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A perspective on multisensory integration and rapid perturbation responses

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ABSTRACT

In order to perform accurate movements, the nervous system must transform sensory feedback into motor commands that compensate for errors caused by motor variability and external disturbances. Recent studies focusing on the importance of sensory feedback in motor control have illustrated that the brain generates highly flexible responses to visual perturbations (hand-cursor or target jumps), or following mechanical loads applied to the limb. These parallel approaches have emphasized sophisticated, goal-directed feedback control, but also reveal that flexible perturbation responses are expressed at different latencies depending on what sensory system is engaged by the perturbation. Across studies, goal-directed visuomotor responses consistently emerge in muscle activity ~100 ms after a perturbation, while mechanical perturbations evoke goal-directed muscle responses in as little as ~60 ms (long-latency responses). We discuss the limitation of current models of multisensory integration in light of these asynchronous processing delays, and suggest that understanding how the brain performs real-time multisensory integration is an open question for future studies.

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1. General introduction

Our ability to move with little effort is the result of complex transformations of sensory data about the state of our body and the world into motor commands suitable for the task. In recent years, there have been substantial advances in our understanding of the computations involved in flexible feedback control (Todorov, 2004; Todorov & Jordan, 2002). Many studies motivated by this framework have used mechanical or visual perturbations as a window into the mechanisms underlying sensorimotor control (Scott, 2004, 2012). Here, we review empirical evidence highlighting the motor system's ability to engage remarkably flexible feedback control strategies following visual or mechanical perturbations.

Although the majority of studies have emphasized goal-directed sensorimotor transformations, these parallel research streams have also highlighted the distinct latencies of sophisticated visual

and proprioceptive feedback responses. A robust finding is that visual feedback can generate task-dependent muscle responses within ~100 ms (Franklin & Wolpert, 2008), while mechanical perturbations evoke goal-directed muscle responses within ~60 ms of a perturbation (long-latency responses; see Scott, 2012). We discuss these findings in light of current models of multisensory integration suggesting that each sensory modality is weighted according to its reliability. Although this normative framework captures many features of sensorimotor control, there are important issues that remain to be resolved. In particular, it remains unknown how the brain combines information with asynchronous time delays to support online movement control.

2. Sophisticated feedback responses to perturbations

2.1. Visual perturbations

The importance of sensory feedback for voluntary control has mobilized intense research efforts in motor neuroscience. In the context of reaching movements, pioneering studies emphasized that the motor system continuously processes sensory feedback to control upper limb reaching movements. This continuous monitoring of sensory information allows us to rapidly alter our movement path when a target changes position during reaching ('target

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jump'; Bridgeman et al., 1979; Carlton, 1981; Georgopoulos, Kalaska, & Massey, 1981; Goodale, Pelisson, & Prablanc, 1986; Prablanc & Martin, 1992; Pélisson et al., 1986; van Sinderen, van der Gon, & Gielen, 1988). Since then, the importance of visual feedback for the online control of action has been further addressed by perturbing the hand-aligned feedback cursor during reaching ('cursor jumps'). These perturbations introduce errors between the ongoing movement path and goal target, and require that participants rapidly adjust their movement to complete the task successfully. The aim of this research is to investigate whether visuomotor corrections are influenced by features of the task such as movement kinematics, direction of the target jump, retinal processing of target attributes, and the effector used to perform the task (Brenner & Smeets, 2003; Oostwoud-Wijdenes, Brenner, & Smeets, 2011, 2013; Pisella, Arzi, & Rossetti, 1998; Sarlegna et al., 2003).

Many studies have demonstrated that visuomotor responses are modulated by features of the task, including the time of the target jump relative to movement onset (Georgopoulos, Kalaska, & Massey, 1981), the shape of the goal target (Knill, Bondada, & Chhabra, 2011), the relevance of visual perturbations to task completion (Franklin & Wolpert, 2008), and the need to alter the movement trajectory to avoid obstacles in the environment (Aivar, Brenner, & Smeets, 2008; Chapman & Goodale, 2010). For example, when a target unexpectedly changes location before or during reaching, the corrective response varies with the time available to adjust the reach plan. Target jumps occurring before the reach lead to the gradual correction of movements directed somewhere between the target locations, whereas target jumps occurring during the reach are initially directed toward the first target, followed by a rapid correction to the new goal (Georgopoulos, Kalaska, & Massey, 1981).

