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Evidence for distinct brain networks in the control of rule-based motor behavior

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Granek JA, Sergio LE. Evidence for distinct brain networks in the control of rule-based motor behavior. *J Neurophysiol* 114: 1298–1309, 2015. First published July 1, 2015; doi:10.1152/jn.00233.2014.—Reach guidance when the spatial location of the viewed target and hand movement are incongruent (i.e., decoupled) necessitates use of explicit cognitive rules (strategic control) or implicit recalibration of gaze and limb position (sensorimotor recalibration). In a patient with optic ataxia (OA) and bilateral superior parietal lobule damage, we recently demonstrated an increased reliance on strategic control when the patient performed a decoupled reach (Granek JA, Pisella L, Stemberger J, Vighetto A, Rossetti Y, Sergio LE. *PLoS One* 8: e86138, 2013). To more generally understand the fundamental mechanisms of decoupled visuomotor control and to more specifically test whether we could distinguish these two modes of movement control, we tested healthy participants in a cognitively demanding dual task. Participants continuously counted backward while simultaneously reaching toward horizontal (left or right) or diagonal (equivalent to top-left or top-right) targets with either veridical or rotated (90°) cursor feedback. By increasing the overall neural load and selectively compromising potentially overlapping neural circuits responsible for strategic control, the complex dual task served as a noninvasive means to disrupt the integration of a cognitive rule into a motor action. Complementary to our previous results observed in patients with optic ataxia, here our dual task led to greater performance deficits during movements that required an explicit rule, implying a selective disruption of strategic control in decoupled reaching. Our results suggest that distinct neural processing is required to control these different types of reaching because in considering the current results and previous patient results together, the two classes of movement could be differentiated depending on the type of interference.

eye-hand coordination; posterior parietal cortex; prefrontal cortex; strategic control; sensorimotor recalibration/adaptation

DECOUPLED VISUOMOTOR CONTROL involves integration of a cognitive rule with a motor action. The use of a computer mouse, for example, incorporates a simple yet concrete transformational rule: move the mouse forward to orient the cursor vertically (using fast, explicit strategic control). There are also situations in which a rule can only estimate the required direction of the motor plan. For example, if the computer mouse was rotated 45°, a corresponding mental transformation could be approximated, but online feedback would predominate. Instead of relying on the rule, an unconscious sensorimotor realignment (Abeele and Bock, 2003; Sulzenbruck and Heuer, 2009) must occur gradually over multiple attempts (using slow implicit sensorimotor recalibration).

If the computer mouse was rotated 90°, orienting the cursor would require a combination of both gradual and discrete processes (Bock et al., 2003; Werner and Bock, 2010) involving strategic control and sensorimotor recalibration depending on target location (Granek et al., 2013; Werner and Bock, 2010). We have previously demonstrated an increased reliance on explicit strategic control during decoupled visuomotor control in a patient with bilateral caudal superior parietal lobule (SPL) damage resulting in optic ataxia (OA) (Granek et al., 2013). We observed that decoupled reach performance during a 90° rotation was more accurate when the movement required an explicit rule (i.e., toward targets along the horizontal axis) relative to a more implicit sensorimotor realignment (i.e., toward targets along the diagonal axes, importantly, not oriented toward the corners of the visual monitor) (Granek et al., 2013), suggesting damage to a distinct connection between the SPL and the dorsal premotor (PMd) cortex (Pisella et al., 2006; Rizzolatti and Matelli, 2003). Furthermore, performance improves in patients with OA following a delay (Revol et al., 2003; Trillenberg et al., 2007), suggesting a reliance on strategic control networks (Honda et al., 1998;Sulzenbruck and Heuer, 2009) via prefrontal communication with an intact inferior parietal lobule (IPL) or infero-temporal cortex (Pisella et al., 2006).

To further demonstrate the independence of neural processes associated with different types of rule-based movement control, one would need to selectively impair movements that rely on explicit rule use without affecting implicitly controlled visuomotor realignment, the inverse to what we have previously demonstrated (Granek et al., 2013). The present study attempts this double dissociation by employing a complex dual task designed to interfere with cognitive-motor integration. We tested a group of healthy individuals with both veridical and 90° rotated cursor feedback, with and without a cognitively demanding secondary task (sequential backward counting). Sequential verbal arithmetic has been suggested to involve a cortical network including the IPL and the prefrontal cortex (Grabner et al., 2009; Simon et al., 2004). We hypothesized that the complex secondary task would activate a similar network thought to be involved in cognitively demanding visuomotor control (Pisella et al., 2006, 2009). On the basis of our working hypothesis of dual streams for decoupled reaching depending on target location, we predicted that the secondary task would interfere with the guidance of a rotated cursor toward horizontal targets, which required the implementation of a strategic rule (e.g., right = up). In contrast, we predicted that the complex secondary task would not affect the movements toward diagonal targets as it did in our previous OA study, which required more sensorimotor recalibration (Granek et al., 2013; Werner and Bock, 2010). Here we report that indeed, one can selectively disrupt movements requiring ex-

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plicit strategic control, complementary to our previous work in which we selectively disrupted movements requiring implicit sensorimotor recalibration. These findings support the existence of distinct cortical networks involved in the control of different aspects of rule-based motor control.

METHODS

Participants. We tested 20 healthy participants (10 men, 10 women; mean age 27 ± 7 yr). All participants gave informed consent, and the study protocol was approved by the York University human participant research ethics committee. All participants were tested using their dominant right hand [handedness score greater than +0.50 (Oldfield, 1971)] and had experience with a computer mouse and laptop touchpad.

Experimental procedure. Participants sat in a darkened room in front of a computer monitor at a distance of 43 cm, aligned with their midsagittal plane. They made sliding finger movements over a touch-sensitive screen (Keytec Magic Touch Screen Model KTMT-1315, sampling rate 100 Hz, Garland, TX) affixed over the computer monitor to displace a cursor from a starting point to one of two horizontal targets (right or left), or to one of two diagonal targets (45° rotated from a vertical line, equivalent to top-right or top-left; Fig. 1*B*). Importantly, contrary to the horizontal targets that were oriented directly perpendicular to the dimly lit computer monitor border, the diagonal targets were not oriented toward any helpful allocentric cues such as the corner of the monitor (Fig. 1*A*). Following a 2-s delay, one of the peripheral visual targets (16 mm in diameter) was presented 120 mm (16° visual angle) from the starting point (25 mm in diameter), always on the vertical monitor. Participants were instructed to move the cursor as accurately and quickly as possible across the touch screen into the target, and were encouraged to maintain a consistent initial arm orientation for the different task conditions of the experiment. Eye movements were monitored at 250 Hz (right eye; EyeLink II, SR Research, Ottawa, Ontario, Canada). The viewing space was calibrated using a nine-point calibration and drift correction was applied between each condition.

