DISCHARGES IN HUMAN MUSCLE AFFERENTS DURING MANUAL TASKS

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Sweden, 2008
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ABSTRACT


Muscle spindles are complex sensory organs that have been strongly implicated in the control and perception of movements. Human muscle spindles in relaxed muscles behave as stretch receptors, responding to the length and velocity of their parent muscles. However, it has been unclear how they discharge during active movements since their discharges are also affected by fusimotor activity and extrafusal contractions. The vast majority of neurophysiological recordings of muscle afferents have been obtained under passive conditions, or active but behaviourally restricted conditions. These restrictions prevent predictions of human muscle afferent activity during purposeful multi-joint movements, naturally occurring during tasks such as hand shaping, grasping or key-pressing.

An experimental protocol was therefore developed which allowed recordings of muscle receptor afferent activity using microneurography during un-restrained wrist and digit movements. Along with single afferent discharges, recordings were obtained of electromyographic activity of major forearm muscles and the kinematics of the wrist and digits. This approach allowed investigations of the factors shaping afferent discharge during everyday manual tasks, i.e., block-grasping and pressing sequences of keys, and during active sinusoidal joint movements. The afferents’ ability to encode information concerning the state of the muscle and joint kinematics during these tasks was also assessed.

The responses of spindle afferents from load-bearing muscles were approximately 90 degrees more phase-advanced than expected on the length of their parent muscles. That is, the discharges of primary muscle spindle afferents were significantly affected by both velocity and acceleration, the discharges of secondary afferents by velocity, and neither afferent type was particularly affected by static muscle length. Accordingly, these afferents failed to encode length, encoded velocity well and acceleration poorly. The representation of muscle length and velocity was, however, significantly improved when the discharge activity of Golgi tendon afferents was taken into consideration along with muscle spindle activity. The discharge of primary afferents during both key-pressing and block-grasping was best correlated to the muscle velocities observed ~100-160 ms in the future. This predictive ability went beyond what could be expected from the spindles’ simultaneous sensitivity to velocity and acceleration, and could thus only be explained by implicating the fusimotor drive. In addition, evidence is presented that the fusimotor control of spindles was contingent on entire movement sequences during the key-pressing task.

It is proposed that the phase relationship between the discharge rate of spindle afferents and the length of their parent muscles is load dependent. Moreover, muscle spindles seem to act as forward sensory models of their parent muscle, which makes sensorial feedback control possible despite neural delays.

Key words: motor control; muscle spindle; Golgi tendon organ; muscle afferent; microneurography; proprioception; sensorimotor; fusimotor; hand; forward model.
This doctoral thesis is based on the following articles. They will be referred to by their roman numerals.


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INTRODUCTION

Any manual endeavour, such as reaching for a cup of coffee, relies heavily on information concerning the mechanical state of the engaged limb. The task of providing this information is charged to a wide range of sensory mechanoreceptors, strategically placed in key areas such as muscle, tendon and skin. In the past, considerable attention was directed to a particular class of complex sensory receptors, tens or hundreds of which are tacked neatly between the fibres of most skeletal muscles. These so-called muscle spindles have been strongly implicated in the control and perception of movements. Spindles have been proposed to play important roles in various functions including in the reflex control of muscle stiffness (Houk, 1976; Sinkjaer et al., 1988), in the establishment and maintenance of body schema (Lackner, 1988), in motor learning and adaptation (Prochazka, 1989), in inter-joint coordination (Sainburg et al., 1993) and in proprioception (Goodwin et al., 1972; Roll and Vedel, 1982). In fact, there is “…a kaleidoscope of functions, in which proprioceptive feedback has been supposed to be involved” (Windhorst, 2007).

Despite the numerous roles proposed for them, it has been hitherto impossible to confirm the contribution muscle spindles make during common multi-joint movements. Technical constraints have discouraged the documentation of spindle afferent activity during ‘natural’ motor behaviours in humans. The majority of neurophysiological recordings of spindle afferents have been obtained under passive or behaviourally restricted conditions. Hence, there has been no record of human spindle activity during everyday actions such as grasping or typing.

In relaxed human muscles, spindle afferents respond to muscle stretch (Edin and Vallbo, 1990a; Bergenheim et al., 2000). Muscle spindle responses to movements imposed on passive muscles can be therefore easily predicted from the anatomy of their parent muscles (Roll et al., 2000; Ribot-Ciscar et al., 2002, 2003). However, such findings may have limited applicability in unravelling the functional role of muscle spindle afferents during active movements. This is because spindle responses during passive stretch and active movements may very well be different: during active movements the muscle spindles are responsive to changes in muscle length, but are also affected by the fusimotor system and by extrafusal muscle contractions (Wilson et al., 1997). For example, it has been shown that human muscle

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1 ‘Parent’ refers to the muscle where the muscle spindle endings reside
spindle afferents discharge more in accordance to changes in contraction strength than changes in muscle length during shortening contractions against an external load (Burke et al., 1978). Similarly, muscle spindle afferents from finger extensor muscles fail to represent joint positions during visually guided finger movements conducted with isotonic loads (Vallbo et al., 1981; Hulliger et al., 1982). During wrist movements, spindle afferents from actively contracting muscles also show poor muscle length sensitivity (Jones et al., 2001). Mathematical models of cat muscle spindles that use length and velocity as main inputs account poorly for their responses in load-bearing muscles (Prochazka and Gorassini, 1998). In short, while spindle afferents from relaxed muscles can signal muscle length, this has not been consistently shown for spindle afferents in actively contracting muscles.

It has been proposed that muscle spindles in the relatively relaxed and lengthening antagonists may provide information concerning limb configurations (Jones et al., 2001). However, natural hand and finger movements are typically associated with extensive co-contractions (Johansson and Westling, 1988; Maier and Hepp-Reymond, 1995); that is, antagonistic muscle may also be contracting during simple movements and this would compromise the ability of spindle afferents to encode the length of these muscles as well. Since previous human studies have focused on spindle responses to isometric contractions or movements at single joints (Vallbo, 1971; Vallbo et al., 1981; Edin and Vallbo, 1990a-b; al-Falahe et al., 1990b; Bergenheim et al., 2000; Jones et al., 2001; Cordo et al., 2002), there is currently a lack of knowledge concerning the nature of muscle spindle activity during important motor events of everyday life.

An experimental protocol was therefore developed which allowed recordings of muscle receptor afferent activity during unconstrained wrist and digit movements (Fig. 1). Along with single afferent activity, the electromyographic activity of all muscles engaged were recorded as well as the kinematics of the wrist and digits. This approach allowed for the investigation of the factors shaping afferent discharge during ‘everyday’ motor tasks such as block-grasping and pressing sequences of keys. In addition, the afferents’ ability to encode information concerning the state of the muscle and joint kinematics during the behavioural tasks was also assessed.
Throughout the experiments, the participants were sitting comfortably on a dentist’s chair, while microneurography from the radial nerve, surface EMG of major forearm muscles and the joint angles of the wrist and digits were recorded. The joint angles were recorded using the Cyberglove™ and complimented by the use of four Polhemus™ 3D sensors, which were placed on the wrist, thumb, index and middle finger. The participants’ forearm was resting on a cushion and was clamped just proximal to the wrist to help prevent movements of the upper arm (i.e. accidental dislocations of the electrodes). In this set-up, they could move their hand and digits freely. Depending on the location of the recorded muscle receptor, the participants had to either conduct a block-grasping task or a key-pressing task.

