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

Running Title: Disrupting cognitive-motor integration

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Abstract

Guiding a reach when the spatial location of the viewed target and the hand movement are not congruent (i.e. decoupled) can rely on the use of explicit cognitive rules (strategic control) or on the implicit recalibration of gaze and the limb position (sensorimotor recalibration). We previously demonstrated, in a patient with optic ataxia (OA) having bilateral superior parietal lobule damage, an increased reliance on strategic control when performing a decoupled reach (Granek et al. 2013). To understand fundamental mechanisms of decoupled visuomotor control more generally and to test whether we could distinguish these two modes of movement control more specifically, we tested healthy participants in a cognitively-demanding dual task. Participants continuously counted backwards while simultaneously reaching towards horizontal (left or right) or diagonal (~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 non-invasive means to disrupt the integration of a cognitive rule into a motor action. Complementary to our previous results observed in patients with OA, 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, since, in considering the current results and previous patient results together, the two classes of movement could be differentiated depending on the type of interference.

Keywords: Eye-hand coordination; Posterior parietal cortex; Prefrontal cortex; Strategic control; Sensorimotor recalibration/adaptation.
1. Introduction

Decoupled visuomotor control involves the 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).

Now, 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. towards targets along the horizontal axis) relative to a more implicit sensorimotor realignment (i.e. towards targets along the diagonal axes, importantly, not oriented towards the corners of the visual monitor) (Granek et al., 2013), suggesting damage to a distinct connection between SPL and the dorsal premotor (PMd) cortex (Pisella et al., 2006; Rizzolatti and Matelli, 2003). Further, performance improves in OA patients following a delay (Trillenberg et al., 2007; Revol et al., 2003), suggesting a reliance on “strategic
control” networks (Sulzenbruck and Heuer, 2009; Honda et al., 1998) 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 relying 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 backwards counting). Sequential verbal arithmetic has been suggested to involve a cortical network including the IPL and the prefrontal cortex (Simon et al., 2004; Grabner et al., 2009). 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; Pisella et al., 2009). Based on 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 towards 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 towards diagonal targets as it did in our previous OA study which required more sensorimotor recalibration (Granek et al., 2013; Werner and, 2010). Here we report that indeed one can selectively disrupt movements requiring explicit 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.

2. Methods

2.1. Participants

We tested 20 healthy participants (10 females) with a mean age of (27 ± 7 years). 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.

2.2. Experimental procedure

Participants sat in a darkened room in front of a computer monitor at a distance of 43 cm, aligned with their mid-sagittal plane. They made sliding finger movements over a touch sensitive screen (Keytec Magic Touch Screen: Model KTMT-1315: Sampling rate: 100 Hz) affixed over the computer monitor in order to displace a cursor from a starting point to one of two horizontal (right or left), or to one of two diagonal targets (45° rotated from a vertical line – ~top-right or ~top-left, Fig. 1B). Importantly, contrary to the horizontal targets which were oriented directly perpendicular to the dimly lit computer monitor border, the diagonal targets were not oriented towards any helpful allocentric cues such as the corner of the monitor (Fig. 1A). Following a two second delay, one of the peripheral visual targets (16mm in diameter) was presented 120 mm (16° visual angle) from the starting point (25mm 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 Ltd.). The viewing space was calibrated using a nine-point calibration and drift correction was applied between each condition.

Figure 1B 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 forwards counting (simple; S) or a dual task requiring simultaneous backwards counting (complex; C). The voice control conditions (VS and RS) were performed to control for speaking in the chin rest and involved consecutive counting from 1-10 repeatedly and involved very little cognitive processing. The backwards counting conditions (VC and RC) involved sequences of backwards counting by either three or seven from different seeds ranging from 90-110 and was much more demanding cognitively relative to forwards counting. The R condition was used to present a situation where 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.

In order to ensure equal understanding of the transformational rules applied in each condition, all participants were verbally informed of the details of the conditions and then were trained on the V condition followed by the R condition until each participant reached a performance plateau for both target types (Fig. 2). Prior to each randomly assigned experimental block, participants were reminded of the nature of each condition and were allowed practice until each participant reported 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. 1B). For the verbal arithmetic baseline, each participant was
verbally instructed on the details of sequential subtraction which depended on the seed number and the subtraction amount. Again, prior to 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 approximately 60 minutes.

