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RESEARCH ARTICLE

Perturbation of cortical activity elicits regional and age-dependent effects on unconstrained reaching behavior: a pilot study

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Abstract

Contributions from premotor and supplementary motor areas to reaching behavior in aging humans are not well understood. The objective of these experiments was to examine effects of perturbations to specific cortical areas on the control of unconstrained reaches against gravity by younger and older adults. Double-pulse transcranial magnetic stimulation (TMS) was applied to scalp locations targeting primary motor cortex (M1), dorsal premotor area (PMA), supplementary motor area (SMA), or dorsolateral prefrontal cortex (DLPFC). Stimulation was intended to perturb ongoing activity in the targeted cortical region before or after a visual cue to initiate moderately paced reaches to one of three vertical target locations. Regional effects were observed in movement amplitude both early and late in the reach. Perturbation of PMA increased reach distance before the time of peak velocity to a greater extent than all other regions. Reaches showed greater deviation from a straight-line path around the time of peak velocity and greater overall curvature with perturbation of PMA and M1 relative to SMA and DLPFC. The perturbation increased positional variability of the reach path at the time of peak velocity and the time elapsing after peak velocity. Although perturbations had stronger effects on reaches by younger subjects, this group exhibited less reach path variability at the time of peak velocity and required less time to adjust the movement trajectory thereafter. These findings support the role of PMA in visually guided reaching and suggest an age-related change in sensorimotor processing, possibly due to a loss of cortical inhibitory control.

Keywords Motor control · Aging · Goal-directed movement · Transcranial magnetic stimulation · Dorsal premotor cortex

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Introduction

Reaching for an object in space forms the basis for many activities of daily living. Contemporary views of goal-directed reaching emphasize the involvement of online processes that make maximal use of somatosensory and visual feedback to control limb trajectory (Elliott et al. 2017). It is thought that two types of online processes regulate early- and late-phase control of reaching. Impulse control occurs early in the movement and involves a comparison of limb kinematics to an internal representation of expectations about limb trajectory. Limb-target control occurs late in the movement and involves real-time error reduction based on the relative positions of the limb and target. Original thinking was that the early, ballistic phase was entirely pre-programmed due to delays in sensory processing (Schmidt et al. 1979), but it has been shown that integration of visual and somatosensory feedback on short timescales enables online control, even for rapid movements performed under severe time constraints (i.e., movement times ≤ 150 ms). In fact, the trajectory of discrete limb movements is adapted to changes in target size and location after movement onset (Heath et al. 1998), late in the movement trajectory (Paulignan et al. 1991) and without conscious awareness (Day and Lyon 2000; Prablanc and Martin 1992). Rapid processing of sensory feedback during goal-directed behavior, therefore, appears to be an important feature of proficient limb control.

Over a half century of animal and human work has attempted to dissociate the role of various cortical motor regions in the planning and execution of goal-directed movement. Different features of activation in primary motor cortex (M1) are linked to limb kinematics (Georgopoulos et al. 1988, 1986; Moran and Schwartz 1999) and kinetics (Dettmers et al. 1995; Scott et al. 2001). However, the unique contribution of supplementary motor area (SMA) and premotor area (PMA), which both interconnect with M1 (Künzle 1978; Pandya and Kuypers 1969; Pandya and Vignolo 1971), remains unclear. SMA, in the medial portion of Brodmann area 6, is thought to be involved in movement preparation (Tanji and Shima 1994) and control of internally generated movement (Krainik et al. 2001; Nachev et al. 2008). Dorsal and ventral PMA, located lateral to SMA but also within Brodmann area 6, are thought to be part of segregated fronto-parietal circuits subserving different aspects of reach-and-grasp movements. Dorsal PMA is thought to be more involved in the reach (Lee and Van Donkelaar 2006) and ventral PMA in the grasp (Davare et al. 2008). Dorsal PMA receives dense projections from the dorsal visual stream, providing a basis for visually guided movement (Tanné-Gariépy et al. 2002). Although a considerable body of animal (Kurata and Hoffman 1994; Rea et al. 1987; Sasaki and Gemba 1986) and human (Davare et al. 2006; Desmurget et al. 1999; Tunik et al. 2005) evidence supports the hypothesis that dorsal PMA is critically involved in the planning and sensory guidance of goal-directed movement, more recent work in non-human primates shows that inactivation of dorsal PMA impairs internally generated but not visually guided movements (Ohbayashi et al. 2016). While dorsal and ventral PMA are interesting in the context of visually guided reaches, we studied only dorsal PMA here and use "PMA" to mean dorsal premotor area. Localization of ventral PMA in humans is also controversial (Grèzes and Decety 2001; Picard and Strick 2001).

Whether the cortical circuitry mediating online control of unconstrained reaching behavior is subject to age-related change is not well understood. Prior work has shown increased end-point error and variability of reaches in older subjects (Poston et al. 2013) and differences in the relative contribution of ballistic and corrective movements (Poston et al. 2009a, b). In these and most other studies, the reach task was simplified by restricting movement to a two-dimensional plane with anti-gravity support of the arm (Poston et al. 2009a, b; Poston et al. 2013; Przybyla et al. 2011; Welsh et al. 2007). Such a reductionist approach has been useful but leaves open the question of whether there is any unique consideration to the problem of countering effects of gravity when a multijoint limb is lifted and extended away from the trunk (Vandenberghe et al. 2010). In such movements, age-related differences in the trajectory of vertical aiming movements are dependent on the verticality of target location (Bennett et al. 2012). Declines in muscle mass (Haddad and Adams 2006), neuromuscular transmission (Vandervoort 2002), and cortical function (Heuninckx et al. 2008) that occur with advanced age are likely to influence the ability to harness passive inertial and gravitational torques to reach the movement endpoint.

The purpose of this exploratory pilot study was to better understand the unique contributions of premotor areas on the control of unconstrained reaching behavior in younger and older adults and to gain insight into the influence of age on control processes mediated by these areas. To accomplish both objectives, double-pulse transcranial magnetic stimulation (TMS) was applied over M1, PMA, SMA, and dorsolateral prefrontal cortex (DLPFC) while younger and older adults performed moderately paced reaches to one of three vertical targets. A 100-ms interstimulus interval was used in these experiments because it has been shown to mainly disrupt cortical processing (Rice et al. 2006). We reasoned that disruptions should increase inhibition of the targeted cortical area (Davranche et al. 2007). Kinematic differences between conditions involving group and/or double-pulse TMS,

therefore, were used to infer a role of age and/or premotor area on the control of unconstrained reaching behavior.

Methods

Participants

Eighteen individuals participated in the study and were recruited into young ($n = 10$, 6 males, 26.4 ± 6.8 years) and old ($n = 8$, 6 males, 67.4 ± 3.1 years) groups. All subjects reported good health, with no history of neurological disease and normal or corrected-to-normal vision. Subjects were right-hand dominant, as established by the Edinburgh inventory (Oldfield 1971). Signed informed consent was obtained from each subject prior to testing in accordance with policies of the local ethics committee and Declaration of Helsinki.

Experimental setup and task

Subjects performed all reaches while seated in a chair with backrest support and a restraint system situated around the trunk to restrict its movement. An adjustable table with a visual stimulus presentation system was placed in front of the subject (Fig. 1A). Three pairs of light emitting diodes (LEDs) represented locations of an upper target (UT), middle target (MT) and lower target (LT). Both the LT and UT were vertically separated 15 cm from the MT. The height and horizontal positions of the MT were aligned to the right shoulder. The distance from the target to the subject was set 5 cm less than a fully extended reach to the MT. The starting position was marked on the table and in line with the targets, 3 cm lower than the LT and 15 cm from the target board.

Subjects were asked to find a comfortable sitting position with the right upper arm in a vertical, adducted position and elbow flexed approximately 90°. The forearm was pronated with the hand resting on the table and the tip of index finger on the starting position. Each target location contained one red (left) and one green (right) LED separated by 1 cm (Fig. 1B). Subjects were instructed to start at rest with the index finger on a starting position marker. Relaxation prior to movement initiation was stressed explicitly. First, one red LED illuminated for 1 s as a preparation cue, indicating the target for the forthcoming reach. A green LED illuminated for 200 ms after an additional 800–1200-ms random delay as a cue to initiate movement. All red LEDs illuminated

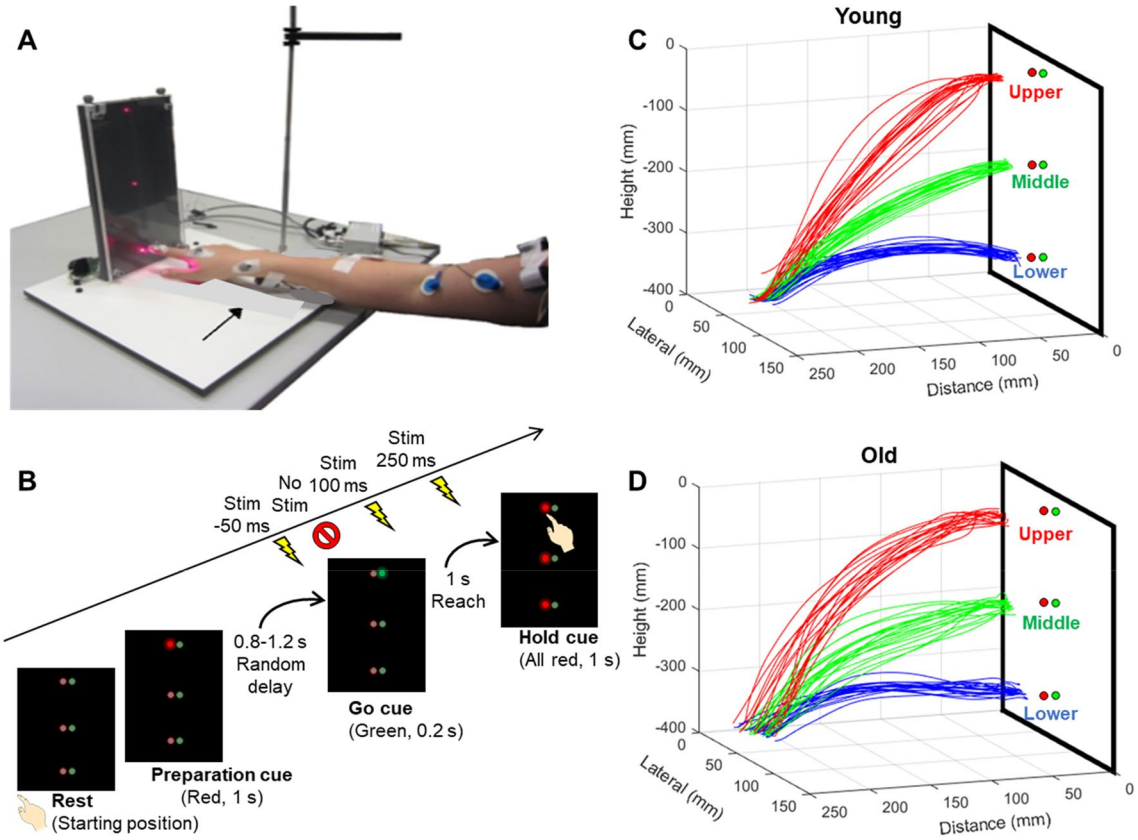

Fig. 1 **A** Visual stimulus presentation system and **B** sequence of events in the unconstrained reaching task. Each stimulation timing is relative to the Go cue. Representative reach paths to the three target location from subjects in the **C** young and **D** old groups