Franklin and Wolpert (2008) disrupted hand-aligned feedback with perturbations that may or may not affect task performance. In this study, subjects made vigorous corrective responses when visual perturbations persisted until the end of movement, but did not respond to transient perturbations where the cursor returned to the actual hand location before the end of the movement. The flexibility of visuomotor responses was further addressed in a task that shifted hand-aligned feedback while subjects reached to rectangular targets oriented parallel or perpendicular to their movement path (Knill, Bondada, & Chhabra, 2011). Knill and colleagues showed that visuomotor responses were sensitive to the accuracy constraints imposed by the goal target, with larger responses observed when the target was parallel versus perpendicular to the movement path. In addition, these corrections are made at similar latencies with the hand or a hand-held tool (Brenner & Smeets, 2003), and when perturbations alter the direction or distance of the goal target (Oostwoud-Wijdenes, Brenner, & Smeets, 2013). Visual perturbation responses have also been shown to update during force-field adaptation (Franklin, Wolpert, & Franklin, 2012), with rapid increases in visuomotor responses that the authors suggested might be linked to uncertainty about the novel dynamics. Such intelligent, context-specific feedback responses suggest that the nervous system continuously converts sensory data into motor commands that reflect the goals and constraints of the task.

An elegant demonstration of this flexibility is that feedback responses depend on the hand's position when a goal target changes location during reaching (Liu & Todorov, 2007; Prablanc, Desmurget, & Gréa, 2003). For example, in the Liu and Todorov (2007) experiment, visual target perturbations were introduced at the start or near the end of target-directed reaching movements. The authors observed incomplete hand-path corrections when target jumps were introduced near the end of the reach, and argued that in order to stop near the target, the motor system became

more sensitive to movement velocity than endpoint accuracy. Using a feedback controller optimizing the balance between movement performance and motor costs, the authors illustrated that distinct response strategies may emerge when the energy cost of reaching the target outweighs the cost of missing the target.

Additional evidence for these time-varying feedback gains was provided in a recent study that measured visuomotor responses to target jumps introduced throughout the time course of point-to-point reaching movements (Dimitriou, Wolpert, & Franklin, 2013). The authors observed systematic modulation of visuomotor responses over the time course of the reach, with the amplitude of feedback responses peaking in the middle of the movement and decaying rapidly near the target. Importantly, these responses were rapidly modified to suit the task demand, as the amplitude of visuomotor responses increased or decreased appropriately when the target was shifted toward or away from the participant.

In short, visual perturbation studies have provided compelling evidence that the brain engages distinct feedback responses when we encounter the same perturbation in different behavioral contexts (Franklin & Wolpert, 2011). Across studies, these visuomotor corrections emerged in muscle responses within ~100 ms of the perturbation and produced differences in hand force or motion patterns after 150 ms (Day & Lyon, 2000; Franklin & Wolpert, 2008; Knill, Bondada, & Chhabra, 2011). As discussed later in this review, these task-dependent changes in muscle activity reflect processing times in both visual and limb motor circuits, and are longer than observed for somatosensory-based corrective responses (50–60 ms). However, in some instances, changes in hand acceleration at 90 ms or faster have been reported for individual subjects following a target jump (Brenner & Smeets, 1997, 2003; Oostwoud-Wijdenes, Brenner, & Smeets, 2011, 2013). Analysis of EMG responses in these tasks is warranted as such fast kinematic changes suggest that target-jump related changes in muscle activity might occur within 60–80 ms, which is faster than reports discussed below.

In macaque monkeys, visual stimuli require 15–35 ms to be processed in the retina (Maunsell et al., 1999). These responses are integrated in lateral geniculate nucleus (LGN) within 30–50 ms of a visual stimulus (Maunsell & Gibson, 1992), and are transmitted to primary visual cortex after 60–100 ms (Schmolesky et al., 1998). In humans, very small stimulus-driven visuomotor responses have been noted in percutaneous recordings of shoulder muscle activity beginning at ~80 ms (Pruszynski et al., 2010), and may produce rapid changes in hand motion (Gomi, Abekawa, & Nishida, 2006; Masson, 1997; Saijo et al., 2005; Whitney, Westwood, & Goodale, 2003). These visuomotor responses may reflect rapid processing in superior colliculus (Dorris, Paré, & Munoz, 1997), which targets the arm muscles via tecto-reticulo-spinal pathways (Stuphorn, Hoffmann, & Miller, 1999). In contrast, it appears the ability to modulate visuomotor response gains for the goal of the ongoing task is expressed later (>120 ms, Franklin & Wolpert, 2008), likely because it engages higher-level cortical processing. The latency of task-dependent visuomotor feedback is consistent with changes in primary motor cortex (M1) processing that begin 100 ms after a target jump perturbation (Georgopoulos et al., 1983).