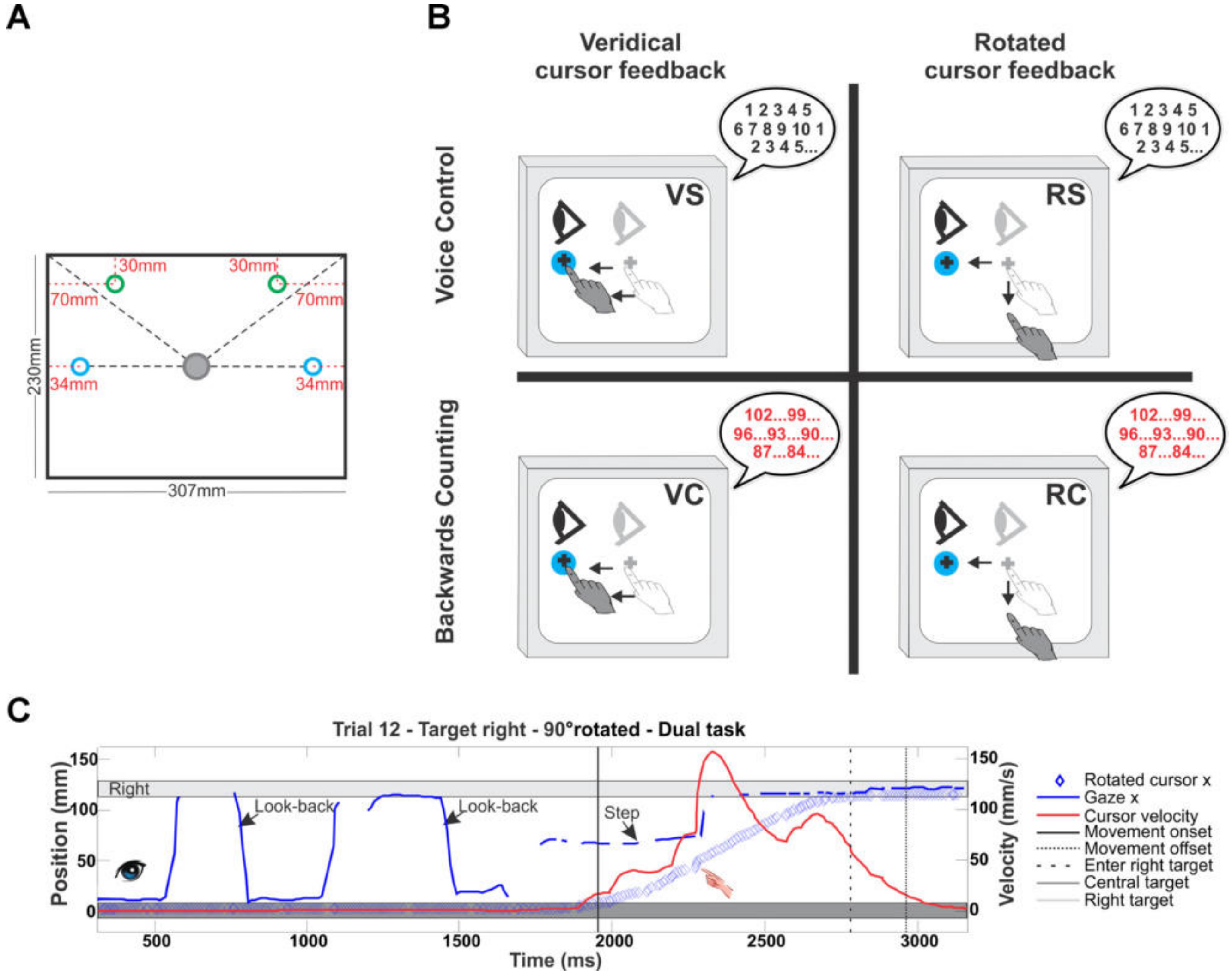


Fig. 1. Experimental procedure schematic and example eye and hand trajectories. *A*: schematic of horizontal (blue) and diagonal (green) target locations. Note that the diagonal targets are not oriented directly toward the corners of the computer monitor. *B*: schematic drawing of the veridical and rotated (90° clockwise) cursor feedbacks. Both conditions were performed concurrently with a simple dual task (forward counting from 1 to 10, blue numbers) and with a complex dual task (backward counting by 3 or 7, red numbers). The blue circles denote the cued position before the movement. Eye and hand symbols in lighter hues denote starting positions. Practice trials were performed before each condition (presented in randomized order) until it was reported that the task was sufficiently familiar for testing to begin. V indicates veridical cursor feedback; R, rotated cursor feedback; S, simple dual task; C, complex dual task. *C*: example eye and hand data during the 90° rotated dual task toward the right visual target (i.e., hand must move upward to orient the cursor to the right). Note the prominent eye movement errors and the slow movement timing.

Figure 1*B* displays a schematic of the experimental conditions. The participants performed a standard condition with veridical cursor feedback (V) and a 90° rotated (clockwise) condition (R) in combination with either a voice control requiring simultaneous forward counting (simple, S) or a dual task requiring simultaneous backward counting (complex, C). The voice control conditions (VS and RS) were performed to control for speaking in the chin rest and involved repeatedly consecutive counting from 1 to 10, and very little cognitive processing. The backward counting conditions (VC and RC) involved sequences of backward counting by either three or seven starting from different numbers between 90 and 110, and was much more cognitively demanding relative to forward counting. The R condition was used to present a situation in which a simple rule could be implemented for the horizontal targets (e.g., right = down), but a more gradual (Werner and Bock 2010), implicit sensorimotor recalibration (Granek et al. 2013) was required for the diagonal targets.

To ensure equal understanding of the transformational rules applied in each condition, all participants were verbally informed of the details of the conditions and were then trained on the V condition followed by the R condition until each participant reached a performance plateau for both target types (Fig. 2). Before each randomly assigned experimental block, participants were reminded of the nature of each condition and were allowed practice until reporting that they understood the task and were comfortable performing it. Following training, each participant performed 40 trials in each of the four randomly assigned experimental conditions (Fig. 1*B*). For the verbal arithmetic baseline, each participant was verbally instructed on the details of sequential subtraction, which depended on the seed number and subtraction amount. Again, before each experimental condition, participants were reminded how the sequential arithmetic was to be performed. Participants were encouraged to continuously count throughout the entire experimental trials including the delay and movement epochs. Importantly, an equal emphasis on speed and accuracy was encouraged for both the verbal and visuomotor tasks. The total testing time was ~60 min.

Data analyses. Trials were included in the hand and eye movement analyses only if they were successfully performed within a maximum of 10 s and performed without an initial hand direction error. A direction error was quantified as a hand movement that was greater than 45° to either side of a straight line between the central and peripheral target occurring in the first half of the ballistic movement.