1 s after the movement initiation cue and remained illuminated for 1 s. Subjects were instructed to arrive at the target approximately 1 s after the initiation cue and maintain contact with the target until all red LEDs extinguished (i.e., for 1 s). The room light was dimmed, so visual feedback of the LED target and hand position was reduced but not eliminated.

Experimental procedure

A fixed pseudorandom sequence of 24 trial types was programmed in Turbo Pascal for DOS (Borland, Austin, TX) with 18 trials in which double-pulse TMS was delivered at one of three timings and six trials with no stimulation. Reach target location varied across all 24 trials within a sequence, covering all combinations of target sequence and stimulation timing twice. Subjects performed a sequence of 24 practice reaches before two to three blocks using the programmed sequence were recorded with the coil at each of the four stimulation locations. This was done partly to help participants learn to approximate a 1-s movement time. Paired stimuli separated by 100 ms were initiated at three different timings relative to the visual cue to initiate movement: 50 ms before cue (− 50 ms), 100 ms after cue (+ 100 ms), and 250 ms after cue (+ 250 ms). Visual cues and double-pulse TMS were controlled by the output of a parallel port of a DOS computer connected to a custom-made trigger box.

Transcranial magnetic stimulation

Double-pulse TMS was applied to left M1, left PMA, left SMA, and right DLPFC using a MagStim Rapid stimulator and standard 70 mm figure-eight coil. Inclusion of contralateral M1 was intended to serve as a positive control to dissociate the unique contributions of PMA and SMA (further explanation below). Although recent work has shown a role of DLPFC in disinhibiting contralateral M1 during bilateral movement preparation (Fujiyama et al. 2016; Verstraelen et al. 2020), ipsilateral DLPFC was intended to serve as a negative control with an expected negligible effect on unilateral reaching. DLPFC is also involved in working memory (Levy and Goldman-Rakic 2000), but there was minimal demand to recall target location in the task paradigm described here.

A mapping procedure was administered in 10–20 space to localize the four brain regions targeted during experimental procedures. Electromyography (EMG) was recorded (1 kHz) from the biceps brachii, long head of triceps brachii, anterior and posterior deltoids using bipolar surface electrodes (2-cm inter-electrode distance) affixed over each muscle belly. The stimulating coil was held tangentially to the scalp overlying M1 and angled 45 degrees laterally and posteriorly (MagStim 200^2, 70 mm figure-eight coil). The location that elicited the largest, peak-to-peak motor-evoked potential (MEP) in the right biceps brachii muscle from the mean of seven single pulses was set as the optimal site. As noted above, the intent for double-pulse TMS was to perturb/disrupt activity in cortical circuits controlling the arm. Biceps brachii was targeted as an exemplar arm muscle because it shows well-formed MEPs and is involved in various phases of the reach. The same procedure was repeated for the tibialis anterior (TA) muscle with the stimulating coil oriented at the midline of the scalp to locate the medial portion of M1. During experimental procedures, M1 stimulation was applied at the biceps brachii optimal site, PMA stimulation was applied 2 cm anterior to this location, SMA stimulation was applied 3 cm anterior of the TA optimal site or 4 cm anterior to the vertex if a MEP could not be elicited in TA, and DLPFC stimulation was applied 8 cm anterior to M1, mirrored to the hemisphere ipsilateral to the reaching arm. Landmarks were established relative to the biceps brachii optimal site as a means to standardize stimulation locations for each region across subjects.

Resting motor threshold (rMT) was determined as the minimum stimulator output needed to elicit a MEP with a peak-to-peak amplitude ≥ 50 μV in the biceps brachii muscle from 5 of 10 consecutive single pulses. Stimulator output was set to 1.0 × rMT for M1, 1.2 × rMT for PMA, 1.5 × rMT for SMA, and 0.8 × rMT for DLPFC. Although the threshold of spinal motor neurons cannot be precisely controlled during a dynamic task, stimulator outputs were intended to drive some degree of brief activation and more prolonged inhibition. Progressively higher stimulator outputs were used for PMA and SMA stimulation to increase the likelihood of measurable effects in absence of an efficient method to determine the intensity needed for such effects. Stimulator outputs were set at the lowest level possible to perturb the brain region targeted by stimulation, while limiting spread of activation to other brain regions. Suprathreshold stimulator outputs have also been used in previous work that aimed to perturb cortical areas during a motor task (Rice et al. 2006). This prior work established threshold based on visible twitch criteria. It is, therefore, likely that stimulator outputs used in the current study, which based rMT on the presence of MEPs, were comparable to or below those used previously.

Motion capture

A ten-camera system (Vicon, Oxford Metrics, UK) in a fixed array along the ceiling edges of a motion capture laboratory acquired the 3-dimensional location of reflective markers (100 Hz) affixed to anatomical landmarks on the arm (acromioclavicular joint, radial and ulnar styloid processes, humeral medial and lateral epicondyles,

metacarpophalangeal joint and distal phalanx of the first finger) and trunk (C7 and T8 spinous processes, sternoclavicular joint, and xiphoid process). Three markers were placed on the stimulating coil, and four markers were placed on the head to track their respective locations. Figure 1 contains sample reach paths from a young (Fig. 1C) and old (Fig. 1D) subject that were reconstructed from motion capture data.

Data analysis

Kinematic data were processed offline using custom software developed in MATLAB™ (The Mathworks, Natick, MA). Data were passed through a low-pass (10 Hz), fourth-order, zero-lag Butterworth filter before further processing. Movement initiation and termination were defined as the instant when velocity of the marker affixed to the metacarpal crossed above and below 5% of peak velocity in the vertical dimension, respectively. All trials were visually inspected to verify the validity of these criteria. Trials were removed from the analysis if movement was evident before the visual cue to initiate the reach, indicating a false start. Trials also were removed if reaction time or movement time was > 2 standard deviations from the mean, indicating missed cues or otherwise unusual kinematics.

Three positional parameters were calculated to characterize the amplitude of the reach path both early and late in the overall movement trajectory under the assumption that composite kinematic features of the reach path would be affected by the perturbation. The 3-dimensional reach vector was defined as the position of the index finger at each instant during the reach. Reach path magnitude was calculated by taking the square root of the sum of squares along each axis to characterize the extent of the reach path to the target. Reach path deviation was calculated by taking the difference between the reach path and a straight-line path to the target to characterize divergence of the reach path. Reach path curvature was calculated as the ratio between the overall length of the reach path and the distance between the position of the 3-dimensional reach vector at movement initiation and termination. Reach path magnitude and deviation were calculated early (i.e., 100 ms after movement initiation) and late (i.e., at the time of peak velocity and 50 ms thereafter) in the movement trajectory. The temporal structure of the reach was characterized by calculating the rise time and time after peak velocity. Finally, positional variability was derived at the time of peak velocity and at the end of the reach path by adapting a previously described formula for computing two-dimensional variability (Hancock et al. 1995) to include a third dimension.

EMG recordings from trials in the − 50 ms condition were inspected to verify the incidence of MEPs in axial muscles integral to the reach (i.e., anterior deltoid, posterior deltoid, triceps longus, and biceps brachii). Recordings from the − 50 ms condition were inspected, specifically, because both pre- and post-stimulation epochs were mostly free of background activation. All trials retained in kinematic analyses were analyzed. EMG recordings were rectified before waveform averaging trials corresponding to each target location. Mean EMG was calculated in the immediate 100 ms preceding stimulation onset. MEPs were detected if EMG increased 2 standard deviations above the mean of the pre-stimulus epoch and remained above this threshold for 15 ms, 10–30 ms after stimulation onset. The incidence of MEPs was expressed as a fraction of the total possible occurrences (3 targets × 18 subjects = 51 possible occurrences) for each muscle. MEP incidence was also calculated by target location.

Statistical analyses

Independent samples *t* tests were used to test for differences between young and old groups in age and rMT. The GLM procedure in SAS (Version 9.4) was used to perform overall *F* tests for detecting independent/interaction effects of brain region, target location, stimulation timing, and age group on kinematic parameters. Specifically, we used a nested multilevel model where observations at level 1 (i.e., the trial) were clustered at level 2 (i.e., brain region, target location, stimulation timing), making observations from the same cluster correlated. In general, correlation under the mixed effects model with compound symmetric structure is recommended. To generalize results to all conditions, we treated the subject-level variables as random effects. Least square means and least square mean differences were computed for classification effects with multiple comparison adjustments (using 2-tailed *t* tests) on *p* values and confidence limits. We chose to model at the trial level to capture systematic trends in within-subject variability. Variability of human movement is well established and likely exacerbated by the lack of constraints on the reaching task described here.

