RESEARCH ARTICLE

Control of Movement

Trial-by-trial modulation of express visuomotor responses induced by symbolic or barely detectable cues

Samuele Contemori,[1] Gerald E. Loeb,[2] Brian D. Corneil,[3,4,5] Guy Wallis,[1] and Timothy J. Carroll[1]

[1]*Centre for Sensorimotor Performance, School of Human Movement and Nutrition Sciences, The University of Queensland, Brisbane, Queensland, Australia;* [2]*Department of Biomedical Engineering, University of Southern California, Los Angeles, California;* [3]*Department of Physiology and Pharmacology, Western University, London, Ontario, Canada;* [4]*Department of Psychology, Western University, London, Ontario, Canada; and* [5]*Robarts Research Institute, London, Ontario, Canada*

Abstract

Human cerebral cortex can produce visuomotor responses that are modulated by contextual and task-specific constraints. However, the distributed cortical network for visuomotor transformations limits the minimal response time of that pathway. Notably, humans can generate express visuomotor responses in arm muscles that are inflexibly tuned to the target location and occur 80–120 ms from stimulus presentation [stimulus-locked responses (SLRs)]. This suggests a subcortical pathway for visuomotor transformations that might involve the superior colliculus and its downstream reticulo-spinal projections. Here we investigated whether cognitive expectations can modulate the SLR. In one experiment, we recorded surface electromyogram (EMG) from shoulder muscles as participants reached toward a visual target whose location was unpredictable in control conditions and partially predictable in cue conditions by interpreting a symbolic cue (75% validity). Valid symbolic cues led to earlier and larger SLRs than control conditions; invalid symbolic cues produced later and smaller SLRs than control conditions. This is consistent with a cortical top-down modulation of the putative subcortical SLR network. In a second experiment, we presented high-contrast targets in isolation (control) or ∼24 ms after low-contrast stimuli, which could appear at the same (valid cue) or opposite (invalid cue) location as the target and with equal probability (50% cue validity). We observed earlier SLRs than control with the valid low-contrast cues, whereas the invalid cues led to the opposite results. These findings may reflect bottom-up attentional mechanisms, potentially evolving subcortically via the superior colliculus. Overall, our results support both top-down and bottom-up modulations of the putative subcortical SLR network in humans.

NEW & NOTEWORTHY Express visuomotor responses in humans appear to reflect subcortical sensorimotor transformation of visual inputs, potentially conveyed via the tecto-reticulo-spinal pathway. Here we show that the express responses are influenced by both symbolic and barely detectable spatial cues about stimulus location. The symbolic cue-induced effects suggest cortical top-down modulation of the putative subcortical visuomotor network. The effects of barely detectable cues may reflect exogenous facilitation mechanisms of the tecto-reticulo-spinal pathway.

low-contrast stimulus; rapid visuomotor response; reaching; subcortical motor control; superior colliculus

INTRODUCTION

Extraction of information about the surrounding environment is crucial to guide motor behavior in everyday life and sport contexts but also to react to threatening events for survival. In higher vertebrates, the availability of the cerebral cortex enables interpretation of surrounding sensory cues and generation of expectations about probable future events.

These expectations can facilitate the transformation of expected sensory information into motor responses, thus reducing the reaction time (RT) (for review see Refs. 1, 2).

Interestingly, extremely rapid (express) muscle activations and inhibitions in response to visual stimuli can be recorded from humans shoulder muscles (3). The initiation time of these early muscle responses is consistently within 80–120 ms after stimulus presentation, regardless of the movement

1507

onset time (3, 4). Therefore, these express visuomotor muscle responses have been called stimulus-locked responses (SLRs; see Ref. 5 for discussion of appropriate nomenclature). Furthermore, the SLR is always directed toward the stimulus location irrespective of whether the task requires movement toward (proreach) or against (antireach) the stimulus (6) or withholding the movement (7). It is worth noting that the short-latency and inflexible stimulus-locked characteristics of SLRs are also properties of express saccades (8, 9). Express saccades are known to be generated subcortically via the superior colliculus and its downstream projections to the reticular formation (10, 11). Indeed, Schiller et al. (12) showed that an obliteration of express saccades, but not longer-latency (>100 ms) saccades, resulted from induced damage of the superior colliculus in monkeys. Therefore, the SLR is proposed to originate from a subcortical visuomotor network akin to that for the express saccades, potentially involving the tecto-reticulo pathway and its downstream projections to the spinal motoneurons and interneurons (for review see Ref. 13).

The occurrence of express saccades increases as a function of collicular pretarget activity level (11, 14), probably via a direct influence on collicular target-related response amplitude. For instance, cuing the target with a prior (~50 ms) stimulus at the same location (i.e., valid cue) has been shown to prime the pretarget activity of superior colliculus neurons and amplify the ensuing target-related response (15). This facilitates both rapid initiation of saccades (15) and neck muscle SLRs (16) compared with no-cued and invalidly cued targets in monkeys, a phenomenon known as attention capture (for review see Refs. 13, 17).These observations suggest that rapid visuomotor behaviors are modulated as a function of pretarget sensory events and their influence on visuomotor networks, including the superior colliculus and its downstream reticulo-spinal circuits.

Critically, the mechanisms behind the cue-induced modulation of express visuomotor behaviors are unclear. The express saccade (15) and neck SLR (16) modulations induced by an ~50-ms prior cue about the target location might originate from a potentiation of the collicular map encoding the cue location via direct retino-tectal projections (bottom-up spatial attention; Ref. 18). Nonetheless, for a ~50-ms cue-target onset asynchrony (CTOA) endogenous cortical contributions cannot be ruled out (top-down orientation of attention; Ref. 18). Top-down modulation mechanisms are also consistent with recent evidence of express saccade vector modulations as a function of prior instructions provided via symbolic cues (19, 20). Furthermore, cue-induced effects on neck SLRs (16) appear to contribute to express orientation of the head. If similar cue-induced modulations of the upper limb muscle SLRs occur during reaching tasks, it would lend support to the hypothesis that similar express processes underlie spatial orientating and recruitment of muscles deputed to reaching functions. Therefore, the purpose of the present study was to delineate the contribution of top-down and bottom-up attentional orientation mechanisms to the SLR of upper limb muscles in humans.

In *experiment 1*, we studied the influence of pretarget signals affording expectations about the location of approaching targets on SLRs. Here, we cued the target location with a symbolic arrow-shaped cue that was validly oriented toward the target location in 75% of trials. Importantly, the cue location was irrelevant to the target position, thus requiring interpretation of the arrow orientation. In *experiment 2*, we tested the hypothesis that SLRs are modulated by bottom-up attentional mechanisms. Specifically, we used a barely detectable spatial cue whose location was relevant to the target position, which appeared shortly (~24 ms) before the target and had a low predictive value (50% validity) for target location. These attributes were designed to minimize strategic top-down contribution to cue processing. These experiments provide evidence about the influence of both top-down and bottom-up neural modulation mechanisms of the SLR and its putative underlying subcortical network, including the superior colliculus. The findings may contribute to our understanding of the neural mechanisms underlying express visuomotor behavior in humans.

MATERIALS AND METHODS

Participants

Sixteen adults participated in *experiment 1* (14 males, 2 females; mean age: 31.6 yr, SD: 6.9), and twelve of them also completed *experiment 2* (11 males, 1 female; mean age: 31.3 yr, SD: 6.0). All participants were right-handed, had normal or corrected-to-normal vision, and reported no current neurological or musculoskeletal disorders. They provided written informed consent and were free to withdraw from the experiment at any time. All procedures were approved by the University of Queensland Medical Research Ethics Committee (Brisbane, Australia) and conformed to the Declaration of Helsinki.

Apparatus

The apparatus used for this study has been previously described by Contemori et al. (5). Briefly, the participants performed target-directed reaching movements with their dominant hand via shoulder extension (rightward) or flexion (leftward) movements in the transverse plane. Because muscle preactivation has proven effective to facilitate SLR expression (5, 6), a constant lateral load of ~5 N was applied in the direction of transverse shoulder extension via a weight and pulley system. This increased the baseline activity of shoulder transverse flexor muscles, including the clavicular head of pectoralis major muscle (PMch).

All stimuli were created in MATLAB with the Psychophysics Toolbox (21, 22) and were displayed on a LCD monitor with a 120-Hz refresh rate ($8.\overline{33}$ ms/refresh cycle) positioned ~57 cm in front of the participants. For *experiment 1*, the target was a full and filled black circle ~2 dva in diameter presented against a light gray background. This created a high target-to-background contrast (luminance: black target, ~0.3 cd/m^2; gray background, ~137 cd/m^2), which has been shown to enhance SLR expression (4). Conversely, in *experiment 2* we used high-contrast (~0.3 cd/m^2) and low-contrast targets, which were both full filled circles ~2 dva in diameter. For each participant, the low-contrast target luminance was customized to visual acuity (see below for details). On average, the low-contrast stimulus luminance was ~119.7 cd/m^2. The luminance was measured with a colorimeter (Cambridge Research System ColorCAL MKII). A photodiode

was attached to the left bottom corner of the monitor to detect a secondary light that was presented coincidentally with the time of appearance of the real target. This allowed us to index the time point at which the stimulus was physically detectable, thus avoiding uncertainties in software execution and raster scanning of the monitor.

Experimental Design

Experiment 1: symbolic cue.

This experiment was designed to investigate the influence of cognitive expectations on express visuomotor responses. The participants were instructed to reach as fast as possible toward a visual target that appeared as a brief flash of a complete circle, features that facilitate SLRs (5, 23). The target location was unpredictable or partially predictable from the orientation of a symbolic arrow-shaped cue (Fig. 1). The stimuli were presented via an emerging target paradigm (Fig. 1) that has proven effective for facilitating the SLR expression in >80% of participants tested with surface electromyogram (sEMG) electrodes (5) and that was motivated by preceding

SLR (24) and oculomotor studies (for review see Ref. 25). To start the trial, the participants aligned their right hand and gaze for 1 s on a fixation spot ("+" sign) located in the center of the screen and below the visual barrier (~9 dva of fixation-target eccentricity). After the fixation period, the central fixation spot could remain unchanged (neutral cue, control condition) or change to an arrow pointing to the future location of the target (valid cue, 75% of cue trials) or in the wrong direction (invalid cue, 25% of cue trials). Note that the physical position of the cue was irrelevant with respect to the future target locations. At ~700 ms after the cue presentation, the target moved downward at constant velocity (~35 dva/s) toward the visual barrier for ~160 ms and always reemerged ("go" signal) below it after ~640 ms from the onset of its movement (i.e., predictably timed stimulus). Therefore, the target was occluded by the barrier for ~480 ms and reemerged after ~1.34 s from the cue presentation (Fig. 1). We decided to use a CTOA of >1 s in order to ensure unambiguous cognitive extrapolation of the arrow orientation. Note that the temporal event timings have been
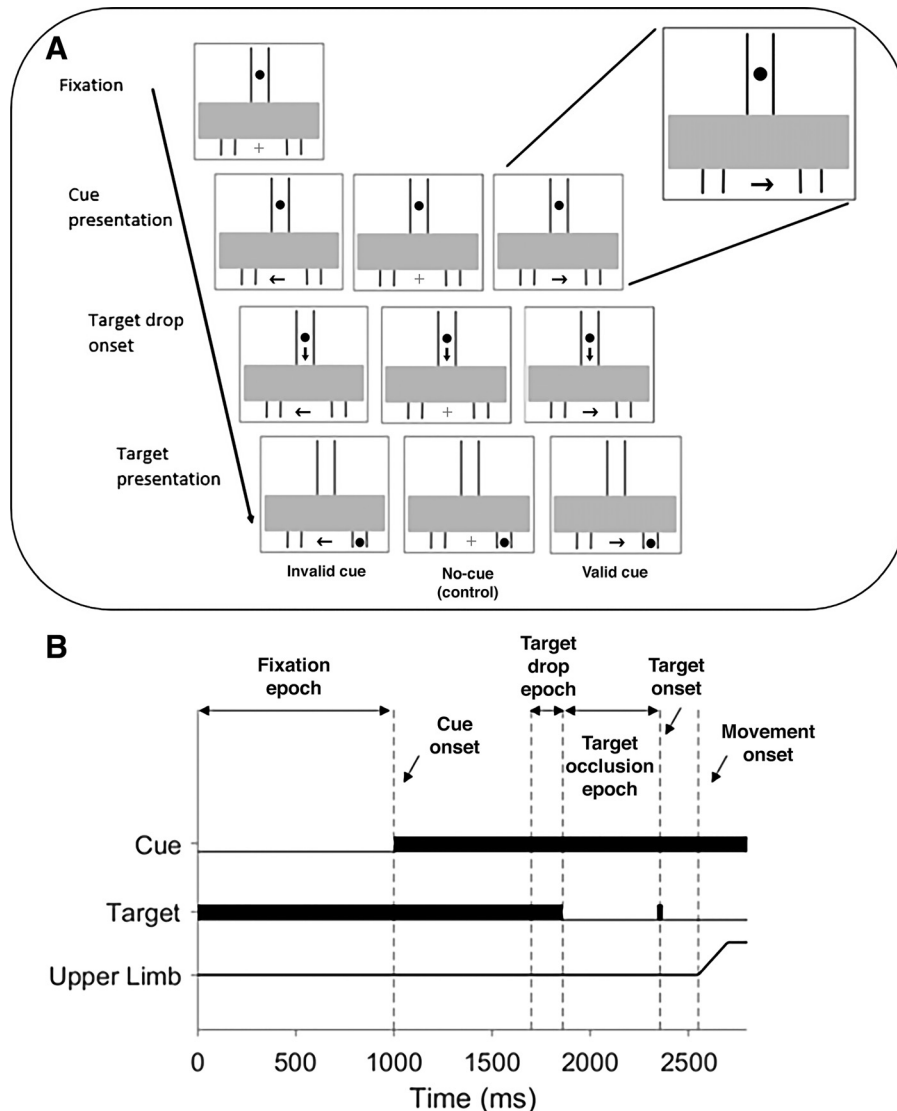