The individual hand movement data were first low-pass Butterworth reverse-filtered at 10 Hz (Matlab; Mathworks, Natick, MA). Hand movement timing was analyzed whereby hand reaction time (HRT) began when the peripheral target was presented and ended at movement onset. Hand movement onsets were scored as the point at which the tangential velocity exceeded 10% of its peak using a custom-written computer algorithm. The hand movement time (HMT) was divided into an acceleration phase prior to peak velocity (hand acceleration time, HAT) and a deceleration/correction phase from peak velocity to the entry of cursor into the peripheral target (hand deceleration time). Peak velocity was recorded as the maximum tangential change in resultant *x* and *y* positions over time between movement onset and when the cursor entered the perimeter of the peripheral target. As a measure of path linearity, the absolute angle (in degrees) of the vector from the starting point to the point of the trajectory that corresponds to the maximum velocity relative to a straight line between the central and peripheral targets was recorded for each trial (angle at peak velocity). Hand movement accuracy and precision were recorded from the participant's absolute movement endpoints relative to each target (absolute error). Further details on the direction (on- and off-axis constant error) and precision (variable error) of the hand movement endpoints were calculated in Supplementary Table S2 (supplementary material for this article is available online at the Journal website).

Eye position data were first low-pass Butterworth reverse-filtered at 50 Hz (Matlab; Mathworks) and were drift-corrected before each trial. Eye movement timing was analyzed whereby eye reaction time (ERT) began when the peripheral target was presented and ended at saccade onset. Eye movement onsets were scored as the point at which the resultant of the *x* and *y* trajectories exceeded 10% of the peak velocity. Eye movement time began at saccade onset and ended when the pupil entered the perimeter of the peripheral target. Eye scan paths were recorded to observe the unrestricted eye movement behavior when the hand was spatially decoupled from gaze direction. Each sampled data point obtained during the experiment that was registered as a blink was interpolated offline using data obtained from the nearest accurate measurement before and after the point. Blinks were detected from a transient reduction in the pupil size measurement, provided by the eye tracking system. To identify saccade-related errors, eye scan path data were recorded from eye movement onset until the entrance of the cursor into the peripheral target. The saccade-related errors were placed into three categories: *1*) steps; *2*) look-backs; and *3*) hand-biased mis-saccades (HBMS). Saccade-related errors were coded only if they occurred greater than 10% (12 mm) of a full saccade (from central to peripheral target) from the target border to ensure we were not enumerating eye movements within the target. The resulting errors were categorized as steps if an eye movement trajectory continued for at least 100 ms. Hypometric saccadic steps were defined as brief saccadic pauses occurring before reaching the peripheral target, whereas hypermetric steps were recorded when these small saccadic pauses occurred beyond the peripheral target toward the border of the computer monitor. Look-backs were counted when participants reversed eye direction (i.e., toward the cursor) a minimum of 20% (24 mm) of the total amplitude from the central target to the peripheral target, holding gaze for at least 100 ms. HBMS were recorded if either or both the initial and final saccadic endpoints were biased (greater than 10% of total distance from central to peripheral target) toward the direction of the hand during the decoupled conditions.

Statistical analyses. All analyses focused on the complex aspect of visuomotor control. The complex aspect for each dependent variable was determined as the relative change in performance between complex (backward counting) and simple (voice control) reaching for each condition and target type. To control for baseline differences across

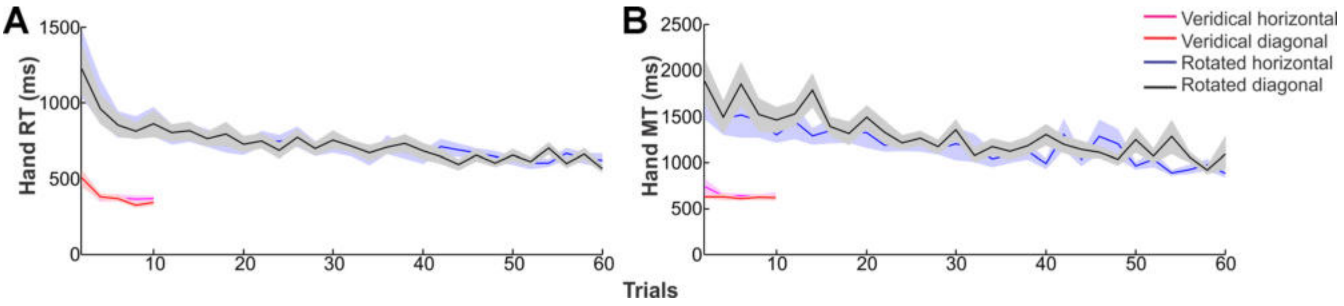


Fig. 2. Hand movement timing during training. Hand reaction time (*A*) and hand movement time (*B*) during training following a verbal explanation for both veridical and rotated conditions. Note the learning plateau for both dependent variables during the last 10 trials for each target type (horizontal and diagonal) in both conditions. Shaded areas denote SE.

participants, we statistically removed (i.e., covaried for) the effects of the simple dual tasks from that of the complex dual tasks. To screen for the effects of sex (men vs. women) on each condition and target type, we initially conducted three-way repeated-measures ANOVAs with condition, target type (horizontal vs. diagonal targets) as within-subject factors, and sex as a between-subject factor. No condition × target type × sex interactions were observed; therefore, all further analyses were pooled across both sexes for each task condition and each target type. All condition × target type ANOVA results were reported with Greenhouse-Geisser-corrected *P* values, and post hoc contrasts were corrected for multiple comparisons (Bonferroni).

RESULTS

If one is relying on a strategic rule to successfully perform a decoupled visually guided reach, the addition of a second cognitively demanding task would interfere with the implementation of the rule into an ongoing motor action. To address this prediction, we initially performed two control analyses. First, we conducted a series of two (condition, veridical vs. rotated) × two (target type, horizontal vs. diagonal) repeated-measures ANOVAs on the effect of the complex aspect of a dual task (see METHODS for details).

During training, although participants predominantly reached a performance plateau during the last 10 trials per target type for each condition of training, some variability in hand movement timing was observed during the rotated condition toward the diagonal targets (see Fig. 2), Importantly, however, no condition × target interactions were observed during training for HRT ($P = 0.95$) or HMT ($P = 0.09$). Thus we were certain that the task was understood and that any differences observed were a result of the addition of the complex secondary task. Second, we tested whether the required division of attention during the complex dual-task conditions selectively impaired performance of the secondary task (sequential backward counting). No differences in counting ($P = 0.27$) or error rates ($P = 0.15$) were observed during SD and RD relative to the voice control. The counting rates increased by 0.003 ± 0.2 numbers counted per second for SD and decreased by 0.06 ± 0.2 numbers counted second for RD, whereas the error rates decreased by 0.1 ± .05 errors per answer for SD and by 0.007 ± 0.06 errors per answer for RD. Consequently, only the primary task revealed selective differences between conditions and targets as a result of the complex dual tasks.

Complex dual tasks impaired eye and hand timing when strategic control was required. To assess both predictive and online updating deficits as a result of performing a secondary task, we analyzed eye and hand movement reaction time and movement time. Figures 3 and 4 show the relative changes in eye and hand movement timing from baseline (voice control) for both target types and conditions. See Supplementary Tables S1–S4 for raw scores of all variables.