2.3. Data analyses

Trials were only included in the hand and eye movement analyses if they were successfully performed within a maximum of ten seconds and performed without an initial hand direction error. A direction error ($DE$) 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 Inc.). 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 in which the tangential velocity exceeded 10% of its peak using a custom-written computer algorithm. The hand movement timing was broken up 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; $HDT$). Peak velocity was recorded as the maximum tangential change in
resultant x and y position 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 the peripheral target was recorded for each trial (\textit{angle at peak velocity}). Hand movement accuracy and precision were recorded from the participant’s absolute movement endpoints relative to each target (absolute error; \(AE\)) Further details on the direction (on- and off-axis constant error; \(CE\)) and precision (variable error; \(VE\)) of the hand movement endpoints were calculated for supplementary table 2.

Eye position data were first low-pass Butterworth reverse filtered at 50 Hz (Matlab, Mathworks Inc.) and were drift-corrected prior to each trial. Eye movement timing was analyzed whereby eye reaction time (\textit{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 in order 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 off-line 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. In order 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) \textit{steps}, 2) \textit{look-backs}, and 3) hand-biased mis-saccades (\textit{HBMS}). Saccade-related errors were only coded 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, while hypermetric steps were recorded when these small saccadic pauses occurred beyond the peripheral target towards the border of the computer monitor. Look-backs were counted when participants reversed eye direction (towards the cursor) a minimum of 20% (24 mm) of the total amplitude from the central to peripheral target, holding gaze for at least 100 ms. HBMS were recorded if the initial and/or final saccadic endpoint was biased (greater than 10% of total distance from central to peripheral target) towards the direction of the hand during the decoupled conditions.

2.4. 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 (backwards counting) and simple (voice control) reaching for each condition and target type. In order to control for baseline differences across 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 (male versus female) on each condition and target type, we initially conducted three-way repeated measures ANOVAs with condition, target type (horizontal versus 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).

3. 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 ten trials per target type for each condition of training, some variability in HMT was observed during the rotated condition towards the diagonal targets (see Fig. 2), Importantly, however, no condition × target interactions were observed for HRT (p = 0.95) or TMT (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 backwards counting). No differences in counting (p = 0.27) and 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, while 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.
3.1. Complex dual task impaired eye and hand timing when strategic control was required

In order 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 1-4 for raw scores for all variables.

Simultaneously counting backwards and reaching slowed down both eye (ERT) and hand (HRT) movement preparation timing by $156.5 \pm 32.9$ ms and $317.3 \pm 50.8$ 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, F₁,₁₈ = 26.1, p = 0.0001). Notably, a condition × target interaction (ANOVA, F₁,₁₈ = 11.6, p = 0.003) was observed during decoupled reaching, specifically towards the horizontal targets relative to the diagonal targets (p = 0.02). A condition × target interaction was also observed for peak velocity (ANOVA, F₁,₁₈ = 15.6, p = 0.001), whereby participants reached a significantly lower peak velocity when counting backwards while guiding the rotated cursor towards 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 towards 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 implicit sensorimotor recalibration between vision and proprioception towards the diagonal targets.

3.2. 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 (AE) and trajectories (angle at peak velocity). Figure 5A displays the ballistic endpoints and trajectories
across all conditions for a typical participant.

The addition of a complex secondary task increased AE 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 $\times$ target interaction (ANOVA, $F_{1,18} = 55.4$, $p = 0.0001$) was observed reflecting an increase in error for the horizontal targets relative to the diagonal targets during a rotated reach ($p = 0.0001$; Fig. 5B). Similarly, analyses of the hand movement trajectories (angle at peak velocity) revealed a condition $\times$ target interaction (ANOVA, $F_{1,18} = 9.0$, $p = 0.007$), whereby the trajectories were more deviated when orienting the cursor towards the horizontal targets relative to the diagonal target during the rotated condition ($p = 0.005$; Fig. 5C).

