THE ROLE OF THE POSTERIOR PARIETAL CORTEX IN COGNITIVE-MOTOR INTEGRATION

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ABSTRACT

When interacting with an object within the environment, one must combine visual information with the felt limb position (i.e. proprioception) in order compute an appropriate coordinated muscle plan for accurate motor control. Amongst the vast reciprocally connected parieto-frontal connections responsible for guiding a limb throughout space, the posterior parietal cortex (PPC) remains a front-runner as a crucial node within this network. Our brain is primed to reach directly towards a viewed object, a situation that has been termed "standard". Such direct eye-hand coordination is common across species and is crucial for basic survival. Humans, however, have developed the capacity for tool-use and thus have learned to interact indirectly with an object. In such "non-standard" situations, the directions of gaze and arm movement are spatially decoupled and rely on both the implementation of a cognitive rule and online feedback of the decoupled limb.

The studies included within this dissertation were designed to further characterize the role of the PPC in different types of visually-guided reaching which require one to think and to act simultaneously (i.e. cognitive-motor integration). To address the relative contribution of different cortical networks responsible for cognitive-motor integration, we tested three patients with optic ataxia (OA; two unilateral – first study, and one bilateral – second study) as well as healthy participants during a cognitively-demanding dual task (third study) on a series of visually-guided reaching tasks each requiring a relative weighting between explicit cognitive control and implicit online control of the spatially decoupled limb. We found that the eye and hand movement performance during decoupled reaching was the most compromised in OA during situations relying on sensorimotor recalibration, and the most compromised in healthy participants during a dual task relying on strategic control. Taken together, these data presented in this dissertation provide further evidence for the existence of alternate task-dependent neural pathways for cognitive-motor integration.

To my inspirations to succeed,

Jaden and Patricia

Keep on being yourselves…

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Glossary of Abbreviations

Abbreviation	Non-Abbreviated Term
aMT	Hand movement time acceleration phase
AD	Alzheimer's Disease
AE	Hand absolute error
ARB	Arbitrary condition
BG	Basal ganglia
BOLD	Blood oxygenated level dependent
C	Coronal condition
C180°	Coronal 180° rotated condition
C90°	Coronal 90° rotated condition
CE	Hand movement constant error
CES	Cumulative effect size
CMT	Hand corrective movement time
dMT	Hand movement time deceleration phase
DE/DR	Direction error
DLPFC	Dorsal lateral prefrontal cortex
EMT	Eye movement time
ERT	Eye reaction time
fMRI	Functional magnetic resonance imaging
H	Horizontal condition
HMT/MT	Hand ballistic movement time
MT	Middle temporal cortex
MST	Medial superior temporal cortex
HR	Horizontal rotated condition
HRT/RT	Hand reaction time
ID	Index of difficulty
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
IPS	Intraparietal sulcus
M1	Primary motor cortex
OA	Optic ataxia
PFv+o	Ventral and orbital prefrontal cortex
PMd	Dorsal premotor region
PMdc	Caudal dorsal premotor region
PMdr	Rostral dorsal premotor region
PMv	Ventral premotor region
POJ	Parieto-occipital junction
PPC	Posterior parietal cortex

S	Para-sagittal condition
S1	Primary sensory cortex
S2	Secondary somatosensory cortex
SFG	Superior frontal gyrus
SMG	Supramarginal gyrus
SPL	Superior parietal lobule
TMT	Total hand movement time
TTR	Time to recovery from a hand direction error
V	Vertical condition
VE	Hand movement variable error
VLPFC	Ventrolateral prefrontal cortex
VR	Vertical rotated condition

Chapter One

General Introduction

As we act upon our thoughts and desires, our ability to interact with the external environment is the only means of escape from the swirling depths of our own minds. We are visual creatures and thus rely on the visual cues within the environment in order to successfully interact with an object of interest. Such visually-guided interactions are crucial to the ability to feed ourselves, take care of our young, or even successfully navigate throughout our environment. In contrast, the ability to think is our only means of control within our environment. Such control over our decisions is necessary for making choices and thus adapting to potential unexpected changes within our environment. Taken together, the ability to think and to act **simultaneously** is what has made us excel as a species. Although the control of movements and cognition have been thoroughly examined as separate entities throughout the literature, the cortical mechanism for combining a cognitive rule with a motor action (termed "cognitive-motor integration") have not been fully established. As such, this dissertation will examine the role of different cortical regions responsible for cognitive-motor integration in a series of "complex" eye hand coordination tasks relying on a relative combination of explicit strategic control and implicit motor control.

What exactly makes one type of eye-hand coordination more complex than another? When one first thinks of complex eye-hand coordination, perhaps a highly skilled athlete comes to mind. For example, a football player propels himself towards a moving football, anticipating the timing and the location of contact between his hand and the ball, and then applies just enough pressure on the ball with his fingertips in order to maintain possession. Although the neural control of this behaviour may appear quite complex, it can actually be controlled quite automatically via the vast reciprocal connections responsible for direct interaction with moving objects. Direct eye-hand coordination has been termed "standard" (Wise, di Pellegrino, & Boussaoud, 1996). On the other extreme, humans have evolved the capacity to incorporate a tool, such as a computer mouse, as an extension of one's end effector (Iriki, Tanaka, & Iwamura, 1996), in order to successfully interact with the external environment. This type of action at first glance appears as a simple task, however, the neural underpinnings required are quite complex. As such, indirect reaching that has been said to employ "non-standard" transformational mappings (Wise et al., 1996). Indirect interaction with objects is not innate (Bo, Contreras-Vidal, Kagerer, & Clark, 2006; Piaget, 1965) and requires the implementation of a cognitive rule (e.g. rightward arm movement = leftward cursor movement) in order to guide the limb to the appropriate spatial location (see Sergio, Gorbet, Tippett, Yan, & Neagu, 2009). This integration of a cognitive rule with a motor action (i.e. cognitive-motor integration) requires greater additional processing time (Gorbet & Sergio, 2009) and has been suggested to be a part of a more indirect neural network (Pisella, Binkofski, Lasek, Toni, & Rossetti, 2006; Pisella, Sergio, Blangero, Torchin, Vighetto, & Rossetti, 2009; Rizzolatti & Matelli, 2003).

Our knowledge of the specific neural underpinnings of these different types of eye-hand coordination is still lacking. The goal of my doctoral work is to tease apart the neural networks responsible for the guidance of different types of complex eye-hand coordination. **The central hypothesis guiding this research is that different types of visuomotor compatibility are processed in separate neural networks.** Specifically, I have begun to address how the human brain plans and executes movements when a rule dictates the relationship between perception and action in situations which rely on explicit strategic relative to situations which rely on implicit guidance of the limb in space. One of my primary goals is to characterize the role of the posterior parietal cortex (PPC) within the cortical network responsible for integrating cognitive rules into motor actions. This work consisted of three separate studies which are described in detail in the following chapters. This introduction will provide a brief overview of how the brain controls reaching movements in situations with direct correspondence between vision and action, and in situations requiring a cognitive rule to be incorporated as a part of the motor plan. The vast cortical networks including some of the highlighted regions included in **Figure 1.1** will be discussed below.

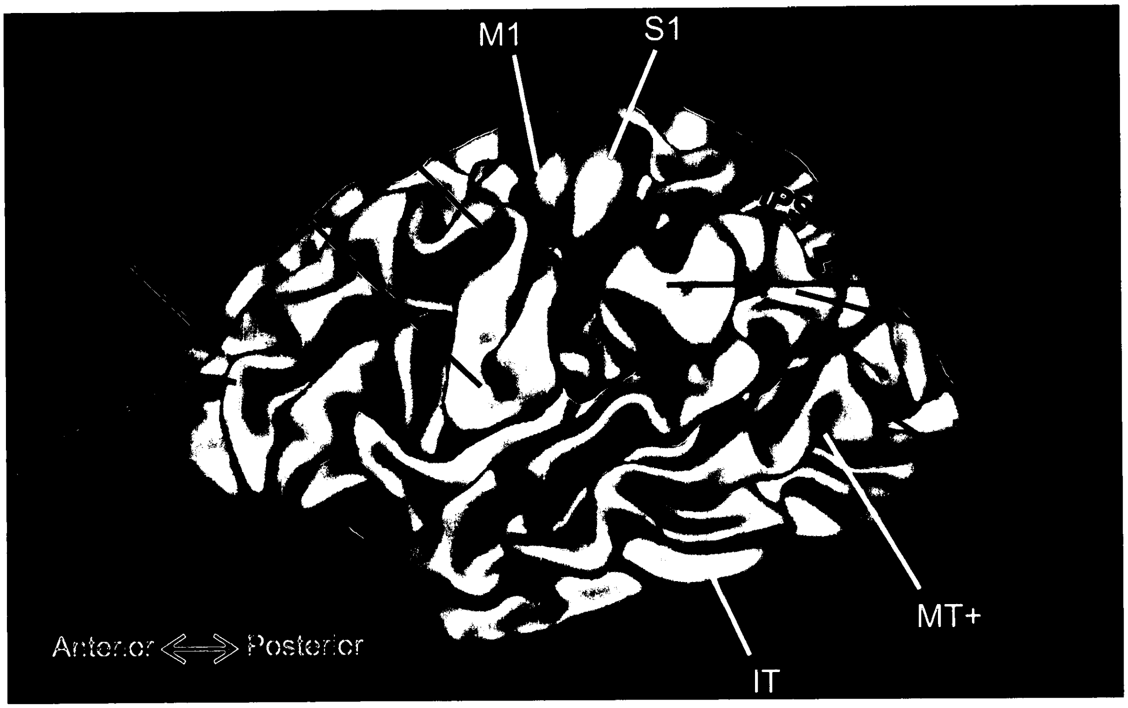

Figure 1.1. A schematic of the human brain viewed from a lateral perspective. The prefrontal cortex (red) is comprised of SFG (superior frontal gyrus), VLPFC, and DLPFC (ventrolateral and dorsolateral prefrontal cortex). The lateral premotor cortex (represented in green) is comprised of PMv and PMd (ventral and dorsal premotor area). The primary motor and sensory cortices (white) are comprised of M1 and S1, respectively. The posterior parietal cortex (blue) is comprised of SPL (superior parietal lobule) which includes the parieto-occipital junction; POJ and area 5; monkey area PEc), and IPL (inferior parietal lobule) which includes the supramarginal gyrus (SMG) and the angular gyrus (AG). The occipital cortex includes V1 (primary visual) and LO (lateral occipital) cortices. The temporal cortex includes IT (inferior temporal cortex) and MT+ (middle temporal complex).

1.1. Eye-hand coordination

The term eye-hand coordination is used often in daily life - especially in sports - as with the common saying "keep your eye on the ball". Consider the example of reaching for a piece of fruit. Throughout the day, we are constantly redirecting our eyes throughout the environment until an object of interest (e.g. an apple) falls upon the retina and its spatial location is initially coded relative to the direction of gaze (Buneo, Jarvis, Batista, & Andersen, 2002; Buneo & Andersen, 2006; Khan, Pisella, Rossetti, Vighetto, & Crawford, 2005). Eye-hand coordination requires a synergistic interaction between two effectors. In fact, our eye and hand movements have been shown to be closely coupled (Johansson, Westling, Backstrom, & Flanagan, 2001; Neggers & Bekkering, 2000; Neggers & Bekkering, 2001; Vercher, Magenes, Prablanc, & Gauthier, 1994) in order to optimize visual monitoring of the moving hand (Crawford, Medendorp, & Marotta, 2004; Johansson et al., 2001). In addition, proprioceptive and motor feedback signals (i.e. efference copies) of gaze position can be used to improve the hand, even when the hand is not visible (Flanagan, Terao, & Johansson, 2008; Prablanc, Echallier, Komilis, & Jeannerod, 1979; Prablanc & Martin, 1992; Prablanc, Desmurget, & Grea, 2003). When saccade locations have been deliberately deviated from the appropriate target locations, however, systematic reaching errors occur (Bock, 1986; Henriques, Klier, Smith, Lowy, & Crawford, 1998; Henriques & Crawford, 2000), emphasizing the strong linkage between eye and hand movements.

In addition to gathering the spatial location of the object, the apple is then analyzed for its many attributes, including its shape, size and colour. It has been proposed that coding the spatial location of the apple utilizes the occipital-to-parietal "dorsal" visual stream, while the specific visual attributes of the apple (i.e. round, red, smooth, etc.) utilizes the occipital-to-temporal "ventral" visual stream (Mishkin, Ungerleider & Macko, 1983). Evidence from two different patients with damage to the inferior temporal (IT) and the posterior parietal cortices (PPC) provided motivation to refine the previous model into the "perception and action model" (Goodale & Milner, 1992). A patient (DF) with lateral occipital (LO; James, Culham, Humphrey, Milner, & Goodale, 2003; just posterior to IT) damage resulting in visual agnosia, with deficits in utilizing appropriate shape, orientation, and colour features for accurate object recognition but accurate reaching and object manipulation, was contrasted with a patient (IG) with caudal superior parietal (encompassing the parieto-occipital junction; POJ) damage resulting in optic ataxia (OA; Blangero, Menz, McNamara, & Binkofski, 2009; Karnath & Perenin, 2005) who had deficits in accurate visually-guided reaching, but preserved object recognition. Recent evidence involving more complex situations, however, have provided evidence that the two streams are not in fact segregated and communication between them is quite necessary (Pisella et al., 2006; Pisella et al., 2009; Rizzolatti & Matelli, 2003).

1.2. Visuomotor compatibility and visually-guided movements

The evolution for the capacity for tool-use in primates has been integral in the development in society. Many primates and even some birds (Hansell & Ruxton, 2008) and invertebrates (Finn, Tregenza, & Norman, 2009) have developed the ability to utilize tools in order to enhance their lives. It appears that those species equipped for tool-use have evolved to form the essential cortical regions responsible for guiding a tool in space. These cortical regions are the last to develop in childhood (Bo et al., 2006; Piaget, 1965) and subsequent damage to these regions can result in a variety of disorders of visually-guided reaching including OA (Perenin & Vighetto, 1988; Pisella et al., 2000), ideomotor apraxia (Buxbaum, Kyle, Grossman, & Coslett, 2007; Goldenberg, 2009), and Alzheimer's Disease (Ghilardi, Gordon, & Ghez, 1995; Tippett & Sergio, 2006; Tippett, Krajewski, & Sergio, 2007). The required calibration involved in accommodating a tool as an extension of an end-effector has been thought to require the combination of the semantic properties of the tool with the mechanical organization required for appropriate manipulation (Frey, 2007). When one has adapted to using a tool, it essentially becomes an extension of the body. The ability to incorporate different types of complex tools as extensions of one's own body schema as been touted as the process of distalization of an end-effector in order to encompass a tool (Arbib, Bonaiuto, Jacobs, & Frey, 2009). For this reason, a tennis player does not lunge to be able to catch a ball, but instead gets oriented at a distance for the sweet spot of the racket to make contact with the ball. In addition to this anecdotal evidence, tools were used to represent body schema in a fascinating experiment on an individual with a right IPL lesion neglect patient (Berti & Frassinetti, 2000). Common with the spatial neglect literature, patient P.P. neglected anything within her peripersonal (close) space, but did not display any impairment for anything far away from her (Berti & Frassinetti, 2000). This changed, however, when she was using a long stick as a tool, and her rightward displacements (implying left spatial neglect) were extended further away from her body (Berti & Frassinetti, 2000). These data imply that the intact left dorsolateral parieto-frontal connections (see below) were able to account for the tool as a part of her own body schema and in this case, further impair her condition. The ability of the brain to incorporate an inanimate object to be a part of one's body schema is truly fascinating.

In the literature, non-standard sensorimotor mappings are divided into two different categories: "arbitrary" and "transformational" (Wise et al., 1996). As the name suggests, arbitrary mappings occur when the relationship between a visual stimulus and the motor response it guides is completely arbitrary. For example, drivers know that a red light indicates that they should apply force to the brake pedal, while a green light indicates that the accelerator pedal should be pressed instead. These learned associations between colours and foot motion are arbitrary. In contrast, while transformational visuomotor mappings also involve dissociated visual cues and motor responses, they use a specific spatial algorithm to relate the position of visual cues to the direction of an action. The common example is using the computer mouse, which is typically used on a horizontal tabletop to control a cursor displayed on a vertical monitor. One must learn the spatial rule that moving the cursor "upward" on the screen requires the hand to move the mouse "forward" on the desk. Non-standard transformational mappings (as opposed to arbitrary mappings) can take two forms: a change in the physical location of the visual stimulus relative to plane of the limb movement, and a cue that signals a required movement in some direction (often opposite) to the cued target location. These different levels of visuomotor compatibility represent two fundamentally different levels of sensorimotor mapping. Adapting to spatial orientation differences (e.g. those where the hand moves in a different location relative to the visual target) is referred to as **sensorimotor recalibration**, and is more **implicit** in nature. Such a recalibration requires a coordinated remapping between different sensory modalities such as vision and proprioception (Bedford, 1993; Clower & Boussaoud, 2000; Lackner & Dizio, 1994), and will produce after-effects if the source of the recalibration is removed (Rossetti, Koga, & Mano, 1993; Welch, Bridgeman, Anand, & Browman, 1993). This represents a different type of information compared to the more cognitive "reversal" conditions, which rely on an explicit rule. An example of this situation would be pushing a boat rudder to the right in order to steer the boat to the left. Adapting to a situation which requires a mental rotation in order to realign the required hand movement relative to the spatial location of the target is referred to as **strategic control** (Bock, 2005; Redding & Wallace, 1996; Redding, Rossetti, & Wallace, 2005), and is more **explicit** in nature. Strategic control can include having to integrate various rules for correctly acquiring a new skill, and does not produce movement after-effects when switching to a related skill. Multiple mappings of this sort can be learned simultaneously, something more difficult for sensorimotor recalibration tasks such as prism adaptation; however, some inter-limb transfer of strategic control has been seen during prism adaptation in healthy controls (Pisella et al., 2004). In both of these cases, the location of gaze direction and hand location have been decoupled. We wish to explore how the different parieto-frontal cortical networks are responsible for planning and guiding such decoupled visually-guided tasks.

1.3. Parieto-frontal networks for sensorimotor transformations

In order to reach accurately for an object of interest, one must transform a sensory signal into a complex pattern of muscle activity. The neurological processes which underlie this seemingly straightforward task are not yet completely understood. Direct interactions with an object have been suggested to be controlled by a "default visuomotor network" (Gorbet, Staines, & Sergio, 2004). This default visuomotor network involves the combined activation of the contralateral primary motor cortex (M1), medial motor areas, lateral premotor areas, PPC activation during the preparatory stages of a direct visuomotor transformation (Gorbet et al., 2004; see **Fig. 1.1**).

Much current research seeks to characterize the role of specific parieto-frontal networks in sensory-guided reaching, with an emphasis on the strong connectivity of the white matter tracts between these areas. Evidence of strong, reciprocal association fibers between the PPC and the lateral premotor regions in the frontal lobe (Marconi et al., 2001; Tanne-Gariepy, Rouiller, & Boussaoud, 2002) have been thought to play a significant role in the preparation and guidance of visually-guided arm movements. Specifically, studies suggest that both superior and inferior parietal lobules (SPL, IPL), separated by the intraparietal sulcus (IPS) within the PPC (see **Fig. 1.1**) are involved in the early processing of sensory input for movement guidance. Different areas of the PPC are known to receive both somatosensory and visual information (Andersen & Buneo, 2002; Cavada & Goldman-Rakic, 1989a), making this region a prime location for the integration of senses and conversion into a motor output. In fact, neurons in the PPC are known to discharge in response to both sensation and movement, and are thus considered crucial in the transformation of visual information needed for motor behaviours (Blangero et al., 2009; Goodale, 1993; Kalaska, 1996; Milner & Harvey, 2006). Further, neuronal activity in PPC is affected by attention (Colby, 1999; Kelley, Serences, Giesbrecht, & Yantis, 2008; Striemer et al., 2009; Yantis et al., 2002), gaze direction (Batista, Buneo, Snyder, & Andersen, 1999; Marzocchi, Breveglieri, Galletti, & Fattori, 2008; Neggers & Bekkering, 2001; Prado et al., 2005), and tool-use (Inoue et al., 2001; Iriki et al., 1996) all relevant to the cognitive-motor integration.

Two major parieto-frontal networks exist connecting the medial PPC (SPL) to the dorsal premotor cortex (PMd) and the lateral PPC (IPL) to the ventral premotor cortex

(PMv). For details on possible parieto-frontal networks for decoupled visuomotor control, see **Fig. 4.8A**). The **dorsomedial** (Tanne-Gariepy et al., 2002; Tomassini et al., 2007), which is also referred to as the dorso-dorsal (Pisella et al., 2006; Pisella et al., 2009; Rizzolatti & Matelli, 2003) parieto-frontal network, arises from the caudal SPL (human homologue to V6a; (Fattori, Breveglieri, Amoroso, & Galletti, 2004; Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003), which is thought to calculate the appropriate visual reach vector goal (Fernandez-Ruiz, Goltz, DeSouza, Vilis, & Crawford, 2007; Hawkins, Sayegh, Yan, Crawford, & Sergio, 2013; Vesia, Prime, Yan, Sergio, & Crawford, 2010) to rostral PMd (PMdr; (Gamberini et al., 2009; Passarelli et al., 2011; Tanne-Gariepy et al., 2002; Tomassini et al., 2007). An intact parietal input into the dorsomedial network has been suggested to be responsible for the accurate guidance of a limb in peripheral vision (Battaglia-Mayer, Ferrari-Toniolo, Visco-Comandini, Archambault, Saberi-Moghadam, & Caminiti, 2012; Battaglini, Muzur, & Skrap, 2003; Hwang, Hauschild, Wilke, & Andersen, 2012). The dorsomedial connections have been implicated in decoupled reaching even in darkness (Marzocchi et al., 2008), with emphasis on the transport phase (Cavina-Pratesi et al., 2010), fast form and motion analyses (Passarelli et al., 2011) with the integration of cognitive visuo-perceptual skills with complex visuomotor skills (Pisella et al., 2013).

Connections from IPL along the superior longitudinal fasciculus to the ventral premotor cortex (PMv) on the inferior frontal gyrus (IFG; (Matelli & Luppino, 2001;

Rozzi et al., 2006) form the **dorsolateral** parieto-frontal pathway (Tanne-Gariepy et al., 2002; Tomassini et al., 2007). Specifically, both the anterior portion of the IPL (supramarginal gyrus; SMG; (Petrides & Pandya, 2009; Rozzi et al., 2006; Rushworth, Behrens, & Johansen-Berg, 2006; Tomassini et al., 2007) and the posterior portion of the IPL (angular gyrus; AG; (Petrides & Pandya, 2009) are connected with PMv. The anterior IPS (AIP) is also connected with PMv (Borra et al., 2008; Matelli, Camarda, Glickstein, & Rizzolatti, 1986; Matelli & Luppino, 2001; Rushworth et al., 2006; Tanne-Gariepy et al., 2002), which is implicated in the online control of grasping (Grol et al., 2007). In addition, PMv/IFG has been shown to be responsible for object grasping in macaques (Rizzolatti, Fogassi, & Gallese, 2002) and in humans (Binkofski et al., 1999; Goldenberg & Spatt, 2009). IFG activation has also been reported during tasks involving increased attention and working memory (Brass & von Cramon, 2002; Derrfuss, Brass, & von Cramon, 2004) and a part of a conflict control network (Petrides & Pandya, 1999). Although these connections have been described separately, weak connections from the medial SPL to AIP and IPL to caudal PMd (PMdc; (Tanne-Gariepy et al., 2002; Wise, Boussaoud, Johnson, & Caminiti, 1997) have been observed in the non-human primates (Borra et al., 2008; Gamberini et al., 2009) which could represent cross-talk between the dorsolateral and the dorsomedial parieto-frontal networks for accurate complex visuomotor control.

IPL is also strongly connected with the prefrontal cortex (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). Specifically, SMG (macaque area PF; Petrides & Pandya, 2009) and its direct connections with the dorsolateral prefrontal cortex (DLPFC; Cavada & Goldman-Rakic, 1989b; Gamberini et al., 2009; Rozzi et al., 2006; Tanne, Boussaoud, Boyer-Zeller, & Rouiller, 1995), as well as AG (macaque area PG; Petrides & Pandya, 2009)) and its direct connections with the ventrolateral prefrontal cortex (VLPFC), could serve as possible connections of rule-base motor control. DLPFC has been commonly thought of as a region for rule-based decision making and as a part of "executive function", specifically activated not only to accommodate for the proper control of a tool (Moll, de Oliveira-Souza, Passman et al., 2000; Saito, Mushiake, Sakamoto, Itoyama, & Tanji, 2005). In addition, the human IFG along with DLPFC have been strongly linked planning functional tool-use gestures with the right hand, when compared with random hand movements (Johnson-Frey, Newman-Norlund, & Grafton, 2005). SMG has also been shown to be connected with VLPFC (Petrides & Pandya, 2006; Tomassini et al., 2007) while AG is also connected with DLPFC (Andersen, Asanuma, Essick, & Siegel, 1990; Petrides & Pandya, 1984). Further, top-down visuomotor control has been suggested to mediated by connections from DLPFC and VLPFC (Luppino, Rozzi, Calzavara, & Matelli, 2003; Tomassini et al., 2007) into the rostral PMd (PMdr). PMd is thought to not only been implicated in the kinematics required for movement preparation (Cisek & Kalaska, 2002) and task selection (Cisek & Kalaska, 2005), but also for suppressing unwanted movements (Koch et al., 2006).

Although cortical spinal tracts exist from PMd, most arise from the primary motor cortex (M1; He, Dum, & Strick, 1993; He, Dum, & Strick, 1995), via the connections from PMdc to M1 (Barbas & Pandya, 1987; Dum & Strick, 2005; Johnson, Ferraina, & Caminiti, 1993; Johnson, Ferraina, Bianchi, & Caminiti, 1996; Tanne et al., 1995). Strong functional links between PMd and M1 have been observed using paired-pulse transcranial magnetic stimulation (TMS; Davare, Andres, Cosnard, Thonnard, & Olivier, 2006; O'Shea, Sebastian, Boorman, Johansen-Berg, & Rushworth, 2007). M1 is located on the precentral gyrus and is thought to represent the kinetics related to specific joint torques underlying the kinematic requirements of a reach (Kalaska, Sergio, & Cisek, 1998; Sergio & Kalaska, 2003; Sergio, Hamel-Paquet, & Kalaska, 2005). M1 is not only thought to code dynamic reaching movements, but also the joint torques responsible for isometric goal-directed movements (Sergio & Kalaska, 2003; Sergio et al., 2005). Taken together, the parieto-frontal connections have been shown to be crucial for the combination of sensory information for the accurate planning and updating of motor control.

1.4. Cortical control of non-standard visually-guided reaching

Non-standard visuomotor transformations require the integration of a cognitive rule with a motor output (i.e. cognitive- motor integration). Cognitive-motor integration involves a large distributed cortical network (Connolly, Goodale, Desouza, Menon, &

Vilis, 2000; Gorbet et al., 2004; Granek, Gorbet, & Sergio, 2010; Toni & Passingham, 1999) and the relative contribution of the different nodes within this network can depend on the requirements of the visuomotor task (see **Fig. 4.8B**).

While the contribution of post-central cortical areas to non-standard sensorimotor mappings is an open area of research, it is well known that higher cognitive functions are related to activity in the frontal areas (Lamar & Resnick, 2004; Lu, Preston, & Strick, 1994; Mesulam, 1990; Mesulam, Nobre, Kim, Parrish, & Gitelman, 2001; Moscovitch, Kapur, Kohler, & Houle, 1995; Petrides, 1997). Many studies have examined the degree to which cell activity in different frontal lobe regions covary with attributes of the sensory input, the motor output, and their various integrated combinations. Dorsal premotor (PMd) neurons have been shown to have both attentional, gaze-related activity and intentional, limb movement activity in response to targets that are both directly presented and arbitrary in nature (Boussaoud & Bremmer, 1999; Boussaoud, 2001; Inoue et al., 2000; Wise et al., 1996). Within the premotor area these effects appear to be preferentially encoded along a rostral-caudal gradient (Boussaoud, 2001; Fujii, Mushiake, & Tanji, 2000), as have been observed with different spectral profiles of the local field potentials within PMdr and PMdc during decoupled visually-guided reaching (Sayegh, Hawkins, Hoffman, & Sergio, 2013). The prefrontal cortex may also contribute to halting the natural spatial linkage between eye and hand movements (Gielen, van den Heuvel, & van Gisbergen, 1984; Gorbet et al., 2004; Neggers & Bekkering, 2000; Neggers &

Bekkering, 2001). The dorsolateral prefrontal cortex (DLPFC) is widely known as an area associated with inhibitory attention (Hoshi & Tanji, 2006; Leung & Cai, 2007), specifically during the preparation and switching of motor programs incorporating tool-use (Moll, de Oliveira-Souza, Passman et al., 2000; Saito et al., 2005). Similarly, it has been proposed that prefronto-striatal connectivity, specifically deriving from the DLPFC, is necessary for the decision to inhibit natural tendencies such as in the case of performing anti-saccades (Bertolino et al., 2009; Durston et al., 2005). The rostral superior frontal gyrus (i.e. polar Brodmann area 10) is known to be involved in rule-based decision making (Leung & Cai, 2007; Murray, Bussey, & Wise, 2000; Rowe, Hughes, Eckstein, & Owen, 2008) and it is strongly interconnected with PMdr. All of these characteristics may be relevant to the processing of visual input, and to the planning of a limb movement requiring the integration of task-specific rules.

