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REVIEW

# Optimal feedback control and the long-latency stretch response

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**Abstract** There has traditionally been a separation between voluntary control processes and the fast feedback responses which follow mechanical perturbations (i.e., stretch "reflexes"). However, a recent theory of motor control, based on optimal control, suggests that voluntary motor behavior involves the sophisticated manipulation of sensory feedback. We have recently proposed that one implication of this theory is that the long-latency stretch "reflex", like voluntary control, should support a rich assortment of behaviors because these two processes are intimately linked through shared neural circuitry including primary motor cortex. In this review, we first describe the basic principles of optimal feedback control related to voluntary motor behavior. We then explore the functional properties of upper-limb stretch responses, with a focus on how the sophistication of the long-latency stretch response rivals voluntary control. And last, we describe the neural circuitry that underlies the long-latency stretch response and detail the evidence that primary motor cortex participates in sophisticated feedback responses to mechanical perturbations.

**Keywords** Reflex · Optimal feedback control · Long-latency · Motor cortex · Stretch response

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## Introduction

The nervous system counters mechanical perturbations applied to the arm with a stereotypical sequence of muscle activity, starting with a short-latency stretch reflex (20–50 ms post-perturbation) and ending with a voluntary response (>100 ms). Occurring between these two events is the enigmatic and often studied long-latency stretch reflex (50–100 ms), which occurs earlier than standard metrics of voluntary reaction time yet can sometimes be modified by a subject's voluntary intent (Crago et al. 1976; Hagbarth 1967; Hammond 1956; Rothwell et al. 1980). The duality of the long-latency reflex, which is on the one hand fast, simple and automatic like the short-latency reflex and on the other hand complex and capable like voluntary control, has yielded a great deal of debate about its functional role in motor behavior and its underlying neural circuitry (Marsden et al. 1983; Matthews and Miles 1988; Shemmell et al. 2010).

A recent theory of motor control, based on optimal feedback control, posits that voluntary motor behavior involves the sophisticated manipulation of sensory feedback (Todorov 2004; Todorov and Jordan 2002). We have previously suggested that one physiological implication of this manipulation is that the long-latency reflex, like voluntary control, should support a rich assortment of behaviors because this reflexive response and the voluntary motor system are intimately linked (Scott 2004). Reflexive

and voluntary responses are related because they both form part of the same feedback control process and engage similar neural circuitry including primary motor cortex. Such a close link between reflexive and voluntary responses makes many experimental predictions but belies the traditional distinctions made between reflexes and voluntary control. Therefore, we avoid the term "reflex" and its associated semantic baggage (Prochazka et al. 2000), favoring instead a simple empirical distinction between relatively slow (i.e., voluntary) and rapid motor responses ($<\sim$100 ms post-perturbation).

In this review, we briefly introduce optimal feedback control as it relates to sensorimotor control and elaborate how this theory, which is formulated at the behavioral level, can nevertheless help reconcile previous findings about the long-latency response. We then review experiments, including classical studies performed many years ago, exploring the sophistication of stretch responses to mechanical perturbations as well as more recent studies motivated by optimal control that re-evaluate and extend our knowledge on these rapid feedback control processes.

## Optimal feedback control

The sensorimotor system is a product of evolution, development, and learning. As previously articulated, these processes act on different timescales to improve behavioral performance, so it is no surprise that many theories of motor behavior take a normative approach based on optimal control principles and that the resulting models are successful at reproducing a wealth of empirical observations (Fagg et al. 2002; Harris and Wolpert 1998; Hogan 1984; Kuo 1995; Kurtzer et al. 2006; Scholz and Schoner 1999; Smeets and Brenner 1999; Todorov and Jordan 2002).

Optimal feedback control is a subfield of optimal control that computes control signals based on the current state of the system and a cost function which describes the performance criteria of a given behavior. The net result is a complex link between sensory feedback signals and motor outputs that changes as a function of the task being performed. Such controllers can reproduce a wide range of motor phenomena at the behavioral level (Todorov 2004), including muscle synergies, goal-directed corrections (Diedrichsen 2007), and apparent controlled variables (Todorov and Jordan 2002). Given the inherent noise in biological systems (Faisal et al. 2008), optimal feedback controllers designed with a rational cost function (i.e., get to the target while penalizing control effort) predict goal-directed movements that are variable from trial-to-trial but remain successful at achieving the behavioral goal. In fact, this variability adheres to a minimum intervention principle, where only those errors that adversely affect the behavioral task are corrected (Todorov and Jordan 2002). Irrelevant errors are ignored because they play no role in reducing the cost and because trying to correct these task-irrelevant errors with a noisy sensorimotor system may actually produce more errors and possibly make them task-relevant, impacting behavioral performance. Consistent with these expectations, many studies have demonstrated that patterns of variability are not random but show considerable organization that is related to the behavioral goal of the motor task (Scholz and Schoner 1999). For example, in a pistol-shooting task, variability occurs predominantly in those directions where the pistol axis intersects the target so that the bullet will successfully hit the target (Scholz et al. 2000).

An optimal feedback controller has several key features. First, such controllers need an explicit definition of task performance (i.e., cost function). The cost function defines the relevant behavioral variables of the task and quantifies their relative weighting. A rational cost function for upright stance may include a term related to maintaining the body's center-of-mass above its base-of-support and a second term that penalizes energy expenditure. In contrast, the cost function for a 100-m sprint would be heavily biased toward minimizing the time to run the distance without a great deal of consideration for energy expenditure. Once the cost function has been established, the complex mathematics of optimal feedback control can be employed to find the control law that best satisfies the cost function given the physical plant being controlled. Critically, the resulting mapping between sensory inputs and motor outputs (i.e., feedback gains) may not be fixed, but vary throughout a behavior.

Second, an optimal feedback controller can handle mapping multiple inputs onto many outputs. In general, such a multiple-input, multiple-output (MIMO) structure is critical for controlling a system with internal interactions, which are a common feature of many systems (Brogan 1991). When taking a shower, for example, increasing the temperature is often linked to increasing the total flow of water. Keeping water flow constant requires knowledge of the interaction between the hot and cold water valves (with respect to both temperature and flow) and is not trivial to solve with simpler control schemes that control the valves independently. Biological systems possess a myriad of complex interactions that could also be addressed by an MIMO control structure. The flexibility afforded by MIMO control allows the nervous system to account for the physical interactions that naturally occur between parts of the body and may permit it to optimize complex high-level cost functions that hinge on such interactions across parts of the body and across sensory modalities. As in the shower example, controlling the shoulder joint will influence

motion of the shoulder, elbow, and wrist because of intersegmental dynamics (Graham et al. 2003; Hollerbach and Flash 1982). Furthermore, generating the optimal response at the shoulder joint may require position information from the elbow when responding to a dog's sudden pull on a leash, force information from the foot when countering the unexpected movements of a bus and visual information when reacting to catch a ball.

Lastly, an optimal feedback controller needs an accurate estimate of the state of the system it is controlling. This can be generated by combining delayed afferent feedback from peripheral sensors and an estimate of current system state based on the descending motor signals. This estimation process can predict changes in the periphery before the corresponding sensory data have arrived, a process that requires knowledge about the dynamical properties of the body—i.e., an internal model (Hwang and Shadmehr 2005; Kawato and Wolpert 1998; Wolpert and Flanagan 2001).

## Optimal feedback control and the stretch response

Although optimal feedback controllers can reproduce a wide range of motor behaviors, the theory does not specifically describe the physiological or neural basis for such control. The formal mathematics of optimal feedback control are incredibly complex (Stengel 1994), and it is highly unlikely that the brain formally solves these equations. In general, determining how a distributed neural network, which includes multiple nested feedback loops, yields near-optimal motor behavior is an important outstanding question in sensorimotor control (Diedrichsen et al. 2010; Scott 2004; Shadmehr and Krakauer 2008).

Where can we start the process of unraveling the physiological mechanisms that underlie optimal feedback control for voluntary movement? It has been well established and is commonly appreciated that the voluntary motor system possesses an incredible capacity to control direction, distance, speed, and accuracy of movement (Shadmehr and Wise 2005). Voluntary control mechanisms can also adjust for current loads and can rapidly learn novel loads (Lackner and Dizio 1994; Nozaki et al. 2006; Shadmehr and Mussa-Ivaldi 1994), visuomotor rotations (Cunningham 1989; Krakauer 2009; Pine et al. 1996) and even arbitrary sensorimotor mappings (Sailer et al. 2005). Yet few studies on voluntary behavior have linked their observations to online feedback control. Optimal feedback control motivates exploring such a link because it emphasizes the importance of using and manipulating sensory feedback to guide voluntary motor behavior. The implication is that feedback mechanisms, such as the response of a muscle to its mechanical stretch (i.e., the stretch "reflex" response), should exhibit a level of sophistication that is similar to voluntary movement because the two systems are inherently linked as part of the same control process. In this context, probing the sophistication of the stretch response provides a window into understanding voluntary control.