In addition to these brain areas, posterior parietal cortex (PPC) is an important structure in the online control of reaching (Desmurget & Grafton, 2000). Evidence for the involvement of PPC was provided by disrupting neural processing with transcranial magnetic stimulation (TMS) during targeted reaching movements (Desmurget et al., 1999). Following a TMS-pulse to PPC, participants were unable to alter their hand motion to correct for target-jump perturbations introduced during the reach. The contribution of PPC to visually-guided movements has also been shown in lesion studies where feedback responses to target jumps

typically consist of two separate movements instead of the single, smooth correction observed in healthy participants (Gréa et al., 2002; Pisella et al., 2000).

An important question is how these rapid visuomotor responses relate to the reliability of sensory feedback. Izawa and Shadmehr (2008) addressed this question with a target jump experiment where they manipulated the uncertainty of target feedback during reaching movements (Fig. 1). The authors noted that early visuomotor responses scaled with the reliability of target feedback, with marked increases in response amplitude when target feedback became more reliable after the target jump. These results were interpreted in the context of Bayesian integration through time (i.e., Kalman filter), in which the estimation of the target location after the jump converges faster or slower toward the new location depending on the reliability of visual feedback about the target location. Importantly, these results indicate that internal priors can be integrated with sensory feedback in real-time and influence hand acceleration in ~ 120 ms, although a little more time was needed to express response modulation as a function of target reliability.

Aside from issues related to the response latency and underlying pathways, the results presented above clearly establish that visual information is processed online and used to guide motor commands in real time. We may therefore expect that this mechanism interacts with information coming from other sensory modalities such as auditory, haptic, or limb afferent feedback. However, the real-time integration of these distinct sensory signals may not be so straightforward because, as we point out in upcoming sections, limb afferent feedback evokes flexible responses at shorter latencies than the visuomotor system.

2.2. Mechanical perturbations

Motor physiology studies have shown that muscle afferent feedback can evoke corrective responses within tens of milliseconds of a mechanical perturbation (see Pruszynski & Scott, 2012). In fact, the motor system produces a stereotyped sequence of muscle activity when the limb is displaced by a mechanical perturbation, beginning with the short-latency stretch reflex (20–50 ms post-perturbation) and ending with a voluntary motor response (>100 ms). Fast feedback loops, such as the short-latency stretch reflex, are sensitive to changes in joint motion (Smeets, Erkelens, & Denier van der Gon, 1990) and background muscle activity

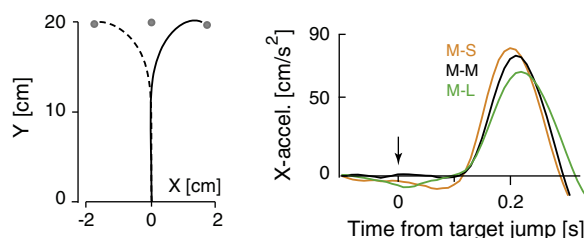


Fig. 1. Left: Hand paths of reaching movements initially directed toward the center target, and corrected toward the novel location of the target following lateral jumps. The targets were displayed as Gaussian blurbs with different variances to manipulate the reliability of sensory feedback relative to the initial target. The right panel presents the lateral hand acceleration following the target jump in three conditions of target variance: the first target had a medium level of variance (M), while the second target had a comparatively smaller (S, yellow trace), equal (M, black) or larger (L, green) level of variance. Observe that the response rate and the peak acceleration scale with the reliability of the second target. This effect was captured by theoretical simulations in which internal estimates (priors) of the target's location were gradually corrected with sensory feedback (Kalman filter). In this framework, the estimate of the target location following the jump converges faster or slower according to the reliability (or inverse of variance) of the sensory feedback. Adapted with permission from Izawa and Shadmehr (2008).

(Bedingham & Tatton, 1984; Matthews, 1986; Pruszynski et al., 2009; Smeets & Erkelens, 1991) but are not easily modified by the task demand without extended experience (see Wolpaw, 1985).