1.4.1. Human imaging studies of brain activity for complex motor behaviours

Brain imaging provides a non-invasive means to explore the human brain during rest and during action. Functional magnetic resonance imaging (fMRI) has served as a useful tool to explore brain activation of behaving participants. As long as motion within the bore of the magnet is conservative and restricted to reduce the effects of motion artifacts, limitless complex eye-hand coordination studies can be undertaken. As such, brain imaging research has revealed an extensive cortical network involved in different types of complex, non-standard reaching (Connolly et al., 2000; Gorbet et al., 2004; Granek et al., 2010; Inoue et al., 2000). In a surprising finding, less overall activation (although still extensive network) was observed during the more complex, non-standard conditions involving a decoupling between what one sees and one does than for direct visuomotor control, putatively due to the required inhibition of the natural tendency to reach towards the direction of gaze (Gorbet et al., 2004). Further, differences between the sexes were observed using both event-related fMRI (Gorbet & Sergio, 2007) and slow cortical potentials (Gorbet, Mader, & Richard Staines, 2010), as more bilateral activation was observed for females than for males. Specifically, during the preparatory stages, females had more activation than the males in the medial frontal gyrus, the ipsilateral premotor cortex, bilateral SPL, and contralateral primary sensorimotor cortex. In contrast, the males only had an increase in cortical activation in the superior temporal gyrus. Keeping these results in mind, it is important that future studies to control for sex differences during analyses. It has also been established that extensive experience with a visuomotor skill can alter brain activity for the subsequent performance of that skill (Haslinger et al., 2004; Jancke, Shah, & Peters, 2000; Krings et al., 2000; Norton et al., 2005; Smith, McEvoy, & Gevins, 1999). Even on a shorter time scale, cortical changes can be observed from the early to the late stages of novel skill learning (Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994). It has also been demonstrated that the cortical control of specific previous experience in decoupled visuomotor (e.g. video games) control can generalize to other non-standard sensorimotor mappings (Granek et al., 2010).

Across participants, within the cortical network for non-standard visuomotor control, the PPC has been established as a predominant contributor to the preparation and execution of this type of non-standard behavior. Specifically, preliminary evidence suggests that SPL is involved in the early planning and IPL is involved in the late planning just prior to movement onset for the "rotation aspect" of a rotated visuomotor transformation **(Fig. 1.2.)**. In addition, within the medial PPC, anterior to the parietal occipital sulcus, an area termed the parietal occipital junction (POJ; Clavagnier, Prado, Kennedy, & Perenin, 2007; Prado et al., 2005); also referred to as SPOC (Gallivan, Cavina-Pratesi, & Culham, 2009; Vesia et al., 2010) in humans and V6A (Galletti, Fattori, Gamberini, & Kutz, 1999; Galletti, Fattori, Kutz, & Gamberini, 1999) and PO (Colby, Gattass, Olson, & Gross, 1988; Lewis & Van Essen, 2000) in non-human primates) has been shown to display increased activity during visuomotor and (Clower et al., 1996) mental (Tagaris et al., 1996) rotations. Additional activation of POJ together with PMdr have been shown to display increased blood oxygen level dependent (BOLD) activity during extra-foveal reaching compared with foveal reaching (Prado et al., 2005), implying a more extensive network as gaze and hand direction begin to become decoupled (for review, see Culham, 2005). In contrast, direct foveal reaching has been shown to rely on the medial intraparietal sulcus (IPS) relative to extra-foveal reaching

(Prado et al., 2005). Greater BOLD activity within the medial superior parietal region (adjacent to POJ) has been shown for anti-pointing relative to pro-pointing during central fixation (Connolly et al., 2000), thus providing evidence for the caudal SPL in inhibiting the natural tendency to reach towards the direction of gaze. Evidence for activation within the human "parietal reach region" within the SPL (Connolly, Andersen, & Goodale, 2003) has been observed during reaching while wearing reversing prism goggles (Fernandez-Ruiz et al., 2007). Here, Fernandez-Ruiz and colleagues (2007) report that the human PRR is responsible formulating the target goal regardless of the hand movement orientation. These reports of decoupled difference vector calculations during decoupled reaching have been since supported by deactivation work using transcranial magnetic stimulation (TMS; Vesia et al., 2010) and in single cell electrophysiology (Hawkins et al., 2013).

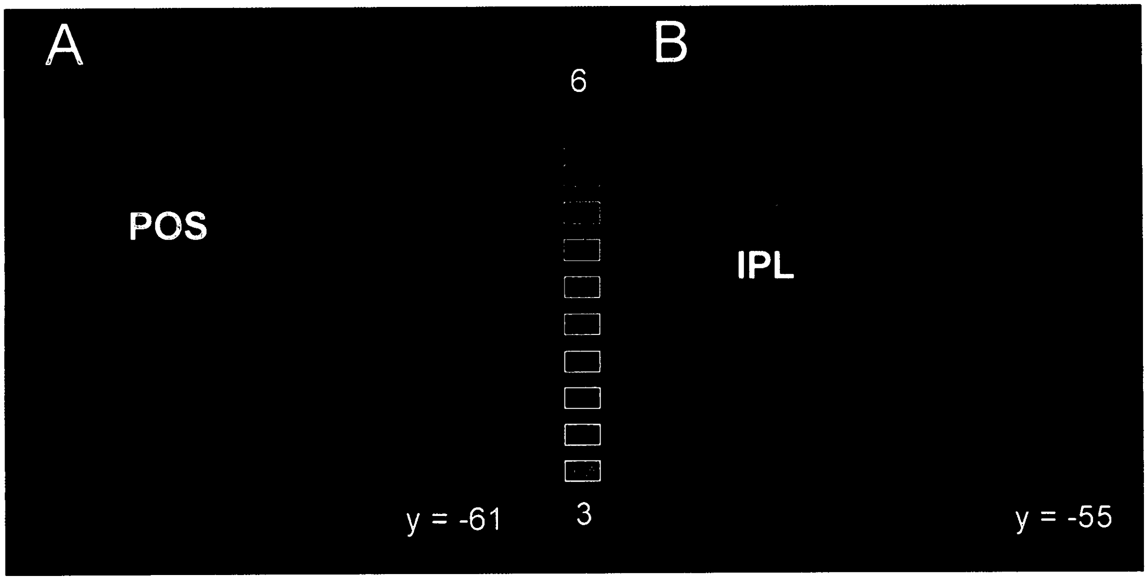

Figure 1.2. fMRI BOLD activation during the preparation of a rotated visually-guided reach. Coronal view during early (A) and late (B) planning during a reach with 180° cursor feedback rotation in contrast with a reach with veridical cursor feedback (preliminary evidence from (Granek et al., 2010). POS; parieto-occipital sulcus, IPL; inferior parietal lobule.

The cortical regions involved in cognitive-motor integration require an increase in attentional demands. The precuneus, thought to be the human PRR (see Filimon, Nelson, Huang, & Sereno, 2009; Jackson et al., 2009) is known to be activated as a result of cognitive control of tasks involving increased spatial attentional demands (Culham et al., 1998), decoupled visually-guided reaching (Gorbet et al., 2004), and increased sequence complexity and duration (Wenderoth, Debaere, Sunaert, & Swinnen, 2005). The SPL, has also been shown to be activated when a shift in attention to different locations in space is required (Kelley et al., 2008; Yantis et al., 2002), which is a crucial component of decoupling gaze from hand movement as in non-standard sensorimotor mappings.

The precentral structures involved in non-standard visuomotor control include the prefrontal and lateral premotor cortices. The prefrontal structures are those previously discussed (Gorbet et al., 2004) to be responsible for the inhibitory attention required to inhibit the natural tendency to couple gaze and hand movement direction (Gielen et al., 1984; Neggers & Bekkering, 2000; Neggers & Bekkering, 2001). Specifically, Gorbet and colleagues (2004) found greater superior frontal gyrus (SFG) as a part of the parieto-frontal network involved in orienting a joystick in the opposite direction of gaze relative to standard sensorimotor mappings, which likely contributed to the overall dimming of the standard default motor cortical network. The rostral SFG is known to be involved in rule-based decision making (Leung & Cai, 2007; Murray et al., 2000; Rowe et al., 2008) and it is strongly interconnected with PMd (Tomassini et al., 2007), a brain area known to be active in non-standard movement control (Batista et al., 1999; Battaglia-Mayer et al., 2001; Boussaoud, Jouffrais, & Bremmer, 1998; Crammond & Kalaska, 1994; Johnson, Coltz, & Ebner, 1999; Shen & Alexander, 1997; Snyder, Batista, & Andersen, 2000). The DLPFC another prefrontal structure which is widely known as an area associated with inhibitory attention (Hoshi & Tanji, 2006; Leung & Cai, 2007), specifically during the preparation and switching of motor programs incorporating tool-use (Moll, de Oliveira-Souza, Passman et al., 2000; Saito et al., 2005). It has been proposed that prefronto-striatal connectivity, specifically deriving from the DLPFC, is necessary for the decision to inhibit natural tendencies such as in the case of performing anti-saccades (Bertolino et al., 2009; Durston et al., 2005). The ventrolateral prefrontal cortex (VLPFC) has been shown to display an increase in BOLD signal for halting the execution of either eye or hand movements, once they have been prepared (Leung & Cai, 2007). In addition, increased activity observed from fMRI (Toni, Ramnani, Josephs, Ashburner, & Passingham, 2001) and positron emission tomography (Toni, Rushworth, & Passingham, 2001) in the ventral prefrontal cortex during arbitrary reaching learning has revealed a possible role in the VLPFC in combining perceptual information with cognitive rules (see Passingham, Toni, & Rushworth, 2000). In the medial frontal cortex, the anterior cingulate cortex activity can predict post-conflict adjustments in the lateral prefrontal cortex as a part of a conflict control network during complex tasks (Kerns et al., 2004; Kerns, 2006). This conflict control network might also apply when monitoring reaches towards a different spatial location than gaze (Connolly et al., 2000; Gorbet et al., 2004). Downstream, PMd has been shown to display greater BOLD activation when participants reached towards a required reach direction that was defined by an arbitrary colour (Amiez, Kostopoulos, Champod, & Petrides, 2006), specifically in an area corresponding to PMdr (Tachibana, Nambu, Hatanaka, Miyachi, & Takada, 2004).

1.4.2. Neurophysiological studies of brain activity in non-standard visuomotor control

Recording from a cellular level in non-human primates allows researchers to confirm much of the imaging data derived from human cortices. 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 (Miyazaki, Nakajima, Shima & Mushiake, 2013). Ablation of the DLPFC can cause deficits in an arbitrary situation (e.g. red circle = leftward arm movement), which associated a cognitive rule with a motor plan (Gaffan & Harrison, 1989). The ventral and orbital component of the prefrontal cortex (PFv+o) has been shown to have a direct involvement in these non-standard attentional processes (see Murray et al., 2000). Specifically, PFv+o has been implicated for the acquisition of arbitrary visuomotor associations where the visual information required for guiding a motor response must be learned (Rushworth et al., 2005). As well, the PFv+o is required for learning the reward value of a visual stimulus (Hornak et al., 2004). Further, lesions of the whit matter connections from the infero-temporal (IT) cortex to the PFv+o, have been shown to interfere with the learning of new arbitrary visuomotor mappings (Gaffan & Harrison, 1988).

The ability to halt an automatic response requires substantial attentional control. Anti-saccades have been a common means for exploring attentional control (see Munoz & Everling, 2004). A key candidate in the execution of eye movements (frontal eye fields; FEF), has been shown to be inhibited by prefrontal structures as its neuronal activity is less for anti-saccades than pro-saccades, and in turn, relaying alternative information to the superior colliculus (SC) a subcortical region involved in eye-movements (Everling & Munoz, 2000). As such, influenced by the altered input from FEF, fixation-related SC neurons have been shown to increase in firing rate, while saccade-related SC neurons displayed a decrease in firing rate when preparing for an anti-saccade, thus halting the natural tendency to look towards a visual stimulus (Everling, Dorris, Klein, & Munoz, 1999).

Downstream, PMd neurons have been shown to differentially respond when successfully (i.e. with improved performance) integrating an arbitrary rule with a motor action (Mitz, Godschalk, & Wise, 1991). PMdr is known to represent the relative position between gaze, hand and target (Pesaran, Nelson, & Andersen, 2006) specifically when incorporating a transformational rule into a motor action during a spatial plane dissociation between gaze and hand movements (Sayegh et al., 2013). Others (Boussaoud

& Wise, 1993a; Boussaoud & Wise, 1993b; di Pellegrino & Wise, 1993; Gail, Klaes, & Westendorff, 2009) have recorded cells in PMd which respond to visual stimuli that instruct movements, thus providing further evidence for PMd in incorporating a cognitive rule with a motor action. Following bilateral ablation of PMd, monkeys struggled in performing previously learned arbitrary associations (Passingham, 1988). Further, PMd's role in receiving inhibitory commands becomes apparent with the administration of a GABA-antagonist (e.g. muscimol) to PMd, whereby monkeys were unable to inhibit well trained movements that have been stored as a motor plan (Sawaguchi, Yamane, & Kubota, 1996). Similarly, muscimol injections in PMd have been shown to disrupt the selection of a motor action which was conditional on a visual stimulus, while sparing movement amplitude and velocity (Kurata, 1994a; Kurata, 1994b).

Postcentrally, neurophysiological recordings in parietal area V6A, the non-human homologue of the human POJ (Fattori et al., 2004; Galletti et al., 2003), have offered further evidence that the medial parieto-occipital cortex is involved in proprioceptive updating as the reach direction has been decoupled from gaze direction (Marzocchi et al., 2008). During a 180° rotation, SPL neurons have been shown to switch their preferred direction towards the movement goal regardless of the visual target feedback (Hawkins et al., 2013), father solidifying the role for SPL in online goal directed reaching during decoupled situations. The introduction of an external tool in a visuomotor task further increases its complexity. A tool, in essence, acts as an extension of one's end-effector (e.g. arm). As such, neurons within the IPL of non-human primates have been shown to expand their receptive fields to account for a tool (e.g. a rake; Iriki et al., 1996; Obayashi et al., 2001), and display task-specific preferential firing (Fogassi et al., 2005), implying the context specificity of the intention of purposeful movements involving a tool within the IPL.

1.4.3. Behavioural findings of decoupled eye-hand coordination

Behavioural studies on decoupled eye-hand coordination have been designed to test the hypotheses that different levels of visuomotor dissociation are processed by distinct yet interdependent neural substrates. Healthy individuals have been shown to display compromised reaching performance when reaching towards a spatial location that is decoupled from gaze direction (Gorbet & Sergio, 2009; Gordon, Ghilardi, & Ghez, 1994; Messier & Kalaska, 1997), suggesting that such movements require additional neural processing relative to direct object interaction. Specifically, when performing non-standard movements (e.g. using a computer mouse), the patterns of spatial errors (direction and extent) of final end-point position were found to differ between the two conditions in spite of the fact that arm movements made in each condition were biomechanically identical (Messier & Kalaska, 1997). Others have observed changes in reaction time (Dassonville, Lewis, & al., 1999; Ghilardi et al., 2000), hand-path curvature (Goodbody & Wolpert, 1999; Gorbet & Sergio, 2009), and learning processes (Clower &

Boussaoud, 2000) when subjects were required to perform non-standard visuomotor tasks, relative to standard ones.

1.5. Posterior parietal cortex and complex behaviour

The PPC has been implicated as a crucial node for integrating both somatosensation and vision and communicating with the frontal cortex for visuomotor control. The function within the PPC changes quite dramatically depending on the sub-region. In fact, it has been argued that distinct functional regions exist within the SPL, with segregated areas for reaching (Batista & Andersen, 2001; Gail & Andersen, 2006), located within the medial bank of the IPS (Snyder, Batista, & Andersen, 1997), and saccades (Andersen, Brotchie, & Mazzoni, 1992), located on the lateral bank of the IPS (Cui & Andersen, 2007; Snyder et al., 1997). Others have argued that SPL neurons respond with a global tuning incorporating the combination of the preferred directions of both eye and hand signals (Battaglia-Mayer et al., 2000; Battaglia-Mayer & Caminiti, 2002). Areas within the IPL have been shown to be responsible for complex tool-use (Buxbaum, Kyle, Tang, & Detre, 2006; Goldenberg & Spatt, 2009; Johnson-Frey et al., 2005), monitoring of hand position relative to the target goal (Fernandez-Ruiz et al., 2007; Vesia et al., 2010), and in complex arithmetic (Lee, 2000; Menon, Rivera, White, Glover, & Reiss, 2000).

1.5.1. Evidence from lesion studies

Working with the patient population offers a unique situation where one can infer function via dysfunction. In addition to being able to perform a series of experiments to identify symptoms characterized with a certain disorder, lesion studies can serve as a tool to decipher the role a given node within a previously identified network (i.e. via neuroimaging). Lesion studies also provide the opportunity to establish not only which areas are "active" during a task, but provide insight into which nodes are crucial for a given task.

Patients with optic ataxia (OA), which is a visuomotor disorder associated with damage to the superior parietal lobule (SPL), with consistent overlap to POJ (Blangero et al., 2009; Karnath & Perenin, 2005), present an ideal population to decipher the role that the SPL plays within the neural network responsible for preparing and guiding different types of visually-guided reaching. OA patients are known to display impaired visually-guided reaching towards extra-foveal targets, with preserved visual and motor function (Jeannerod, 1986; Perenin & Vighetto, 1988). Specifically, OA patients have been shown to display predominant gaze-biased misreaching (i.e. hypometric reaching) towards peripheral targets in the contralesional visual field, while using the contralesional limb (Blangero et al., 2008; Perenin & Vighetto, 1988), Conversely, an intact SPL is generally not required for reaching directly towards a foveally-acquired target (Perenin & Vighetto, 1988; Rossetti et al., 2005). Preliminary findings of a bilateral OA patient demonstrate that an intact caudal SPL is crucial for decoupled visually-guided reaching, particularly in situations involving a visuomotor rotation (Sergio et al., 2009). Similarly, specific lesions to macaque V6A (Battaglini et al., 2002) and PEc (Battaglia-Mayer et al. 2012) reported acute gaze-biased misreaching (Battaglini et al., 2002; Galletti et al., 2003), although the symptoms were followed by a quick recovery, thought to perhaps be a result of compensatory activity of neighboring parietal connections (Battaglini et al., 2002; Battaglini et al., 2003).

Incorporating a tool as an extension of the hand requires the brain to adapt to the suddenly longer arm require and thus the entire body scheme must be re-learned and calibrated. The accommodation of the spatial properties of the tool has been thought to be involved in the left IPL (Inoue et al., 2001; Iriki et al., 1996; Obayashi et al., 2001) and its direct connections with PMv (Tanne-Gariepy et al., 2002; Tomassini et al., 2007). This predominantly left-dominant parieto-frontal network has been shown to be crucial in choosing the appropriate distal limb orientation for purposeful tool-use (Buxbaum et al., 2006; Goldenberg & Spatt, 2009; Johnson-Frey et al., 2005), which is considered to be "cognitive" in nature (Buxbaum, Sirigu, Schwartz, & Klatzky, 2003; Buxbaum et al., 2007). Patients with left IPL damage have been shown to produce ideomotor (limb) apraxia, which has been characterized by the inability to perform purposeful movements involving a tool along with retained knowledge of the meaning of the tool (Leiguarda & Marsden, 2000). An intact left IPL has been shown to be associated with improved performance on appropriate hand gestures specifically during the grasp-to-use condition (Osiurak et al., 2008). Interestingly, patients with left hemispheric damage do not display deficits in the appropriate selection of a novel tool to perform certain tasks, relative to healthy controls (Goldenberg & Hagmann, 1998). The impairment in purposeful movements involving a tool implies a predominant misorientation of the distal joints associated with meaningful manipulation, with spared ability to grasp and transport an object and to associate an object with semantic meaning.

Damage to the right IPL has been shown to lead to spatial neglect, where the patient is impaired in attending to the left visual field (for review, see Husain & Nachev, 2007). Based on evidence from patients with neglect, the right IPL in humans (Mort et al., 2003; Vallar & Perani, 1986) and the right superior temporal gyrus in non-human primates (Karnath, Ferber, & Himmelbach, 2001) could be a crucial node as a part of a visuo-perceptual network (Pisella et al., 2013) since such patients with neglect show non-lateralized deficits of anti-saccade (Butler et al., 2009) anti-reaching (Rossit et al., 2011), and complex motor programming towards the affected visual field (Mattingley, Husain, Rorden, Kennard, & Driver, 1998).

Individuals diagnosed with Alzheimer's (AD) have been suggested to experience parieto-frontal disconnect (Bonni et al., 2013) and parietal hypoperfusion (Johnson et al., 2005), both potentially leading to performance deficits during complex visuomotor tasks. In particular, AD participants have been shown to struggle during decoupled eye-hand coordination with spared direct visuomotor control (Ghilardi et al., 1999; Ghilardi et al., 2000), even in early stages (Tippett & Sergio, 2006; Tippett et al., 2007). Even patients diagnosed with mild cognitive impairment show deficits in decoupled eye-hand coordination, however, only in situations which require two levels of dissociation (e.g. spatial plane change in addition to a visuomotor rotation: (Salek, Anderson, & Sergio, 2011). These changes may reflect differences in information processing by the brain to account for the altered correspondence between sensory input and motor response.

Arithmetic is known to be a cognitively-demanding task. Parietal lesions resulting in deficits in calculations (acalculia; (Ardila & Rosselli, 2002) have provided insight to the crucial involvement of the parietal lobe in calculations. Primary acalculia (a component of "Gertsmann Syndrome") is thought to result from left IPL damage (Mazzoni, Pardossi, Cantini, Giorgetti, & Arena, 1990) and has been shown to lead to impaired oral calculations (see Ardila & Rosselli, 2002). Evidence for the left AG in sequential memorized mathematics (e.g. verbally reporting multiplication tables) has been shown with correlations between BOLD activations and the lesion site of a patient with acalculia (Lee, 2000). These specific deficits of the left AG correspond with imaging data which link verbal arithmetic to the verbal system (Dehaene & Cohen, 1997; Dehaene, Piazza, Pinel, & Cohen, 2003; Lee & Kang, 2002) and for recalling stored arithmetic facts retrieved from long-term memory (Grabner et al., 2009).

1.6. A brief overview of the three projects described in this dissertation

The purpose of this research is to understand how the brain incorporates visual and cognitive-rule information into a motor act, a skill essential to our everyday function. Here we describe the role of the different regions of the PPC within the cortical network responsible for preparing and guiding different types of cognitive-motor integration. We present fundamental and clinical projects which will advance our understanding of one of our most basic behaviours: how we interact with objects in the world around us.

The current dissertation focuses on three projects designed to quantify performance changes in human behaviour, using a parietal stroke patient population (OA) and a healthy adult population in which we "overloaded" the neural networks thought to be responsible for the implementation of a secondary task. These studies will categorize behavioural effects under different task conditions, and characterize the contribution of different cortical areas to the underlying neural control systems. This approach will contribute to our fundamental understanding of how the brain controls movement. Guiding a decoupled limb involves the ability to predict hand location without direct vision, and with impaired proprioceptive updating observed in OA (as seen in reaches in the dark: Blangero et al., 2007), patients may be required to rely on strategic control in such situations. In the studies presented in this dissertation, each task was designed to involve a different **weighting** between strategic control and sensorimotor recalibration.

The task manipulations, in which participants were instructed to foveate the visual targets, involved moving the limb to targets when there was either 1) a rotated cursor feedback between viewed hand motion and actual hand motion (180°, more strategic control and 90°, more sensorimotor recalibration), 2) a change in the plane of the displayed visual stimulus (vertical) relative to plane of the limb movement (familiar horizontal and non-familiar para-sagittal planes) and 3) an arbitrary symbol that signals a specific movement direction (strategic control). These different mapping levels are used to explore the integration of different types of information into a reach.

The distinction between the 180° and 90° visuomotor rotations is predicated on the assumption that movements in the opposite direction to the cursor feedback (180°) rely on strategic control by utilizing a discrete inversion of the horizontal and vertical axes, while movements made under a 90° cursor feedback rotation rely heavily on sensorimotor recalibration, utilizing a gradual visuomotor adaptation. The support for this assumption comes from previous studies in which neurologically healthy adults showed minimal behavioral performance degradation with 180° cursor feedback rotation versus no rotation (Abeele & Bock, 2001; Cunningham, 1989). In contrast, it has been demonstrated that reach performance declines as feedback rotation moves from 0° to 90°, improves from 90° to 180°, and then declines again from 180° to 270° (Bock, Abeele, & Eversheim, 2003; Werner & Bock, 2007). These data support the idea of two 'functional modules' or control modes (Bock, 2013), in which a simple 'move in opposite direction' requirement employs a quick to implement rule-based strategy while intervening angles – maximizing at 90° – employ a gradual recalibration (Bock, 2013; Sergio et al., 2009).

Further, the targets for the centre-out reach task were placed either along a horizontal axis or along a diagonal axis. We also make the assumption that, when moving under conditions of rotated visual feedback, targets placed on a horizontal line will rely on explicit rule-based strategic control more than targets placed on a diagonal line. Use of allocentric cues are important for visuomotor adaptations, which have been shown to be represented in extrinsic coordinates (Krakauer, Pine, Ghilardi, & Ghez, 2000). Our assumption is thus based on the idea that in our task one is able to rely on allocentric cues for movement guidance to horizontal targets, since a straight path to these targets is aligned with the horizontal borders of the target display monitor (and perpendicular to the vertical border just beyond the target). In contrast, one would not be able to rely on allocentric cues to plan a straight path to targets placed diagonally from the central target since the computer monitor the monitor corner was not along a diagonal line from the start location. Hence although participants might have an approximate rule for the diagonal targets using allocentric cues (e.g. top-left target is close to a bottom-right movement), this rule could only be used as a guideline since the surrounding allocentric cues were not precise enough to devise a predictive motor plan; a gradual recalibration between senses would be required. Comprehension of the cognitive rule has not been shown to be sufficient for successful adaptation in off-axis situations (Benson, Anguera,

& Seidler, 2011; Mazzoni & Krakauer, 2006; Werner & Bock, 2007). In addition, it has been shown that learning of a left-right inversion towards diagonal targets (similar to a 90° rotation) involved responses which were initially aimed at or opposite to the targets, followed by a gradual change towards the visual target to compensate for the x-axis inversion (Werner & Bock, 2010). In contrast, only a transient increase in variability was observed during a left-right inversion towards targets along the ordinal axes (Werner & Bock, 2010). Lastly, in our previous work with this patient she showed success during a horizontal spatial plane transformation (Pisella et al., 2009), which may reflect cortical activation changes (Granek et al., 2010) as a result of previous experience with a similar decoupled task (e.g. using a computer mouse). Improvements in grasping deficits have been previously observed in OA towards familiar objects (Jeannerod, Decety, & Michel, 1994). Thus we also introduced a decoupling involving motion in a para-sagittal plane to reduce the effect of familiarity on movement performance. In summary, we employ a series of non-standard movements having varying levels of well-categorized canonical and less-categorized non-canonical orientations and directions, which thus follow a spectrum of strategic control to sensorimotor recalibration.

Since we were the first to test the "natural" scan path behaviour of OA patients during decoupled visually-guided reaching, our second exploratory objective throughout the following three projects was to examine the potential eye-movement errors utilized to compensate for the hand-movement impairments. As such, we formulate the following hypotheses and predictions describing the potential hand and eye movement errors in rule-based visuomotor control during situations relying on a relative contribution of sensorimotor recalibration and strategic control:

Project #1: To identify the role of the caudal SPL during different levels of non-standard visually-guided reaching. In order to further examine the role of the SPL during situations when the hand location has been decoupled from gaze, we studied two unilateral OA patients (MFL and CF) and eight aged-matched controls in a series of non-standard visuomotor tasks where the subjects were free to foveate the targets, but were required to move their hand while incorporating both cognitive and spatial algorithms.

Objective #1: To identify the motor error patterns in patients with damage to their SPL in situations in which participants were free to foveate the visual targets but their hands were spatially decoupled (spatial plane changes and visual feedback rotations) from the direction of gaze.

Hypothesis: Different forms of visuomotor compatibility are subserved by different parieto-frontal networks.

Prediction. The damaged SPL, seen in OA, is involved in decoupled reaching such as a visuomotor rotation between the eyes and the hand, but not for direct reaching or the ability to make arbitrary sensorimotor mappings.

Objective #2: To identify the eye-hand strategies employed by OA patients during

reaching under standard and non-standard situations.

Hypothesis: The superior parietal lobule formulates and maintains a "difference vector" between the felt hand and the viewed action goal.

Prediction. OA patients will perform additional eye movements which will aid in the continuous monitoring of the ongoing hand motion and target goal.

Project #2: To identify the role of the caudal SPL during different levels of non-standard visually-guided reaching relying on strategic control versus sensorimotor recalibration. The first project indicated that there was some independence between the networks, but to explicitly examine whether these two types of coordination are represented independently, we were fortunate enough to work with a bilateral optic ataxic patient. In order to examine the role of the caudal SPL during situations when the hand location has been decoupled from gaze, but can either be performed with the aid of explicit strategies or with the reliance on implicit sensorimotor recalibration, we studied a bilateral OA patients (IG) and six aged-matched controls in a series of non-standard visuomotor tasks. Again, subjects were free to foveate the targets, but were required to move their hand while incorporating both cognitive and spatial algorithms, but only in some situations could explicit strategies be employed.

Objective #1: To identify the effects of plane changes and visual feedback rotations on motor error patterns in bilateral OA during situations where explicit strategic

control can be utilized versus situations relying on implicit sensorimotor recalibration (i.e. realignment between proprioception and vision).

Hypothesis: An intact SPL is integral for situations requiring sensorimotor recalibration, but not for situations where strategic control can be useful.

Prediction. The damaged caudal SPL, damaged in OA, is involved crucial for the implicit realignment of the decoupled proprioceptive and visual input, especially during 90° rotated cursor feedback, and towards the diagonal visual targets. Performance will improve during the 180° rotated cursor feedback (i.e. move eyes and hand in the opposite direction) and towards a horizontal target, where strategic control can be implemented. In addition, allowing free head movement (during "gaze" conditions) will enable natural (Biguer, Prablanc, & Jeannerod, 1984) and synergistic (Pelz, Hayhoe, & Loeber, 2001) head movmements and thus will improve performance during decoupled visually-guided reaching. Her ability to adapt to a change in a spatial plane (either horizontal or para-sagittal) between the viewed target and motor output or to make direct eye and eye-hand movements will not be as affected based on previous evidence in this patient (Pisella et al., 2009).

Objective #2: To identify the eye-hand strategies employed by IG during decoupled visually-guided reaching where explicit strategic control can be utilized versus situations relying on sensorimotor recalibration.

Hypothesis: The superior parietal lobule formulates and maintains a "difference vector" between the felt hand and the viewed action goal predominantly when relying on implicit sensorimotor recalibration.

