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The long-latency reflex is composed of at least two functionally independent processes

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Pruszynski JA, Kurtzer I, Scott SH. The long-latency reflex is composed of at least two functionally independent processes. *J Neurophysiol* 106: 449–459, 2011. First published May 4, 2011; doi:10.1152/jn.01052.2010.—The nervous system counters mechanical perturbations applied to the arm with a stereotypical sequence of muscle activity, starting with the short-latency stretch reflex and ending with a voluntary response. Occurring between these two events is the enigmatic long-latency reflex. Although researchers have been fascinated by the long-latency reflex for over 60 years, some of the most basic questions about this response remain unresolved and often debated. In the present study we help resolve one such question by providing clear evidence that the human long-latency reflex during a naturalistic motor task is not a single functional response; rather, it appears to reflect the output of (at least) two functionally independent processes that overlap in time and sum linearly. One of these functional components shares an important attribute of the short-latency reflex (i.e., automatic gain scaling, sensitivity to background load), and the other shares a defining feature of voluntary control (i.e., task dependency, sensitivity to goal target position). We further show that the task-dependent component of long-latency activity reflects a feedback control process rather than the simplest triggered reaction to a mechanical stimulus.

upper limb; feedback; background load; intent; spatial target

RECENT THEORIES OF MOTOR CONTROL propose that coordinated movement involves the intelligent manipulation of sensory feedback (Todorov and Jordan 2002). This suggestion has reignited interest in the long-latency reflex, a natural candidate to mediate an intelligent feedback signal because it occurs very quickly in response to a mechanical perturbation and exhibits a wide range of sophistication (Diedrichsen et al. 2010; Scott 2004).

Despite a wealth of research on the long-latency reflex spanning over 60 years, some basic questions remain unresolved. For example, many studies have established that the long-latency reflex includes contributions from multiple neural pathways at various levels of the neuraxis (Gomi and Osu 1998; 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. 1977a; Matthews et al. 1990; Phillips 1969). It is largely unknown, however, whether these separate neural contributors endow the long-latency reflex with unique functional capabilities (Kimura et al. 2006; Matthews 2006; Shemmell et al. 2009).

In this study, we address this important issue by testing whether the long-latency reflex can be decomposed into functionally distinct components, which presumably reflect different neural contributors. Our approach builds on previous experiments, which showed that the sequence of muscle activity following a mechanical perturbation is decreasingly sensitive to preperturbation muscle activation (short latency > long latency; voluntary = none) (Pruszynski et al. 2009) but increasingly sensitive to task constraints as manipulated by goal-target position (short latency = none; long latency < voluntary) (Pruszynski et al. 2008a). On the basis of these results, it is reasonable to suggest that the intermediate sensitivity of the long-latency reflex reflects a functionally discrete response with feedback gains somewhat sensitive to both parameters (Fig. 1*A*) (Jaeger et al. 1982; Prochazka 1989). Alternatively, we suspected that the intermediate nature of long-latency activity occurs because it reflects the temporal overlap of two distinct processes (Crago et al. 1976; Rothwell et al. 1980), one sensitive only to preperturbation muscle activity and another sensitive only to goal-target position (Fig. 1*B*).

We can test between these possibilities because, under reasonable assumptions, they make different predictions about how the sensitivity of the long-latency reflex to preperturbation muscle activity and target position should interact. The discrete hypothesis predicts that larger preperturbation muscle activity will yield greater sensitivity to target position (Fig. 1*C*) because it assumes that both factors act to preset the sensitivity of a discrete response. In contrast, the overlap hypothesis predicts that target-dependent activity is independent of preperturbation muscle activity because it assumes these factors are processed by two independent contributors (Fig. 1*D*) whose outputs sum linearly, as when muscle activity evoked by transcranial electrical stimulation over primary motor cortex is superimposed on the long-latency stretch reflex (Day et al. 1991).

Our results are consistent with previous studies demonstrating that the long-latency response reflects the temporal overlap of multiple contributors (Gomi and Osu 1998; Kimura et al. 2006; Kurtzer et al. 2010; Lewis et al. 2004; Lourenco et al. 2006; Matthews and Miles 1988; Shemmell et al. 2009). Critically, we provide the clearest evidence to date that the long-latency response reflects the temporal overlap of at least two distinct components that sum linearly and contribute different functional capabilities. The first functional component is sensitive to preperturbation muscle activity but not target

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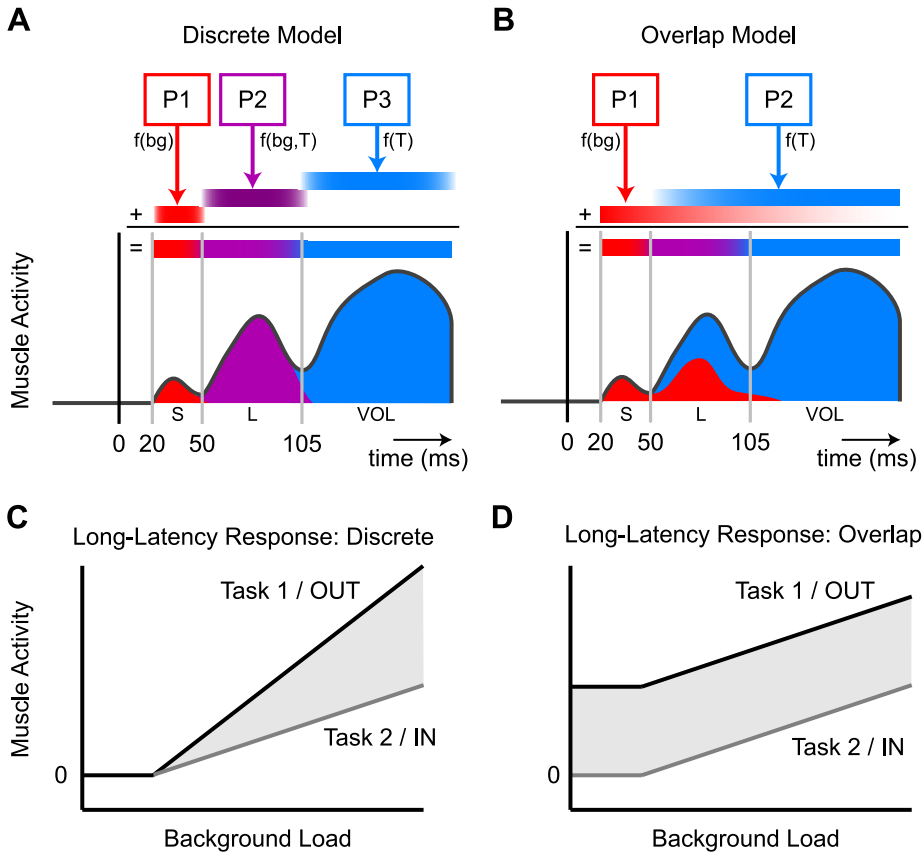