Between the short-latency and voluntary responses is the long-latency muscle stretch response (50–105 ms post-perturbation), which includes responses generated by spinal (Ghez & Shinoda, 1978; Matthews, 1984) and cortical circuits (Evarts, 1973; Pruszynski et al., 2011). A striking attribute of long-latency feedback responses is that, unlike the short-latency stretch reflex, these rapid responses do not reflect simple responses to changes in muscle length, but instead integrate multijoint motion information (Gielen, Ramaekers, & van Zuylen, 1988; Lacquaniti & Soechting, 1986) and are modulated by the behavioral task and prior instructions (Colebatch et al., 1979; Crago, Houk, & Hasan, 1976; Doemges & Rack, 1992; Krutky et al., 2010; Lacquaniti, Borghese, & Carrozzo, 1991; Lee & Tatton, 1982; MacKinnon, Verrier, & Tatton, 2000; Marsden, Merton, & Morton, 1981; Rothwell, Traub, & Marsden, 1980). In this section, we define the latency of flexible feedback responses relative to changes in muscle activity following a mechanical perturbation. Many studies have noted that muscle force generation in the upper limb may require up to an additional 50 ms to be observed in limb kinematics (Cavanagh & Komi, 1979; Norman & Komi, 1979), and depending on the size of task modulation in the long latency response, typically produces task-dependent differences in limb motion within 120–180 ms of a mechanical perturbation (Cluff & Scott, 2013; Crevecoeur, Kurtzer, & Scott, 2012; Nashed, Crevecoeur, & Scott, 2012; Omrani, Diedrichsen, & Scott, 2013; Pruszynski, Kurtzer, & Scott, 2008).

Feedback corrections in the long-latency time window are remarkably flexible, and can be modified by the spatio-temporal constraints of the task (Crevecoeur et al., 2013; Pruszynski, Kurtzer, & Scott, 2008), bimanual control (Dimitriou, Franklin, & Wolpert, 2012; Omrani, Diedrichsen, & Scott, 2013), and evolving sensorimotor decisions (Selen, Shadlen, & Wolpert, 2012). These flexible feedback responses can rapidly implement distinct motor strategies, such as the ability to re-route movements around obstacles blocking the path to the target (Nashed, Crevecoeur, & Scott, 2014), and integrate visual information about targets that appear in the environment (Yang et al., 2011). Despite substantial amounts of noise in muscle recordings, feedback responses in the long-latency epoch correlate with the kinematics of corrective movements on a trial-by-trial basis (Crevecoeur et al., 2013). This key result establishes that feedback responses are a direct contributor to behavioral performance rather than the simple consequence of external perturbations.

Although the foregoing studies have focused on the flexibility of upper limb perturbation responses, it is important to note that rapid and flexible feedback control has been documented extensively in the lower limb following whole-body postural perturbations (Horak & Nashner, 1986; Nashner, 1976). Recently, Safavynia and Ting (2013) used support-surface perturbations to address whether lower limb muscle responses are best accounted for by global features of the task such as center-of-mass kinematics, or by local aspects such as individual joint motion patterns. The authors found that lower-limb muscle activity was well reconstructed by center-of-mass motion delayed by ~ 100 ms, which corresponds to long-latency processing delays for the lower limb. Thus, task-dependent sensory processing regulates long-latency responses in both the upper and lower limbs.

We have so far focused on feedback responses that can be flexibly modified to suit the needs of many behavioral tasks. It is important to recognize these flexible feedback responses are only possible if the motor system has knowledge of how the body should move in response to external forces or forces generated

by muscles. How does the motor system modify feedback responses to suit the task demand? A number of studies have shown that the voluntary motor system rapidly updates our motor commands using error feedback obtained from the previous reaching trial when we are exposed to novel loads (Wolpert, Diedrichsen, & Flanagan, 2011), and M1 plays a critical role in this adaptation process (Gandolfo et al., 2000; Li, Padoa-Schioppa, & Bizzi, 2001; Sanes & Donoghue, 2000). Given the functional complexity and shared neural substrates engaged by voluntary actions and feedback responses to perturbations, a compelling hypothesis is that motor learning plays a key role in flexible feedback control.