Prediction. IG will utilize additional eye movements in order to continually monitor and recalibrate the difference vector during decoupled visually-guided reaches relying on implicit sensorimotor recalibration relative to decoupled visually-guided reaches relying on strategic control.

Project #3: To further differentiate the alternative cortical connections during different levels of non-standard visually-guided reaching relying on strategic control versus sensorimotor recalibration. To further differentiate the fundamental mechanisms of decoupled visuomotor control, we tested healthy participants in a cognitively-demanding dual task. Participants continuously counted backwards while simultaneously reaching with either veridical or rotated (90°) cursor feedback. By increasing the overall neural load and selectively compromising the potential overlapping neural circuits responsible for strategic control, the dual task served as a non-invasive means to disrupt the integration of a cognitive rule with a motor action.

Objective #1: To identify the motor effects of increasing the neural load in healthy participants by simultaneously performing a cognitively-demanding secondary task (sequential backwards counting) during decoupled and coupled visually-guided reaching.

Hypothesis: Dual task will interfere with motor performance during decoupled visually-guided reaching differently depending on the relative reliance on strategic control versus sensorimotor recalibration.

Prediction: Dual task will lead to impaired motor control during rotated visually-guided reaching tasks towards the **horizontal** targets which rely on strategic control to a greater extent than the diagonal targets, which rely on implicit sensorimotor recalibration.

Objective #2: To identify the eye-hand strategies employed by healthy participants to compensate for the increased neural load when simultaneously performing a cognitively-demanding secondary task and decoupled visually-guided reaching in situations where explicit strategic control can be utilized versus situations relying on sensorimotor recalibration.

Hypothesis: Alternate parieto-frontal networks are responsible for those decoupled visually-guided reaches leaned via strategic control versus those learned via sensorimotor recalibration.

Prediction. Healthy participants will perform additional eye movements in order to compensate for the decoupled visually-guided reaches learned via strategic control versus those implicitly incorporated as a part of the motor plan via sensorimotor recalibration.

Chapter Two

The role of the caudal superior parietal lobule in updating hand location in peripheral vision: further evidence from optic ataxia

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Abstract

Patients with optic ataxia (OA), who are missing the caudal portion of their superior parietal lobule (SPL), have difficulty performing visually-guided reaches towards extra-foveal targets. Such gaze and hand decoupling also occurs in commonly performed non-standard visuomotor transformations such as the use of a computer mouse. In this study, we test two unilateral OA patients in conditions of 1) a change in the physical location of the visual stimulus relative to the plane of the limb movement, 2) a cue that signals a required limb movement 180° opposite to the cued visual target location, or 3) both of these situations combined. In these non-standard visuomotor transformations, the OA deficit is not observed as the well-documented field-dependent misreach. Instead, OA patients make additional eye movements to update hand and goal location during motor execution in order to complete these slow movements. Overall, the OA patients struggled when having to guide centrifugal movements in peripheral vision, even when they were instructed from visual stimuli that could be foveated. We propose that an intact caudal SPL is crucial for any visuomotor control that involves updating ongoing hand location in space without foveating it, i.e. from peripheral vision, proprioceptive or predictive information.

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

Introduction

Humans typically gaze and reach directly toward objects they interact with, a situation that has been termed "standard" (Wise et al., 1996). In tool-use however, the direction of our gaze and the object that we are manipulating are often in different spatial locations (e.g. driving). These "non-standard" situations require the mapping between stimulus and response to be learned and calibrated (Wise et al., 1996). Commonly performed "non-standard" situations often include the integration of various transformational (e.g. push computer mouse forward to move cursor upward) or arbitrary (e.g. green light means push gas pedal) rules. Such cognitive visuomotor associations are preserved in (OA; Pisella et al., 2006; Pisella et al., 2009; Rossetti, Pisella, & Vighetto, 2003), suggesting that the caudal superior parietal lobule (SPL) damaged in these patients is not crucial for this ability. However, neuroimaging findings give evidence of an involvement of the posterior parietal cortex (PPC) in non-standard visuomotor mapping (see below), the nature of which is unclear. Here, we put forward that the involvement of the SPL is related to another characteristics of "non-standard" situations: they often include having to guide actions outside the field of view or in peripheral vision. Both the explicit strategic control of non-standard transformational mappings (Bedford, 1993; Bock, 2005; Clower & Boussaoud, 2000; Lackner & Dizio, 1994; Redding & Wallace, 1996; Redding et al., 2005) and the implicit adaptation to spatial orientation differences between sensory modalities (e.g. vision and proprioception; (Gordon, Ghilardi, Cooper,

& Ghez, 1994; Messier & Kalaska, 1997) imply an ability to know or predict hand location during motor execution without direct vision. The updating and sensorimotor transformation of proprioceptive information has recently been shown to be impaired in OA (Blangero et al., 2007), which indicates that OA patients may need to look at their hand in such situations.

Brain imaging research has revealed overlapping yet distinct cortical networks involved in different types of non-standard reaching (Connolly et al., 2000; Gorbet et al., 2004; Granek et al., 2010; Inoue et al., 2000). A common cortical region activated during non-standard reaching is the PPC, which has been established as a predominant contributor to the preparation and execution of this type of non-standard behaviour. Within the PPC, the caudal portion of SPL (delimited ventrally by the intraparietal sulcus and posteriorly by the parietal occipital sulcus), is known to be directly connected to the rostral dorsal premotor cortex (PMd; (Tanne-Gariepy et al., 2002) and to constitute the visual dorsal stream (Pisella et al., 2006). The intraparietal sulcus and the SPL have been shown to display increased activity during visuomotor adaptation (Clower et al., 1996) and during mental rotation (Tagaris et al., 1996). Similarly, greater activity within the medial superior parietal region has been observed for anti-pointing relative to pro-pointing during central fixation (Connolly et al., 2000). Alternatively, other studies have concluded from endpoint errors that anti-pointing relies on a visuo-perceptual network which can be dissociated from the direct visuomotor network which supports pro-pointing (Blangero, Khan, Rode, Rossetti, & Pisella, 2011; Heath, Maraj, Gradkowski, & Binsted, 2009).Based on evidence from patients with neglect, this visuo-perceptual network could include the inferior parietal lobule (Mort et al., 2003; Vallar & Perani, 1986) and the superior temporal gyrus (Karnath et al., 2001), since such patients with neglect (contrary to patients with unilateral OA; (Blangero et al., 2011) show non-lateralised deficits of anti-saccade (Butler et al., 2009) and anti-reaching (Rossit et al., 2011). The process common to pro- and anti-pointing involving the most caudal portion of the SPL might thus be the control of a reach towards an extra-foveal position (Prado et al., 2005). An extensive PPC network is involved even as gaze and hand direction begin to become decoupled (for review, see Culham, 2005). In addition, neurophysiological recordings in area V6A, a monkey medial area at the parieto-occipital junction (Fattori et al., 2004; Galletti et al., 2003), have offered further evidence that neurons within the medial parieto-occipital cortex are involved in proprioceptive updating in situations in which gaze direction has been decoupled from reach direction (Marzocchi et al., 2008).

Patients with optic ataxia (OA), which is a visuomotor disorder that is associated with damage to the caudal SPL (Blangero et al., 2009; Karnath & Perenin, 2005), present an ideal population to decipher the role that the visual dorsal stream plays within the neural network responsible for preparing and guiding different types of visually-guided reaching. With preserved primary visual and motor function, OA patients typically exhibit misreaching (Perenin & Vighetto, 1988) and impaired visuomotor on-line control

(Blangero et al., 2008). We have recently proposed that the deficit associated with OA is a combination of a faulty coding of extra-foveal locations in their contralesional visual field (Field effect) and a faulty proprioceptive transformation of the location of their contralesional hand for reaching in the whole space (Hand effect: Blangero et al., 2007; Perenin & Vighetto, 1988; Pisella et al., 2006; Pisella et al., 2009). This proprioceptive transformation is necessary in conditions restricting visual feedback of the hand (as in the dark; Blangero et al., 2007) or in conditions where a provided visual feedback is decoupled from real hand location or direction. The involvement of caudal SPL in visually-guided reaching toward extra-foveal targets has been well accepted as well as the spared performance of OA patients in "standard" conditions of direct visually-guided reaching in free vision (Pisella et al., 2006; Pisella et al., 2009; Rossetti et al., 2003). However, the question remains if caudal SPL is a crucial component in guiding a reach within peripheral visual space when one is free to foveate the target, but the limb motion is spatially decoupled from gaze direction, a skill used in everyday life.

In order to address the role of the caudal SPL in situations in which the hand location is decoupled from gaze, we investigated a series of non-standard visuomotor tasks. The participants were briefly trained to perform visuomotor tasks that required the application of both cognitive and spatial algorithms in order to align a cursor with a foveated visual target using their hand. The spatial algorithms included the manipulation of cursor feedback rotation and the spatial plane of the hand movement (performed in isolation and in combination).

The first aim of the present study was to test the role the dorsomedial parieto-frontal neural pathway from caudal SPL to rostral PMd (PMdr; Tanne-Gariepy et al., 2002) in performing different types of non-standard visuomotor mappings. Specifically, we predicted that an intact caudal SPL served as a crucial node for the preparation and guidance of visually-guided reaches in situations in which the hand was spatially decoupled from gaze direction. In contrast, we predicted that an intact caudal SPL was neither crucial for the control of standard, spatially coupled visually-guided reach movements, nor for the control of arbitrary mappings (which also do not involve eye-hand decoupling). We therefore expect larger spatial endpoint errors or increased movement timings in patients relative to controls in the non-standard conditions, even if the subjects are free to look at the target. This deficit under conditions of eye-hand decoupling may reflect an inability to process simultaneously the decoupled hand and eye targets without an intact caudal SPL (Jackson et al., 2009). This inability may be explained in two ways which lead to two different predictions.

The first explanation is that the caudal SPL represents extrafoveal locations (of the hand or the goal) as we postulated previously (Blangero et al., 2007; Pisella et al., 2009). Along this positional hypothesis (developed in McIntosh, Mulroue, Blangero, Pisella, & Rossetti, 2011), lateralised effects would concern the right visual target which forces the patients to monitor their hand location (from proprioception or from the cursor) in their left (contralesional) visual space. In contrast, in visuomotor rotation conditions, where the visual target location has to be intentionally remapped to its symmetrical location in the opposite visual field for anti-pointing, it is expected that only the left visual target presentation will be affected. Indeed, it is known from recent results that only targets presented in the left (contralesional) visual space will be erroneously remapped for anti-reaching (Blangero et al., 2011). Given these opposing effects, along the positional hypothesis (Blangero et al., 2007; Pisella et al., 2009) we are unlikely to observe lateralised spatial effect of target presentation side.

An alternative explanation is that the key factor is neither the hand location nor the extrafoveal goal location per se, but rather their spatial relationship (allocentric coding), such that the deficit is determined by the direction of the required movement. This directional dependence could arise if the dorsal stream in each hemisphere subserves contralaterally-directed orienting behavior (cf. Kinsbourne, 1970). According to this 'directional' hypothesis (also more recently developed by McIntosh et al., 2011), a unilateral optic ataxic patient with field dependent misreaching would fail when contralesionally-directed guidance is required (leftward movements in our left OA patients). In such a case, we should observe a lateralised deficit depending on the motor goal, which is opposite to the side of visual target presentation in visuomotor rotation conditions. However, other authors (Schenk, 2006; Thaler & Goodale, 2011) have hypothesized that this guidance based on allocentric coding relies more on the ventral visual stream system (because it is impaired in patient D.F. with visual agnosia and is processed slower than target-directed coding).

The second aim of the present study was to explore the “natural” eye scan path behavior of OA patients in situations in non-standard conditions (for eye-hand coordination strategies in direct (standard) reaching conditions, see Gaveau et al., 2008). In our non-standard conditions, the decoupling of the spatial targets of the effectors was not due to extra-foveal reaching during central fixation – as done in most previous work with OA patients – but due to having the eyes and hand move to different locations in space. We predict that OA patients will not be able to simply saccade towards the target and maintain fixation during the performance of a decoupled visually-guided reach (control behavior), but will rely on additional eye movements in order to successfully complete the task (i.e. to recalibrate their hand and goal locations using central vision). The more complex the condition is, the more we may observe a tendency of the patients to make additional eye movements. Indeed, the patients may compensate their deficit by alternating several eye movements between the goal and the hand locations (either by looking at the real hand or by looking at the visual feedback cursor) in order to recalibrate visually their hand location.

Methods

Ethics statement

All participants signed informed consent and the study protocol was approved by the York University human participant research ethics committee, certificate number 2008-098.

Subjects

The participants were two patients with dorsal visual stream damage (CF, male, age 30; MFL, female, age 60) and eight healthy age-matched controls (four controls - two female - per patient; mean ages 30 ± 4 and 59 ± 5). All participants were tested for handedness (Oldfield, 1971). Control subjects were tested using their dominant right hand (handedness score greater than +0.50), while the patients were tested with both hands. MFL is predominantly left handed (although trained to use her right hand as a child; her handedness score was left-handed, -0.53). CF is predominantly right-handed (although his handedness score indicated ambidextrous, +0.33). CF reported to be an avid video-gamer, with a self-reported skill level of 8/10 prior to brain injury (although he reported a decrease in ability to 4/10 post-injury) and practiced 2-3 hours/week, while MFL had no video-game experience. All subjects had experience with a computer mouse and/or laptop touch pad.

Patient details

At the time of testing, patient CF was a 30-year-old male who suffered a watershed posterior infarct six years earlier, resulting in distributed and asymmetrical bilateral lesions of the occipito-parietal region (Brodmann's areas 18, 19, 7, 5 and 2) with a minute extension to the semiovale centers (**Fig. 2.2** – top row). At the time of testing, most lesions were asymptomatic; he exhibited chronic unilateral left optic ataxia, thought to be the consequence of intra-parietal sulcus lesion only in the right hemisphere, as well as larger SPL and white matter damage in the right hemisphere, probably causing a parieto-frontal disconnection from intra-hemispheric fibres lesions (**Fig. 2.2** – top row; for other behavioral details, see Blangero et al., 2008; Khan et al., 2005).

At the time of testing, patient MFL was a 60-year-old female who suffered from haemorrhagic stroke in the right hemisphere 16 years earlier. The lesion damaged the caudal part of the intraparietal sulcus and of the SPL (**Fig. 2.2** – bottom row). Following this focal lesion in the right hemisphere, MFL exhibited unilateral left optic ataxia (for an example of her behavior, see (Blangero et al., 2011).

Patients were given a set of standard clinical tests involving visual field topography (Goldman perimetry), sensory stimulation tests (visual and tactile extinction), neurological evaluation of reflexes and muscle tone and joint movements. Neither patient exhibited any purely motor, somatosensory or visual deficits, or any sign of neglect (on standard line bisection, star cancellation and drawing tasks).

Experimental procedure

Subjects sat in front of a computer monitor (41 cm from screen), head-fixed (with a chin rest), in a darkened room, and made sliding finger movements over a touch sensitive screen (Keytec Magic Screen: Model KTMT-1315: Sampling rate: 100 Hz) from a center target (with a four second delay) to one of four peripherally presented targets (up, down, left, right). The targets were presented 95 mm (13° visual angle) from the central target and were 25mm in diameter on the vertical monitor. Subjects were instructed to move as accurately and quickly as possible, across the touch screen and encouraged to maintain a consistent initial arm orientation for the different task conditions of the experiment. Right eye movements were monitored (Cambridge Systems, 250 Hz and EyeLink II, 250 Hz). The viewing space was calibrated using a nine-point calibration and drift correction was applied between each condition.

The subjects performed four conditions and a single arbitrary condition (**Fig. 2.1A**), each of which consisted of 20 trials. All conditions were performed in randomly assigned blocks, towards randomly presented visual targets. Initial training (up to 40 trials) was performed by all subjects prior to each condition until each subject reported that they were adequately prepared to ensure equal understanding of the task. Importantly, in order to emulate a natural environment, all subjects were instructed to look at the visual target (i.e. foveal acquisition), but were not restricted to a certain eye scan path. In the darkened room, the border of the computer monitor and the hand were still visible with peripheral vision. The subjects performed a single standard reaching task

('Vertical'; V), in which reaching movements were performed directly on the touch screen which was placed directly over the vertically-displayed monitor, and the cursor feedback reflected veridical finger motion. Subjects also performed three non-standard transformational reaching tasks involving two basic manipulations employed both separately and in combination:

A 'Horizontal' (H) condition, in which reaching movements were performed on a touch screen which was placed in the horizontal plane in front of the vertically-displayed monitor, a 'Vertical Rotated' (VR) condition, in which reaching movements were performed on a touch screen which was placed directly over the monitor, but the cursor feedback that reflected finger motion was rotated 180°, and a 'Horizontal Rotated' (HR) condition, involving a combination of the two manipulations, whereby reaching movements were performed on a touch screen which was placed in the horizontal plane in front of the vertically-displayed monitor and the cursor feedback reflected finger motion that was rotated 180°.

The unilateral OA patients (MFL and CF) were tested on the standard and the three non-standard transformational reaching tasks using both hands (to explore possible hand effects). In order to assess general strategic control in each of our patients relative to the control group, a single non-standard arbitrary association reaching task (ARB) was performed by the OA patients with their contralesional limb, while the controls used their dominant limb. Briefly, the ARB condition consisted of four different symbols presented in the center of the monitor which each represented a different target location, whereby the subjects were given feedback of the target at the completion of a successful trial. The maple leaf symbol was shown to represent the top target, the Bentley™ symbol reflected the left target, the Acura™ symbol reflected the right target and the Blue Jay™ symbol reflected the bottom target.

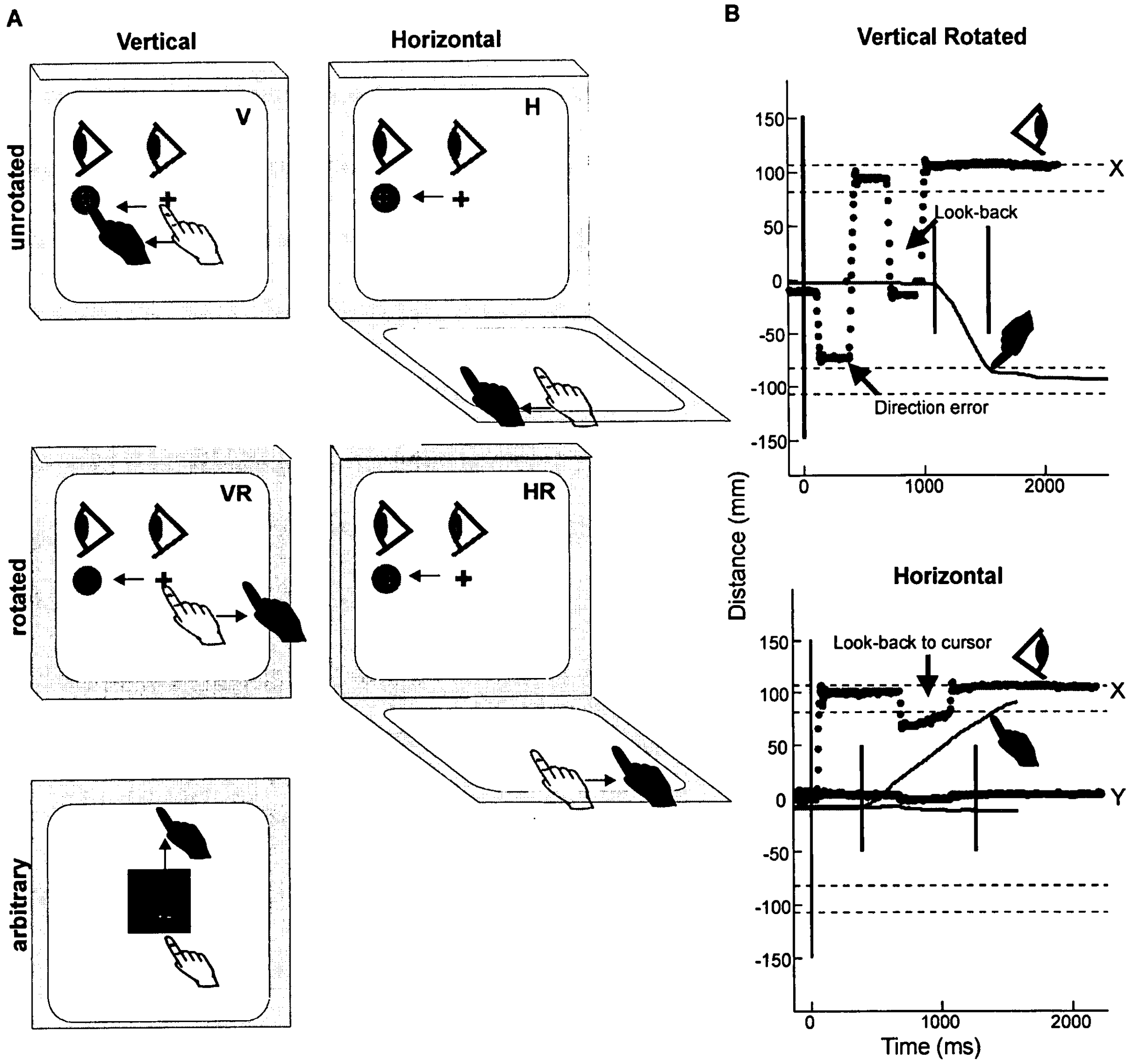

Figure 2.1. Task procedure, example patient eye data. (A) Schematic drawings of the standard center-out reaching movement towards one of four peripheral targets. Reaching movements were done both directly (vertical) and in two basic manipulations: spatial plane dissociation (horizontal) and 180° visuomotor rotation (vertical rotated) employed both separately and in combination (horizontal rotated), as well as a single arbitrary

association task. In the arbitrary condition, the maple leaf symbol is shown to indicate a required upward hand and eye movement. (B) Example x (gray dots) and y (black dots) eye position (in mm) for OA patients towards right (positive x) peripheral target during the VR and H conditions. Gray lines represent x hand position and black line represents y hand position (positive is upward) from movement onset to movement offset (short black lines). Horizontal dashed lines demark the location of peripheral targets, while long vertical black lines represent the go signal. Note that the look-back in the H condition was to the cursor representation of the hand, not the hand itself, while the look-back in the VR condition was to the hand.

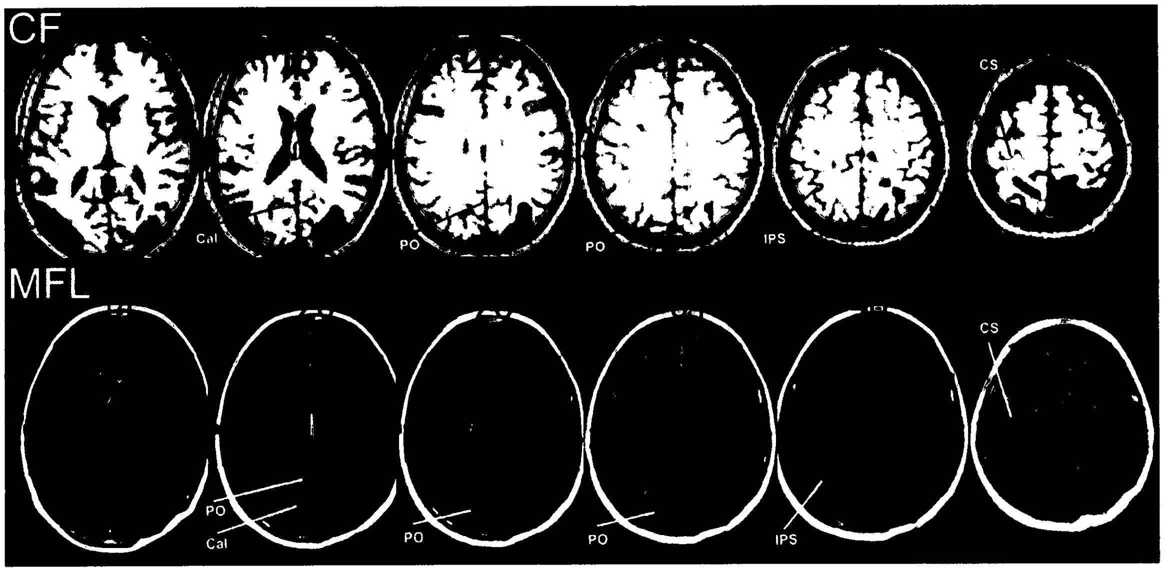

Figure 2.2 Anatomical MRI scan slices of patient CF (first row) and patient MFL (second row). The z-coordinates of the axial slices are indicated in blue. Occipital and parietal lesions were mapped and colored in green and red, respectively. The major sulci are indicated to guide the localization of the lesions (Cal: calcarine, PO: parieto-occipital, IPS: intra-parietal, CS: central). Note that these MRI scans were acquired at the acute stage of the strokes and that at the time of testing no visual field defect was associated with the occipital lesions. The patients' lesions overlap to the greatest extent at the level of the right caudal superior parietal lobule, which is the pertinent anatomical substrate of their common chronic visuomotor deficits.

Data analysis

Trials were only included in the hand movement timing, path, and endpoint analyses if they were successfully performed within a maximum of eight seconds without a 180° hand direction reversal (hand path errors were enumerated in a separate analysis).

An index of difficulty (ID) for each subject using 11 dependent variables (i) was computed as a measure of how demanding eye-hand decoupling (NS; non-standard, our VR, H, and HR conditions) was relative to direct visuomotor control (S; standard, our Vertical condition) by using the following formula:

$$ID = \sum_{i=1}^{11} \frac{NS - S}{S + NS}$$

Hand movement timing was analyzed whereby hand reaction time (**RT**) began when the peripheral target was presented and ended at movement onset. Hand movement onsets were scored as the point at which the resultant of the x and y trajectories exceeded 10 % of the peak velocity using a custom-written computer algorithm; the scored point was then verified visually for each trial (i.e. before any corrective movements). The hand ballistic movement time (**MT**) for all conditions began from the hand movement onset and ended at the first point in which the movement slowed to 10% peak velocity. In order to quantify the timing for corrective movements, we analyzed corrective movement time (**CMT**), which began at the end of MT (10% peak velocity) of a given trial and ended when the cursor entered the perimeter of the peripheral target (trial completion).

The individual hand movement paths were first low-pass Butterworth reverse filtered at 10 Hz (Matlab, Mathworks Inc.). Hand movement paths were recorded as direction errors (**DR**) if the first half of the paths in each trial deviated 180° or 45° (errors classified separately) from a straight line towards the cued direction. Hand movement accuracy parameters were determined from the participant's mean movement endpoints for each target location and analyzed separately for distance errors (**on-axis CE**) and for direction errors (**off-axis CE**),. Endpoint precision (variable error, **VE**) was determined by the distance of the endpoints of the individual movements from their mean movements.

Eye scan paths were also tested in order to observe the un-restricted eye movement behavior when the hand was spatially decoupled from gaze direction. The eye scan paths were only analyzed for a given trial if the corresponding hand movement trial was successfully completed. Eye movement onset was determined at 10% peak saccadic velocity following central fixation. Each sampled data point obtained during the experiment that was registered as a blink was smoothed 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. Eye scan path data were recorded from eye movement onset up until 1500 msec of peripheral target hold in order to be able to identify saccade-related errors. The saccade-related errors were placed into three categories: 1) initial direction errors (**DE**), 2) **look-**

backs, and 3) **steps** to catch up the target. DE were defined as initial primary saccades towards the wrong target (at least 90° away from the correct target) travelling a minimum of 50% of the distance between the central and peripheral target. Look-backs were counted when subjects reversed eye direction (towards the hand or the cursor) a minimum of 20% of the total amplitude from the central to peripheral target, holding at least 100 msec. Saccade-related errors were categorized as 'steps' if an eye movement was at least 10% of a full saccade from central to peripheral target, holding for at least 100 msec. 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 location towards the boarder of the computer monitor.

Statistics

The data from the individual patients and the controls were analyzed separately. For the control group (n=8), we conducted two-way repeated measures ANOVAs with condition and target as within-subject factors, and age (younger group - 30 ± 4 vs. older group - 58 ± 5) as a between-subject factor in order to address possible age by condition interactions. All ANOVA results were reported with Greenhouse-Geisser-corrected p-values, and post hoc comparisons were corrected for multiple comparisons (Bonferroni).

Inter-group analyses were performed on MFL and CF separately using modified t-tests (Crawford, Garthwaite, & Porter, 2010; each hand separately) and were compared with the control group for each visual target, in order to screen for hand and/or visual field effects (i.e. target direction). Importantly, for accurate comparison of each case (MFL and CF), the modified t-tests utilized in the current study adjusted the critical t-value depending on the variability (i.e. standard deviation) and group size of our control group (for details, see (Crawford et al., 2010). Therefore, alpha levels for all inter-group analyses were adjusted to 5% at $p' < 0.05$ (Crawford et al., 2010). In addition, an index of the number of standard deviation units that each case differed from a randomly chosen control subject (i.e. 'effect size') was calculated for each modified t-test to demonstrate the magnitude of the difference between groups (Crawford et al., 2010). One exception was during the comparison of the number of initial saccadic direction errors between the patients and the control group. Since the control group did not perform such errors (mean 0 ± 0), no statistical comparison could be performed.

Results

Because the patients were 30 years apart in age, we tested two different age-matched control groups. Importantly, no condition by age interactions were observed within the control group for any dependent variable ($p > 0.05$). Therefore, all inter-group analyses were performed for each OA patient relative to the entire control group ($n=8$). For details on the individual dependent variables see below.

Index of difficulty

We calculated an index reflecting the performance demand of the different non-standard transformational conditions relative to the standard condition (see Methods for details). For each subject, the index of difficulty (ID) was always positive, indicating that decoupling gaze and hand target location was more challenging than direct visuomotor control (**Fig. 2.3**).

Control group. Control subjects varied in their performance depending on the level of eye-hand decoupling (main effect of condition; ANOVA, $F_{2,11} = 26.3$, $p<0.0001$), whereby VR was more demanding than H ($p<0.05$) and HR was more demanding than both VR and H ($p<0.05$).