Here, we review both classical and recent findings which suggest that stretch responses, and particularly the long-latency stretch response, possess many functional attributes that are commonly reserved for voluntary movement and expected by an optimal feedback control process: task dependency, MIMO mappings, and knowledge of limb dynamics. We then suggest that such functional similarity can be readily understood if one appreciates that both long-latency responses and voluntary control share similar neural substrates, including primary motor cortex.

## Task dependency of stretch responses

One expectation of an optimal feedback control process is that the control law that maps sensory input to motor output should be sensitive to the ongoing behavior. Consider how a subject should respond to the same mechanical perturbation applied during the maintenance of posture or in the middle of a reach. When in posture, the subject needs to counter the applied perturbation and maintain their current position. But when reaching, the subject should not maintain their current position. Rather, the response should be directed toward the final reach target that they are trying to attain. It has been well established that the nervous system accounts for the current behavioral context such that the same sensory information may evoke a robust motor correction, yield no response, or even assist the perturbation (Hasan 2005).

Consistent with the notion of modifiable feedback responses, over 60 years of research has established that stretch responses are task-dependent in a variety of experimental settings using a range of devices and focusing on different behaviors and muscle groups. Despite this wide array of approaches, most of the experiments can be categorized into one of three different types of task dependency. One class of studies explores how the long-latency response is modulated by subject intent. In these studies, subjects are given an explicit instruction on how they should respond to an upcoming perturbation. A second class focuses on changing the behavioral context and demonstrating that the demands of the task implicitly modify the long-latency response. A third class investigates how the long-latency response is modulated when the main goal of the task remains constant but the surrounding environment is changed.

### Explicit modulation by subject intent

Peter Hammond was the first researcher to describe the long-latency response (Hammond 1955). With a simple

motor, pulley, and clutch, he tethered a human subject's wrist with a cable and pulled the hand in such a way that extended the elbow and caused a concomitant stretch of the biceps muscle. The imposed stretch evoked a multi-peaked sequence of muscle activity. The first peak, occurring 20–50 ms after the perturbation, was the well-described short-latency response (Pierrot-Deseilligny and Burke 2005), whose monosynaptic contribution had been originally described in the seminal work of Charles Sherrington (Liddell and Sherrington 1924). The second peak, which was substantially larger and occurred 50–100 ms following the perturbation, was termed the long-latency stretch response.

Quite literally, in the second experiment investigating this multi-peaked sequence of muscle activity, Hammond probed its task dependency by asking subjects to respond to an unpredictable perturbation based on a verbal instruction provided prior to each trial (Hammond 1956) (Fig. 1a). The short-latency response evoked by the perturbation was not sensitive to the instruction. Remarkably, however, the long-latency response was larger when the subjects were told to "resist" the perturbation than when they were asked to "let go". In a control experiment, a very small perturbation was applied and subjects were instructed to resist it as soon as possible. This small perturbation did not evoke the multi-phasic sequence of muscle activity attributed to the short- and long-latency stretch response mechanisms, but did yield a slowly rising response at ~100 ms, which was deemed a voluntary muscular response. These seminal studies led to the conclusion that the long-latency stretch response was not voluntarily generated—because it occurred prior to voluntary reaction time—but that it could nevertheless be modulated by a subject's voluntary intent because it was sensitive to verbal instructions. Although these responses have sometimes been called "triggered reactions" (Crago et al. 1976; Shemmell et al. 2010), they scale with the size of an unexpected perturbation so that they cannot be entirely preplanned (Pruszynski et al. 2011b).

The finding that long-latency responses are modulated by subject intent is incredibly robust. It has been investigated for a wide range of muscles at the elbow (Colebatch et al. 1979; Crago et al. 1976; Evarts and Granit 1976; Hagbarth 1967; Rothwell et al. 1980), wrist (Calancie and Bawa 1985; Jaeger et al. 1982; Lee and Tatton 1982), finger (Capaday and Stein 1987; Marsden et al. 1981; Rothwell et al. 1980), ankle (Gottlieb and Agarwal 1979, 1980; Ludvig et al. 2007), and jaw (Pearce et al. 2003).

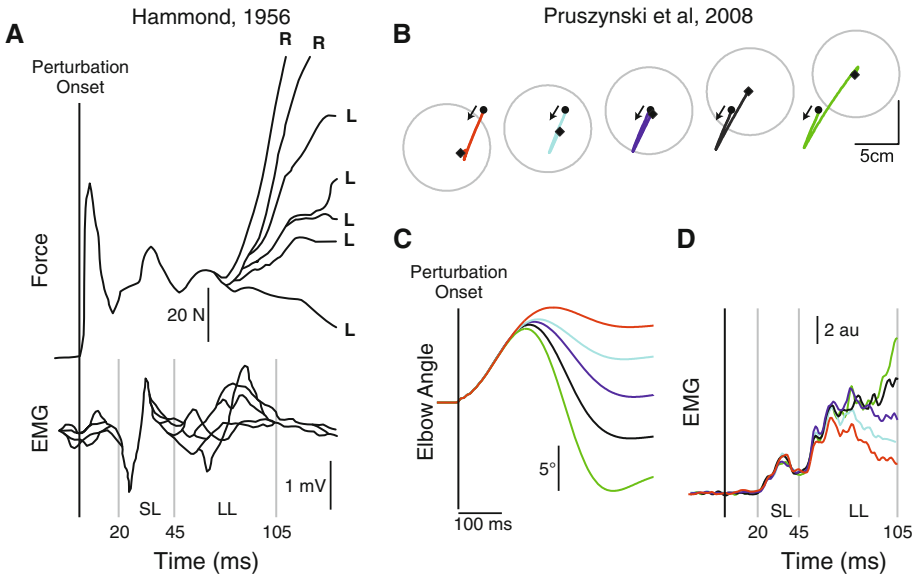


**Fig. 1** Modulation by subject intent. **a** Example of how subjects can categorically modulate the long-latency stretch response according to verbal instruction. Subjects were verbally instructed to respond to a mechanical perturbation with one of two verbal instructions ("resist"/"let go"). *The upper panel* depicts force traces from individual trials aligned on perturbation onset and labeled according to the instruction. *The bottom panel* is the corresponding muscle activity, which shows modulation in the long-latency stretch response (LL) but not the short-latency stretch response (SL). **b** Example of how subjects can continuously modulate their long-latency stretch response in accordance to spatial target position. Subjects were instructed to respond to an unpredictable mechanical perturbation by placing their hand inside one of the five presented spatial targets. *Each plot* represents exemplar hand kinematics as a function of target position. Subjects began each trial at *the filled black circle*, and *the black diamond* indicated final hand position. *The small arrows* indicate the approximate direction of motion caused by the perturbation. **c** Temporal kinematics for the elbow joint aligned on perturbation onset. **d** Pooled EMG aligned on perturbation onset and normalized to pre-perturbation muscle activity. Note that the long-latency stretch response exhibits graded modulation as a function of target position. **a** is modified with permission from (Hammond 1956). **b–d** are modified with permission from (Pruszynski et al. 2008)

Furthermore, the phenomenon is readily observable using a range of verbal instructions including "resist/let go" (Colebatch et al. 1979; Rothwell et al. 1980), "flex/extend" (Hagbarth 1967), and "compensate/do not intervene" (Crago et al. 1976). Although these pioneering studies have established that the long-latency response is modulated by subject intent, their use of verbal instructions has limited the range of questions that could be asked to the small subset of behaviors where verbal instructions have a reliable interpretation, generally at the extremes of behavior. So it is possible to ask the subject to "resist as quickly as possible after the perturbation" or "let go as quickly as possible after the perturbation" but it is unlikely that subjects could reliably "resist 50%", "resist 23%", or "resist 50% with the elbow and 75% with the shoulder". The limited range of verbal instructions is an impediment to exploring the fine and nuanced capabilities expected of the long-latency response predicted by optimal control.