We recently addressed this hypothesis by examining how muscle stretch responses were altered in a reach adaptation task (Cluff & Scott, 2013). In this study, subjects performed reaching movements in the presence of velocity-dependent elbow loads while mechanical perturbations were used to measure feedback responses throughout the course of learning. We found that as subjects began adapting to the load, they also began modulating their motor responses within ~ 65 ms of a perturbation (Fig. 2, i.e., long-latency epoch). These intelligent feedback corrections mirrored changes in voluntary control, peaked at the asymptote of learning, and decayed rapidly when the load was removed. Moreover, long-latency responses scaled with the strength of the viscous elbow load used during training and were thus updated based on the task demand.

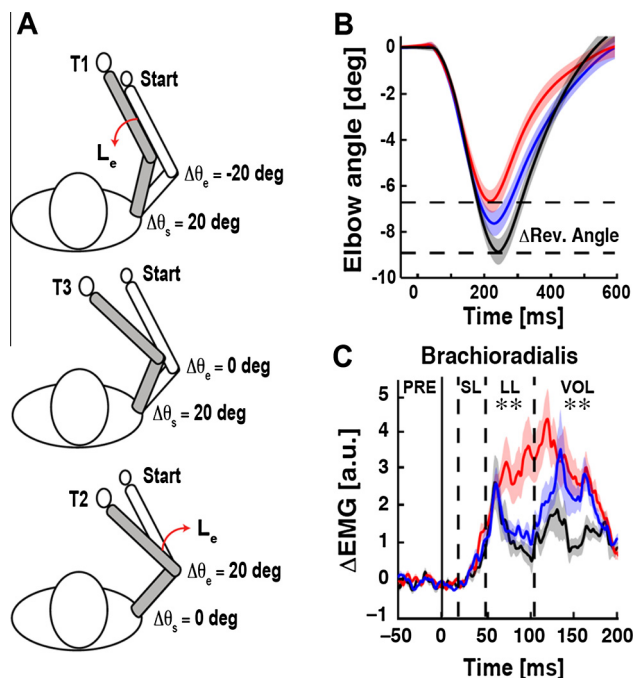


Fig. 2. Adaptation of muscle stretch responses. (A) Overhead representation of the target and limb configuration. Subjects reached to training targets that required elbow motion (T2) or combined shoulder and elbow motion (T1). We implemented a viscous elbow load that required additional muscle activity to reach the training targets. Subjects also reached to a separate probe target, which required only shoulder motion and did not alter muscle activity during unperturbed movements (T3). On certain trials, a mechanical perturbation extended the subject's elbow while reaching to the probe target (T3). (B) Adaptation-related changes in elbow motion following a perturbation (mean $\pm$ SEM). Data are aligned to perturbation onset. Black, red, and blue traces denote the baseline, adaptation, and washout blocks, respectively. Observe the change in elbow reversal when subjects responded to the perturbation in the adaptation block. (C) Perturbation responses of the brachioradialis muscle (mean $\pm$ SEM). Data are plotted in the same format as in (B). Note that for similar initial elbow motion, differences in the muscle response emerge in the long-latency time period (LL; ~ 65 ms). Data are aligned to perturbation onset and dashed vertical lines separate the different time periods of the muscle response. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Adapted from Cluff and Scott (2013).

Our findings illustrate that the motor system exploits knowledge of acquired internal models both during voluntary actions and rapid feedback responses to perturbations. These results are compatible with knowledge of multijoint limb dynamics expressed in the long-latency epoch (Kurtzer, Pruszynski, & Scott, 2008, 2009), and show that long-latency responses incorporate knowledge of environmental loads that have only been observed over longer time scales during reaching (>100 ms; Wagner & Smith, 2008) or postural control prior to reach onset (Ahmadi-Pajouh et al., 2012). Collectively, these findings suggest that motor learning plays an integral role in the generation of flexible feedback control strategies.

While most studies emphasize flexible control expressed during the long-latency epoch, there remains an important question regarding how these responses are generated. Indeed, participants accurately respond to the direction and amplitude of perturbations randomized across trials (Crevecoeur, Kurtzer, & Scott, 2012; Pruszynski, Kurtzer, & Scott, 2011), making it unlikely that pre-programmed feedback responses are stored and triggered for each possible perturbation. However, in some circumstances a simple readout of sensory signals is not feasible because sensorimotor feedback delays can generate instability. How does the nervous system resolve this issue? In theory, it is possible to partially compensate for the effect of sensorimotor delays by relying on state estimation (Wolpert & Ghahramani, 2000). Given the similarity between voluntary control and feedback responses to perturbations, we suspected that state estimation must also be engaged during the long-latency epoch.