OA patients versus control group. MFL struggled in all conditions when gaze and hand position were decoupled relative to control participants (VR: $t = 2.9$, $p'<0.05$, effect size = 3.1, H: $t = 5.1$, $p'<0.01$, effect size = 5.4, HR: $t = 3.8$, $p'<0.01$, effect size = 4.1), while the index of difficulty was significantly higher than controls only in VR ($t = 2.4$, $p'<0.05$, effect size = 2.5) for CF.

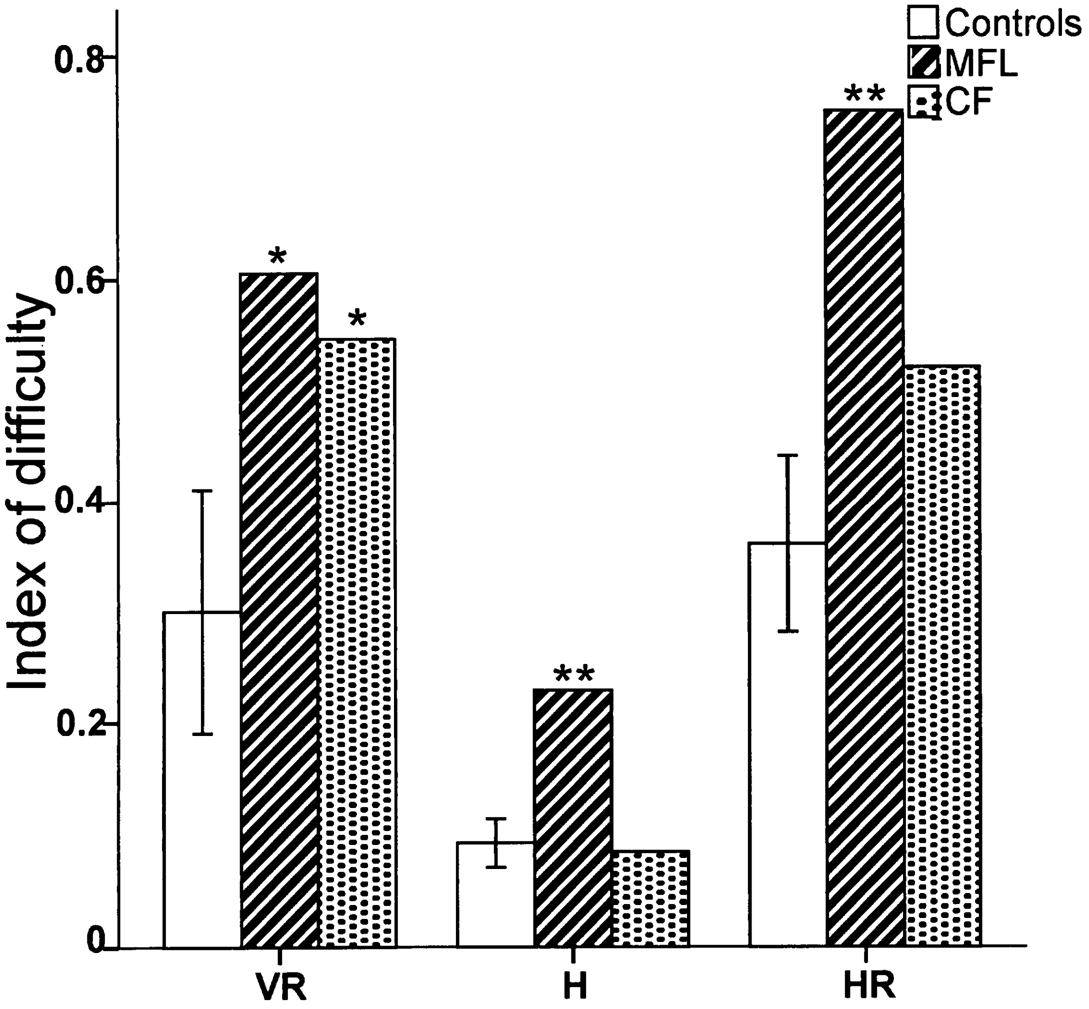

Figure 2.3. Index of difficulty for the decoupled non-standard conditions relative to the standard condition. A positive number from 0-1 indicates that the decoupled conditions were more difficult than the standard conditions across all significant dependent variables. Note the marked increase in ID for both patients in the Vertical Rotated (VR) condition relative to the controls. Error bars denote 95% Confidence Intervals. *p'< 0.05; **p'<0.01.

Hand movement timing

Control group. Within-group analyses were conducted on movement timing to determine a baseline of difficulty depending on the condition and the target. Condition main effects were observed for movement preparation (RT; ANOVA, $F_{2,14} = 11.4$, $p<0.001$), ballistic movement timing (MT; ANOVA, $F_{2,10} = 6.2$, $p<0.05$), and online movement correction (CMT; ANOVA, $F_{1,9} = 4.9$, $p<0.05$). Post hoc comparisons revealed longer RT for VR compared with H, and HR compared with H and V ($p<0.05$). Target direction did not influence movement timing parameters within this group ($p>0.05$).

OA patients versus control group. Unexpectedly, MFL exhibited timing differences relative to controls in the standard condition (V) for her RT and in the arbitrary condition (ARB) for her MT, suggesting that timing effects in this patient could be an unspecific tendency to be more cautious than controls before or during motor execution.

Pooled across both hands and all visual targets, MFL also displayed longer RT than the control group for all non-standard conditions (H: $t = 3.0$, $p'<0.05$, effect size = 3.1; VR and HR: $t > 5.4$, $p'<0.001$, effect size > 5.8). Across all visual targets, CF displayed slower RT than the control group only when using his left (affected) hand during HR ($t = 2.6$, $p'<0.05$, effect size = 2.8). Both MFL and CF revealed an overall deficit (both hands, all visual targets) of MT, relative to the control group, for VR (MFL:

$t = 2.8$, $p' < 0.05$, effect size = 3.0; CF: $t = 3.6$, $p' < 0.01$, effect size = 3.8). In addition, both MFL and CF took longer to correct their movements (CMT) compared to the control group during VR while using their right (unaffected) hands, across all visual targets (MFL: $t = 2.8$, $p' < 0.05$, effect size = 3.0; CF: $t = 2.4$, $p' < 0.05$, effect size = 2.6). MFL also displayed an increase in CMT in condition HR across hand and target ($t = 2.6$, $p' < 0.05$, effect size = 2.8).

In summary, decoupling the spatial location of the foveally-acquired visual target and the hand motion required to reach that target led to a slowing of preparation, initial movement execution, and online movement correction in these OA patients, independent of the target and with no consistent hand effect (see **Tab. 2.1**).

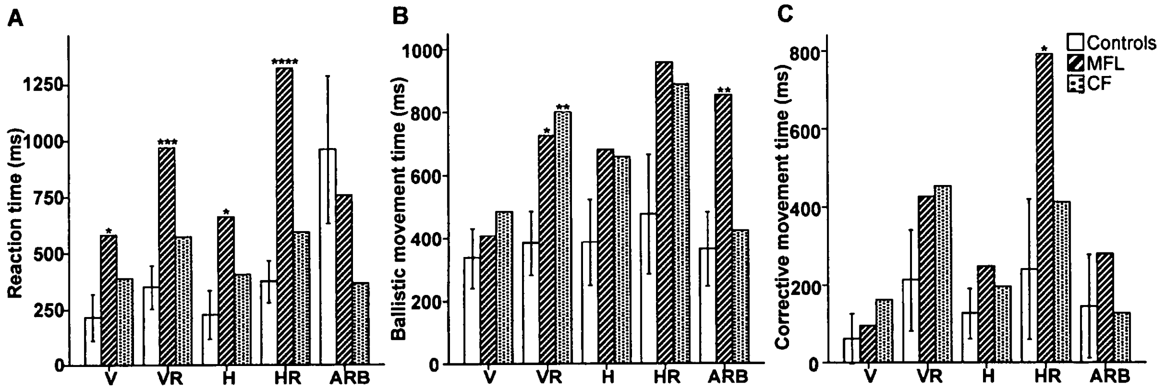

Figure 2.4. Hand movement timing data for MFL, CF, and the control group. Mean reaction times (A) ballistic movement times (B) and corrective movement times (C) in msec for both groups for the five conditions (V = Vertical; VR = Vertical Rotated; H = Horizontal; HR = Horizontal Rotated; ARB = Arbitrary) across all targets. Both hands were pooled for MFL and CF. Error bars denote 95% Confidence Intervals. $*p' < 0.05$; $**p' < 0.01$; $***p' < 0.001$; $****p' < 0.0001$.

Table 2.1. Hand movement timing significant differences separated by hand and visual target between MFL and CF compared with the control group

Group	Variable	Condition	Hand	Target	t-Value	Effect size
MFL	RT	V	L	L,B	>3.9**	>4.2
		V	R	T,L,B	>2.7*	>2.9
		VR	L,R	R,T,L,B	>3.7**	>3.9
		H	L	R,T,B	>2.8*	>2.9
		H	R	R,T,L,B	>2.8*	>2.9
		HR	L,R	R,T,L,B	>3.2*	>3.4
	MT	VR	L	L	3.1*	3.3
		VR	R	R,T,L	>3.4*	>3.6
		H	L,R	L	>2.5*	>2.6
		HR	L	T	2.9*	3.1
		HR	R	T,L	>2.9*	>3.1
		ARB	L	L	3.6**	3.8
	CMT	V	R	L	3.5**	3.7
		VR	R	T	11.2****	11.9
		H	L	R	5.9***	6.2
		HR	L	T,B	>2.7*	>2.9
CF	RT	VR	L	B	3.6**	3.9
		VR	R	L	2.6*	2.7
		HR	L	R,T	>2.7*	>2.9
		HR	R	R	2.7*	2.9
	MT	V	L	R	2.6*	2.7
		VR	L,R	R,L,B	>2.6*	>2.7
		H	L	B	2.5*	2.6
		H	R	R,B	>2.7*	>2.9
		HR	L	L	3.1*	3.3
	CMT	V	R	T	2.5*	2.7
		VR	L	R	2.7*	2.9
		VR	R	T	3.8**	4.1
		HR	R	R	2.6*	2.8

Table 2.1 note: Dependent variables (RT = reaction time; MT = ballistic movement time; CMT = corrective movement time) were tested with separated modified t-tests ($p' < 0.05$) for each condition (V = vertical; VR = vertical rotated; H = horizontal; HR = horizontal rotated) for each hand and each visual target (R = right; T = top; L = left; B = bottom). *$p' < 0.05$; **$p' < 0.01$; ***$p' < 0.001$; ****$p' < 0.0001$.

Hand endpoints

Control group. Within-group analyses were conducted on the control group for hand position following the initial ballistic movement, however, no differences in endpoint accuracy (CE) or precision (VE) were observed ($p>0.05$). The controls only made 180° hand direction reversals (i.e. did not implement non-standard rule) during the conditions involving a visuomotor rotation (VR/HR; ANOVA, $F_{2,11} = 5.2$, $p<0.05$).

OA patients versus control group. Both OA patients displayed a systematic undershoot (i.e. negative on-axis CE) of the targets in non-standard visuomotor conditions (**Figs. 2.5B,C,D**, and **2.6A**). This finding was accompanied by relatively very little direction error (i.e. off-axis CE; **Fig. 2.6B**). Indeed, neither OA patient displayed a hand movement bias towards the computer monitor in those conditions in which the hand was moving in a horizontal spatial plane while viewing the target on a vertical monitor (H/HR; see **Figs. 2.5C,D**). 180° hand movement direction reversals were observed in patients during visuomotor rotation conditions (VR and HR), as in control subjects, but significantly more than the control group for MFL with her right (unaffected, non-dominant) hand, and for CF when required to move into his affected (left) visual field (right visual target; see **Tab. 2.2** for details). CF was also more variable (VE) than controls during visuomotor rotations (VR and HR) when using his left (affected) hand and when right visual targets were presented, a situation cumulating hand and field effects. CF also produced hypometric reaching errors (on-axis CE) significantly higher than controls in all non-standard conditions (H, VR and HR), but they were observed with both hands and only when the top target was presented. For MFL, VE was also higher than controls overall in HR (**Fig. 2.6C**), with the left (affected) hand when the right visual target was presented in H, and with the right (unaffected) hand when the left visual target was presented in VR. In summary, differences in hand endpoints parameters between OA patients and controls were observed only in non-standard visuomotor conditions, with no systematic hand or visual field biases across the conditions.

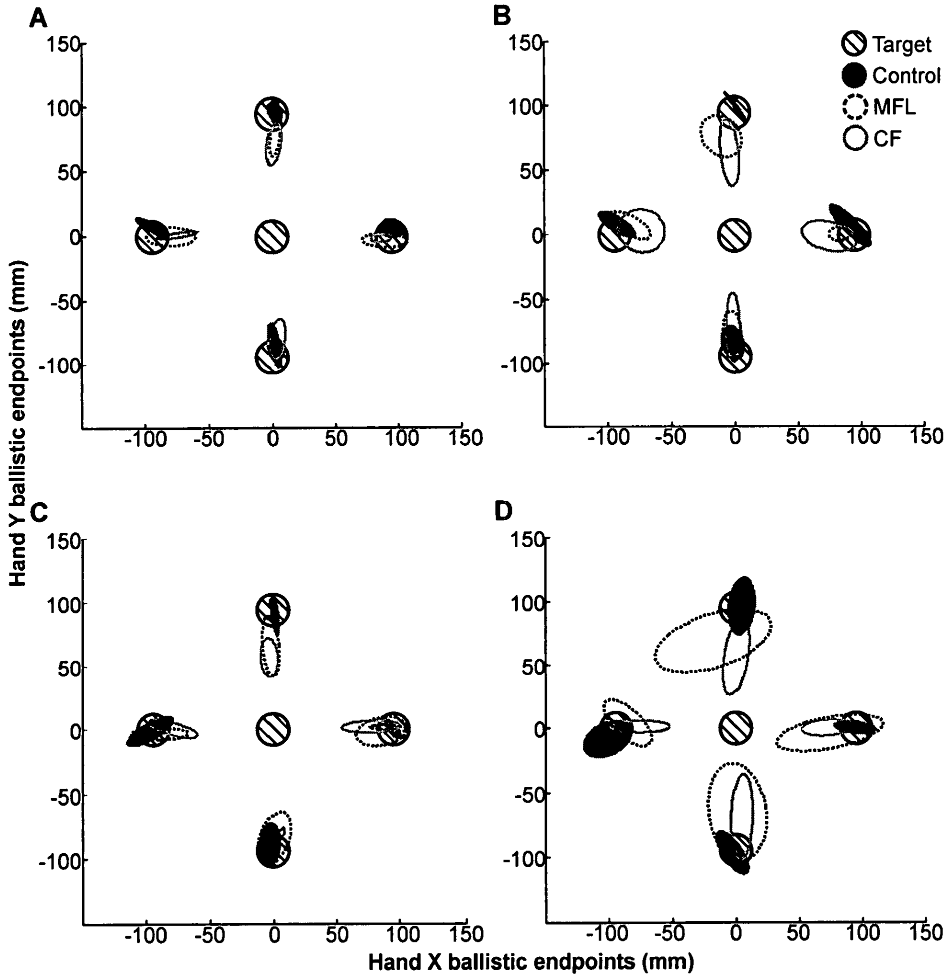

Figure 2.5. Individual hand endpoint ellipses for MFL, CF, and a typical control subject. Hand movement endpoints to four peripheral targets from the home target in (A) Vertical (B) Vertical Rotated (C) Horizontal (D) Horizontal Rotated. Both hands were pooled for MFL and CF. Open and filled ellipses represent 95% confidence intervals for patients and a typical control, respectively. Circles with cross-hatching represent starting and ending target location. Note that the systematic undershoot seen in both patients is not seen in the horizontal conditions in the + y direction towards the monitor.

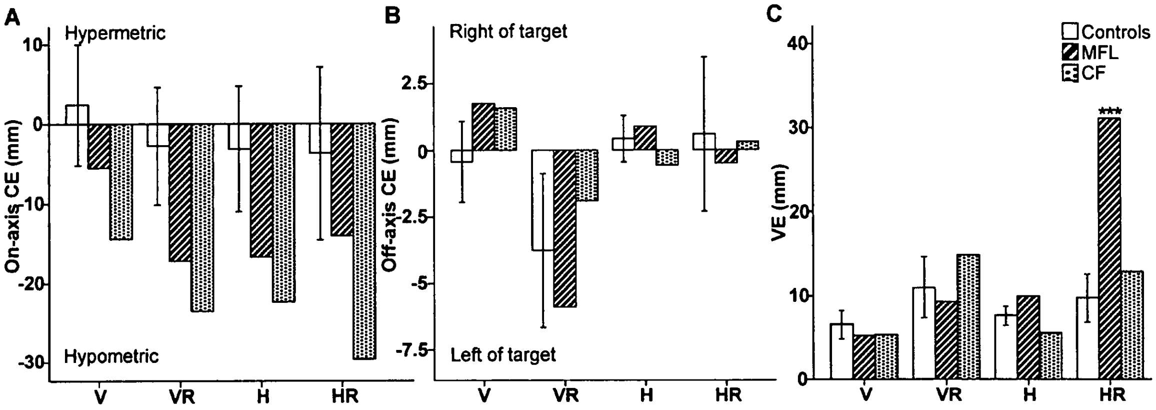

Figure 2.6. Ballistic hand endpoint data for MFL, CF, and the control group. Hand movement (A) on-axis constant error (B) off-axis constant error (C) variable error (in mm) for four conditions (V = Vertical; VR = Vertical Rotated; H = Horizontal; HR = Horizontal Rotated) across all targets. Both hands were pooled for MFL and CF. Error bars denote 95% Confidence Intervals. ***p'<0.001.

Table 2.2. Hand movement endpoint and error significant differences between MFL and CF compared with the control group

Group	**Variable**	**Condition**	**Hand**	**Target**	**t-Value**	**Effect**
MFL	On-axis CE	VR	R	T	-2.6*	-2.7
	Off-axis CE	VR	R	R	-2.6*	-2.8
		HR	R	T	-3.2*	-3.5
	VE	VR	R	L	5.8***	6.2
		H	L	R	7.2***	7.6
		HR	R	R,T,L,B	>7.1***	>7.5
	DR 180°	VR	R	R	2.9*	3.1
		HR	R	R,T,L,B	>2.9*	>3.1
CF	On-axis CE	VR	R	T	-2.5*	-2.7
		H	L,R	T	<3.6**	<3.8
		HR	L,R	T	<4.2**	<4.5
	VE	VR	L	R	5.6***	6.0
		HR	L	R,B	>2.6*	2.8
	DR 180°	VR	L,R	R	>2.9*	>3.1
		HR	L	R	7.0***	7.4

Table 2.2 note: Dependent variables (CE = constant error; VE = variable error; DR 180°= direction reversals in the opposite direction) were tested with separated modified t-tests (p'<0.05) for each condition (V = vertical; VR = vertical rotated; H = horizontal; HR = horizontal rotated) for each hand and each visual target (R = right; T = top; L = left; B = bottom). *p'<0.05;**p'<0.01;***p'<0.001.

Eye movement errors

Although the hand data for the OA patients demonstrated impaired performance during the initial ballistic phase of non-standard, decoupled movements, they eventually did complete all trials within the given time limit (eight seconds). The reason for their overall success becomes clear when looking at the eye movement data. Although all subjects were instructed to foveally acquire the target, several oculomotor errors were observed in the OA patients (see **Fig. 2.7**).

Control group. For the most part, the control group followed the given instructions and spontaneously kept their eyes on the peripherally cued (presented) visual target. One exception was a condition main effect for the number of look-backs (ANOVA, $F_{2,12} = 16.7$, $p<0.0001$), whereby controls performed significantly more look-backs towards their hand position during the rotated conditions (VR/HR) relative to V and H ($p<0.05$).

OA patients versus control group. Both OA patients performed more oculomotor errors than the control participants (**Fig. 2.7**; for specific hand and target details, see **Tab. 2.3**). During the performance of HR, both MFL and CF performed initial saccades towards the goal location of the upcoming hand movement (eye directional errors), while none of the control subjects performed such errors (no statistical comparisons could be made, see Methods).

MFL relied on additional hypometric steps with either hand and across all visual targets than the controls did during HR (t = 4.6, p′<0.001, effect size = 4.9). CF relied on hypometric steps only while using his right (unaffected) hand towards the right visual target during H and the top visual target during HR (**Tab. 2.3**).

MFL performed more overall “look-backs” towards her hand in VR (either hand, all visual targets, t = 5.9, p′<0.001, effect size = 6.2) and towards the cursor in HR (t = 9.4, p′<0.0001, effect size = 10.0) than control subjects did. CF did perform a greater number of look-backs during all the decoupled conditions (VR, H, HR) when orienting the cursor towards the top or the right visual target (**Tab. 2.3**).

Lastly, both MFL and CF performed more “hypermetric steps” than the control group towards the frame of the computer monitor during the decoupled conditions (VR, H, HR; t > 8.6, p′<0.0001, effect size > 9.1), CF already performing more hypermetric steps during direct visuomotor control (V; t = 10.9, p′<0.0001, effect size = 11.5).

In summary, both patients made more eye-movement errors compared to control subjects, particularly during the execution of decoupled visuomotor tasks, with no systematic hand or visual field biases across the conditions (**Tab. 2.3**).

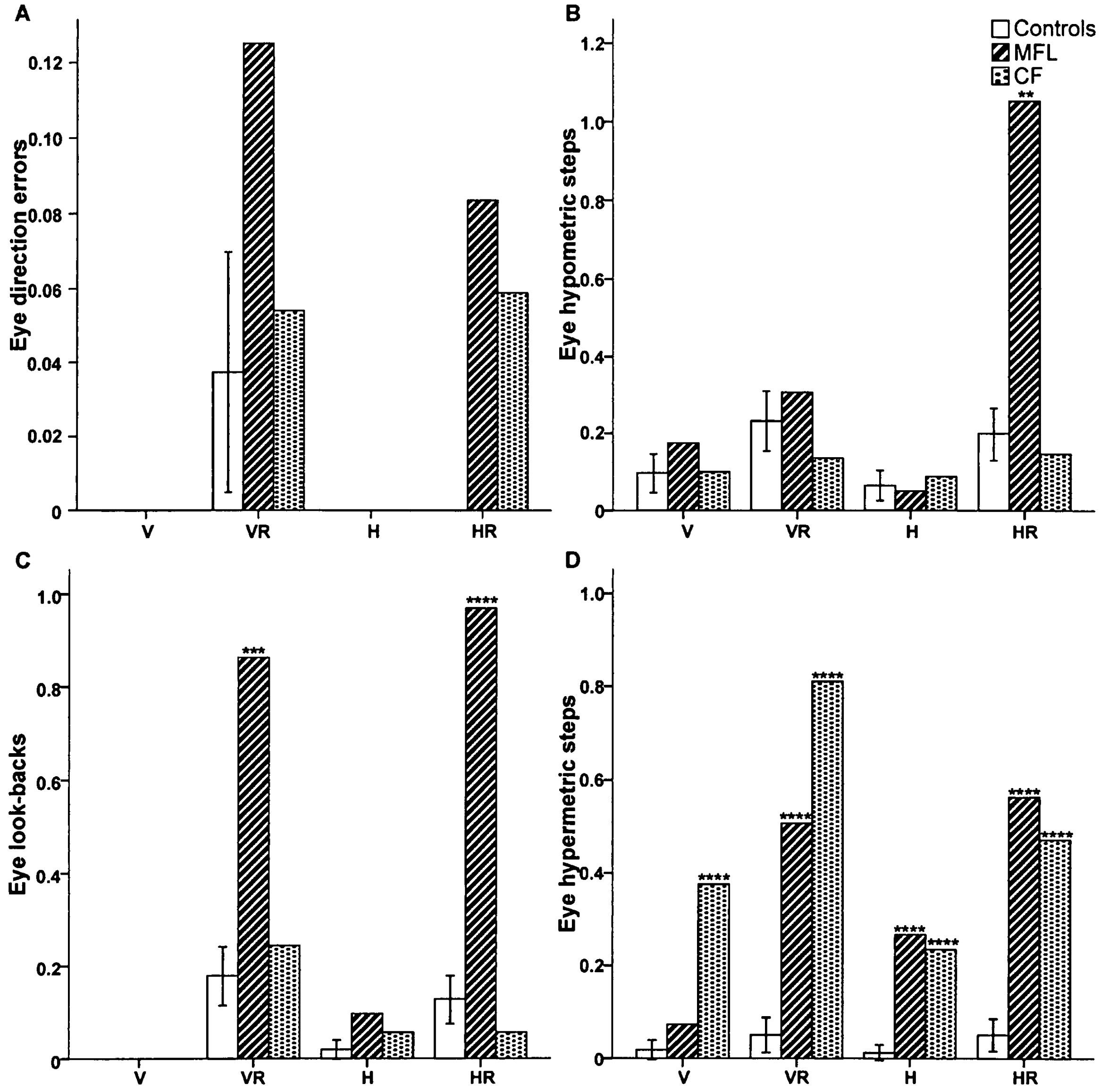

Figure 2.7. Mean eye errors performed by MFL, CF, and the control group. (A) Eye direction errors (B) hypometric steps (C) look-backs (D) hypermetric steps that have been normalized as a ratio per trial across all targets for four conditions (V = Vertical; VR = Vertical Rotated; H = Horizontal; HR = Horizontal Rotated). Both hands were pooled for

MFL and CF. Note an increase in oculomotor errors for both MFL and CF during the conditions with rotated visual feedback (VR/HR). Error bars denote 95% Confidence Intervals. + No statistical comparison between the case and the control group could be performed because the control group had a mean and variance of zero. $^{**}p' < 0.01$; $^{***}p' < 0.001$; $^{****}p' < 0.0001$.

Table 2.3. Eye movement error significant differences between MFL and CF compared with the control group

Group	Variable	Condition	Hand	Target	t-Value	Effect size
MFL	DE	VR	L,R	R	>4.1**	>4.4
		HR	R	R,T	+	+
	Look-backs	VR	L	R,B	>4.9**	>5.2
		VR	R	R,T,L,B	>2.6*	>2.7
		H	L	L	3.3*	3.5
		H	R	T,B	>4.2**	>4.4
		HR	L	T,L,B	>2.9*	<3.1
		HR	R	R,T,L,B	>4.1**	>4.4
	Hypo-steps	V	L	B	4.2**	4.5
		HR	L	R,T,B	>4.3**	>4.6
		HR	R	T,L,B	>2.9*	>3.1
	Hyper-steps	V	R	T	18.8****	20.0
		VR	L	R,L,B	>3.5**	>3.7
		VR	R	R,T,L,B	>3.7**	>3.9
		H	L	L,B	>7.6***	>8.1
		H	R	R,L	>7.7***	>8.1
		HR	L	T,B	>7.1***	>7.6
		HR	R	R,L,B	>13.2****	>14.0
CF	DE	HR	R	T	+	+
	Look-backs	VR	R	R	2.7*	2.9
		H	R	T	3.2*	3.4
		HR	L	R,T	>3.2*	>3.4
		HR	R	T	2.5*	2.7
	Hypo-steps	H	R	R	4.0**	4.3
		HR	R	T	4.3**	4.6
	Hyper-steps	V	L	R,T,L,B	>7.4***	>7.9
		V	R	R,L	>5.8***	>6.2
		VR	L,R	R,T,L,B	>2.7*	>2.9
		H	L	R,T,L	>2.7*	>2.9
		H	R	R,T,L,B	>7.4***	>8.1
		HR	L	R,T,L,B	>3.1*	>3.2
		HR	R	R,L,B	>5.3**	>5.6

Table 2.3 note: Dependent variables (DE = initial direction error; Look-backs = look-backs to hand or cursor; Hypo-steps = hypometric saccadic steps; Hyper-steps = hypermetric saccadic steps) were tested with separated modified t-tests (p'<0.05) for each condition (V = vertical; VR = vertical rotated; H =

horizontal; HR = horizontal rotated) for each hand and each visual target (R = right; T = top; L = left; B = bottom). + No statistical comparison between the case and the control group could be performed because the control group had a mean and variance of zero. *p′< 0.05 ; **p′<0.01; ***p′<0.001; ****p′<0.0001.

Discussion

The alterations in eye-hand coordination observed in the present experiment suggest a critical role for caudal SPL in non-standard visually-guided reaching, i.e. when gaze and hand direction are decoupled. The patients' hand endpoints revealed no directional errors but increased variable errors and hypometric errors during non-standard conditions in several specific comparisons with controls. In addition, unlike controls, the OA patients performed many eye movements during non-standard conditions, both exhibiting a frequent number of hypermetric step errors compared to control subjects and eye movement reversals during visuomotor rotations.

Overall, in both patients, we found no obvious and systematic differences in reaching or eye-movement parameters as a function of which hand was used, which target was reached or which direction the movement was guided. Since we found no consistent lateralised deficits, the directional hypothesis, based on allocentric directional coding, can be discarded._Instead, we suggest that the deficits seen in these unilateral OA patients reflect a global deficit in the initial decoupling and online monitoring of non-standard visually-guided reaches. The monitoring of peripheral vision involves covert spatial attention, and SPL has been shown to be integral for such covert attention shifts (Kelley et al., 2008; Pisella et al., 2009; Striemer et al., 2007; Vesia et al., 2010; Yantis et al., 2002). Without an intact SPL, patients with optic ataxia may have lost their ability to attend to and represent extrafoveal **goal and hand** locations (Pisella et al., 2009). Along this 'positional' hypothesis (developed by McIntosh et al., 2011), a unilateral optic ataxic patient with field dependent misreaching (field effect) would fail in all conditions decoupling hand and eye, especially if the eye does not remain still on the target. Indeed, if the eyes gaze the ongoing hand to an extrafoveal location, current hand position may be well represented but the intended target may not; conversely, if the eyes gaze the target, the intended goal may be well represented but the current hand position may not. In the one case, the impaired visuomotor system knows where the hand is, but not where to go; in the other, it knows where to direct the hand to, but not where from. In either case, the smooth visuomotor guidance will fail (McIntosh et al., 2011).

The involvement of caudal superior parietal lobule in strategic control?