Figure 1. A: timeline of no-cue (control) and valid and invalid cue conditions of experiment 1. A zoomed view of the symbolic arrow-shaped cue is shown at top right. In these examples the target appears to the right, so the right column of panels shows the temporal events for a valid cue trial, whereas the left column of panels shows the temporal events for an invalid cue trial. B: schematic diagram of temporal events in the cue conditions. After 1 s of fixation, the central cross bar for fixation remained unchanged in the control condition, whereas it was substituted by an arrow cue pointing toward the exact future location of the target (valid cue, 75% of cue trials) or in the wrong direction (invalid cue, 25% of cue trials). After ~700 ms from cue presentation, the target started moving downward from the stem of the track at constant velocity of ~35 dva/s until it passed behind the barrier (occlusion epoch) for ~480 ms and reappeared underneath it at ~640 ms from the onset of its movement. The target appeared transiently by making 1 single flash of ~8-ms duration.

adjusted by rounding the values to the nearest ten milliseconds (full monitor scanning occurred every $8.\overline{33}$ ms, see *Apparatus*).

On each trial, gaze-on-fixation was checked online with an EyeLink 1000 Plus tower-mounted eye tracker device (SR Research Ltd., Ottawa, ON, Canada) at a sampling rate of 1,000 Hz. If the fixation requirement was not met, participants received an error message and the trial was repeated. Each participant completed 10 blocks of 72 reaches/block (36 for each direction), with each block consisting of 46 valid, 16 invalid, and 10 neutral cues, randomly intermingled.

Experiment 2: low-contrast cue.

In this experiment, we aimed to investigate whether the SLR is modified by spatially cuing the target location with barely detectable cues. For each participant, we initially set the target luminance threshold for stimulus detection as a function of visual acuity via an adaptive (staircase) procedure (26). The task was the same as the control conditions in *experiment 1*, but the circle started moving downward immediately after 1 s of fixation (Fig. 2) and the luminance of the target flashing underneath the barrier was changed trial by trial depending on preceding response. Specifically, we generated an array of 22 logarithmic scaled steps of luminance ranging from high-contrast target luminance ($\sim$0.3 cd/m^2) to background luminance ($\sim$137 cd/m^2). The participants were required to reach toward the first target flash they perceived below the barrier as soon as possible and to guess the target location by moving arbitrarily right or left if nothing was perceived. If the movement direction was correct (see below), then the target luminance was made dimmer (i.e., closer to background color) by selecting the next luminance level in the array (i.e., 1 step up). By contrast, if the movement was incorrect, the target luminance was made four times darker than the last flashed target (i.e., 4 steps down in the array; this only happened when the target was at least 5 steps dimmer than the high-contrast target). No-movement trials were also classified as incorrect movements. Furthermore, random jumps of target luminance were used in order to avoid trial-by-trial dependencies (26). The staircase procedure was terminated after 10 reversals (i.e., wrong reach made after a correct response) of the target luminance, which occurred on average after $\sim$65 trials. The final low-contrast stimulus used in *experiment 2* (Fig. 2) had the average luminance used in the 10 trials before the last reversal, corresponding to correct stimulus detectability on $\sim$80% of presentation as per the "1 up/4 down" staircase approach (26).

For the main experiment, we used four unique target conditions: *1*) high-contrast (control) target appearing alone underneath the barrier; *2*) low-contrast target appearing alone underneath the barrier; *3*) low-contrast cue appearing at the location of the high-contrast target (valid cue); *4*) low-contrast cue appearing at the opposite location of the high-contrast target (invalid cue). In the cue conditions, the high-contrast target was validly or invalidly cued with equal probability (i.e., 50% cue validity). The low-contrast cue appeared three frames ($\sim$24 ms) before the high-contrast target, by making a single flash of $\sim$8-ms duration (Fig. 2). Importantly, the dim luminance, short CTOA, and irrelevant validity (50%) of the low-contrast cues were designed to minimize the involvement of cortical networks in cue processing. We presented the low-contrast cue at locations that were relevant to the possible target locations in order to facilitate target-related responses (1), potentially via a spatial selection benefit mechanism (27). The brief $\sim$24-ms CTOA was chosen to facilitate cue-target integration and avoid inhibition of return. Specifically, cue-target integration is proposed to facilitate the target processing because of temporal-spatial contiguity between cue and target (28). By contrast, inhibition of return is a phenomenon known to reverse the cue-induced facilitation effects (1) if the target is presented >200 ms after the peripheral cue (Ref. 29, for review see Ref. 17). On each trial, the target that moved toward the barrier was always a full and filled black circle, thus making it impossible for the participants to predict the target condition from trial context. The participants were instructed to reach as fast as possible toward the first perceived target flash underneath the barrier and to guess the target location by reaching arbitrarily right or left if no stimulus was detected. They completed 10 blocks of 64 reaches/block, with each block consisting of 16 trials of each of the four different target conditions, randomly intermingled.

Data Recording

Surface EMG (sEMG) activity was recorded from the clavicular head of the right pectoralis muscle (PMch) and the posterior head of the right deltoid muscle (PD) with double-differential surface electrodes (Bagnoli-8 system; Delsys Inc., Boston, MA). The quality of the signal was checked with an oscilloscope before the start of recording. The sEMG signals were amplified by 1,000, filtered with a 20- to 450-Hz-bandwidth filter by the native Delsys Bagnoli-8 Main Amplifier Unit, and full-wave rectified after digitization without further filtering. Arm motion was monitored by a three-axis accelerometer (Dytran Instruments, Chatsworth, CA). The sEMG and kinematic data were sampled at 2 kHz with a 16-bit analog-digital converter (USB-6343-BNC DAQ device; National Instruments, Austin, TX). Data synchronization was guaranteed by starting the recording of the entire data set at the frame at which the target started moving toward the barrier.

Reaction time (RT) was monitored by running a cumulative sum analysis (30) on the acceleration signal, as described by Contemori et al. (5). To minimize the occurrence of anticipatory responses, we monitored the RT online and sent an error message if the participants moved before the target onset time or responded in <130 ms from target presentation ($\sim$3 trials/block). This RT cutoff was adopted because 130 ms has been recently shown to be the critical time to prepare a target-directed response (31). Furthermore, the initiation of a movement requires agonist muscle activation and antagonist muscle inhibition to generate enough net joint torque to overcome limb inertia and produce angular acceleration at the joint. If a target-directed movement occurs faster than 130 ms, the potential short-latency sEMG response occurring in the SLR epoch (i.e., 80–120 ms from target onset) could be contaminated by an anticipatory voluntary response. This would make it impossible to distinguish the SLR from the muscle activity that is time-locked with the voluntary movement initiation. To further reduce
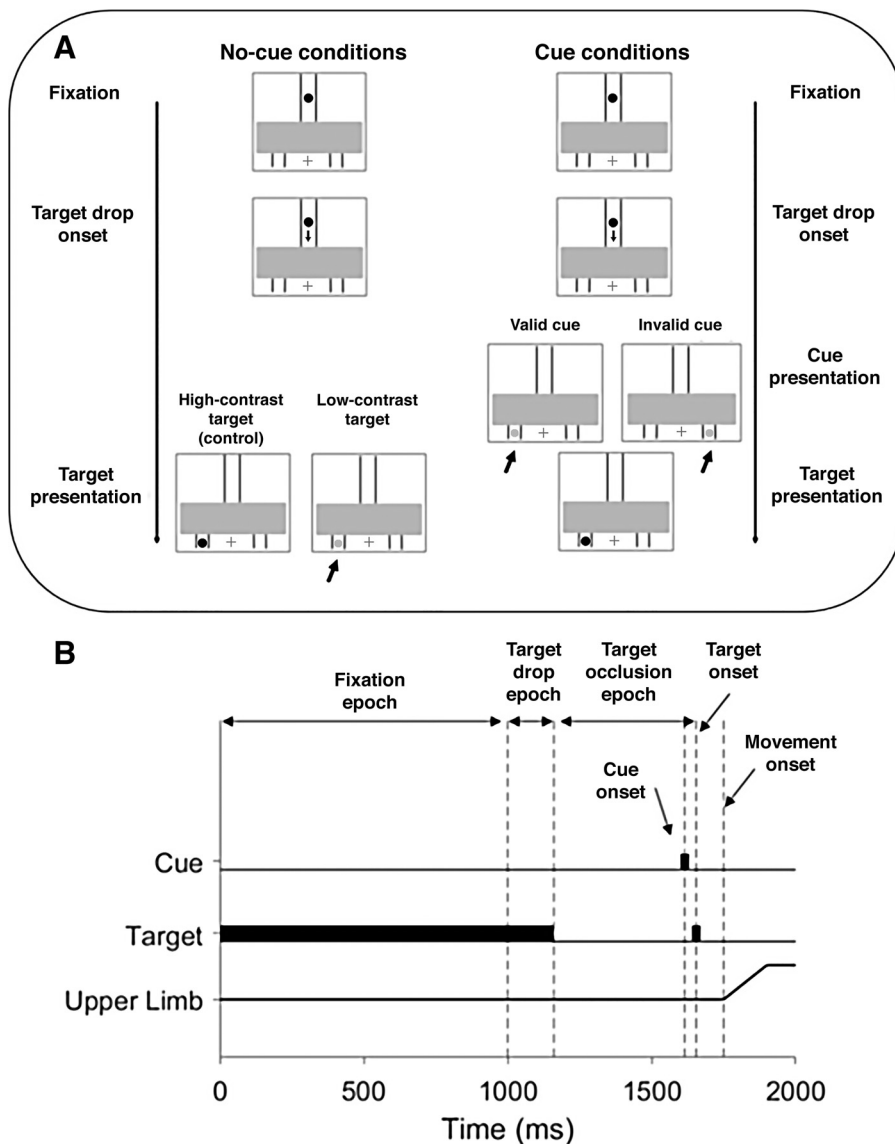
Figure 2. *A*: timeline of high-contrast (control condition) target, low-contrast (dim gray dot) target, valid cue, and invalid cue conditions of *experiment 2* (arrows indicate the low-contrast stimulus position). In these examples the high-contrast target appears to the *left*, so the valid cue condition is satisfied when the low-contrast stimulus (dim gray dot) appears to the *left*, whereas it appears to the *right* in the invalid cue condition. The low-contrast cue appeared with equal probability at the same (valid cue) or opposite (invalid cue) location of the ensuing high-contrast target (i.e., 50% cue validity). *B*: schematic diagram of temporal events in the cue conditions. After 1 s of fixation at the central cross bar, the target started moving downward from the stem of the track at constant velocity of ∼35 dva/s until it passed behind the barrier (occlusion epoch) for ∼480 ms. The low-contrast cue appeared after ∼616 ms from the trial start and stayed on for ∼8 ms. The high-contrast target reemerged transiently (1 single flash of ∼8-ms duration) underneath the barrier after ∼640 ms from the trial start. Therefore, the temporal gap between the low-contrast cue and the high-contrast target was ∼24 ms.

this risk, we adopted a more conservative RT cutoff for offline data analysis, by excluding trials with RT < 140 ms (∼7% of the trials). We also excluded trials with RT > 500 ms (<1% of the trials) as indicative of inattentiveness.