Fig. 1. Candidate models and experimental predictions. *A*: schematic showing typical evoked muscle activity following a mechanical perturbation. The vertical black line indicates perturbation onset, and the multiphasic trace (black line) represents muscle activity recorded by a surface electrode. The color coding underneath the trace represents the processes that actually contribute to the observed muscle activity. In the discrete model, 3 processes uniquely contribute to 1 of the 3 principal epochs of evoked muscle activity: the short-latency reflex (S), the long-latency response (L), and voluntary response (VOL). Process 1 (P1) is sensitive to preperturbation muscle activity as manipulated by background load (bg) but not task constraints as manipulated by spatial target position (T), P2 is somewhat sensitive to both bg and T, and P3 is sensitive only to T. *B*: the layout of this schematic is the same as the discrete model in *A*. However, in the temporal overlap model, the phasic events are caused by 2 processes that overlap during the long-latency epoch: P1, which is sensitive only to bg, and P2, which is sensitive only to T. *C*: predictions made by the discrete model when simultaneously manipulating bg and T. Note the multiplicative interaction between the 2 parameters whereby larger bg induces greater sensitivity to T (OUT and IN refer to spatial target position, the type of task constraint used in this study; see METHODS). *D*: predictions made by the overlap model. Note that the amount of modulation associated with T is independent of bg.

position, like the short-latency reflex, and the second functional component is sensitive to target position but not preperturbation muscle activity, like voluntary control. By leveraging our simple experimental approach, we further show that the task-dependent component, as modulated by spatial target position, does not reflect the simplest triggered reaction (Crago et al. 1976; Ravichandran et al. 2009) to a mechanical perturbation because it is sensitive to perturbation magnitude on a trial-by-trial basis even when the perturbation magnitude is unpredictable.

A preliminary account of this work has been presented in abstract form (Pruszynski et al. 2008b).

METHODS

Subjects and Apparatus

A total of 17 volunteers (11 males and 6 females, age 21–36 yr) participated in at least one of the three experiments presented in this study. All subjects were neurologically unimpaired, had normal/corrected vision, and gave informed consent according to a protocol approved by the Queen's University Research Ethics Board.

All experiments were performed in a robotic exoskeleton (KINARM; BKIN Technologies, Kingston, ON, Canada), which permits combined flexion and extension movements of the shoulder and elbow in the horizontal plane and can independently apply mechanical loads to the shoulder and/or elbow (Scott 1999). Target lights and simulated hand feedback were provided in the horizontal plane. Direct vision of the hand was occluded and hand feedback was removed before perturbation onset so that all perturbation responses were guided entirely by proprioception.

Experimental Paradigm

Experiment 1: two-target task. Subjects (n = 11) maintained their hand in a small central area (radius = 0.3 cm) while countering a background load (±2 Nm at elbow) that activated either the elbow flexors (negative background loads) or extensors (positive background loads) before perturbation onset (Fig. 2, *A–E*). Subjects were then shown a large peripheral target (radius = 20 cm) located on either the medial or lateral aspect of their hand and thus requiring predominantly elbow flexion or extension movements, respectively. After a 1- to 4-s random hold period, a rapid step-torque perturbation (±2 Nm at the elbow) displaced the hand either toward (IN condition) or away from (OUT condition) the peripheral target. It is important to emphasize that the OUT and IN conditions/targets were defined relative to the perturbation being applied. For perturbations that extended the elbow and thus stretched the elbow flexor muscles, OUT and IN targets were located on the medial and lateral aspect of the hand, respectively. For flexion perturbations, which stretched the elbow extensor muscles, OUT and IN targets were located on the lateral and medial aspect of the hand, respectively.

Subjects were required to quickly place their hand into the displayed target following the perturbation. After completing the trial, subjects were provided visual feedback to indicate success (target filled green) or failure (target filled red) based on set speed and accuracy criteria. A successful trial required the subjects to place their hand inside the peripheral target within 300 ms of perturbation onset and then remain inside the target for the next 1,000 ms. Fifteen successful repeats were performed in each condition (2 background loads, 2 perturbation loads, 2 targets; mean success rate = 98%) for a total of 120 trials presented in random order. Of these eight conditions, four were analyzed for each muscle, since we did not evaluate shortening responses. As such, the stretched muscle always needed to respond more vigorously for the OUT target than the IN target.

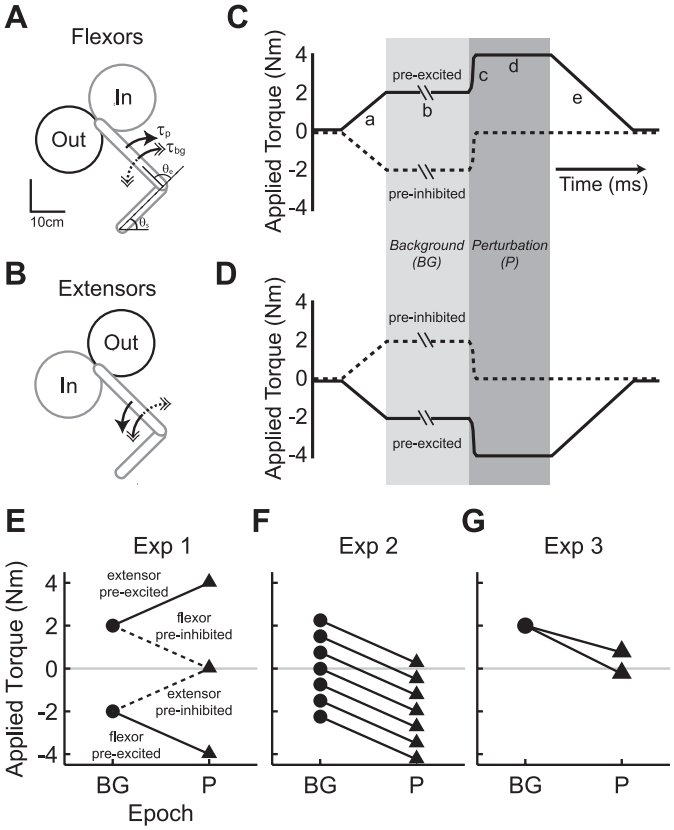

Fig. 2. Apparatus and experimental paradigm. *A* and *B*: subjects were presented with 1 of 2 large peripheral targets (PT; radius = 20 cm) located on the medial or lateral aspect of their hand when it was at the central starting position (CT). Target locations were chosen such that the applied flexion/extension perturbations displaced the hand either into (IN) or out of (OUT) the target. The central starting position was placed at the tip of the index finger when shoulder (θ_s) and elbow angles (θ_e) were 45° and 90°, respectively. Applied perturbations (solid arrows at elbow), background loads (double arrows), and target positions were different for studying elbow flexors (*A*) and extensors (*B*). *C* and *D*: timeline for an individual trial for studying elbow flexors (*C*) and extensors (*D*): *a*, both the CT and PT appeared while a background load (BG) was slowly introduced (rise time = 500 ms); *b*, hand feedback was removed while subjects maintained their hand at the CT. *c* and *d*, after 1–4 s, a rapid step (1,250-ms duration) perturbation (P) was introduced that stretched/lengthened the muscle of interest; *e*, the background load was slowly removed (fall time = 1 s) while performance feedback was provided to the subject. *E*, *F*, and *G*: schematic representation of conditions in *experiments 1*, *2*, and *3*, respectively. The horizontal axis represents loads applied at the elbow joint during the BG and P epochs. Positive and negative loads in the BG epoch preactivate extensor and flexor muscles, respectively. Positive and negative changes in load between the BG and P epochs stretch the extensor and flexor muscles, respectively.