Muscle spindles

Muscle spindles are found in most striate muscles of all mammals and their structure and efferent supply are well known (Matthews, 1972). The spindles are encapsulated, fusiform in shape, and 5-10 mm in length. The vast majority of spindles are mechanically situated in parallel with the skeletal (i.e. ‘extrafusal’) fibres of the muscle they inhabit, although exceptions have been observed microscopically (Swett and Eldred, 1960) and functionally (Burke et al., 1987). The main components comprising the muscle spindle organs are the receptor endings and their respective afferent axons, the intrafusal fibres and the efferent axons innervating them. There are three major types of intrafusal muscle fibres (Kucera and Dorovini-Zis, 1979; Taylor et al., 1999), the ‘dynamic’ bag₁, ‘static’ bag₂ and chain fibres, whose central regions are mostly non-contractile. There are two kinds of
muscle spindle receptor endings, the primary receptor (or ‘annulospiral’ ending) and the secondary receptor or ‘flower-spray’ ending. The two types of sensory ending are located around the non-contractile regions of the intrafusal fibres, and respond with action potentials to the stretch of these regions. Only the primary endings spiral around the bag 1 fibre, however. A typical muscle spindle may contain several bag 1 and bag 2 fibres, and 2-11 chain fibres. A number of muscle spindles, like some of those found in compound spindles in the neck (Price and Dutia, 1989), lack bag 1 fibres altogether. More recent research shows that human muscle spindles from deep neck muscles may lack bag 1 or bag 2 fibres (Liu et al., 2003). There can also be a considerable number of intrafusal fibres (i.e. ~10% in one muscle) which display atypical features (Soukup et al., 2003).

In addition to external mechanical transients on the capsule itself, intrafusal stretch may result from stretching the whole muscle or by the actions of efferent motor axons. The efferent axons are of two main groups, γ and β, with the former exclusively supplying intrafusal fibres whereas the latter bifurcates to supply both intrafusal and extrafusal fibres. The γ and β axons can be further divided into ‘static’ or ‘dynamic’ axons (Matthews, 1962; Emonet-Dénand et al., 1975; Barker et al., 1976). The axons of the primary muscle spindle endings constitute the primary or ‘type Ia’ afferents and the axons of the secondary endings are the secondary or ‘type II’ afferents. A single muscle spindle may give rise to 1-2 type Ia afferents and up to 5 secondary afferents.

The two types of afferent vary considerably in their responses. The current consensus relates the discharges of type Ia afferents to both static muscle length and the rate of muscle length changes (i.e. ‘velocity’), and those of type II afferents to static length (Pearson and Gordon, 2000). The dynamic fusimotor activity increases the gain of the afferents’ responses to muscle stretch, whereas the static activity increases their base-line discharge but decreases the gain to muscle stretch (Prochazka, 1996). Through fusimotor activation of different intrafusal fibres, it has been possible to estimate the effects of each intrafusal type on muscle afferent discharges. Chain fibres bias afferent discharges and decrease stretch sensitivity, bag 2 fibres have a biasing effect but also reduce the stretch sensitivity of Ia afferents and increase it for type II afferents, and activation of bag 1 fibres increase the dynamic stretch sensitivity of type Ia afferents (Emonet-Dénand et al., 1977; Taylor et al., 1992, 2000; Prochazka, 1996; Durbaba et al., 2001, 2003).
*Golgi tendon organs*

Golgi tendon organs are encapsulated sensory organs, of 0.2-1 mm in length, respond to tension in a small set of motor units, and are found near musculotendinous junctions, i.e. are placed in series with the extrafusal muscle fibres (Prochazka, 1996). Accordingly, Golgi tendon organs are particularly sensitive to contraction, and so their ‘type Ib’ afferents have been found to primarily encode the actively produced muscle force (Crago *et al.*, 1982). Although the above is not always the case for individual type Ib afferents, averaging across the responses of these afferents still provides a good representation of contractile force (Horcholle-Bossavit *et al.*, 1990).
METHODOLOGICAL SUMMARY

Neurophysiological techniques

Microneurography

Signals in single muscle receptor afferents were obtained using microneurography (Vallbo and Hagbarth, 1968). First, a thin non-insulated electrode (200 μm diameter) was inserted percutaneously in the radial nerve of the right arm, ~10 cm proximal to the elbow (Fig. 2). The precise location of the nerve was progressively defined by providing low-intensity electrical impulses through the electrode and monitoring the consequent reactions. Subjective reports of elicited cutaneous sensations pertaining to the dorsum of the hand or contractions of the extensor muscles were indicative of close proximity to the nerve. At this stage, another electrode which was insulated but for the tip, was used to penetrate the nerve. Once in the radial nerve, small adjustments were made to the location of the insulated electrode until the activity of a single afferent could be isolated in the neurogram i.e. single action potentials with amplitudes substantially higher than that of the background 'multi-unit' activity. Identification of single action potentials was made semi-automatically under visual control, using criteria based on the shape of single action potentials (Edin et al., 1988).

Throughout the microneurography recordings, the participants were seated in a dentist’s chair with their right arm resting on a mobile ramp and supported by a vacuum pillow around their forearm and a cushioned clamp just proximal to the wrist (Figs. 1-2). In this position, the participants could move their wrist and digits freely. This particular posture and the fixation of the forearm were necessary precautions against dislocations of the electrode. Even slight movements of the head or shoulders could cause an accidental

Figure 2. Microneurography. On the left, the tungsten electrodes used for microneurography; a pin is also shown for visual reference. On the right, the location of the microneurographic recording is marked with a rectangle.
dislocation of the electrode. Depending on the parent muscle of the recorded muscle receptor afferent, the participants had to conduct one of two motor tasks, i.e. a block-grasping task or a key-pressing task as described below (on p.8).

Afferent identification

The parent muscle of an afferent was identified by palpation and by the afferent’s responses to passive joint movements and active contractions. Muscle spindle afferents were discriminated from Golgi tendon organ afferents by their different responses to passive movements and isometric contractions (Edin and Vallbo, 1990a). A lack of responses or inconsistent responses to muscle stretch and static muscle length were indicative of a Golgi tendon organ afferent. Higher discharge levels at the beginning and during isometric contraction, rather than during muscle relaxation following the contraction, were also indicative of a type Ib afferent (Paper II: Fig. 4AB). Muscle spindle afferents were subdivided into type Ia and type II depending on the variability of their interspike intervals during passive isometric conditions (Nordh et al., 1983), responses to lengthening of the relaxed muscle (Edin and Vallbo, 1990a), and their response to a sudden relaxation following isometric contraction (Edin and Vallbo, 1990b). Specifically, a variable or poor response to static length but pronounced responses to fast length changes imposed on the relaxed parent muscle were indicative of a type Ia afferent (cf., Fig. 7AB). A clear sensitivity to static muscle length increases and regular interspike intervals during static conditions were indicative of a type II afferent (cf., Fig. 10, p.20). Single afferents from skin receptors were discarded by moving the electrode. Unlike muscle receptor afferents, skin afferents are not responsive to muscle palpation or to voluntary muscle activation, but are very responsive to localised cutaneous stimuli.

EMG recordings

Electromyographic (EMG) recordings were made from all major forearm muscles involved in wrist and digit movements and accessible by surface electrodes: the radial wrist extensor (m extensor carpi radialis), the radial wrist flexor (m flexor carpi radialis), the ulnar wrist flexor (m flexor carpi ulnaris), the ulnar wrist extensor (m extensor carpi ulnaris), the common finger extensors (m extensor digitorum communis or m indicis proprius) and flexor (m flexor digitorum superficialis), and the thumb abductor muscle (m abductor pollicis longus). The optimal recording site for each muscle was identified with help of a hand-held EMG recording probe during isometric contractions. Custom-build surface electrodes (Ø 2 mm; 12 mm apart) were
coated with electrode jelly and attached to the skin at the optimal sites using double-sided adhesive tape. The activity in the short and long RWE (*m. extensor carpi radialis brevis et longus*) cannot be distinguished by surface electrodes although subtle differences can be demonstrated in intramuscular EMG recordings (Riek et al., 2000). However, because the experimental sessions lasted 4-5 hours, intramuscular EMG recordings were not feasible.