The accelerometer signal also allowed us to identify correct and wrong responses. Specifically, we searched for the first peak/valley of acceleration subsequent to the RT index to define the initial movement direction. We then compared the movement direction with the target location. If the target location did not correspond with the movement direction, the trial was classified as incorrect and discarded (see RESULTS). This analysis was run online for the staircase procedure adopted in *experiment 2* to customize the low-contrast target luminance on each participant's visual acuity (see above).

Data Analysis

Indexing the presence, timing, and magnitude of SLRs.

The presence of a candidate SLR was identified with a time series receiver operator characteristic (ROC) analysis. This

analysis allowed us to index the point in time at which the location of the target could be discriminated [discrimination time (DT)] from the sEMG trace (3).

We first tested whether the muscle response initiation covaried with the RT. Specifically, for every muscle sample and tested condition not showing anticipatory activity (for details see Ref. 5), we sorted the correct trials according to RT and subdivided the sEMG trials into two equally sized trial sets by doing a median split on the RT data (Fig. 3, *A* and *D*). We then ran separate ROC analyses on the fastest 50% (fast trial set) and the slowest 50% (slow trial set) of the trials, and we calculated the area under the ROC curve (AUC) for both fast and slow trial sets. The AUC values range from 0 to 1, where a value of 0.5 indicates chance discrimination and a value of 1 or 0 indicates perfectly correct or incorrect discrimination, respectively. We set the thresholds for discrimination at 0.65 (Fig. 3, *B* and *E*); this criterion exceeds the 95% confidence intervals of data randomly shuffled with a bootstrap procedure. The time of earliest discrimination was defined as the time after stimulus onset at which the
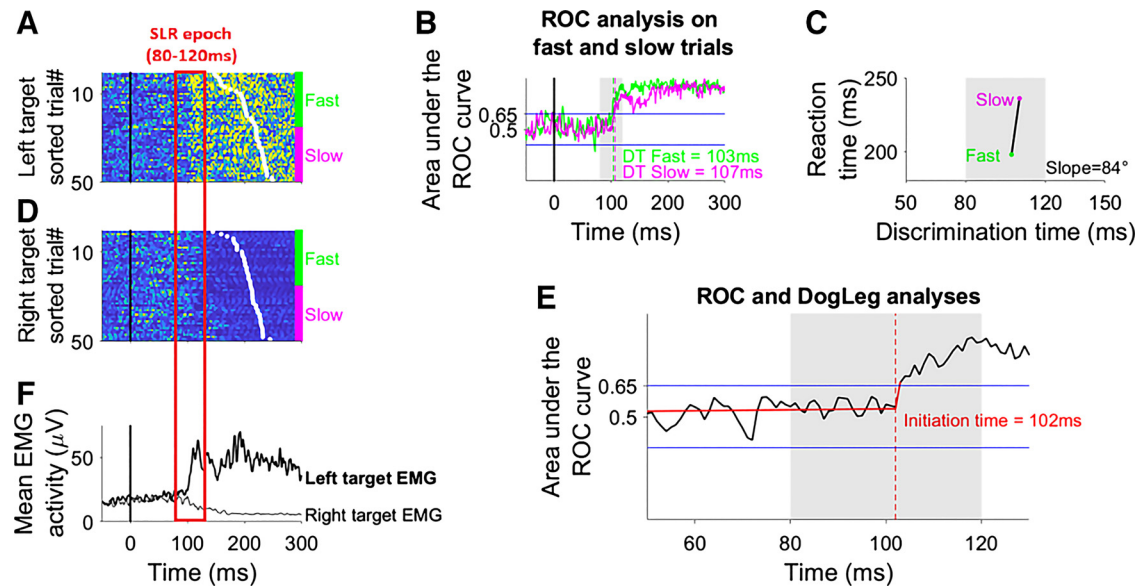
Figure 3. Exemplar surface electromyogram (sEMG) activity from the clavicular head of pectoralis major of a participant who exhibited a stimulus-locked response (SLR) in the control condition of *experiment 1* (*participant 8*, Table 1). *A*, *D*, and *F*: the muscle acts as agonist and antagonist for left (*A*) and right (*D*) targets, respectively. Rasters of rectified surface sEMG activity from individual trials are shown (darker yellow colors indicate greater sEMG activity; *A* and *D*) as are the traces of the mean sEMG activity (*F*; thick line = left target EMG; thin line = right target EMG). Data are aligned on visual target presentation (solid black vertical line at *time 0*) and sorted according to reaction time (white dots within the rasters).The open red rectangle indicates the time window in which an SLR is expected (80–120 ms from target onset).The SLR appears as a column of either rapid muscle activation (*A*) or inhibition (*D*) time-locked to the stimulus onset in both the fastest 50% (green bar) and the slowest 50% (magenta bar) of the trials. *B*: receiver operator characteristic (ROC) analysis showing the point in time at which the target location can be discriminated [discrimination time (DT)] from muscle activity for the fast (green line) and slow (magenta line) sets of trials. The DT is identified by the first time frame at which the area under the ROC curve surpasses the value of 0.65 (*top* blue line in *B*) and remains over this threshold for 15 ms (vertical dashed lines in *B*; see MATERIALS AND METHODS). The candidate SLR was identified if the target location was discriminated by the sEMG trace within the SLR epoch (gray patch) for both of the fast and slow trial sets. *C*: a line connecting the fast and slow DTs that are plotted for the slowest and fastest half of voluntary reaction times; the line slope is shown. For this participant, both the early and late DTs are inside the SLR epoch (gray patch) and the line slope exceeds 67.5°, thus indicating the presence of a visuomotor response that is more time-locked to the stimulus onset than to the reaction time. *E*: the initiation time (dashed red line) obtained by running the ROC analysis on the full set of trials and fitting a two-piece "DogLeg" linear regression on the ROC curve to determine the point in time at which the ROC curve started to deviate positively toward the discrimination threshold (intersection point between the red lines; see MATERIALS AND METHODS).

AUC overcame the defined threshold and remained above that threshold level for at least 15 ms. The candidate SLR was considered only if both fast and slow trial discrimination times were within 80–120 ms after target presentation (5, 6). To test whether or not the DT covaried with the RT, we associated the fast and slow DTs with the average RT of fast and slow data sets (4), and we fitted a line to the data to test if the DT did not covary with the RT (i.e., line slope >67.5°, Fig. 3C; for further details see Ref. 5). In this case, we ran the ROC analysis on all trials to determine the all-trials set DT (Fig. 3E). Finally, we defined the SLR initiation time by running a two-piece "DogLeg" linear regression analysis (32, 33) recently adopted by Contemori et al. (5) to index the point in time at which the time series ROC curve begins to deviate positively toward the 0.65 discrimination threshold (Fig. 3E). Importantly, this analysis allowed us to define the EMG response initiation time regardless of the slope of the ROC curve as it deviated toward the discrimination threshold (5).

To quantify the SLR amplitude, on each trial we measured the mean sEMG activity recorded in the 10 ms subsequent to the DT of the slow trial sets (5). This method allowed us to quantify the muscle activity enclosed in a short time window in which the earliest target-related EMG response had been identified (i.e., DT within 80–120 ms from target onset time) for both the fast and slow trial sets.

Cue-induced effect dimension.

In this study, we expected to observe cue-induced modifications of the volitional and express visuomotor responses relative to control conditions. This would indicate that cue information was encoded by some neural circuit to bias the ensuing target-related response. We quantified the RT and SLR (initiation time and magnitude) differences between control and cue conditions as both absolute and percentage changes from control conditions (Eq. 1):

$$\text{cue} - \text{induced increase } (\%) = \left[\frac{(Cv - CCv)}{Cv}\right] \times 100 \qquad (1)$$

where Cv represents the control value and CCv the cue condition value.

For the RT and SLR initiation time, we concluded that the cue exerted an advantaging effect if it led to shorter latencies than control (i.e., positive cue-induced percentage increase). By contrast, we concluded that the cue exerted a disadvantaging effect if it led to longer latencies than control conditions (i.e., negative cue-induced percentage increase). For the SLR magnitude, we inverted the order of members of the subtraction in Eq. 1: (Cv − CCv) → (CCv − Cv). This allowed us to index the cue-induced percentage increase as positive (i.e., cue advantage effect) if the SLR size was larger in cue than control conditions and negative (i.e., cue disadvantage

effect) if the SLR had a larger magnitude in control than cue conditions.

Statistical Analysis

Statistical analyses were performed in SPSS (IBM SPSS Statistics for Windows, version 25; SPSS Inc., Chicago, IL) and MATLAB (version R2018b; The MathWorks, Inc., Natick, MA). Results were analyzed with t test and repeated-measure ANOVA models as the normality of the distributions was verified by the Shapiro–Wilk test. When ANOVA revealed a significant main effect or interaction, we computed the partial eta squared (η_p^2) to estimate the effect size and ran paired sample t tests for post hoc comparisons.

The Pearson chi-square test with Bonferroni correction was run to analyze changes in SLR prevalence between predicable and unpredictable conditions. For correlation analyses, the Pearson coefficient (r) was computed to index the strength of association between variables. For all tests, statistical significance was designated at $P < 0.05$.

Formal within-participant statistical comparisons could not be conducted if SLRs occurred infrequently across the different target conditions. In this circumstance, we used a single-subject statistical analysis that aimed to test the reliability of the time series ROC analysis to compare different stimulus conditions at the single-subject level (5). Briefly, for each target condition we generated 1,000 bootstrapped data sets from the original set of trials. We then ran the ROC and DogLeg analyses on each bootstrapped data set to determine the distribution of SLR initiation time and magnitude. To test the statistical significance of the contrasts between the different target conditions, we compared one randomly resampled set of values from one target condition distribution with one randomly resampled set of values from the

other target condition distribution (i.e., 1,000 unique data comparisons for each of the 3 dependent variables). If the values for one target condition were larger or smaller than for the other target condition in >95% (i.e., >950) of cases, we concluded that the difference between the two target conditions was significant (for further details see the data supplement to Ref. 5).

RESULTS

Experiment 1: Symbolic Cue

Task performance.

The proportion of correct reaches toward the target differed among the different symbolic cue conditions (main effect of cue condition: $F_{2,15} = 20.3$, $P < 0.001$, $\eta_p^2 = 0.58$). The post hoc analysis revealed that the prevalence of correct reaches was significantly lower in the invalid cue condition (78.3 ± 16.1%) than in the control (94.9 ± 4.5%; $t = 4.6$, $P < 0.001$) and valid cue (96.4 ± 2.8%; $t = 4.5$, $P < 0.001$) conditions, whereas no significant difference was observed between the neutral and valid cue conditions. The fact that the highest error rate was observed with invalid cues suggests that the participants were biased to move toward the cued location. However, in the majority of invalid cue trials they correctly used the target spatial information to orient the final visuomotor response.