Within this straightforward two-by-two experimental design (2 target positions, 2 background loads), the difference in evoked muscle activity for the same background load but different spatial targets was termed target-dependent activity (OUT − IN), and the difference in evoked muscle activity for the same spatial target but different background loads was termed load-dependent activity (preexcited − preinhibited). According to the overlap hypothesis, target-dependent activity should remain constant for both the preexcited and preinhibited background loads. Similarly, load-dependent activity should remain constant for both the IN and OUT spatial target positions.

Experiment 2: two targets and multiple background loads. Our second experiment tested whether target-dependent activity is constant across a wide range of background loads as predicted by the overlap hypothesis. Subjects (n = 8) were presented with two spatial target locations (IN and OUT, as in *experiment 1*) and seven initial background loads (±2.25, ±1.5, ±0.75, and 0 Nm at the elbow). The perturbation always stretched the elbow flexor muscles (−2.25 Nm) (Fig. 2*F*). A total of 20 successful repeats were performed in each condition, and the trial order was randomized across subjects (7 background loads, 1 perturbation loads, 2 target locations; mean success rate = 96%) for a total of 280 trials.

Experiment 3: two perturbation magnitudes. Our third experiment tested whether the target-dependent component of the long-latency response incorporated information from the current trial or whether it reflected the release of a preplanned sequence of muscle activity triggered by perturbation onset. Subjects (n = 8) countered a background load that inhibited the elbow flexor muscles (+2.5 Nm) and were presented with one of two perturbation magnitudes that stretched the elbow flexors (−1.25, −2.5 Nm) (Fig. 2*G*). Note that we only presented the subject with the OUT target, since pilot studies revealed that the IN target was never sufficient to elicit any evoked activity for these background loads and perturbation magnitudes (see also *experiments 1* and *2*). As such, OUT target activation in this experiment was equivalent to target-dependent activity in *experiments 1* and *2* (i.e., target-dependent activity = OUT − IN = OUT − 0 = OUT).

Forty successful repeats were performed in each condition (1 background load, 2 perturbation loads, 1 target location; mean success rate = 97%) for a total of 80 trials presented in a random order. At the end of the experiment, we collected 10 trials with a background load exciting the elbow flexor muscles (+2.5 Nm) for the purposes of normalization (see *Signal Processing*).

Electromyography

Surface electromyography (EMG) was collected according to previously reported procedures (Kurtzer et al. 2008; Pruszynski et al. 2008a, 2010). In *experiments 1* and 2, EMG was recorded from four muscles involved with flexion or extension at the elbow joint: brachioradialis (monoarticular flexor), biceps long head (biarticular flexor), triceps lateral head (monoarticular extensor), and triceps long head (biarticular extensor). Note that one muscle sample in *experiment 1* was not included in the analysis because it yielded no observable signal. In *experiment 3*, EMG was recorded only from biceps. After the skin was cleaned, electrodes (DE-2.1; Delsys, Boston, MA) were placed on the muscle belly parallel to the muscle fibers; the reference electrode was placed on the ankle. EMG signals were amplified (gain = 10^3–10^4), band-pass filtered (20–450 Hz), and then digitized at 1 kHz.

Consistent with many previous studies (Bonnet 1983; Crago et al. 1976; Lee and Tatton 1975; Mortimer et al. 1981; Mutha and Sainburg 2009; Nakazawa et al. 1997; Rothwell et al. 1980; Shemmell et al. 2009), including our own (Kurtzer et al. 2008, 2009; Pruszynski et al. 2008a, 2009), we defined three separate epochs of rapid muscle activity: the short-latency reflex (20–45 ms), the long-latency response (50–105 ms), and the voluntary response (120–180 ms). We also calculated mean muscle activation in a baseline epoch before perturbation onset (−100–0 ms).

Signal Processing

Joint and hand position signals were obtained directly from the KINARM device with a sampling rate of 1 kHz. These signals were then low-pass filtered (20 Hz, 2-pass, 6th-order Butterworth). After digitization, EMG signals were band-pass filtered (25–250 Hz, 2-pass, 6th-order Butterworth), full-wave rectified, and normalized by their mean activity during the baseline epoch in the most excitatory background load condition available in each experiment (2 Nm in *experiment 1*, 2.25 Nm in *experiment 2*, and 2.5 Nm in *experiment 3*). See Pruszynski et al. (2008a) for detailed signal processing procedures.

Data Analysis

Kinematics data were analyzed in two ways. First, we compared the effect of preperturbation muscle activity on final hand position for both target positions (i.e., preexcited vs. preinhibited for both the IN and OUT targets). We calculated the 95% confidence ellipse of hand positions at 350 ms postperturbation, a time when all subjects had stabilized their hand within the goal target. Final hand position was deemed significantly different if the calculated confidence ellipses did not overlap. Second, we analyzed the effect of preperturbation background load on initial elbow displacement (50 ms postperturbation) conditions using an ANOVA with four factors: subject, perturbation direction, target position, and background load. We chose a time of 50 ms postperturbation because kinematics at this time could be attributed almost exclusively to changes in intrinsic muscle properties rather than postperturbation changes in muscle activity (Brown et al. 1999). More exhaustive kinematics analysis of these tasks can be found in our previous studies (Pruszynski et al. 2008a, 2009).

Muscle activity was compared using a paired *t*-test. In all cases, we compared the mean muscle activity in a specific predefined epoch (see above). We shifted muscle activity for preinhibited conditions to account for a small temporal delay observed in their response. Specifically, we calculated the time (average, trial by trial) when each muscle reached half of its peak activity in the preinhibited/OUT and preexcited/OUT conditions. We then calculated the average temporal shift across muscles and applied it to the entire population of muscle samples. Similar results were found when using sample-specific shifts. It is important to emphasize that some of our predictions are trying to establish a null finding and thus are prone to type II errors. To permit easier interpretation of this possibility, we provide the *t*-statistic, degrees of freedom, and *P* value for each comparison.

When comparing the population of muscles, we performed a standard linear regression focusing on muscle activation across conditions or between epochs. The populations were deemed significantly different if the resulting linear regression included a slope parameter whose 95% confidence interval did not include the unity line (i.e., a slope of 1). A similar correlation was performed using single-trial data. In these cases, the correlation was done for each individual muscle across specific conditions, and a *t*-test evaluated whether the resulting correlation coefficients (r) were statistically different from each other. In all cases, the statistical threshold was set at 0.05.

Akaike's Information Criterion.

In *experiment 2*, we used Akaike's information criterion (AIC) to determine whether the amount of target-dependent activity in the long-latency epoch was independent of the preperturbation background load (i.e., a constant function, see below). AIC is a technique for choosing a parsimonious model from a set of candidates by balancing how well the model fits the data and its complexity (Burnham and Anderson 2002). Model quality is proportional to the likelihood (£) of a candidate model (θ') given the experimental data (x), and complexity is accounted for by K, the number of free parameters in the candidate model: $\mathrm{AIC} = -2 \log (£\theta'|x)] + 2K$. Under the assumption that model errors are Gaussian with equal variance, the model quality term can be simplified to the square root of the sum of squared error (RSS), which was calculated via either linear regression or constrained nonlinear optimization (*fmincon* in MATLAB; The MathWorks, Boston, MA). When nonlinear optimization was used, the procedure was restarted 1,000 times from random initial locations in an attempt to locate the global best fit.