**Kinematic measurements**

The Polhemus Fastrak™ motion tracking system (Skill Technologies Inc., Arizona, USA) and the CyberGlove™ (Immersion Corporation, CA, USA) were used for recording digit and wrist kinematics. The CyberGlove™ allows recordings of wrist, metacarpophalangeal, and interphalangeal joint angles (flexion, extension, abduction and adduction) with a nominal resolution of ~0.5°. Each of the 18 sensors of the CyberGlove™ was calibrated for each participant according to predetermined angles obtained using custom-build wooden blocks. Polhemus Fastrak™ sensors provide azimuth, elevation and roll angles with an accuracy of 0.15 degrees, and can be fixated anywhere on the hand or digits. The relevant null angles were defined as those occurring when the participants kept the wrist and digits extended and the thumb fully abducted.

**Behavioural tasks**

The participants were familiarized with the two behavioural tasks used in this thesis – i.e., block-grasping and key-pressing – before the microneurography recordings commenced. Due to the simplicity of the tasks, only a few minutes of practice were necessary before the participants achieved proficiency. The participants were carefully instructed to execute the tasks at speeds which they were comfortable with and felt represented the speeds they would employ when conducting such tasks in everyday life.

**Block-grasping**

In the block-grasping task, the participants were asked to use the thumb and their index or middle finger to grasp one of a total of seven wooden blocks that was driven in their grasp by the experimenter (Fig. 3). Each block was presented ~30 cm from the participant’s hand, and they performed the task under full visual control. After driving the block into the participants hand, the experimenter released the block when the participants made contact with the object. They had received prior instructions to release the block when the experimenter again grasped the block after several seconds of holding.
Each trial started and ended with the finger and thumb in apposition. The seven wooden blocks were presented in sequence and they differed only in their widths in increments of 10 mm (30–90 mm).

Figure 3 also shows the digit and wrist angular changes as well as the resulting muscle length changes while a single block was grasped, held and then released. The participants’ grasping behaviours were very similar when they received blocks as during the microneurography recordings, when they themselves transferred the object from the left hand to the right hand, and when they performed normal reaching-and-grasping movements (Paper II: Fig. 2).

Key-pressing

In the key-pressing task, the participants were asked to use their wrist and middle finger to press sequences of keys on a custom-build numeric key pad (Fig. 4A; cf., Fig. 2). The keypad had nine buttons (Ø 5mm, arranged 3×3) that required a normal force of ~1.5 N to be pressed. The position of the key pad was adjusted so that, by having the wrist at ‘zero angles’, participants could reach the middle key (‘5’) with the tip of the middle finger.
Figure 4. The key-pressing task. A, Throughout the key-pressing task, the hand was in a semi-pronated position so that radial deviations of the wrist coincided with vertical movements against gravity (i.e. ‘UP’). B, The key-pressing task involved pressing different sequences of three keys. Key ‘5’ was always the first and last key in each sequence and never the middle key. Movements from key ‘5’ towards keys ‘2-3-6’ and movements towards key ‘5’ from keys ‘4-7-8’ required flexion and/or ulna deviation of the wrist joint, and so induced elongation of the Radial Wrist Extensor (RWE) muscle. The Ulnar Wrist Extensor (UWE) was mostly affected by radial deviations, so was elongated substantially during movements from key ‘5’ towards keys ‘1-4-7’, and during movements to key ‘5’ from keys ‘3-6-9’. C, For the purpose of further analyses, each key sequence was divided in nine phases: 100 ms before and after each key and one phase which included the actual keypresses.

All sequences were comprised of three keys, the first and last key was always the 5 key, but the second key (i.e. ‘target’ key) could be any key but 5 (Fig. 4BC). All sequences were presented in a spatially congruent manner on a visual display in front of the participants. Each sequence was presented 300 ms after pressing the terminal 5 key of the previous sequence, and the concurrent sequence remained on display until the terminal 5 key was pressed. Sequences were presented in blocks of eight. The interval between blocks of sequences was about 10 s. A sound was triggered whenever an incorrect key was pressed.

Data processing

Kinematics

Changes in muscle length, or more precisely tendon excursions, were calculated from the measured joint angles by simple transformations of the angular data using published coefficients (Elliot and McGrouther, 1986; Smutz et al., 1998; Pigeon et al., 1996). The first and second derivatives of muscle length (i.e. ‘velocity’ and ‘acceleration’), were calculated using moving
windows whose size corresponded to low-pass filtering DC-10Hz for the wrist data of Study I and DC ~17Hz for the digit and wrist data of Study II. All analyses of the key-pressing task focussed on the key sequences associated with significant muscle length changes of the afferents’ parent muscles. Therefore, different key sequences were associated with each of the two wrist extensor muscles (cf., Fig. 4B). For both muscles there were three key sequences with consistent initial muscle length increase and three key sequences with initial length decrease.

Afferent population responses

From the spike trains recorded from each single afferent, a continuous signal representing the instantaneous discharge was created. This signal corresponded to the inverse of the duration of each interspike interval. Afferent population responses were created from the empirically observed discharges; such averaged responses are less affected by noise present at the single afferent level (Faisal et al., 2008).

In Study I, for each discrete movement to and from all keys associated with significant muscle length changes, 100 ensemble responses were generated by averaging the discharge rates of single afferents. More specifically, the ensemble responses were created by picking at random one of the recorded responses of all single afferents for which at least two repetitions without key-pressing errors had been obtained. The number of afferents contributing to the ensemble responses thus varied slightly depending on the key of interest. Of the 15 recorded Ia afferents from the RWE muscle, 12-14 contributed to the type Ia ensemble responses from the RWE muscle whereas 4-8 of the 8 type II afferents contributed type II ensemble responses from the UWE muscle. The degree to which the ensemble responses were representative of the ‘true’ population responses was determined by correlating the randomly generated responses for each movement (n=100, N=1200) with the grand weighted mean. As Figure 5 shows, all ensemble responses were good representations of ‘true’ populations except the UWE type Ia ensemble. Since the validity of the latter was questionable, it was not used when investigating the relationship between ensemble responses and observed kinematics.
Figure 5. Validation of the ensemble responses pertaining to the key-pressing task. A, The histograms represent r values when each randomly generated average was correlated with the grand mean. The median r value obtained for the type Ia and type II ensemble were 0.87 and 0.90, respectively. B, The same as in A but pertaining to the UWE. The type Ia and type II median r values were 0.68 and 0.95, respectively. RWE - radial wrist extensor; UWE - ulnar wrist extensor.

As for the key-pressing task, the data of the block-grasping task (Study II) were used to generate ‘population responses’, averaged kinematic and EMG variables. The averaged population responses were cross-validated by employing a bootstrapping methodology. A ‘grasping’ and a ‘releasing’ phase was defined for each single block-grasping trial (Fig. 11 on p.20). A data matrix containing one data series for each recorded afferent, variable, block size and phase was first compiled. From this matrix 100 averaged responses of populations were created, each comprising a random sample of ~60% of the available afferents (8/13 type Ia; 3/5 type II afferents; 5/9 type Ib; a total of 3 afferent types × 2 phases × 7 block sizes × 100 replicates = 4,200 generated population responses). The median r obtained when correlating all averaged population responses from a subset of type Ia afferents with the corresponding average calculated from all type Ia afferents was 0.96 (range between the upper and lower quartiles was 0.04), for type II 0.91 (range 0.17), and for type Ib 0.93 (range 0.09). Averaged kinematic and parent EMG signals were generated in a similar way but based on participants not on single afferents.