We recently tested for such extensive sophistication by introducing a paradigm that can examine the long-latency response under a wide range of behaviors akin to the dominant methodology used to study the volitional motor system (Shadmehr and Wise 2005). Rather than verbal instructions, subjects were shown a target while they maintained posture at a central position and were instructed to respond to an unpredictable perturbation by quickly placing their hand inside the displayed target (Pruszynski et al. 2008). This approach allowed us to quantify how rapid responses are modulated as a function of target position. Unlike the ambiguity of verbal instructions, target metrics such as position, size, and shape, along with timing constraints, explicitly define the goal of the task and can be monitored and controlled. Our results indicate that the long-latency response is not limited to categorical changes at behavioral extremes. Like voluntary control, the long-latency response is sensitive to fine changes in target position. For example, when we distributed five targets at various distances from the central position, we found that the magnitude of the long-latency response was largest for the furthest target and smallest for the closest target (Fig. 1b–d). Critically, we found a continuous increase for the intermediate targets that mirrored activity during the voluntary response. A similar pattern was present for target positions distributed around the hand. Long-latency responses were tuned to the two-dimensional position of the hand, indicating that they incorporate the multi-joint requirements of the task.

Another advantage of the visuospatial paradigm is that the temporal presentation of the target can be precisely controlled. Recently, we varied the time between the presentation of the spatial target and the application of a mechanical perturbation, which allowed us to determine how much time the nervous system required to modify fast feedback responses. Again, we confirmed that the short-latency response was modified regardless of how long the subject had to view the spatial target. In contrast, the long-latency response was reliably modulated when the target was presented only 100 ms before perturbation onset, which is on the timescale of voluntary reaction time (Yang et al. 2011). Taken together, our findings suggest that long-latency stretch responses are flexibly and quickly modulated by spatial target position, making them a viable candidate for modulating motor actions during day-to-day human behavior.

## Implicit modulation by behavioral context

Although subject intent robustly modifies the long-latency stretch response, such manipulation is so direct that it may not reflect the natural state of affairs where a subject changes from one behavior to another and does not explicitly focus on modulating their rapid motor responses. In fact, there exists substantial evidence that changing the functional goal of a task leads to changes in the long-latency response without an explicit instruction.

An elegant demonstration of such task dependency occurs in the so-called tea cup experiment (Marsden et al. 1981). In that study, subjects were exposed to mechanical perturbations that destabilized their body by pulling on their left hand while crouching and either holding onto a table or grasping a tea cup with their right hand. The principle result was that the long-latency response of right arm muscles was different depending on what the right arm was doing. If it was gripping the table, the long-latency response in extensor muscles was activated in response to the perturbation such that it would help stabilize the subject. If the subject was gripping an unsupported handle, the long-latency response was absent, presumably because any activation in that muscle would not help stabilize the body. And if they were holding a cup of tea, the long-latency response was reversed to ensure that the liquid remained in the cup. Similarly, it has been shown that rapid grip responses to unanticipated object loading account for the directional nature of the gravitational force such that responses are smaller when the perturbation acts against gravity (i.e., up) than when it acts with gravity (Hager-Ross et al. 1996).

Another example of how behavioral context modulates the long-latency response arises when subjects are engaged in maintaining the position of their hand versus maintaining a set level of force/torque (Dietz et al. 1994; Doemges and Rack 1992a, b; Hore et al. 1990). In these experiments, subjects are presented with a display that indicates either their joint position or their joint torque. Their task is to maintain this set level in the presence of mechanical perturbations. Short-latency stretch responses are not

modulated by the task constraints. They are only sensitive to the pre-perturbation muscle activity. In contrast, the long-latency response is larger when perturbations are applied in the position control task than in the force control task.

It is important to emphasize that task-dependent modulation is not limited to the upper limb, which is the focus of this review. In fact, many of the original studies focused on the control of upright posture (Jacobs and Horak 2007; Nashner 1977). For example, when a subject is standing on a platform that can suddenly move, their long-latency response is governed by the length of the platform (Horak and Nashner 1986). When the platform is longer than the foot, subjects recruit long-latency responses in ankle muscles to counter the perturbation, but when the platform is shorter than the foot, subjects utilize a hip strategy to counter the same perturbation. Changing the response according to the platform length is critical to task success. Because the short platform was much shorter than the foot (9 cm), using the ankle strategy in this context would cause the feet to rotate off the support surface. In contrast, the hip strategy allows the subject to move their center-of-mass relative to their base-of-support and thus stay upright without generating torque around the ankle.

## Effect of environmental constraints

Generating appropriate feedback responses requires not only an appreciation of the goal of the task but also the environment within which the task is taking place. Indeed, several studies have demonstrated that changing the mechanical properties of the environment leads to an appropriate change in the long-latency response (Akazawa et al. 1983; Dietz et al. 1994; Perreault et al. 2008). In these studies, subjects typically held on to a robot which simulated either a stiff or compliant environment and thus affected how well they could maintain their hand at a given position. When the same perturbation was applied in these two situations, the long-latency response was larger for the compliant environment. The observation that long-latency responses are larger in the compliant environment has led to the proposal that they act to regulate the stability of the limb (Shemmell et al. 2010). However, it is important to recognize that a stiff environment implies that feedback responses will be relatively ineffective. Therefore, the long-latency response may be depressed because the nervous system recognizes that responding will not change anything with respect to the task goal.

The long-latency response also accounts for interactions with external force fields during reaching (Kimura et al. 2006). In that study, subjects made straight reaches in a predictable force field that pushed their right hand away from its intended target. When a perturbation was unexpectedly applied just before subjects entered the force field, the long-latency response was modified to appropriately counter deviations generated by the force field. Specifically, rightward force fields evoked increased activity in flexor muscles, and leftward force fields evoked increased activity in extensor muscles. This demonstration of predictive modulation associated with a voluntary movement is evidence that the long-latency stretch response is closely coupled to the voluntary motor system.

Recent work has advanced the known capabilities of the long-latency response by demonstrating that task-dependent regulation of limb stiffness is sensitive to the direction of environmental stability (Krutky et al. 2010). Subjects were exposed to destabilizing environments that acted like springs with negative stiffness such that position errors in a particular direction were amplified. These environments were oriented so that the instability could be aligned or orthogonal to the direction of maximal endpoint stiffness of the limb. Unlike the short-latency response, the long-latency response was preferentially increased in those muscles that contribute to countering perturbations along the direction of instability. Interestingly, this increase only occurred when the magnitude of the environmental instability exceeded the mechanical stiffness of the limb in the perturbation direction, a result which suggests that long-latency responses account for the mechanical properties of both the environment and the limb. The direction dependence of the long-latency response is important since many tasks compromise limb stability for particular directions and the mechanical properties of the upper limb are direction specific (Hogan 1984). For example, when using a screwdriver, there is substantial stability along the screw but a great deal of instability in off-axis directions. The observed sophistication during the long-latency response is consistent with the known attributes of voluntary control where patterns of muscular co-contraction account for the directional instability present in various environments (Burdet et al. 2001; Franklin et al. 2003).

The environment has a powerful effect on the short-latency stretch response because it is profoundly modulated by pre-perturbation muscle activity. The result of this sensitivity is that the same perturbation in an environment that activates the muscle a little or a lot will evoke a small or large short-latency response (Bedingham and Tatton 1984; Matthews 1986; Stein et al. 1995; Verrier 1985) (Fig. 2a). This gain-scaling phenomenon was originally proposed as a mechanism to keep the short-latency response useful over a range of load contexts (Marsden et al. 1976a). However, the presence of gain scaling may actually impede this goal because, under the assumption of a relatively linear relationship between a muscle's activity and its force production (Hof 1984; Lawrence and Deluca 1983; Milner-Brown and Stein 1975), the motor output