Results

Subjects completed all research procedures within a single testing session. An average of 65 ± 9 trials (mean ± SD) were performed in the no-stimulation condition and at each stimulation timing for each subject. A subset of trials was removed from each condition based on the rejection criteria described above: no-stimulation (14.9 ± 7.5%), 50 ms before cue (8 ± 8.5%), 100 ms after cue (7 ± 9.1%), and 250 ms after cue (6.5 ± 9.2%). Ages of young and old groups were 26 ± 7 and 67 ± 3 years, respectively. There was no significant difference in rMT between young (52.7 ± 10.3%) and old (65.9 ± 17.3%) groups ($t_{16} = -1.9$, $p = 0.084$), although

the old group had a trend towards a higher rMT, which is consistent with previous work (Oliviero et al. 2006).

Prior to testing for kinematic differences, reaction times were examined in stimulation and no-stimulation conditions to determine if there was a cueing effect of stimulation. Such an effect might bias movement kinematics via earlier movement initiation. A mixed model on reaction time ($F_{9,4157} = 10.39$, $p < 0.001$, $\eta^2 = 0.16$) revealed an effect of stimulation timing with − 50 and + 100 ms conditions producing significantly (all $p < 0.001$) reduced reaction times relative to no-stimulation and 250-ms conditions (Fig. 2). Given evidence of a cueing effect, preliminary models excluded the no-stimulation condition and focused on the regional effect of stimulation at all three timings.

Models revealed a distinct pattern of regional but not temporal effects. PMA stimulation increased magnitude of

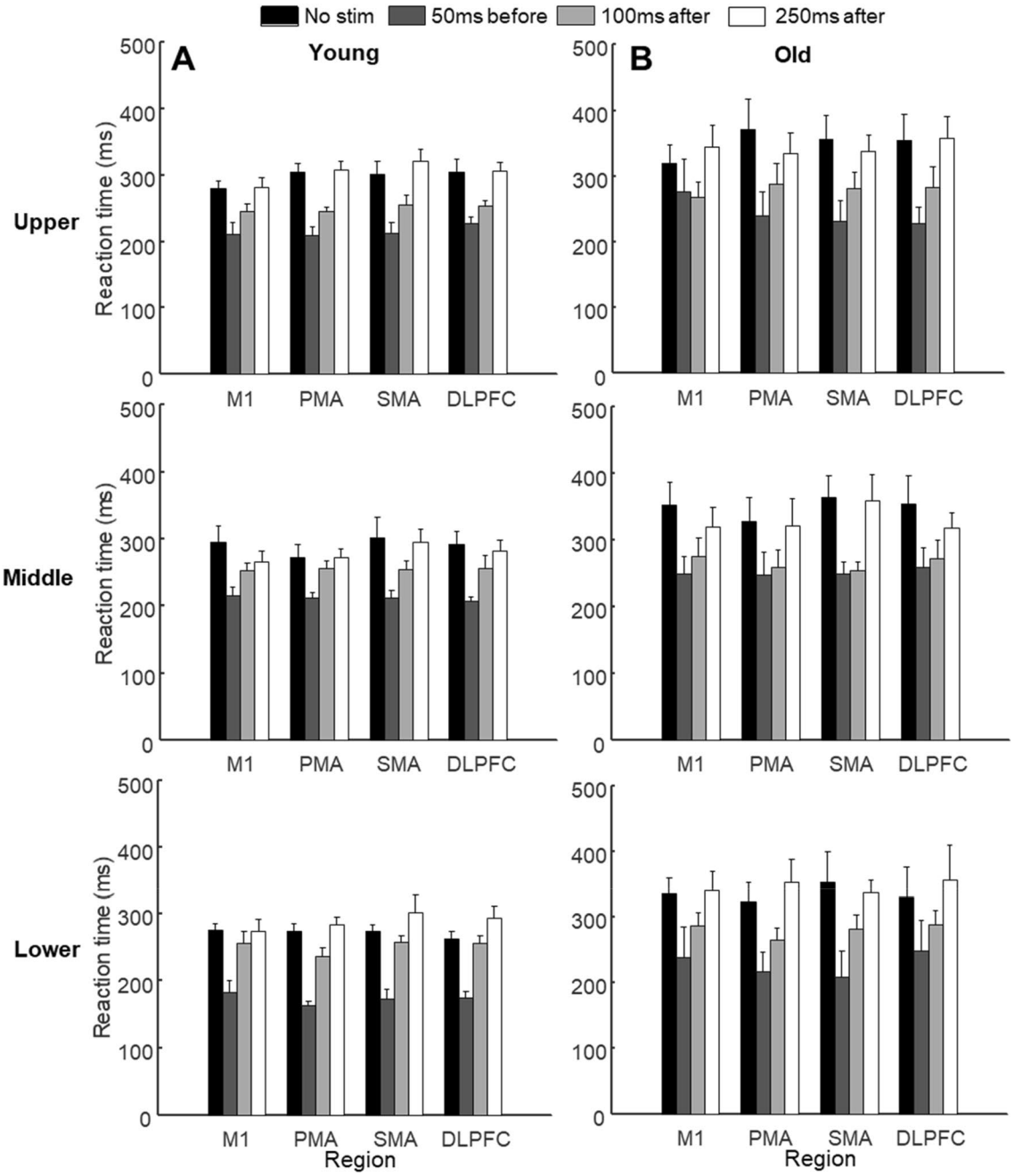

Fig. 2 Group means of reaction time in young (**A**) and old (**B**) groups at each target location (rows) under no-stimulation and stimulation conditions. Note the reduced reaction time for both groups at each target location under 50 ms before cue and 100 ms after cue stimulation conditions. Error bars reflect standard deviation

the reach path at 100 ms after movement onset to a greater extent than all other regions (M1, $t = 4.452$, $p < 0.0001$; SMA, $t = 3.694$, $p = 0.0002$; DLPFC, $t = 8.603$, $p < 0.0001$, $\eta^2 = 0.02$). Reach path magnitude at 100 ms after movement onset was also greater for M1 and SMA relative to DLPFC ($t = 4.182$, $p < 0.0001$ and $t = 4.947$, $p < 0.0001$, respectively, $\eta^2 = 0.01$). Mixed models for reach path deviation revealed that M1 and PMA stimulation increased deviation to an extent that was similar yet greater than SMA and DLPFC stimulation throughout the reach, including 100 ms after movement onset (M1 > SMA, $t = 3.46$, $p = 0.0005$, M1 > DLPFC, $t = 2.992$, $p = 0.0028$; PMA > SMA, $t = 2.992$, $p = 0.0028$, PMA > DLPFC, $t = 2.992$, $p = 0.0028$; $\eta^2 = 0.01$), at the time of peak velocity (M1 > DLPFC, $t = 2.992$, $p = 0.0028$; PMA > SMA, $t = 5.104$, $p < 0.0001$, PMA > DLPFC, $t = 4.624$, $p < 0.0001$, $\eta^2 = 0.04$), and 50 ms after the time of peak velocity (M1 > SMA, $t = 2.32$, $p = 0.0272$, M1 > DLPFC, $t = 4.07$, $p < 0.0001$; PMA > SMA, $t = 2.21$, $p = 0.0204$, PMA > DLPFC, $t = 1.763$, $p = 0.078$; $\eta^2 = 0.02$). The same pattern was observed for reach path curvature (M1 > SMA, $t = 2.792$, $p = 0.0053$, M1 > DLPFC, $t = 3.927$, $p < 0.001$, $\eta^2 = 0.02$; PMA > SMA, $t = 3.792$, $p = 0.0002$, PMA > DLPFC, $t = 4.919$, $p < 0.0001$, $\eta^2 = 0.01$).

In summary, preliminary statistical models revealed distinct patterns in regional effects of the perturbation. Since reaction time did not differ between no-stimulation and 250-ms stimulation conditions, a final set of statistical models included only these conditions to avoid the confound of reaction time effects while also preserving the ability to observe pure regional effects of the perturbation. Thus, all levels of brain region (4), target location (3), and age group (2) were retained,but only 2 level of stimulation timing (no-stimulation and 250-ms stimulation) were included in these models.

For reach path magnitude, an effect for brain region was only evident early in the movement trajectory (100 ms after movement onset ($F_{8,4157}$) = 8.1, $p < 0.001$, $\eta^2 = 0.16$, Fig. 3). Exemplar reach path magnitudes with stimulation to each cortical region are shown in Fig. 4. Similar to preliminary statistical models, reach path magnitude at 100 ms after movement onset was greater with PMA stimulation relative to all other regions (M1, $t = 2.899$, $p = 0.0038$, SMA, $t = 3.6$, $p = 0.0003$, and DLPFC, $t = 6.162$, $p < 0.0001$). M1 and SMA stimulation also produced a greater reach path magnitude than DLPFC ($t = 3.175$, $p = 0.0002$ and $t = 2.997$, $p = 0.0031$, respectively, $\eta^2 = 0.01$). Effects of stimulation on reach path magnitude were greater in the young relative to the old group ($p < 0.001$ and $p < 0.001$, respectively, $\eta^2 = 0.01$), and a region by group interaction ($p = 0.04$, $\eta^2 = 0.01$) was detected. There was a significant effect of target ($p < 0.001$) and a target by group interaction ($p < 0.02$), such that increased demands to counter the effects of gravity at successively higher target locations decreased reach path magnitude (UT < MT < LT) with the young group exhibiting greater magnitudes.