Analyses

Statistical methods

Statistical tests were performed using either STATISTICA® or MatLab®, choosing a significance level of p<10^{-2} for all tests (applying compensations for multiple tests when appropriate). In the key-pressing task, the experimental paradigm included symmetrical movements around the central
5 key of the keyboard, and therefore muscle lengths, velocities and accelerations should in theory all be pair-wise uncorrelated. Length and velocity were indeed uncorrelated for both muscles ($r^2$<0.02) but length and acceleration were statistically significantly correlated but to such a small degree that it was ignored in the regression analyses ($r^2$<0.20). The data used for regression analyses showed, however, a high degree of auto-correlation which if not taken into account would have led to inflated p values. For the data pertaining to both the block-grasping and key-pressing task, the effective sampling rate was estimated to be ~20 Hz (Dawdy and Matalas, 1964). Accordingly, all regressions in Study I and II were performed on data that was down-sampled to 20 Hz, i.e., each data point represented the average in a 50 ms window. The impacts of kinematic variables and EMG on the discharge rates were determined by means of non-linear regression analyses under the assumption that if all other factors were constant, neither length, nor velocity or acceleration could have had a negative impact on the discharge of spindle afferents. The effect of EMG on the other hand was not constrained and could thus have either a negative or a positive impact. The non-linear regression model for the impact analyses is represented by the following equation:

\[
\text{Discharge rate} = k_1 + |k_2| \cdot \text{Len} + |k_3| \cdot \text{Vel} + |k_4| \cdot \text{Acc} + k_5 \cdot \text{EMG}
\]

Eq. 1

‘Len’, ‘Vel’, and ‘Acc’ represent the instantaneous muscle length, velocity and acceleration, respectively, and $k_1$-$k_5$ represent the constants determined by the regression. Kinematic variables were recreated from the ensemble discharges of the afferents using the following equation:

\[
\text{Kinematic variable} = k_1 + k_2 \cdot I_a + k_3 \cdot I_I + k_4 \cdot I_b
\]

Eq. 2

‘Kinematic variable’ corresponds to the instantaneous muscle length, velocity or acceleration; ‘$I_a$’, ‘$I_I$’ and ‘$I_b$’ correspond to the instantaneous ensemble discharge of type Ia, type II and type Ib afferents, respectively; $k_1$-$k_4$ represent the constants determined by the regression. Different combinations of populations were created by forcing one or two of the coefficients $k_2$-$k_5$ to zero.

PLS modelling

To assess whether the fusimotor drive differed depending on the key sequence, we determined if it was possible to calculate the functional end-points of the key-pressing task, i.e., the spatial location of variable key ‘T’ of each sequence (cf., Fig. 4B, p.10), from the muscle spindle afferent responses. The mean discharge rate and standard deviation for each of the 9 phases depicted in Figure 4C were determined for each afferent and each key sequence. Accordingly, $8 \times 9$ means and standard deviations corresponding to
8 target keys and 9 phases were tabulated for each recorded afferent. For a specific phase of a specific key sequence a population response was created by generating a vector containing random numbers with the same population mean and standard deviation as the individual afferents. The locations of the keys were represented by the true x-y coordinates of the keys with an arbitrarily chosen origo (cf., Fig. 4A).

Modelling was performed using Partial Least Squares (also called Projection to Latent Structures, PLS) analysis (Eriksson et al., 1999). This was a preferred method for analysing the key-pressing data, because it can deal with correlations among independent variables, missing data and multiple dependent variables. The PLS method is a multivariate extension of Principal Components Analysis (PCA). In PCA, a covariance matrix pertaining to the standardised equivalents of the independent variables is used for creating eigenvectors; in geometrical terms, this corresponds to a rotation of the standardised axes, so that one axis essentially assumes the dimension along which most data variance is observed (i.e., the rotated axis constitutes a ‘principal component’ or ‘latent variable’). The dimension where the second-largest variability is observed will become a second principal component and is used along with the first principal component to define a plane (additional principal components define a hyper-plane). The coordinates of the points with respect to the newly formed plane are called scores, and can be thought of as new and more ‘compact’ independent variables. The required transformations between the original independent variables and the scores is accomplished by the ‘loads’ or ‘weights’ (i.e. coefficients); in geometric terms, weights describe the coordinate transformations required to rotate the original axes in order to obtain the final configuration (e.g. orientation of a plane).

In PLS, successive linear combinations of the independent variables are extracted and optimised to explain both dependent and independent variable variation. More specifically, the axis rotations that take place in PLS seek to account for both the variability in independent-variable and dependent-variable space. In contrast to the PCA, therefore, the PLS iteratively maximises the covariance between latent independent variables and latent dependent variables, and does not attempt to maximise the degree to which it accounts for variance in independent variables. The dependent-variable scores are in turn used to predict the original dependent values through ordinary least squares procedures. In effect, PLS allows predictions of multiple dependent variables from a set of independent variables. In our case, the dependent variables were the x-y coordinates of the target keys. Matlab® was used for data tabulations, generating simulated afferent
responses, probability calculations and data displays while PLS analyses were performed using SIMCA-P®. Calculation of probabilities for correct and false identification of key sequences was performed using Bayesian probability calculus. The set of x-y coordinates calculated from the PLS model represented the likelihood of observing a specific x-y coordinate given a certain key (cf., Fig. 15 on p.25).
SUMMARY OF STUDIES & RESULTS

Study I

In this first study, we recorded the activity of muscle spindle afferents in the radial wrist extensor (RWE) and ulnar wrist extensor (UWE), while participants performed the key-pressing task which demanded precise control of the wrist. We simultaneously recorded the EMG of the four major wrist muscles as well as the kinematics of the wrist and digits. During the key-pressing task the RWE was contracting concentrically and acting as an anti-gravity muscle, whereas the UWE was contracting eccentrically (Fig. 6).

Further analyses showed that the responses of the muscle spindle afferents from the RWE were approximately 90 degrees more phased advanced than expected on the length of their parent muscle. As such, only velocity and acceleration significantly affected the discharges of single type Ia afferents (Fig. 7) and of the population of type Ia afferents (Fig. 8) during the key-pressing task. Type II afferent discharges from the same muscle were significantly affected only by velocity (Fig. 8).

The same kinematic dependence was observed in both type Ia and type II afferents from the RWE during voluntary sinusoidal wrist movements. On the other hand, the discharges of type II afferents from the UWE were affected by muscle length and velocity, while the type Ia afferents from this muscle were too variable to allow reliable analyses (cf., Fig. 5B). Accordingly, only the wrist ulnar-radial angular velocity was well encoded by the

Figure 6. Different activation patterns of wrist extensor muscles during the key-pressing task. The radial wrist extensor (RWE) and the ulnar wrist extensor (UWE) fulfilled different mechanical roles during the key-pressing task. Namely, repeated ANOVAs indicated that RWE electromyographic activity was higher when the muscle was at a short length and shortening (i.e. concentric contractions). The opposite effects were seen for the UWE (eccentric contractions). The data used were of 19 participants and were z-transformed for each participant before analysis. Vertical bars represent ±SE.
Figure 7. Responses of a typical type Ia muscle spindle afferent from the radial wrist extensor. A, During passive joint movements this Ia afferent (65-02) showed poor responses to static length but pronounced dynamic responses particularly evident during small rapid length changes (grayed area) shown on an expanded time scale in (B) and it discharged vigorously during isometric contractions (C). D, During key-pressing, however, the afferent’s discharge was characterized by bursting and pauses apparently related to the second derivative of muscle length (‘acceleration’). In particular, note the discharge onset when acceleration reversed from negative to positive (grayed areas).
**Figure 8.** *Ensemble responses of muscle spindle afferents from the radial wrist extensor.* **A,** Averaged length, velocity, acceleration and EMG signals along with the corresponding ensemble discharges of type Ia afferents (n=15) and type II afferents (n=8) from the radial wrist extensor (RWE), for a long key 3 and a short key 7. EMG was z transformed before averaging. Shaded areas around means represent ±SD. **B,** Qualitative comparisons of ensemble discharge profiles and kinematic variables having the most significant impacts on the discharge rates. The kinematic variables were rescaled by eye to make a good fit to the discharge profiles using red for acceleration and blue for velocity (as in A). **C,** Reconstructions of the observed ensemble discharge rates shown in (A) by regression: solid lines represent the observed values and dots the values predicted from linear regressions using the kinematic signals and RWE EMG as independent predictors. For the key sequences shown, both acceleration and velocity significantly affected type Ia ensemble discharges from the RWE, and velocity alone sculpted the type II discharges from the same muscle.
combination of afferent populations, and ulnar-radial angle itself was well encoded only during periods of UWE lengthening (Paper I: Fig. 7). Joint angular acceleration was rather poorly encoded throughout.