Simultaneously counting backward and reaching slowed down both eye (ERT) and hand (HRT) movement preparation timing by 156.5 ± 32.9 ms and 317.3 ± 50.8 ms, respectively, regardless of condition or target type. Neither ERT ($P = 0.56$) nor HRT ($P = 0.57$), however, displayed a condition × target interaction. In contrast, both eye and hand movement execution timing were differentially affected by condition and target type during the complex dual task. Specifically, we observed a condition × target interaction for EMT (ANOVA $F_{1,18} = 22.9$, $P = 0.0001$). Importantly, post hoc comparisons revealed a greater increase in EMT for the horizontal targets relative to the diagonal targets during the rotated condition ($P = 0.0001$). We also found that the secondary cognitive task interfered with the hand movements to horizontal targets to a much greater extent than the diagonal movements. Hand movements took longer in the rotated condition than the veridical condition during the acceleration phase (HAT, main effect of condition, ANOVA $F_{1,18} = 26.1$, $P = 0.0001$). Notably, a condition × target interaction (ANOVA $F_{1,18} = 11.6$, $P = 0.003$) was observed during decoupled reaching, specifically toward the horizontal targets relative to the diagonal targets ($P = 0.02$). A condition × target interaction was also observed for peak velocity (ANOVA $F_{1,18} = 15.6$, $P = 0.001$), whereby participants reached a significantly lower peak velocity when counting backward while guiding the rotated cursor toward the horizontal targets relative to the diagonal targets ($P = 0.0001$).

In summary, the preparation of eye and hand movement was similarly affected by the performance of a concurrent cognitively demanding task. Notably, however, eye and hand movement execution was most compromised by the complex dual task when orienting a rotated cursor toward the horizontal targets, a movement that required the use of an explicit rule and could be guided by accurate allocentric cues. Eye and hand kinematics were considerably less affected by the complex secondary task when the movement employed a learned im-

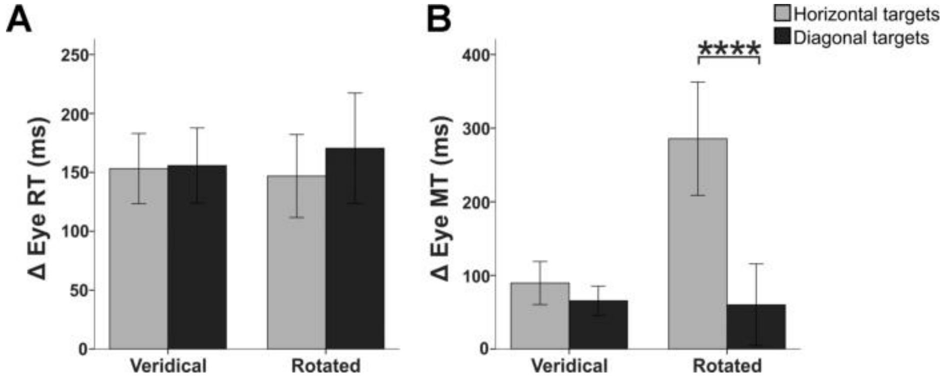


Fig. 3. Eye movement timing. Change in eye reaction time (*A*) and eye movement time (*B*) compared with control conditions for the complex dual-task conditions [i.e., both horizontal (right and left, gray bars) and diagonal (top-right and top-left, black bars) targets]. Error bars denote SE. ****$P < 0.0001$ [significance (Bonferroni-corrected) of post hoc condition by target comparisons].

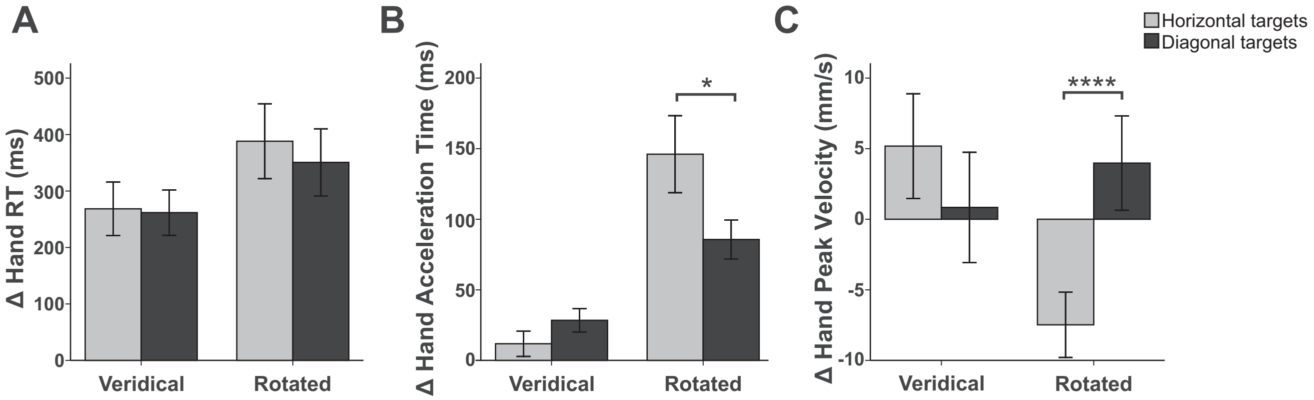


Fig. 4. Hand movement timing. Change in hand reaction time (*A*), hand acceleration time (*B*), and peak velocity (*C*) compared with control conditions for the complex dual-task conditions [i.e., both horizontal (right and left, gray bars) and diagonal (top-right and top-left, black bars) targets]. Note the increase in hand movement timing and decrease in velocity when orienting toward the horizontal targets. Error bars denote SE. $^{*}P < 0.05$, $^{****}P < 0.0001$ [significance (Bonferroni-corrected) of post hoc condition by target comparisons].

plicit sensorimotor recalibration between vision and proprioception toward the diagonal targets.

Complex dual task impaired ballistic hand motor command when strategic control was required. If the complex secondary task was successful in interfering with the implementation of a cognitive rule into a motor plan, the initial ballistic movements would be inaccurate, thus resulting in an increased reliance on online sensorimotor updating. To address the integrity of the ballistic motor plan, we conducted analyses of initial hand movement endpoints (absolute error) and trajectories (angle at peak velocity). Figure 5*A* displays the ballistic endpoints and trajectories across all conditions for a typical participant.