For reach path deviation, there was reversal in trends such that regional effects were only evident *late* in the movement trajectory (at peak velocity: ($F_{8,4157}$) = 15.11, $p < 0.001$, $\eta^2 = 0.24$, Fig. 5; 50 ms after peak velocity: ($F_{8,4157}$) = 8.98, $p < 0.001$, $\eta^2 = 0.08$, Fig. 6). Exemplar reach path deviations with stimulation to each cortical region are shown in Fig. 7. Just as preliminary models showed, reach path deviation was similar for M1 and

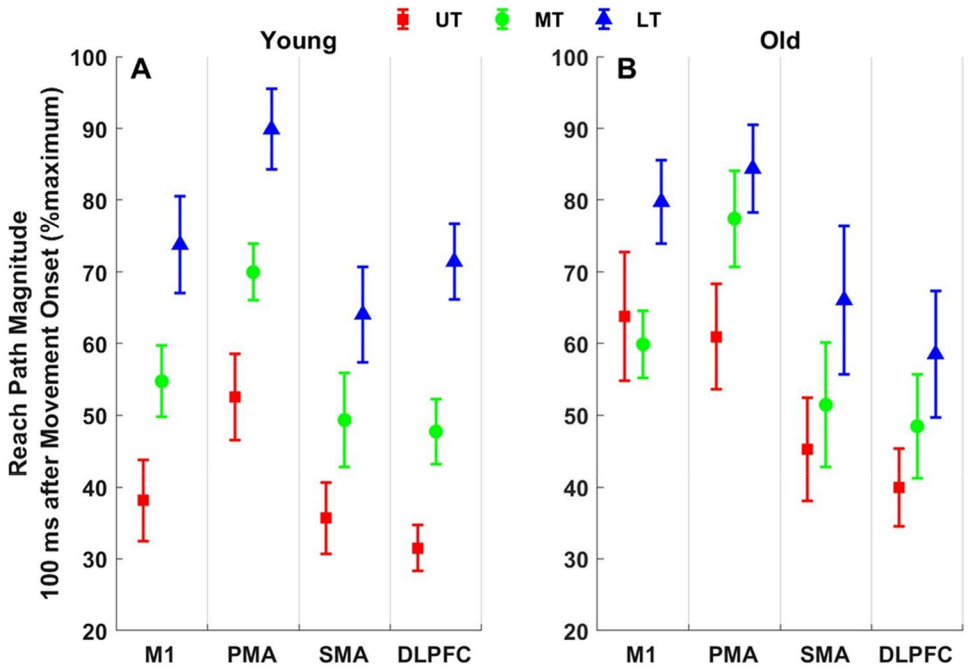

Fig. 3 Regional effects of cortical perturbations on relative reach path magnitude 100 ms after movement onset in young (**A**) and old (**B**) groups at each target location under the +250-ms stimulation condition. Error bars represent standard error. Reach magnitudes across trials for all regions were normalized to the maximum magnitude across trials for each subject

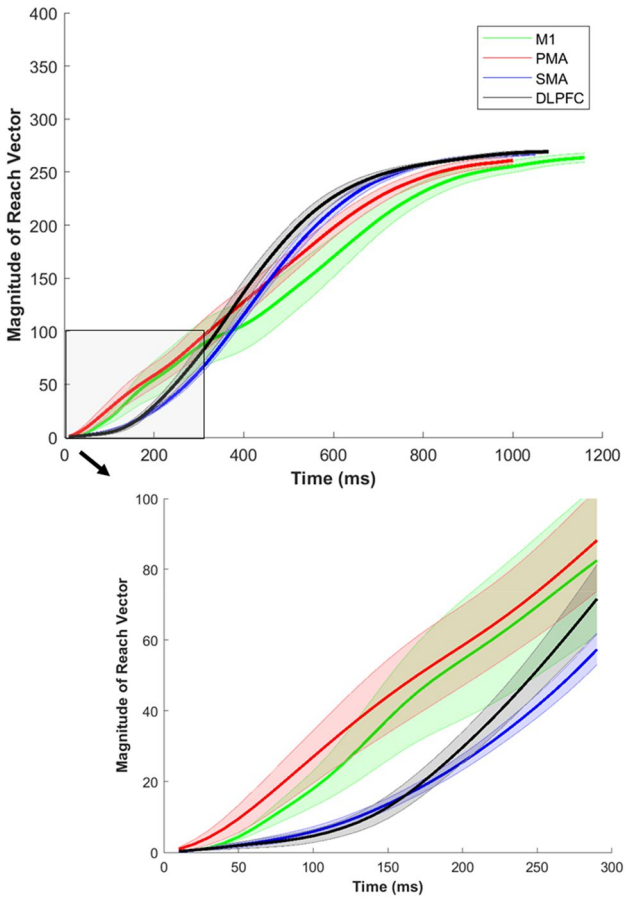

Fig. 4 Exemplar reach path magnitude from a single subject under the 250-ms stimulation condition. The top plot illustrates magnitude of the reach vector over the entire reach, whereas, the bottom plot depicts only the first 300 ms of the reach to more clearly show regional differences detected at 100 ms after movement onset. Traces represent the mean of all trials when stimulation was applied to a particular region, and shaded areas correspond to standard error

PMA, with both regions increasing deviation beyond DLPFC and SMA stimulation at both the time of peak velocity (M1 > SMA, $t = 2.694$, $p = 0.0071$, M1 > DLPFC, $t = 2.423$, $p = 0.016$; PMA > SMA, $t = 3.428$, $p = 0.0006$, PMA > DLPFC, $t = 3.161$, $p = 0.002$, $\eta^2 = 0.01$) and 50 ms thereafter (M1 > SMA, $t = 2.65$, $p = 0.0081$, M1 > DLPFC, $t = 2.401$, $p = 0.0016$; PMA > SMA, $t = 3.414$, $p = 0.0007$, PMA > DLPFC, $t = 3.167$, $p = 0.0015$, $\eta^2 = 0.05$). Consistent with trends for reach path magnitude, the effects of stimulation on reach path deviation were significantly greater in the young relative to the old group ($p < 0.001$ and $p < 0.001$, respectively), but no significant region by group interaction was observed. As with reach path magnitude, there was also a significant effect of target at both time points (both $p < 0.001$) and target by group interactions ($p < 0.001$ and $p < 0.001$, respectively). However, reverse trends were observed such that increased demands to counter the effects of gravity at successively higher target locations *increased* reach path deviation (UT > MT > LT) with the younger group exhibiting greater deviations, regardless of stimulation condition.

Regional effects were also detected for overall reach path curvature ($F_{8,4157}) = 15.66$, $p < 0.001$, $\eta^2 = 0.26$ Fig. 8). Exemplar reach path curvatures with stimulation to each cortical region are shown in Fig. 9. In addition, similar to preliminary and final models on reach path deviation, M1 and PMA stimulation produced comparable increased curvature that was greater than SMA (M1, $t = 2.988$, $p = 0.0028$; PMA, $t = 4.005$, $p < 0.001$, $\eta^2 = 0.02$) and DLPFC (M1, $t = 3.59$, $p = 0.0003$; PMA, $t = 4.613$, $p < 0.0001$, $\eta^2 = 0.04$) stimulation. Reach path curvature was greater in the young group ($t = 3.68$, $p = 0.0002$, $\eta^2 = 0.01$). Although a region by group interaction was not detected, there were region by target($p = 0.01$) and group by target ($p = 0.008$) interactions.

Separate models were used to examine the effects of perturbations on peak velocity of the reach and on the overall time-course of the movement trajectory. Mixed model analysis showed that stimulation increased peak velocity ($F_{8,4157}) = 59.28$, $p < 0.001$, $\eta^2 = 0.08$). There were also effects of group ($p < 0.001$) and target ($p < 0.001$), with older subjects exhibiting higher peak velocities relative to younger subjects and lower peak velocities at successively higher targets (UT < MT < LT). Mixed model analysis of the time-course of the movement revealed an effect of stimulation on the time that elapsed before ($F_{8,4157}) = 3.75$, $p < 0.001$, $\eta^2 = 0.01$) and after ($F_{8,4157}) = 1.95$, $p = 0.001$, $\eta^2 = 0.01$) peak velocity (Fig. 10). Stimulation reduced the rise time to peak velocity but increased the time that elapsed after peak velocity. Although stimulation produced stronger effects on the amplitude of reach kinematics in younger subjects, this group also exhibited less time before ($p < 0.001$) and after peak velocity ($p < 0.001$) despite reaching lower peak velocities. Mixed model analysis revealed that stimulation increased 3-dimensional variability of the reach path at the time peak of velocity ($F_{8,4157}) = 2.04$, $p < 0.001$, $\eta^2 = 0.20$) but not at movement termination ($p = 0.6$). There was an effect of group at both points with older subjects showing greater variability at the time of peak velocity ($p < 0.001$) and movement termination ($p < 0.001$).

Acknowledging that stimulation was applied at or above rMT to three of the four brain regions, EMG recordings were inspected to determine the incidence of MEPs in the peristimulus time window (10–30 ms after stimulation onset). Overall, MEPs in shoulder and elbow muscles were evident in fewer than half of all cases (Fig. 11). M1 stimulation produced a slightly higher overall incidence of MEPs (33.9%) relative to PMA stimulation (29.1%). Stimulation to both regions generated higher rates of MEPs relative to SMA (16.9%) and DLPFC (0%) stimulation. M1 stimulation elicited MEPs in deltoid muscles

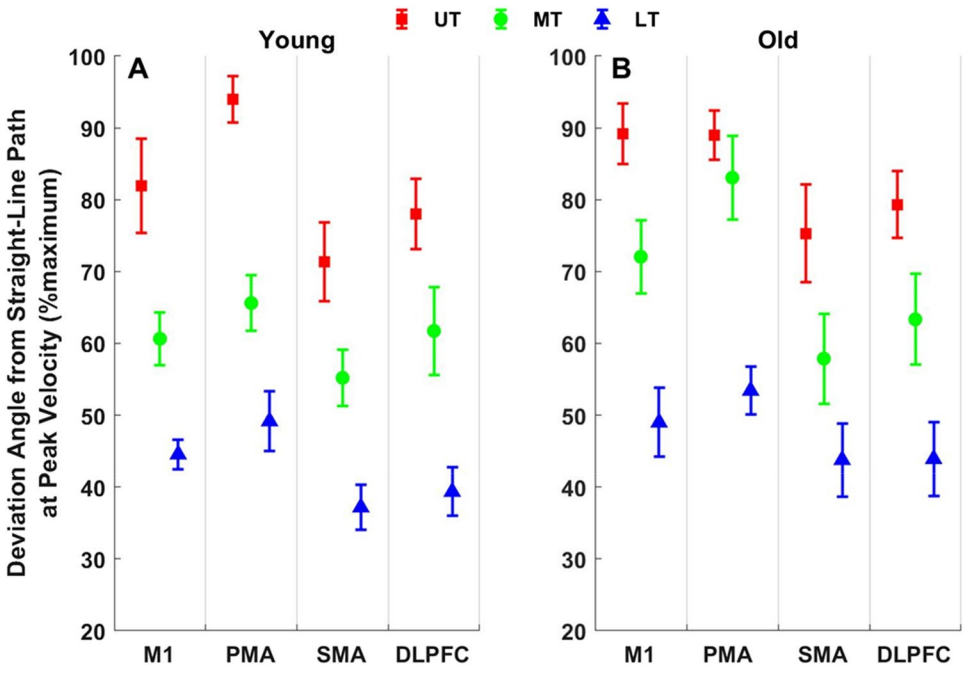

Fig. 5 Regional effects of cortical perturbations on reach path deviation at the time of peak velocity in the young (**A**) and old (**B**) groups at each target location under the 250-ms stimulation condition. Error bars represent standard error. Reach deviations across trials for all regions were normalized to the maximum deviation across trials for each subject