**Study II**

The second study describes the discharges of muscle receptor afferents recorded from the digit extensor and thumb abductor muscles whilst the participants performed a block-grasping task (cf., p.8). EMG activity of all pertinent muscles was recorded along with wrist and digit kinematics. The discharges of single muscle afferents during block-grasping were more phase-advanced than expected from previous studies and from the afferents’ own responses to imposed stretches of their relaxed parent muscle (Figs. 9-10).

As for the key-pressing task, the type Ia ensemble responses from the finger extensor and thumb abductor muscles were found to be significantly sensitive to both acceleration and velocity (Fig. 11). Similarly, type II afferents responded mostly to velocity. Golgi tendon organ afferents were

![Figure 9. Responses of a type Ia muscle spindle afferent from the finger extensor.](image-url)

**A**, During length changes imposed on the relaxed parent muscle by the experimenter, the type Ia afferent showed poor responses to static length but clear dynamic responses.

**B**, The afferent also responded to voluntary near-isometric contractions.

**C**, The afferent’s responses when the participant grasped, held and subsequently released wooden blocks of increasing size (40, 50 and 60mm). Instead of discharging preferentially during phases of muscle stretch, the afferent displayed high discharge rates when the second derivative of muscle length ('acceleration') was positive (signified by the vertical gray bars). The highest discharge rates were observed when both 'acceleration' and 'velocity' were positive.
also recorded during block-grasping, and they were significantly affected only by EMG activity of their parent muscle.

In addition, the study showed that the encoding of muscle length and velocity by afferents was significantly improved when the ensemble activity of Golgi tendon afferents was taken into consideration along with muscle spindle activity (Fig. 12).

Study II study also demonstrated that both single afferents and ensemble discharges failed to signal the moment of coming into contact with the

![Figure 10. Responses of a type II muscle spindle afferent from the thumb abductor. A, The type II afferent responded to passive muscle stretch of the relaxed muscle and also displayed a certain degree of sensitivity to static length increases B, The afferent also responded during voluntary near-isometric contractions C, The afferent’s responses when the participant grasped, held and subsequently released wooden blocks of increasing size (40-50-60mm). This afferent discharged preferentially during phases of muscle stretch (signified by the vertical gray bars). No consistent relationship between static muscle length increase and discharge rate could be noted by simply observing the behaviour of the afferent during block-grasping.](image-url)
object during block-grasping (Paper II: Fig. 8). Lastly, it was shown that afferents were unable to represent object size. As with Study I, the results of this study were discussed in terms of the interactions between tendon compliance, muscle fascicle length changes and the type of load the muscle is acting upon.

Figure 11. Afferent population responses during the block-grasping task. Superimposed averaged ensemble responses across all type Ia, II and Ib afferents during the grasping (left column) and releasing phases (right column) across all block-sizes. The grasping phase included fingertip spacing and grasping a block and the release phase included the release of the block and the return of the digits into apposition. Both periods were 800 ms long and were fixed in time with respect to the peak negative and positive muscle velocity, respectively, with the grasping phase starting 400 ms before and the release phase 300 ms before this event. The displayed kinematic and EMG signals were averaged across all participants whom contributed with an afferent recording. The periods between the vertical dashed lines mark the 800 ms periods used in the regression analyses. Note the apparent lack of any significant length dependence of the afferent discharges.
Figure 12. Population encoding of muscle length and velocity. A, Muscle velocity versus instantaneous discharge rates of afferent populations (top row) and observed velocity versus that predicted from linear regression with various combinations of populations as the independent variables (bottom row). Data from both the grasping and releasing phases were included. Solid lines represent significant regression lines ($p<10^{-6}$). The $r$ values for combinations which included Ib afferents were significantly higher than those of any other combination including, in particular, the combination of only type Ia and II. B, As in A, but relating to muscle length instead of muscle velocity. The $r^2$ value of the combination comprised of Ia and Ib afferents was significantly higher than that for both the combination of Ia and II and the combination of II and Ib afferents ($p<10^{-4}$).

Study III

In the third study we investigated the possibility that spindle Ia discharges were more closely related to future than to current sensory states. This exploration was inspired by the fact that muscle spindles are complex organs whose output is shaped by both the current sensory state of the muscle and an efferent command; i.e. the ‘inputs’ to the spindle match those of the so-called ‘forward sensory model’ (Wolpert and Miall, 1996; Wolpert and Ghahramani, 2000). Therefore, if fusimotor activity biases the spindle responses as an ‘efferent copy’ would affect a forward model, one may hypothesise that spindle afferent discharge relates more to future sensory
states (e.g. in terms of length, velocity etc.) than to concurrent states. Using simple cross-correlation, we re-examined the data presented in Study I and II and showed that type Ia discharges do indeed encode future muscle velocity significantly better than current velocity. Importantly, this capability went beyond what could be expected from kinematic autocorrelations and the ability of type Ia afferents to simultaneously signal acceleration and velocity (Fig. 13).

Afferent discharges were well correlated with future muscle states during some phases of the key-pressing task, but there were some occasions where deviations in discharge rates could not be attributed to current muscle state or to immediate future states. At certain phases during the key-pressing task, for example, the 5 key was pressed to terminate one sequence and then again to begin the following sequence. Although there were no notable changes in muscle length, velocity or EMG during these periods, there were distinct changes in the single afferent discharge (Fig. 14).

Figure 13. Real-time prediction of future muscle velocity from type Ia discharges observed during block-grasping. A, The discharges of a type Ia afferent population (n=13; ‘grasping’ phase; cf., Fig. 11) plotted against the velocity of their parent muscles at the same time as the discharge (0 ms) and at other times in the future. The ensemble discharge showed the maximum correlation with the velocity ~160 ms in the future (r=0.82). B, Correlation between type Ia ensemble discharge at time t and muscle velocity for time advances 0-400 ms, i.e., v(t+Δt); filled circles correspond to data in A. Also shown is the correlation between the actual v(t+Δt) and v(t)+a(t)·Δt, i.e., the best correlation expected if the spindle output was a mere consequence of velocity and acceleration sensitivity. At 160 ms, the r value obtained using the ensemble discharge was significantly higher than with v(t)+a(t)·Δt, p<10^-4. C, Auto-correlations of the muscle velocity and acceleration observed during the block-grasping task. Colored areas correspond to 90% confidence intervals.
Further analyses showed that during a 100 ms period immediately before pressing the first 5 key and immediately after the final 5 key of a sequence (i.e., phases 1 and 9; cf., Fig. 4C on p.10), the discharge of several muscle spindle afferents differed depending on the target key of the sequence, and this was apparent immediately before executing each sequence and immediately after executing the sequence (Paper III: Fig. 3A,B).

The above findings suggested that some afferents were affected by the fusimotor system in a sequence-specific manner; in other words, afferent discharges appeared to be under fusimotor control contingent on entire movement sequences. In order to investigate whether or not this was true for populations of afferents, we compared the predicted x-y coordinates of the
target key of each sequence generated from the afferent discharges of a muscle spindle population (n=36) against predictions made from the kinematic state and EMG levels of their parent muscles (cf., ‘PLS modelling’ on p.13). The predictive abilities of the two PLS models are shown in Figure 15A.