We compared four models relating muscle activity to background load for each muscle sample: *1*) a constant function, *2*) a linear function, *3*) two linear functions that were piecewise continuous, and *4*) a sigmoid. The models were chosen because they include the possibility of no change with background load as well as changes that incorporate no saturation or saturation at either or both extremes. Candidate models were compared in two ways. First, the candidate model with the lowest AIC score was deemed the best candidate model. Second, we determined how often a candidate model was acceptable by calculating the difference between its AIC score and that of the best candidate model: $\Delta\mathrm{AIC} = \mathrm{AIC} - \min(\mathrm{AIC})$. If this difference was less than a typically chosen threshold ($\Delta\mathrm{AIC} < 4$), the model was deemed acceptable (Burnham and Anderson 2002).

RESULTS

Experiment 1: Target-Dependent Responses Persist When Load-Dependent Activity is Fully Suppressed

Our first experiment required subjects to maintain their hand at a central location while countering a background load and then respond to a sudden mechanical perturbation by moving their hand to a visually defined spatial target (Fig. 2). Background loads could either excite or inhibit the muscle before the perturbation, and targets were positioned such that the same perturbation could displace the hand either into the target (IN) or away from the target (OUT).

Although the differences in background load were notable, they did not have a large effect on subject behavior (Fig. 3). No subjects showed a significant difference in final hand position as a function of background load for either the elbow flexor or elbow extensor conditions (for exemplar, see overlap of 95% confidence intervals, Fig. 3, *A* and *D*), suggesting that subjects were planning to move to a relatively constant position in space. We also found no statistical difference in initial elbow displacement (50 ms postperturbation) as a function of background load and thus preperturbation muscle activation (ANOVA, $F_{1,87} = 1.7$, $P = 0.2$; see METHODS). The modest effect of background load on joint displacement may be surprising given previous suggestions that activity-dependent changes in intrinsic muscle stiffness are an important stabilizing mechanism for the upper limb (Franklin and Milner 2003; Gomi and Osu 1998; Mussa-Ivaldi et al. 1985). However, this finding is consistent with our previous empirical and modeling work showing that intrinsic muscle properties are modestly affected by changes in preperturbation muscle activity (Pruszynski et al. 2009), especially at the relatively low levels of muscle activity employed in the present experiments.

As expected from previous experiments that studied the same factors in isolation, each of the four experimental conditions (2 background loads, 2 target locations) yielded a qualitatively different pattern of activity for the same mechanical perturbation, which stretched the muscle of interest (see METHODS). This result is depicted for an exemplar elbow extensor muscle (triceps lateral) in Fig. 4*A*. When the muscle was preinhibited (applied extension background load) and the perturbation (applied elbow flexion) displaced the hand into the displayed target (preinhibited/IN condition), we observed no substantial muscle activity in the short-latency, long-latency, or voluntary epochs. In contrast, preexciting the muscle (applied flexion background load) and applying the perturbation for the same target location (preexcited/IN) yielded distinct phasic events in the short-latency and long-latency epochs but no substantial voluntary response. When the muscle was preexcited and the perturbation displaced the hand away from the presented target (preexcited/OUT), the evoked muscle activity appeared phasic, as for the preexcited/IN condition, but was substantially more robust in the long-latency and voluntary epochs. Finally, when

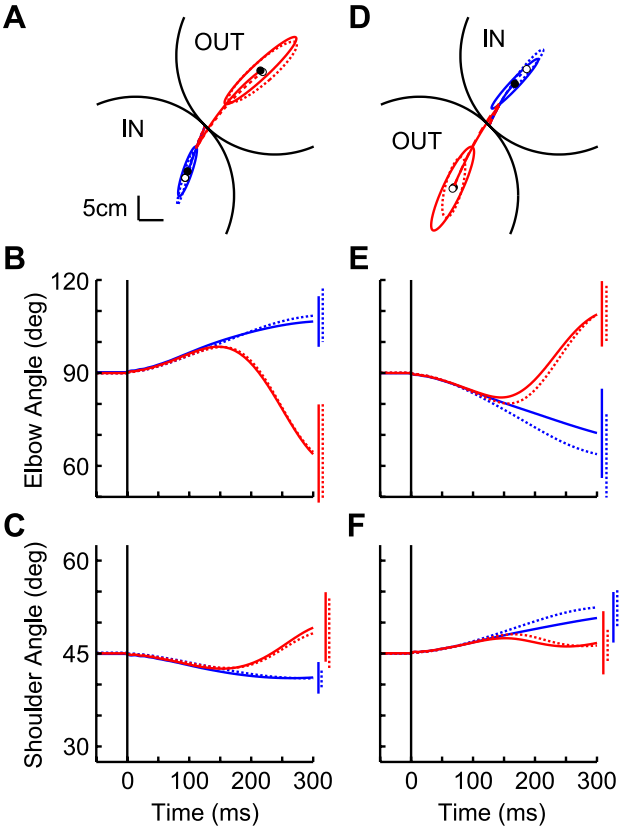

Fig. 3. Hand kinematics: *experiment 1*. *A*: spatial hand position from a representative subject for a perturbation that stretched the elbow extensor muscles. Traces correspond to the mean response for the IN (blue) and OUT (red) targets, under both excitatory (solid) and inhibitory (dashed) background loads. Filled (preexcited) and open circles (preinhibited) represent the mean hand position 300 ms after perturbation onset, and the surrounding ellipses indicate the 95% confidence intervals of these endpoints. *B* and *C*: temporal kinematics of the elbow and shoulder. The horizontal axis represents time after perturbation onset (black vertical line), and the vertical axis represents the joint angle, which is initially 45° and 90° for the shoulder and elbow, respectively. The vertical lines to the right of each trace represent the 95% confidence interval of the corresponding trajectory 300 ms after perturbation onset. They are offset from one another for clarity. *D–F*: same format as in *A–C* for perturbations that stretched the elbow flexor muscles.

the muscle was preinhibited and the perturbation displaced the hand away from the target (preinhibited/OUT), the evoked activity appeared as a slowly growing response beginning near the onset of the long-latency epoch and continuing through the voluntary response with no discernable separation.

Despite the differences in evoked activity for each experimental condition, target-dependent activity was strikingly constant for both background loads, and load-dependent activity was strikingly constant for both target positions (Fig. 4*B*). Similar results were observed across the population of collected elbow muscle samples that act to flex or extend the elbow joint (Fig. 5). In fact, the only notable difference was a small temporal delay when the muscle was inhibited before the perturbation. On average, muscles reached half of their peak activity ~5 ms earlier when they were preexcited, which is consistent with previous studies and likely reflects the additional slack present in muscle fibers when they are inhibited before the stretch (Proske et al. 1993). On the basis of this result, all subsequent analyses were performed after the preinhibited responses was shifted by 5 ms. Note that all figures showing raw EMG signals in time are not shifted.