Incorporating a cognitive rule into a visuomotor task can lead to slower visuomotor control. The increased time required for processing an appropriate motor plan (i.e. motor strategy) for an upcoming peripherally-guided movement has been previously shown as a successful means of eliminating the ballistic visuomotor control deficits seen in OA patients (Milner, Dijkerman, McIntosh, Rossetti, & Pisella, 2003; Revol et al., 2003; Rice et al., 2008). In the present study we demonstrate preserved strategic control in the OA patients (Rossetti et al., 2005), based on their successful performance during the arbitrary mapping task relative to controls. Arbitrary visuomotor transformations have been shown to involve the integration of ventrolateral prefrontal inputs into PMdr

(Hanakawa, Honda, Zito, Dimyan, & Hallett, 2006). While a recent study has found evidence for the involvement of foci within the PPC in processing arbitrary mappings (Tosoni, Galati, Romani, & Corbetta, 2008), in the present study neither OA patient had difficulty preparing for them. Overall, these data imply that an intact caudal SPL is not imperative for the successful completion of cognitive-motor integration in arbitrary situations.

In addition, the OA patients were able to learn the cognitive rules of the 180° feedback rotation, although their performance did not fully match that of controls. Previous work has suggested that 180° feedback rotation tasks require cognitive-rule integration rather than more implicit mental rotation required for other amounts of feedback rotation (e.g. 60°) (Bock, 2005). In addition, both OA patients in the current study were able to utilize the horizontal touch screen as a tool to guide a cursor toward the visual target on the vertical plane. Taken together, our findings suggest that the capacity to learn the appropriate rules in order to compute different levels of non-standard visuomotor transformations is preserved in OA. In contrast, the required implicit realignment of visual and proprioceptive discrepancies (i.e. sensorimotor recalibration) during decoupled visually-guided reaching appears to have been compromised. Despite intact strategic control, the increased reliance on proprioceptive inputs during decoupled visually-guided reaching (Jackson, Newport, Mort, & Husain, 2005; Jackson et al., 2009; Pellijeff, Bonilha, Morgan, McKenzie, & Jackson, 2006) suggests that the deficits seen in these unilateral OA patients are indeed a result of impaired sensorimotor recalibration.

Visuomotor rotation versus spatial plane dissociation

One main finding was that unilateral OA patients did not reach towards the actual direction of gaze when the gaze and reach target were decoupled by virtue of being in different spatial planes (gaze on vertical monitor, hand moving over horizontal table). Rather, their reaching bias occurred in the plane that the hand was moving in. This finding confirms our previous demonstration of this preserved behavior in a bilateral OA patient (Pisella et al., 2009). In a similar situation, Alzheimer Disease (AD) patients were not able to accommodate such spatial plane differences, instead producing hand movements that were towards the physical location of the viewed monitor (Ghilardi et al., 1999). We have proposed previously that AD patients may be experiencing a disconnection between prefrontal and parietal areas, areas whose connectivity is likely important for cognitive-motor integration (Sergio et al., 2009; Tippett & Sergio, 2006; Tippett et al., 2007). The current study's findings that OA patients have no specific trouble when dissociating the plane of eye and hand movements suggest that an intact, independent neural pathway is used in such condition, potentially the left dorsolateral parieto-frontal network (Tanne-Gariepy et al., 2002) that is involved in choosing the appropriate distal limb orientation for purposeful tool-use, or the same integration of ventrolateral prefrontal inputs into rostral PMd (Hanakawa et al., 2006) as involved in arbitrary visuomotor transformations.

For OA patients, visuomotor rotation led more often than plane dissociation to pathological behavior. It may be because plane dissociation simply requires transposing a motor plan to another location within the same hemifield, whereas inverting the direction of eye and hand motion may involve a transfer towards or away from the unilateral patient's damaged hemisphere (for the left and right targets). Alternatively, visuomotor rotations result in a larger dissociation between proprioception and vision. In addition to the dissociation between peripheral vision of the hand and foveal vision of the cursor being moved to the target, the hand also has to be guided in a direction opposite to the cursor. Whether this is due to the demands of computing an inverted difference vector (Heath, Maraj, Maddigan, & Binsted, 2009), the greater inhibition requirements in these conflicting situations (Heath, Maraj, Gradkowski et al., 2009; Munoz, Armstrong, Hampton, & Moore, 2003; Munoz & Everling, 2004) or a more extensive network for 'anti-movement' versus 'postural adjustment' type tasks, remains an open question.

Oculomotor errors during non-standard reaching in optic ataxia

The second main finding in the present experiment is that the OA patients were unable to simply look at a target and then reach or guide a cursor to that target as instructed. Rather, they made a number of eye-movement errors which allowed them to ultimately complete the trials. We believe that these errors reflect oculomotor strategies that these patients have developed in order to successfully interact with the external world, particularly in situations in which gaze and reach direction are decoupled. We propose that the most parsimonious explanation for the eye-movement behaviors observed in these patients is that 1) they serve to assist in locating the upcoming spatial location of the goal of the hand movement (i.e. priming that location), and 2) they serve to update the difference vector between the current location of the hand and the goal of the movement.

The OA patients performed the greatest number of saccadic errors during the performance of both tasks involving a visuomotor rotation (VR/HR). These eye-movements likely served to prime the remembered location of the upcoming goal requirement (cursor to the target). This behavior has been previously shown during a series of object manipulation tasks (Flanagan, Bowman, & Johansson, 2006; Johansson et al., 2001) . The authors of these studies proposed that a series of eye movements towards the edges of an object about to manipulated, the upcoming target, and the end-goal of the movement often preceded the hand movement in order to successfully predict the spatial location and timing of the upcoming hand movements. In the present context, during the performance of HR, both OA patients utilized initial saccadic direction errors towards the transformed (cursor) location of the upcoming hand movement direction, something that none of the control participants did.

We also suggest that these OA patients are often updating the difference vector between their eye and hand using vision. Previous work using transcranial magnetic stimulation suggests that the dorsolateral PPC may be crucial for maintaining a difference vector between the current hand location and the desired movement goal (Vesia, Yan, Henriques, Sergio, & Crawford, 2008). In the present study, support for this idea comes from the look-backs and the hypermetric steps performed by the OA patients. These additional eye movements may provide a means to re-couple the natural linkage between eye and hand movements (Gaveau et al., 2008; Gorbet & Sergio, 2009; Jackson et al., 2009; Neggers & Bekkering, 2000; Neggers & Bekkering, 2001). Overall, the OA patients performed the most hypermetric steps during the decoupled visually-guided reaches. The additional hypermetric saccades were most likely performed by the OA patients in order to utilize an additional cue within the environment (to replace the peripherally-viewed hand) in order to complete the task. The increase in oculomotor errors performed by CF towards the end of the movement may reflect the online control deficits seen previously during target jump paradigms (Blangero et al., 2008). We suggest that the additional saccades performed by the OA patients may serve to foveally update the relative position of the end-effector (hand/cursor) and the visual target in order to recalibrate the hand movement goal.

Overall, these scan-path data reiterate the role of an intact caudal SPL in simultaneously representing and integrating proprioceptive (intrinsic) and visual (extrinsic) information for successful planning of visually-guided reaching (Ren et al., 2006), especially as the eye and the hand movements become spatially decoupled (Jackson et al., 2005; Jackson et al., 2009; Pellijeff, Bonilha, Morgan, McKenzie, & Jackson, 2006b).

Hypometric reaching in optic ataxia

Hypometric reaching deficits in extra-foveal reaching seen in primates with caudal SPL damage (for example, (Battaglini et al., 2002; Blangero et al., 2010) may be partially explained by a role of this region in covert attention changes (Kelley et al., 2008; Yantis et al., 2002) between eye and goal locations. As well, the reported gaze-biased undershooting of extra-foveal targets could result from an increased reliance on coding of the decoupled reach and gaze directions in intrinsic (limb postural) coordinates (Jackson et al., 2005; Pellijeff et al., 2006). Without the benefits of overt visual updating of limb position (Desmurget et al., 1999; Flanagan et al., 2006; Khan et al., 2007; Prablanc et al., 1979), decoupled reaching deficits seen in OA patients may reflect difficulty with the conversion from the eye-centered (extrinsic) coordinates of the visual goal (Batista et al., 1999; Buneo & Andersen, 2006; Dijkerman et al., 2006; Fernandez-Ruiz et al., 2007; Khan et al., 2007; Khan et al., 2005; Medendorp, Goltz, Vilis, & Crawford, 2003; Newport, Hindle, & Jackson, 2001) into the limb-centered (intrinsic) coordinates needed to guide the decoupled limb (Jackson et al., 2005; Jackson et al., 2009; Khan et al., 2007; Pellijeff et al., 2006). Previously, it was thought that a limb-centered reference frame is only required later in the movement correction phase (Batista et al., 1999).

Similar to previous reports (Perenin & Vighetto, 1988; Rossetti et al., 2003), in the present study, the OA patients did not display initial hypometric reaching during direct visuomotor control (i.e. standard condition in free vision). Both OA patients did, however, undershoot their hand during the decoupled visually-guided reaches relative to the standard condition (negative on-axis CE, **Figs. 2.4 & 2.5A**). In contrast to previous work on unilateral OA patients utilizing central fixation paradigms (Blangero et al., 2008; Perenin & Vighetto, 1988), no obvious misreaching to the contralateral visual field (field effect) or by the affected hand (hand effect) were observed. It may be that testing left handed and ambidextrous patients may reduce laterality in eye-hand coordination, however previous work with these patients (Blangero et al., 2007; Blangero et al., 2008; Blangero et al., 2011; Khan et al., 2005) suggests that this is not the case. Rather, not preventing direct (foveal) vision of the target eliminated the visual field effect (as predicted) and the hand effect in these patients. Note that the hand effect is reduced when the hand is calibrated by vision at the start and movement is performed in lighting conditions (Blangero et al., 2007). Overall, the OA patients appear to display a global motor deficit when relying on decoupled proprioceptive and visual inputs when they are able to foveate the visual target.

Conclusions

The results of this study suggest that the right dorsal stream missing in both of the OA patients that we studied (i.e. caudal SPL and its direct connection to rostral PMd) is a critical component of the global network involved in overcoming the natural coupling of eye and hand movements. Despite preserved strategic control, we suggest that an intact caudal SPL is crucial for maintaining and updating hand location in peripheral vision in situations requiring decoupled eye-hand coordination.

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Chapter Three

Decoupled visually-guided reaching in optic ataxia: differences in motor control between canonical and non-canonical orientations in space

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Abstract

Guiding a limb often requires both the contribution of explicit, strategic control and implicit sensorimotor recalibration when the spatial location of the target for gaze and limb movement are not congruent (i.e., decoupled). To further understand the neural mechanisms underlying these different types of visuomotor control, we tested a patient with bilateral caudal superior parietal lobule (SPL) damage resulting in optic ataxia (OA), and six age-matched controls on a series of center-out reaching tasks. The tasks comprised 1) directing a cursor that had been rotated within the same spatial plane as the visual display (either 180°/quick strategic control, or 90°/gradual sensorimotor recalibration), or 2) moving the hand along a different spatial plane than the visual display (horizontal/familiar, or para-sagittal/unfamiliar). To further understand how the brain controls movement when using explicit representations of canonical spatial orientations/directions or when using implicit representations of non-canonical spatial orientations/directions during decoupled eye-hand coordination, all conditions were performed towards horizontal (which can be guided from strategic control) and diagonal (requiring on-line trajectory elaboration and updating by sensorimotor recalibration) visual targets. The bilateral OA patient performed much better in non-standard situations in which explicit representations of spatial orientations and reliable allocentric cues could be utilized. Relative to neurologically intact adults, her performance suffered in situations in which relevant allocentric cues or canonical spatial orientations could not guide her movements, and she was therefore required to rely on the implicit sensorimotor recalibration of her decoupled limb. We propose that an intact caudal SPL is crucial for any decoupled visuomotor control, particularly when relying on the realignment between vision and proprioception.

Keywords: Eye-hand coordination; Superior parietal lobule; Strategic control; Sensorimotor recalibration/adaptation; Visuomotor control.

Introduction

The evolution of the human cerebrum has enabled us to interact indirectly with objects via the use of tools. Tool-use requires combining the semantic properties of the functionality of the tool, with the appropriate orientation of the distal musculature (Frey, 2007). In addition, top-down control is needed to inhibit the natural tendency to directly interact with a viewed object (Gielen et al., 1984; Gorbet & Sergio, 2009; Neggers & Bekkering, 2000; Neggers & Bekkering, 2001; Sergio et al., 2009). The integration of an explicit cognitive rule with a motor action has been referred to as **strategic control** (Bock, 2005; Redding & Wallace, 1996; Redding et al., 2005). However, motor skills which require something other than direct object interaction (i.e. "standard" sensorimotor mapping; Wise et al., 1996) also require a coordinated remapping between different sensory modalities such as vision and proprioception (Granek, Pisella, Blangero, Rossetti, & Sergio, 2012). The adaptation by the brain to spatial orientation differences has been referred to as **sensorimotor recalibration** (Bedford, 1993; Clower & Boussaoud, 2000; Lackner & Dizio, 1994), and comprises a control mode that is more gradual and does not involve conscious awareness (Jimenez, Vaquero, & Lupianez, 2006; often referred to as 'implicit' learning). In both these explicit and implicit situations, a spatial algorithm must be integrated into the motor plan in order to accurately compute the relative positions of the visual cues with the required direction of the limb (i.e. "non-standard mapping"; Wise et al., 1996), and are crucial for everyday activities such as using a computer mouse or driving a car.

Although an extensive cortical network for non-standard visuomotor control has been established using brain imaging (Connolly et al., 2000; Gorbet et al., 2004; Granek et al., 2010; Inoue et al., 2000; Toni & Passingham, 1999), their distinct components (i.e. strategic control versus sensorimotor recalibration) have not been fully characterized. Our first objective in the current study was to determine if different cortical networks were involved in strategic control versus sensorimotor recalibration. To address this objective, we examined the performance on a series of non-standard eye-hand coordination task by an adult with bilateral caudal SPL lesions resulting in optic ataxia (OA), relative to neurologically intact adults. Previous observations in OA have revealed that a damaged caudal SPL (Blangero et al., 2009) can lead to deficits in online updating of limb position in eye-hand coordination (Blangero et al., 2008; Grea et al., 2002; Khan et al., 2005; Khan et al., 2007; Pellijeff et al., 2006; Pisella et al., 2000) with field and hand effects (Blangero et al., 2008). OA patients typically misreach when guiding a limb in peripheral space towards extra-foveal targets (Khan et al., 2005; Perenin & Vighetto, 1988) which has been shown to activate the POJ (Prado et al., 2005). These deficits observed in OA to extend to situations which require the peripheral guidance of the decoupled limb towards foveal visual targets in lighting conditions (Granek et al., 2012). In contrast, “standard” eye-hand coupling, which in the dark relies on the medial intraparietal sulcus (IPS; Prado et al., 2005) also lesioned in most OA patients, is generally spared in lighting condition which provides vision of the hand (Pisella et al., 2006; Pisella et al., 2009; Rossetti et al., 2003). Guiding a decoupled limb involves the ability to predict hand location without direct vision, and with impaired proprioceptive updating observed in OA (as seen in reaches in the dark; Blangero et al., 2007), patients may be required to rely on strategic control in such situations. As such, we hypothesized that an intact caudal SPL is crucial for situations relying on sensorimotor recalibration, but not for situations in which strategic control is more useful. From this hypothesis, we predicted that the damaged caudal SPL seen in OA would cause performance impairments in situations that relied predominantly on an implicit realignment of the decoupled proprioceptive and visual input. These performance impairments would be beyond the visuomotor deficits such as slow and inaccurate motor predictions (Granek et al., 2012) and deficits in automatic online updating observed previously (Battaglia-Mayer et al., 2012; Grea et al., 2002; Pisella et al., 2000). In contrast, we predicted that IG's performance would improve although still be compromised relative to controls (Granek et al., 2012) during movements for which strategic control would be employed.

There are a variety of motor behavioral tasks one may use to employ rule-based movement control in order to examine cognitive-motor integration. In the present study, each task was designed to involve a different **weighting** between strategic control and sensorimotor recalibration. The task manipulations, in which participants were instructed to foveate the visual targets, involved moving the limb to targets when there was either 1) a rotated cursor feedback between viewed hand motion and actual hand motion (180° and 90°), or 2) a change in the plane of the displayed visual stimulus (vertical) relative to plane of the limb movement (familiar horizontal and non-familiar para-sagittal planes for this patient, see (Pisella et al., 2009). All conditions were performed both "head-fixed" (in a chin rest) and "head-free". The head-free conditions were implemented in order to explore the potential benefits of synergistic (Pelz et al., 2001) and more "naturalistic" head-eye movements during reaching (Biguer et al., 1984). Further, the targets for the center-out reach task were placed either along a horizontal axis or along a diagonal axis. The distinction between two types of non-standard movement control in this paradigm is predicated on the assumption that movements in the opposite direction to the cursor feedback (180° rotation condition) rely on strategic control, while movements made under a 90° cursor feedback rotation rely heavily on sensorimotor recalibration. The support for this assumption comes from previous studies in which neurologically healthy adults showed minimal behavioral performance degradation with a 180° cursor feedback rotation versus no rotation (Abeele & Bock, 2001; Cunningham, 1989). In contrast, it has been demonstrated that reach performance declines as feedback rotation moves from 0° to 90°, improves from 90° to 180°, and then declines again from 180° to 270° (Bock et al., 2003; Werner & Bock, 2007). These data support the idea of two 'functional modules' or control modes (Bock, 2013), in which a simple 'move in opposite direction' requirement employs a quick to implement rule-based strategy while intervening angles – maximizing at 90° – employ a gradual recalibration (Bock, 2013; Sergio et al., 2009). We also make the assumption that, when moving under conditions of rotated visual feedback, targets placed on a horizontal line will rely on explicit rule-based strategic control more than targets placed on a diagonal line. Use of allocentric cues are important for visuomotor adaptations, which have been shown to be represented in extrinsic coordinates (Krakauer et al., 2000). Our assumption is thus based on the idea that in our task one is able to rely on allocentric cues for movement guidance to horizontal targets, since a straight path to these targets is aligned with the horizontal borders of the target display monitor (and perpendicular to the vertical border just beyond the target). We have previously reported the reliance of additional saccades towards the computer monitor boarder (i.e. "hypermetric steps") in OA patient CF towards horizontal and vertical targets (Granek et al., 2012). In contrast, one would not be able to rely on allocentric cues to plan a straight path to targets placed diagonally from the central target since the computer monitor the monitor corner was not along a diagonal line from the start location. Hence although participants might have an approximate rule for the diagonal targets using allocentric cues (e.g. top-left target is close to a bottom-right movement), this rule could only be used as a guideline since the surrounding allocentric cues were not precise enough to devise a predictive motor plan; a gradual recalibration between senses would be required. Comprehension of the cognitive rule has not been shown to be sufficient for successful adaptation in off-axis situations (Benson et al., 2011; Mazzoni & Krakauer, 2006; Werner

& Bock, 2007). Lastly, in our previous work with this patient she showed success during a horizontal spatial plane transformation (Pisella et al., 2009), which may reflect cortical activation changes (Granek et al., 2010) as a result of previous experience with a similar decoupled task (e.g. using a computer mouse). Improvements in grasping deficits have been previously observed in OA towards familiar objects (Jeannerod et al., 1994). Thus we also introduced a decoupling involving motion in a para-sagittal plane to reduce the effect of familiarity on movement performance. In summary, here we employ movements having varying levels of well-categorized canonical and less-categorized non-canonical orientations and directions, which thus follow a spectrum of strategic control to sensorimotor recalibration.

Our second exploratory objective was to examine what the effects of decoupled eye-hand coordination were on motor error patterns in bilateral optic ataxia during situations where strategic control would be used versus situations where sensorimotor recalibration would be used. We hypothesized, based on our results with unilateral OA patients (Granek et al., 2012) that an intact caudal SPL formulates and maintains a "difference vector" between the felt hand and the viewed action goal only when relying on sensorimotor recalibration. Specifically, we predicted that IG would perform additional saccades and additional head movements (when allowed) in order to continually monitor and recalibrate the required difference vector between limb, gaze, and visual target locations during situations relying primarily on sensorimotor recalibration.

Methods

All participants signed informed consent and the study protocol was approved by the York University human participant research ethics committee.

Participants

The participants tested in the current study were one patient with dorsal visual stream damage (IG, age 44) and six healthy age-matched controls (three females), mean age 39 ± 9. 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). All participants had experience with a computer mouse and laptop touchpad.

Patient details

At the time of testing, IG was a 44 year old woman who suffered from an ischemic stroke related to acute vasospastic angiopathy in the posterior cerebral arteries established with an angiogram. Magnetic resonance imaging revealed a hyperintense signal on T2 sequencing that was fairly symmetrically, located in the posterior parietal and upper and lateral occipital cortico-subcortical regions (**Fig. 3.1C**). Reconstruction of the lesion

(Talairach & Tournoux, 1988) indicated that it involved mainly Brodmann's areas 19, 18, 7, a limited part of area 39. This therefore included the parieto-occipital sulcus and the caudal part of the intraparietal sulcus. IG was given a set of standard clinical tests involving visual field topography (Goldman perimetry), sensory stimulation tests (visual and tactile extinction), neurological evaluation of reflexes and muscle tone and joint movements. Visual fields showed a partial right inferior homonymous quadrantanopia (visual scotoma). The patient did not exhibit any purely motor or somatosensory deficit, any sign of sensory extinction or any sign of neglect during conventional testing (on standard line bisection, star cancellation and drawing tasks) but she demonstrated bilateral optic ataxia (Blangero et al., 2009; Karnath & Perenin, 2005). OA patients typically display in impaired online peripheral guidance of a limb (Khan et al., 2005; Perenin & Vighetto, 1988) with improved accuracy when given more processing time as in delayed reaching (Rossetti et al., 2005), along with preserved low-level visual and motor function (Pisella et al., 2006; Pisella et al., 2009; Rossetti et al., 2003). Reaching and grasping inaccuracy predominated for her right hand in her right peripheral hemifield. However, visually elicited hand movements were generally accurate when performed in foveal vision. Note that IG initially showed simultanagnosia, which prevented her to see the target and her hand at the same time, which could lead to a contradictory result (Newport, Brown, Husain, Mort, & Jackson, 2006). In the present experiment, however, IG was tested when the bilateral optic ataxia persisted without associated clinical simultanagnosia.

Experimental procedure

Participants sat in a darkened room in front of a computer monitor placed 41 cm away, aligned with their mid-sagittal plane. They made sliding finger movements over a touch sensitive screen (Keytec Magic Screen: Model KTMT-1315: Sampling rate: 100 Hz) in order to displace a cursor from a central target to one of two horizontal (right or left), or to one of two diagonal (45° rotated from a vertical line – approximately top-right or approximately top-left) targets. Importantly, contrary to the horizontal targets which are oriented directly perpendicular to the dimly lit computer monitor boarder, the diagonal targets were not oriented directly towards any helpful allocentric cues such as the corner of the computer monitor. Following a two second delay, one of the peripheral visual targets (16mm in diameter) was presented 110 mm (15° visual angle) from the central target (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. Participants were instructed to perform a saccade towards the peripherally-cued visual target and to maintain fixation of the target until the end of the trial. Eye movements were monitored at 250 Hz (right eye, Cambridge Systems and EyeLink II). The viewing space was calibrated using a nine-point calibration and drift correction was applied between each condition.

Figure 3.1A displays a schematic of all of the experimental conditions. The participants performed a single standard condition and four decoupled conditions. There were two ways in which the visual target could be decoupled from the required hand movement: a change in the spatial plane of the hand movement or a change in the motion of the viewed cursor relative to the motion of the hand (rotated visual feedback). In the standard condition and the rotated visual feedback conditions, the touch screen was placed over the computer monitor (C, in a coronal plane). The touch screen was also placed in two other spatial planes: horizontal (H, lying flat in front of the participant aligned with their midline) and para-sagittal (S, affixed to a custom mount in line with the subject's right shoulder). The para-sagittal plane was chosen to ensure that control of a spatial plane dissociation was not aided by previously learned rules involving a computer mouse and/or laptop touchpad (such as in H). Thus, the horizontal and para-sagittal planes represented two decoupled conditions, since the visual targets were always presented on the computer monitor. Within the coronal plane (where the touch screen was placed on the monitor), cursor feedback rotation was altered either 180° (e.g. move hand leftward to displace cursor rightward) or 90° clockwise (e.g. move hand upward to displace cursor rightward). Thus the cursor feedback rotations in the plane of the computer monitor represented the other two decoupled conditions, C90° and C180°. The C90° 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 implicit mental rotation of the cursor was required for the diagonal targets. In order to test for effects of head restraint, each condition was performed with the head being restrained using a chin rest (eye), and with the head not restrained (gaze).

In order to ensure equal understanding of the transformational rules applied in each condition, all participants were trained prior to each randomly assigned block until each subject reported that they were adequately prepared. IG felt cognitively prepared following training for a total of six trials for C, 12 for H, 27 for S, 30 for C180°, and 40 for C90°. The control subjects reported to adequately prepared following training for a mean total of 12.2 trials for C, 22.6 for H, 30.6 for S, 21.2 for C180°, and 37.7 for C90°. Following training, each participant performed 40 trials (20 eye trials, 20 gaze trials per participant) in each of the five experimental conditions (**Fig. 3.1A**). In addition, in order to ensure proper oculomotor control in the patient, participants performed a sixth condition in which all participants performed 40 saccades (20 eyes only trials, 20 gaze only trials) towards the peripherally-cued targets without any hand movements.

For gaze conditions, the relative changes in absolute translation and roll of the head were extrapolated from the change in position of an infrared camera positioned on the middle of the forehead (Cambridge Systems and EyeLink II) relative to four infrared calibration points. These relative changes in translation and roll were verified with video from a head-mounted video camera. In order to emulate a natural environment, all subjects were instructed to look at the visual target (i.e. foveal acquisition), but were not restricted to a certain eye path. In the darkened room, the border of the computer monitor and the hand were still visible with peripheral vision.

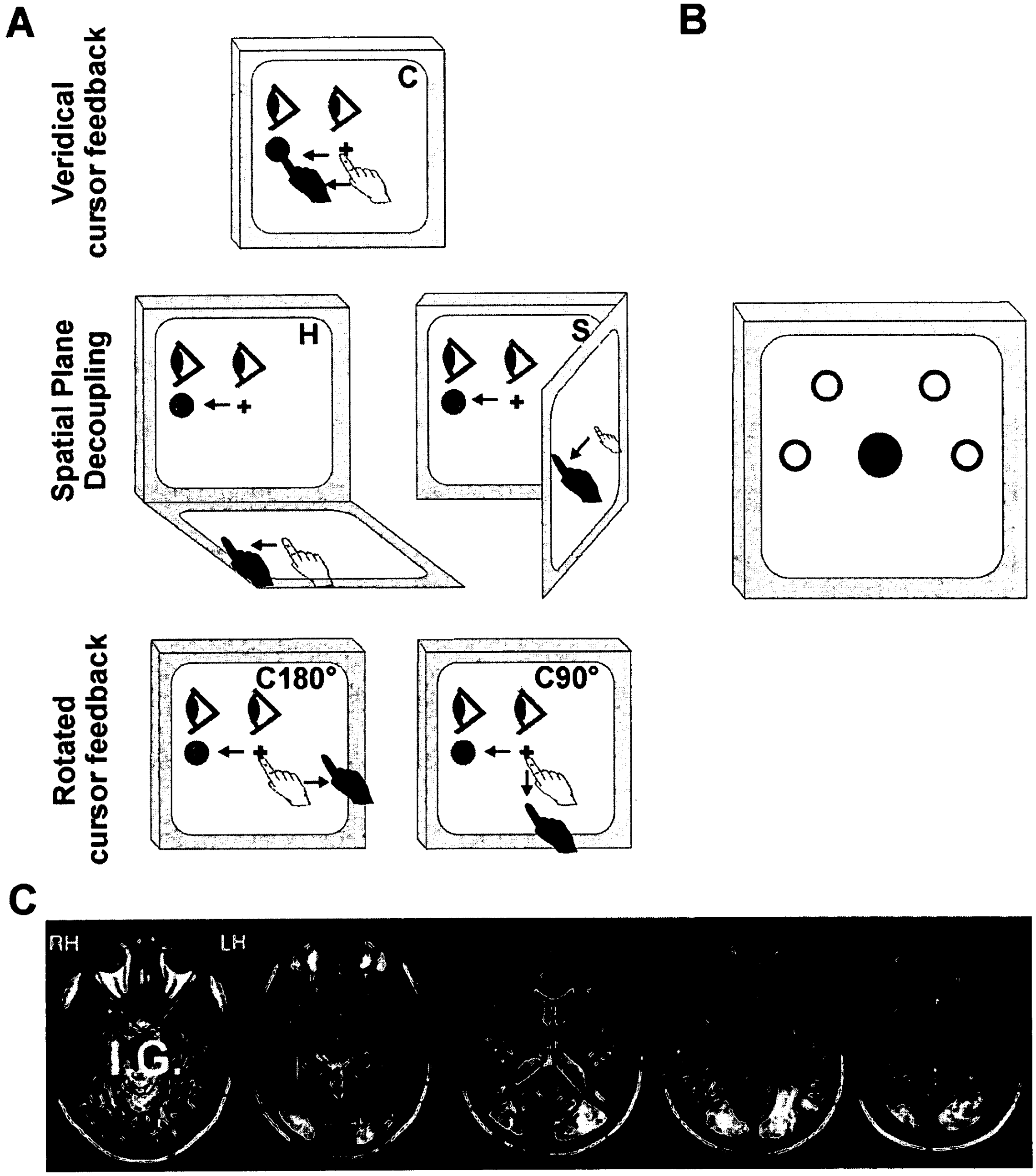

Figure 1. Task procedure, anatomical MRI scan slices. (A) Schematic drawing of the standard center-out reaching movement (C, coronal) and the two basic manipulations:

spatial plane (H, horizontal; S, para-sagittal) and cursor feedback rotation (C180°/90°). The visual stimuli were always presented on the vertical monitor. The gray 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. All conditions were performed both head-fixed and head-free in addition to a control eye (head-fixed) and a control gaze (head-free) condition. (B) Schematic of horizontal (black) and diagonal (gray) target locations. Note that targets in lower hemifield were not tested to avoid IG's scotoma. (C) Axial T2-weighted MRI scans of IG's cortex revealed fairly symmetrical lesions located in the posterior parietal and upper and lateral occipital cortico-subcortical regions (mainly BA 19, 18 and 7, and a limited part of area 39 and the IPS).

