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Physiological and Biomechanical Analyses of Rigidity in Parkinson's Disease

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1. Introduction

Parkinson's disease is one of the most common movement disorders characterized by bradykinesia, rigidity, resting tremor and postural instability (Fahn, 2003). It affects nearly five million elderly people worldwide (de Lau & Breteler, 2006). As the population ages, the incidence and prevalence of Parkinson's disease are expected to increase dramatically (Dorsey et al., 2007; Tanner & Goldman, 1996; Tanner & Ben-Shlomo, 1999). Rigidity is one of the clinical hallmark symptoms that characterize and define Parkinson's disease. Rigidity is one form of the increased muscle tone, which is defined as a resistance to a passive movement. Rigidity is clinically characterized by an increase in muscle tone, and is felt as a constant and uniform resistance to the passive movement of a limb persisting throughout its range (Bantam, 2000; Fung & Thompson, 2002; Hallett, 2003). There are two types of rigidity: plastic or lead-pipe rigidity, in which resistance remains uniform, constant and smooth, such as experienced when bending a piece of lead; and cogwheel rigidity, in which tremor is superimposed on increased tone, giving rise to the perception of intermittent fluctuation in muscle tone. The latter is principally attributable to the combination of plastic rigidity and tremor.

In addition to being a key element of parkinsonian rigidity, increased muscle tone also characterizes spasticity which is a common motor symptom in a few other neurological disorders, such as multiple sclerosis, stroke and cerebral palsy. Spasticity is clinically described as an increased resistance to passive movement due to hyperexcitability of stretch reflex (Lance, 1980; Rymer & Katz, 1994). Rigidity and spasticity share the characteristic feature of the increased muscle tone to a passive movement. However, the unique lead-pipe resistance can distinguish the increased muscle tone in rigidity from that associated with spasticity. In particular, the differentiation between rigidity and spasticity is not straightforward in a clinical scenario (Fung & Thompson, 2002).

Rigidity generally responds well to dopaminergic medication and surgical intervention. Thus, it is used as a diagnostic criterion and to evaluate the efficacy of therapeutic interventions (Prochazka et al., 1997). Clinical examination and assessment of rigidity is determined by an examiner's perception of resistance while rotating the limb at major joints, based upon the Unified Parkinson Disease Rating Scale (Fahn & Elton, 1987; Goetz et al., 2008). A better understanding of the physiological and biomechanical characteristics of rigidity merits scientific significance and clinical implication. In this chapter, studies on

elucidation of the physiological mechanisms and biomechanical quantification of parkinsonian rigidity will be reviewed and the latest research on this topic will be presented.

2. Physiological studies of parkinsonian rigidity

2.1 Reflex responses to passive stretch

The history of studying the pathophysiology of rigidity can be traced back to nearly a century ago. Forester's observation (1921) that parkinsonian rigidity is reduced by the dorsal root section suggested that rigidity could be of reflex origin, although other equally plausible explanations are possible. The most widespread view was that rigidity arose from the increased response of muscle receptors to externally imposed stretch. This view was supported by earlier experiments (Pollock & Davis, 1930; Rushworth, 1960), demonstrating that rigidity was substantially reduced by dorsal root section or local anesthetic block.

However, illustration by microneurographic recordings from muscle nerves has provided evidence that increased muscle afferent discharge (due to increased fusimotor drive) was not sufficient to explain the presence of rigidity (Burke et al., 1977). Recent studies using electrophysiological techniques demonstrated that monosynaptic segmental stretch reflexes showed no significant differences between individuals with Parkinson's disease and healthy controls (Bergui et al., 1992; Delwaide, 1985; Delwaide et al., 1986; Meara and Cody, 1993; Rothwell et al., 1983). Numerous studies on stretch reflexes have also shown that most reflexes (H-reflex, tendon jerks and tonic vibration reflex), considered to be principally mediated by Ia afferents and to be spinal in origin, appear normal in Parkinson's disease (Burke et al., 1972a; Dietrichson, 1971; Lance et al., 1973). In brief, there is no evidence that Ia muscle afferent pathway might explain the pathophysiological basis of parkinsonian rigidity.

If the response of the spinal machinery to muscle primary spindle afferent input is intact in Parkinson's disease, supraspinally mediated reflexes might well play a role in the pathophysiology of rigidity. Lee and Tatton (1975) were the first to demonstrate that long-latency stretch reflexes in forearm muscles were exaggerated in patients with Parkinson's disease. This observation was subsequently confirmed by several other investigators who studied rigidity in the same or different muscle groups (Berardelli et al., 1983; Cody et al., 1986; Mortimer & Webster, 1979; Rothwell et al., 1983). Some studies found a quantitative association between the degree of increase in long-latency stretch reflex and the clinically assessed degree of rigidity (Mortimer & Webster, 1979; Berardelli et al., 1983), whereas others found that no correlation existed between the two based on a larger number of patients (Cody et al., 1986; Rothwell et al., 1983). The lack of a consistent correlation might be because rigidity is often assessed using a sustained static stretch whereas long-latency stretch reflexes is elicited by transient and brisk muscle stretches (Marsden, 1990). However, it is certain that patients with parkinsonian rigidity show a marked increase in long-latency stretch reflexes, compared with healthy controls (Marsden, 1990; Fung & Thompson, 2002), though there is no universal agreement as to the origin of the long-latency stretch reflexes (Matthews, 1991). In addition, the tonic muscle response to slow and sustained stretch is reported to be exaggerated in Parkinson's disease (Dietrichson, 1971; Andrews et al., 1972).

Findings obtained from the aforementioned studies provide partial explanations for increased resistance, *i.e.*, one of the two elements defining parkinsonian rigidity. However,

they cannot account for the constancy and uniformity of resistance which is uniquely associated with rigidity. Recent studies have shed light on the underlying mechanism of the uniform nature of parkinsonian rigidity (Xia & Rymer, 2004; Xia et al., 2011). Evidence indicates that shortening reaction and stretch-induced inhibition play pivotal roles in the genesis of lead-pipe characteristics of rigidity.

2.2 Responses to passive shortening – Shortening reaction

Besides abnormal muscle responses to stretch, anomalous reactions in the shortened muscles during a passive joint motion have also been described in Parkinson's disease. More than a century ago, Westphal (1877, 1880) observed muscular contraction in the passively shortened skeletal muscles. Before he observed this phenomenon, he had already studied the muscular contraction in lengthening or stretched muscles. Thus, he named it 'paradoxer Muskel-contraction'. At that time, he also described enhanced activation of tibialis anterior corresponding to the shortening phase in patients who had great difficulty in passively aiding imposed movement. The phenomenon he observed is often referred to as "Westphal's phenomenon". Later, Sherrington (1909) described analogous findings in both the spinal dog and the decerebrate cat under the name "shortening reaction'. This term has been used since then.