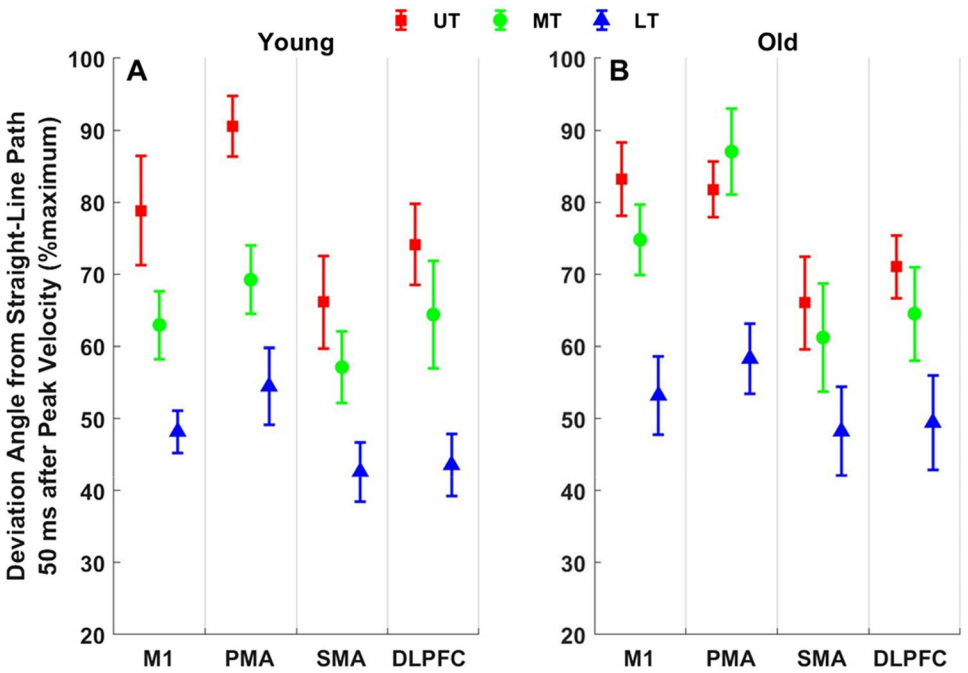

Fig. 6 Regional effects of cortical perturbations on reach path deviation 50 ms after the time of peak velocity in the young (**A**) and old (**B**) groups at each target location under the 250-ms stimulation condition. Error bars represent standard error. Reach deviations across trials for all regions were normalized to the maximum deviation across trials for each subject

more frequently than PMA stimulation (32.4% and 19.4%, respectively), and a comparable rate was observed to a lesser extent for elbow muscles (35.3% and 39.2%, respectively). The incidence of deltoid MEPs elicited by M1 and PMA stimulation remained fairly constant across target locations (UT: 30.3% vs 21.5%; MT: 36.6% vs 18.4%; LT: 30.3% vs. 18.4%). There was some consistency for MEPs elicited in triceps across target locations, but there was a more distinct disparity in biceps MEPs at successively higher target locations (LT: 29.4% vs. 23.5%, MT: < 1% vs. 29.4% UT: < 1% vs. 41.2%).

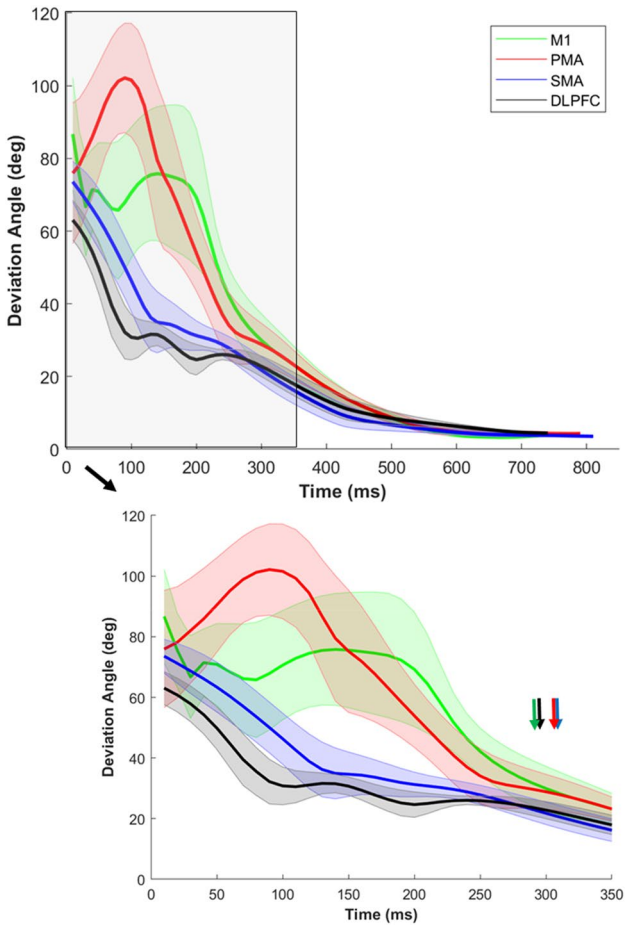

Fig. 7 Exemplar reach path deviation from a single subject under the 250-ms stimulation condition. The top plot illustrates deviation of the reach vector from a straight-line path over the entire reach, whereas, the bottom plot depicts only the first 350 ms of the reach to more clearly show regional differences detected late in the movement trajectory at the time of peak velocity and 50 ms thereafter. Arrows indicate the time of peak velocity. Traces represent the mean of all trials when stimulation was applied to a particular region, and shaded areas correspond to standard error

Discussion

Summary

Consistent with prior work (Poston et al. 2009a, b; Poston et al. 2013), differences in reach profiles were observed between age groups with notably shorter reaction times evident in the younger group and greater variability of reach path trajectories in the older group. Double-pulse TMS to any brain region 50 ms before and 100 ms after the onset of the visual cue to initiate movement shortened reaction times, complicating the analysis of regional effects. While some of the early effects on reach path could have been due to differences in reaction time, regional effects were detected with the perturbation of PMA increasing early movement magnitude and later deviation from a straight-line path.

The comparison of no-stimulation and 250-ms post-go cue stimulation avoided the confound of differing reaction times. This timing should mainly inhibit output neurons in each region non-specifically, although the 10 Hz paired-pulse technique likely involves a complex and dynamic interaction between ongoing activity, local circuitry, and recurrent/lateral inhibition. In this comparison, regional effects of the perturbation were detected both early and late in the reach. Perturbation of PMA, in particular, increased the magnitude of reach paths early, likely contributing to greater deviation from a straight-line path later in the movement trajectory. Although there are multiple possible explanations for why effects of the perturbation were more prominent in the reach paths of younger subjects (e.g., greater integrity of cortical circuitry and lesser co-contraction), this group was able to more efficiently adjust to the perturbation as evidenced by less positional variability at the time of peak velocity and less time required after peak velocity to reach the target. Our findings, therefore, suggest an age-related change in online control of reaching behavior that may be due to reduced cortical inhibitory control.

Findings from similar perturbation studies support a role for PMA in action inhibition (Duque et al. 2012; Parmigiani and Cattaneo 2018). Inhibitory rTMS of PMA also has been shown to compromise learned behaviors involving the selection of motor responses (Chouinard et al. 2005; Mochizuki et al. 2005). While both SMA and PMA are likely to have modulatory effects on M1, intracortical microstimulation of PMA in non-human primates has been shown to induce effects on M1 that are stronger than those elicited by SMA (Côté et al. 2020). In the current study, movement onset occurred after the second pulse, indicating that disruptive effects of the perturbation preceded movement onset. Acknowledging that double-pulse TMS of PMA had the greatest effect on forward movement early in the reach (i.e., reach path magnitude), our findings might suggest that motor commands were run off without the guidance of sensory feedback, requiring adaptation later in the movement trajectory. We, therefore, interpret the effects of the perturbation as a release of a braking mechanism, whether through direct inhibition of PMA or of local circuits in M1.