Data analyses

We calculated an index reflecting the overall performance decrements observed during eye-hand decoupling for patient IG relative to the control group. The index was computed as the cumulative absolute **effect size** (Crawford et al., 2010) for the 17 hand and eye timing, trajectory and error variables (see **Tabs. 3.1 and 3.2**). Cumulative effect size (CES) was calculated for each decoupled condition (H, S, C180°, and C90°), and for each target type (horizontal versus diagonal; see **Fig. 3.2**).

Trials were only included in the hand and eye movement analyses if they were successfully completed within a maximum of ten seconds and performed without an initial hand direction error (**DE**). An error was quantified as a hand movement that deviated greater than 45° to either side of a straight line between the central and peripheral target for three consecutive time bins occurring in the first half of the ballistic movement. These initial miscalculations were enumerated in a separate analysis. For each DE, we calculated the time to recovery (**TTR**), which was recorded from the time from the inaccurate hand movement onset (see below) until the time point in which the trajectory was reversed towards the correct target location.

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 ballistic movement time (**HMT**) for all conditions began from the hand movement onset and ended at the first point in which the movement slowed to 10% peak velocity. The automatically scored onset and offset was verified visually for each trial (before any overlapping corrective movements). In order to quantify the timing for corrective movements, we analyzed corrective movement time (**CMT**), which began at the end of HMT (10% peak velocity) of a given trial and ended when the cursor entered the perimeter of the peripheral target (trial completion). For summary purposes, we also report total movement time (**TMT**), which began at hand movement onset and ended when the cursor entered the perimeter of the peripheral target. **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. Path linearity was measured using hand movement paths (**path length**), which were recorded as the distance travelled from movement onset to when the cursor entered the perimeter of the peripheral target. In addition, 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 (**angle at peak velocity**). Hand movement accuracy parameters were determined from the participant's mean movement endpoints for each target location and analyzed separately for distance errors (**on-axis CE**) and for direction errors (**off-axis CE**). Endpoint precision (variable error, **VE**) was determined by the distance of the endpoints of the individual movements from their mean movements. For summary purposes, we also report absolute error (**AE**), which was the resultant of on- and off-axis CE.

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 (**ERT**) began when the peripheral target was presented and ended at saccadic 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 un-restricted eye movement behavior when the hand was spatially decoupled from gaze direction. The eye scan paths were only analyzed for a given trial if the corresponding hand movement trial was successfully completed. 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 be able to identify saccade-related errors, eye scan path data were recorded from eye movement onset until hand movement onset (early errors: “priming”) and from hand movement onset until entrance of peripheral target (late errors: "online updating"). 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 only coded if they occurred greater than 10% (11 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 subjects reversed eye direction (towards the cursor) a minimum of 20% (22 mm) of the total amplitude from the central to peripheral target, holding 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.

Statistical analyses

In order to determine if successful learning occurred following training in each task (albeit not necessarily complete visuomotor adaptation), initial paired t-tests were performed for each participant between the first five trials and the last five trials performed for each condition and each target type. After confirming a performance plateau for all participants, the data from the individual patient and the control group were analyzed separately. To screen for the effects of head movement (eye versus gaze) on each condition, we initially conducted three-way repeated measures ANOVAs with condition, target type (horizontal versus diagonal targets), and head movement as within-subject factors on the control group. For patient IG, we initially conducted fixed-effect intra-subject ANOVAs also with condition, target type and head movement as within-subject factors. No condition × head-movement interactions were observed following either statistical test. Therefore, all further analyses were pooled across head-movement conditions for each task condition. Since IG's baseline data (i.e. direct visuomotor control) did not differ from the control group for any dependent variable ($p' > 0.05$), all further analyses focused on the eye-hand "decoupling" (i.e. complex – simple) aspect of non-standard visuomotor control. IG's data was presented as the mean change in her "decoupled" relative to her "standard" performance for each condition and each target type. For the control group, eye-hand decoupling was determined as the relative change in performance between complex and simple reaching for each dependent variable and each target type. In order to control for baseline differences across control subjects, we statistically removed (i.e. covaried for) the effects of the simple task from that of the complex tasks. All ANOVA results were reported with Greenhouse-Geisser-corrected p-values, and post hoc comparisons were corrected for multiple comparisons (Bonferroni).

Inter-group analyses were performed using modified t-tests (Crawford et al., 2010; Granek et al., 2012) and were compared with the control group for each visual target type. Importantly, for accurate comparison of a case to a control group, the modified t-tests utilized in the current study adjusted the critical t-value depending on the variability (standard deviation) and group size of our control group (for details, see Crawford et al., 2010). Therefore, alpha levels for all inter-group analyses were adjusted to 5% at $p' < 0.05$ (Crawford et al., 2010). In addition, an index of the number of standard deviation units that each case differed from a randomly chosen control subject ("effect size") was calculated for each modified t-test to demonstrate the magnitude of the difference between groups (Crawford et al., 2010). One exception was during the comparison of the change in the number of eye "look-backs" between IG and the control group. In this case, the control group did not perform such errors (mean 0 ± 0), and therefore, no statistical comparison could be performed.

In order to assess the level of eye-hand coupling in both IG and our control subjects, separate correlation analyses were performed between the eye and the hand reaction times (ERT and HRT) for the both the direct and the decoupled conditions.

Results

Following training, no differences ($p > 0.05$) in timing, trajectory and endpoint variables were observed across participants between the first five trials and the last five trials performed for each condition and target type. Having established that motor performance had reached a plateau, we could then assess cognitive-motor integration accurately. Further, to determine the effect of head restraint in an experimental setting, we tested all conditions with both head restraint (eye movement only) and head movement (gaze). Importantly, for all of the dependent variables tested, no task condition × head condition interactions were observed within the control group or within intra-subject analyses for patient IG ($p>0.05$). Therefore, all inter-group analyses were pooled across both head conditions (eye and gaze) for each task condition. In addition, IG's control condition performance (eye movement/gaze without hand movement) and standard eye-hand coordination performance (i.e. direct interaction with the viewed target) did not differ from the control group across all tested dependent variables. Thus, IG's oculomotor control was not compromised and she was able to look at and reach directly to a freely viewed target without difficulty, similar to our control participants. Therefore, since both the patient and control groups performed at a similar level in these standard situations, we focused our analyses on the visuomotor control of the more complex decoupled eye-hand movements (see Methods for details).

Cumulative effect size

We calculated an index reflecting the overall performance decrements of eye-hand decoupling for patient IG relative to the control group (i.e. cumulative effect size; CES, see Methods for details). The CES was the greatest for patient IG during the performance of visuomotor rotations, specifically the 90° rotation (C90°), and towards the diagonal targets (**Fig. 3.2A**). For details on the dependent variables comprising the CES, see below.

Hand and eye movement timing

In order to assess both predictive and online updating deficits as a result of OA, we analyzed eye and hand movement preparation and execution. **Figure 3.3** shows the overall changes in hand and eye movement timing from baseline (direct, standard visuomotor control) for all subjects across the four decoupled conditions. For details on condition × target type interactions and hand movement timing details between IG and the control group, see **Table 3.1.**

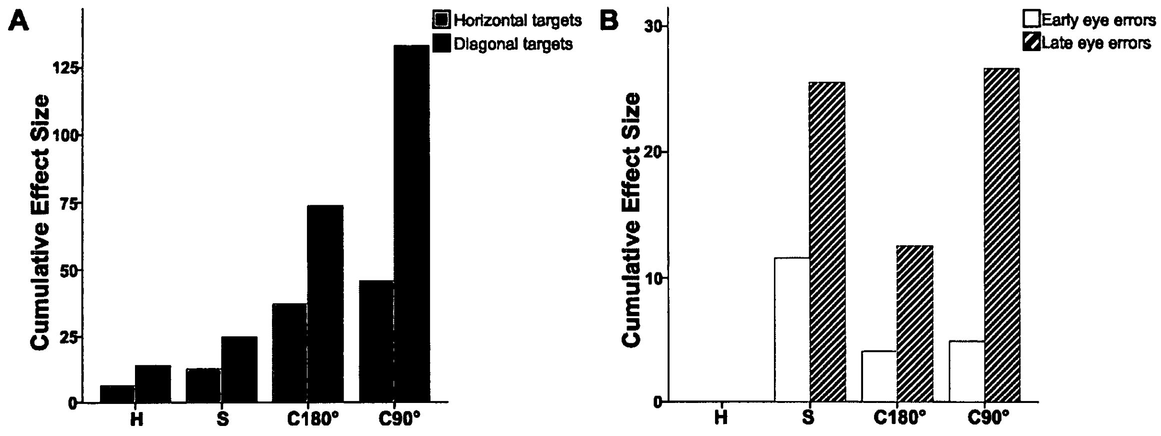

Figure 3.2. Cumulative effect size for decoupled conditions relative to the control subjects. (A) Cumulative number of standard deviation units (i.e. cumulative effect size; CES) in which IG differed from control group during the decoupled conditions by target type (horizontal = light gray, diagonal = dark gray). Note the increase in CES during the rotated visuomotor tasks (C180°/C90°) and towards the diagonal targets. (B) CES for eye errors prior to hand movement onset (early; white bars) and after hand movement onset (late; hashed bars). Note the increases in CES during decoupled visuomotor control after hand movement onset.

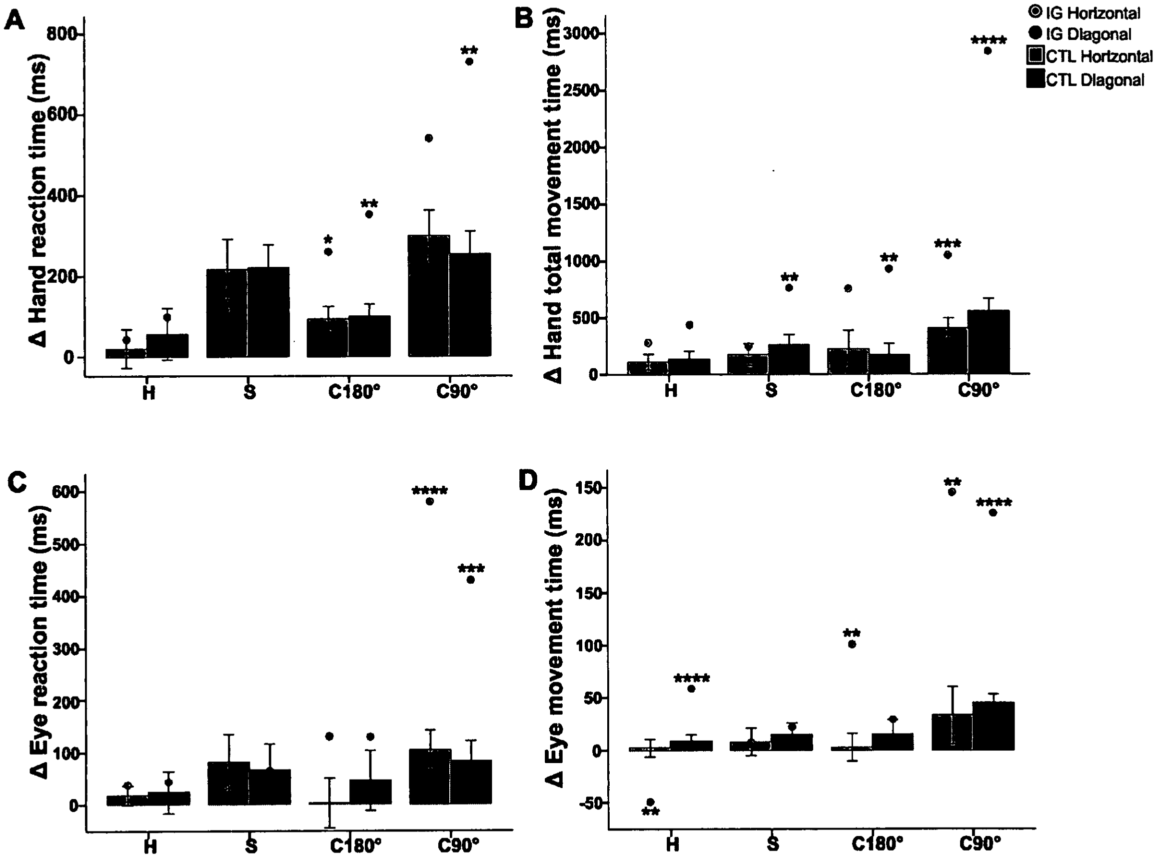

Figure 3.3. Hand and eye movement timing data IG and the control group. Mean change in (A) hand and (C) eye reaction times and (B) hand and (D) eye total movement times in ms for both groups for the four decoupled conditions (H = horizontal; S = para-sagittal; C180° = coronal 180°; C90° = coronal 90°) relative to standard reaching for each target type (horizontal versus diagonal). Both eye and gaze conditions were pooled for each subject. Error bars denote 95% Confidence Intervals. *p'<0.05; **p'<0.01; ***p'<0.001; ****p'<0.0001.

Control group. Within-group analyses were conducted on hand and eye movement timing decrements in order to determine a baseline of difficulty depending on the condition and the target type. Condition main effects were observed for hand movement preparation (HRT; ANOVA, $F_{2,6} = 18.9$, $p<0.01$), and online movement correction (HCMT; ANOVA, $F_{2,8} = 20.8$, $p<0.001$). Post hoc comparisons revealed longer HRT for C90° compared with C180° and S compared with H ($p<0.05$), as well as longer HCMT for C90° relative to C180°, and H ($p<0.05$), and C90° relative to S ($p<0.01$). Whether the movement was to a diagonal versus a horizontal target did not influence the hand movement timing parameters for each condition within this control group ($p>0.05$).

Eye movement timing analyses within the control group revealed a condition × target type interaction for eye movement preparation (ERT; ANOVA, $F_{2,7} = 5.8$, $p<0.05$) and a main effect of condition for eye movement execution (EMT; ANOVA, $F_{2,8} = 12.9$, $p<0.01$). Post hoc comparisons revealed longer ERT for C90° compared with C180° and H for horizontal targets, as well as longer EMT for C90° relative to H across both target types ($p<0.05$).

OA patient versus control group. Relative to the control group, patient IG showed the greatest increase in hand movement timing for C90° towards the diagonal targets. Across target types, IG displayed longer HRT than the control group did for both conditions involving rotated cursor feedback (C180°/C90°: $t > 4.2$, $p'<0.01$, effect size > 4.5). For

C90°, IG displayed a greater increase in HRT than the control group only towards the diagonal targets (see **Tab. 3.1**). We observed different patterns of performance difficulty for the different types of decoupling (plane change, feedback rotation) presented to IG. She displayed an overall deficit (across target types) for total movement execution (TMT), relative to the control group, for S and C180° ($t > 3.1$, $p' < 0.05$, effect size > 3.3), and for C90° ($t = 18.1$, $p' < 0.0001$, effect size = 18.1). The differences between groups in C180° were predominantly driven by increases in hand movement timing during the ballistic phase (HMT) for both target types, while the differences for S and C90° were predominately comprised of increased hand movement timing during the corrective phase (HCMT) towards the diagonal targets (see **Tab. 3.1**). These deficits in movement timing can also be explained in terms of hand movement velocity. Across targets, IG's peak velocity was the most compromised, relative to the control group, during C90° ($t = 7.4$, $p' < 0.001$, effect size = 8.0), whereby she slowed down the most towards the diagonal targets **(Tab. 3.1)**.

Similarly, eye movement timing analyses revealed an overall decline in performance for patient IG relative to controls for C90°, although target type was not as large an influence on her deficits **(Figs. 3.3C,D)**. For the performance of C90°, IG displayed an overall greater decline than the control group did for eye movement preparation (ERT: $t = 11.8$, $p' < 0.0001$, effect size = 12.7) and for eye movement execution (EMT: $t = 10.3$, $p' < 0.001$, effect size = 11.2). For details on eye movement timing between conditions and target types see **Table 3.2**.

In summary, decoupling the spatial location of the foveally-acquired visual target and the hand motion required to reach that target led to a slowing of preparation and execution of both hand and eye movements in this OA patient. This decline in performance was most apparent during the 90° visuomotor rotation and was exacerbated when orienting towards off-axis, diagonal targets (i.e. where a cognitive rule is not as relevant and online sensorimotor recalibration is required).

Eye-hand coupling

We analyzed the impact that eye movement planning (ERT) hand on hand movement planning (HRT) in both direct and decoupled situation. As such, to assess eye-hand coupling across conditions and targets for IG and the control group, we ran correlation analyses.

IG displayed the strongest eye-hand coupling for both direct reaching ($r=0.63$; $p<0.0001$) and for C90° ($r=0.64$; $p<0.0001$), along with a moderate correlation for H ($r=0.40$; $p<0.01$). ERT and HRT were not correlated for S or C180° ($p>0.05$). The control group displayed moderate eye-hand coupling during both direct ($r=0.42$; $p<0.0001$) and C90° ($r=0.45$; $p<0.0001$), along with low correlations for S ($r=0.24$; $p<0.001$) and C180° ($r=0.19$; $p<0.01$). No correlation was observed in the control group for H ($p>0.05$).

Table 3.1. Hand movement significant differences between IG and the control group separated by visual target type for each condition

Target type	Dependent Variable	Condition	IG: mean Δ in performance	Controls: mean Δ in performance (± 95%) CI)	t-Value	Effect size
Diagonal	HRT	C180°	354.4 ms	99.5 ± 31.9 ms	5.0**	5.4
		C90°	733.5 ms	253.0 ± 57.0 ms	5.6**	6.1
	HMT	C180°	434.6 ms	130.8 ± 90.7 ms	3.2*	3.4
	HCMT	S	500.3 ms	101.1 ± 84.3 ms	3.4*	3.7
		C180°	447.2 ms	46.6 ± 24.4 ms	10.8***	11.7
		C90°	2487.8 ms	309.1 ± 126.0 ms	15.4****	16.6
	Peak velocity	H	-46.7 ms/s	11.2 ± 17.9 mm/s	-2.8*	-3.0
		S	-42.7 ms/s	17.8 ± 19.72 mm/s	-3.1*	-3.3
		C180°	-61.0 ms/s	6.1 ± 19.0 mm/s	-3.2*	-3.5
		C90°	-69.0 ms/s	-4.5 ± 8.3 mm/s	-6.8***	-7.4
	On-axis CE	C180°	-12.1 mm	0.3 ± 1.0 mm	-10.2***	-11.0
		C90°	-29.3 mm	-4.1 ± 3.7 mm	-4.0**	-4.3
	Off-axis CE	S	6.5 mm	0.8 ± 0.9 mm	4.7**	5.1
		C180°	6.2 mm	-1.0 ± 1.1 mm	6.3**	6.9
		C90°	13.7 mm	-4.2 ± 4.3 mm	3.3*	3.5
	VE	H	7.6 mm	2.5 ± 2.3 mm	3.2*	3.5
		S	14.1 mm	5.1 ± 2.7 mm	2.9*	3.1
		C180°	11.5 mm	3.8 ± 1.6 mm	3.8*	4.1
		C90°	19.1 mm	9.2 ± 2.5 mm	2.1*	2.8
	Path length	C180°	32.6 mm	14.6 ± 6.6 mm	10.6***	11.4
		C90°	62.3 mm	26.6 ± 8.9 mm	3.7*	4.0
	Angle at peak	S	12.2°	2.6 ± 1.1°	6.2**	6.7
		C180°	11.6°	2.4 ± 1.4°	5.5**	5.9
		C90°	25.9°	3.1 ± 1.4°	17.1****	18.5
	DE	C180°	0.11/trial	0.02 ± 0.02/trial	3.4*	3.7
		C90°	0.11/trial	0.02 ± 0.02/trial	3.4*	3.7
	TTR	C90°	2613.5 ms	410.5 ± 101.1 ms	18.1****	19.6

Table 3.1. Continued

Horizontal	HRT	C180°	261.2 ms	91.9 ± 30.0 ms	3.8*	4.1
	HMT	C180°	408.3 ms	52.6 ± 62.1 ms	5.1**	5.5
		C90°	316.6 ms	73.0 ± 77.0 ms	4.6**	5.0
	HCMT	H	98.7 ms	26.2 ± 10.4 ms	4.8**	5.2
		C90°	702.7 ms	220.0 ± 85.7 ms	4.5**	4.8
	Peak velocity	C180°	-56.2 ms/s	-10.0 ± 13.8 mm/s	-2.9*	-3.2
		C90°	-57.0 ms/s	-21.5 ± 9.3 mm/s	-4.4**	-4.8
	On-axis CE	H	-11.2 mm	-4.3 ± 1.7 mm	-2.8*	-3.1
		C90°	-29.0 mm	-10.9 ± 4.1 mm	-3.2*	-3.4
	Off-axis CE	H	3.9 mm	-0.6 ± 1.2 mm	3.5*	3.7
	VE	C90°	14.9 mm	4.5 ± 2.6 mm	5.5**	5.9
	Path length	C180°	24.0 mm	7.2 ± 3.7 mm	5.2**	5.6
	TTR	C180°	1622.0 ms	439.5 ± 0 mm	4.2**	4.5

Table 3.1 note: Significant differences (p'<0.05) between IG and the control group for each hand movement variable (HRT = hand reaction time; HMT = hand ballistic movement time; HCMT = hand corrective movement time, CE = constant error, VE = variable error, DE = direction errors, TTR = time to recovery from a direction error) for each visual target type (diagonal versus horizontal). Modified t-tests were performed on the relative changes for IG and the control group (± 95% CI) from complex to simple for each decoupled condition (H = horizontal; S = para-sagittal; C180° = coronal 180° rotated; C90° = coronal 90° rotated). Note the increase in impairments for IG towards diagonal relative to horizontal targets. Negative t-values and effect size values for on-axis CE and peak velocity represent impaired performance for IG. *p'<0.05; **p'<0.001; ***p'<0.001; ****p'<0.0001.

Hand movement endpoints and trajectories

Analyses of hand movement endpoints of the initial ballistic motor plan, as well analyses of the entire trajectory were performed to assess the integrity of the predictive motor plan and the online correction in OA. **Figure 3.4** displays the ballistic endpoint across all conditions for IG and for a typical control subject. For examples of full hand and eye movement trajectories between diagonal and horizontal targets during decoupled eye-hand coordination, see **Figure 3.5**.

Control group. Within-group analyses were conducted on the control group for the hand position following the initial ballistic movement as well as the full hand movement trajectory. Although their initial motor commands were predominantly accurate, the control group displayed differences in on-axis CE between decoupled visuomotor tasks across both target types (ANOVA, $F_{2,7} = 7.6$, $p<0.05$), and differences in off-axis CE towards horizontal targets (ANOVA, $F_{1,5} = 8.6$, $p<0.05$). Post-hoc comparisons revealed hypometric on-axis CE for C90° relative to C180° and greater (rightward) off-axis CE (i.e. hand bias towards gaze) for C90° compared with H. We also observed changes in hand movement path length (ANOVA, $F_{2,6} = 10.1$, $p<0.05$) between decoupled reaching tasks. However, corrected post-hoc comparisons did not reveal specific differences between conditions. No differences in hand movement precision (VE) or in the number of direction errors (DE) were observed between the conditions ($p>0.05$).

OA patient versus control group. IG displayed greater hand endpoint errors following the ballistic portion of the movement in decoupled eye-hand situations, especially when attempting to move the cursor towards the diagonal targets (**Figs. 3.4B-E, 3.6D**). For complete details on IG's deficits in accuracy and precision, see **Table 3.1**.

IG displayed an overall increase in absolute hand endpoint errors (AE) towards diagonal targets during C90° (**Fig. 3.6D**, $t = 6.9$, $p' < 0.001$, effect size = 7.5). In terms of distance, IG's initial motor plan was the most hypometric (gaze-biased, on-axis CE) relative to controls during C180° towards the diagonal targets. Similarly in terms of direction, IG's initial motor plan (off-axis CE) was least accurate during C180°, also towards the diagonal targets (see **Tab. 3.1**). During C90°, IG's positive (rightward) increase in off-axis CE, relative to controls, reflected a hand position bias towards the direction of gaze. IG was the least precise (reflecting a noisy motor plan), when orienting towards diagonal targets during H, S, and C180°, and lacked precision for all targets during C90°.

Similar to that observed for endpoint accuracy, IG displayed compromised hand movement trajectories during decoupled eye-hand coordination towards diagonal targets (**Fig. 3.5A**). Across target types, IG's path length was the most compromised during C180°, relative to the control group ($t = 12.1$, $p' < 0.0001$, effect size = 13.1). We also observed longer path lengths in the C90° rotation condition when orienting towards off-axis (diagonal) targets (**Tab. 3.1**). Her angle at peak velocity during C90° was the greatest, relative to the control group, when attempting to accurately implement the appropriate cognitive rule towards the diagonal targets (**Tab. 3.1**). IG only made more initial reversals in direction compared to the control group during visuomotor rotations (C180°/C90°) towards diagonal targets, not horizontal targets (DR variable, **Tab. 3.1**). Further, her overall time to recover from these initial direction errors (TTR; for details, see Methods), was greater than the controls ($t = 4.0$, $p' < 0.01$, effect size = 4.4), especially when such errors were performed during C90° towards diagonal targets ($t = 18.1$, $p' < 0.0001$, effect size = 19.6).

In summary, differences in hand endpoint and trajectory parameters between the OA patient and the control group were observed predominantly towards diagonal targets, a situation where a strategic rule was not as useful to guide the initial motor plan of decoupled-eye hand movements.

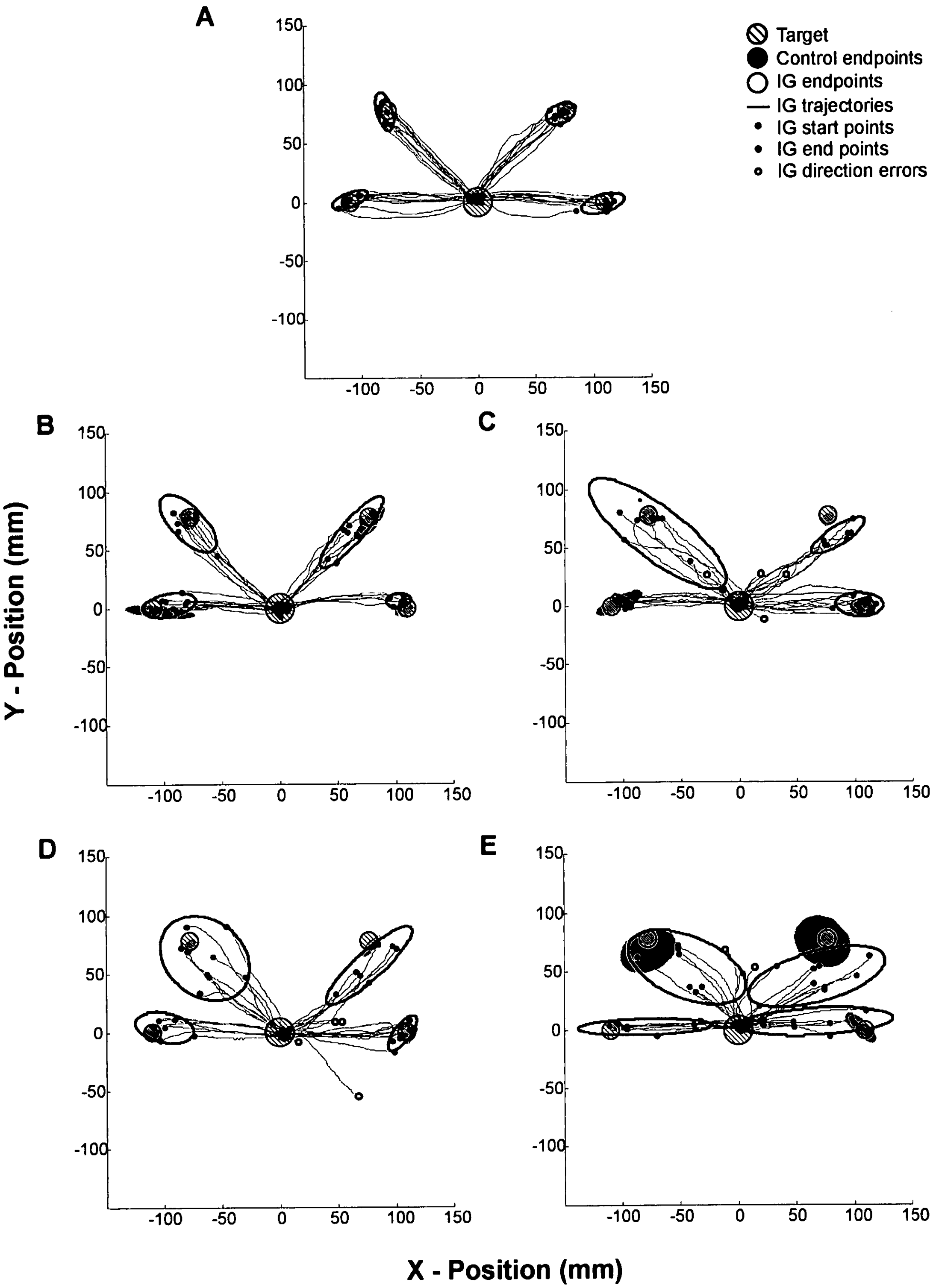
A
B
C
D
E
Target
Control endpoints
IG endpoints
IG trajectories
IG start points
IG end points
IG direction errors
150
100
50
0
-50
-100
-100
-50
0
50
100
150
Y - Position (mm)
X - Position (mm)

Figure 3.4. Individual hand endpoint ellipses for IG and a typical control subject. Hand movement trajectories endpoints of ballistic motor plan to four peripherally-cued targets from the home target in (A) coronal (B) horizontal (C) para-sagittal (D) coronal 180° and (E) coronal 90°. Both eye and gaze conditions were pooled for all subjects. Open and filled ellipses represent 95% confidence intervals for IG and a typical control, respectively. Trajectories (green lines), start points (closed red circles), endpoints for successful trial (closed blue circles) and direction error trials (open black circles) represent IG's data only. Circles with cross-hatching represent starting and ending target location. Note the systematic endpoint errors for IG during decoupled reaching especially when orienting towards the diagonal (off-axis) targets, and the accurate reaching for the control subject.