Application of electromyographic (EMG) recording method has demonstrated that inappropriate activation of shortened muscles occurs widely in basal ganglia disorders (Rondot & Metral, 1973), and most prominently in Parkinson's disease (Andrews et al., 1972; Angel, 1983; Berardelli & Hallett, 1984; Rondot & Metral, 1973; Xia & Rymer, 2004). An example of shortening reaction is illustrated in Fig. 1B (Xia et al., 2011). During the passive wrist flexion movement, flexor muscles were progressively shortened. There occurred strong muscle activations in the wrist flexor muscles. Shortening reaction has been reported to be manifested in both upper and lower limb muscles. Some investigators suggested that shortening reaction plays an important role in the pathophysiology of rigidity (Angel, 1983; Rondot & Metral, 1973), given that it represents a reflex action that agonistically assists with a passive movement in contrast to antagonistic opposition of a motion caused by stretch reflex. Correlational analysis showed that there was no direct relationship between shortening reaction and changes in muscle tone (Berardelli & Hallett, 1984).

Nevertheless, the neural mechanism of the shortening reaction was virtually unknown. Since shortening reaction was first reported a century ago, very little attention has been paid to exploring its underlying physiology. Shortening reaction is the opposite of stretch reflex, a topic that has been extensively studied for a long period of time. In contrast, only a limited number of studies were conducted to understand and characterize shortening reaction, and these previous studies simply monitored muscle electromyographic activity (Andrews et al. 1972; Angel, 1983; Berardelli et al. 1983; Berardelli and Hallett, 1984; Rondot and Metral, 1973). The importance of shortening reaction in the pathophysiology of parkinsonian rigidity is undoubtedly underestimated. Utilization of both EMG recording and joint torque measure has provided us with useful information to reveal the role of shortening reaction in mediating rigidity in Parkinson's disease (Xia & Rymer, 2004; Xia et al., 2011). A parallel mechanism responsible for mediating parkinsonian rigidity is stretch-induced inhibition which will be discussed in the next section.
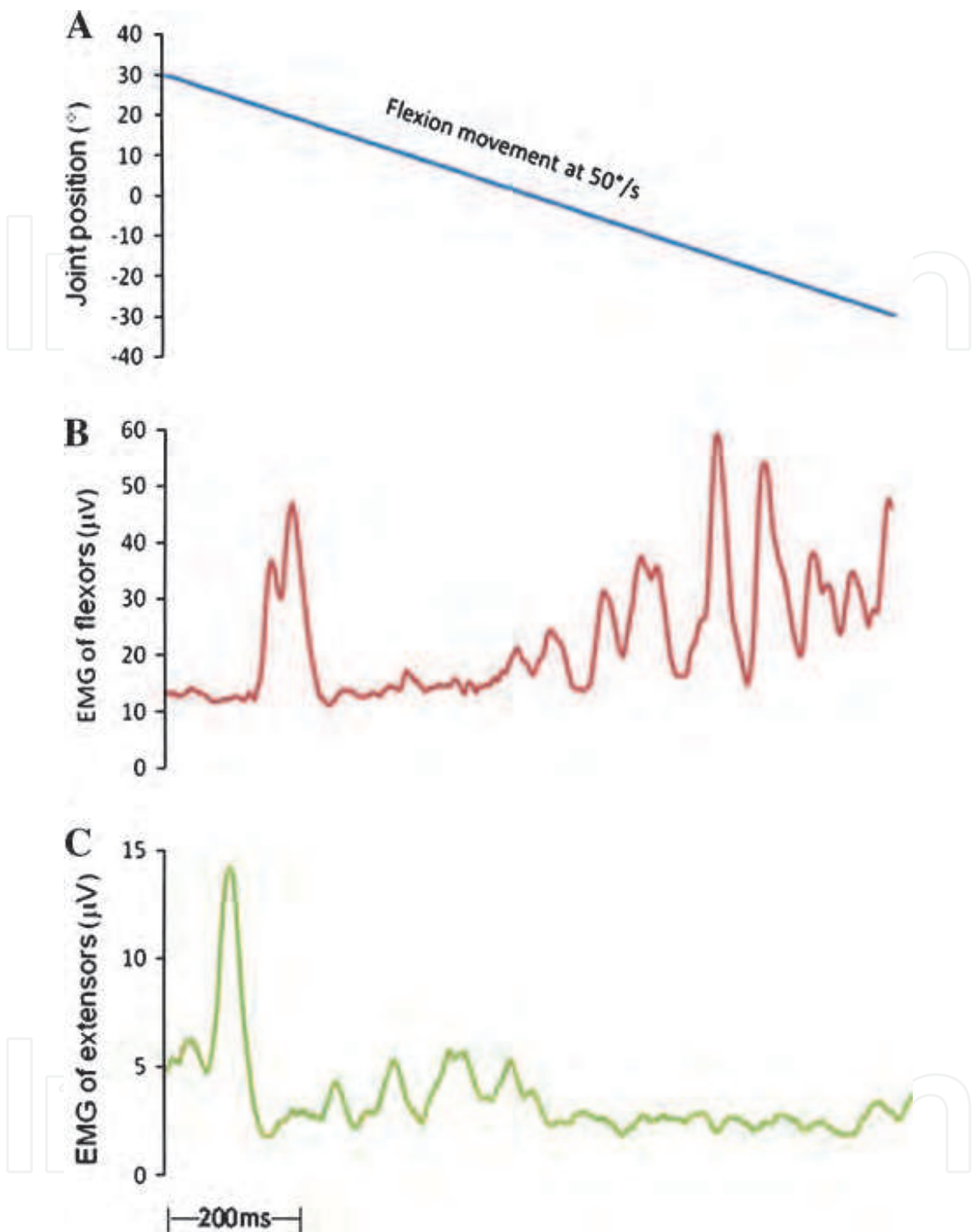
Fig. 1. Kinematic and EMG recordings during passive flexion movement obtained from a patient after an overnight withdrawal of medication (Off-medication). **A.** Wrist joint position during the passive flexion movement; the subject's wrist joint was externally rotated from 30 degree to -30 degree at 50°/s. **B.** Shortening reaction was recorded in shortened flexors in the Off-medication state in a parkinsonian subject. There was an increased EMG activation in passively shortened muscles. **C.** Stretch-induced inhibition was observed in the stretched extensor muscles during the same movement. There was an EMG reduction, when the stretch exceeded the neutral position and the muscle length was elongated [from Xia et al. (2011) with permission].

2.3 Lengthening reaction or stretch-induced inhibition

In addition to shortening reaction, Sherrington (1909) also observed in the above-noted animal preparations that "… *when an examiner bent the knee against the knee-extensor's contraction, the examiner felt the opposition offered by the extensor gave away almost abruptly at a certain pressure; the knee could then be flexed without opposition ...*". He named this phenomenon "lengthening reaction". Lengthening reaction was demonstrated in both spinal dog and in decerebrate rigidity of the cat, yet the reaction was recognized to have differential features in the two preparations. In his monograph, he also pointed out that muscles, exhibiting shortening reaction and lengthening reaction, were all extensor muscles. The distinction of the flexor and extensor muscle groups has been documented in parkinsonian rigidity (Mera et al., 2009; Xia et al., 2006).