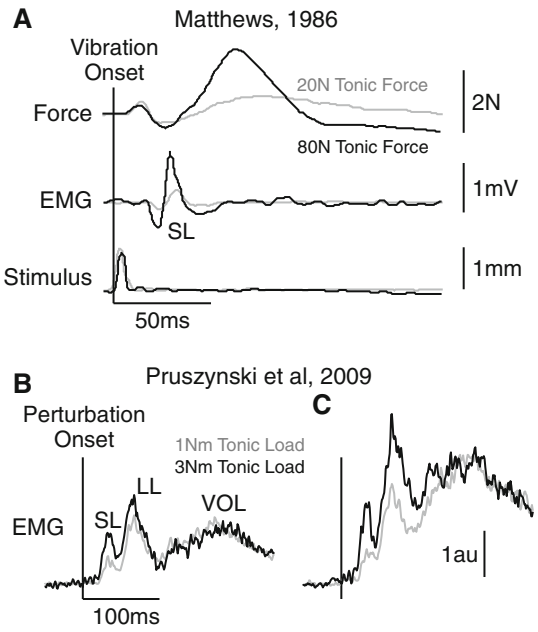


**Fig. 2** Sensitivity to background load. **a** Example of automatic gain scaling during the short-latency stretch response. The first and second rows depict force and biceps muscle activity in response to a vibratory stimulus caused by tapping the tendon. Using a tendon tap ensured that only the short-latency stretch response (SL) is elicited. All traces are aligned on stimulus onset, and the two lines correspond to two levels of initial force. Note that both force and muscle responses are substantially larger with the higher level of initial force even though the magnitude of the tendon tap is similar. **b** Example of how automatic gain scaling is reduced for the long-latency stretch response. Muscle activity in response to the same mechanical perturbation at two levels of tonic load. Using a step-torque perturbation and requiring the subjects return to the initial target after the perturbation ensured that they generated both short-latency (SL) and long-latency (LL) responses. As in (**a**), the short-latency stretch response shows substantial gain scaling but this effect is reduced in the long-latency stretch response and absent at ~100 ms post-perturbation. **c** Same as (**b**) but for a larger perturbation magnitude. Note that pre-perturbation differences in muscle activity have been removed in both (**b**) and (**c**) to permit direct comparison of the phasic activity following mechanical perturbation. **a** is modified with permission from (Matthews 1986). **b**, **c** are modified with permission from (Pruszynski et al. 2009)

should reflect the magnitude of the perturbation regardless of the initial conditions. Since the gain-scaling phenomenon is caused by the size-recruitment principle of the motoneuron pool (Capaday and Stein 1987; Kernell and Hultborn 1990; Slot and Sinkjaer 1994), its presence in the short-latency epoch appears to reflect an inadequacy of the short-latency response to account for the size-recruitment principle.

We recently investigated whether the temporal evolution of automatic gain scaling to test whether the long-latency stretch response accounts for the state of the motoneuron pool (Pruszynski et al. 2009). Our experimental approach was straightforward. Subjects were instructed to maintain their hand at a small central target in the presence of various background loads and randomly occurring step-torque perturbations. Unlike previous studies that used short servo-controlled position perturbations and verbal instructions such as "do not intervene" (Matthews 1986; Ruegg et al. 1990; Stein et al. 1995; Verrier 1985), our use of spatial targets and step-torque perturbations elicited robust muscle responses in the short-latency, long-latency, and voluntary (>100 ms post-perturbation) epochs. And since subjects were required to stabilize their hand at the same position before and after the perturbation, we could also quantify changes in steady-state muscle activity. Consistent with previous studies, we found that the short-latency activity, but not steady-state muscle activity, showed substantial gain scaling and that limb displacement was significantly reduced with larger background loads (Fig. 2b, c). Critically, our results revealed that gain scaling was quickly attenuated during the long-latency response and was statistically absent within ~100 ms of perturbation onset.

## Selective integration of sensory feedback

An important feature of an optimal feedback controller (and many other types of modern control systems) is the ability to incorporate multiple sensory input signals into each motor output (Brogan 1991). The presence of an MIMO control structure would permit the sensorimotor control system to account for its many internal interactions and to route sensory feedback to a variety of motor effectors as appropriate for the task constraints. The ability of the motor system to adapt and use sensory signals from various locations and modalities during feedback control is exemplified by our ability to use cutaneous signals from light finger contact to stabilize whole-body standing posture (Jeka and Lackner 1994).

### Flexible routing of sensory information

The short-latency stretch response can coordinate the contraction of multiple muscles. At the simplest level, the monosynaptic response activates not just the muscle being excited but also its functional synergists. An additional synapse via an inhibitory interneuron means that exciting one muscle will yield inhibition in its antagonists. More complex coordination is possible at the spinal level. For example, when a noxious stimulus is applied to the leg, cutaneous afferents yield activation of flexor muscles in the stimulated leg and extensor muscles in the other leg (Sherrington 1910). This rapid flexion and crossed-extension response means that stepping on a nail results in a rapid response to lift the stimulated leg and bear the weight of the body with the other leg.

The long-latency response can route sensory feedback in a much more flexible manner. For example, in the tea cup experiment described above, when the subject was pulled forward by their left arm, a long-latency stretch response was also routed to the muscles of the toe, which were not stretched by the perturbation but could contribute to maintain the subject's balance (Marsden et al. 1981). Long-latency responses are also routed across finger muscles when subjects are exposed to perturbations during an object manipulation task (Cole et al. 1984). If a perturbation is applied to the thumb, the long-latency response appears on both thumb and forefinger muscles as they both contribute to compensating for the load and thus help satisfy the goal of the task (Fig. 3a). Interestingly, this coupling is influenced by task constraints. If the subject is making rhythmic movements that mimic a grasping motion but without the presence of an object, then the application of a perturbation does not result in a coordinated response across the thumb and forefinger.

Recent work has demonstrated that feedback responses are also coordinated across the two limbs (Diedrichsen 2007; Dimitriou et al. 2011; Mutha and Sainburg 2009; Ohki and Johansson 1999). In an elegant study, Diedrichsen (2007) asked subjects to reach with two hands to two separate spatial targets (two-cursor condition) or make the same bimanual movements to move a cursor presented at the spatial average location of the two hands (single-cursor condition) to a single spatial target. When forces were applied in the two-cursor condition, only the hand that received the force could ultimately counter the applied load. In contrast, when the same perturbation was applied in the one-cursor condition, both hands could counter the disturbance applied to one of the hands. The results indicate that subjects were optimal with respect to a simple cost function by recruiting only one hand in the two-cursor condition and efficiently splitting the response between the hands in the one-cursor condition. The work of Diedrichsen (2007) did not record muscle activity and the behavioral responses occurred with a large enough delay (~180 ms with respect to velocity) that the phenomenon did not necessarily reflect the action of the long-latency stretch response. However, further investigation in a similar task designed specifically to elicit the long-latency stretch response showed that it was present only in the muscles of the perturbed arm for the two-cursor task but appears in muscles of both arms for the one-cursor condition (Mutha and Sainburg 2009). More recently, Dimitriou et al. demonstrated that the long-latency response can integrate information across the limbs by engaging subjects in a virtual tray-holding task (Dimitriou et al. 2011). In this task, a perturbation applied to one limb will tend to tilt the tray and spill the virtual drinks, while a perturbation

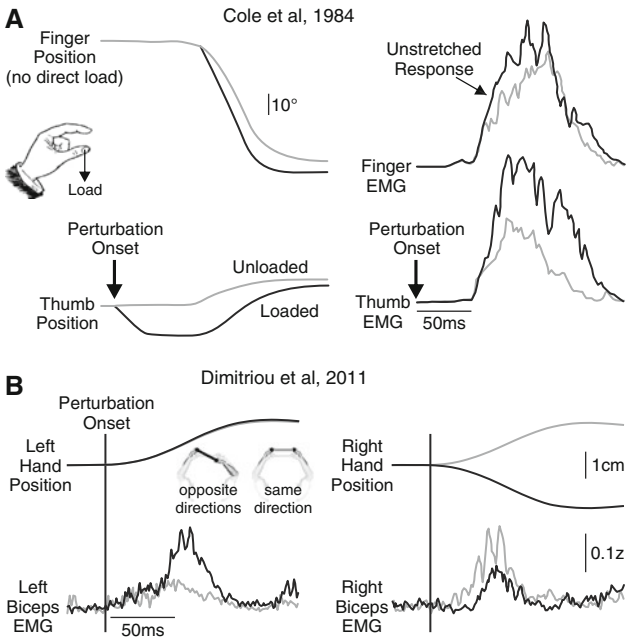


**Fig. 3** Transfer of stretch responses between fingers and arms. **a** Example of how the long-latency response can be coordinated between the finger and thumb in a pinching task. *The left column* depicts finger and thumb kinematics in unloaded (*grey lines*) and loaded (*black lines*) trials. In unloaded trials, subjects were instructed to bring the finger and thumb together and generate a set level of pinching force. In loaded trials, an unexpected force was applied to thumb as indicated by *the arrow*. Although no load was applied on the finger, its kinematic trajectory is modified to maintain the required pinch contact. *The right column* depicts muscle activity from both the finger and thumb for the same conditions. Critically, the finger response mediating the coordination of the pinch occurs ~60 ms post-perturbation, which corresponds to the latency of the long-latency stretch response in the fingers. **b** An example of how the long-latency response can be coordinated across limbs. Subjects were engaged in a virtual tray holding task and instructed to maintain the orientation but not position of the tray. Perturbations could be applied to the hands such that the tray was either displaced (no response required, *left inset*) or rotated (response required, *right inset*). Critically, the trials were interleaved, and the movement of the left hand was identical for both conditions so that generating the appropriate response in the left arm muscles required integrating information from the right arm within a single trial. The top row depicts left and right hand position aligned on perturbation onset. The bottom row depicts the left and right muscle activity aligned on perturbation onset. Note that appropriate changes in muscle activity (black > grey in left panel) occur during the long-latency stretch response. **a** is modified with permission from (Cole et al. 1984). **b** is modified with permission from (Dimitriou et al. 2011)

applied to both arms will displace but not tilt the tray and thus keep the drinks from falling. Their results indicate that the long-latency response of both arms is consistent with task-level goal and, because all of their perturbation conditions were randomly interleaved, that the long-latency response of one arm can be modulated online within a single trial based on sensory information from the other arm (Fig. 3b).