The addition of a complex secondary task increased absolute error for the rotated task to a greater extent than for the veridical task (main effect of condition, ANOVA $F_{1,18} = 11.9$, $P = 0.005$). As with the eye and hand movement timing, a condition × target interaction (ANOVA $F_{1,18} = 55.4$, $P = 0.0001$) was observed, reflecting an increase in error for the

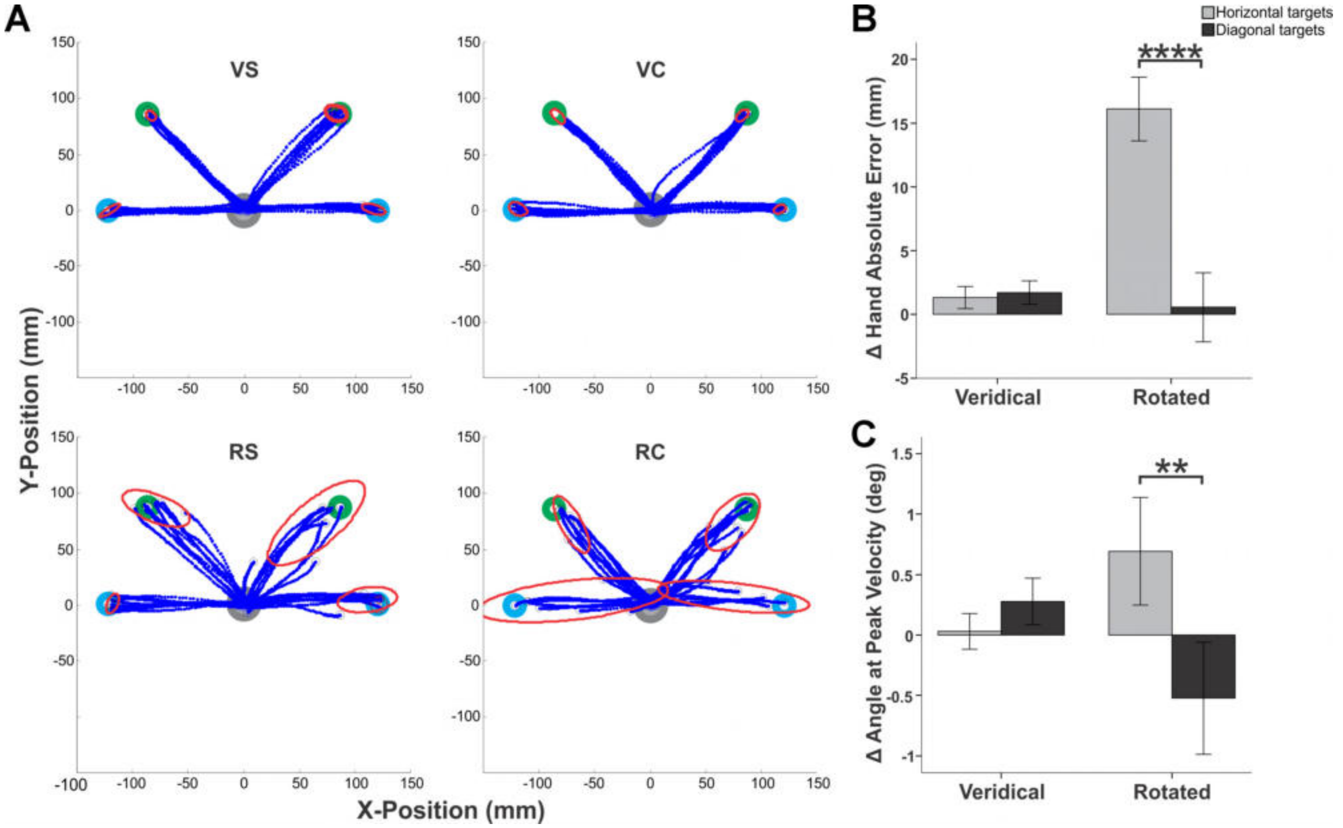


Fig. 5. Hand movement trajectories and endpoints. *A*: example trajectories and endpoints of a typical subject performing the veridical simple (VS), veridical complex (VC), rotated simple (RS), and rotated complex (RC) tasks. Ellipses denote 95% CI of landing point following ballistic hand motor plan. Note the increased deficits toward the horizontal targets during the rotated complex condition. Group changes in hand absolute error following ballistic reach (*B*) and hand angle at peak velocity (*C*) during the complex dual task conditions relative to the simple, backward counting controls. Error bars denote SE. $^{**}P < 0.01$, $^{****}P < 0.0001$.

horizontal targets relative to the diagonal targets during a rotated reach ($P = 0.0001$, Fig. 5*B*). Similarly, analyses of the hand movement trajectories (angle at peak velocity) revealed a condition × target interaction (ANOVA $F_{1,18} = 9.0$, $P = 0.007$), whereby the trajectories were more deviated when orienting the cursor toward the horizontal targets relative to the diagonal target during the rotated condition ($P = 0.005$, Fig. 5*C*).

Similar to what we observed for hand and eye movement times, differences in hand endpoint and trajectory parameters during the complex dual task relative to the voice control revealed the greatest errors when moving toward the horizontal targets during the rotated condition.

Additional eye movements were performed for the complex dual task during visuomotor rotation toward horizontal targets but not diagonal targets. If a decoupled task that is not implicitly incorporated into a motor plan is interfered with, as we propose with our complex dual task, the guidance of the decoupled limb will become more difficult. Although all participants were instructed to foveate the peripherally cued visual target, eye movements were not restricted. Our previous work has shown that different visuomotor mappings can affect both eye and hand kinematics (Gorbet and Sergio 2009). Under these natural conditions, and similar to our previous reports in patients with OA (Granek et al., 2012, 2013), we observed four basic types of eye movement errors. However, in the current situation, our complex dual task interfered with the eye movements toward the horizontal targets (Fig. 5) rather than the diagonal targets as is observed in patients with bilateral OA (Granek et al., 2013).

Across eye-movement errors, we observed a main effect of condition (ANOVA $F_{1,18} = 7.5$, $P = 0.01$) and a condition × target interaction (ANOVA $F_{1,18} = 48.1$, $P = 0.0001$), predominantly as a result of the greater number of errors during the rotated task toward the horizontal targets relative to the diagonal targets ($P = 0.0001$). Specifically, addition of the complex secondary task led to a condition × target interaction for the number of additional pauses prior to acquiring the peripheral target (i.e., hypometric steps; ANOVA $F_{1,18} = 52.8$, $P = 0.0001$). This interaction was influenced predominantly by the increase in hypometric steps toward the horizontal targets during the rotated condition ($P = 0.0001$). The complex dual task also led to increased pauses beyond the peripheral target toward the computer monitor border (i.e., hypermetric steps) during the rotated condition relative to the veridical condition (main effect of condition, ANOVA $F_{1,18} = 7.2$, $P = 0.02$). Similarly, the complex dual task influenced the number of look-backs toward the cursor during the rotated condition relative to the veridical condition (main effect of condition, ANOVA $F_{1,18} = 9.9$, $P = 0.006$). In terms of target differences, participants performed more of these look-backs (condition × target interaction, ANOVA $F_{1,18} = 5.3$, $P = 0.03$) during the rotated condition toward the horizontal targets relative to the diagonal targets ($P = 0.005$). Finally, the introduction of the complex secondary task influenced the number of saccades that were biased toward the direction of the decoupled limb (i.e., HBMS) during the rotated condition relative to the veridical condition (main effect of condition, ANOVA $F_{1,18} = 4.7$, $P = 0.04$). We observed a condition × target interaction (ANOVA, $F_{1,18} = 31.1$, $P = 0.0001$), again driven by the increase in errors toward the horizontal targets relative to the diagonal targets during the rotated condition ($P = 0.0001$).

To summarize, more eye movement errors were observed as a result of the interference of complex dual task predominantly during the rotated condition toward the horizontal targets—a situation that relies more on rule-based motor control than implicit sensorimotor recalibration.