State estimation can provide stability but it is prone to errors if the internal models, or priors, provide erroneous estimates of the state of the body. We recently exploited this aspect of internal priors to address whether state estimation was also engaged during rapid feedback responses (Crevecoeur & Scott, 2013). We used an upper limb postural control task with mechanical perturbations to show that subjects modulated their motor response within 60 ms according to their expectations about the perturbation profile (Fig. 3). A simple feedback control model coupled with a state estimator designed to account for feedback delays reproduced this response modulation. These results are compatible with the computation of the present state of the body based on delayed sensory signals, and therefore represent a sensory prediction in the sense that the feedback signal is extrapolated forward in time to estimate the present state of the limb. Such a prediction requires an internal model of the relationship between perturbation profiles and joint motion, and it appears that this model is quickly updated for the perturbation context. These results suggest that rapid state estimation may be the keystone of flexible long-latency feedback control.

Extensive evidence has linked the flexibility of feedback responses in the long-latency epoch with the contribution of transcortical pathways involving cerebellum (Strick, 1979), primary somatosensory cortex (Fromm & Evarts, 1982), and primary motor cortex (Cheney & Fetz, 1984; Desmedt, 1978; Matthews, 1991; Pruszynski, Kurtzer, & Scott, 2011). Across non-human primate studies, neural responses in M1 typically reflect knowledge of the task within 40–50 ms of a perturbation (Tanji & Evarts, 1976), which is ~ 15 ms before the onset of long-latency responses in the upper limb (Pruszynski, Kurtzer, & Scott, 2011). This conduction delay is consistent with microstimulation studies in primate (Cheney & Fetz, 1984) and TMS studies in humans (Merton & Morton, 1980) noting a 10–20 ms delay between M1 stimulation and the onset of upper limb muscle activity.

There is extensive evidence that cerebellum is involved in predicting the sensory consequences of descending motor commands (Bastian, 2006; Doya, 1999; Miall & King, 2008; Miall et al., 2007; Wolpert, Miall, & Kawato, 1998), with cerebellar deficits causing impairments in a range of motor tasks (Bastian, Zacksowski, &

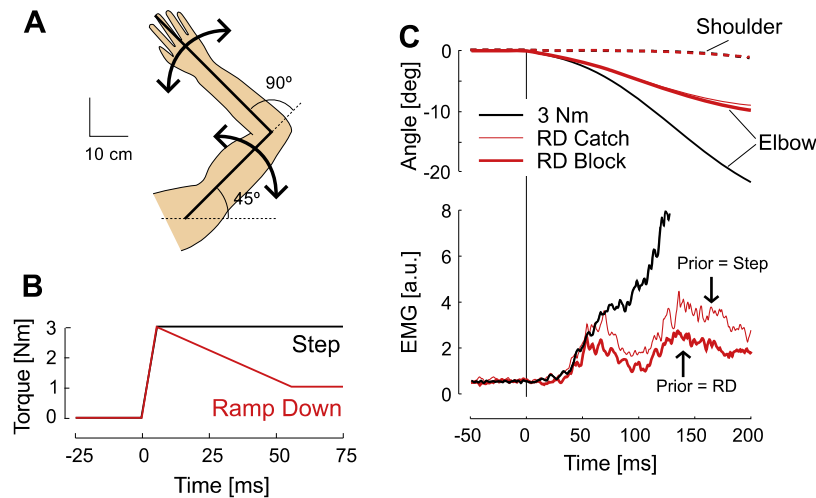


Fig. 3. (A) Overhead representation of the initial joint configuration. Equal amounts of torque were applied on the shoulder and elbow joints. (B) Illustration of the distinct time-varying torque profiles used in the experiment. Exemplar profiles are the step torque (black) and Ramp-Down perturbations (red, RD). (C) (Top) Perturbation-related changes in joint angles following an extension load. Ramp down profiles were either randomly interleaved with step perturbations (RD Catch), or presented in blocks (RD Block). Observe that the shoulder did not move until ~150 ms after the perturbation. Bottom: Response of an elbow flexor muscle (brachioradialis). Observe that for similar perturbation, muscle response to the RD perturbation presented as a catch trial follows the step response until >60 ms. When the same profile is expected, the motor responses diverges from the step response at ~45 ms, showing that internal priors about the profile rapidly influence the motor response. Adapted from [Crevecoeur and Scott \(2013\)](#).