## Accounting for properties of the musculoskeletal system

Optimal feedback control suggests that motor outputs should be crafted for the physical plant they are controlling. This capability can be accomplished by flexibly routing sensory information among multiple muscles (Gielen et al. 1988; Koshland et al. 1991; Perreault et al. 2008; Soechting and Lacquaniti 1988). For example, the long-latency stretch response accounts for the mechanical action of multi-articular muscles (Gielen et al. 1988) (Fig. 4a). If a subject's task is to supinate their hand and a pronation perturbation is applied, the coordinated response (at both short and long latencies) includes a contribution from biceps which crosses the elbow and helps supinate the hand. However, countering the pronation perturbations with the biceps muscle results in unwanted elbow flexion. This elbow flexion ultimately needs to be countered to prevent unwanted movement at the elbow. The short-latency response is only recruited by the locally stretched muscles, so it does not provide this compensation. In contrast, the long-latency response is evoked in the triceps muscles, which generates elbow extensor torque. Furthermore, long-latency inhibition is present in brachialis, a monoarticular elbow flexor. The flexibility of the system is incredible. For pronation perturbations of the hand, the biceps and triceps act in concert as agonists and the brachialis is an antagonist. For extension perturbations at the elbow, the biceps and brachialis are coupled as agonists, and the triceps act as antagonists.

The above example provides an elegant demonstration that the long-latency response can intelligently coordinate the activity of multiple muscles of the limb. Such coordination could allow the long-latency response to account for the complex mechanical interactions that occur in multi-joint systems like the human arm. An essential feature of the arm is that single-joint torque will cause multi-joint motion and that single-joint motion can only result from multi-joint torque (Graham et al. 2003; Hollerbach and Flash 1982). A wealth of research has demonstrated that self-initiated (i.e., voluntary) movements account for the complex mechanical properties of the limb, a fact often cited as a hallmark of voluntary motor sophistication (Hwang and Shadmehr 2005; Kawato and Wolpert 1998; Wolpert and Flanagan 2001).

There is evidence that long-latency responses can account for the mechanical properties of the limb (Koshland et al. 1991; Kurtzer et al. 2009, 2008; Soechting and Lacquaniti 1988). Recently, we applied known loads to the shoulder and elbow, which yielded particular motion patterns at these two joints (Kurtzer et al. 2008). We could then directly test whether stretch responses are sensitive to local joint motion or whether they integrate motion from

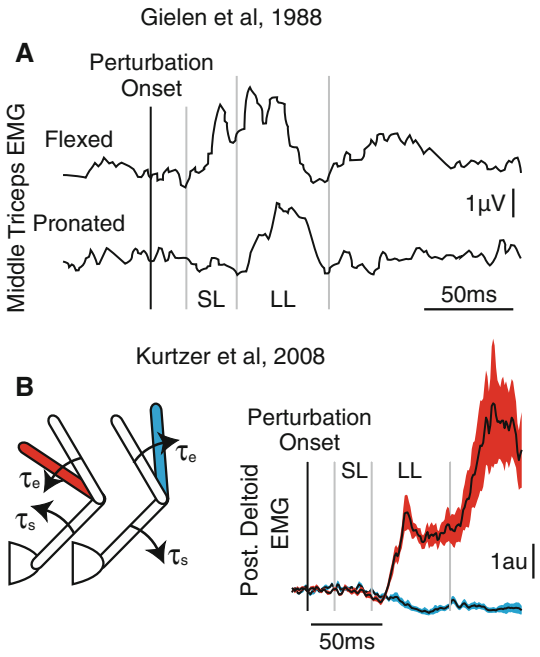


**Fig. 4** Sensitivity to muscle and limb mechanics. **a** Example of how the long-latency response can account for muscle mechanics. The *top* and *bottom rows* depict muscle activity (*middle triceps*) in response to a mechanical perturbation that flexed or pronated the arm, respectively. Flexion torque perturbations stretched the triceps, and the resulting response included both short-latency (SL) and long-latency (LL) stretch responses. In contrast, pronation torque perturbations do not have a mechanical effect on the triceps muscles, and they evoked only a long-latency stretch response. This pattern of activation is similar to what is seen during self-initiated movements and can be explained by the need to counter undesired contributions from responses in the multi-articular biceps muscle (see text). **b** Example of how the long-latency response can account for limb dynamics. Subjects were instructed to maintain their hand at a central target while countering unpredictable step-torque perturbations applied to both the shoulder and elbow. Critically, shoulder and elbow torque magnitudes were chosen so that they caused substantial elbow motion but almost no shoulder motion. The traces on the right panel depict muscle activity aligned on perturbation onset. Note that even though the shoulder muscle was neither stretched nor slackened by the mechanical perturbation, there is still a robust long-latency stretch response (both excitatory and inhibitory) in the posterior deltoid muscle. This pattern is appropriate to counter the underlying torque, which indicates that the neural circuits contributing to the long-latency stretch response account for the intersegmental dynamics of the limb. **a** is modified with permission from (Gielen et al. 1988). **b** is modified with permission from (Kurtzer et al. 2008)

both the shoulder and elbow in a manner appropriate to counter the underlying torque (Graham et al. 2003; Hollerbach and Flash 1982). In our first experiment, we applied either pure shoulder torque or pure elbow torque. Both of these perturbations resulted in the same shoulder motion but different elbow motion. We then tested whether monoarticular shoulder muscles respond to shoulder motion or to the underlying shoulder torque. Our results indicate that not all stretch responses were equal. The short-latency response was the same in both conditions,

indicating that it responded only to local joint motion. In contrast, the long-latency response, like voluntary control, was sensitive to motion at both joints and generated a larger response for the shoulder torque perturbation than the elbow torque perturbation. In our second experiment, we applied combined shoulder and elbow torque perturbations such that the shoulder did not move. If stretch responses account for the limb's mechanical properties, they should still respond to this perturbation even though the joint is not moving. Again, we found that the short-latency response mirrored the local joint motion and was not evoked by these perturbations. In contrast, we found a robust long-latency response that appropriately countered the underlying torque perturbation (Fig. 4b).

### The short-latency stretch response: stereotyped but not immutable

The short-latency stretch response is the fastest neuromuscular response to a mechanical perturbation. Since this response occurs 20–50 ms following a mechanical perturbation, it must be mediated by mono- and oligo-synaptic pathways at the spinal level (Kandel et al. 2000; Pierrot-Deseilligny and Burke 2005). The largest contribution to the short-latency response comes from the monosynaptic pathway (Burke et al. 1984) where sensory fibers arising from the primary spindle endings (group IA) in a given muscle directly target motoneurons which innervate the same muscle and its synergists (Liddell and Sherrington 1924; Pierrot-Deseilligny and Burke 2005). It is the monosynaptic component of the short-latency response that is elicited by tapping a tendon with a hammer, a valuable clinical tool for identifying neurological dysfunction.

The short-latency response is generally thought to be an extremely stereotyped "knee-jerk" response that simply reflects the present state of spinal circuitry. Indeed, the short-latency response displays limited sophistication under many experimental settings, as emphasized in this review, but it is not completely immutable and can be modulated under some conditions. For example, the short-latency response is profoundly modulated at the transition between posture and movement (Mortimer et al. 1981) or between stance and walking/running (Duysens et al. 1993; Komiyama et al. 2000). In general, there is substantial evidence that the short-latency response changes dramatically over the course of cyclical movements such as gait (Akazawa et al. 1982; Capaday and Stein 1986; Forssberg et al. 1975; Zehr et al. 2003), sinusoidal tracking (Dufresne et al. 1980; Johnson et al. 1993), or hand cycling (Zehr and Chua 2000). Note that all of these behaviors tend to be cyclical in nature, suggesting that spinal processing in this context is substantially different compared to spinal processing during goal-directed reaching or postural control.