DISCUSSION

Overall, our results demonstrate that the divided attention required during the cognitively challenging dual task selectively impaired the implementation of a cognitive rule into a motor plan while sparing implicit sensorimotor control. The addition of a cognitively challenging secondary task introduced an increased neural load that required divided attention. The increase in neural load could have interfered with overall neural processing as well as some more specific interference with spatial processing. Although daily activities often require simultaneous performance of two different tasks such as walking and talking, dividing one's attention impairs even familiar tasks (Neider et al., 2011), potentially due to bottlenecking (Pashler, 1990) of shared sensory resources (Taylor and Ivry, 2012). As such, dual tasks have been utilized experimentally as a noninvasive means to causally impair a wide range of behaviors including drawing (Martin and Henriques, 2010; Martin et al., 2013), walking (Bock, 2008; Neider et al., 2011), and arithmetic (Lee and Kang, 2002). The complex dual task employed in the current study did in fact selectively impair the conditions requiring the greatest strategic control, supporting our working hypothesis of a distinct, independent pathway for this mode of control. As predicted, the most robust deficits were observed during the rotated-feedback complex dual-task condition toward the horizontal relative to the diagonal targets, implying alternate movement control depending on target location. These deficits included slower eye and hand movements, as well as additional pauses in eye trajectory and instances of looking back toward the cursor or the hand. We suggest that these additional eye movements were performed to enable the recoupling of gaze and cursor/hand location to generate and maintain an accurate difference vector (Granek et al., 2012; Shadmehr and Wise, 2005). Free gaze toward the visual target has been associated with the onset of error reduction during decoupled visuomotor learning, implying the influence of explicit gaze location strategies on implicit visuomotor learning (Rand and Rentsch 2015). It appears that the visuomotor adaptation suppressed its generalization to the horizontal targets, a situation in which it was possible to use an explicit, strategic rule to guide movement in some parts of the workspace. To accurately generalize the results found in the current study across other targets in the workspace, one would require testing these decoupled movements toward other target orientations (e.g., vertical orientations). The target locations in the current study were chosen to replicate those performed by patient I.G. in our previous OA study (Granek et al., 2013). Those target directions were chosen to prevent any visual targets presented in the lower hemifield in which the patient with OA who was tested had a visual scotoma.

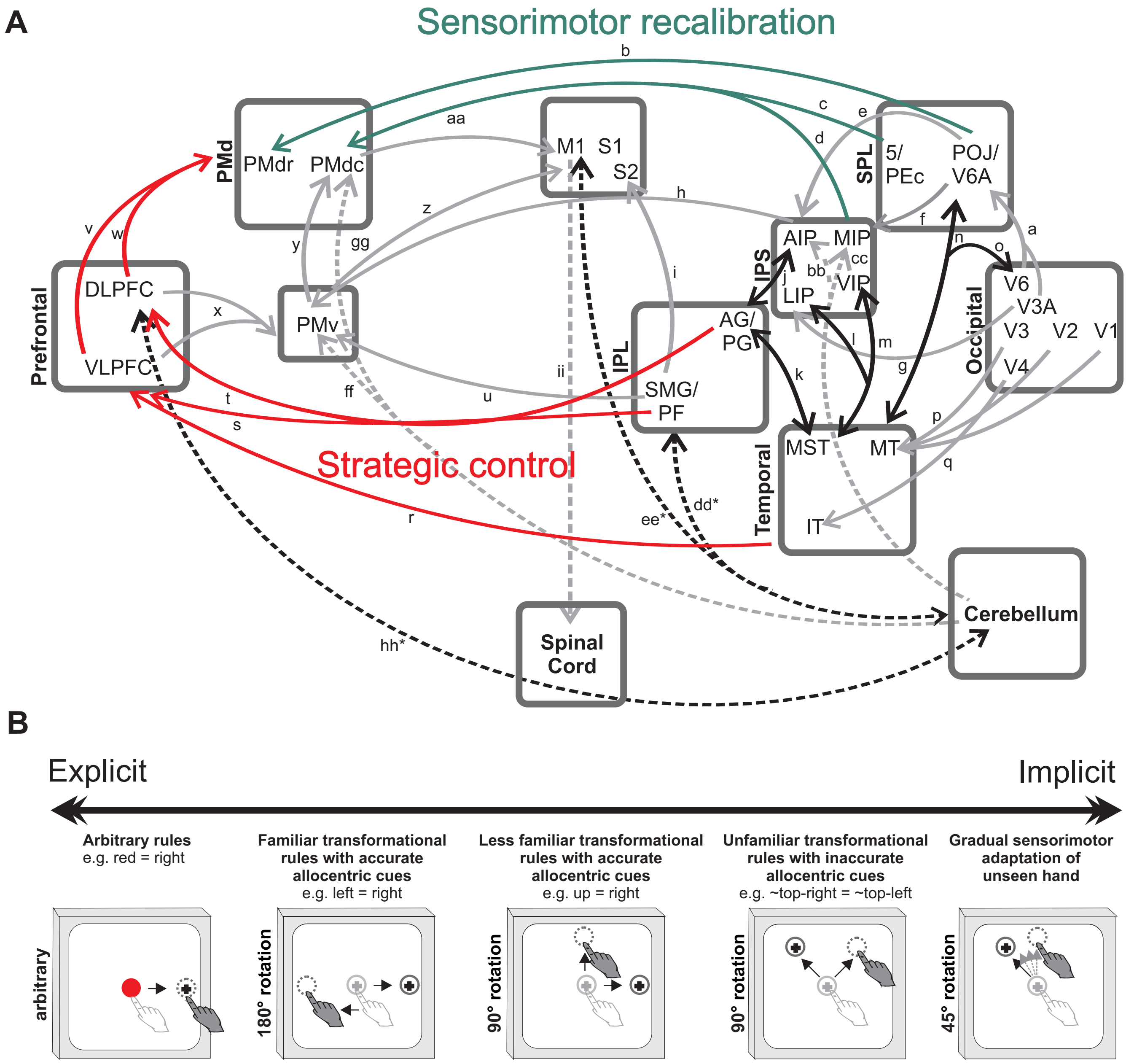
Interestingly, in the current study, the complex dual task did not selectively impair the planning of the two types of rule-based movements. In a previous dual-task study, only slight saccadic RT deficits (~39 ms) and intact hand RT were observed following a 2-s delay during eye-hand coordination using a stylus with veridical cursor feedback (Bekkering et al., 1994). Because our conditions also consisted of a long delay (2 s), participants were able to plan the upcoming eye and hand movements concurrently with the verbal arithmetic with equal accuracy regardless of condition or target orientation. Perhaps selective planning deficits such as those observed during a dual task for a 90° rotated choice reaction time task (Eversheim and Bock, 2001) might have been observed in our task, testing an interference with strategic control if the delay was shorter. In contrast, implementation of the cognitive rule was most impaired during the RC condition (rotated-feedback/backward counting) movement toward the horizontal targets, a task learned primarily via strategic control (Granek et al., 2013; Werner and Bock, 2010). In the current study, impaired implementation of the cognitive rule with the motor action was apparent in the acceleration phase of the hand acceleration timing and the endpoint errors of the ballistic hand motor plan (for details see Supplementary Table S2). The observed deficits in cognitive-motor integration might have reflected an impaired categorical representation of the motor goal, which can be overridden by short-term sensorimotor feedback required during a decoupled reach (see Rossetti, 1998), thus potentially disrupting the transformation from extrinsic to intrinsic coordinates (McIntyre et al., 2000). In the current study, the online correction phase of movement was less affected during the complex dual task. Because continuous visual feedback is crucial for automatic visuomotor adaptation (Hinder et al. 2010; Taylor et al. 2014), it is probable that the more gradual learning of the visuomotor rotation toward the diagonal targets required more online updating relative to the more discrete learning of the horizontal targets. It has been suggested that a flexible interplay between explicit, rule-based learning and implicit, adaptive learning of a forward model exists during decoupled visuomotor learning (Taylor et al. 2014). Specifically, explicit, strategic aiming during the initial stages of visuomotor learning tends to predominantly influence target errors with only a subtle effect on the sensory prediction during implicit, gradual sensorimotor recalibration (Benson et al. 2011; Taylor et al. 2014). Thus in the current study, guiding the rotated cursor toward the horizontal targets relied predominantly on the initial angle estimation based on the learned cognitive rule, resulting in less visuomotor adaptation and consequently more disruption from the complex dual task. Further work is required to confirm the exact stage of disruption of movement control toward different target directions.