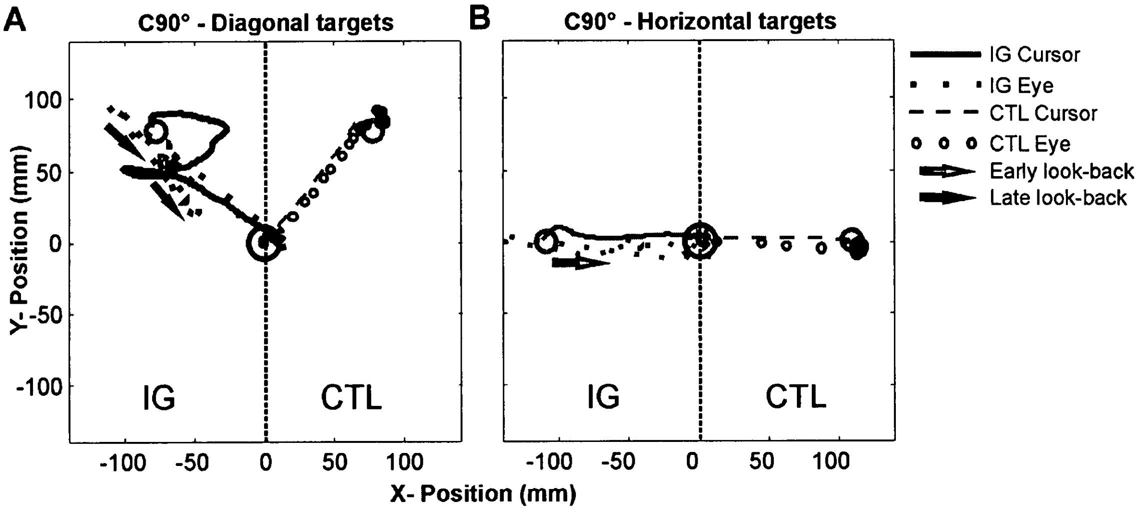

Figure 3.5. Example trials during coronal 90° condition towards diagonal and horizontal targets for IG and a typical control subject. Example hand (represented by the rotated cursor) and eye movement trajectories for the entire trial towards (A) diagonal and (B) horizontal targets. Note for IG (left side) the increase in path length towards diagonal targets and the increase in online (late) look-backs (closed arrows), and relatively accurate hand movement trajectories accompanied by an early look-back (closed arrow) towards the horizontal target.

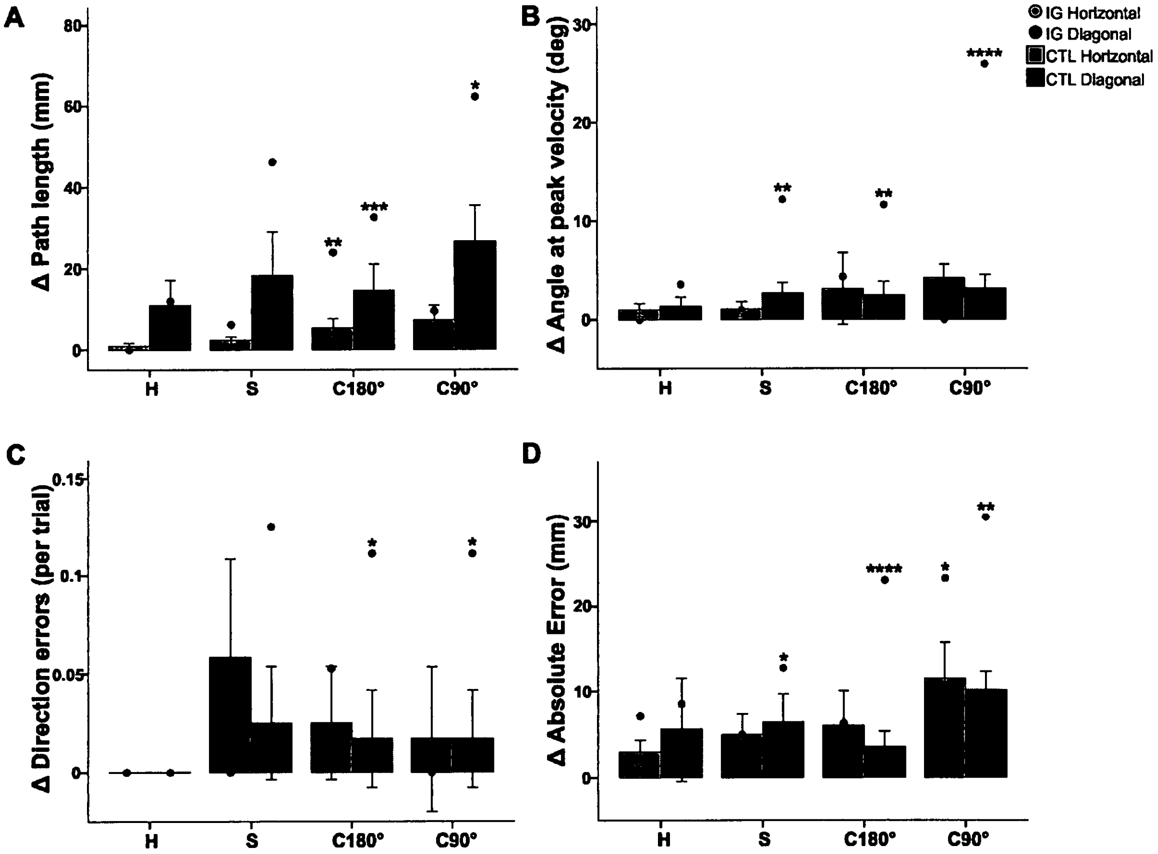

Figure 3.6. Trajectory and ballistic hand endpoint data for IG and the control group. Change in hand movement (A) path length (in mm) (B) angle at peak velocity (in degrees) (C) direction errors (per trial) and (D) absolute error (in mm) for IG (circles) and controls (bars) for the four decoupled conditions (H = horizontal; S = para-sagittal; C180° = coronal 180°; C90° = coronal 90°), relative to standard reaching, for each target type (horizontal = light gray, diagonal = dark gray). Both eye and gaze were pooled for all subjects. Error bars denote 95% Confidence Intervals. *$p' < 0.05$; **$p' < 0.01$; ***$p' < 0.001$; ****$p' < 0.0001$.

Eye movement errors

Although the hand data for this OA patient demonstrated impaired performance, IG did complete all trials within the given time limit (10 seconds). The reason for her successful completion of each trial becomes clear when looking at the eye movement data. Although all subjects were instructed to foveate the peripherally-cued visual target, eye movements were not restricted. Similar to previous results observed in unilateral OA patients (Granek et al., 2012), several additional oculomotor errors were observed in this bilateral OA patient (see **Fig. 3.7**).

Control group. For the most part, the control group followed the given instructions and spontaneously performed accurate saccades, keeping their eyes on the peripherally presented visual target (**Fig. 3.5**). The control group did, however, perform a greater total number of eye movement errors during C90° than H (ANOVA, $F_{2,6} = 14.0$, $p<0.01$), a result which was predominantly driven by the additional pauses during their saccades prior to hand movement onset (i.e. "early" hypometric steps; ANOVA, $F_{1,6} = 9.7$, $p<0.05$).

OA patient versus control group. IG performed more oculomotor errors than the control participants, predominantly for C90° (**Fig. 3.7**; for specific target-type details, see **Tab. 3.2**). IG performed the greatest number of erroneous eye movements, relative to the control group, during the online control of the decoupled limb (i.e. after the start of the hand movement; see **Fig. 3.2B**).

We observed that there were four basic types of eye movement errors in this patient. First, IG primarily relied on looking back ("look-backs") to either her hand or the cursor during decoupled eye-hand coordination. Although IG performed more look-backs overall than the controls did for movements made in a para-sagittal plane ($t = 19.6$, $p' < 0.0001$, effect size = 21.1) and for C180° ($t = 8.1$, $p' < 0.001$, effect size = 8.8), she relied predominantly on such additional saccades for C90° ($t = 39.2$, $p' < .0001$, effect size = 42.4), specifically towards diagonal targets (**Tab. 3.2**). Second, we observed that IG performed a greater number of hypometric steps (across targets) than did the controls did during C90° ($t = 3.1$, $p' < 0.05$, effect size = 3.3), pausing the eye movement to allow a temporal coupling (i.e. "catching up") between the eye and hand movements. Third, we found that IG performed a greater number of eye movements beyond the target towards the computer monitor border than the control group did, but only during C180° and towards the horizontal targets (**Tab. 3.2**). Fourth, IG produced a greater amount of hand-biased mis-saccades (HBMS; $t = 9.0$, $p' < 0.001$, effect size = 9.7) than the controls did, again specifically towards the diagonal targets (**Tab. 3.2**) rather than the horizontal ones.

In summary, during decoupled eye-hand movements, IG made more eye movement errors than the control subjects did - particularly during the online correction phase - when implicit control of the peripherally-guided limb was required (for example, in situations where the cursor feedback was rotated 90° and the target was not presented along the horizontal axis).

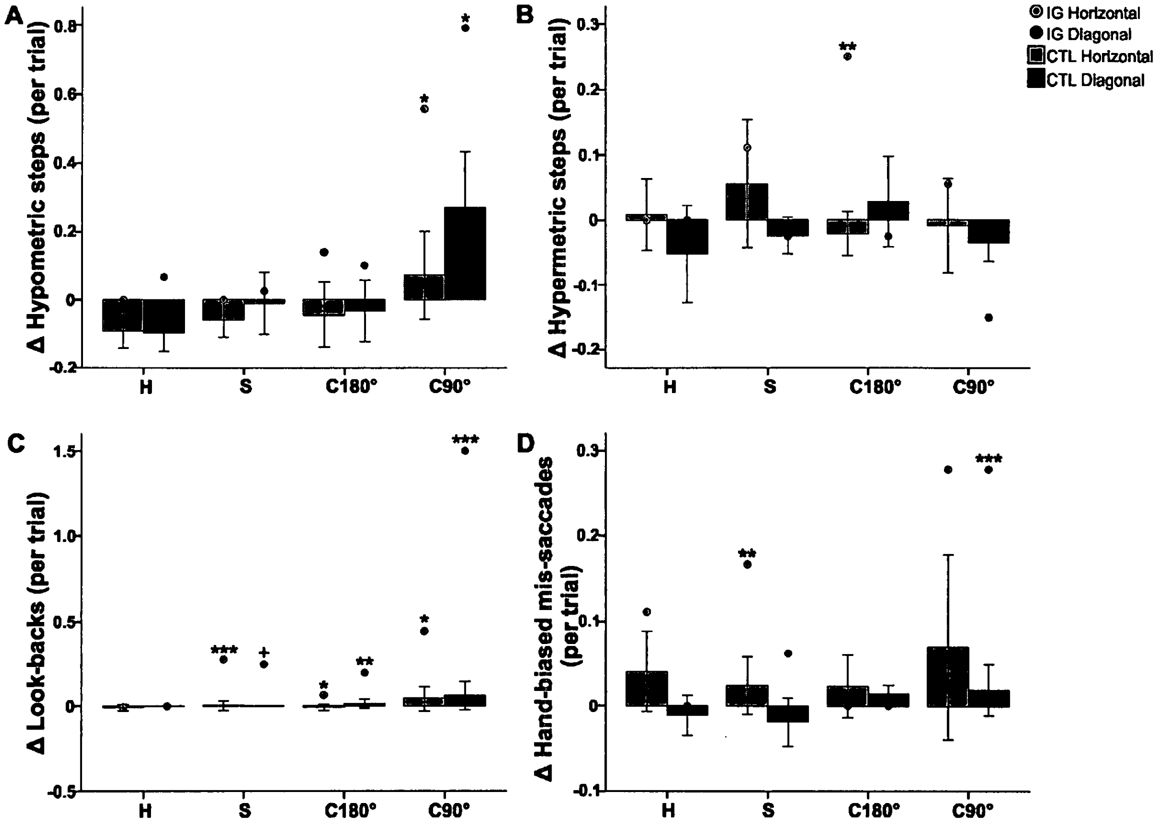

Figure 3.7. Eye errors performed by IG and the control group. Change in eye (A) hypometric steps (B) hypermetric steps (C) look-backs and (D) hand-biased mis-saccades for IG (circles) and controls (bars) for the four decoupled conditions (H = horizontal; S = para-sagittal; C180° = coronal 180°; C90° = coronal 90°) for each target type (horizontal = light gray, diagonal = dark gray) relative to standard reaching. Eye and gaze conditions were pooled for all subjects. Note a marked increase in look-backs for IG during the performance of C90° towards diagonal targets. *p'<0.05; **p'<0.01; ***p'<0.001.

Table 3.2. Eye movement significant differences between IG and the control group separated by visual target type for each condition

Target type	**Dependent Variable**	**Condition**	**IG: mean Δ in performance**	**Controls: mean Δ in performance (± 95% CI)**	**t-Value**	**Effect size**
Diagonal	ERT	C90°	429.9 ms	82.8 ± 39.1 ms	7.3***	7.9
	EMT	H	59.1 ms	9.0 ± 8.3 ms	7.2***	7.8
		C90°	225.2 ms	45.5 ± 8.2 ms	15.6****	16.8
	Hypometric	C90°	0.79/trial	0.27 ± 0.16/trial	2.7*	2.9
	Look-backs	S	0.25/trial	0 ± 0/trial	+	+
		C180°	0.2/trial	0.01 ± 0.07/trial	6.1**	6.6
		C90°	1.5/trial	0.06 ± 0.03/trial	10.4***	11.2
	HBMS	C90°	0.28/trial	0.02 ± 0.03/trial	7.1***	7.7
Horizontal	ERT	C90°	577.5 ms	104.6 ± 37.7 ms	11.8****	12.8
	EMT	H	**-49.2 ms**	**2.4 ± 8.3 ms**	**-5.2****	**-7.4**
		C180°	100.7 ms	2.8 ± 12.9 ms	5.5**	5.9
		C90°	224.9 ms	32.9 ± 27.4 ms	6.2**	6.7
	Hypometric	C90°	0.56/trial	0.07 ± 0.13/trial	2.8*	3.0
	Hypermetric	C180°	0.25/trial	-0.02 ± 0.03/trial	4.5**	4.9
	Look-backs	S	0.28/trial	0.0008 ± 0.03/trial	7.7***	8.3
		C180°	0.06/trial	-0.008 ± 0.02/trial	3.2*	3.5
		C90°	0.44/trial	0.04 ± 0.07/trial	3.8*	4.1
	HBMS	S	0.17/trial	0.02 ± 0.03/trial	4.2**	4.6

Table 3.2 note: Significant differences (p'<0.05) between IG and the control group for each eye movement variable (ERT = eye reaction time; EMT = eye movement time; HBMS = hand-biased mis-saccades) for each visual target type (diagonal versus horizontal). Modified t-tests were performed on the relative changes for IG and the control group (± 95% CI) from complex to simple for each decoupled condition (H = horizontal; S = para-sagittal; C180° = coronal 180° rotated; C90° = coronal 90° rotated). Bold implies control group performed worse than IG. + No statistical comparison between the case and the control group could be performed because the control group had a mean and standard deviation of zero. *p'<0.05; **p'<0.001; ***p'<0.001; ****p'<0.0001.

Head movement

In order to observe behavior in a more "natural" environment, we repeated all conditions "head-free". During such gaze conditions, we recorded the change in cumulative head movement (translation and roll, see Methods) for decoupled reaching relative to standard reaching. Although allowing free head movement (i.e. not head-fixed) did not improve hand or eye performance in either group, we did observe inter-group differences between IG and the controls for the amount of head movement during decoupled reaching (**Fig. 3.8**). IG utilized more head movement than the controls did during the performance of C90°, for both horizontal ($t = 14.9$, $p' < 0.0001$, effect size = 16.1) and for diagonal ($t = 7.2$, $p' < 0.001$, effect size = 7.7) targets. In addition, we observed that IG moved her head even less in C180° than in standard reaching and therefore had significantly less change in head movement than the control group did for both horizontal ($t = -6.1$, $p' < 0.01$, effect size = -6.6) and diagonal ($t = -3.1$, $p' < 0.05$, effect size = -3.4) targets.

In summary, although free head movements did not improve hand or eye movement performance in any participant, IG performed larger head movements in one of the more challenging conditions (C90°; see **Fig. 3.1A**).

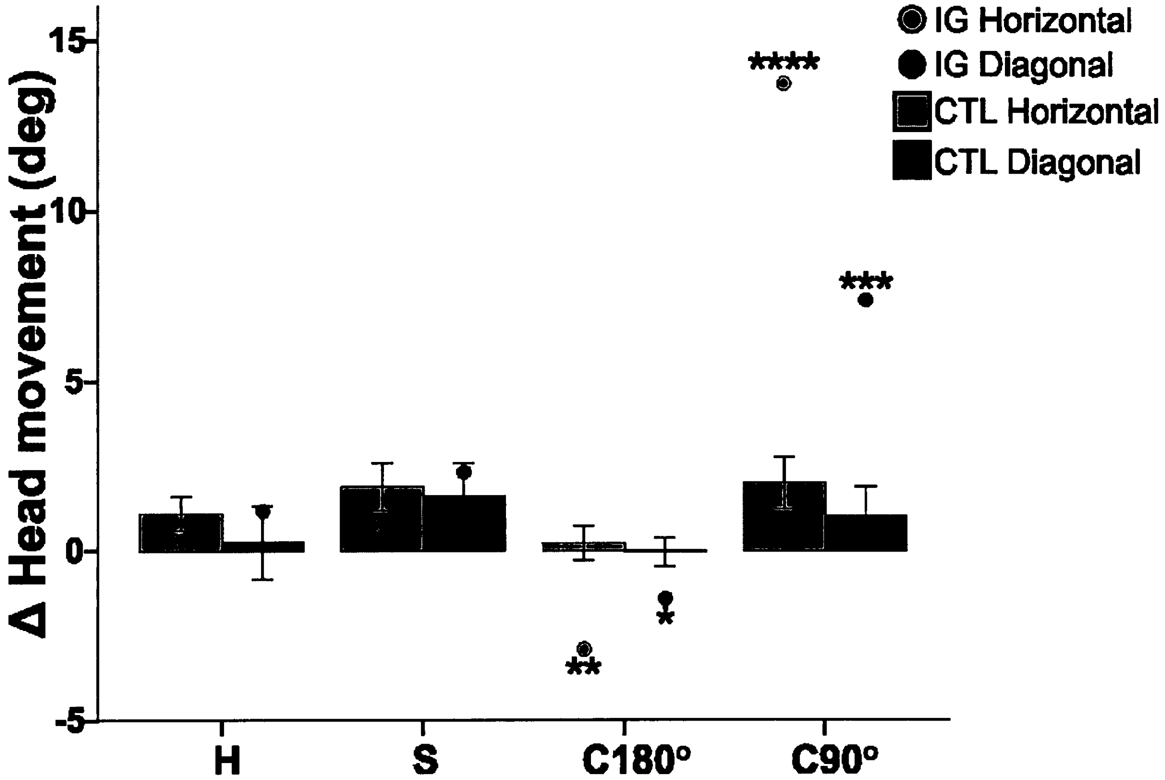

Figure 3.8. Cumulative head movement for IG and the control group. Change in head movement (in degrees) during head-free (gaze) conditions for IG (circles) and controls (bars) for the four decoupled conditions (H = horizontal; S = para-sagittal; C180° = coronal 180°; C90° = coronal 90°) for each target type (horizontal = light gray, diagonal = dark gray) relative to standard reaching. Note a marked increase in head movement during C90°. *p'<0.05; **p'<0.01; ***p'<0.001; ****p'<0.0001.

Discussion

The alterations in eye-hand performance observed in this bilateral OA patient expand our understanding of the role that the caudal SPL plays in non-standard visually-guided reaching (Granek et al., 2012). Eye-hand decoupling in non-standard visuomotor control involves the integration of a strategic motor plan with the ongoing monitoring of the current state estimate of the relative limb, gaze, and goal positions. The current study was designed to tease apart the involvement of the caudal SPL with these two major contributors to the guidance of decoupled gaze and limb during non-standard visuomotor control.

As predicted, IG demonstrated an inability to accurately update her limb position in non-canonical situations when she could not rely on strategic control. Although IG's bilateral caudal SPL damage manifested itself as an overall impairment in online processing during decoupled eye-hand coordination, her impairment worsened in situations where a cognitive rule was not as useful (e.g. during C90° towards diagonal targets). That is, we observed movement control impairment for non-canonical orientations. In such a situation, IG attempted to compensate for her slow and inaccurate hand movements by utilizing several additional eye movements (e.g. looking back to the representation of current hand location from the visual target). While many of the eye movements were done after hand movement onset (**Fig. 3.2B**), there were also a number of instances where the eye movement paused until the hand movement had 'caught up' to the location of gaze, a behavior similar to that seen in bilateral OA patients who delayed their hand movement onset until the completion of a corrective saccade during a target jump (Gaveau et al., 2008). These additional eye movements and instances of eye-hand re-coupling potentially served as a means to update the hand/cursor position relative to the target. We suggest that this online updating of a decoupled difference vector (Vesia et al., 2008) would be useful for the generation of corrective sub-movements (Novak, Miller, & Houk, 2002) required to complete the complex movement.

Strategic control versus sensorimotor recalibration of a decoupled limb in optic ataxia

Strategic control plays an integral role in cognitive-motor integration. However, cognitive rules alone are not sufficient; the incorporation of a rule into a motor plan must be complimented by online sensorimotor recalibration of a decoupled limb in space. Similar to previous reports in OA (Granek et al., 2012; Rossetti et al., 2005), in the current study IG displayed intact strategic control, particularly for well-categorized canonical movements. Her deficits were the greatest when forced to predominantly rely on sensorimotor recalibration. These decrements were observed in the form of increased planning and execution time for the eye and the hand, hypometric reaching, and increased hand path length. Her deficits were markedly smaller for mappings which relied predominantly on explicit rule integration, suggesting an independent pathway for processing strategic control in non-standard visually-guided reaching (see below).

It has been previously demonstrated during the early learning of off-axis (e.g. 45°) rotations that explicit strategies reduce initial hand endpoint errors, but ultimately get overridden by implicit visuomotor adaptation (Benson et al., 2011; Mazzoni & Krakauer, 2006; Werner & Bock, 2007). In contrast, cognitive rules were previously useful for patient IG (horizontal spatial plane dissociation) after a brief training (Pisella et al., 2009). Therefore, a flexible balance appears to exist when learning the rules needed for strategic control versus the making the gradual adaptation needed for sensorimotor recalibration during decoupled eye-hand coordination. In the current situation, although all participants had an adequate comprehension of the required rule for each task, and were performing at a plateau during the task, they were not necessarily fully adapted to the different transformational manipulations. In fact, each participant had very little difficulty switching between the randomly assigned conditions (i.e. showed no after effects), indicating that all conditions involved a strong explicit component. However, the implicit component of each condition and target type becomes apparent when observing the deficits seen as a result of OA. We observed a linear increase in performance difficulty for patient IG relative to the control group (i.e. CES; see **Fig. 3.2A**) from a canonical condition (H; similar to a computer mouse) towards the horizontal (on-axis) targets, to a non-canonical condition (C90°) towards the diagonal (off-axis) targets. The increased performance deficits observed in patient IG relative to the controls during C90°

towards diagonal targets confirm that even an adequate comprehension of a rule is not sufficient to adapt to non-canonical off-axis situations (Benson et al., 2011; Mazzoni & Krakauer, 2006; Werner & Bock, 2007). In contrast, IG's relatively successful performance in the horizontal plane towards horizontal targets indicates that learning of a rule is sufficient in situations with reliable allocentric cues and previous experience. An alternative explanation is that the C90° condition was simply more difficult than the other conditions. Evidence for an increase in cognitive demand for C90° was observed as increases in RT as well as eye and hand movement errors performed by the control group. However, equal performance across targets by the control group implies a specific deficit observed for IG towards the diagonal targets. These findings suggest that an intact caudal SPL is not crucial for decoupled eye-hand movements when relying on a cognitive rule or a stereotyped motor plan (formulated via previous experience), but is integral for the implicit realignment of decoupled vision and proprioception during novel situations or where there is no reliable rule. This latter situation likely requires the close monitoring of visual and proprioceptive information processed in this region of the brain, while the former situation could rely on intact fronto-temporal circuits for movement planning and guidance (see below).

Further evidence for intact strategic control in OA is apparent from IG's eye- and head-movement performance. IG performed additional saccades during the more complex conditions (C90°; see **Fig. 3.7**) potentially as a means to recalibrate the required difference vector in order to compute accurate corrective movements (Granek et al., 2012). During the gaze conditions, IG moved her head the most relative to her body (translation and roll) during the performance of C90°, towards the horizontal targets, which involved a simple rule (up = right; see **Fig. 3.8**). These movements, perhaps performed as a means to gain additional proprioceptive information about the location of her effectors relative to the visual goal, did not improve her performance however. In contrast, in a situation where her eyes and hand were going the opposite directions (C180°) and could rely on rule-based guidance, IG moved her head less than the controls did, a finding similar to "gaze-anchoring" (Neggers & Bekkering, 2000; Neggers & Bekkering, 2001). Overall, when available, IG utilized any potential aids in order to compute the required motor plan in decoupled eye-hand coordination.

Potential neurological substrates for decoupled visuomotor control

Although the dorsal stream of the proposed perception-action model (Milner & Goodale, 1995) has been well accepted as a primary network for the control of "vision for action", it has become clear that it is not entirely functionally segregated from the control of "vision for perception" (Brogaard, 2011; Pisella et al., 2006; Pisella et al., 2009; Schenk & McIntosh, 2010). Instead, the dorsal stream appears to contribute to the integration of cognitive visuo-perceptual skills (cognitive) with complex visuomotor skills (Pisella et al., 2013). As such, it has become apparent that overlapping yet distinct cortical networks exist which control the specific components involved in decoupled eye-hand coordination.

Notably, damage to a crucial node involved in the peripheral guidance of limb in space (caudal SPL; Granek et al., 2012; Perenin & Vighetto, 1988; Pisella et al., 2000) appears to result in an inability to successfully integrate the two proposed streams. Such egocentric guidance of conflicting visual and proprioceptive information in peripheral space (Blangero et al., 2007; Granek et al., 2012) and online updating required following target displacement (Blangero et al., 2008; Clavagnier et al., 2007; Grea et al., 2002; Khan et al., 2005; Khan et al., 2007; Pisella et al., 2000) are primarily affected from dorsal stream damage. This suggests that the OA deficit includes an impaired integration of conscious awareness of eye-centered metrics with transient online representations of limb-centered metrics. Supporting the contribution of this brain region to non-standard visuomotor mapping, we have observed reduced firing rates in caudal SPL neurons in (intact) non-human primates performing similar eye-hand decoupled reaching tasks (Hawkins et al., 2013). Taken together, we propose that the caudal SPL contributes to the required inhibition of the natural tendency to reach towards where one looks by monitoring the relationships between the behavioral goal and the location of the involved effectors in space, and communicating this information to frontal lobe structures involved in planning the biomechanical details of the specific movement.

The current data provide evidence of a functional spectrum from explicit to implicit control of non-standard, decoupled visuomotor control. Reaching in a well-learned canonical situation such as in the horizontal plane (H: when using a computer mouse), or with the aid of a simple rule such as in the 180° rotated visual feedback condition (C180°: right = left) does not rely fully on an intact caudal SPL. Rather, the premotor cortex may receive indirect inputs from more *ventral* connections into the prefrontal cortex via the infero-temporal cortex or via the IPL (Pisella et al., 2006), which may carry the crucial information to guide the movement. Evidence in support of these alternate connections comes from reach studies employing a long delay between the cue and the movement (Blangero et al., 2008; Revol et al., 2003). Such connections require more processing time (Thaler & Goodale, 2011) and carry rule-based and allocentric information, which is impaired in patients such as DF with lateral occipital (James et al., 2003) ventral stream damage (Schenk, 2006). Fast, implicit guidance of a limb in peripheral space, on the other hand, relies on the combination of peripheral perception of motion with an appropriate reach vector command. It has since been suggested by (Milner & Goodale, 2006) that the motion sensitive area MT, an area previously thought to be explicitly within the dorsal stream, and its connections with MST and IPL (Maunsell & van Essen, 1983; Rozzi et al., 2006), may serve as an integral node in the suggested interaction between dorsal and ventral streams (Buxbaum, 2007; Husain & Nachev, 2007; Pisella et al., 2006; Schenk & McIntosh., 2010).

Difference vector computation in optic ataxia

Decoupled eye-hand coordination requires ongoing overt foveal monitoring of the visual target with covert peripheral visual feedback of the limb and cursor position, along with proprioceptive feedback of the decoupled limb position. If the generated motor plan has been miscalculated, a difference vector must be continually updated online to compensate accordingly. Such a miscalculation will, in the OA patient, result in hypometric reaching (towards the direction of gaze) when reaching towards extra-foveal targets (Battaglini et al., 2002; Blangero et al., 2010; Perenin & Vighetto, 1988), proprioceptive targets (Blangero et al., 2007), and foveated visual targets decoupled from the moving limb (Granek et al., 2012).