Reaction time effects

TMS interacts with human behavior through a few modalities, the pulsed magnetic field induced in the brain being just one of them. The solenoid-like vibration of the coil causes a clicking sound and tactile sensation. Induced electric currents in the scalp cause significant stimulation of sensory and motor nerves. These non-specific peripheral effects lead to brain input through cranial and cervical spinal nerves,

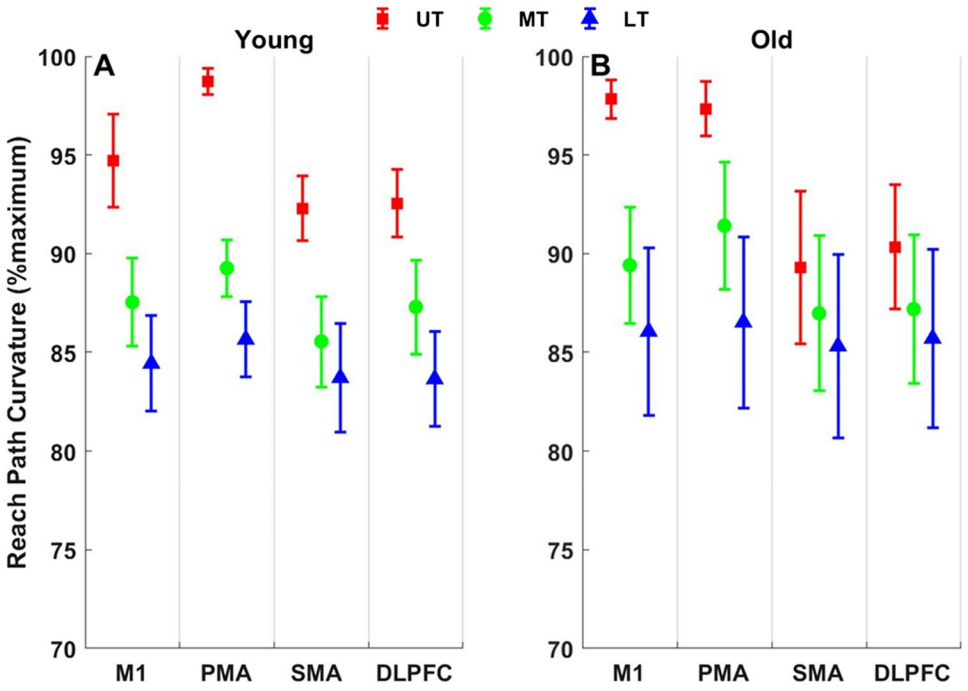

Fig. 8 Regional effects of cortical perturbations on reach path curvature in the young (**A**) and old (**B**) groups at each target location under the 250-ms stimulation condition. Error bars represent standard error. Reach curvature across trials for all regions were normalized to the maximum curvature across trials for each subject

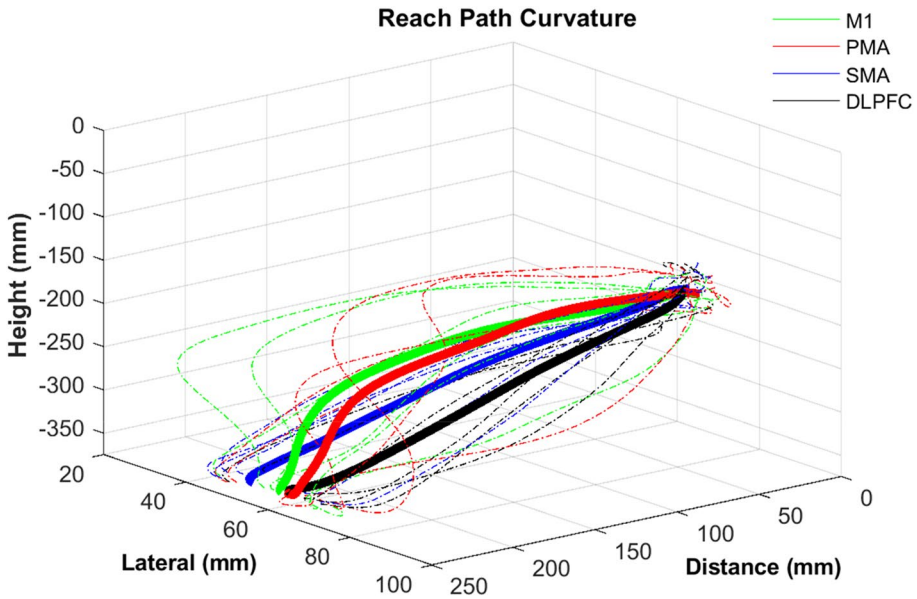

Fig. 9 Exemplar reach path curvature from a single subject under the 250-ms stimulation condition. Bold traces represent the mean of all trials when stimulation was applied to a particular region, and dashed traces correspond to individual trials

affecting some central sensorimotor processing (Xu-Wilson et al. 2011). It is, therefore, important to first understand effects of stimulation on reaction time and also distinguish whether these effects are regionally specific. There was a non-specific regional effect on reaction time, with stimulation just before and after the go cue shortening the reaction time. There was also a non-specific effect on positional variability early (i.e., at peak velocity) but not late (i.e., at termination) in the movement trajectory.

Auditory cues tend to produce faster reaction times than visual cues (Woodworth and Schlosberg 1954), so it is unsurprising that an auditory cue occurring after a visual cue could shorten reaction time. The sound produced by discharge of the coil was not intended as a cue but, since reaction times were shortened by more than would be expected from the auditory-visual cue effect (~ 30 ms), it is likely that there was some cueing effect of stimulation. While the pulses should not have elicited startle-like reactions, given that pulses occurred frequently and were not excessively

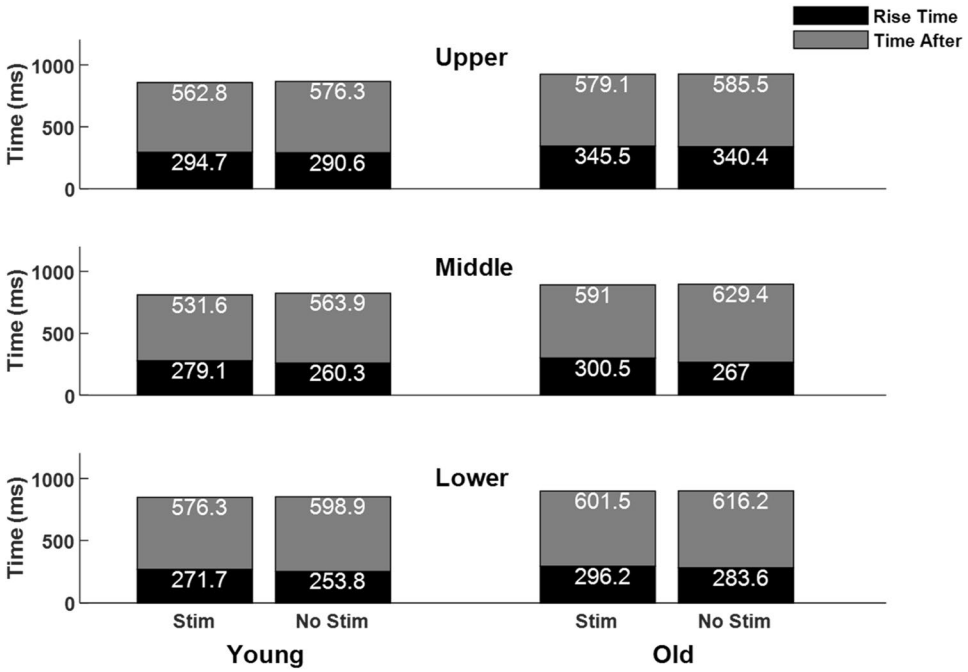

Fig. 10 Stacked bar plot showing rise time and time after peak velocity under no-stimulation and 250-ms stimulation conditions. Note the decreased rise time and increased time after peak velocity with stimulation. In addition, note slower rise time and time after peak velocity in the old group

loud, coil discharge seems to have an indirect effect on reaction time.

Effects on the early impulse-control phase

The initial phase of a reaching movement can be characterized as a ballistic, approximately straight-line trajectory towards the target. The perturbation imposed by stimulation could interfere with movement planning and execution in two general ways: (a) a short-term increase in the level of activation in neurons that are already activated and/or (b) an inhibition of neurons over a longer period, reducing the duration and frequency of spiking. These effects would be delayed by time required for central conduction and excitation–contraction coupling. The fact that the perturbation over PMA increased early reach path magnitude suggests a role for PMA as a brake on movement during the time-range studied, a role consistent with known effects in action selection (Chambers et al. 2006). This is based on the argument that, without a strong time dependence of stimulation, local inhibitory effects would have dominated any lasting effects.

Effects on the later limb-target control phase

Later effects of the cortical perturbation, measured at the time of peak velocity (i.e., after peak acceleration), reduced movement efficiency and increased positional variability. Increased curvature and deviation from a straight-line path are consistent with a secondary effect of the perturbation and the role of PMA in enabling online control (Lee and Van Donkelaar 2006). Perturbation of PMA tended to have the strongest effect on deviation of the reach path in most subjects, despite a lack of statistical difference between PMA and M1. There was no uniform pattern to the deviation, implying that inhibition of activity reduced corrections to limb trajectory introduced in the initial, ballistic phase. Alternatively, changes in the reach path observed early were compensated for later. In both interpretations, PMA likely contributes to the homing-in phase which is consistent with the two-component theory of goal-directed aiming (Elliott et al. 2010) and likely influenced by age-related factors (Helsen et al. 2016; Van Halewyck et al. 2015).

Gravity effects, compensation, and age

An initial hypothesis was that there would be specific regional control of the antigravity components of reaching movements. In particular, SMA seemed a likely node in the network for antigravity control, serving a role in production of antigravity postural adjustments (Goel et al. 2019; Richard et al. 2017). While target height affected kinematics, there was no specificity with regard to regional effects of stimulation. The lack of regional effects might suggest that the antigravity and vertical aspects of the movement shared a common cortical control mechanism. A feature of reaching without antigravity support is the role of elbow flexors in every phase of the reach. Despite that the elbow eventually extends, the elbow flexors lift the forearm off the support surface, act eccentrically to control gravity-actuated forward extension and, then, support the forearm at the end-point of the reach. This strategy is consistent with minimization in co-contraction and energy use in practiced movements.