The short-latency response can also be systematically modified by providing extensive exposure to the same experimental condition and direct reinforcement of response magnitude (Christakos et al. 1983; Wolf and Segal 1996; Wolpaw et al. 1983). These results suggest the short-latency response is modifiable with repeated exposure to the same condition but that the timescale of such modulation dramatically exceeds the typical length of an experimental session. This is in stark contrast to long-latency or voluntary responses, which can be modulated by naïve subjects within milliseconds or seconds of a spatial instruction and with minimal practice (Colebatch et al. 1979; Soechting et al. 1981; Yang et al. 2011).

The general inflexibility of the short-latency response is surprising as there are several mechanisms that can modulate the spinal circuitry. At the behavioral level, performing the Jendrassik maneuver by interlocking the hands and pulling is known to raise the sensitivity of the short-latency response that follows a tendon tap (Zehr and Stein 1999). Physiologically, it is well established that the gamma-motoneurons modulate the sensitivity of muscle spindles (Hulliger 1984) and that they can be activated independently of alpha-motoneurons that drive the extrafusal muscle fibers and cause movement (Goodwin and Luschei 1975; Loeb and Duysens 1979; Taylor and Cody 1974). The nervous system could, in principle, use gamma-activation to regulate the sensitivity of feedback responses at all latencies without affecting motor output (Prochazka 1989).

Recently, it has been demonstrated that monkey spinal interneurons receive descending input from cortical areas and exhibit task-specific preparatory activity (Prut and Fetz 1999). The implication is that cortical networks, which mediate a range of sophisticated voluntary behavior, have access to the spinal cord and should be able to tune that circuitry to an upcoming perturbation. Presumably, these signals could modify the short-latency stretch response. However, in that study, the muscles were silent in the preparatory period. This silence could allow for systematic subthreshold changes in muscle activity associated with the cortical preparation, which would not be visible in the recorded muscle activity (Capaday and Stein 1987). The implication is that the short-latency stretch response is tightly linked to the state of the motoneuron pool; if so, the observed preparatory activity in spinal interneurons may disappear if the muscles were activated.

## Neural basis of the long-latency stretch response

When Hammond first observed the long-latency response, he immediately proposed that this phase of muscle activity could reflect one of the two potential pathways (Hammond

1955, 1956). One option was that it traversed the same spinal pathway as the short-latency response but travelled along slower afferent fibers. Alternatively, the long-latency response could travel along the same fast afferents but traverse a longer route through the nervous system. This simple suggestion ignited a long-standing debate about the neural origin of the long-latency response (Matthews 1991). Below, we review the evidence supporting spinal and cortical contributions to the long-latency stretch response.

## Spinal contributions to the long-latency response

The principle motivation for attributing the long-latency stretch response to a spinal mechanism is that spinalized cats and monkeys still exhibit muscular activity in the long-latency epoch (Ghez and Shinoda 1978; Miller and Brooks 1981; Tracey et al. 1980). These results clearly demonstrate that a transcortical pathway is not required to evoke long-latency activation, but it is unclear how similar this pathological response is to that observed in intact animals and humans.

One possible spinal mechanism is that the sensory information which generates the long-latency stretch response utilizes slower afferents originating from the secondary spindle ending (group II). Since these afferents have transmission speeds approximately half that of group IA afferents (group I: 72–120 m/s; group II: 36–72 m/s) (Kandel et al. 2000), their timing would be appropriate for the generation of the long-latency response for at least some muscles of the upper limb. Support for this hypothesis comes from various sources. Muscle vibration fails to excite the long-latency response as seen when the muscle is stretched by a mechanical perturbation (Matthews 1984; Matthews and Pickup 1985). Since the primary muscle spindle is robustly excited by the vibratory stimulus, the lack of a long-latency stretch response has been taken as evidence that it does not use this type of sensory information, implicating instead a spinal pathway mediated by group II afferents. Group II transmission is further supported by recent observations that the muscle relaxant tizanidine, which selectively depresses transmission by group II afferents, yields a reduction in the long-latency response for muscles of the upper and lower limbs (Grey et al. 2001; Meskers et al. 2010).

Not all the reported evidence provides positive support for a group II pathway. For example, a smart controller would ignore that vibratory stimulus since it did not evoke movement and interfere with task success. Therefore, the lack of response may reflect a control strategy rather than insensitivity to information originating from the primary spindle afferent. Further contradictory results come from studies that systematically slow the speed of afferent conduction by cooling the arm. Critically, the absolute size of the slowing is proportional to the cross-sectional diameter of the fibers and their pre-cooled conduction velocity (Paintal 1965). This physical fact means that cooling the arm will have a greater effect on the timing of the long-latency response if it traverses a spinal pathway via slower afferents than a cortical pathway via faster afferents. Indeed, in an elegant series of experiments, Peter Matthews found clear evidence that cooling the arm slowed the long-latency response by an amount that could not correspond to a spinal pathway (Matthews 1989). Thus, at least for the muscles of the hand, a substantial portion of the long-latency response does not appear to traverse a spinal pathway via group II afferents.

Long-latency responses may also reflect the synchronization or reverberation of the group IA afferents which generate the short-latency stretch response (Hagbarth et al. 1981; Schuurmans et al. 2009). Specifically, the application of a mechanical perturbation causes robust excitation and synchronization of the primary spindle endings. The synchronization at perturbation onset may then cause the afferent fibers to enter their refractory period at around the same time and subsequently recover around the same time. This second phase of activation may appear in the long-latency time window, suggesting that the long-latency stretch response merely reflects the ongoing action of the short-latency response. Such an explanation is attractive and can account for the phasic nature of the short- and long-latency responses, but it predicts that the long-latency response should always be smaller than the short-latency response. This suggestion is incompatible with the observation that the long-latency response is often much larger than the short-latency response (Crago et al. 1976; Hammond 1956; Rothwell et al. 1980) and that the long-latency response can appear even in the total absence of a short-latency response (Gielen et al. 1988; Kurtzer et al. 2008; Soechting and Lacquaniti 1988).

## Cortical contributions to the long-latency response

There is substantial evidence suggesting that the long-latency response involves a transcortical pathway through primary motor cortex. Philips first made this suggestion based on anatomical observations that area 3a of primary somatosensory cortex projects to primary motor cortex and that there exist direct projections from primary motor cortex to spinal motoneurons (Phillips 1969). Given the relatively direct route and the speed of the fibers that mediate primary muscle spindle activation (group IA, conduction velocity $\sim$100 m/s), there is sufficient time for an afferent signal to reach sensorimotor cortex and return to the periphery (a distance of 1–2 m) before the onset of the long-latency stretch response.

Several studies investigated the relative timing of the short- and long-latency response as a test of the transcortical hypothesis. In an elegant series of experiments, Marsden et al. hypothesized that if both the short-latency and long-latency responses were mediated by the same fast afferent fibers, then the relative timing between the short-latency and long-latency stretch response should be different across muscles (Marsden et al. 1973, 1976b). This prediction arises because each muscle has a somewhat different relationship between its distance to the spinal cord (which determines the short-latency timing) and its distance to the brain (which would determine the long-latency timing). In contrast, if the long-latency response traverses the same circuit as the short-latency response but using the slower afferents, then the timing of both the responses should be proportional to the distance from that muscle to the spinal cord. Their results were quite clear. The timing of the short-latency response, elicited by a tendon tap, was 13 and 23 ms for a muscle of the shoulder (infraspinatus) and thumb (long flexor), respectively. But the long-latency response occurred 27 and 22 ms later in the same muscles. This excess latency is consistent with the distance between the given muscle and the brain rather than a simple ($\sim$2x, given reasonable physiological estimates) increase that would occur if the afferent signals traversed slower (group II) afferents to the spinal cord and returned to the muscle along a similar population of alpha-motoneurons.

Clinical studies have shown that lesions in the dorsal columns and in the sensorimotor cortex can abolish the long-latency response (Lee and Tatton 1978; Marsden et al. 1977; Soechting and Lacquaniti 1988), but these results cannot unequivocally establish the presence of a transcortical pathway since the dysfunction could be caused by a change in cortical modulation of spinal circuits. More interesting, therefore, are results from subjects who suffer from Klippel-Fiel syndrome (Capaday et al. 1991; Matthews et al. 1990), a rare disease caused by a bilateral bifurcation of the descending motor cortical projections whose prime symptom is the presence of undesired bilateral (mirror) movements. When these subjects counter mechanical perturbations applied to the forefinger, they demonstrate unilateral short-latency responses but bilateral long-latency stretch responses. That is, stretching the left forefinger muscle (Matthews et al. 1990: first dorsal interosseous; Capaday et al. 1991: flexor pollicis longus) elicits the typical long-latency response in the left forefinger muscle and an inappropriate evoked response in the unperturbed right forefinger muscle. Since the bifurcation of motor pathways in these subjects occur at the cortical level, these results imply that cortical structures at least partly mediate the long-latency response.