The well-know clasp-knife phenomenon associated with human spasticity, appears to be the equivalent of the lengthening reaction (Burke et al., 1970, 1971). The clasp-knife reflex is characterized by an abrupt decline in muscle force that occurs when a spastic limb is moved beyond a certain joint angle. There is a common ground between lengthening reaction in animal preparations (Burke et al., 1972b; Rymer et al., 1979) and clasp-knife reflex in human spasticity in that the essential feature of both phenomena is the sudden release of the resistance due to continuous stretch of the elongated muscle, hence also referred to as "stretch-induced inhibition" (Rymer et al., 1979). The physiological framework previously established or explored in the context of the lengthening reaction or stretch-induced inhibition has recently been investigated in parkinsonian rigidity (Xia & Rymer, 2004; Xia et al., 2011).

Fig. 1C illustrates a stretch-induced inhibition recorded from a parkinsonian patient in the Off-medication state. During the passive flexion movement (Fig. 1A), there was a large initial stretch reflex in the wrist extensor muscles. The initial stretch reflex was followed by a period of sustained activity and curtailed by an evident decline when the progressive movement approached at almost the neutral position and the muscle length of the extensors was elongated, demonstrating the stretch-induced inhibition (Fig. 1C). It is noted that both shortening reaction and stretch-induced inhibition occur during the same movement phase (Fig. 1). The importance and functional role stretch-induced inhibition and the above described shortening reaction may have played in parkinsonian rigidity will be explained and discussed in Section 3.

3. Pathophysiological mechanisms of lead-pipe rigidity

This session will begin with an overview of the basic principles of muscle mechanics. When an active muscle is stretched, the muscle force output increases proportionally with the increasing muscle length. The dependence of muscle force on muscle length gives rise to a "spring-like" behavior (Gordon et al., 1966; Matthews, 1959; Rack & Westbury, 1969). This spring-like property of skeletal muscle has been shown to play a key role in the maintenance of posture and control of movement. A limb's posture is maintained when the forces exerted by agonist and antagonist muscle groups are equal and opposite.

Rotational movements about human joints are promoted by a resultant torque which is a summation of the individual contributions of agonist muscles minus contributions of antagonist muscles, where a single torque is mathematically defined as the product of force times the moment arm for each muscle. The corresponding measure of rotational position is the joint angle, which determines the length of each muscle acting on the joint. Ultimately, it

is the torque-angle relationship that serves to characterize the musculature of the joint as a whole (Feldman, 1966). Given the phenomenon that individual muscles are characterized by the length-tension relationship or spring-like property, thus the net torque-angle relation, arising from the summation of the stretched muscles and shortening muscles in normal subjects, manifests a steep curve. Fig. 2A shows that the net torque-angle characteristics of the joint arising from the summation of the spring-like properties of the stretched flexor muscle and shortening extensor muscle display spring-like behavior in healthy subjects, which is characterized by a steep torque-angle curve.

However, the natural spring-like property can be altered, generating a relatively flat torque-angle relationship that is equivalent to a plastic sensation perceived in parkinsonian rigidity. Such a flattened torque-angle relationship can be resulted from either the impact of a shortening reaction or a stretch-induced inhibition or a combination of the two. In the case of parkinsonian rigidity (Figs. 2B-2D), the torque produced by the stretched muscles (i.e., wrist flexors in this example) is increased due to the exaggerated long-latency stretch reflexes (Lee & Tatton, 1975) and enhanced tonic muscle responses (Dietrichson, 1971). There are two ways in which a joint could generate relatively constant torque with the changing joint position. Firstly, if there is an inappropriate shortening reaction in parkinsonian rigidity, the increasing force generated by the stretched flexor is offset by increasing activation of the shortening extensor. This muscle interaction could lead to a flat net torque-angle relationship, and promote the perception of the constant rigidity. Fig. 2B shows the potential interactions between stretched and activated shortening muscle in the presence of a shortening reaction. Another possibility, shown in Fig. 2C, is that a reduction in activation of stretched muscle at an elongated muscle length counteracts the otherwise gradual increase in muscle force (i.e., spring-like or elastic-like muscle force) as the muscle length of the stretched flexors is elongated throughout the stretch. Due to this counteracting effect, the net torque is relatively constant throughout the rotation of the limb. During the passive flexion or extension movement, one group of muscles is shortened whereas the other group is stretched. Both shortening reaction and stretch-induced inhibition have counteracting effects within a specified movement, generating the promotion of constant rigidity (uniformity) as defined in rigidity. Fig. 2D schematically illustrates the net torque resulting from a combined effect of the two mechanisms.

During passive movements, one group of muscles is shortened whereas the other group of muscles is stretched. Thus, the two mechanisms are potentially generating counteracting effects on the net torque resistance simultaneously. However, a dissociation of the two mechanisms is not readily available and technically challenging. Application of a biomechanical model (Holzbaur et al., 2005) implemented through the Software for Interactive Musculoskeletal Modeling (Delp & Loan, 1995) made it possible to quantify the torque generated by shortening muscles and by stretched muscles, separately, and to identify which mechanism predominates. Our findings obtained through the biomechanical modeling approach indicate that both shortening reaction and stretch-induced inhibition contribute significantly to the lead-pipe nature of parkinsonian rigidity (Xia et al., 2011). During the passive flexion movement, shortening reaction plays a predominant role in the genesis of lead-pipe rigidity, whereas stretch-induced inhibition is a primary contributor to the manifestation of lead-pipe rigidity during the passive extension movement. The knowledge gained from these studies provides new insights into the biomechanical and