Reaction time also differed significantly between symbolic cue conditions (main effect of cue condition: $F_{2,15} = 27.6$, $P < 0.001$, $\eta_p^2 = 0.65$). The post hoc analysis showed significantly shorter RTs for valid than control cue conditions and significantly longer RTs with invalid than other cue conditions (Fig. 4A). Furthermore, validly cuing the target led to significantly positive percentage differences relative to control
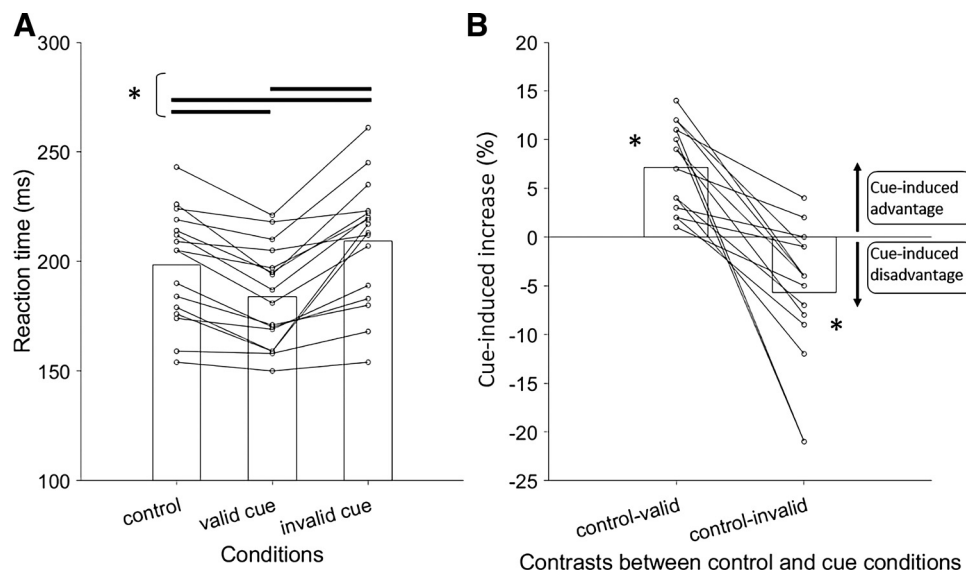

Figure 4. *A*: the latency of correct reaches in the control (198 ± 25 ms), valid (184 ± 23 ms), and invalid (209 ± 28 ms) cue conditions of *experiment 1* (see MATERIALS AND METHODS; data are reported as means ± SD). The reaction time was significantly shorter for valid than control cue conditions (*$P < 0.001$) and significantly longer with invalid than other cue conditions (control vs. invalid, *$P = 0.003$; valid vs. invalid, *$P < 0.001$). *B*: the percentage increase relative to control conditions induced by validly (7 ± 4.4%) or invalidly (−5.6 ± 7.3%) cuing the target location with the arrow-shaped symbolic cues (see MATERIALS AND METHODS). Positive increment means that cuing the target location advantaged the volitional movement initiation, whereas negative increment indicates disadvantaging cue-induced effects on reaction time. The cue-induced percentage increase was significantly positive with valid cues (*$P < 0.001$) and significantly negative with invalid cues (*$P = 0.004$). Each black line represents 1 participant, and the bars represent the mean values.

Table 1. *Occurrences of positive SLRs in PMch and PD across participants in all 3 cue conditions tested in experiment 1*

Participant	Control		Valid		Invalid	
	PMch	PD	PMch	PD	PMch	PD
1	✓	✓	✓	✓	✓	
2	✓		✓		✓	
3			✓			
4	✓		✓			
5	✓		✓	✓		
6			-			
7	✓		✓			
8	✓		✓		✓	
9	✓		✓			
10	✓	✓	✓	✓	✓	
11						
12	✓		✓		✓	
13			✓			
14	✓		✓			
15	✓		✓			
16	✓		✓		✓	
Total SLRs (*n*)	12	2	14	3	6	0
SLR prevalence (%)	75	12.5	87.5	18.75	37.5	0

Occurrences of positive stimulus-locked responses (SLRs; ✓) in the clavicular head of the pectoralis major muscle (PMch) and the posterior deltoid (PD) across participants in all 3 cue conditions tested in *experiment 1.*

conditions (Fig. 4*B*), whereas significantly negative cue-induced percentage increments resulted from invalidly cuing the target (Fig. 4*B*). These findings indicate that the participants used the cue information to improve their task performance.

Identified SLRs.

To be classified as an SLR, the target location had to be discriminated from the sEMG signal within 80–120 ms after the stimulus presentation in both fast and slow trial sets without, or with minimal, covariation with the volitional RT (see MATERIALS AND METHODS). For the PMch, the conditions for positive SLR detection were satisfied in both control and valid cue conditions in 12 of 16 participants, but only 6 of them also expressed an SLR in the invalid cue condition and 2 participants did not express any SLR (Table 1). Notably, the valid cue condition promoted SLR generation among two participants who were otherwise negative SLR producers in the other task conditions (i.e., *participants 3* and *13*; Table 1). These observations resulted in significantly lower SLR prevalence for invalid cues than for control (chi-square test; *P* = 0.033, chi-square = 4.6, df = 1) and valid cue conditions (chi-square test; *P* = 0.003, chi-square = 8.5, df = 1). Notably, the high SLR prevalence in the control cue condition is consistent with recent studies (5, 24) that used similar versions of the emerging target paradigm described here. This confirms the effectiveness of the paradigm for eliciting SLRs.

The fact that many fewer SLRs were observed for the PD (Table 1) is consistent with the effects of isolated shoulder transverse extensor muscle preloading, which enhances the pretarget activity of the PMch but not that of the PD (5). Given the low occurrence of SLRs for the PD, only the PMch was considered for statistical comparisons between the different cue conditions.

Cuing the target location influenced the timing and amplitude of SLRs. For the exemplar participant in Fig. 5, the sEMG signal started to deviate from baseline 87 ms after target presentation for the valid cue condition and at 95 ms for the neutral cue condition (Fig. 5*C*). For the invalid cue condition, the muscle started to encode the target location at 121 ms from its presentation and, therefore, after the SLR epoch (Fig. 5*C*). Furthermore, SLR magnitude was larger for the valid (76 μV) than neutral (55 μV) cue conditions. Therefore, the valid cue condition led to positive percentage increase in SLR initiation time (8.4%) and magnitude (38.2%) relative to control conditions.

Similar trends were observed across the 12 participants who produced an SLR to the control and valid cue conditions (Table 1). The initiation time was significantly shorter, and the SLR magnitude significantly larger, in the valid than the control cue condition (Fig. 6, *A* and *C*). In addition, we observed significantly positive cue-induced percentage increase for both SLR initiation time and magnitude relative to the control condition (Fig. 6, *A* and *C, insets*). These results indicate a cue-induced SLR facilitation relative to control conditions when the target appeared at the expected location.

To complete the description of cue-induced effects on SLR expression, we ran a one-way repeated-measures ANOVA analysis with cue validity (3 levels: neutral, valid, invalid) as within-participant factor for the six participants who exhibited an SLR among all three cue conditions (Table 1). A significant cue validity main effect was found for initiation time ($F_{2,5}$ = 10.3, *P* = 0.004, η_p^2 = 0.67) and SLR magnitude ($F_{2,5}$ = 9.87, *P* = 0.026, η_p^2 = 0.52). For all six subjects the invalid cue conditions resulted in an increase in SLR latency and a decrease in SLR magnitude relative to the other cue conditions (Fig. 6, *B* and *D*), consistent with SLR inhibition effects when the expected and actual target locations were mismatched.

Experiment 2: Low-Contrast Cue

Task performance.

The occurrence of correct reaches was ~95% for control and valid low-contrast cue conditions, ~90% in the invalid low-contrast cue condition, and ~85% for the single low-contrast target condition. The one-way repeated-measures ANOVA analysis showed a main effect for task condition ($F_{2,11}$ = 4.9, *P* = 0.007, η_p^2 = 0.31). The post hoc analysis evidenced a significantly lower correct response rate for the low-contrast target than the control (paired *t* test: *t* = 4.3, *P* = 0.001) and valid cue (paired *t* test: *t* = −3.7, *P* = 0.003) conditions, whereas no significant difference was observed between the invalid cue and other task conditions. These results suggest that target detection was impaired, but not fully obliterated, by the presentation of stimuli that were around the threshold for correct detection. Furthermore, the data indicate that participants moved correctly toward the high-contrast target even when it was preceded by the low-contrast cue at the opposite location.

A significant task condition main effect ($F_{2,15}$ = 27.6, *P* < 0.001, η_p^2 = 0.73) was found for RT. The RT was significantly longer in the low-contrast condition than in all of the other target conditions and significantly longer for the invalid cue
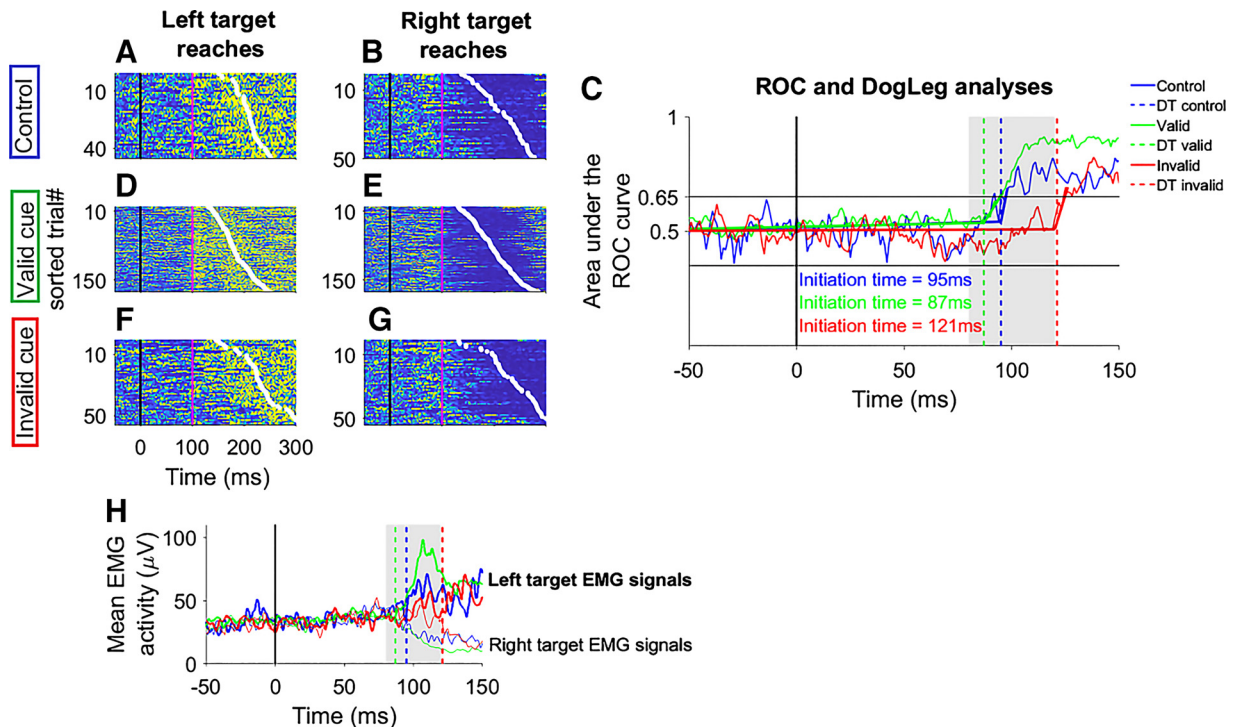
Figure 5. Surface electromyogram (sEMG) activity of the pectoralis major clavicular head muscle of an exemplar participant who completed *experiment 1* and exhibited a stimulus-locked response (SLR) in control and valid cue conditions but not in invalid cue condition (*participant 5*, Table 1). For each cue condition, rasters of rectified sEMG activity from individual trials are shown (*A, B, D–G*; same format as Fig. 2). The solid magenta line indicates the expected initiation time of the SLR (~100 ms from target onset). *H*: a zoomed view of the mean sEMG activity (thick lines = left target reaches; thin lines = right target reaches); the vertical dashed lines show the initiation time of the target-related muscle response. The initiation time was indexed as the point in time at which the receiver operator characteristic (ROC) curve started to positively diverge toward the 0.65 discrimination threshold (see MATERIALS AND METHODS). *C*: a zoomed view of ROC and DogLeg analyses that were run to index the initiation time of the target-related EMG response. For this participant, the ROC curve starts to deviate earlier in valid (87 ms, intersection between the straight green lines) than control (95 ms, intersection between the straight blue lines) cue conditions and after the SLR epoch in the invalid cue condition (121 ms, intersection between the straight red lines). DT, discrimination time.

condition than the control and valid cue conditions (Fig. 7A). Furthermore, validly cuing the target led to significantly faster RTs than control conditions (Fig. 7A). The absolute cue-induced changes were consistent with the percentage cue-induced changes relative to control conditions (Fig. 7B). These findings indicate that the low-contrast stimulus biased the volitional reaching behavior despite its low saliency for movement initiation, its temporal proximity (~24 ms) to the high-contrast target, and its lack of predictive value (50% validity) for signaling the location of the high-contrast target.

Identified SLRs.