To summarise, clearly better predictions of the finger-tip coordinates were obtained from the model based on spindle discharges (‘PLS-MS’) rather than the model based on kinematic and EMG signals (‘PLS-MLVE’). This was especially apparent during the beginning and end of each key sequence (i.e. phases 1 and 8-9). The performance of the PLS models was further assessed by comparing the models’ predictive errors and sensitivity estimates (Fig. 16). As expected from inspecting Figure 15, the PLS-MLVE model produced more erroneous responses than the PLS-MS model.

Figure 15. Predicting fingertip coordinates from muscle spindle afferent responses and muscle states. A, Mean x-y coordinates of the finger-tip when pressing the variable target key of a sequence (i.e. middle key of each sequence, i.e. phase 5, cf. panel B) predicted from a PLS model which was based on muscle spindle afferent discharges (top row) and another based on muscle length, velocity and EMG (bottom row) during phases 1-9 (cf., inset in panel B). B, PLS model predictions from muscle spindle discharges for phases 1-5; from top to bottom: histograms of predicted fingertip coordinates during phase 5, area containing 90% of the predicted coordinates, and at the bottom, the areas with a probability of > 0.9 that the target key of the sequence was correctly predicted; inset at the top of panel B depicts the colour coding of target keys.
Figure 16. Assessing the performance of PLS models. Constant (A) and variable prediction error (B), and prediction sensitivity, i.e., the probability of correct identification of the variable target key (C) of the PLS model based on muscle spindle afferents (PLS-MS) and on muscle length, tendon velocity and EMG (PLS-MLVE; solid lines represent median values; coloured zones 50% of the distribution). D, Median maximum difference in discharge depending on the variable target key ‘T’, as well as the median discharge rate, and median coefficient of discharge variation across all afferents.

Whereas the PLS-MS sensitivity around the time the target key was pressed (phases 4-6; Fig. 16C) was understandable given the afferents’ dependence on the muscle states, this did not explain the high sensitivity during phases where the muscle lengths, velocities and EMG activation levels were similar irrespective of the target-key pressed during phase 5. During the period with highest sensitivity, the afferents showed both their largest contrast in discharge rates between keys and their lowest coefficient of variation (Fig. 16D), both factors that should promote good predictions. Periods with low sensitivity were associated with the lowest overall discharge rates and the largest coefficient of variation. This relationship between the overall discharge rates and discharge variation did not, however, explain the patterns of sensitivity for the periods immediately before, during and after pressing the target key 'T', nor when the 5 key following the target key was pressed. In short, the quality of prediction appears not to have been a simple function of the contrast in discharge rates among keys or of discharge variability.
DISCUSSION

This thesis is based on a compilation of three studies that generated several new findings concerning muscle afferent responses. The discharge rates of primary muscle spindle afferents can represent accelerations in addition to velocities, and the discharge of primary and secondary afferents does not necessarily represent muscle length. These findings challenge the role of muscle spindles as the main source of hand posture information. However, combining type Ib discharges together with muscle spindle afferent discharges significantly improves the representation of kinematic signals. The findings also counter the widely held belief that muscle spindles provide unambiguous information concerning the properties of manipulated objects. Most importantly, a novel role for muscle spindles in sensory prediction is supported, which makes possible the use of sensory signals in feedback control despite sensorimotor delays. Since the pertinent afferent activity was recorded during the execution of common manual actions under 'physiological' conditions, the applicability of such findings to everyday life is straightforward. In what follows, I shall discuss the aforementioned findings and their implications.

Unexpected phase advances

Taken together, the results of Study I and II showed that spindle afferent responses from load-bearing muscles were roughly 90 degrees more phase-advanced than expected on the length of their parent muscle. These results contradict the consensus according to which type Ia afferents signal muscle length and velocity and type II signal length during 'natural' movements (Pearson and Gordon, 2000). Instead, three unexpected phenomena were observed as a direct result of the additional spindle phase advance: type II afferents signalled velocity on par or better than type Ia afferents, neither afferent type could substantially signal muscle length, and type Ia afferents were able to signal acceleration and velocity. Although the majority of muscle spindle morphological studies and afferent recordings have been conducted in cats, there is no reason to believe that the encoding capabilities of human muscle spindle endings differ fundamentally to those of other mammals (Poppele and Kennedy, 1974; Kakuda, 2000). In order to explain the presence of the unexpected phase advances therefore, one must look beyond the encoding capabilities of the isolated muscle spindle ending.

A likely reason for the unexpectedly large phase advance in spindle responses must be common to the primary and secondary spindle endings of a muscle, and take into account the novel conditions under which the recordings were
made (i.e. varying shortening and lengthening velocities and contraction levels of the parent muscles). Fusimotor activity alone does not seem to provide a plausible explanation, as it modifies the spindles’ sensitivity to length and velocity but not the phase relationship of either type Ia or type II afferents (Matthews and Stein, 1969; Hulliger et al., 1977; Cussons et al., 1977; Baumann and Hulliger, 1991). There have been reports of increases in spindle phase advance when stretching relaxed muscles that had just previously been exposed to fusimotor activity (Brown et al., 1969). While this phenomenon has been called upon to explain spindle discharge patterns during chewing in alert monkeys (Goodwin and Luschei, 1975), it does not explain the phase-advanced responses of spindle afferents from the radial wrist extensor, which was continuously acting against gravity in the key-pressing task.

Another possible explanation is that the muscles were acting against a viscous load constituted by antagonists, the skin and connective tissues. Given that the mechanical properties of both contracting fascicles and tendons are dominated by stiffness, their lengths will be proportional to the tendon force. But if the muscle is acting on a viscous load, the force will be 90 degrees phase advanced on the length, and hence both type Ia and II discharges should appear phase advanced. Future comparative studies will hopefully shed more light on this issue. Nevertheless, it is now well established that the muscle fascicle compartment ‘measured’ by the spindle afferents is not always in phase with the whole muscle-tendon complex (Hoffer et al., 1989; Griffiths, 1991; Fukunaga et al., 1997; Kawakami et al., 2002). Indeed, even slight contractions alter the relationship between fascicle lengths and whole muscle-tendon length (Herbert et al., 2002).

If series elasticity represented by some tendons acts so that changes in overall muscle-tendon length differ significantly from those of muscle fascicles (Loram et al., 2005), estimates of muscle lengths cannot rely solely on receptors encoding the length of muscle fascicles. In retrospect, therefore, it should not be particularly surprising that afferent predictions of length and velocity significantly improved when the responses of Ib afferents were incorporated in the predictive models (cf., Fig. 12). Such analyses have a distinct physiological underpinning in spinal cord circuitry; namely, spinal inter-neurons and spino-cerebellar neurons are known to receive both “length-related” and “force-related” sensory inputs, creating what has been interpreted as mixed kinematic-kinetic representations (Windhorst, 2007). In such a framework, the role of afferent inputs from Golgi tendon organs would be to disambiguate spindle inputs. Representations of static and dynamic joint positions can also be provided by stretch-sensitive skin
mechanoreceptors as shown in neurophysiological (Edin and Abbs, 1991; Edin, 1992, 2001, 2004; Aimonetti et al., 2007) and behavioural studies (Edin and Johansson, 1995; Collins and Prochazka, 1996; Collins et al., 2005).