The discrete hypothesis predicts that target-dependent activity should be modified by the background load. In contrast, the overlap hypothesis predicts that target-dependent activity should be the same for both background loads. Consistent with the overlap hypothesis, we found no statistical difference in target-dependent activity as a function of background load for the long-latency epoch (paired *t*-test, $t_{42} = 1.5$, $P = 0.14$) or during the voluntary response ($t_{42} = 0.62$, $P = 0.5$; Fig. 6*A*). At the level of individual muscles, a linear regression comparing target-dependent activity for the two background loads yielded slope terms that were not significantly different from unity (long latency: mean slope = 1.01, 95% confidence interval = [0.87 1.15]; voluntary: 1.01, [0.94 1.09]), and we found a robust correlation between target-dependent activity in the preexcited and preinhibited conditions (long latency: $r = 0.69$; voluntary: $r = 0.91$). Analogous statistical results were found when load-dependent activation was compared as a function of target position.

Experiment 1: Evidence for the Overlap Hypothesis Provided by Trial-by-Trial Correlations Across Epochs

An interesting prediction of the overlap hypothesis is that trial-by-trial correlations between the short-latency, long-latency, and voluntary epochs should be systematically related to the background load and target condition presented to the subject. Specifically, correlations between the long-latency and voluntary epochs should be higher when the muscle is preinhibited and the subject is pushed away from the target (preinhibited/OUT) than when the muscle is preexcited and pushed away from the target (preexcited/OUT). This is because when the muscle is preinhibited, the long-latency response is putatively dominated by a single (target-dependent) component that also dominates the voluntary epoch (see Fig. 1*B*). In contrast, when the muscle is preexcited, long-latency activity is composed of two components, one of which (load dependent) is essentially absent during the voluntary response and thus would reduce any correlation between these epochs. Note that the discrete hypothesis does not predict any particular pattern of correlations across conditions because each of the epochs is independent of one another.

The empirical results were strikingly consistent with the predictions made by the overlap hypothesis. Trial-by-trial correlations between the long-latency and voluntary epochs were significantly higher when the muscle was preinhibited and pushed away (preinhibited/OUT) from the target than when it was preexcited and pushed away (preexcited/OUT) from the target (mean $r = 0.44$ vs. 0.18, $t_{42} = 3.9$, $P < 0.001$; Fig. 6*B*). Note that the resultant correlation coefficient is impressively high given the noisy nature of EMG signals. A control analysis between two subdivisions of the voluntary epoch (spaced 15 ms apart, like that between the long-latency and voluntary epoch, 120–143 and 158–180 ms) yielded a mean trial-by-trial correlation coefficient that was not significantly higher ($r = 0.51$, $t_{42} = -1.1$, $P = 0.3$).

A related prediction can be made about the relationship between short-latency and long-latency activity. Higher correlations should occur when the muscle is preexcited and pushed into the target (preexcited/IN) than when the muscle is preex-

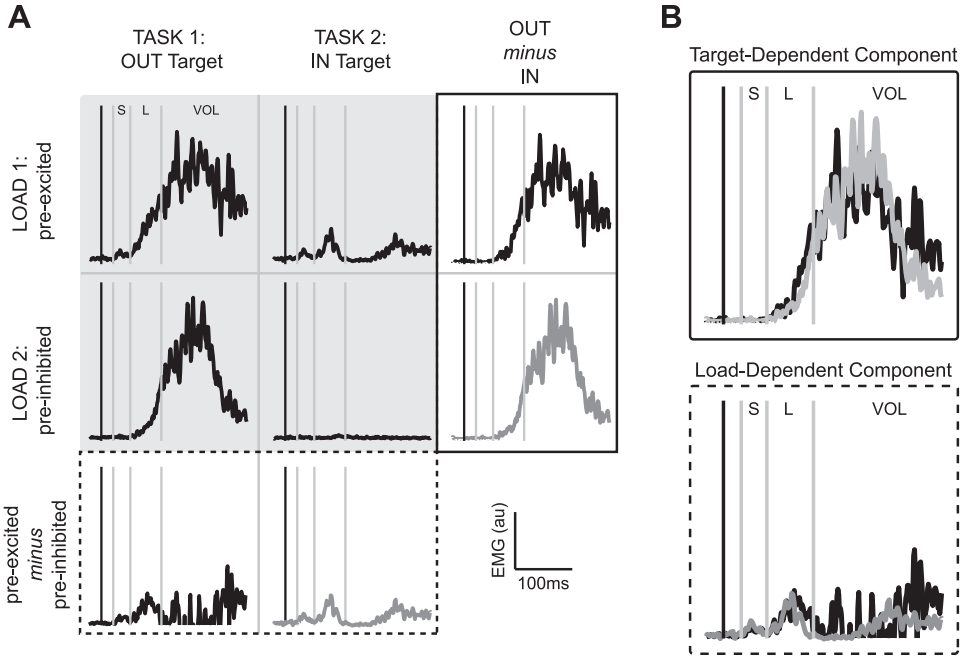

Fig. 4. Exemplar muscle activity: *experiment 1*. *A*: muscle activity from a single, representative subject and muscle (*subject 8*, triceps long). The horizontal axis represents time aligned on perturbation onset (black vertical line). Thin gray lines within each panel approximate divisions between the response epochs: short latency (S), 20–45 ms; long latency (L), 50–105 ms; and voluntary (VOL), 120–180 ms. The panels with a shaded background are actual experimental conditions (see Fig. 2*E*). Panels at *right* (solid box) depict the difference in activity for the same background load condition but different target locations (OUT − IN) and thus represent target-dependent activity. Panels at *bottom* (dashed box) depict the difference in activity for the same target locations but different background load condition (preexcited − preinhibited) and thus represent background load-dependent activity. For clarity, only positive values are displayed, although the subtraction process could, in principle, yield negative values. EMG, electromyogram. *B*: an overlay of the load-dependent and task-dependent components. The same data as in *A* are placed on the same axes to highlight their similarity.

cited and pushed out of the target (preexcited/OUT). This is because the former condition results in a unitary contribution to the long-latency epoch from the load-dependent component, which putatively dominates the short-latency reflex. Our results were again compatible with the overlap hypothesis. Trial-by-trial correlations were significantly higher for the preexcited/IN condition than for the preexcited/OUT condition (mean $r = 0.13$ vs. 0.005, $t_{42} = 2.1$, $P < 0.05$; Fig. 6*C*). A control analysis revealed that the correlations found in the preexcited/OUT condition were not significantly lower than trial-by-trial correlations between two subdivisions of the long-latency epoch (spaced 5 ms apart, 50–73 and 78–105 ms, $r = 0.12$, $t_{42} = 0.2$, $P = 0.8$).

Experiment 2: Target-Dependent Activity is Constant Across a Wide Range of Background Loads

The results of our first experiment support the overlap hypothesis by demonstrating that target-dependent activity in the long-latency epoch is independent of background load. However, this observation may reflect our choice of a particular inhibitory background load, which yielded no phasic activation in the long-latency epoch for the IN target. To address this limitation, our second experiment tested whether target-dependent activity is constant across a wide range of background loads. The experimental protocol was identical to *experiment 1* except that subjects were presented with seven potential background loads rather than two (Fig. 2*F*).

As expected, we observed a systematic increase in the long-latency response for both the IN and OUT targets as the background load was increased (Fig. 7*A*). We also found that for the same background load, activity in the long-latency epoch was larger for the OUT target than for the IN target. Despite these changes in overall activity, qualitative inspection of target-dependent activation suggested that it was constant across background loads (Fig. 7*B*).