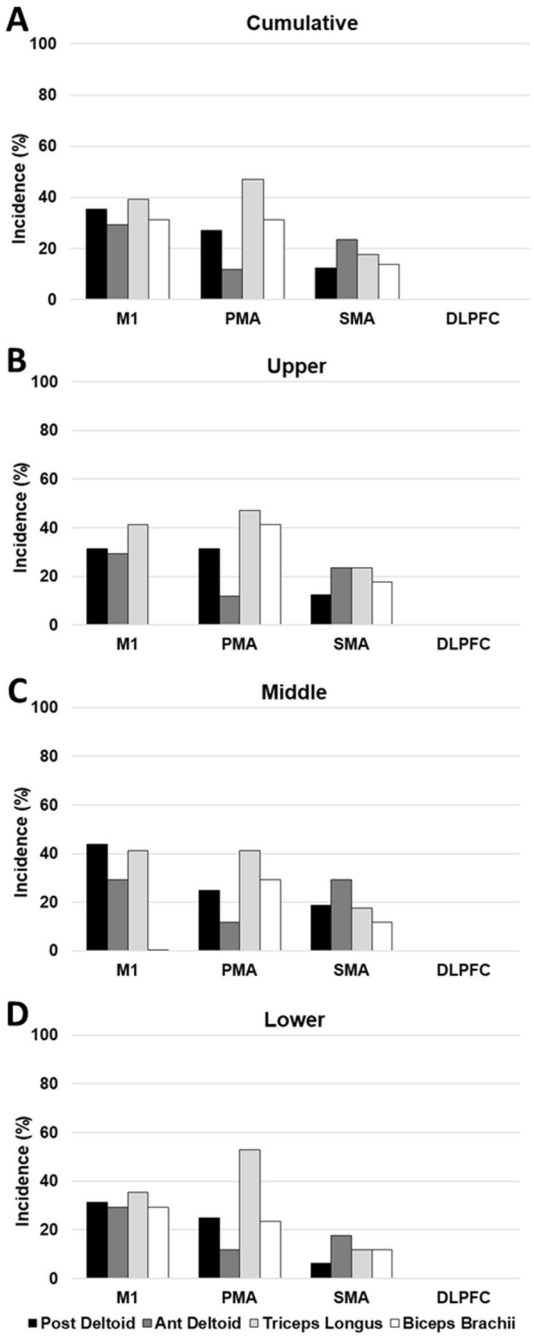

Fig. 11 MEP incidence from perturbations to each brain region overall (**A**) and for upper (**B**) middle (**C**) and lower (**D**) target locations. Bars correspond to posterior deltoid (black), anterior deltoid (dark gray), long head of the triceps (light gray), and biceps brachii (white)

The perturbation increased reach path magnitude within 100 ms of movement onset to a greater extent in the young group. Reaching against gravity reduced movement amplitude, particularly in the old group, but there was no interaction to suggest an increased level of activity in antigravity motor representations that could be accessed by TMS. The effect of double-pulse TMS in this study was to increase forward movement regardless of stimulation location. It is possible that other regions, such as the reticular formation, play more of a role in the postural aspect of unsupported reaching (Stuphorn et al. 1999) and this general effect might be more related to activation of the reticular formation.

More curved reach paths were exhibited at successively higher targets, which might reflect a compensatory strategy to offset the increased magnitude early and deviation late in the movement trajectory while also countering the effects of gravity. If so, such a compensation might require increased time after peak velocity to allow for online control processes to hone the reach vector into the target. In this study, the perturbation increased the time spent after peak velocity but to a lesser extent in the young group.

Younger subjects showed more sensitivity to stimulation effects both early in the impulse-control phase (i.e., reach path magnitude), later in the limb-target control phase (i.e., reach path deviation), and throughout the entire movement (i.e., reach path curvature) which might be explained by one or more factors. The temporal pattern of reach-related activity could be more spread out in older individuals, reducing effects of the perturbation at any particular time. Cortical processing is reduced in older individuals which may be due to an age-related decline in the integrity of cortical circuits. It is, therefore, possible that stimulation did not engage circuitry to the same extent as in younger individuals. As part of preliminary analyses from these experiments, we found a higher amount of co-activation in the axial muscles of older subjects. The resulting joint stiffness may have reduced brief changes in neuronal activity elicited by stimulation. Despite more prominent effects of the perturbation on initial reach path trajectories, younger subjects were more readily able to adjust and coordinate the timecourse of the remaining movement, presumably by processing sensory feedback more efficiently.

Limitations

A major limitation of this study is sample size, both in number of subjects and number of reaches. The latter was restricted due to concern about fatigue but could have been handled by multiple sessions or fewer trial types. With further refinement of the experimental paradigm used in this study, it is reasonable to test a larger number of participants over a broader age range. Another limitation of the study was the lack of neuronavigation-guided stimulation. The scalp locations and coil orientations for stimulation were selected by surface anatomy and relationships with optimal sites for two muscles. While we would have preferred to use stereotactic neuronavigation, this would have been in concert with such functional anatomy to confirm distance from M1. Future work should investigate use of MRI functional and

anatomical markers for non-primary motor areas and control areas.

Confounds

MEPs were elicited on some trials and broadly represent the interaction of stimulation with a cortical motor system that is not at rest. The incidence of MEP was dependent on target height, but different for M1 and PMA. A greater demand to overcome gravity at higher target locations could explain the increased incidence of MEPs for PMA stimulation, but not the reverse effect for M1. Localization of TMS current is subject to the size and shape of the induced magnetic field. While several square centimeters of cortical surface receive significant currents, the effects are more restricted due to threshold effects (Romero et al. 2019). Therefore, while TMS over M1, PMA, and SMA may affect neighboring areas—and in the case of SMA, the contralateral homolog—those effects are not likely to significantly affect neuronal activity. But SMA stimulation has other limitations, in terms of its distance from the scalp and variability in location (Immisch et al. 2001). This was an undesired effect of the TMS paradigm used in this study. It is not possible to tell if the MEP was directly evoked from M1 regardless of coil position due to spread of induced current from non-M1 locations to M1 vs. through activation of the region to which the stimulation was directed. The mechanism of TMS pulse train interference depends on depolarizing current entering neurons; the effects include excitation and recurrent inhibition of various neuronal elements. Ideally, MEP occurrence would have been reduced further, but the procedure for doing so was impractical with the setup used. As a first investigation into unconstrained reaching, we also wanted to ensure the stimulation would have measurable effects, and therefore, opted for stronger as opposed to weaker stimulation.

The idea that regional effects were driven, at least in part, by inhibition within these cortical areas was drawn from the literature using the same or similar technique. This interpretation is consistent with our observation that PMA stimulation increased movement amplitude in a manner that rivaled or exceeded M1 stimulation, the latter of which was intended to serve as a positive control given its predominant role in movement execution. In addition, the relatively low time dependence of effects is more consistent with a longer lasting inhibition than with selective increased activation in dynamically activated subsets of neurons.

Future directions

The primary objective of this study was to demonstrate the disruptive effects induced by brief trains of TMS in exploring the functional role of cortical regions in controlling unconstrained reaches against gravity. A goal for this study is to inform future work examining the role of these brain regions on motor control after stroke to explain and facilitate the recovery of arm function. Before addressing this goal directly, it will be important to refine the method further. For example, it has been shown that the timing of disruption can be achieved with single stimuli or paired stimuli to different cortical areas (i.e., PMA and M1, Duque et al. 2012). In addition, titrating stimulation intensities may be useful in distinguishing between excitatory and inhibitory effects.

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Author contributions MAU analyzed data and drafted the manuscript. JT analyzed data and wrote parts of the manuscript. CWL analyzed data. GPM did statistical analysis and writing. NK and LW had a primary role in data collection and protocol development. OL, SPS, and IJ contributed to design and interpretation of the experiments. GFW conceived of the project and was involved in every aspect of it. All the authors approved the final version of the manuscript.

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Declarations

Conflict of interest On behalf of all the authors, the corresponding author states that there is no conflict of interest.

References

Bennett SJ, Elliott D, Rodacki A (2012) Movement strategies in vertical aiming of older adults. Exp Brain Res. https://doi.org/10.1007/s00221-011-2947-x

Chambers CD, Bellgrove MA, Stokes MG, Henderson TR, Garavan H, Robertson IH, Mattingley JB (2006) Executive "brake failure" following deactivation of human frontal lobe. J Cogn Neurosci. https://doi.org/10.1162/089892906775990606

Chouinard PA, Leonard G, Paus T (2005) Role of the primary motor and dorsal premotor cortices in the anticipation of forces during object lifting. J Neurosci. https://doi.org/10.1523/JNEUROSCI.4649-04.2005

Côté SL, Elgbeili G, Quessy S, Dancause N (2020) Modulatory effects of the supplementary motor area on primary motor cortex outputs. J Neurophysiol. https://doi.org/10.1152/JN.00391.2019

Davare M, Andres M, Cosnard G, Thonnard JL, Olivier E (2006) Dissociating the role of ventral and dorsal premotor cortex in precision grasping. J Neurosci. https://doi.org/10.1523/JNEUROSCI.3386-05.2006

Davare M, Lemon R, Olivier E (2008) Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. J Physiol. https://doi.org/10.1113/jphysiol.2008.152603

Davranche K, Tandonnet C, Burle B, Meynier C, Vidal F, Hasbroucq T (2007) The dual nature of time preparation: neural activation and suppression revealed by transcranial magnetic stimulation of the motor cortex. Eur J Neurosci. https://doi.org/10.1111/j.1460-9568.2007.05588.x

Day BL, Lyon IN (2000) Voluntary modification of automatic arm movements evoked by motion of a visual target. Exp Brain Res. https://doi.org/10.1007/s002219900218

Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST (1999) Role of the posterior parietal cortex in updating reaching movements to a visual target. Nat Neurosci. https://doi.org/10.1038/9219

Dettmers C, Fink GR, Lemon RN, Stephan KM, Passingham RE, Silbersweig D, Frackowiak RSJ (1995) Relation between cerebral activity and force in the motor areas of the human brain. J Neurophysiol. https://doi.org/10.1152/jn.1995.74.2.802

Duque J, Labruna L, Verset S, Olivier E, Ivry RB (2012) Dissociating the role of prefrontal and premotor cortices in controlling inhibitory mechanisms during motor preparation. J Neurosci. https://doi.org/10.1523/JNEUROSCI.4299-12.2012

Elliott D, Hansen S, Grierson LE, Lyons J, Bennett SJ, Hayes SJ (2010) Goal-directed aiming: two components but multiple processes. Psychol Bull 136(6):1023–1044. https://doi.org/10.1037/a0020958

Elliott D, Lyons J, Hayes SJ, Burkitt JJ, Roberts JW, Grierson LEM, Bennett SJ (2017) The multiple process model of goal-directed reaching revisited. Neurosci Biobehav Rev. https://doi.org/10.1016/j.neubiorev.2016.11.016

Fujiyama H, Van Soom J, Rens G, Gooijers J, Leunissen I, Levin O, Swinnen SP (2016) Age-related changes in frontal network structural and functional connectivity in relation to bimanual movement control. J Neurosci. https://doi.org/10.1523/JNEUROSCI.3355-15.2016

Georgopoulos AP, Schwartz AB, Kettner RE (1986) Neuronal population coding of movement direction. Science. https://doi.org/10.1126/science.3749885