In humans, there is currently no reason to doubt that the representation of movement parameters is multi-modal (Collins et al., 2000, 2005; Weerakkody et al., 2007). Given the abundance of muscle spindles and cutaneous receptors in mammalian bodies, a quest for a ‘dominant’ mechanoreceptor in proprioceptive signalling seems misguided (Stein et al., 2004). However, the relative weight of populations of different receptors may vary systematically, even under ‘natural’ circumstances. For example, one approach may be to explore the extent to which different receptor groups contribute to the proprioception of different body parts. The distribution of mechanoreceptor densities around the body should carry a major clue (e.g. dependence on cutaneous receptors for lip proprioception and a heavy reliance on muscle spindles for neck/head proprioception). Tendon vibration (Goodwin et al., 1972) and cutaneous vibration (Weerakkody et al., 2007) can be used in conjunction with psychophysical measurements in order to address such issues.

**Spindles inform on acceleration**

A novel observation made in this thesis is that spindle afferent responses can also be associated with acceleration. Thus far, several models of spindle afferents have taken into account muscle length and velocity but not acceleration and yet the simulated responses match well experimentally-obtained spindle responses (Hasan, 1983; Prochazka and Gorassini, 1998; Mileusnic et al., 2006). However, these models have not been shown to work well for muscle spindles residing in muscles actively working against loads (Prochazka and Gorassini, 1998). There is evidence that signals related to limb acceleration play a role in motor control. For example, in a study of the reflexes evoked by postural and vestibular disturbances, Fitzpatrick et al. (1996) found unexpectedly large phase advances which they suggested might be attributed to central nervous processes. The current findings indicate that some of this additional phase advance may in fact be attributed to phase advances in the muscle afferent discharges themselves. Phase advanced signals are beneficial for feedback control, since they can counteract phase lags that are introduced by external loads or that are inherent in the control apparatus (e.g. sluggish muscle contraction dynamics).
In addition, recent evidence has surfaced which documents the use of acceleration-related afferent signals in more advanced sensorimotor transformations. Specifically, by studying the responses of cats to a sudden loss of balance, Lockhart and Ting (2007) successfully reproduced the cats’ muscle activation patterns by considering the position, velocity and acceleration of the cats’ centre of mass. The estimated feedback gains obtained with healthy cats were compared to those intoxicated with pyridoxine, known to destroy large diameter afferents (Stapley et al., 2002). The main difference was a significantly reduced acceleration feedback gain in the intoxicated cats, which the authors suggested was likely due to a loss of type Ia afferents.

**Spindles can signal future sensory states**

In Study III, muscle spindles were shown to fulfil the criteria for neurophysiologically identifying a ‘forward sensory model’ (Wolpert and Miall, 1996). Their inputs were the current kinematic state of their parent muscle and a corollary\(^2\) command related to the $\alpha$-motor command (‘effeference copy’, $\alpha$-$\gamma$ coactivation or $\beta$ innervation); their output was an estimate of a future kinematic state, beyond what was expected from autocorrelations and multiple kinematic sensitivities. Although no similar results have been previously reported, the apparent prerequisites for such a predictive capability – i.e., simultaneous responsiveness to more than one kinematic variable and fusimotor influence – are known to exist for muscle spindles of various species (Prochazka, 1996).

The signals of muscle spindles have long been associated with movement regulation. Physiological delays, however, speak against the use of sensory information in feedback control. Yet, behavioural evidence has shown that on-line error feedback control does occur (e.g. Cordo, 1990; Sainburg et al., 1999). The lack of proprioceptive input has been associated with increased variability of rapid single-joint movements (Forget and Lamarre, 1987), and severe deficits in the coordination of multi-joint movement (Sainburg et al., 1993). The coordination of discrete movement sequences of durations 210 ms and longer requires proprioceptive information concerning velocity and position (Cordo et al., 1994). Furthermore, vibrating the biceps branchii tendon during forearm movements (Cordo et al., 1995) and the wrist extensor tendons during wrist movement (Verschueren et al., 1998) strongly implicate muscle spindles in feedback control.

\(^2\) ‘Corollary’ is used throughout to mean any efferent signal which can influence sensory processing (Crapse and Sommer, 2008)
Effective feedback control becomes feasible by means of forward models. That is, forward models circumvent sensorimotor delays because reactions to motor errors are based on the state of the limb close to the time of reaction, rather than on the state of the limb prevalent at the time the error occurred (Desmurget and Grafton, 2000). Behavioural evidence of precisely this has been recently made available in a study of perturbed arm movements (Wagner and Smith, 2008), leading the authors to suggest the existence of a forward model which predicts limb velocity in 'real-time'. Regardless of whether muscle spindles should be literally considered as 'forward models', their velocity estimates are sufficiently advanced to match the minimum delay required for trajectory corrections during reaching movements (i.e., 80-100 ms; Paillard, 1996).

Forward models are currently believed to reside in central structures such as the cerebellar cortex (Scott, 2004) and the cerebellum (Miall et al., 1993). Evolution may have also favoured placing forward sensory models within muscles for several reasons. First, the incorporation of multiple forward models in the peripheral nervous system can certainly ease the computation requirements placed on central structures. Second, unlike a corollary send from a central to another central structure, the muscle spindle is more likely to receive a reliable corollary of the motor command entering the final common pathway. In the case of β fibres, for example, the efferent axon reaching the spindle is simply a bifurcation of the α-motor axon reaching the skeletal muscle fibres; such corollaries should be less concerned with trial-to-trial variability in transmission and noise (Faisal et al., 2008). The main advantage of placing a forward sensory model within an effector, however, is simply that current sensory state can be directly encoded and incorporated into future predictions rather than estimated in a feed-forward manner through a probably less accurate structure called a 'forward dynamic model' (Wolpert and Miall, 1996). Dynamic models use a copy of the motor command and knowledge of system dynamics to produce estimates of current state, which are then fed to forward sensory models as inputs. Such models aim to “compensate for sensorimotor delays and to reduce the uncertainty in the state estimate that arises because of noise inherent in both sensory and motor signals” (Wolpert and Ghahramani, 2000). But predicting and controlling the dynamic state of a multi-joint system is a notoriously difficult task (e.g., Hogan et al., 1987), especially so due to joint interaction torques (Hollerbach and Flash, 1982). Nevertheless, even with

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3 As is proposed to occur in the cortico-ponto-cerebellar system (Ugolini and Kuypers, 1986; Ramnani, 2006).
impeccable knowledge of system and environmental dynamics, forward models in the CNS can still be inaccurate, since their output ultimately depends on expected motor outcomes and not on the actual forces acting on effectors; as mentioned above, the accuracy of central predictions is subject to “motor noise”, owing to variability in neuronal transmission and muscle fibre function. Therefore, by directly encoding current state as it is immediately affected by system and environmental dynamics, as well as using more reliable corollaries of the motor commands reaching the periphery, muscle spindles justify their role as forward sensory models.

It should be emphasised that any predictions stemming from muscle spindles only concern the state of the parent muscle, which in turn may relate to joint angles, future movement directions etc. Higher-level neural circuits are necessary for creating representations of a more elaborate nature. In the case of hand position and velocity, for example, central structures may not create sensory predictions from a ‘dynamic model’, but may use proprioceptive information to construct a more pertinent or detailed neural representation. Indeed, proprioceptive information from the hand is known to be necessary for up-dating internal models (Ariff et al., 2002). Thus, an interesting implication is that the CNS may create a representation of the sensorimotor system which is directly based on predictive proprioceptive information, advanced 100 ms or so in time.