We quantified the constancy of target-dependent activity by comparing the ability of four candidate models to relate long-latency activity to background load. For each muscle sample, we fit the muscle activity in the long-latency epoch with four candidate models [*1*) constant, *2*) linear, *3*) piecewise linear, and *4*) sigmoid] and evaluated their ability to represent target-dependent activity. We then ranked each model for every muscle sample using the AIC, an information-theoretic approach for choosing a parsimonious model that takes into account both quality of fit and model complexity (Burnham and Anderson 2002) (see METHODS). Matching our qualitative observations, both the IN and OUT target conditions yielded robustly increasing responses that were rarely well described by a constant model (best model: IN = 0%, OUT = 17%; adequate model: IN = 3%, OUT = 31%) (Fig. 7*C*). Strikingly, target-dependent activity (OUT − IN, Fig. 7*C*) was almost always well explained by a constant model (best = 61%; adequate = 91%), suggesting that despite substantial and systematic changes in the overall response, target-dependent activity was constant across background loads.

Experiment 3: Target-Dependent Activity Is Not a Simple "Triggered Reaction"

Our first two experiments demonstrated that long-latency activity in human subjects performing a simple motor task reflects the temporal overlap of two independent components. In our third experiment, we showed the utility of the present experimental approach by using it to address a long-standing question about long-latency activity.

Some authors have suggested that task-dependent activity (i.e., the target-dependent component in this task) is generated by a simple "triggered reaction" whereby a motor plan is formulated in advance of the perturbation and then released by its occurrence (Crago et al. 1976; Houk 1978; Shemmell et al. 2009). Such a simple triggered reaction would reflect an open-loop release of motor commands rather than a closed-loop feedback response that is adjusted as a function of current sensory information. Testing this hypothesis was straightforward with our approach. We used a large inhibitory back-

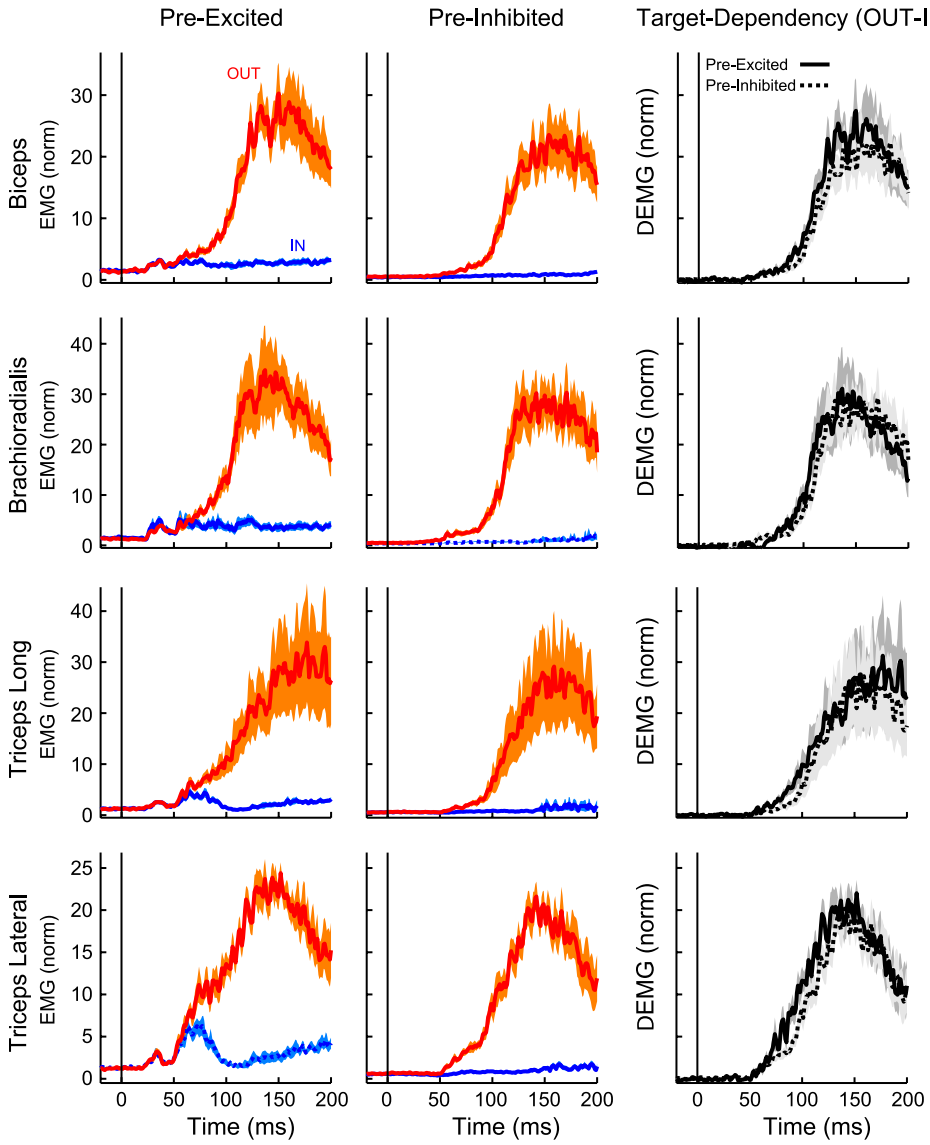

Fig. 5. Population muscle activation: *experiment 1*. Each row of panels presents the average muscle activation across subjects aligned on perturbation onset (black vertical line). Panels in the *left* and *middle* columns represent activation patterns when the muscle was preexcited and preinhibited, respectively. Panels in the *right* column plot the mean target-dependent activity calculated by subtracting the evoked response for the 2 target locations (OUT − IN) for both the excitatory (solid) and inhibitory (dashed) background loads. Note that target dependency is remarkably similar regardless of initial background load.

ground load and the OUT target to isolate target-dependent activity and then randomly applied one of two perturbation magnitudes (small: 1.25 Nm; large: 2.5 Nm; Fig. 2*G*). Note that the OUT target activity under these conditions is essentially equivalent to target-dependent activity (see METHODS, *experiment 3*). Since the subjects could not predict which perturbation magnitude would occur, the triggered reaction hypothesis would predict that, on average, the muscle response would be the same for both perturbation magnitudes, because the nervous system would not know which response to prepare and trigger. In contrast, a more sophisticated mechanism would evaluate the sensory information about the magnitude of the perturbation on every trial and scale the target-dependent activity appropriately (i.e., generate a larger response for the larger perturbation). Our results clearly reject the notion of the simplest triggered reaction that can only plan one response, since all subjects significantly scaled the magnitude of long-latency activity (paired *t*-test: $t_7 = 3.6$, $P < 0.01$; Fig. 8*A*). In fact, doubling the perturbation magnitude (from 1.25 to 2.5 Nm) yielded an approximately twofold increase in target-dependent muscle activity (mean = 2.2, 95% confidence interval = [1.6, 2.8]), suggesting that target-dependent activity accurately reflected the perturbation magnitude on the current trial (Fig. 8*B*).

DISCUSSION

To our knowledge, the present work is the first to demonstrate that task-dependent muscle activity in the long-latency epoch (as modulated by target position) is independent of preperturbation muscle activity and, conversely, that load-dependent activity (as modulated by preperturbation muscle activity) is independent of target position. As such, these observations provide clear evidence that long-latency activity in the present context is not a functionally discrete event as commonly implied when it is referred to as the long-latency or transcortical reflex. Rather, long-latency muscle activity in an awake human performing a naturalistic motor task appears to reflect the temporal overlap of at least two functionally independent components.