Experiment 2 was completed by 12 participants who also participated in *experiment 1*. In 10 of them we detected an SLR on the PMch muscle either when the high-contrast target appeared alone (control condition) or when it was validly cued by the low-contrast stimulus, but only 5 of them had an SLR also for the invalid cue condition (Table 2). The presentation of the low-contrast stimulus alone elicited an SLR in only two participants, who also had an SLR in the control and valid cue conditions but not in the invalid cue condition (see *participants 1* and *3* in Table 2). Finally, two participants did not exhibit any SLR (i.e., *participants 4* and *8*, Table 2). Akin to *experiment 1*, a sufficient number of SLRs for

statistical comparisons between the target conditions was obtained only for the PMch muscle (Table 2).

Given that the same 10 participants expressed an SLR to control and valid cue conditions (i.e., *participants 1–3*, *5–7*, and *9–12*, Table 2), we only considered the control condition to test whether the SLR prevalence was significantly different across conditions. The chi-square test returned a significantly higher ($P < 0.05$) SLR prevalence for control than both low-contrast target ($P = 0.001$, chi-square = 10.7, df = 1) and invalid cue ($P = 0.035$, chi-square = 4.4, df = 1) conditions. This suggests that the low-contrast target was a less salient stimulus for SLR generation than the high-contrast target. Furthermore, cuing the high-contrast target with an invalid low-contrast cue impaired, but did not completely obliterate, the SLR expression.

Figure 8 shows the results of one exemplar participant who participated in *experiment 2* (i.e., *participant 12*, Table 2). For this participant, the ROC curve started to deviate from chance earlier for the valid (81 ms; Fig. 8I) and later for the invalid (110 ms; Fig. 8L) cue relative to control conditions (97 ms; Fig. 8C). By contrast, in the low-contrast target condition the sEMG signal started to encode the location in 130 ms after the stimulus presentation (Fig. 8F), thus after the SLR epoch (i.e., 80–120 ms after stimulus onset time). The size of the SLR was similar between the high-contrast target (28 μV)
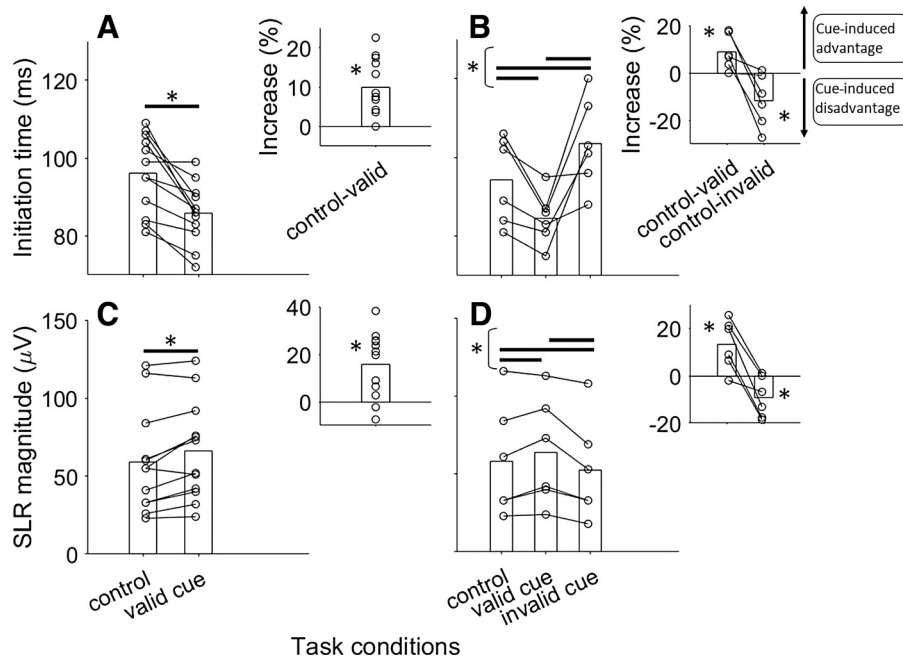
Figure 6. Latencies and magnitude of the express visuomotor responses in *experiment 1*. *A* and *C*: the results from 12 participants who exhibited a stimulus-locked response (SLR) in control (initiation time, 96 ± 10 ms; magnitude, 59 ± 33 µV; data are reported as means ± SD) and valid (initiation time, 86 ± 8 ms; magnitude, 66 ± 32 µV) cue conditions (see Table 1). *Insets*: the percentage increase induced by validly cuing the target location relative to control conditions (initiation time, 9.8 ± 7.5%; magnitude, 15.8 ± 13.9%). *B* and *D*: the results of 6 participants who exhibited an SLR in control (initiation time, 94 ± 11 ms; magnitude, 58 ± 38 µV), valid (initiation time, 84 ± 7 ms; magnitude, 64 ± 34 µV), and invalid (initiation time, 104 ± 11 ms; magnitude, 52 ± 33 µV) cue conditions (see Table 1). *Insets*: the percentage increase induced by validly (initiation time, 8.9 ± 7.3%; magnitude, 13.3 ± 10.5%) and invalidly (initiation time, −11.6 ± 11%; magnitude, −9.1 ± 8.6%) cuing the target location relative to control conditions. Positive cue-induced increase means that cuing the target location advantaged the SLR expression, whereas negative increase means disadvantaging cue-induced effects. Each black line represents 1 participant, and the bars represent the mean values. Validly cuing the target location with the symbolic arrow cue led to significantly (*$P < 0.01$) faster (*A*) and larger (*C*) SLRs than control conditions and to significantly positive (*$P < 0.01$) percentage increase relative to control conditions (*A* and *C*, insets). The SLRs were significantly (*$P < 0.05$) faster (*B*) and stronger (*D*) than control with valid cues and significantly (*$P < 0.05$) slower (*B*) and smaller (*D*) than control with invalid cues. Moreover, validly cuing the target location led to significantly (*$P < 0.05$) positive percentage increase relative to control conditions, whereas significantly (*$P < 0.05$) negative cue-induced percentage increase resulted from invalid cues (*B* and *D*, insets).

and valid cue (25 µV) conditions, whereas a smaller SLR magnitude was observed for the invalid cue condition (16 µV).

Similar trends were observed across the 10 participants who expressed an SLR in control and valid cue conditions (Table 2). More precisely, the SLR initiation time was significantly earlier for the valid (∼81 ± 2 ms) cue than control (∼90 ± 5 ms) conditions (Fig. 9A). Furthermore, we observed a significantly positive cue-induced percentage increase of the initiation time relative to the control condition (Fig. 9A, inset). By contrast, no significant difference was found between the valid cue and control conditions for the SLR magnitude (Fig. 9C). These results suggest that the SLR latency can be shortened by the presentation of a low-contrast stimulus appearing shortly in advance of, and at the same location as, a high-contrast target.

The exemplar participant's results (Fig. 8) were also consistent across the five participants who exhibited an SLR in the high-contrast, valid cue, and invalid cue conditions (i.e., participants 2, 5, 7, 11, and 12, Table 2). For these participants, we observed a significant task condition main effect for the initiation time ($F_{2,4}$ = 6.9, P = 0.018, η_p^2 = 0.63) but not for the SLR magnitude ($F_{2,4}$ = 1.89, P = 0.213, η_p^2 = 0.32). Post hoc analysis showed significantly faster SLRs with the valid than the invalid cue condition (Fig. 9B). The SLR latency was also ∼10 ms shorter in the control than the invalid cue

condition (Fig. 9B), but this difference was not statistically significant. Invalid low-contrast cues led to negative percentage changes of SLR timing (Fig. 9B, inset) and magnitude (Fig. 9D, inset) relative to control conditions that were not statistically significant. The absence of statistical significance, however, does not provide strong evidence that no effect exists, given the small sample size available for this analysis. In combination with the low prevalence of SLR activity in the invalid cue condition (41.7%, Table 2), the data strongly suggest that cuing the location of high-contrast targets with barely detectable cues can modulate the SLR expression according to the compatibility between the expected and actual stimulus positions.

In Fig. 10 are shown the data of one participant (S1) who produced an SLR in control, low-contrast target, and valid cue conditions but not in the invalid cue condition (i.e., participant 1, Table 2). A similar SLR distribution was observed in only one other participant (S2) of *experiment 2* (i.e., participant 3, Table 2). The results of these subjects are reported in Table 3. For these subjects, we ran a single-participant statistical analysis (see MATERIALS AND METHODS; Ref. 5).

For both participants, the initiation time was significantly shorter ($P < 0.05$) with the valid cue condition than other conditions and significantly longer than control with the low-contrast target condition. The SLR magnitude was
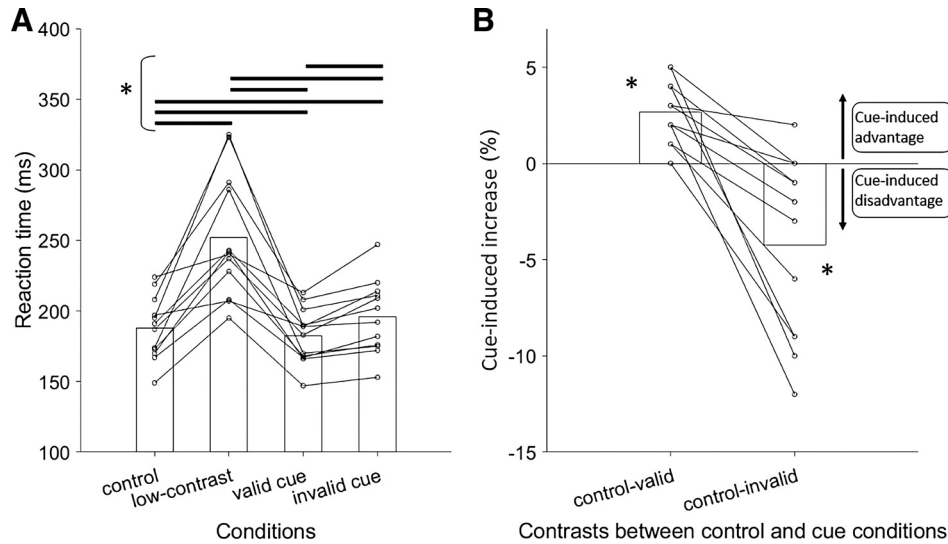
Figure 7. *A*: latency of correct reaches toward high-contrast targets (control condition; 188 ± 22 ms), low-contrast targets (252 ± 44 ms), and high-contrast targets cued by low-contrast stimuli appearing at the same (valid cue; 183 ± 20 ms) or opposite (invalid cue; 196 ± 26 ms) location (data are reported as means ± SD). The reaction time was significantly longer in the low-contrast condition than in all of the other target conditions (control vs. low contrast, *P < 0.001; low contrast vs. valid, *P < 0.001; low contrast vs. invalid, *P < 0.001), significantly longer for the invalid cue condition than the control (*P = 0.005) and valid cue (*P < 0.001) conditions, and significantly shorter for the valid cue condition than the control condition (*P < 0.001). *B*: the percentage increase relative to control conditions induced by validly (2.7 ± 1.5%) or invalidly (−4.2 ± 4.6%) cuing the target location with the low-contrast cues (same format as Fig. 4). Significantly positive cue-induced increase was observed with valid cues (*P < 0.001), whereas the negative cue conditions led to negative cue-induced percentage increase relative to the control conditions (*P = 0.004). Each black line represents 1 participant, and the bars represent the mean values.

significantly larger (*P* < 0.05) with the valid cue than the low-contrast target condition. The size of the SLR was also larger in the control than the low-contrast target condition, but this difference was statistically significant (P < 0.05) only for *S1*. These results indicate that some participants are capable of producing SLRs to both high-contrast and low-contrast stimuli. However, low-contrast targets have less saliency for the generation of rapid and large SLRs compared with high-contrast targets.

Table 2. *Occurrences of positive SLRs in PMch and PD across participants in all 4 task conditions tested in experiment 2*

Participant	Control		Low-Contrast		Valid		Invalid	
	PMch	PD	PMch	PD	PMch	PD	PMch	PD
1	✓		✓		✓			
2	✓				✓		✓	
3	✓		✓		✓			
4								
5	✓				✓		✓	
6	✓				✓		-	
7	✓	✓			✓	✓	✓	
8								
9	✓				✓			
10	✓				✓			
11	✓				✓		✓	
12	✓				✓		✓	
Total SLRs (n)	10	1	2	0	10	1	5	0
SLR prevalence, %	83.3	8.3	16.7	0	83.3	8.3	41.7	0

Occurrences of positive stimulus-locked responses (SLRs; ✓) in the clavicular head of the pectoralis major muscle (PMch) and the posterior deltoid (PD) across participants in all 4 task conditions tested in *experiment 2*. *Participants 1–12* correspond to participants *8, 7, 1, 11, 9, 4, 10, 15, 12, 14, 5,* and *13,* respectively, in Table 1.