Most importantly, however, predictive proprioceptive signals can be used for feedback control only if such information is contrasted with an expected or desired state. The discharge rates of cerebellar Purkinje cells signal information related to limb position and velocity present at approximately 100 ms in the future (Coltz et al., 1999; Roitman et al., 2005), which has been promoted as evidence of the cerebellum’s role as a forward sensory model (Pasalar et al., 2006; Ebner and Pasalar, 2008). A proposed site for comparisons of proprioceptive and cerebellar signals is the inferior olive (Ramnani, 2006), as it receives proprioceptive afferent information from the spinal cord and corollary information from the cerebellum. If the proprioceptive and cerebellar systems are intimately linked in their sensorimotor feedback roles, it should be of no surprise that cerebellar and sensory neuropathy patients display similar motor deficits (Diener and Dichgans, 1992; Gordon et al., 1995), and a distinct inability to counter the effects of joint interaction torques (Sainburg et al., 1993; Bastian et al.,

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4 Noise and variability certainly also affect afferent signals, but averaging across populations of afferents counters such effects (Faisal et al., 2008), which is the approach adopted in Study I and II.
Since muscle spindles under fusimotor control can act as forward sensory models, a role for fusimotor activity may be to adjust the sensitivity to length, velocity and acceleration in order to incorporate the effects of intended actions on future sensory states, given the current sensory state. In its simplest form, a modulation of spindle gain can even be simply adjusted to skeleto-motor activation. In a lengthening muscle, for example, decreasing the spindles’ overall gain in accordance with future parent muscle force probably facilitates a rough estimation of future kinematics. More accurate predictions are to be created if spindle sensitivity to length, velocity and acceleration are finely tuned; however, fusimotor actions cannot adjust spindle sensitivity to a particular kinematic variable alone, but rather adjust the overall spindle gain (Matthews, 1981). If this extends to common manual tasks, humans may learn to control the fusimotor system in order to find optimal combinations of sensitivities to length, velocity and acceleration, even if the three cannot be independently adjusted.

Evidence of $\alpha$-$\gamma$ dissociation

There were some occasions where deviations in discharge rates could not be attributed to current muscle state or to immediate future states (cf., Fig. 14). In addition, fusimotor activity during the key-pressing task was found to be contingent on entire key-sequences (cf., Figs. 15-16). That the afferents discharged differently depending on subsequent or previous keystrokes – in the absence of differentiated surface EMG activity – suggests that the fusimotor activity was dissociated from skeletomotor activity (i.e. ‘$\alpha$-$\gamma$ dissociation’). The main reason for the signs of $\alpha$-$\gamma$ dissociation during key-pressing may be the nature of the task itself. During both key-pressing and block-grasping, the participants performed fast and unconstrained movements, had to position their fingers accurately and apply force, and were making and braking contact between their fingertips and objects. Although the participants grasped blocks of different sizes in the one task, the movement sequence was the same across trials (i.e. grasp opening followed by grasp closing).

As recently pointed out, a universal role of corollary discharges across species is to facilitate motor sequences (Crapse and Sommer, 2008). A parsimonious explanation for the presence of $\alpha$-$\gamma$ dissociation in the key-pressing study, therefore, relates to the serial execution of different movement sequences, requiring different temporal and spatial coordination of several muscles. If
so, this may explain the failure to demonstrate significant dissociations between fusimotor and skeletomotor activity in previous microneurography studies with humans, even after increasing the precision requirements (Kakuda et al., 1996), or learning to cope with disturbances (al-Falahe et al., 1990a). Also, this may explain why we found evidence for sequence-specific fusimotor drive in a task that was simple to execute once the participants understood it but still obviously required clever coordination of the muscles actuating the digits and the wrist. Given the spindles’ ability to signal future kinematic states, it is tempting to speculate whether the purpose of the sequence-specific and probably α-γ dissociated fusimotor activity was to refine state predictions. Since this fusimotor activity was evidently unrelated to the current state of the muscle, it may have represented the influence of the synergists associated with each particular sequence; that is, the sensorimotor system may account for the effects of motor commands send to a parent muscle and to its synergists on the future state of the parent muscle.

**A role for muscle spindles in sensory cancellation?**

While position and movement sense is currently believed to result from multi-modal sensory integration, the specific role of muscle spindle afferents in this respect is, in fact, still unclear. The main evidence linking primary spindle afferent responses to movement sense has been based on tendon vibration studies. However, the illusions evoked by vibrating passive muscles are slow and small in amplitude (Roll and Vedel, 1982), depend on context (Rabin and Gordon, 2006) and show significant latencies following the onset of vibrations (Cordo et al., 2005). If primary spindle afferents, on the other hand, contribute by communicating future rather than current states, this may explain why vibratory stimuli of relaxed muscles induce illusory movements with significant delays.

Nevertheless, in addition to a role in motor control, forward sensory models have also been proposed to facilitate our sense of self. That is, the process by which sensation produced by the self (‘re-afference’) and sensations induced by environmental influences (‘ex-afference’) has been suggested to involve a comparison between predicted and actual sensory states (Wolpert and Flanagan, 2001; Cullen, 2004). Hence, in establishing velocity re-afference, both types of muscle spindle ending are likely contributors towards this goal.
CONCLUSIONS

1. During active movements, muscle spindle responses were found to be ~90° more phase advanced on muscle length than expected from previous studies in animals and humans. Consequently, the discharge of type Ia afferents was correlated to velocity and acceleration of their parent muscle, whereas that of type II afferents was correlated with velocity.

2. A parsimonious explanation for this phase advance is that muscle fascicle length (as ‘measured’ by the muscle spindles) is proportional to the force generated by the muscle, and that the muscles were acting on a predominantly viscous load. This entails that information from muscle spindle afferents is load-dependent.

3. Combining muscle spindle and Golgi tendon organ activity generated better representations of muscle kinematics than using spindle activity alone. The discharge of type Ib afferents is related to contractile force. Since this force is proportional to the length of in-series elastic elements of muscles, this explains why type Ib responses may disambiguate muscle spindle signals.

4. Muscle spindles under fusimotor control can act as forward sensory models. Their inputs are the current kinematic state of their parent muscle and a corollary motor command, whereas their output is an estimate of a future kinematic state. We demonstrate that type Ia afferents predict muscle velocity ~100-160 ms in the future.

5. The fusimotor input to the muscle spindles was found to be contingent on planned movement sequences and not strictly coupled to the α-motor activity.

6. A likely role of the γ motor system is to adjust spindle sensitivity to incorporate the effects of imminent action on future muscle states, thereby enabling muscle spindles to act as forward models.

7. Finally, the ability of muscle spindles to act as forward sensory models implies that sensorimotor learning includes learning to control the fusimotor system.
ACKNOWLEDGEMENTS

I would like to express my appreciation to all the people that have contributed -one way or another- to the successful completion of this doctoral project. However, the contribution of quite a few individuals warrants particular mention:

I would first like to thank my supervisor, Benoni B. Edin, for initiating me into the art of microneurography and to the science of neurophysiology, and for being enthusiastic, patient and optimistic throughout. Next is Anders Bäckström, for bringing stoicism back into fashion but mostly for his technical help. I would also like to thank Micael Andersson, for all the matlab tips and his advice on physics, for occasionally being a gym buddy and for always being a friend. Sven-Olof Johansson, for creating excellent microneurography electrodes and the key-pressing apparatus. Roland Johansson for impeccable advice on scientific and presentational matters. Göran Westling for his technical help and for building gadgets of sorts. My comrade in arms Daniel Säfström, I would like to thank for his advice, for all of the stimulating discussions on various topics and for his contagious gentlemanly disposition. Anna Theorin, for all of her help and support over the years. Inga-Lill Bäckström, for help with all administrative issues. Herbert Silvenius, Erika Dahlin and CJ Olsson for all of their help and encouragement. My appreciation also goes out to all the participants in my microneurography experiments, for their discomfort was not in vain. To my beloved wife, Linnea Dimitriou, for her love and support but mostly for showing me that life can be without compromise. Last but not least, I would like to thank my family in Cyprus, in Sweden, in Athens and in London for all of their encouragement and love.

Sincerely,

Michael Dimitriou

December - 2008
REFERENCES


Matthews, P.B. (1962). The differentiation of two types of fusimotor fibre by their effects on the dynamic response of muscle spindle primary endings, *Quarterly Journal of Experimental Physiology and Cognate Medical Sciences*, vol. 47, pp. 324-333