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

3.3. Additional eye movements were performed for the complex dual task during visuomotor rotation towards 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 OA patients (Granek et al., 2012; Granek et al., 2013), we observed four basic types of eye movement errors. However, in the current situation, our complex dual task interfered with the eye movements towards the horizontal targets (Fig.5) rather than the diagonal targets as seen in 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 $\times$ target interaction (ANOVA, $F_{1,18} = 48.1$, $p = 0.0001$), predominantly as a result of the increased number of errors during the rotated task towards the horizontal targets relative to the diagonal targets ($p = 0.0001$). Specifically, the addition of the complex secondary task led to a condition $\times$ 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 towards the horizontal targets during the rotated condition ($p = 0.0001$). The complex dual task also led to increased pauses beyond the peripheral target towards 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” towards 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 $\times$ target interaction; ANOVA, $F_{1,18} = 5.3$, $p = 0.03$) during the rotated condition towards 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 towards 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 towards the horizontal targets relative to the diagonal targets during the rotated condition ($p = 0.0001$).

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

4. 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 non-invasive 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 towards 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 towards the cursor or the hand. We suggest that these additional eye movements were performed to enable the recoupling of gaze and cursor/hand location in order to generate and maintain an accurate difference vector (Granek et al., 2012; Shadmehr and Wise, 2005). Free gaze towards 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 which was possible to use an explicit, strategic rule to guide movement in some parts of the workspace. In order to accurately generalize the results found in the current study across other targets in the workspace, one would require testing these decoupled movements towards other target orientations (e.g. vertical orientations). The target locations in the current study were chosen to replicate those performed by patient IG 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 optic ataxic patient 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 two second delay
during eye-hand coordination using a stylus with veridical cursor feedback (Bekkering et al., 1994). Since our conditions also consisted of a long delay (two seconds), 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, the implementation of the cognitive rule was the most impaired during the RC condition (rotated-feedback/backwards counting) movement towards the horizontal targets, a task learned primarily via strategic control (Granek et al., 2013; Werner and Bock, 2010). In the current study, the impaired implementation of the cognitive rule with the motor action was apparent in the acceleration phase of the hand acceleration timing (HAT) and the endpoint errors of the ballistic hand motor plan (for details see Supplementary Table 2). 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. Since 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 towards 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 towards 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 in order to confirm the exact stage of disruption
of movement control towards different target directions.

Our previous work with a bilateral OA patient (Granek et al., 2013) revealed an impaired
dorso-dorsal (Pisella et al., 2006; Rizzolatti and Matelli, 2003) parieto-frontal network for
implicit sensorimotor recalibration, since performance in OA improved during situations relying
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, rather than
improved, performance when guiding the rotated cursor towards 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. Based on 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. 6A). 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. 6B). 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.

It has been established that cognitive-motor integration involves a distributed parieto-frontal network (Granek et al., 2010; Connolly et al., 2000; Gorbet et al., 2004; Toni and Passingham, 1999; Chouinard and Goodale, 2009). The addition of a cognitively-demanding secondary task such as sequential backwards 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; Lee and Kang, 2002; Dehaene et al., 2003) 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 thought to utilize 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 utilized alternative procedural strategies than memory recall. Strategic control can rely on transformational rules (Wise et al., 1996) and has been suggested (Miller, 2000; Rougier et al.,
to be largely mediated by top-down control via connections from DLPFC into PMdr in non-human (Matelli and Luppino, 2001; Luppino et al., 2003) 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 prefrontal patients suffer during successive operations such as backwards 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 6A provides a schematic of and provides details for 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 SPL activation is observed (Himmelbach et al., 2009). Similarly, hand endpoint performance was shown to improve when OA patients 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 towards potentially useful allocentric cues (i.e. perpendicular to computer monitor border) was selectively impaired during the complex rotated condition. Finally, cortical networks are the focus of our study, given the
cortical damage of 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, recognized as crucial for on-line monitoring of visuomotor adaptation (Donchin et al. 2012; Shmuelof and Krakauer 2011) by learning a forward model in order 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 backwards counting performed in the current dual task study might interfere with visuospatial attention as the participant could be mentally comparing the numbers. We believe that this is not the case since the backwards counting was consistent across participants, target directions, and conditions. It would be interesting however to compare different types of cognitive overloading (including multiplication) in order to further examine the specifics of the bottlenecking of resources. Regardless, the current complex dual task required participants to allocate finite resources in order to complete the concurrent tasks. These resources appear to be overlapping to a greater extent when guiding a rotated cursor towards 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). Further, the possibility remains that decoupled reaching towards different target directions might use alternative spatial codes. It has been proposed that different reaches can be performed utilizing 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 towards 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 towards 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.