It is important to emphasize that our results not only demonstrate the presence of two functionally independent compo-

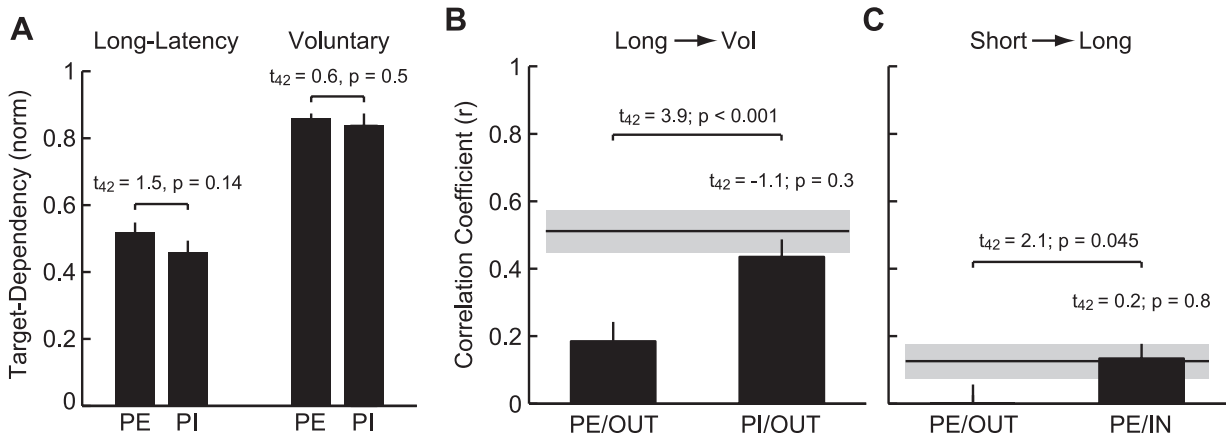

Fig. 6. Group analysis and trial-by-trial correlations: *experiment 1*. *A*: comparison of target-dependent activation in the epochs of interest normalized to their overall magnitude of activation; the normalization factor is mean muscle activity in that epoch for the OUT target condition and preexcited background load. A value of 0 indicates no target dependency, and a value of 1 indicates that target dependency was as large as the overall level of activity when the muscle was preexcited for the OUT target. Error bars indicate SE. PE, preexcited; PI, preinhibited. *B*: each bar represents one of the experimental conditions, including a particular background load (PE, PI) and target position (IN, OUT). The vertical axis represents the average trial-by-trial correlation between the long-latency and voluntary epochs. The horizontal bar represents the correlation in a control analysis comparing 2 subcomponents of the voluntary response in the PI/OUT condition (i.e., best-case scenario). All error bars indicate SE. *C*: the same format as in *B* except that the comparison is made between the short- and long-latency epochs and different conditions are contrasted. The horizontal bar represents the correlation between 2 subcomponents of the long-latency epoch in the PE/IN condition.

nents but also provide a powerful experimental paradigm for manipulating their contribution. We expect that future studies will use our approach to "dissect" the long-latency response into its constituent parts, which will further our understanding of the functional and structural organization of rapid feedback responses.

For example, a straightforward application of our approach allowed us isolate target-dependent activity. We could then directly show that target-dependent activity does not reflect the simplest preplanned triggered reaction (Crago et al. 1976; Houk 1978), a long-standing hypothesis in the field, because it was clearly sensitive to perturbation magnitude on a trial-by-trial basis even though the perturbation magnitude was unpredictable. These findings are not consistent with studies focused on rapid responses to postural perturbations, where triggered reactions appear to be remarkably stereotyped (Nashner et al. 1979; Nashner and Cordo 1981). Rather, our results parallel the object manipulation (Johansson and Westling 1984, 1988) and speech production (Abbs et al. 1984; Abbs and Gracco 1984) literature, where triggered reactions are considered flexible, goal-directed responses that actively account for various parameters of the sensory input. Although we favor the latter conceptualization, it is important to emphasize that our present findings do not rule out the possibility that the nervous system is capable of preparing multiple responses and triggering the appropriate one based on various parameters of the current sensory stimulus, as has been reported for motor responses to startling auditory stimuli under some conditions (Carlsen et al. 2009). Future experiments using our experimental approach can address this question by testing whether the magnitude of the target-dependent component is a continuous function of perturbation magnitude or whether it is limited to preparing a relatively limited number of discrete responses.

Our paradigm may resolve other prominent findings in the literature. For example, Rothwell et al. (1980) found that long-latency activity, like the voluntary response, was sensitive to the predictability of the mechanical perturbation. This result led them to speculate that the long-latency response reflects an "interaction between a reflex of long-latency and a subsequent very rapid voluntary event." Our results empirically demonstrate that their speculation was correct insofar as target-dependent activation in the long-latency epoch was well correlated with target-dependent activation in the voluntary epoch. Further experiments using our approach can isolate target-dependent activity, determine whether it is the source of task-dependency in a host of experimental situations (Diedrichsen et al. 2010; Kurtzer et al. 2008; Marsden et al. 1981), and empirically establish its similarity to voluntary control.

Our experimental approach can also be used to isolate the load-dependent component of long-latency activity. On this front, the overlap model indicates that load-dependent activity consists to two distinct phases of activation, an initial period of excitation in the short-latency epoch and a second peak in the long-latency epoch (Fig. 1*B*). This is consistent with past suggestions that the long-latency response is caused by the reactivation of primary spindle afferents following their synchronization during the short-latency reflex and subsequent refractory period (Schuurmans et al. 2009). Alternatively, it may be that the load-dependent component of long-latency activity is mediated by slower secondary muscle afferents that yield a distinct phasic burst of activation at a longer latency (Grey et al. 2001; Matthews 1984). Although our present results cannot distinguish between these possibilities, future experiments could focus directly on the load-dependent component when testing between these hypotheses. Such studies may well demonstrate that the load-dependent component itself reflects the overlap of multiple contributors. Our findings do not rule out the possibility that the two functionally independent components we identified can be further subdivided. They do, however, predict that all the potential subcomponents of load-dependent activity will not be sensitive to task constraints as modulated by spatial target position and that all potential subcomponents of task-dependent activity will not be sensitive to preperturbation muscle activity.