Further support for a transcortical pathway comes from single-cell recordings in monkeys. In general, many studies have emphasized the robust presence of afferent signals in primary motor cortex (for review, see (Hatsopoulos and Suminski 2011)) without focusing directly on the long-latency stretch response (Evarts 1973; Evarts and Fromm 1977; Fetz et al. 1980; Flament and Hore 1988; Herter et al. 2009; Lamarre et al. 1978; Lemon and Porter 1976; Lucier et al. 1975; Murphy et al. 1978; Rosen and Asanuma 1972; Scott and Kalaska 1997; Suminski et al. 2010; Wolpaw 1980; Wong et al. 1978). For example, the pioneering work of Evarts and Granit demonstrated that neurons in primary motor cortex are very quickly modulated by a mechanical perturbation of the wrist (Evarts and Granit 1976). The activity of M1 neurons was later shown to precede and correlate with long-latency responses in a variety of motor tasks (Evarts and Tanji 1976; Fromm and Evarts 1977; Picard and Smith 1992; Pruszynski et al. 2011a). More direct evidence comes from the study of corticomotoneuronal cells, which project directly from primary motor cortex to motoneurons and can be identified using spike-triggered averaging. Many corticomotoneuronal cells produce post-spike facilitation in their target muscles prior to the onset of long-latency activity and have total loop times compatible with initiating the long-latency response (Cheney and Fetz 1984) (Fig. 5a). Furthermore, the observed facilitation is stronger for spikes during a torque pulse than during a static hold, implying that CM cells are causally involved in generating the long-latency response when the muscle is stretched (Fig. 5b).

Neurophysiological evidence in human subjects also suggests a role for primary motor cortex in generating the long-latency response. As with single-cell recordings in monkeys, several studies using positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and even intraoperative single-cell recordings have emphasized the robust presence of afferent signals in human primary motor cortex (Goldring and Ratcheson 1972; Naito et al. 1999, 2002;Weiller et al. 1996). Some work in this regard has even implicated primary motor cortex as a critical node for the somatic perception of limb movement (Naito et al. 1999, 2002). More specifically related to the long-latency response is the observation that scalp potentials localized to primary motor cortex, occurring prior to the long-latency response, are graded according to the magnitude of the perturbation in parallel with the recorded muscle activity (Abbruzzese et al. 1985). Furthermore, several groups have shown a supra-linear interaction between the long-latency response elicited by a mechanical perturbation and transcranial magnetic stimulation applied over primary motor cortex (Day et al. 1991; Palmer and Ashby 1992). This interaction, which does not occur for the short-latency response, is evidence that the long-latency response and magnetic stimulation are physically co-localized at the site of stimulation, primary motor cortex.

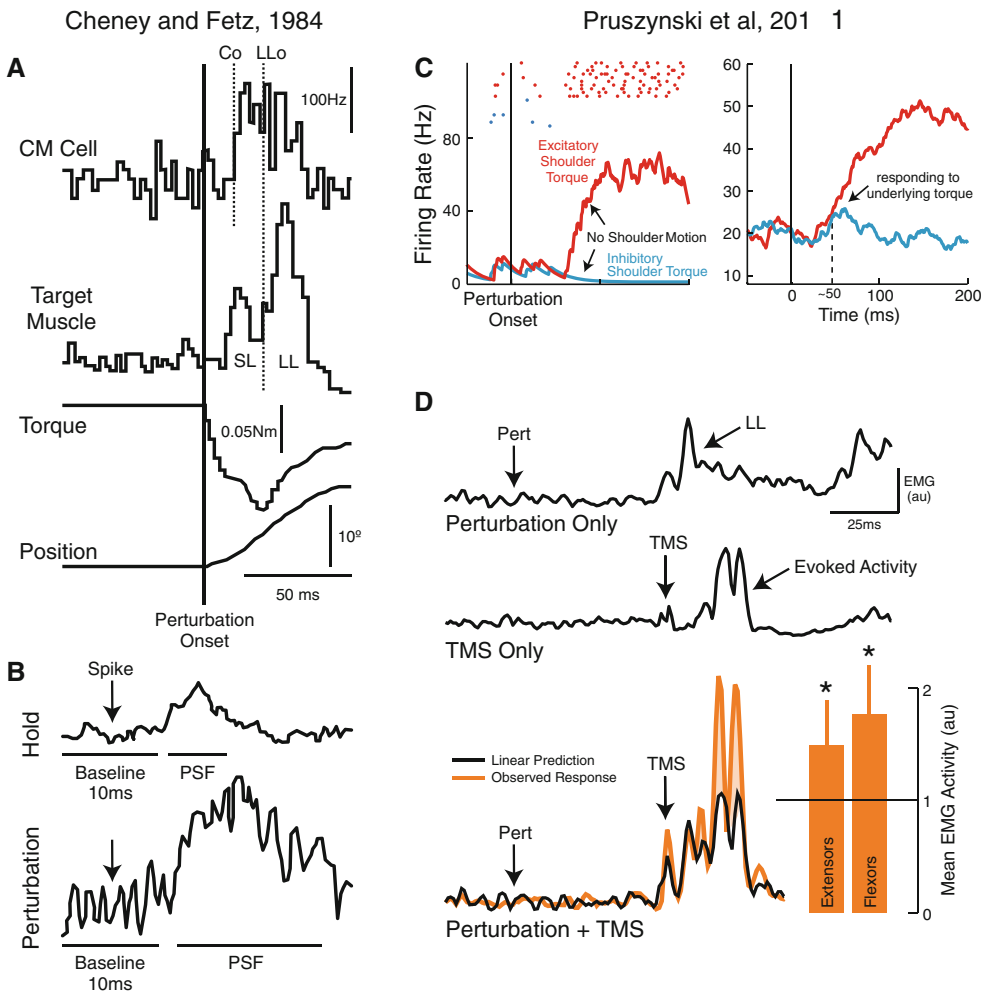


**Fig. 5** Cortical mechanisms underlying the long-latency stretch response and its sophistication. **a** Recordings from a corticomotoneuronal (CM) cell in primary motor cortex and its target muscle applied in response to transient torque perturbations. Note that all the traces are aligned on perturbation onset and that the perturbation stretched the target muscle. The two vertical dashed lines indicate the onset of the CM activity (Co) and the onset of the long-latency response in the target muscle (LLo). Note that the CM activity precedes the long-latency stretch response by ~10–20 ms. **b** Spike-triggered averages in the target muscle during static wrist extension (*top*) and during the torque pulse responses (*bottom*). The increased post-spike facilitation (PSF) during the torque pulse epoch indicates a causal contribution of this CM cell to the long-latency stretch response in the target muscle. **c** The left and right panels depict the response of an exemplar shoulder-like neuron (*left*) and the population of shoulder-like neurons (*right*) to a mechanical perturbation that causes pure elbow motion as in Fig. 4b. Note that the shoulder-like neurons respond to the underlying shoulder torque even though the local motion information from the shoulder is ambiguous. **c** Evoked responses in a shoulder muscle when applying only a mechanical perturbation as in Fig. 4b (*top*), only TMS over primary motor cortex (*middle*), or when the two stimuli were paired to occur on the target muscle during the long-latency stretch response (*bottom*). The *vertical arrow* in each trace depicts when the indicated stimulus was presented. The black trace in the bottom panel is the predicted activity if the two stimuli are independent, and the orange trace is the observed result. The observed supra-linear response suggests that the mechanical perturbation and the stimulation interact at the site of stimulation which, along with control conditions (not shown), provides causal evidence that primary motor cortex contributes this type of sophistication during the long-latency stretch response. The *bar graphs* are statistical results across the population of analyzed muscles. **a**, **b** are modified with permission from (Cheney and Fetz 1984). **c**, **d** are modified with permission from (Pruszynski et al. 2011a)

## Neural contributions to the functional sophistication of the long-latency responses

As outlined above, many studies have established that the long-latency response includes contributions from multiple neural pathways (Kimura et al. 2006; Kurtzer et al. 2010; Lewis et al. 2004; Lourenco et al. 2006; Matthews and Miles 1988; Shemmell et al. 2009), including the spinal cord (Cody et al. 1986; Eklund et al. 1982; Ghez and Shinoda 1978; Matthews 1984; Miller and Brooks 1981; Schuurmans et al. 2009; Tracey et al. 1980) and cerebral cortex (Capaday et al. 1991; Cheney and Fetz 1984; Evarts 1973; MacKinnon et al. 2000; Marsden et al. 1977; Matthews et al. 1990; Phillips 1969). Far less is known about

the specific functional capabilities provided via these separate neural contributors (Matthews 2006). For example, a particularly elegant sequence of experiments by Lourenco et al. (2006) demonstrated that electrical stimulation of a mixed nerve can excite the innervated wrist muscles at two distinct latencies within the long-latency epochs. The first phase of activation is likely caused by a spinal pathway via group II afferents, and the second phase likely reflects a cortical pathway via group I afferents. However, the authors were unable to establish the functional contribution of each pathway because the constraints of the experimental approach did not permit the subjects to be engaged in a meaningful motor task.