In Fig. 10*J*, short-latency responses can be observed at ∼100 ms in the invalid cue trials before the muscle started responding to the high-contrast target (arrow in Fig. 10*J*). This reflects the erroneous activation/inhibition of the PMch and underlies the negative deflection below 0.5 chance level of the ROC curve within the SLR epoch (arrow inside the gray patch in Fig. 10, *K* and *L*). Some express motor signals encoding the low-contrast cue location appear to have been delivered to the muscles. Such express visuomotor responses to a barely detectable stimulus might then be rapidly overridden by a response to a more salient target, at least when both visual events occur within a short temporal interval. This hypothesis remains tentative, however, because this phenomenon was observed in only one participant.

DISCUSSION

Experiment 1: Symbolic Cue

The reaching task in this study required rapid identification of the target location relative to hand position in order to program the reaching direction and associated coordination between the agonist/antagonist muscles. The arrow-shaped cue provided symbolic information regarding the future target location, but its physical location was uninformative, as it appeared midway between the two possible target locations (Fig. 1*A*). That is, the target position could be predicted only by interpreting the arrow orientation. When this information was valid, the RT was shorter than in control conditions. However, this cue-induced benefit turned into a behavioral cost (i.e., delaying RT) when the cue was invalid. These observations are consistent with an overt attention orientation mechanism (1) that reflects cortical perception about the expected task.
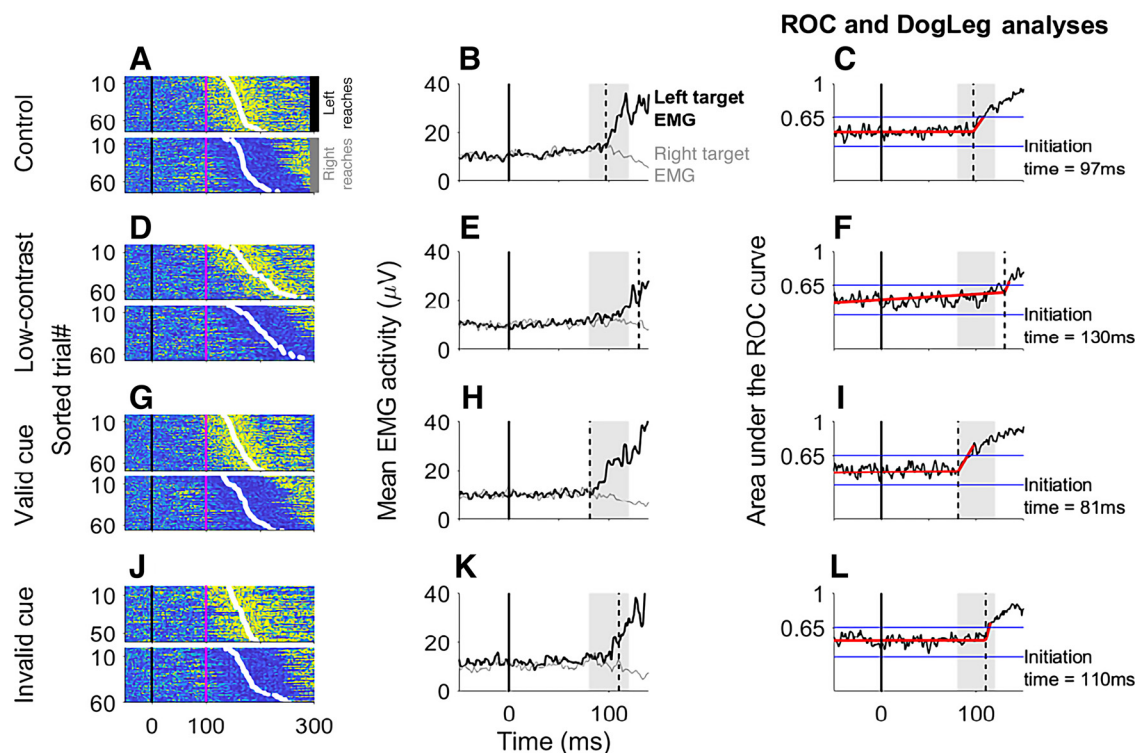
Figure 8. *A*, *D*, *G*, and *J*: surface electromyogram (sEMG) activity of the pectoralis major clavicular head muscle of an exemplar participant who completed *experiment 2* and exhibited a stimulus-locked response (SLR) in control (*A*), valid (*G*), and invalid (*J*) cue conditions but not in low-contrast target condition (*D*) (*participant 12*, Table 2). For each condition, rasters of rectified sEMG activity from individual trials are shown (same format as Fig. 5). *B*, *E*, *H*, and *K*: zoomed views of the mean sEMG activity; the vertical dashed lines show the initiation time of the target-related muscle response (see MATERIALS AND METHODS; same format as Fig. 5). *C*, *F*, *I*, and *L*: for this participant, the receiver operator characteristic (ROC) curve starts to deviate at 97 ms in control (*C*), 81 ms in valid (*I*), and 110 ms in invalid (*L*) cue conditions, whereas the initiation time in the low-contrast target condition (*F*) was at 130 ms and thereby after the SLR epoch (gray patch).

In mammalian species, the neural networks involved in cortical attention orientation comprise complex feedback loops between prefrontal, parietal, and sensory cortices and thalamic, basal ganglia, and brain stem structures (for review see Refs. 18, 34). For instance, Moore and Armstrong (35) showed that microstimulation of the frontal eye field (FEF) enhanced neural activity of area V4 in monkeys. Furthermore, the enhanced activity in area V4 was restricted to visual neurons encoding the visual field corresponding to the saccade that could be triggered by the FEF neurons undergoing the stimulation procedure. This suggests a cortico-cortical modulation mechanism by which higher-level premotor and motor areas can modify the activity of sensory cortices, such as those deputed to the processing of visual information. The symbolic cue-induced RT advantages may underlie enhanced sensitivity of the cortical visual map encoding the cued location, consistent with an endogenous prioritization to sensory events occurring at the expected location. By contrast, the neural populations encoding the noncued locations could be disengaged by suppressing cortico-cortical feedback signals (18, 34). This may result in a longer time to override the cue-driven expectation and transform the unexpected stimulus in the corresponding target-directed reach, consistent with the increase of volitional RTs with the invalid symbolic cues.

The prior information obtained from the interpretation of the symbolic cue also influenced the temporal and magnitude components of the SLR. Specifically, validly cuing the target location reduced the SLR initiation time and enlarged the SLR amplitude compared with control conditions, whereas the opposite was observed with invalid symbolic cues. The SLR is the biomarker of a neural network that can rapidly generate muscle responses, which are computed in a hand-centric reference frame (36). We and others have proposed previously that this neural network may include the midbrain superior colliculus and its downstream connections with the brain stem reticular formation, which then projects to interneurons and motoneurons in the spinal cord (3–7, 23, 24, 36, 37). Thus, according to this proposal, sensorimotor transformation of visual events is not an exclusive duty of high-level cortical sensorimotor areas. Given that the symbolic cue required cognitive extrapolation, we propose that the cue-induced SLR modifications reflect a cortical top-down modulation of the putative subcortical SLR network, including the superior colliculus.

A possible contribution of the superior colliculus to SLR is supported by evidence of collicular involvement in the production of express saccades (10–12). Notably, the mechanisms behind the generation of express saccades are consistent with the low-level visual processing and rapid visuomotor transformation operated by the superior colliculus. Indeed, this phylogenetically old structure can encode the location of visual stimuli via a transient visual burst
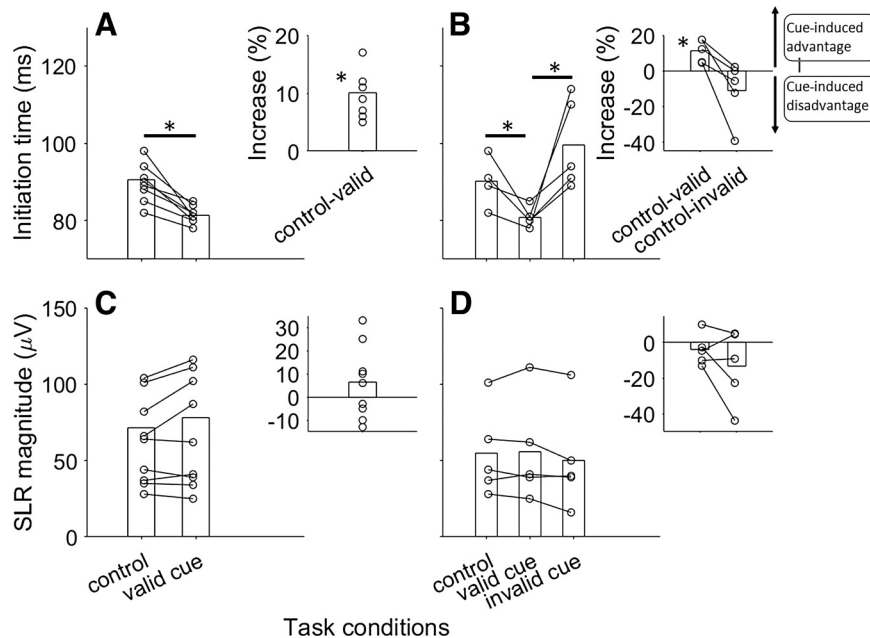
Figure 9. Latencies and magnitude of the express visuomotor responses in *experiment 2* (same format as Fig. 6). *A* and *C*: the results of 10 participants who exhibited a stimulus-locked response (SLR) in control (initiation time, 91 ± 5 ms; magnitude, 72 ± 40 µV; data are reported as means ± SD) and valid (initiation time, 81 ± 2 ms; magnitude, 78 ± 45 µV) cue conditions (see Table 2). *Insets*: the percentage increase induced by validly cuing the target location relative to control conditions (initiation time, 10.1 ± 0.5%; magnitude, 6.4 ± 14.8%). *B* and *D*: the results of 5 participants who exhibited an SLR in control (initiation time, 90 ± 6 ms; magnitude, 55 ± 29 µV), valid (initiation time, 81 ± 3 ms; magnitude, 56 ± 34 µV), and invalid (initiation time, 100 ± 11 ms; magnitude, 50 ± 34 µV) cue conditions (see Table 2). *Insets*: the percentage increase induced by validly (initiation time, 11.3 ± 6.4%; magnitude, −4.1 ± 8.9%) and invalidly (initiation time, −11 ± 16.8%; magnitude, −13.2 ± 20.6%) cuing the target location relative to control conditions. Validly cuing the target location with the low-contrast cue led to significantly faster SLRs than control condition (*A*, *P < 0.01; *B*, *P < 0.05) and to a significantly positive cue-induced percentage increase relative to control condition (*A*, inset, *P < 0.01; *B*, inset, *P < 0.05). Furthermore, valid low-contrast cues led to significantly (*P < 0.05) faster SLRs than invalid cue conditions (*B*).

starting within ∼40–70 ms from the stimulus presentation, regardless of its goal-related relevance (e.g., target vs. distractor stimulus; Ref. 38). This transient visual response is then transformed into a motor burst with a very short visual-to-motor phase lag, which justifies the striking rapidity (∼70–100 ms; Ref. 38) of target-directed express saccades.

The midbrain superior colliculus receives direct retinal inputs, but it is also mutually interconnected with cortical areas responsible for the cascade of neural operations that transforms visual events into motor actions (i.e., visual, parietal, and frontal cortices; Ref. 38). Peel et al. (39) reported activity decrements of the superior colliculus neurons when the frontal eye field (FEF) in monkeys was cryogenically inactivated. More recently, Dash et al. (40) showed that FEF inactivation correlated with reduced occurrence of express saccades relative to control conditions. Furthermore, behavioral studies have shown modulation of the express saccade vector as a function of explicit cue-driven instructions (19, 20). Critically, these findings indicate that the cortical top-down signals to the superior colliculus can modulate the express visuomotor transformations operated by this midbrain structure. Cortical signals affording explicit expectations (e.g., target location) may be conveyed to the superior colliculus and modulate its express visuomotor functions.