physiological underpinnings of this common symptom in patients with Parkinson's disease. The use of this approach may offer a means of assessing the efficacy of rehabilitation programs and therapeutic interventions. Efficacy of anti-Parkinson medication on the biomechanical and physiological characteristics associated with parkinsonian rigidity will be discussed in later section of this Chapter.
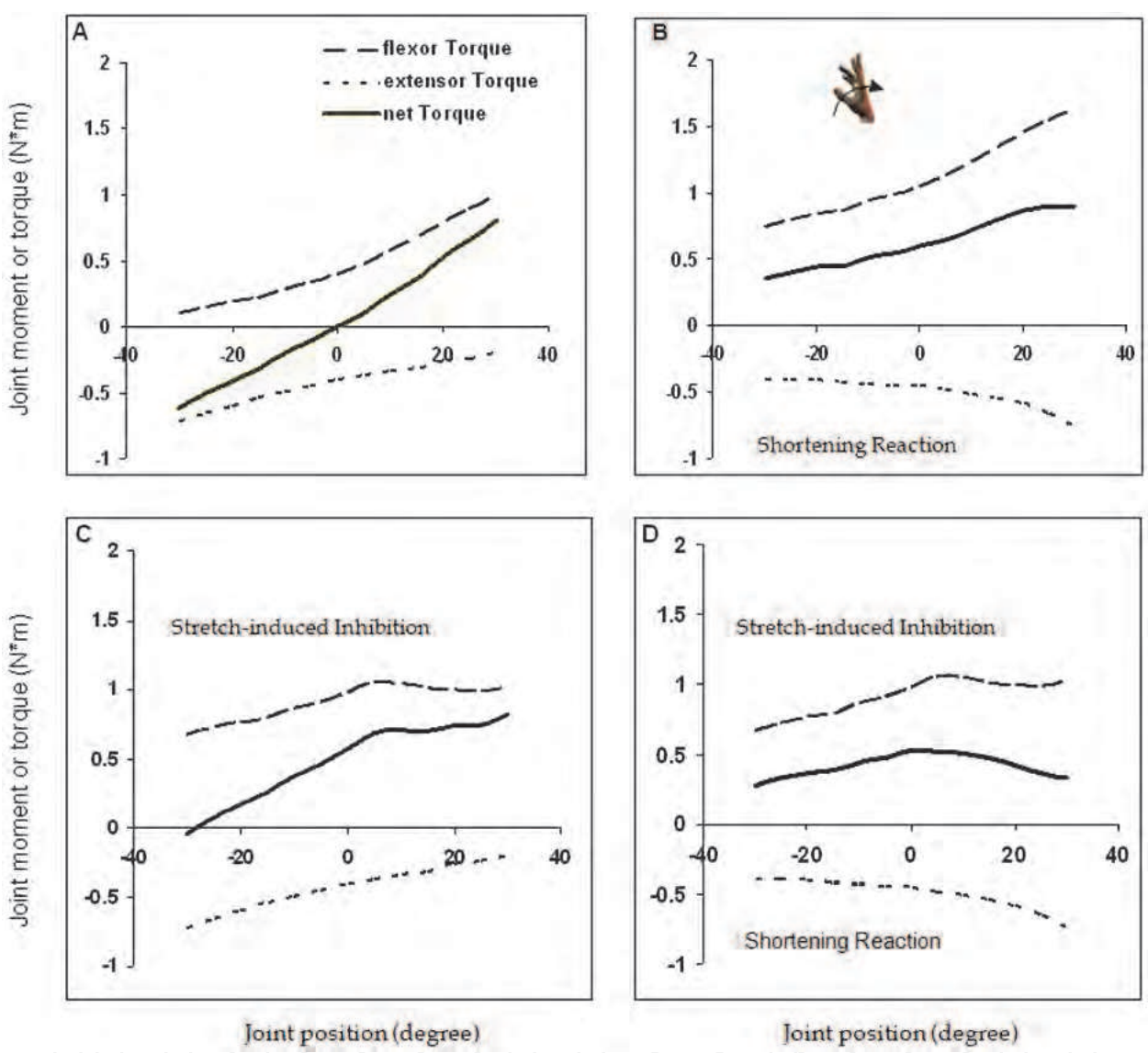

Fig. 2. Schematics of the net (solid line) torque-angle relationship showing four possible types of interactions between stretched and shortening muscles during extension of a right wrist. **A**: torque-angle relationship characterizing spring-like property of the stretched flexor and shortening extensor muscles in healthy subjects; **B**: the potential impact of a shortening reaction in the extensor muscles (contributing to extensor torque), inducing a flattened net torque-angle relation and promoting the perception of the constant rigidity; **C**: the effect of a stretch-induced inhibition in flexor muscles, causing spring-like force generated by a muscle stretch to decline as the muscle length increases. **D:** The combined effect of shortening reaction and stretch-induced inhibition on the net torque. The units and torque curves are arbitrary.

4. Non-neural factor responsible for parkinsonian rigidity

Evidence has indicated that in addition to neural-mediated abnormal muscle reflex responses, the non-neural component also contributes to parkinsonian rigidity (Dietz, 1987; Dietz et al., 1981; Watts et al., 1986). The non-neural component includes visco-elastic (i.e., mechanical) properties of muscle fiber and passive connective tissues. Dietz et al. (1981) examined ten patients with parkinsonian rigidity aiming to identify the physiological mechanism with respect to altered muscle activity to account for impaired gait pattern in Parkinson's disease. Compared to healthy control subjects, parkinsonian patients exhibited significantly stronger EMG activity in tibialis anterior during the swing phase of gait, while the strength and timing of EMG activity recorded from triceps surae were similar in two groups of participants. The authors stated that the increased muscle tone in parkinsonian rigidity cannot be explained by the electrical activity of the antagonist muscle groups of the limb, since there was no co-contraction of tibialis anterior and triceps surae muscles. It was concluded that the altered mechanical properties of muscle fibers were mainly responsible for the increased muscle tone in rigidity. This conclusion was also drawn by Watts et al. (1986) who examined elbow joint of patients with Parkinson's disease and normal controls by using a torque motor. Even in patients with relatively mild symptoms, the upper limb was stiffer than controls in the totally relaxed state with no EMG activity present. The study findings suggested that changes in the passive mechanical properties of the upper limb likely accounted for greater passive stiffness. Using the torque motor, natural progression of the disease can be quantified and followed.

Evidence indicates that neural and non-neural mechanisms operate in parallel, both contributing to parkinsonian rigidity. However, there is no simple and easy solution in differentiation and quantification of the neural and non-neural components because clinical measures of rigidity consist of the two parallel components. Using advanced technology and computational algorithm, a few sophisticated approaches have been developed to segregate the two responsible factors and quantify the individual component contributing to the overall joint stiffness (Kearney et al., 1997; Meinders et al., 1996; Sinkjaer et al., 1993; Sinkjaer & Magnussen, 1994; Zhang & Rymer, 1997). One approach, termed as parallel-cascaded system identification technique, was initially applied to separate the overall stiffness into neural reflex stiffness and non-neural mechanical stiffness at ankle joint in normal healthy adults (Kearney et al., 1997; Mirbagheri et al., 2000). Subsequently, the system identification approach has been applied to characterize the dynamic joint stiffness and to quantify the neural and non-neural contribution to the abnormal muscle tone in spasticity associated with upper motor neuron syndromes, such as stroke and spinal cord injury (Alibiglou et al., 2008; Galiana et al., 2005; Mirbagheri et al., 2001, 2009, 2010). The validity of this method has been demonstrated as well as its efficiency, accuracy and advantages by Mirbagheri et al. (2000) and Alibiglou et al. (2008).

More recently, we have applied the parallel-cascaded system identification technique to make a distinction between the neural and non-neural contributions to rigidity in patients with Parkinson's disease (Xia et al., 2010). Patients participated in the protocol under two medication states: initially under a temporary overnight withdrawal of dopaminergic medication and then after the resumption of medication. The results have shown that both neural and non-neural components contributed to parkinsonian rigidity, with the neural component being predominating over the non-neural to the overall rigidity. Medication therapy caused a reduction of torque resistance in the neural reflex torque, but did not

decrease the non-neural mechanical torque. This observation appears to be attributed to the mechanism of anti-Parkinson medication therapy.