Our previous work with a patient with bilateral OA (Granek et al., 2013) revealed an impaired dorso-dorsal (Pisella et al., 2006; Rizzolatti and Matelli, 2003) parieto-frontal network for implicit sensorimotor recalibration, because performance in OA improved during situations in which patients relied on strategic control (e.g., 90° rotation, horizontal targets). In contrast, and in support of our working hypothesis, the complex dual task employed here revealed impaired performance rather than improved performance when guiding the rotated cursor toward the horizontal targets, thereby selectively disrupting movements that relied on the integration of an explicit rule. These data, when considered in the context of our previous work, provide further evidence for independent cortical processes depending on the mode of movement control by creating a double dissociation between the cortical area of disruption (through either damage or interference) and the type of movement that became impaired. On the basis of these data and numerous other anatomical and physiological studies of the brain during reach behavior, we present a schematic of putative cortical networks involved in the control of rule-based behavior (Fig. 6*A*). In addition, we propose that rule-based visuomotor control involves a continuum between explicit and implicit control depending on the details of the task (Fig. 6*B*). The movement control system could thus employ the distinct networks suggested to varying degrees depending on the nature of the task requiring cognitive-motor integration.

Fig. 6. Putative cortical networks and example tasks requiring a relative contribution of strategic control and sensorimotor recalibration. *A*: schematic of the possible cortical connections based on a collaboration of human and macaque connection experiments (see lowercase letters below) involved in strategic control (red) sensorimotor recalibration (green). Cross-talk between networks is indicated by black double arrows, other intermediate connections are shown in gray. Dashed lines imply subcortical connections, asterisks imply indirect connections via thalamus/pons. Note that although most cortico-cortical connections are drawn with arrows pointing in one direction, most connections are reciprocal. VLPFC and DLPFC represent ventrolateral and dorsolateral prefrontal cortices, respectively; PMv, PMdr, and PMdc represent the ventral, rostral, and caudal dorsal premotor areas, respectively. M1 and S1 represent primary motor and primary sensory cortices, respectively. S2, secondary somatosensory cortex. The posterior parietal cortex includes the superior parietal lobule (SPL), which includes the parieto-occipital junction (POJ) and area 5 (monkey area PEc). The inferior parietal lobule (IPL) includes the supramarginal gyrus (SMG) and angular gyrus (AG). The SPL and IPL are separated by the intraparietal sulcus (IPS), which consists of anterior (AIP), lateral (LIP), ventral (VIP), and medial (MIP) divisions. The occipital cortex includes visual association areas V1 (primary visual) and V2, V3, V3a, V4, and V6. The temporal cortex includes the inferior (IT), middle (MT), and medial superior (MST) temporal cortices. *a*) (Galletti et al., 2001; Grol et al., 2007; Shipp et al., 1998), *b*) (Caminiti et al., 1999; Gamberini et al., 2009; Matelli et al., 1998; Marconi et al., 2001; Passarelli et al., 2011; Shipp et al., 1998; Tanne et al., 1995), *c*) (Bakola et al., 2010), *d*) (Grol et al., 2007; Tanne-Gariepy et al., 2002; Tomassini et al., 2007), *e*) (Borra et al., 2008; Gamberini et al., 2009), *f*) (Passarelli et al., 2011; Tanne et al., 1995), *g*) (Nakamura et al., 2001), *h*) (Matelli et al., 1986; Matelli and Luppino, 2001; Rozzi et al., 2006; Rushworth et al., 2006; Tanne-Gariepy et al., 2002), *i*) (Cavada and Goldman-Rakic, 1989a; Rozzi et al., 2006), *j*) (Borra et al., 2008), *k*) (Maunsell and van Essen, 1983), *l*) (Boussaoud et al., 1990; Maunsell and van Essen, 1983), *m*) (Maunsell and van Essen, 1983), *n*) (Colby et al., 1988; Passarelli et al., 2011), *o*) (Galletti et al., 2001), *p*) (Maunsell and van Essen, 1983), *q*) (Maunsell and van Essen, 1983), *r*) (Petrides and Pandya, 2002; Tanne et al., 1995), *s*) (Petrides and Pandya, 2006, 2009; Rozzi et al., 2006; Tomassini et al., 2007), *t*) (Cavada and Goldman-Rakic, 1989b; Petrides and Pandya, 2006, 2009; Rozzi et al., 2006), *u*) (Petrides and Pandya, 2009; Rozzi et al., 2006; Rushworth et al., 2006; Tomassini et al., 2007), *v*) (Luppino et al., 2003; Tomassini et al., 2007), *w*) (Luppino et al., 2003; Matelli and Luppino, 2001; Tomassini et al., 2007), *x*) (Tomassini et al., 2007), *y*) (Dum and Strick, 2005; Marconi et al., 2001), *z*) (Dancause et al., 2006a, 2006b), *aa*) (Barbas and Pandya, 1987; Dum and Strick, 2005; Johnson et al., 1993, 1996; Tanne et al., 1995), *bb*) (Clower et al., 2005), *cc*) (Prevosto et al., 2009), *dd**) (Clower et al., 2001; Dum and Strick, 2003; Glickstein et al., 1985; May and Andersen, 1986), *ee**) (Clower et al., 2005; Dum and Strick, 2003; Kelly and Strick, 2003), *ff*) (Clower et al., 2005), *gg*) (Hashimoto et al., 2010), *hh**) (Dum and Strick, 2003; Kelly and Strick, 2003; Middleton and Strick, 2001), and *ii*) (He et al., 1993, 1995). *B*: schematic of the relative explicit vs. implicit requirements of different nonstandard tasks involving cognitive-motor integration.