Selectively manipulating the activity of the topographically organized collicular visual map according to expected locations may increase the response to congruent sensory events and diminish the response to unexpected stimuli. For example, the presentation of temporally and spatially

predictable targets facilitates the initiation of target-directed saccades within the express range (∼100 ms; Refs. 8, 41). This suggests a contribution of cognitive expectation to the generation of express visuomotor responses. Moreover, expecting a stimulus to occur at a defined position correlates with inhibition of activity of the superior colliculus neurons encoding the locations distant from the saccadic goal (42). This suggests that rapid collicular visuomotor transformations are modulated as a function of the pretarget collicular activity, which can be biased by cortical top-down signals originating from expectations about future sensory events. This cortical top-down priming might underlie a top-down attention orienting mechanism to increase the saliency of expected stimuli on the collicular visual map and to inhibit the responses to unexpected targets (18). Notably, the cortical top-down SLR modulation hypothesis is consistent with recent evidence of SLR facilitation induced by temporal stimulus predictability and by briefly flashed stimuli, which activate both ON and OFF responses in superior colliculus (5). This neural mechanism may underlie the faster and larger SLRs observed when the target appeared in an expected location and the slower and smaller SLRs expressed with invalid cues relative to control conditions.

Experiment 2: Low-Contrast Cue

The use of low-contrast targets resulted in delayed RT and impaired SLR expression relative to control conditions. Only two participants exhibited an SLR for the low-contrast target
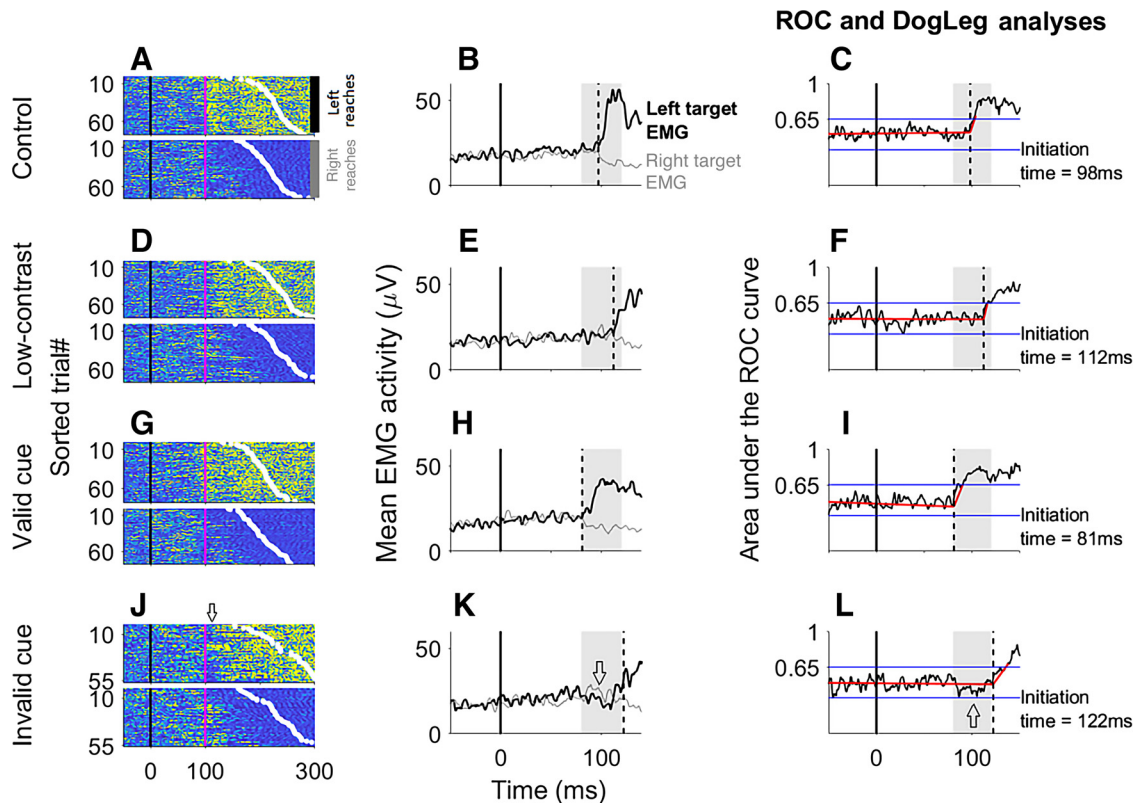
ROC and DogLeg analyses

Figure 10. Surface electromyogram (sEMG) activity of the pectoralis major clavicular head muscle of a participant who exhibited a stimulus-locked response (SLR) in control (*A*), low-contrast target (*D*), and valid (*G*) conditions but not in the invalid cue (*J*) condition (*participant 1*, Table 2). For each condition, rasters of rectified sEMG activity from individual trials (*A*, *D*, *G*, and *J*) and mean EMG traces (*B*, *E*, *H*, and *K*) are shown, as are the outcomes of the time series receiver operator characteristic (ROC) and DogLeg linear regression analyses (*C*, *F*, *I*, and *L*; same format as Fig. 8). For this participant, the ROC curve starts to deviate at 98 ms in control (*C*), 112 ms in low-contrast target (*F*), and 81 ms in valid cue (*I*) conditions, whereas the initiation time in invalid target condition (*L*) is at 122 ms and thereby after the SLR epoch (gray patch). In *J*, the arrow indicates short latency responses at ∼100 ms that are consistent with the low co-contrast cue location, before the muscle started responding to the high-contrast target. These rapid responses reflect the short-latency (∼100 ms) EMG activation for right targets and inhibition for left targets of the average EMG signal (arrow inside the gray patch in *K*) and underlie the negative deflection below 0.5 chance level of the ROC curve within the SLR epoch (arrow inside the gray patch in *L*).

condition (*participants 1* and *3*, Table 2), and it was delayed and smaller than that expressed with the high-contrast target condition. These results are consistent with previous work showing that both visual responses in the superior colliculus (43) and the SLR (4) are delayed as the target-to-background contrast is reduced.

Despite its low detectability, the low-contrast stimulus led both to RT and SLR modulations when it was used as a cue for the high-contrast target. Specifically, the valid low-contrast cues reduced both the RT and SLR latency relative to control conditions, whereas the invalid cues led to the opposite effects. Furthermore, invalid low-contrast cues obliterated the SLR in 5 of 10 participants who exhibited it in

control and valid cue conditions (Table 2). These phenomena are unlikely to originate from the same neural mechanisms proposed for the symbolic cue effects. The symbolic cue was predictive for target location (i.e., 75% validity) and required interpretation of the arrow orientation, which we enabled experimentally by a CTOA > 1 s. By contrast, the low saliency, brief CTOA (∼24 ms), and irrelevant validity (50%) attributes of the low-contrast cue were designed to limit cortical processing of the cue before the high-contrast target presentation. Notably, this is consistent with the large behavioral cost (i.e., delayed RT) of the low-contrast stimulus when it represented the target to reach (i.e., low-contrast condition; Fig. 7A). Furthermore, incorrect (i.e., cue directed)

Table 3. *Results of 2 participants who exhibited an SLR in the control, low-contrast target, and valid cue conditions of experiment 2*

Participant		Control	Low Contrast	Valid
S1	SLR initiation time, ms	97 [90–104]	112 [102–122]	81 [73–90]
	SLR magnitude, µV	42 [38–46]	28 [21–35]	41 [36–46]
S2	SLR initiation time, ms	94 [88–100]	112 [104–120]	84 [77–91]
	SLR magnitude, µV	78 [54–102]	48 [24–72]	85 [72–92]

Results of 2 participants who exhibited a stimulus-locked response (SLR) in the control, low-contrast target, and valid cue conditions of *experiment 2*. Data are reported as median [95% confidence interval].

reaches occurred in only ~10% of the invalid cue trials, which indicates that participants moved toward the high-contrast target even when it was preceded by the low-contrast cue appearing in the opposite visual hemifield. This suggests that the low-contrast stimulus did not have sufficient salience to systematically drive the voluntary reaching movement toward the cued (i.e., incorrect) location before the presentation of the high-contrast target.

In addition to its sensory and motor function (38, 44, 45), the superior colliculus is proposed to contribute to mechanisms of bottom-up attention orientation (18, 34). Bottom-up attention evolves rapidly after a sensory event and is exclusively sensitive to the physical attributes of the stimulus, such as its spatial location (18). Neural correlates of bottom-up attention orientation in the superior colliculus have been reported in nonhuman primates, and there is some evidence that perturbations of superior colliculus activity can influence both conscious perception and volitional motor behavior (13, 18, 34). For instance, Müller et al. (46) showed that microstimulation of superior colliculus neurons improved perceptual task performance when visual stimuli appeared at locations encoded by the stimulated collicular neurons. Furthermore, Zénon and Krauzlis (47) reported a perception deficit for stimuli presented at a location encoded by visual collicular neurons that were previously inactivated but not for distracting stimuli presented outside the inactivated collicular receptive field. More recently, Bogadhi et al. (48) showed that superior colliculus inactivation modulates neural correlates of spatial and object-selective attention and event detection on the superior temporal sulcus in monkeys. Overall, these findings suggest that the superior colliculus can bias cortical mechanisms of stimulus detection and selection. Furthermore, Fecteau et al. (15) showed an increase of target-related collicular response and a corresponding reduction of target-directed saccade onset time when the target was validly cued by another stimulus appearing at the same location ~50 ms in advance. A 50-ms CTOA is arguably sufficient time for bottom-up collicular modulation of target processing in primary visual cortex, but this mechanism seems less plausible for the ~24-ms CTOA and low-contrast cues of *experiment 2*.

We propose that the cue-induced SLR modifications reported here reflect a spatiotemporal integration of the low-contrast and high-contrast stimuli accomplished subcortically through the tecto-reticulo-spinal circuits rather than via cortical top-down feedback mechanisms. More specifically, we propose that the express visuomotor response in the valid cue conditions was faster than control because it was superimposed upon residual activity in the superior colliculus originating from the low-contrast cue. Functionally, this might aid the onset of rapid visuomotor responses to visual stimuli spatially congruent with weak sensory events that were recently experienced.

Methodological Considerations and Future Directions

Cuing the target location had consequences for both RT and SLRs, which may reflect modulation mechanisms of top-down origin for the symbolic cues and bottom-up origin for low-contrast cues. It is unclear, however, which cue type provided the strongest modulation of the SLR expression, at least for the cue paradigms adopted here. Future studies should use different versions of our cuing paradigms to further delineate the neural mechanisms behind this express visuomotor behavior in humans.

In this study, we reasoned that the effects of the symbolic cue reflected a cortical top-down priming of visuomotor networks, including the putative subcortical SLR network, but there are alternative interpretations that might explain our observations. In the no-cue (i.e., control) conditions of *experiment 1*, the target appeared randomly to the left or right of participants' dominant hand. Given the absence of prior information (i.e., no cue) about the probable target location, two distinct and competing motor programs could be prepared and coexist in the subcortical circuitry until the program compatible with the actual target location was chosen and released. The integration between visual and motor preparation signals could be facilitated if the competition between prepared motor programs is resolved, at least partially, before the stimulus presentation by cuing the target location with the symbolic arrow cue. This would be expected to potentiate the SLR expression when the stimulus appears at a location congruent with the cue-related motor program and impair it when the prepared motor program mismatches the target location. For example, visual inputs to the superior colliculus might quickly trigger the nodes that are involved in the release of prepared responses (e.g., brain stem reticular formation nuclei; for review see Refs. 49, 50). It is noteworthy that these hypotheses are consistent with the positive and negative cue-induced SLR changes observed in *experiment 1*. Motor preparation mechanisms cannot underlie the effects of low-contrast cues, however, because they were barely detectable, had weak predictive value (50%), and appeared too shortly (~24 ms) before the high-contrast target to allow the pretarget preparation of a specific motor response. Nonetheless, we acknowledge that neural mechanisms consistent with motor preparation might contribute to SLR generation and therefore should receive attention for future investigations on this express visuomotor behavior.