A few studies have observed flexible responses in primary motor cortical neurons to mechanical perturbations applied to the limb (Fromm and Evarts 1977; Picard and Smith 1992; Tanji and Evarts 1976; Wolpaw 1980). For example, Evarts and Tanji trained monkeys to respond to a mechanical perturbation by either pulling or pushing the perturbing handle. They found that neurons in primary motor cortex signaled the instructed action (Tanji and Evarts 1976) and then subsequently responded to the perturbation with two distinct components (Evarts and Tanji 1976). First, there was a relatively short-latency response occurring ~20–50 ms post-perturbation that was not modulated according to the instruction and a second, longer component starting ~50 ms post-perturbation which depended on the prior instruction. Interestingly, neurons in the dentate nucleus of the cerebellum have also been shown to be sensitive to the instructed action (Strick 1983) and deactivating these neurons by cooling leads to selective removal of the later response in primary motor cortex (Vilis et al. 1976). Taken together, these findings suggest that the dentate nucleus may be an important node for rapidly implementing a desired action and thus modulating fast feedback mechanisms traversing primary motor cortex, including the long-latency stretch response.

We have recently investigated whether the transcortical pathway contributes to the ability of the long-latency stretch response to account for the mechanical properties of the limb (Pruszynski et al. 2011a). We used the same single- and multi-joint perturbation tasks described earlier (Kurtzer et al. 2009, 2008) to examine when shoulder-related cells in primary motor cortex of monkeys appropriately respond to the applied torque. Unlike muscles that have clear anatomical actions, we had to identify shoulder-related neurons in primary motor cortex based on their response to steady-state motor outputs as the monkey countered various combinations of shoulder and elbow loads (Herter et al. 2009). Like Evarts and Tanji (1976), the earliest response to the mechanical loads (20–50 ms post-perturbation) did not distinguish between the various loading conditions (see Fig. 2 in Pruszynski et al. 2011a). Critically, the shoulder-related neurons increased their firing for the appropriate load at the shoulder starting 50 ms after perturbation onset (Fig. 5b) and about 20 ms before shoulder muscles appropriately responded to the applied shoulder load. Since shoulder motion itself provides ambiguous information about the underlying shoulder torque and since the only other piece of available information arises at the elbow, these findings indicate that primary motor cortex integrates elbow and shoulder motion to identify and counter the applied torque load. We further established a causal link between primary motor cortex and the ability of the long-latency stretch response to account for the mechanical properties of the limb by applying transcranial magnetic stimulation over human primary motor cortex. Specifically, we evoked activity in shoulder muscles and found that the stimulation potentiated the long-latency response even when the shoulder joint was not displaced by the mechanical perturbation (Fig. 5d). Any potentiation of the shoulder muscle response (Day et al. 1991; Lewis et al. 2004; Palmer and Ashby 1992) in this condition must reflect the impact of elbow afferent information onto a cortical circuit controlling shoulder muscles since local shoulder afferents are not physically affected by the perturbation.

Several studies have used transcranial magnetic stimulation to link specific neural structures to the functional capabilities of the long-latency response by using a stimulation protocol that disrupts cortical processing and then observing what functional properties of the long-latency response are affected. Kimura et al. (2006) showed that disrupting sensorimotor cortex did not completely abolish the long-latency response; rather, the stimulation specifically impaired the ability of the long-latency response to predictively compensate for external force fields during reaching. The same approach has been used to show that interfering with primary motor cortex does not change long-latency activity associated with the verbal instructions given to the subject but does affect long-latency activity associated with the stability of the environment, suggesting that only the latter functionality relies on a circuit that includes primary motor cortex (Shemmell et al. 2009).

Although both of these stimulation studies demonstrated an important neuroanatomical distinction between particular functional aspects of the long-latency response, their use of transcranial magnetic stimulation was limited because it acted as a categorical probe of a particular neural area. We have recently shown the long-latency response consists of multiple functionally independent components that appear to sum linearly (Pruszynski et al. 2011b). One of these components is sensitive to pre-perturbation muscle activity (Pruszynski et al. 2009), and another is sensitive to the subject's intention to move to spatial targets (Pruszynski et al. 2008). Although this paradigm did not

explicitly test the neural circuitry, it allowed us to robustly control each functional component and determine their features in isolation, how they interact, and how they develop over time. These findings coupled with the TMS results and single-cell recordings strongly emphasize that the long-latency response is not a unitary event; rather, activity in the long-latency window reflects inputs from multiple neural generators which can contribute unique functional capabilities.

## Conclusions

The present review highlights the sophisticated properties of the long-latency stretch response in the upper limb and its underlying neural circuitry. We hope that this review makes clear that such sophistication has been appreciated for almost 60 years, with many classical studies demonstrating that the long-latency stretch response can be altered by various experimental factors including the instruction given to a subject, the behavioral context within which the mechanical perturbation occurs, and the constraints of the surrounding environment. We also emphasize that recent interest in optimal feedback control as a theory of voluntary motor behavior has renewed interest in exploring the sophistication of fast feedback control mechanisms such as the long-latency stretch response (Scott 2004). In this new theoretical context, studies have moved beyond the classical notions about adaptive feedback responses to show that the sophistication of the long-latency stretch response rivals many features of voluntary control, including parametric sensitivity to task constraints, selective integration of sensory input, and the ability to account for the complexities of limb mechanics. These new studies emphasize that the long-latency stretch response provides a useful window into the control mechanisms that underlie movement—be they corrective or planned—and highlight the difficulty of separating the voluntary from the reflexive.

There is certainly value in continuing to explore the sophistication of fast feedback responses, and there are many avenues to pursue. For example, it would be fruitful to determine whether the long-latency stretch response is modified as subjects learn to compensate for an external force field, a hallmark of motor sophistication which has previously been shown to occur relatively quickly following a mechanical disturbance (Franklin et al. 2007; Wagner and Smith 2008). Furthermore, the long-latency stretch response is only one of a host of feedback responses which can contribute to motor behavior, and it is important to consider the role and capabilities of feedback responses driven by other modalities such as vision (Franklin and Wolpert 2008; Goodale et al. 1986; Knill et al. 2011; Pelisson et al. 1986, 2000; Pruszynski et al. 2010; White and Diedrichsen 2010; Gritsenko and Kalaska 2010) and how these multiple feedback mechanisms are integrated by the motor system. Lastly, we believe that many of the critical outstanding questions revolve around how various neural pathways and circuits participate in the observed feedback responses. Our general opinion is that the transcortical pathway endows the long-latency stretch response with many of its sophisticated qualities. But the long-latency response also includes spinal and brainstem contributions, and the transcortical pathway integrates information from a host of brain areas including cerebellum, posterior parietal cortex, and frontal cortex. A key challenge for future studies, therefore, is to unravel how the various different pathways and circuits contribute to the sophistication of the long-latency stretch response.

In the long run, it is clearly important to formalize the relationship between the various feedback pathways and theoretical notions about optimal feedback control. This is a difficult process since optimal feedback control is formulated at the behavioral level and provides no explicit links to the underlying neurophysiology (Diedrichsen et al. 2010; Scott 2004; Shadmehr and Krakauer 2008). Adding the various levels of complexity requires many additional empirical studies and substantial additions to an already complex set of mathematical equations and formalisms. Nevertheless, we believe that this effort is critical to developing our understanding of the neural control of movement, and we hope that future studies on feedback mechanisms will begin to develop, formulate, and test their hypotheses in a common formal framework based on physiologically realistic models of optimal feedback control.

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