It has been established that cognitive-motor integration involves a distributed parieto-frontal network (Chouinard and Goodale, 2009; Connolly et al., 2000; Gorbet et al., 2004; Granek et al., 2010; Toni and Passingham, 1999). The addition of a cognitively demanding secondary task such as sequential backward counting has been shown to activate a similar network including the left angular gyrus (AG) (Dehaene and Cohen, 1997), a region activated during increased task complexity, and the dorsolateral prefrontal cortex (DLPFC) (Grabner et al., 2009), a region activated when initiating a complex task (Menon et al., 2000). Specifically, the left AG has been implicated in sequential memorized mathematics (Lee, 2000; Menon et al., 2000) due to its link with the verbal system (Dehaene and Cohen, 1997; Dehaene et al., 2003; Lee and Kang, 2002) and with the recall of stored arithmetic facts (Grabner et al., 2009). Adjacent activations just inferior (Simon et al., 2002) and mesial (Simon et al., 2004) to the left AG have been observed as a part of the network involved in the linkage between arithmetic and language (Simon et al., 2004). In the current study, the tasks believed to use more automatic and implicit motor control were less affected than those involving more cognitive-motor integration, implying independent cortical resources from sequential verbal arithmetic.

A more distributed (Grabner et al., 2009) and varying (Rosenberg-Lee et al., 2009) parieto-frontal network has been observed for verbal arithmetic when participants used alternative procedural strategies than memory recall. Strategic control can rely on transformational rules (Wise et al., 1996) and has been suggested (Miller, 2000; Murray et al., 2000; Rougier et al., 2005) to be largely mediated by top-down control via connections from DLPFC into rostral PMd (PMdr) in nonhuman (Luppino et al., 2003; Matelli and Luppino, 2001) and human (Tomassini et al., 2007) primates. DLPFC neurons can



bias downstream connections as they respond to both the initiation of the interrupting (secondary) task and the resumption of the primary task (see Miyazaki et al. 2013). Ardila and Rosselli (2002) suggest that patients with prefrontal damage suffer during successive operations such as backward counting with the tendency to preserve the same pattern within their answers (e.g., 100 − 7 = 93, 83, 73...), which was an error observed during the complex dual task in the current study. Downstream, PMdr is known to represent the relative position between gaze, hand, and target (Pesaran et al., 2006) during rule-based motor control (Sayegh et al., 2013).

The question remains how cognitive information from the prefrontal cortex and sensory information from the parietal cortex are combined to devise a motor plan for decoupled reaching. Figure 6*A* contains a schematic depiction of possible alternative connections. Briefly, evidence in support of indirect parieto-frontal communication for decoupled eye-hand coordination comes from reach studies on extra-foveal reaching in patients with OA. When the task employs a long delay between the cue and the movement (see Schenk, 2006), a combination of compensatory temporal lobe and intact superior parietal lobe activation is observed (Himmelbach et al., 2009). Similarly, hand endpoint performance was shown to improve when patients with OA had more time for processing the remembered representation of the movement goal (Revol et al., 2003; Trillenberg et al., 2007) and when grasping objects with familiar allocentric cues (Jeannerod et al., 1994). In the current study, orienting a rotated cursor toward potentially useful allocentric cues (i.e., perpendicular to the computer monitor border) was selectively impaired during the complex rotated condition. Finally, cortical networks are the focus of our study, given the cortical damage experienced by the patients in our previous work upon which this experiment was based. However, one cannot present a schematic of brain networks for visual-proprioceptive integration during reach without including the cerebellum, which is recognized as being crucial for on-line monitoring of visuomotor adaptation (Donchin et al. 2012; Shmuelof and Krakauer 2011) by learning a forward model to reduce sensory prediction errors (Shadmehr et al. 2010). We include a number of relevant cerebellar-cortical connections in our model, and are at present exploring the contribution of this structure to cognitive-motor integration in ongoing imaging work (Gorbet and Sergio, 2014).

In addition to our working hypothesis of different brain networks for different types of decoupled reaching, the differences in behavior observed in the current study might reflect variations in competition for cognitive resources. Specifically, one might argue that the backward counting performed in the current dual task study might interfere with visuospatial attention because the participant could be mentally comparing the numbers. We believe that this is not the case because backward counting was consistent across participants, target directions, and conditions. It would be interesting, however, to compare different types of cognitive overloading (including multiplication) to further examine the specifics of the bottlenecking of resources. Regardless, the current complex dual task required participants to allocate finite resources to complete the concurrent tasks. These resources appear to be overlapping to a greater extent when guiding a rotated cursor toward horizontal targets relative to diagonal targets during the complex dual task.

One factor that was not controlled for in the current study was the consistency of accurate allocentric cues depending on target direction. Providing a perpendicular line of reference for the diagonal targets would further demonstrate the importance of such cues for aiming and guiding of a rotated cursor. Indeed, the importance of allocentric cues during decoupled reaching is the topic of ongoing research in our group (Chen et al. 2011, 2014). Furthermore, the possibility remains that decoupled reaching toward different target directions might use alternative spatial codes. It has been proposed that different reaches can be performed using either a slower or a faster neural system state (Smith et al., 2006). In such a case, the slower system is thought to respond weakly to error, but to show strong adaptive responses at the end training (Smith et al., 2006), which could reflect a more gradual sensorimotor recalibration (Bock et al., 2003; Bock, 2013) required for decoupled reaching toward the diagonal targets. In contrast, the fast system is thought to respond strongly to errors, but to show little or no adaptive responses by the end of training (Smith et al., 2006), and could reflect a more quick strategic control (Bock et al., 2003; Bock, 2013) required for decoupled reaching toward the horizontal targets. Bringing these two concepts together, the present data suggest that distinct neural system states could take the form of independent brain networks to process the different types of reach.

Conclusions. In summary, we observed selective performance declines during the implementation of eye and hand motor plans depending on target location. When simultaneously performing a 90° visuomotor rotation with a cognitively demanding dual task, increased reliance on a cognitive rule (toward horizontal targets) was more susceptible to disruption, whereas reliance on sensorimotor recalibration (toward diagonal targets) was more preserved. Our previous patient study found the opposite pattern. Together, these data suggest that sensorimotor recalibration to a visuomotor rotation appears to shut down and limit its generalization when it is possible to use an explicit, strategic rule to guide movement in some parts of the workspace. In addition, there appears to be relative contributions of distinct neural pathways underlying the control of these different types of reach because one class of movement was impaired to a greater extent than the other.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.A.G. and L.E.S. conception and design of research; J.A.G. performed experiments; J.A.G. and L.E.S. analyzed data; J.A.G. and L.E.S. interpreted results of experiments; J.A.G. prepared figures; J.A.G. drafted manuscript;

J.A.G. and L.E.S. edited and revised manuscript; J.A.G. and L.E.S. approved final version of manuscript.

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