Conclusions

This study has shown that cuing the location of a visual target modulates express visuomotor responses in humans. Symbolic cues appear able to modify express visuomotor behavior via cortical top-down feedback signals to the putative subcortical SLR network, including the superior colliculus and its downstream reticulo-spinal circuits. These phenomena illustrate a mechanism by which cognitive expectations can modulate the critical nodes for SLR generation to speed up the visuomotor responses to expected visual events. By contrast, the effects of low-contrast cues appear to reflect bottom-up facilitation mechanisms, potentially evolving subcortically via the superior colliculus. These mechanisms might aid the spatiotemporal integration of spatially congruent visual signals along the tecto-reticulo-spinal pathway and facilitate rapid response initiation when a salient stimulus follows a weak visual event. Overall, our findings help to constrain models of the neural mechanisms responsible for express visuomotor responses in humans.

REFERENCES

1. **Posner MI.** Orienting of attention: then and now. *Q J Exp Psychol (Hove)* 69: 1864–1875, 2016. doi:10.1080/17470218.2014.937446.

2. **van Ede F**, **de Lange FP**, **Maris E.** Attentional cues affect accuracy and reaction time via different cognitive and neural processes. *J Neurosci* 32: 10408–10412, 2012. doi:10.1523/JNEUROSCI.1337-12.2012.

3. **Pruszynski JA**, **King GL**, **Boisse L**, **Scott SH**, **Flanagan JR**, **Munoz DP.** Stimulus-locked responses on human arm muscles reveal a rapid neural pathway linking visual input to arm motor output. *Eur J Neurosci* 32: 1049–1057, 2010. doi:10.1111/j.1460-9568.2010.07380.x.

4. **Wood DK**, **Gu C**, **Corneil BD**, **Gribble PL**, **Goodale MA.** Transient visual responses reset the phase of low-frequency oscillations in the skeletomotor periphery. *Eur J Neurosci* 42: 1919–1932, 2015. doi:10.1111/ejn.12976.

5. **Contemori S**, **Loeb GE**, **Corneil BD**, **Wallis G**, **Carroll TJ.** The influence of temporal predictability on express visuomotor responses. *J Neurophysiol* 125: 731–747, 2021. doi:10.1152/jn.00521.2020.

6. **Gu C**, **Wood DK**, **Gribble PL**, **Corneil BD.** A trial-by-trial window into sensorimotor transformations in the human motor periphery. *J Neurosci* 36: 8273–8282, 2016. doi:10.1523/JNEUROSCI.0899-16.2016.

7. **Atsma J**, **Maij F**, **Gu C**, **Medendorp WP**, **Corneil BD.** Active braking of whole-arm reaching movements provides single-trial neuromuscular measures of movement cancellation. *J Neurosci* 38: 4367–4382, 2018. doi:10.1523/JNEUROSCI.1745-17.2018.

8. **Paré M**, **Munoz DP.** Saccadic reaction time in the monkey: advanced preparation of oculomotor programs is primarily responsible for express saccade occurrence. *J Neurophysiol* 76: 3666–3681, 1996. doi:10.1152/jn.1996.76.6.3666.

9. **Fischer B**, **Boch R.** Saccadic eye-movements after extremely short reaction-times in the monkey. *Brain Res* 260: 21–26, 1983. doi:10.1016/0006-8993(83)90760-6.

10. **Edelman JA**, **Keller EL.** Activity of visuomotor burst neurons in the superior colliculus accompanying express saccades. *J Neurophysiol* 76: 908–926, 1996. doi:10.1152/jn.1996.76.2.908.

11. **Dorris MC**, **Paré M**, **Munoz DP.** Neuronal activity in monkey superior colliculus related to the initiation of saccadic eye movements. *J Neurosci* 17: 8566–8579, 1997. doi:10.1523/JNEUROSCI.17-21-08566.1997.

12. **Schiller PH**, **Sandell JH**, **Maunsell JH.** The effect of frontal eye field and superior colliculus lesions on saccadic latencies in the rhesus monkey. *J Neurophysiol* 57: 1033–1049, 1987. doi:10.1152/jn.1987.57.4.1033.

13. **Corneil BD**, **Munoz DP.** Overt responses during covert orienting. *Neuron* 82: 1230–1243, 2014. doi:10.1016/j.neuron.2014.05.040.

14. **Dorris MC**, **Klein RM**, **Everling S**, **Munoz DP.** Contribution of the primate superior colliculus to inhibition of return. *J Cogn Neurosci* 14: 1256–1263, 2002. doi:10.1162/089892902760807249.

15. **Fecteau JH**, **Bell AH**, **Munoz DP.** Neural correlates of the automatic and goal-driven biases in orienting spatial attention. *J Neurophysiol* 92: 1728–1737, 2004. doi:10.1152/jn.00184.2004.

16. **Corneil BD**, **Munoz DP**, **Chapman BB**, **Admans T**, **Cushing SL.** Neuromuscular consequences of reflexive covert orienting. *Nat Neurosci* 11: 13–15, 2008. doi:10.1038/nn2023.

17. **Klein RM.** Inhibition of return. *Trends Cogn Sci* 4: 138–147, 2000. doi:10.1016/S1364-6613(00)01452-2.

18. **Baluch F**, **Itti L.** Mechanisms of top-down attention. *Trends Neurosci* 34: 210–224, 2011. doi:10.1016/j.tins.2011.02.003.

19. **Edelman JA**, **Kristjánsson A**, **Nakayama K.** The influence of object-relative visuomotor set on express saccades. *J Vis* 7: 12, 1–13, 2007. doi:10.1167/7.6.12.

20. **Edelman JA**, **Mieses AM**, **Konnova K**, **Shiu D.** The effect of object-centered instructions in Cartesian and polar coordinates on saccade vector. *J Vis* 17: 2–2, 2017. doi:10.1167/17.3.2.

21. **Brainard DH.** The Psychophysics Toolbox. *Spat Vis* 10: 433–436, 1997. doi:10.1163/156856897X00357.

22. **Pelli DG.** The VideoToolbox software for visual psychophysics: transforming numbers into movies. *Spat Vis* 10: 437–442, 1997. doi:10.1163/156856897X00366.

23. **Kozak RA**, **Kreyenmeier P**, **Gu C**, **Johnston K**, **Corneil BD.** Stimulus-locked responses on human upper limb muscles and corrective reaches are preferentially evoked by low spatial frequencies. *eNeuro* 6: ENEURO.0301-19.2019, 2019. doi:10.1523/ENEURO.0301-19.2019.

24. **Kozak AR**, **Cecala AL**, **Corneil BD.** An emerging target paradigm evokes fast visuomotor responses on human upper limb muscles. *J Vis Exp* 162: e61428, 2020. doi:10.3791/61428.

25. **Fiehler K**, **Brenner E**, **Spering M.** Prediction in goal-directed action. *J Vis* 19: 10–21, 2019. doi:10.1167/19.9.10.

26. **Kingdom FA**, **Prins N.** Adaptive methods. In: *Psychophysics*. San Diego, CA: Academic Press, 2016, p. 119–148.

27. **Hommel B**, **Colzato L.** Visual attention and the temporal dynamics of feature integration. *Vis Cogn* 11: 483–521, 2004. doi:10.1080/13506280344000400.

28. **Lupiáñez J**, **Martín-Arévalo E**, **Chica AB.** Inhibition of return: attentional disengagement or detection cost? *Psicológica* 34: 221–252, 2013.

29. **Wright RD**, **Richard CM.** Location cue validity affects inhibition of return of visual processing. *Vision Res* 40: 2351–2358, 2000. doi:10.1016/S0042-6989(00)00085-7.

30. **Basseville M**, **Nikiforov IV.** *Detection of Abrupt Changes: Theory and Application (Information and System Sciences Series)*. Englewood Cliffs, NJ: Prentice Hall, 1993.

31. **Haith AM**, **Pakpoor J**, **Krakauer JW.** Independence of movement preparation and movement initiation. *J Neurosci* 36: 3007–3015, 2016. doi:10.1523/JNEUROSCI.3245-15.2016.

32. **Carroll TJ**, **McNamee D**, **Ingram JN**, **Wolpert DM.** Rapid visuomotor responses reflect value-based decisions. *J Neurosci* 39: 3906–3920, 2019. doi:10.1523/JNEUROSCI.1934-18.2019.

33. **Pruszynski JA**, **Kurtzer I**, **Scott SH.** Rapid motor responses are appropriately tuned to the metrics of a visuospatial task. *J Neurophysiol* 100: 224–238, 2008. doi:10.1152/jn.90262.2008.

34. **Knudsen EI.** Neural circuits that mediate selective attention: a comparative perspective. *Trends Neurosci* 41: 789–805, 2018. doi:10.1016/j.tins.2018.06.006.

35. **Moore T**, **Armstrong K.** Selective gating of visual signals by microstimulation of frontal cortex. *Nature* 421: 370–373, 2003. doi:10.1038/nature01341.

36. **Gu C**, **Pruszynski JA**, **Gribble PL**, **Corneil BD.** Done in 100 ms: path-dependent visuomotor transformation in the human upper limb. *J Neurophysiol* 119: 1319–1328, 2018. doi:10.1152/jn.00839.2017.

37. **Gu C**, **Pruszynski JA**, **Gribble PL**, **Corneil BD.** A rapid visuomotor response on the human upper limb is selectively influenced by implicit motor learning. *J Neurophysiol* 121: 85–95, 2019. doi:10.1152/jn.00720.2018.

38. **Boehnke SE**, **Munoz DP.** On the importance of the transient visual response in the superior colliculus. *Curr Opin Neurobiol* 18: 544–551, 2008. doi:10.1016/j.conb.2008.11.004.

39. **Peel TR**, **Dash S**, **Lomber SG**, **Corneil BD.** Frontal eye field inactivation diminishes superior colliculus activity, but delayed saccadic accumulation governs reaction time increases. *J Neurosci* 37: 11715–11730, 2017. doi:10.1523/JNEUROSCI.2664-17.2017.

40. **Dash S**, **Peel TR**, **Lomber SG**, **Corneil BD.** Frontal eye field inactivation reduces saccade preparation in the superior colliculus but does not alter how preparatory activity relates to saccades of a given latency. *eNeuro* 5: ENEURO.0024-18.2018, 2018. doi:10.1523/ENEURO.0024-18.2018.

41. **Dorris MC**, **Olivier E**, **Munoz DP.** Competitive integration of visual and preparatory signals in the superior colliculus during saccadic programming. *J Neurosci* 27: 5053–5062, 2007. doi:10.1523/JNEUROSCI.4212-06.2007.

42. **Dorris MC**, **Munoz DP.** Saccadic probability influences motor preparation signals and time to saccadic initiation. *J Neurosci* 18: 7015–7026, 1998. doi:10.1523/JNEUROSCI.18-17-07015.1998.

43. **Marino RA**, **Levy R**, **Boehnke S**, **White BJ**, **Itti L**, **Munoz DP.** Linking visual response properties in the superior colliculus to saccade behavior. *Eur J Neurosci* 35: 1738–1752, 2012. doi:10.1111/j.1460-9568.2012.08079.x.

44. **Gandhi NJ**, **Katnani HA.** Motor functions of the superior colliculus. *Annu Rev Neurosci* 34: 205–231, 2011. doi:10.1146/annurev-neuro-061010-113728.

45. **Basso MA**, **May PJ.** Circuits for action and cognition: a view from the superior colliculus. *Annu Rev Vis Sci* 3: 197–226, 2017. doi:10.1146/annurev-vision-102016-061234.

46. **Müller JR**, **Philiastides MG**, **Newsome WT.** Microstimulation of the superior colliculus focuses attention without moving the eyes. *Proc Natl Acad Sci USA* 102: 524–529, 2005. doi:10.1073/pnas.0408311101.

47. **Zénon A**, **Krauzlis RJ.** Attention deficits without cortical neuronal deficits. *Nature* 489: 434–437, 2012. doi:10.1038/nature11497.

48. **Bogadhi AR**, **Katz LN**, **Bollimunta A**, **Leopold DA**, **Krauzlis RJ.** Midbrain activity shapes high-level visual properties in the primate temporal cortex. *Neuron* 109: 690–699.e5, 2020. doi:10.1016/j.neuron.2020.11.023.

49. **Marinovic W**, **Tresilian JR.** Triggering prepared actions by sudden sounds: reassessing the evidence for a single mechanism. *Acta Physiol (Oxf)* 217: 13–32, 2016. doi:10.1111/apha.12627.

50. **Carlsen AN**, **Maslovat D.** Startle and the StartReact effect: physiological mechanisms. *J Clin Neurophysiol* 36: 452–459, 2019. doi:10.1097/WNP.0000000000000582.