5. Biomechanical quantification of parkinsonian rigidity

In clinic, parkinsonian rigidity is examined and assessed using a numerical rating scale which is known as the Unified Parkinson Disease Rating Scale (Fahn & Elton, 1987; Goetz et al., 2008). However, the nature of this assessment tool is highly qualitative and subjective because it is largely dependent on examiners' individual interpretation and experience (Patrick et al., 2001; Prochazka et al., 1997). When the actual change in rigidity resulting from treatment is small, it may be challenging for the examiners to detect. This can limit ability for evaluation of treatment effectiveness especially in large multi-center clinical drug trials in which a large number of investigators are involved, because differences can exist between different examiners (i.e., inter-rater) and between assessments performed on different visits by a given examiner (i.e., intra-rater) with respect to the efficacy of treatment. Reliability studies have demonstrated varying degrees of inter-rater reliability with respect to rigidity component of clinical rating tools, ranging from low, moderate, very good to excellent (Martinez-Martin, 1993; Rabey et al., 1997; Richards et al., 1994; Van Dillen & Roach, 1988). A need for more accurate evaluations has been expressed to improve the management of symptoms in patients with Parkinson's disease (Obeso et al., 1996; Ondo et al., 1998; Ward et al., 1983).

During the past several decades, considerable efforts have been made aiming to quantify assessment of parkinsonian rigidity by means of biomechanical measures. A variety of quantitative methods have been developed to measure the dynamics of joint stiffness associated with rigidity (Lee et al., 2002; Prochazka et al., 1997; Teräväinen et al., 1989; Watts et al., 1986; Wiegner & Watts, 1986). The underlying approach is to measure the amount of imposed force resistance to externally generated passive movement about the examined joint. The passive movements applied in earlier studies were induced either by a torque motor (Fung et al., 2000; Mak et al., 2007; Shapiro et al., 2007; Watts et al., 1986; Xia et al., 2006) or generated by an examiner to closely resemble a clinical setting (Caligiuri, 1994; Endo et al., 2009; Patrick et al., 2001; Prochazka et al., 1997; Sepehri et al., 2007). Variables described in these previous studies included peak torque (Mak et al., 2007), impulse (i.e., an integral of torque with respect to time; Fung et al., 2000), work score which is calculated as a torque integral with respect to joint angular position (see Fig. 3; Fung et al., 2000; Mak et al., 2007; Shapiro et al., 2007; Teräväinen et al., 1989; Xia et al., 2006, 2009), elastic coefficient (Endo et al., 2009), and mechanical impedance calculated based on the force imposed and displacement of the movement (Patrick et al., 2001; Prochazka et al., 1997).

There are a few advantages of quantification by force or torque measures over quantification by EMG. Torque-based assessment of rigidity is more objective and reliable than EMG-derived evaluation. However, there are limitations in estimation of using surface EMGs as its measures are susceptible to the placement of electrodes, condition of soft tissues and concerns of cross-talk. Biomechanical measures using torque can avoid the limitations inherent in EMG measures. In addition, non-neural contribution to parkinsonian rigidity is also included in torque measures but is not reflected in EMG recordings. Previous studies have shown that correlation is relatively weak between clinical degree of rigidity and EMG quantification of rigidity while correlation is found to be much stronger between clinical degree of rigidity and torque quantification of rigidity (Endo et al., 2009; Levin et al., 2009;

Park et al., 2010; Teräväinen et al., 1989). Evidence indicates that torque measure has proven to be a more objective and robust way for assessing rigidity, compared to EMG evaluation of rigidity.
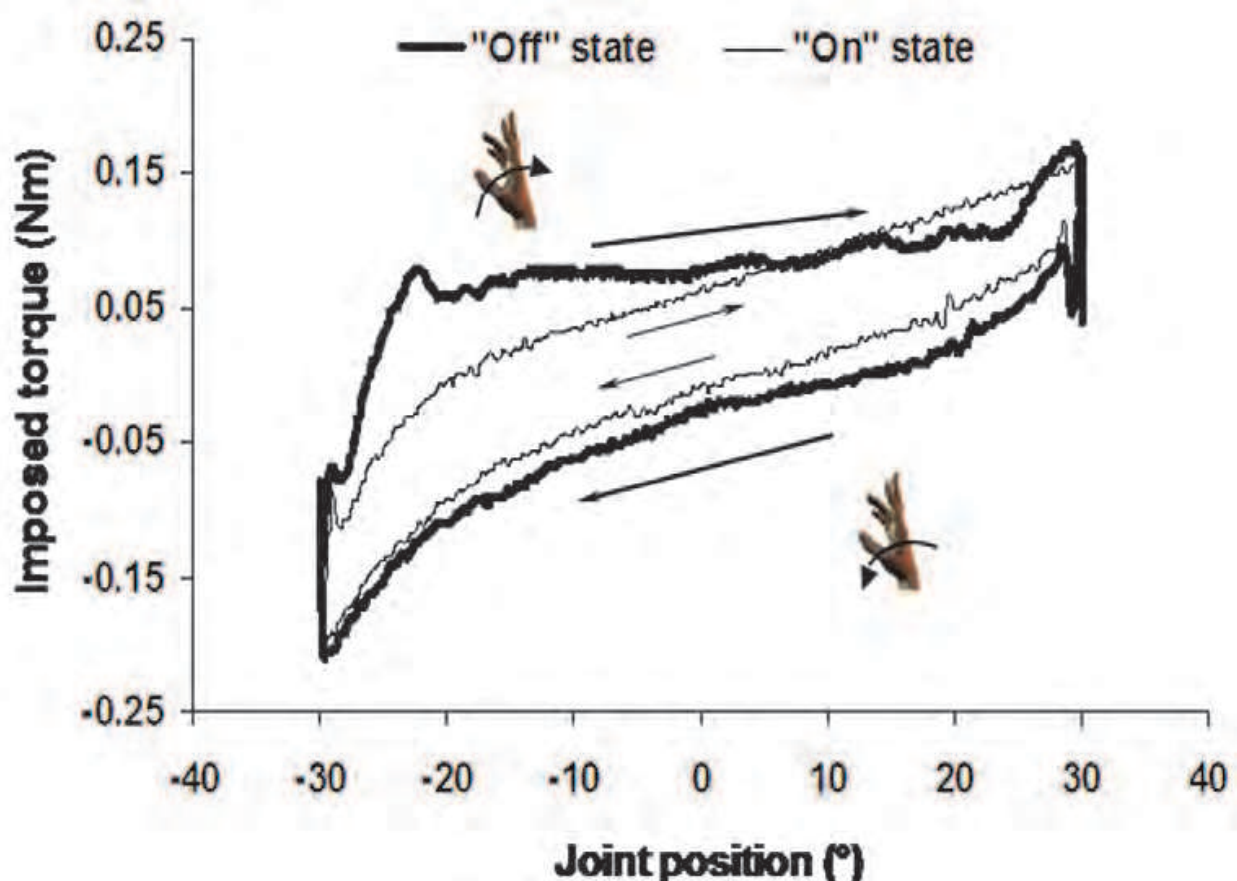

Fig. 3. Torque-angle relationship in a parkinsonian subject in the Off-medication (thicker line) and On-medication (thinner line) states. The subject's more affected side was tested. The upper traces represent imposed extension movements and the lower traces flexion movements. The wrist joint was externally rotated at 50 °/s between 30° flexion and 30° extension shown as a loop. The subject was instructed to remain relaxed. The work, used to quantify the degree of rigidity, was equivalent to the areas inside the loop of torque-angle plots in the respective medication states [from Xia et al. (2006) with permission].