5. 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 (towards horizontal targets) was more susceptible to disruption, while reliance on sensorimotor recalibration (towards 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, since one class of movement was impaired to a greater extent than the
other.

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Figure Captions

Figure 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 towards 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 1-10; blue numbers) and with a complex dual task (backwards counting by 3 or 7; red numbers). The blue circles denote the cued position before the movement. Light eye and hand symbols 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 = 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 towards 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 2. Hand movement timing during training. Hand (A) reaction time and (B) movement time during training following a verbal explanation for both veridical and rotated conditions. Shaded areas denote SEM. Note the learning plateau for both dependent variables during the last 10 trials for each target type (horizontal and diagonal) in both conditions.

Figure 3. Eye movement timing. Change in eye (A) reaction time and (B) movement time for the complex dual task conditions compared with control conditions to both horizontal (right and left; gray bars) and diagonal (top-right and top-left; black bars) targets. Asterisks represent
Figure 4. Hand movement timing. Change in hand (A) reaction time (B) acceleration time and (C) peak velocity for the complex dual task conditions compared with control conditions to both horizontal (right and left; gray bars) and diagonal (top-right and top-left; black bars) targets. Asterisks represent significance (Bonferroni corrected) of post-hoc condition by target comparisons. Error bars denote SEM. *p<0.05; ****p<0.0001. Note the increase in hand movement timing and decrease in velocity when orienting towards the horizontal targets.

Figure 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) task. Ellipses denote 95% CI of landing point following ballistic hand motor plan. Note the increased deficits towards the horizontal targets during the rotated complex condition. Group changes in (B) hand absolute error following ballistic reach and (C) hand angle at peak velocity during the complex dual task conditions relative to the "simple" backwards counting controls. Error bars denote SEM. **p<0.01; ****p<0.0001.

Figure 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, while other intermediate connections are shown in gray. Dashed lines imply subcortical connections, and 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 (ventrolateral) and DLPFC (dorsolateral) prefrontal cortices; PMv (ventral premotor area); PMdr, and PMdc (rostral and caudal dorsal premotor areas). M1 (primary motor) and S1 (primary sensory) cortices; S2 (secondary somatosensory cortex); posterior parietal cortex includes the SPL (superior parietal lobule) including POJ (parieto-occipital junction) and area 5 (monkey area PEc), and IPL (inferior parietal lobule) including SMG (supramarginal gyrus) AG (angular gyrus); SPL and IPL are separated by the IPS which includes AIP (anterior), LIP (lateral), VIP (ventral), and MIP (medial) intraparietal sulcus; occipital cortex includes V1 (primary visual) and V2, V3, V3a, V4, V6 (visual association areas); temporal cortex includes IT (inferior temporal cortex), MT (middle temporal cortex), and MST (medial superior temporal cortex).
Petrides and Pandya, 2002), s) (Petrides and Pandya, 2006; Tomassini et al., 2007; Rozzi et al., 2006; Petrides and Pandya, 2009), t) (Petrides and Pandya, 2009; Rozzi et al., 2006; Cavada and Goldman-Rakic, 1989b), (Petrides and Pandya, 2006) u) (Rozzi et al., 2006; Tomassini et al., 2007; Rushworth et al., 2006; Petrides and Pandya, 2009) 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) (Marconi et al., 2001; Dum and Strick, 2005), z) (Dancause et al., 2006b; Dancause et al., 2006a), aa) (Barbas and Pandya, 1987; Tanne et al., 1995; Johnson et al., 1993; Johnson et al., 1996; Dum and Strick, 2005), 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; He et al., 1995). (B) Schematic of the relative explicit versus implicit requirements of different non-standard tasks involving cognitive-motor integration.