[Thach, 2000; Bastian et al., 1996; Day et al., 1998](#)). In addition to its involvement in estimating the state of the body during voluntary actions, cerebellum also responds to external loads during the long-latency time window ([MacKay & Murphy, 1979; Strick, 1979, 1983](#)). Cerebellar dysfunction is linked to oscillatory ([Flament, Vilis, & Hore, 1984; Vilis & Hore, 1977, 1980](#)), delayed and reduced amplitude feedback responses ([Kurtzer et al., 2013](#)). From this perspective, cerebellum is involved in generating flexible feedback responses and may be implicated in estimating the state of our body and world both during voluntary actions and over the rapid time scales involved in feedback responses to mechanical perturbations.

In summary, perturbation studies have provided compelling evidence that the brain engages flexible, goal-directed feedback responses when we encounter the same perturbation in different behavioral contexts. However, they also highlight distinct latencies in the emergence of sophisticated visual and proprioceptive feedback responses, with visual feedback influencing motor responses after ~100 ms (see [Franklin & Wolpert, 2011](#)), and mechanical perturbations consistently evoking goal-directed muscle responses within ~60 ms (long-latency responses; see [Scott, 2012](#)). These two lines of research clearly point out that the latency of goal-directed feedback depends on what sensory system is engaged by the perturbation.

3. Perspective questions on multi-sensory integration

Although the studies discussed above have focused on visual or mechanical perturbations, the perturbations that we encounter in our daily lives often engage both sensory systems simultaneously. For example, visual and limb afferent feedback are available when someone unexpectedly bumps our arm in a crowded cocktail party, and we have to make a rapid corrective movement to avoid spilling our drink. How does the brain combine multiple sources of sensory information to generate a single motor response? As we point out below, most studies have focused on how the brain combines sensory signals with different variances in conditions where substantive amounts of time were given to integrate sensory signals. Differences in processing times during rapid motor responses have received little attention in comparison. In light of the fast

capabilities of the voluntary motor system these differences in processing times across sensory systems represent an important challenge for real-time feedback control.

The general problem of sensory integration has mobilized intense research efforts, leading to the idea that the brain combines information from distinct sensory modalities in a statistically optimal way ([Angelaki, Gu, & DeAngelis, 2009; Körding, 2007](#)). In this framework, optimality is used in the sense that the internal encoding of a movement variable (e.g., the position of our hand) is the most reliable given the noisy sensory information available. Maximum likelihood estimation and Bayes' theorem provide a formal description of how distinct sources of sensory feedback should be combined with internal expectations about the task. In the simple case of cue combination, the problem is to estimate a variable, μ , based on two sources of information X and Y with expected values $E(X) = E(Y) = \mu$ and non-zero variances σ_X^2 and σ_Y^2 . What is our best guess for μ ? The answer is a linear combination of X and Y with a weighting factor $0 < \lambda < 1$ (we call Z this best guess):

$$Z = \lambda X + (1 - \lambda)Y, \quad (1)$$

where λ is determined by the signal variances as follows:

$$\lambda = \frac{\sigma_Y^2}{\sigma_X^2 + \sigma_Y^2}. \quad (2)$$

In this framework, perceptual estimates rely heavily on the most reliable source of information as determined by the weighting factor λ . However, it is worth noting that sensory cues can be reweighted independently of their variances when these cues are inaccurate ([van Beers et al., 2011](#)) and violate the assumption that $E(X) = E(Y) = \mu$.

Empirical evidence for optimal multisensory integration has been provided in a variety of laboratory tasks that examined how we make perceptual judgments, or by looking at the distribution of endpoint motor errors where sensorimotor delays can be ignored. For instance, in a seminal study Ernst and Banks demonstrated that humans optimally weight visual and haptic feedback to estimate the size of an object ([Ernst & Banks, 2002](#)). In another study, [Körding and Wolpert \(2004\)](#) demonstrated that participants learn priors about the distribution of shifts in their hand-aligned cursor during reaching, and scaled their compensation for these

lateral cursor shifts with the reliability of the cursor flashed during the reach. In practical situations, this means that learning our opponent's strategies and combining these expectations with sensory data can improve performance during sports, such as hockey, soccer or tennis. Perhaps the most skilled athletes are able to learn these priors very well, giving the impression that they are one step ahead of their opponents.