Application of biomechanical measures has also enabled us to investigate more profoundly some of the characteristics associated with parkinsonian rigidity, thus further increasing our understanding of this motor symptom. Firstly, only through the measures of torque resistance and joint position, can lead-pipe nature of rigidity be examined and revealed (Mera et al., 2009; Xia & Rymer, 2004; Xia et al., 2006, 2011). The slope of torque-angle curve was used to quantify the degree of lead-pipe property. The smaller slopes represent higher degrees of constant and uniform resistance through the range of passive movement. The torque-angle slopes are smaller when patients were tested in the untreated conditions, and become greater in the treated conditions (Xia & Rymer, 2004; Xia et al., 2006).
Secondly, rigidity has been thought to be plastic with respect to direction of the movement (Berardelli et al., 1983; Delwaide, 2001). However, recent studies employing the

biomechanical measures have demonstrated that rigidity associated with extension movement is more evident as compared to rigidity during flexion movement in the upper limb including the wrist and elbow (Mera et al., 2009; Park et al., 2010; Xia et al., 2006). These authors used mechanical parameters, such as work, torque-angle slope and visco-elastic parameter, to evaluate the difference and distinction between the passive flexion and extension movements.

Thirdly, parkinsonian rigidity has traditionally been considered to be independent of velocity in contrast to spasticity which is highly velocity-dependent (Lance, 1980). The notion of velocity-independency of rigidity might be anecdotal. As such, this view has been examined by a few recent studies. Lee et al. (2002) studied hypertonia at the elbow joint in patients with Parkinson's disease and patients with hemiparesis as compared to control subjects. Four different stretching velocities were applied, ranging from 40 to 160 °/s. The authors concluded that both rigidity and spasticity have approximately equal velocity-dependent property. Quantitative measure of trunk rigidity in patients with Parkinson's disease also revealed a velocity-dependent feature (Mak et al., 2007). Our results on the effect of movement velocity on rigidity concurred with those reports. Velocity-dependency of rigidity was also demonstrated at the wrist joint of patients with Parkinson's disease (Xia et al., 2009) in which both slow velocity at 50 degree/second and fast speed at 280 °/s were applied. The results showed that the work done during the fast movement was significantly larger than the work associated with the slower movement. The accumulating evidence has pointed out the velocity-dependency of parkinsonian rigidity.

Fourthly, compared to the effect of movement velocity on quantitative analysis of parkinsonian rigidity, effect of displacement amplitude on rigidity has thus far sparsely been investigated, except for one study by Teräväinen et al. (1989). To determine the optimal angular velocity and displacement amplitude for detecting abnormal muscle tone, four movement amplitudes or central ranges of motion, ranging from ±15, ±20, ±25 to ±30 degrees, were applied to examine rigidity at the wrist joint in 29 patients with Parkinson's disease. The results showed that the larger movement amplitudes were more sensitive for detecting parkinsonian rigidity and had stronger correlation with the clinical scores of rigidity. Given the situation that some clinicians rotate the limb back and forth rapidly in the mid-range whereas others focus on the extremes of range of motion or the entire range of motion with slow stretches (Prochazka et al., 1997), it is important and significant to explore the influence of displacement amplitude on objective measurements of rigidity. We recently conducted a study aiming to examine the effect of displacement amplitude. Twenty four patients participated in the experiment under treated (On-medication) and untreated (Off-medication) conditions, with the more affected side of the wrist joint tested. Passive movements of wrist flexion and extension were imposed with two displacement amplitudes, ±30 degree and ±45 degree, respectively, at either 50 °/s or 280 °/s, and the order of movement pattern was presented in a random fashion. Figure 4 depicts and compares the torque-angle plots associated with two ranges of motion: 60 degree (Fig. 4A) and 90 degree (Fig. 4B), in a parkinsonian subject under the two medication conditions. The work score was calculated to quantify rigidity, and was normalized to the range of motion to validate the comparison. Clearly, there is a difference in the area of the torque-angle loop between the two displacement amplitudes or the ranges of motion. Figure 4B shows that the extreme joint position, the larger displacement amplitude, caused increase in rigidity work score.
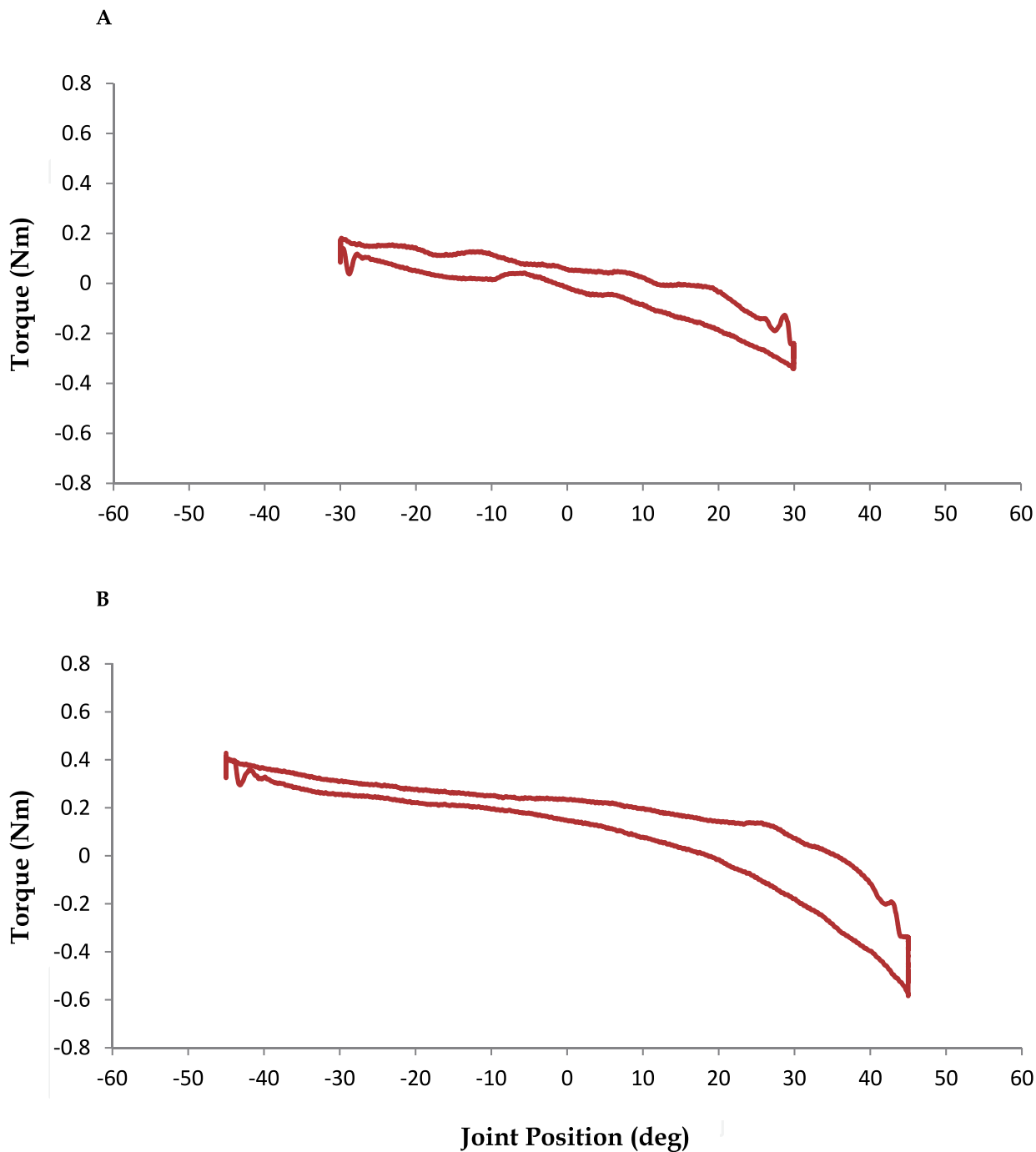
A