Georgopoulos AP, Kettner RE, Schwartz AB (1988) Primate motor cortex and free arm movements to visual targets in three-dimensional space. II. Coding of the direction of movement by a neuronal population. J Neurosci. https://doi.org/10.1523/jneurosci.08-08-02928.1988

Goel R, Nakagome S, Rao N, Paloski WH, Contreras-Vidal JL, Parikh PJ (2019) Fronto–parietal brain areas contribute to the online control of posture during a continuous balance task. Neuroscience. https://doi.org/10.1016/j.neuroscience.2019.05.063

Grèzes J, Decety J (2001) Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum Brain Mapp. https://doi.org/10.1002/1097-0193(200101)12:1%3c1::AID-HBM10%3e3.0.CO;2-V

Haddad F, Adams GR (2006) Aging-sensitive cellular and molecular mechanisms associated with skeletal muscle hypertrophy. J Appl Physiol. https://doi.org/10.1152/japplphysiol.01227.2005

Hancock GR, Butler MS, Fischman MG (1995) On the problem of two-dimensional error scores: measures and analyses of accuracy, bias, and consistency. J Mot Behav. https://doi.org/10.1080/00222895.1995.9941714

Heath M, Hodges NJ, Chua R, Elliott D (1998) On-line control of rapid aiming movements: unexpected target perturbations and movement kinematics. Can J Exp Psychol. https://doi.org/10.1037/h0087289

Helsen WF, Van Halewyck F, Levin O, Boisgontier MP, Lavrysen A, Elliott D (2016) Manual aiming in healthy aging: does proprioceptive acuity make the difference? Age (dordr) 38(2):45. https://doi.org/10.1007/s11357-016-9908-z

Heuninckx S, Wenderoth N, Swinnen SP (2008) Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci 28(1):91–99. https://doi.org/10.1523/JNEUROSCI.3300-07.2008

Immisch I, Waldvogel D, van Gelderen P, Hallett M (2001) The role of the medial wall and its anatomical variations for bimanual antiphase and in-phase movements. Neuroimage 14(3):674–684

Krainik A, Lehéricy S, Duffau H, Vlaicu M, Poupon F, Capelle L, Marsault C (2001) Role of the supplementary motor area in motor deficit following medial frontal lobe surgery. Neurology. https://doi.org/10.1212/WNL.57.5.871

Künzle H (1978) An autoradiographic analysis of the efferent connections from premotor and adjacent prefrontal regions (areas 6 and 9) in macaca fascicularis. Brain Behav Evol. https://doi.org/10.1159/000123780

Kurata K, Hoffman DS (1994) Differential effects of muscimol microinjection into dorsal and ventral aspects of the premotor cortex of monkeys. J Neurophysiol. https://doi.org/10.1152/jn.1994.71.3.1151

Lee JH, Van Donkelaar P (2006) The human dorsal premotor cortex generates on-line error corrections during sensorimotor adaptation. J Neurosci. https://doi.org/10.1523/JNEUROSCI.3898-05.2006

Levy R, Goldman-Rakic PS (2000) Segregation of working memory functions within the dorsolateral prefrontal cortex. Exp Brain Res. https://doi.org/10.1007/s002210000397

Mochizuki H, Franca M, Huang YZ, Rothwell JC (2005) The role of dorsal premotor area in reaction task: comparing the. Exp Brain Res 167:414–421

Moran DW, Schwartz AB (1999) Motor cortical representation of speed and direction during reaching. J Neurophysiol. https://doi.org/10.1152/jn.1999.82.5.2676

Nachev P, Kennard C, Husain M (2008) Functional role of the supplementary and pre-supplementary motor areas. Nat Rev Neurosci. https://doi.org/10.1038/nrn2478

Ohbayashi M, Picard N, Strick PL (2016) Inactivation of the dorsal premotor area disrupts internally generated, but not visually guided, sequential movements. J Neurosci. https://doi.org/10.1523/jneurosci.2356-15.2016

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia. https://doi.org/10.1016/0028-3932(71)90067-4

Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, Di Lazzaro V (2006) Effects of aging on motor cortex excitability. Neurosci Res 55(1):74–77. https://doi.org/10.1016/j.neures.2006.02.002

Pandya DN, Kuypers HGJM (1969) Cortico–cortical connections in the rhesus monkey. Brain Res. https://doi.org/10.1016/0006-8993(69)90141-3

Pandya DN, Vignolo LA (1971) Intra- and interhemispheric projections of the precentral, premotor and arcuate areas in the rhesus monkey. Brain Res. https://doi.org/10.1016/S0006-8993(71)80001-X

Parmigiani S, Cattaneo L (2018) Stimulation of the dorsal premotor cortex, but not of the supplementary motor area proper, impairs the stop function in a STOP signal task. Neuroscience. https://doi.org/10.1016/j.neuroscience.2018.10.005

Paulignan Y, MacKenzie C, Marteniuk R, Jeannerod M (1991) Selective perturbation of visual input during prehension movements—1. The effects of changing object position. Exp Brain Research. https://doi.org/10.1007/BF00229827

Picard N, Strick PL (2001) Imaging the premotor areas. Curr Opin Neurobiol 11(6):663–672

Poston B, Van Gemmert AW, Barduson B, Stelmach GE (2009a) Movement structure in young and elderly adults during goal-directed movements of the left and right arm. Brain Cogn 69(1):30–38. https://doi.org/10.1016/j.bandc.2008.05.002

Poston B, Van Gemmert AWA, Barduson B, Stelmach GE (2009b) Movement structure in young and elderly adults during goal-directed movements of the left and right arm. Brain Cogn. https://doi.org/10.1016/j.bandc.2008.05.002

Poston B, Van Gemmert AWA, Sharma S, Chakrabarti S, Zavaremi SH, Stelmach G (2013) Movement trajectory smoothness is not associated with the endpoint accuracy of rapid multi-joint arm movements in young and older adults. Acta Physiol (oxf). https://doi.org/10.1016/j.actpsy.2013.02.011

Prablanc C, Martin O (1992) Automatic control during hand reaching at undetected two-dimensional target displacements. J Neurophysiol. https://doi.org/10.1152/jn.1992.67.2.455

Przybyla A, Haaland KY, Bagesteiro LB, Sainburg RL (2011) Motor asymmetry reduction in older adults. Neurosci Lett. https://doi.org/10.1016/j.neulet.2010.11.074

Rea GL, Ebner TJ, Bloedel JR (1987) Evaluations of combined premotor and supplementary motor cortex lesions on a visually guided arm movement. Brain Res. https://doi.org/10.1016/0006-8993(87)90962-0

Rice NJ, Tunik E, Grafton ST (2006) The anterior intraparietal sulcus mediates grasp execution, independent of requirement to update: new insights from transcranial magnetic stimulation. J Neurosci. https://doi.org/10.1523/JNEUROSCI.1641-06.2006

Richard A, Van Hamme A, Drevelle X, Golmard JL, Meunier S, Welter ML (2017) Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation. Neuroscience. https://doi.org/10.1016/j.neuroscience.2017.06.047

Romero MC, Davare M, Armendariz M, Janssen P (2019) Neural effects of transcranial magnetic stimulation at the single-cell level. Nat Commun 10(1):2642. https://doi.org/10.1038/s41467-019-10638-7

Sasaki K, Gemba H (1986) Effects of premotor cortex cooling upon visually initiated hand movements in the monkey. Brain Res. https://doi.org/10.1016/0006-8993(86)90422-1

Schmidt RA et al (1979) Motor-output variability: a theory for the accuracy of rapid motor acts. Psychol Rev. https://doi.org/10.1037/0033-295X.86.5.415

Scott SH, Gribble PL, Graham KM, Cabel DW (2001) Dissociation between hand motion and population vectors from neural activity in motor cortex. Nature. https://doi.org/10.1038/35093102

Stuphorn V, Hoffmann KP, Miller LE (1999) Correlation of primate superior colliculus and reticular formation discharge with proximal limb muscle activity. J Neurophysiol. https://doi.org/10.1152/jn.1999.81.4.1978

Tanji J, Shima K (1994) Role for supplementary motor area cells in planning several movements ahead. Nature. https://doi.org/10.1038/371413a0

Tanné-Gariépy J, Rouiller EM, Boussaoud D (2002) Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. Exp Brain Res. https://doi.org/10.1007/s00221-002-1078-9

Tunik E, Frey SH, Grafton ST (2005) Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. Nat Neurosci. https://doi.org/10.1038/nn1430

Van Halewyck F, Lavrysen A, Levin O, Boisgontier MP, Elliott D, Helsen WF (2015) Factors underlying age-related changes in discrete aiming. Exp Brain Res 233(6):1733–1744. https://doi.org/10.1007/s00221-015-4247-3

Vandenberghe A, Levin O, De Schutter J, Swinnen S, Jonkers I (2010) Three-dimensional reaching tasks: effect of reaching height and width on upper limb kinematics and muscle activity. Gait Posture. https://doi.org/10.1016/j.gaitpost.2010.07.009

Vandervoort AA (2002) Aging of the human neuromuscular system. Muscle Nerve. https://doi.org/10.1002/mus.1215

Verstraelen S, van Dun K, Duque J, Fujiyama H, Levin O, Swinnen SP, Meesen RLJ (2020) Induced suppression of the left dorsolateral prefrontal cortex favorably changes interhemispheric communication during bimanual coordination in older adults—a neuronavigated rTMS study. Front Aging Neurosci. https://doi.org/10.3389/fnagi.2020.00149

Welsh TN, Higgins L, Elliott D (2007) Are there age-related differences in learning to optimize speed, accuracy, and energy expenditure? Hum Mov Sci 26(6):892–912. https://doi.org/10.1016/j.humov.2007.04.004

Woodworth RS, Schlosberg H (1954) Experimental psychology (Rev.). Holt, New York

Xu-Wilson M, Tian J, Shadmehr R, Zee DS (2011) TMS perturbs saccade trajectories and unmasks an internal feedback controller for saccades. J Neurosci 31(32):11537–11546. https://doi.org/10.1523/JNEUROSCI.1584-11.2011