Motor dysfunction from a number of clinical conditions, including Parkinson's disease (Tatton and Lee 1975), stroke

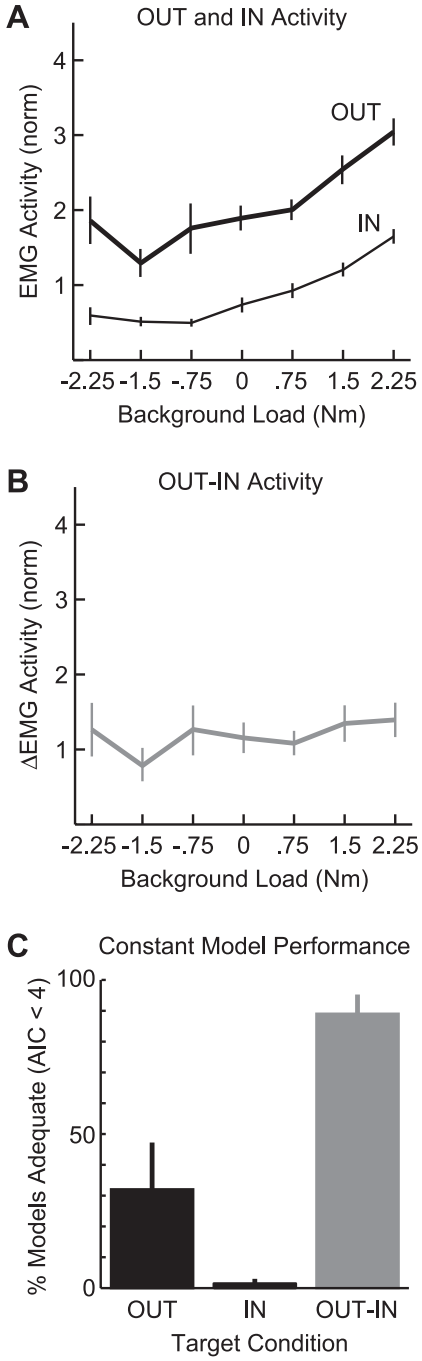

Fig. 7. Group analysis: *experiment 2*. *A*: the change in long-latency activity for the same mechanical perturbation as a function of background load (horizontal axis) for 2 target locations (OUT, thick line; IN, thin line). Error bars indicate SE. *B*: the same format as in *A* except for target-dependent activation (OUT − IN). The error bars represent the average SE when the difference calculation was bootstrapped. *C*: results of Akaike's information criterion (AIC) analysis on each individual muscle sample, demonstrating the proportion of times that a constant model was adequate for explaining the relationship between background load and muscle activation in the long-latency epoch. Bars represent muscle activity for the OUT target, IN target, and the difference between them (OUT − IN). Again, error bars indicate average SE and arise because the procedure (OUT − IN calculation) was bootstrapped to estimate the variability.

(Marsden et al. 1977b), and cerebellar atrophy (Mauritz et al. 1981), has been linked to abnormal long-latency responses (Rothwell 1990). For example, the rigidity of Parkinsonian patients may be caused by the fact that they show increased long-latency responses (Tatton and Lee 1975). These subjects are also less capable of modulating their long-latency response according to verbal task constraints (Bloem et al. 1995), which may be correlated with their difficulty initiating movements. Our results suggest that these abnormalities may reflect the dysfunction of particular functional components of the long-latency response. Establishing such a link is an important avenue for future research because it may help clarify the pathophysiology of Parkinson's disease and other disease states.

As highlighted by Peter Matthews (2006), several previous studies have demonstrated that multiple neural generators can contribute to long-latency activity in principle but have left open the important question of whether/when they do contribute in practice (Gomi and Osu 1998; Kurtzer et al. 2010; Lourenco et al. 2006; Matthews and Miles 1988). For example, in a particularly impressive sequence of experiments, Lourenco et al. (2006) clearly showed that electrical stimuli applied to a

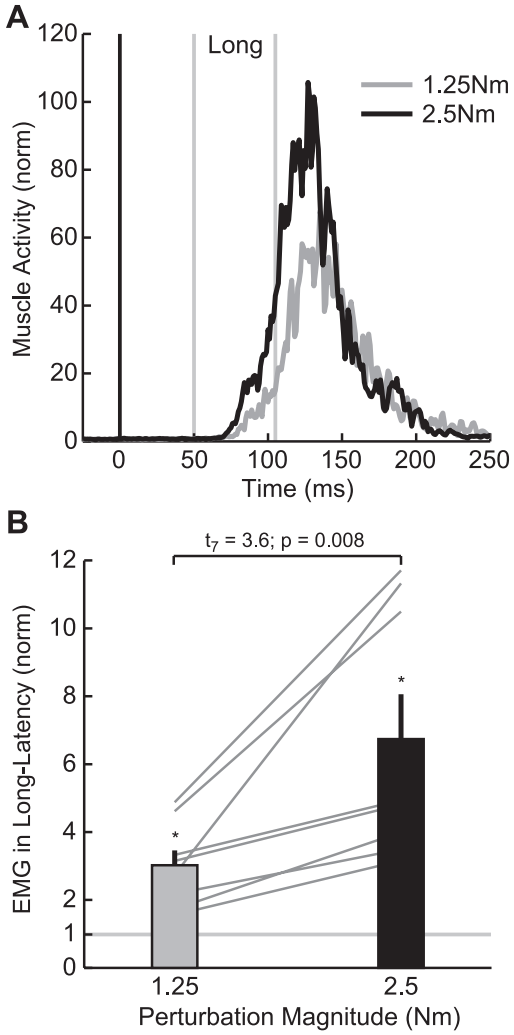

Fig. 8. Group analysis: *experiment 3*. *A*: average muscle activity when the muscle is preinhibited but perturbation magnitude is unpredictable (small, 1.25 Nm, gray; large, 2.5 Nm, black). The horizontal axis represents time relative to perturbation onset (black vertical line), and the vertical axis depicts normalized muscle activity. *B*: mean activation in the long-latency epoch across subjects. Each thin gray line represents data for a single subjects. and error bars indicate SE. Both conditions yielded significant evoked activity within the long-latency epoch (1-sided *t*-test > 1, $^*P < 0.05$).

mixed nerve can excite wrist muscles at two different latencies within the long-latency epoch. Further experimental manipulations led the authors to conclude that the two phases of excitation are likely caused by a spinal pathway via group II afferents and a cortical pathway via group I afferents. Although their physiological evidence is convincing, the functional contribution of each pathway could not be tested because the constraints of their experimental approach meant that their subjects were not engaged in a meaningful motor task. Coupling their results with our own, it is natural to speculate that load-dependent activity reflects a spinal circuit, like the short-latency reflex, and that target-dependent activity involves a cortical pathway, like voluntary control.

The few experiments that have linked neural structures to the functional capabilities of long-latency activity have used transcranial magnetic stimulation (TMS) to systematically interfere with cortical processing (Kimura et al. 2006; Shemmell et al. 2009). For example, the elegant work of Kimura et al. (2006) showed that disrupting sensorimotor cortex did not eliminate long-latency activity but did impair its predictive modulation according to the directionality of a force field that subjects were about to reach through. Similarly, Shemmell et al. (2009) used the same technique to demonstrate that interfering with primary motor cortex affects long-latency activity associated with the stability of the environment but not the verbal task instructions given to the subject, suggesting that only the former functionality relies on a circuit including primary motor cortex.

Although both of these studies demonstrated an important neuroanatomical segregation between various aspects of long-latency activity, they were fundamentally limited because their TMS intervention only acted as a categorical probe of a given neural circuit. In contrast, our behavioral paradigm did not explicitly test the neural circuitry, but it did permit greater control over each functional component based on simple changes in background load and spatial target position. Accordingly, we were able to clearly demonstrate the presence of independent functional components, show how these components interact, determine how their activity is related across epochs, and establish the features of a single component in isolation. Despite these differences, it is important to emphasize that the TMS findings are complementary to our own. Together they form a foundation for understanding long-latency activity as a temporal designation that incorporates the output of multiple neural generators that can contribute unique functional properties.

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DISCLOSURES

S. H. Scott is associated with BKIN Technologies, which commercializes the KINARM robot used in this study.

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