B

Joint Position (deg)

Fig. 4. Comparison of torque-position traces of passive flexion and extension movements of two ranges of motion: 60° (A) and 90° (B) at angular velocity of 50° /s from a subject with Parkinson's disease tested in the Off-medication state. The rigidity score, quantified by the integral of the torque with respect to angular position (Nm-deg), increased in response to the greater range of motion. Upper traces are associated with extension movements while lower traces are associated with flexion movements [from Powell et al. (in press) with permission].

Finally, the phenomenon that rigidity can be reinforced by a concurrent ipsi- or contra-lateral voluntary activation has recently been further quantified using biomechanical measures (Hong et al., 2007; Powell et al., 2011). Figure 5 illustrates torque-angle traces of the entire cycle of flexion and extension movements when a subject with PD was tested in the Off-medication condition. Torque resistance was elevated by the presence of contra-lateral activation (Active condition) as compared to the Passive condition. There is an obvious difference in the contained area of torque-angle plots between the Passive and Active conditions. These studies aimed to provide quantitative data and objective evaluation of clinical assessment of rigidity as a component of the Unified Parkinson Disease Rating Scale (Fahn & Elton, 1987; Goetz et al., 2008). The type of voluntary activations applied in clinical examinations include a variety of motor acts such as tapping fingers, fist opening–closing or heel tapping. The use of reinforcing maneuvers was originated and first investigated by Jules Froment, a French neurologist, in the 1920's (Broussolle et al., 2007). Froment studied muscle tone at the wrist joint while the subject was in different positions, at rest in a sitting position, and standing in stable and unstable postures. In addition to clinical examination, Fremont also conducted experiments recording activity of forearm extensors using a myograph. He described an increased resistance to passive movements of a limb about a joint during the presence of a voluntary action of a contralateral body part. Due to his contributions to the study of parkinsonian rigidity, the activation or facilitation test has been referred to as the "Froment maneuver". The impact of facilitation test is significant as it has been formalized in the motor scale of the Unified Parkinson Disease Rating Scale. The maneuver is particularly used to detect increased muscle tone at an early stage of the disease when rigidity is not otherwise manifested during the examination.

6. Effect of anti-Parkinson medication on physiological and biomechanical measures of rigidity

Rigidity generally responds well to anti-Parkinson medication. Several studies have examined the changes in muscle activation, joint torque resistance and torque-angle slope associated with rigidity reduction as a result of medication therapy (Kirollos et al., 1996; Mera et al., 2009; Powell et al., 2011; Xia & Rymer, 2004; Xia et al., 2006, 2009). Following a standard protocol, patients are tested initially in the Off-medication state, *i.e.*, 12 hours after the last dose of medication when the majority of the beneficial effects of medication therapy are eliminated (Defer et al., 1999). Twelve-hour overnight withdrawal of medication has been broadly used to examine the effect of medication on motor performance and on basal ganglia function (Brown & Marsden, 1999; Corcos et al., 1996; Jahanshahi et al., 2010; Robichaud et al., 2004; Tunik et al., 2004). After the initial tests are completed, patients are retested approximately one hour after taking their regular dose of medication in the On-medication state. These studies have demonstrated that stretch-reflex and shortening reaction are diminished following the treatment (Powell et al., 2011; Xia & Rymer, 2004). The same effects are observed in the changes associated with torque resistance (Kirollos et al., 1996; Mera et al., 2009; Xia et al., 2006, 2009). Further, torque-angle curves associated with the On-medication test become steeper, manifesting the spring-like feature and the typical length-tension relationship (Gordon et al., 1966; Matthews, 1959; Rack & Westbury, 1969; Xia et al., 2006, see Fig. 2).
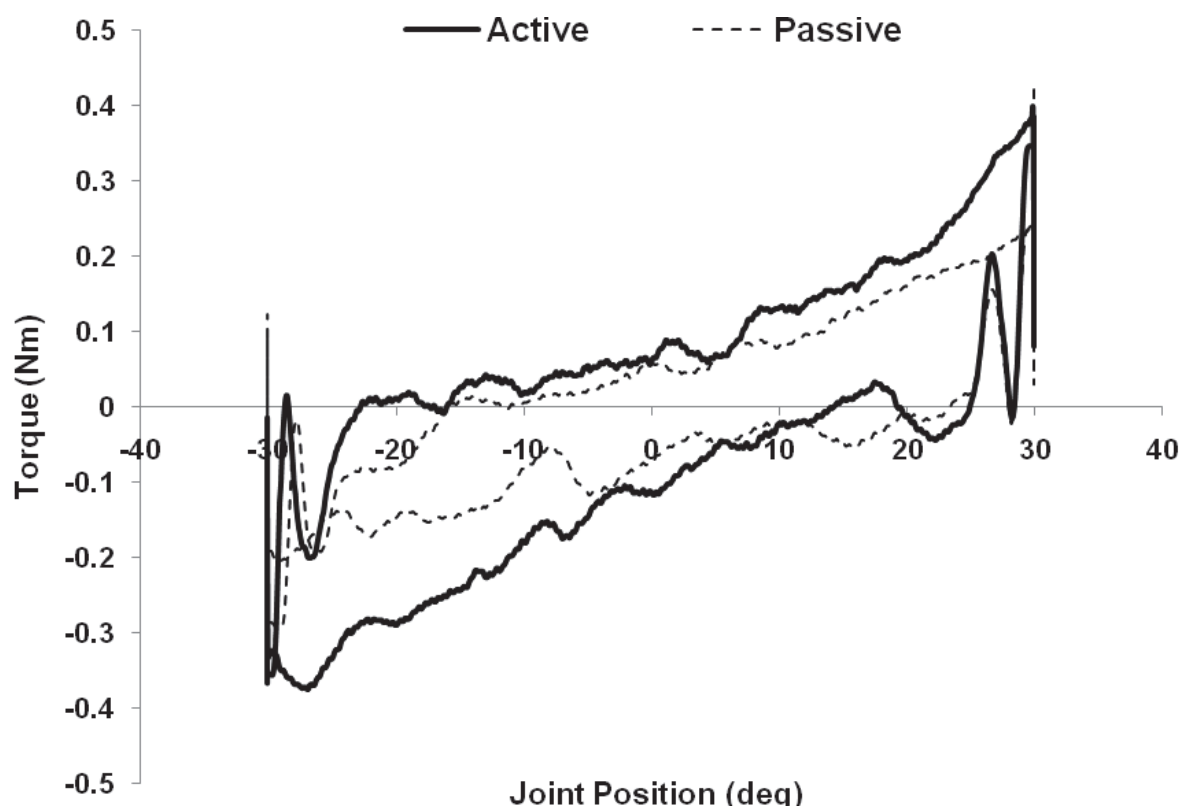
Fig. 5. Comparison of torque-angle traces between the Passive (dashed) and Active (solid) conditions recorded in a subject with Parkinson's disease under the Off-Medication condition. Under the Active condition, passive movement of the wrist joint was concurrent with a contra-lateral hand gripping activation at 20% of maximal voluntary contraction. Rigidity score, calculated as the integral of the torque with respect to position for the entire cycle of flexion and extension movements, was enhanced under the Active condition. Upper traces are associated with the passive extension movement and the lower ones with the flexion movement [from Powell et al. (2011) with permission].