This powerful model captures many features of sensorimotor control, including cue combination, decision making and motor planning (Fetsch et al., 2009; Kording et al., 2007; Trommershauser et al., 2005; Wolpert & Landy, 2012), but does not explicitly consider the issue of time delays or how they may affect the integration process. The issue of time delays becomes increasingly important if we consider the different latencies at which visual and mechanical perturbations engage flexible feedback responses (Cameron, de la Malla, & López-Moliner, 2014).

Indeed, evidence suggests that delays are an important factor when we integrate sensory streams with distinct processing times. Corneil et al. (2002) addressed the question of asynchronous sensory feedback by asking participants to locate visual and/or auditory targets. The authors emphasized that responses to auditory stimuli were faster but less accurate than responses to visual stimuli. Importantly, responses to combined auditory and visual stimuli were as fast as the auditory responses, and as accurate as the visual responses taken independently. These results emphasized that differences in latencies across sensory modalities potentially play an important role in the process of combining them. In fact, previous work on auditory-visual interactions have focused on the distribution of saccade latencies following stimulus presentation (Colonius & Arndt, 2001; Corneil et al., 2002; Harrington & Peck, 1998), in which differences in processing times are the most critical parameters. It is worth pointing out that the problem of multiple delays may also arise in unimodal sensory integration, for instance when coordinating afferent feedback from the upper and lower limbs in full-body motor tasks.

To date, studies addressing the effect of multiple delays have not provided a cohesive framework to understand how the brain processes asynchronous sensory signals. For instance, it has been suggested that binocular cues (such as disparity and vergence) are more important during online control because they are processed faster than monocular cues (Greenwald, Knill, & Saunders, 2005). In contrast, other studies have concluded that monocular cues may be processed more rapidly than binocular cues during reaching (van Mierlo et al., 2009), or that differences of tens of milliseconds between sensory streams are irrelevant for the nervous system given the temporal resolution of neural processing (van Mierlo, Brenner, & Smeets, 2007). Using a reaching task with combined visual and mechanical perturbations, Franklin and colleagues suggested that vision and limb afferent feedback may be processed separately, with proprioception dominating visual processing at faster latencies, while the visual contribution is evident much later in the response (>200 ms after perturbation onset; Franklin et al., 2008). To our knowledge, it remains unclear whether or not the brain accounts for distinct sensory delays, and how this process affects perceptual judgments and online motor control.

In fact, probabilistic models handling neural variability do not explicitly handle the problem of time delays, and studies addressing differences in sensory processing times have not directly addressed the problem of sensory reliability. As we reviewed above, visual and mechanical perturbations evoke flexible feedback responses that engage internal models and priors. Thus, future studies need to combine visual and mechanical perturbations to explicitly describe how the brain handles multiple delays for real-time multisensory integration.

This question is challenging because, unlike visual feedback that can be shifted or altered during a task, limb afferent feedback cannot be easily manipulated, although it is expected to play an important role in real-time sensory integration. The classic view is that (static) perceptual judgments are dominated by vision (Welch & Warren, 1980). However, studies have since shown that estimation varies with the direction-dependent properties of visual and proprioceptive noise (Van Beers, Sittig, & van der Gon, 1999; Van Beers, Wolpert, & Haggard, 2002), and with the sensory modality used to represent the goal target (McGuire & Sabes, 2009; Tagliabue & McIntyre, 2011). In the context of online control, limb afferent feedback appears to be associated with surprisingly low levels of noise following a perturbation. Indeed, the motor system can accurately resolve limb position while responding to perturbations approaching the natural variability of postural control and reaching (Crevecoeur, Kurtzer, & Scott, 2012). In addition to relatively low levels of variance following a perturbation, sensorimotor delays associated with limb afferents are relatively constant across a range of perturbation magnitudes and levels of background muscle activity (Crevecoeur, Kurtzer, & Scott, 2012; Pruszynski, Kurtzer, & Scott, 2011). Finally, limb afferent feedback is always present. This contrasts with the visual system, where feedback reliability and delays can be easily manipulated using virtual reality displays or by altering stimulus features such as target luminance and color (Pisella, Arzi, & Rossetti, 1998; Veerman, Brenner, & Smeets, 2008; White et al., 2009). Although technically challenging, we believe that the question of real-time multisensory integration is critical to understanding how neural processing relates to the online generation of motor commands.

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