Effects of deep brain stimulation of the subthalamic nucleus in conjunction with medication have also been evaluated on the work rigidity and clinical rigidity scores in patients with Parkinson's disease (Shapiro et al., 2007). Subjects' elbow joints were tested under four experimental conditions determined by various combinations of medication (Off vs. On) and deep brain stimulation (Off vs. On) status. Treatment by deep brain stimulation reduced rigidity as indicated by work score and by rigidity score on the Unified Parkinson Disease Rating Scale. The results suggested that the surgical treatment may be more effective in alleviating rigidity in the upper limb of parkinsonian patients than medications administered at pre-surgery dosage level.

7. Interaction of rigidity with other motor symptoms

Parkinson's disease is characterized by both motor and non-motor related symptoms. Motor symptoms, often referred to as cardinal symptoms, include bradykinesia (slowness and decreased amplitude of movement), muscle rigidity, tremor-at-rest, and postural instability.

According to the diagnostic criteria, clinical diagnosis is based on two cardinal features of the disease (Fahn & Sulzer, 2004; Lang & Lozano, 1998). Parkinson's disease is a heterogeneous disease both across different patients and during the natural progression of the same patient. The heterogeneity of the disease among different patients is reflected by multiple sub-types of Parkinson's disease, i.e., akinetic-rigid type, tremor-predominant type, and postural instability gait difficulty sub-type (Burn et al., 2006; Hallett, 2003; Jankovic et al., 1990). Bradykinesia is labeled as a negative symptom due to its describing the poverty and slowing of voluntary movement, whereas rigidity and tremor are referred to as positive motor symptoms.

Many clinical studies have indicated that the distinctions are significant among the hallmark motor symptoms although they share similarities and common origins (Elias et al., 2008). The distinctive nature has also been revealed by Temperli and coauthors (2003) who studied the reappearance of the clinical signs of Parkinson's disease when subthalamic nucleus deep brain stimulation was switched off in 35 patients treated with implanted deep brain stimulators. Authors reported that a sequential pattern of return of motor signs was observed, with a fast worsening of tremor within 10 to 15 minutes, followed by a smoother, slower worsening of bradykinesia and rigidity over half an hour to an hour, and finally a slow and steady worsening of axial signs over three to four hours. When switching the stimulation "on" again, all motor signs improved with a similar pattern. It was concluded that the four major parkinsonian signs may respond to brain stimulation by different mechanisms.

8. Clinical interventions of Parkinson's disease

Our knowledge and understanding of Parkinson's disease have dramatically increased over the past years, consequently shifting the descriptions of this disease. Parkinson's disease, previously considered to be characterized by only motor symptoms (bradykinesia, rigidity, resting tremor and postural instability), is now viewed as a disease affected by both motor symptoms and a range of non-motor symptoms such as depression, disturbed sleeping patterns, fatigue, hallucination, cognitive impairments, changes in ability to taste or smell and a few other domains. Only during the last couple of decades or so, non-motor related symptoms have begun receiving attention in medical and research communities. As a result, a number of clinical rating tools have been developed to target specific or general non-motor symptoms (Brown et al., 2005; Chaudhuri et al., 2007).

Rigidity is treated as part of parkinsonian motor symptoms. Among the motor symptoms of Parkinson's disease, bradykinesia and rigidity are the signs that are most responsive to medication and surgical treatments. A variety of pharmacological and surgical interventions are available for the management of Parkinson's disease. Levodopa was the first major breakthrough in the treatment of Parkinson's disease, and still remains the "gold standard" in the management of symptoms. Levodopa is converted in the brain into dopamine to replenish the brain's dwindling supply in patients with Parkinson's disease. The introduction of dopamine agonists was a milestone in the treatment of parkinsonian symptoms. In contrast to levodopa, dopamine agonists act directly on dopamine receptors in the brain, and thus can help alleviate the symptoms of Parkinson's disease. Based on preclinical observation, there is an increasingly popular theory known as continuous dopamine agonist stimulation that helps to prevent the occurrence of long-term complications.

However, with the treatment of medication on advanced stage of this progressive disease, many patients experience motor complications, which is broadly classified as "wearing off reactions", "On-Off reactions", dyskinesia, confusion, sleepiness, hallucination, and low blood pressure when standing (Stacy, 2009). In patients who are severely affected or in those who fail to respond satisfactorily to pharmacological therapy, surgical treatments have reportedly been effective in reducing symptoms and improving function. These include pallidotomy, thalamotomy and subthalamotomy, and high frequency deep brain stimulation via electrodes implanted in the globus pallidus, thalamus (a "relay station" deep in brain), or subthalamic nucleus. Rigidity can be specifically improved by subthalamic nucleus deep brain stimulation (Temperli et al., 2003).

9. Conclusion

Evidence has indicated that no single mechanism can account for parkinsonian rigidity, which is influenced by a multitude of physiological phenomena and biomechanical features. Treatment of rigidity primarily involves an administration of dopaminergic medication. However, serious side effects usually occur after a few years' drug treatment. Therefore, rehabilitative programs are highly desirable for patients with Parkinson's disease. A better understanding of the comprehensive characteristics of parkinsonian rigidity is crucial for designing effective evidence-based exercise program and physical therapy intervention. An objective assessment of rigidity is essential for evaluating the efficacy of therapeutic interventions, especially in large clinical studies in which trials are conducted across multiple centers.

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11. References

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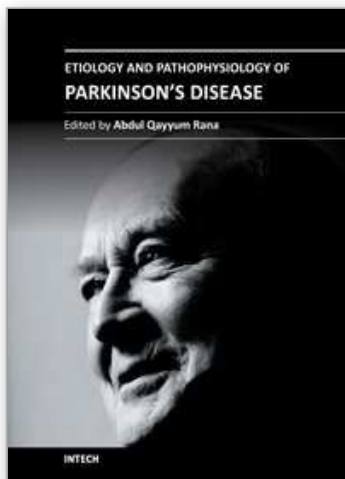
Etiology and Pathophysiology of Parkinson's Disease

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This book about Parkinson's disease provides a detailed account of etiology and pathophysiology of Parkinson's disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinson's disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinson's disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinson's disease.

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