Distinct functional regions have been proposed within the SPL, with segregated areas for reaching (parietal reach region; PRR; Batista & Andersen, 2001; Gail & Andersen, 2006), located within the medial bank of the IPS (Snyder et al., 1997), and saccades (parietal eye fields; PEF; Andersen et al., 1992), located on the lateral bank of the IPS (Cui & Andersen, 2007; Snyder et al., 1997). According to this segregated view, depending on the location of the lesion site, the decoupled eye-hand coordination deficits seen in OA patients could result from either impaired eye-centered coding within the PEF or a breakdown of limb-centered coding within PRR. Others have suggested the impairment in OA to result from the conversion of eye- to limb-centered coordinates may result from the inability to simultaneously represent spatial orientations of decoupled end effectors when guiding a limb in peripheral visual space (Jackson et al., 2005). Thus, during decoupled eye-hand coordination OA patients may have difficulty transforming eye-centered information about the visual goal into a limb-centered motor goal (Jackson et al., 2005; Jackson et al., 2009; Khan et al., 2007; Pellijeff et al., 2006). Alternatively, evidence for reaching deficits resulting from temporary deactivation of parietal area PEc in non-human primates (Battaglia-Mayer et al., 2012), has been thought to result from a breakdown in the **combination** of the preferred direction of eye and hand position relative to a visual target goal into a common state within the dynamic, context-dependent global tuning field of individual parietal neurons (Battaglia-Mayer et al., 2000; Battaglia-Mayer & Caminiti, 2002). Thus, without a functioning SPL, the frontal cortex may not be provided with updated accurate eye-hand position signals (see Battaglia-Mayer & Caminiti, 2002). This breakdown of the global tuning field could explain the altered neural outputs (spikes; Hawkins et al., 2013) from SPL and inputs (local field potentials; Sayegh et al., 2013) into PMdr when required to formulate and maintain an accurate difference vector during decoupled eye hand coordination.

In the present study, we observed that IG had the greatest deficits for those decoupled conditions in which she could not rely on external allocentric aids (such as the computer monitor border) and/or accurate cognitive rules (such as hand up = cursor right). When forced to rely predominantly on online updates from conflicting proprioceptive and visual information, IG displayed impaired hand movement correction when attempting to adjust for inaccurate ballistic movements. In attempt to compensate for impaired online updating in peripheral vision, IG overtly foveated the cursor position via additional eye movements (look-backs). Such overt foveal updating of limb or target position has been previously shown to be beneficial for predicting upcoming hand movements (Desmurget et al., 1999; Flanagan et al., 2006; Khan et al., 2007; Prablanc et al., 1979). Additional evidence for IG's reliance on her vision for her hand movements comes from the high correlation between her eye and hand movement planning timing. Similar to her direct reaching, C90° IG's hand movements varied relative to her eye movements to allow for efficient eye-hand coupling.

We propose that the deficits seen in this OA patient arise as a result of a failed transformation between guiding sensory information and required limb movement when strategic control is not possible. Our findings support the involvement of caudal SPL in the monitoring of gaze, limb, and target location needed for difference vector computation in decoupled reaching, a computation required for successful visuomotor transformations. The question remains if IG's extensive previous experience has enabled neuroplasticity for complex visuomotor control and therefore can be accurately generalized to other OA patients. In fact, compensatory activity has been observed for IG in both occipito-temporal and in occipito-parietal regions surrounding her lesions during both immediate and delayed extra-foveal reaching (Himmelbach et al., 2009). However, similar observations of a reliance on strategic control during decoupled visually-guided reaching in a newly-tested OA patient MFL (Granek et al., 2012) provide evidence that IG's deficits result from her caudal SPL lesions. Further, IG's deficits are in line with the documented role of the caudal SPL in coding the required difference vector during decoupled reaching (Fernandez-Ruiz et al., 2007; Hawkins et al., 2013; Vesia et al., 2010).

Conclusions

The results of this study suggest that the caudal SPL missing in OA is a critical component for guiding a decoupled limb in space. We suggest that an intact caudal SPL is crucial for maintaining and updating the decoupled hand location in peripheral vision, specifically in situations where strategic rules and allocentric cues are not useful. In addition, we suggest that a relative weighting of strategic control and sensorimotor recalibration is required depending on the type of decoupled visually-guided reach.

Acknowledgments

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Chapter Four

Disrupting the integration of a cognitive rule into a motor action in decoupled eye-hand coordination using a dual task paradigm

Joshua A. Granek and Lauren E. Sergio

Abstract

Guiding a limb that has been decoupled from gaze, even when free to foveate the visual target, 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 reaching under a 90° cursor feedback rotation condition (Granek, Pisella, Stemberger, Vighetto & Sergio, 2013). We observed that performance with OA improved when orienting a rotated cursor towards horizontal targets which can be performed using an explicit rule (up = right) relative to diagonal targets requiring more sensorimotor realignment. Here, to further differentiate the fundamental mechanisms of decoupled visuomotor control, we tested healthy participants in a cognitively-demanding dual task. Participants continuously counted backwards while simultaneously reaching 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 dual task served as a non-invasive means to disrupt the integration of a cognitive rule with a motor action. Complementary to the results seen in OA, the dual task led to greater performance deficits during the rotated condition towards horizontal targets, implying a selective disruption of strategic control of decoupled reaching. Our results suggest that independent neural pathways underlie the control of these different types of reaching, since one class of movement was interfered with to a greater extent than the other.

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

Introduction

Rule-based 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 rule: move the mouse forward to orient the cursor vertically (i.e. explicit strategic control). There are also situations, however, 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 can be approximated, but online feedback would predominate. Instead of relying on the rule, an unconscious (Abeele & Bock, 2003; Sulzenbruck & Heuer, 2009) sensorimotor realignment must gradually occur over multiple attempts (i.e. implicit sensorimotor recalibration). We propose that rule-based visuomotor control involves a continuum between explicit and implicit control depending on the details of the task.

Evidence for a rapid "automatic" cortical network has been identified from patients with optic ataxia (OA; Pisella et al., 2000), experiencing caudal superior parietal lobule (SPL) damage (Blangero et al., 2009; Karnath & Perenin, 2005). An intact dorso-dorso (Pisella et al., 2006; Pisella et al., 2009; Rizzolatti & Matelli, 2003) connections serve, at least in part, integral for accurate online updating (Grea et al., 2002; Pisella et al., 2000) and peripheral guidance of a limb (Granek et al., 2012; Perenin & Vighetto, 1988). Based on evidence for improved movement performance following a long delay in OA (Blangero et al., 2008; Revol et al., 2003; Trillenberg et al., 2007) it has been suggested that these patients relied on prefrontal communication with intact ventral circuits including the infero-temporal cortex or the inferior parietal lobule (IPL; Pisella et al., 2006). These alternative connections have been proposed as "strategic control" networks (Honda et al., 1998; Sulzenbruck & Heuer, 2009). We have previously demonstrated an increased reliance on explicit strategic control in a bilateral OA patient when reaching under a 90° cursor feedback rotation condition (Granek et al., 2013). We observed that performance in OA improved when eye, hand and head strategies were utilized, specifically during rotated cursor feedback towards horizontal (on-axis) targets involving an explicit rule (up = right) relative to diagonal (off-axis) targets involving a more implicit sensorimotor realignment.

Thus motivating the current study employed to tease apart the putative cortical networks involved in the control of rule-based motor control. Using a non-invasive dual-task paradigm, 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). Similar to previous reports in decoupled visuomotor control (Connolly et al., 2000; Gorbet et al., 2004; Granek et al., 2010), sequential verbal arithmetic has been suggested to involve a distributed cortical network including the left inferior parietal lobule (IPL) and the prefrontal cortex (Grabner et al., 2009; Simon et al., 2004). We hypothesized that the secondary task would activate a similar network thought to be involved in slow, cognitively demanding visuomotor control (see Pisella et al., 2006; Pisella et al., 2009). Specifically, in contrast with OA, we predicted that the secondary task would interfere with the combination of the strategic rule with the required motor action when guiding the rotated cursor towards the horizontal targets (e.g. right = up), while sparing the sensorimotor recalibration required for the diagonal targets.

Methods

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.

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 Screen: Model KTMT-1315: Sampling rate: 100 Hz) in order to displace a cursor from a central target to one of two horizontal (right or left), or to one of two diagonal (45° rotated from a vertical line – ~top-right or ~top-left) targets. Importantly, contrary to the horizontal targets which are oriented directly perpendicular to the dimly lit computer monitor boarder, the diagonal targets were not oriented towards any helpful allocentric cues such as the corner of the monitor. Following a two second delay, one of the peripheral visual targets (16mm in diameter) was presented 120 mm (16° visual angle) from the central target (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). The viewing space was calibrated using a nine-point calibration and drift correction was applied between each condition.

Figure 4.1B displays a schematic of the experimental conditions. The participants performed a standard condition and a 90° rotated condition in combination with either forwards counting (control) or backwards counting (dual). The control condition was performed to control for speaking in the chin rest and involved consecutive counting from 1-10 repeatedly and involved very little cognitive load. The dual task involved sequences of backwards counting by either three or seven from different seeds ranging from 90-110 and was much more demanding than forwards counting. The C90° 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 implicit mental rotation of the cursor was required for the diagonal targets.

In order to ensure equal understanding of the transformational rules applied in each condition, all participants were trained prior to each randomly assigned block until each subject reached an equal performance plateau for both target types (see **Fig 4.2**) and reported that they were cognitively prepared. Following training, each participant performed 40 trials in each of the four experimental conditions (**Fig. 4.1B**).

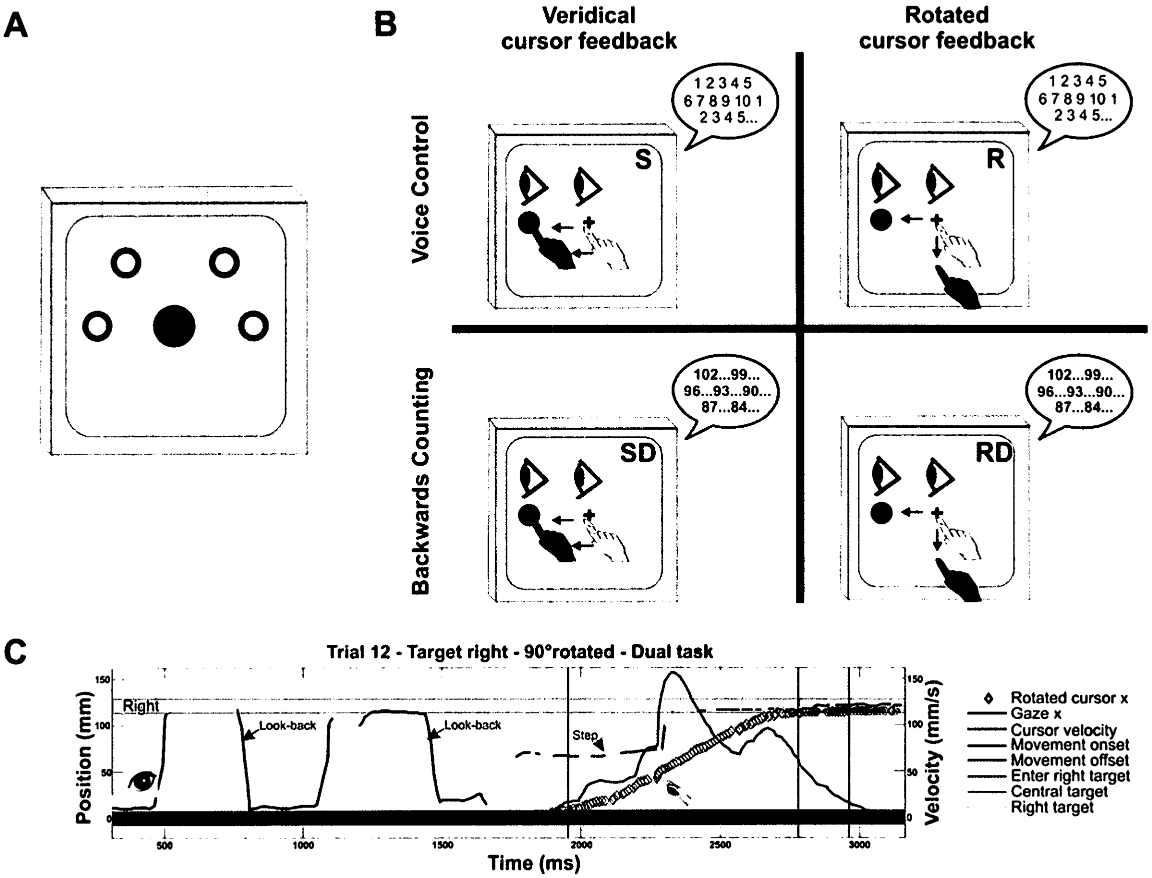

Figure 4.1. Experimental procedure schematic and example eye and hand trajectories. (A) Schematic of horizontal (blue) and diagonal (green) target locations. (B) Schematic drawing of the veridical and rotated (90° clockwise) cursor feedbacks. Both conditions were performed concurrently with a voice control (forward counting from 1-10; blue numbers) and with a dual task (backwards counting by 3 or 7; red numbers). The green 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. S = standard; R= rotated; D =dual. (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.

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 (**DE**). An 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. These initial miscalculations were enumerated in a separate analysis. For each DE, we calculated the time to recovery (**TTR**), which was recorded from the time from the inaccurate hand movement onset (see below) until the time point in which the trajectory was reversed towards the correct target location.

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 (time to peak velocity; aMT) and a deceleration/correction phase (time from peak velocity to the entry of the peripheral target; dMT). **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 (**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**).

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 (**ERT**) began when the peripheral target was presented and ended at saccadic 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 un-restricted 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 be able to identify saccade-related errors, eye scan path data were recorded from eye movement onset until hand movement onset (early errors: "priming") and from hand movement onset until entrance of peripheral target (late errors: "online updating"). 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 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 subjects reversed eye direction (towards the cursor) a minimum of 20% (24 mm) of the total amplitude from the central to peripheral target, holding 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.

Statistical analyses

All analyses focused on the "dual task aspect" of visuomotor control. The dual task 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 subjects, we statistically removed (i.e. covaried for) the effects of the simple task from that of the complex 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).

Results

If one is relying on strategic rule to successfully perform a decoupled visually-guided reach, the addition of a secondary cognitively-demanding task would interfere with the implementation of rule into a motor action. To address this prediction, we conducted a series of 2 (condition: standard vs. rotated) × 2 (target type: horizontal vs. diagonal) repeated measures ANOVAs on the effect of the "dual task aspect" (see **Methods** for details). Following a performance plateau within the last ten trials per target type for each condition during training (see **Fig. 4.2**) no condition × target interactions were observed for HRT ($p = 0.95$) or TMT ($p = 0.09$). Thus, we could then be certain that the task was understood and the differences observed were as a result of the addition of the secondary task. The required division of attention during the dual task conditions did not selectively impair performance of the secondary task (sequential backwards counting). During the dual task, no differences were found between the standard and the rotated conditions for the change in counting rate ($p = 0.27$) or the error rate ($p = 0.05$) from the voice control. Consequently, only the primary task revealed selective differences between conditions and targets as a result of the dual task.

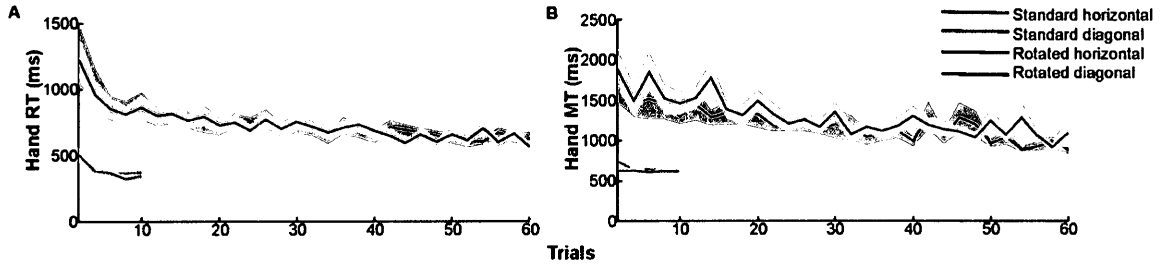

Figure 4.2. Hand movement timing during training. Hand (A) reaction time and (B) movement time (ms) during training following a verbal explanation for both standard and rotated conditions. Shaded areas denote SEM. Note the learning plateau for both dependent variables during the last 10 trials for each target type (horizontal and vertical) in both conditions.

Dual task impairs eye and hand movement timing during visuomotor rotation towards horizontal targets

In order to assess both predictive and online updating deficits as a result performing a secondary task, we analyzed eye and hand movement reaction time and movement time. Figure 3 shows the relative changes in hand and eye movement timing from baseline (voice control) for both target types and conditions.

Simultaneously performing two tasks regardless of condition or target type slowed down both eye and hand movement preparation timing (ERT/HRT; see Fig. 3), although neither ERT ($p = 0.56$) nor HRT ($p = 0.57$) displayed a condition × target interaction. In contrast, both eye and hand movement timing were differentially affected by condition and target type during the dual task. A condition × target interaction was observed for EMT (ANOVA, $F_{1,18} = 22.9$, $p = 0.0001$). Post hoc comparisons revealed a greater increase in EMT for the horizontal targets relative to the diagonal targets during the rotated condition ($p = 0.0001$). Hand movements were overall longer in the rotated condition during the acceleration phase (aMT; main effect of condition; ANOVA, $F_{1,18} = 26.1$, $p = 0.0001$). A condition by target interaction (ANOVA, $F_{1,18} = 11.6$, $p = 0.003$) revealed a greater increase in aMT towards the horizontal targets relative to the diagonal targets ($p = 0.02$). A condition by target interaction was also observed for peak velocity (ANOVA, $F_{1,18} = 15.6$, $p = 0.001$). Participants decreased their peak velocity the most towards the horizontal relative to the diagonal targets during the rotated condition (p =

0.0001).

Despite equal eye and hand movement preparation deficits across condition and targets during the dual task, eye and hand movement execution was the most compromised by the dual task when orienting a rotated cursor towards the horizontal targets.

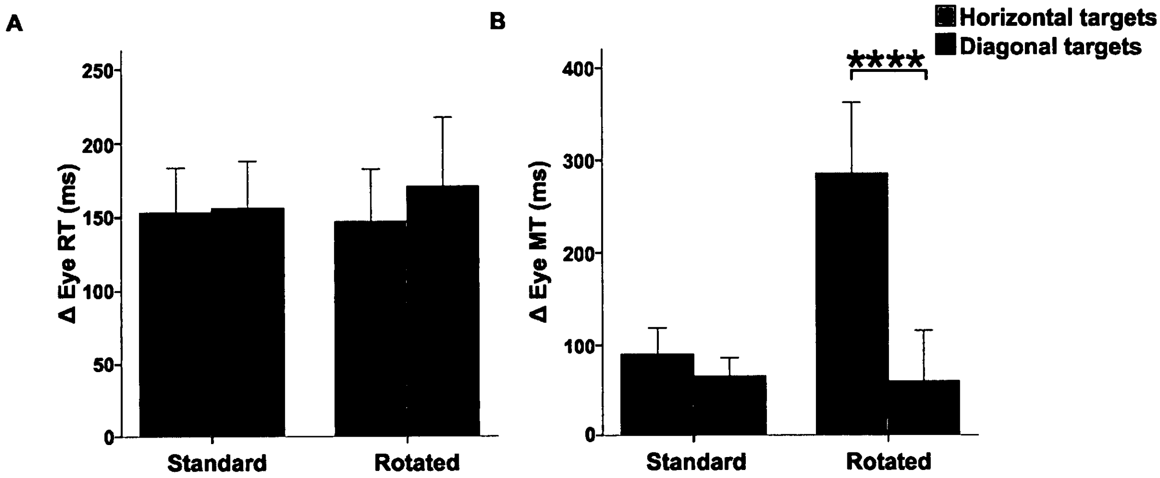

Figure 4.3. Eye movement timing. Change in eye reaction time (A) and movement time (B) for dual task conditions compared with control conditions to both horizontal (right and left; gray bars) and diagonal (top-right and top-left; black bars) targets. Asterisks represent significance (Bonferroni corrected) of post-hoc condition by target comparisons. Error bars denote SEM. ****p<0.0001.

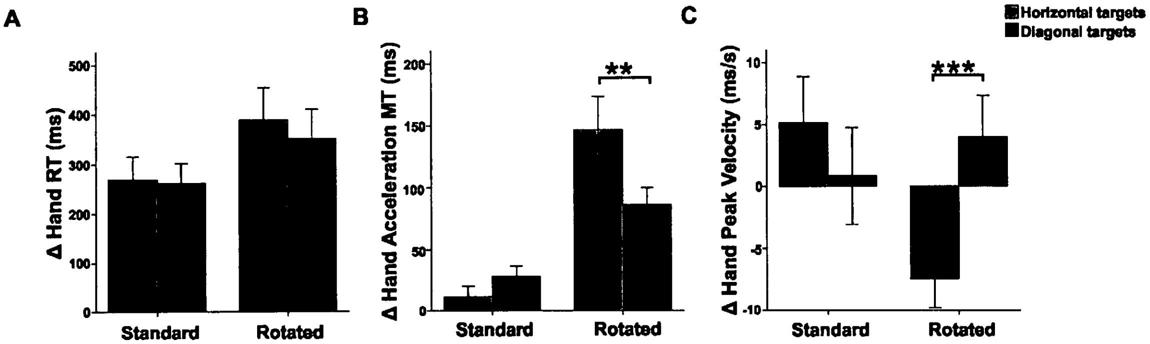

Figure 4.4. Hand movement timing. Change in hand reaction time (A), movement time (B), and peak velocity (C) for dual task conditions compared with control conditions to both horizontal (right and left; gray bars) and diagonal (top-right and top-left; black bars) targets. Asterisks represent significance (Bonferroni corrected) of post-hoc condition by target comparisons. Error bars denote SEM. **p<0.01;***p<0.001.

Dual task impairs ballistic hand motor command during visuomotor rotation towards horizontal targets

If the dual 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 hand movement endpoints (AE), as well as the angle at peak velocity. Figure 4 displays the ballistic endpoint across all conditions for a typical participant. For examples of full hand and eye movement trajectories between diagonal and horizontal targets during decoupled eye-hand coordination, see Figure 5.

The addition of secondary task increased AE for the rotated task to a greater extent than for the standard task (main effect of condition; ANOVA, $F_{1,18} = 11.9$, $p = 0.005$). A condition × 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 ($p = 0.0001$). Similarly, analyses of the hand movement trajectories (angle at peak velocity) revealed a condition × target interaction (ANOVA, $F_{1,18} = 9.0$, $p = 0.007$), where the trajectories were more deviated when orienting the cursor towards the horizontal targets relative to the diagonal target during the rotated condition ($p = 0.005$).

Differences in hand endpoint and trajectory parameters between during the dual task relative to the voice control revealed the greatest errors when orienting towards the horizontal targets during the rotated; a situation where a strategic rule was more useful and thus could be interfered with.

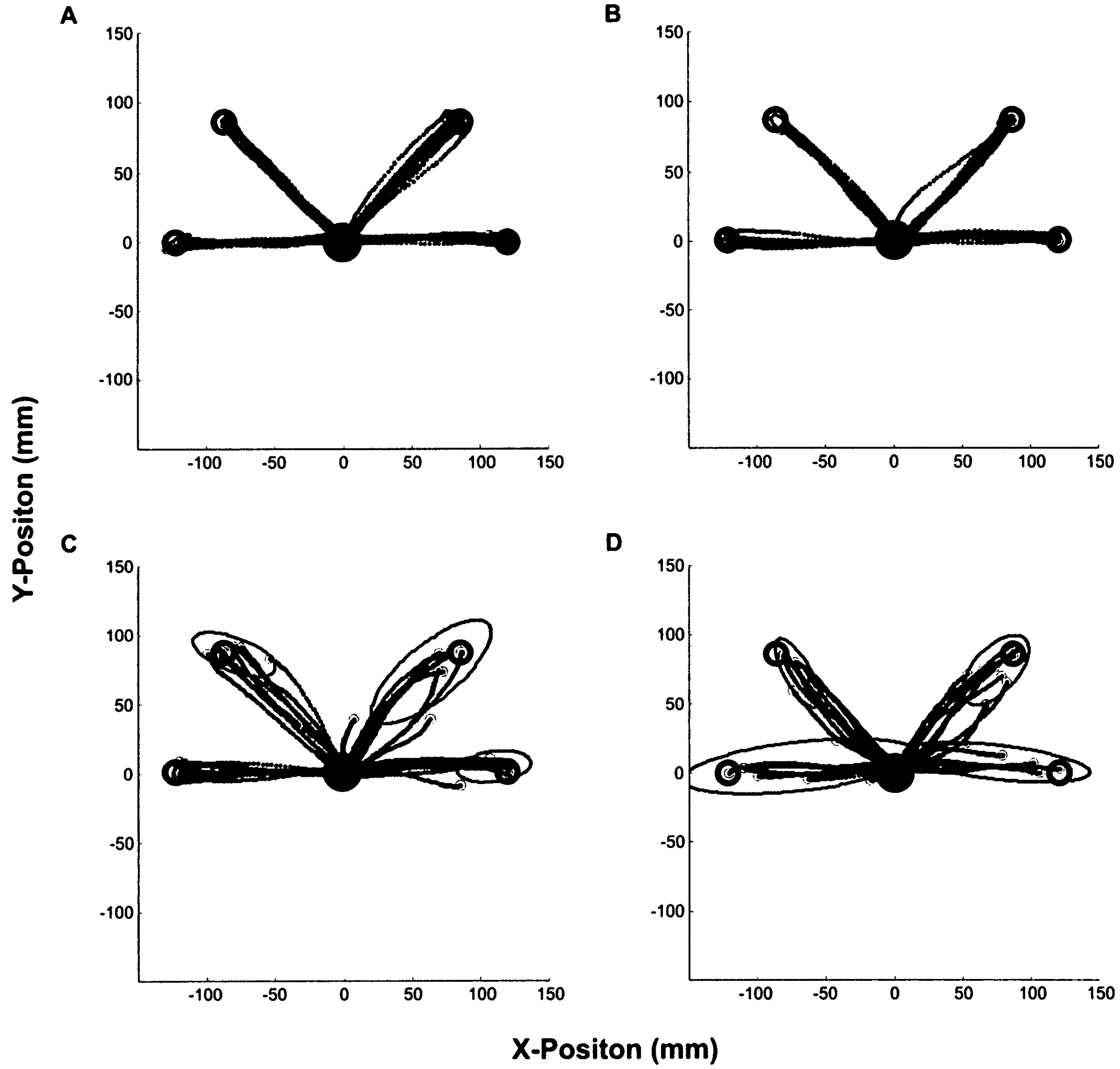

Figure 4.5. Individual hand movement trajectories and endpoints. Example trajectories and endpoints of a typical subject performing the standard (A), standard dual (B), rotated (C), and rotated dual (D) task. Ellipses denote 95% CI of landing point following ballistic hand motor plan. Note the increased deficits towards the horizontal targets during the rotated dual condition.

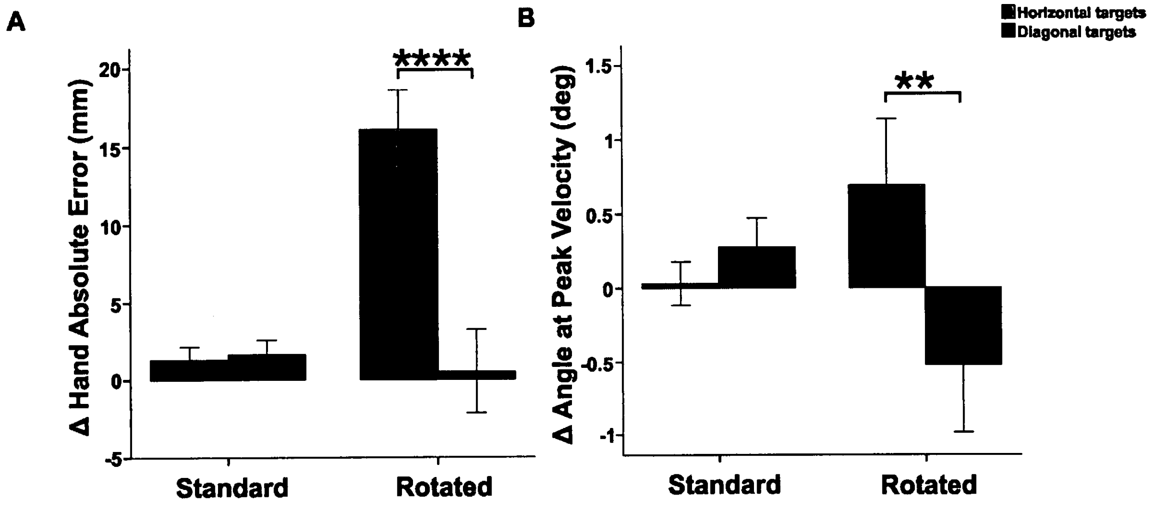

Figure 4.6. Hand ballistic endpoints and angle at peak velocity. Change in (A) hand absolute error following ballistic reach and (B) and hand angle at peak velocity during the two dual task conditions relative to the backwards counting controls. Error bars denote SEM. **p<0.01;****p<0.0001.

Additional eye movements are performed for dual task during visuomotor rotation towards horizontal targets

If a decoupled task that is not implicitly incorporated into a motor plan is interfered with as with our dual task, the guidance of the decoupled limb will become more difficult. Although all subjects were instructed to foveate the peripherally-cued visual target, eye movements were not restricted. As such, similar to our previous reports in OA patients (Granek et al., 2013; Granek et al., 2012), we observed four basic types of eye movement errors. However, in the current situation, our dual task interfered with the eye movements towards the horizontal (see **Fig.4.7**) rather than the diagonal targets as seen in bilateral OA (Granek et al., 2013).

A main effect of condition (ANOVA, $F_{1,18} = 7.5$, $p = 0.02$) and a condition × target interaction (ANOVA, $F_{1,18} = 48.1$, $p = 0.0001$) was observed for all eye-movement errors, 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 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, $F_{1,18} = 52.8$, $p = 0.0001$), influenced predominantly by the increase in hypometric steps towards the horizontal targets during the rotated condition ($p = 0.0001$). The 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 standard condition (main effect of condition; ANOVA, $F_{1,18} = 7.2$, $p = 0.0001$). The dual task also influenced the number of "look-backs" towards the cursor during the rotated condition relative to the standard condition (main effect of condition ANOVA, $F_{1,18} = 9.9$, $p = 0.006$). Similarly, participants performed more of these "look-backs" (condition × target interaction; ANOVA, $F_{1,18} = 5.3$, $p = 0.03$) during the rotated condition towards the horizontal targets relative to the diagonal targets ($p = 0.01$). Finally, the introduction the 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 standard condition (main effect of condition; ANOVA, $F_{1,18} = 4.7$, $p = 0.04$). A condition × target interaction was observed (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 ($p = 0.0001$).

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

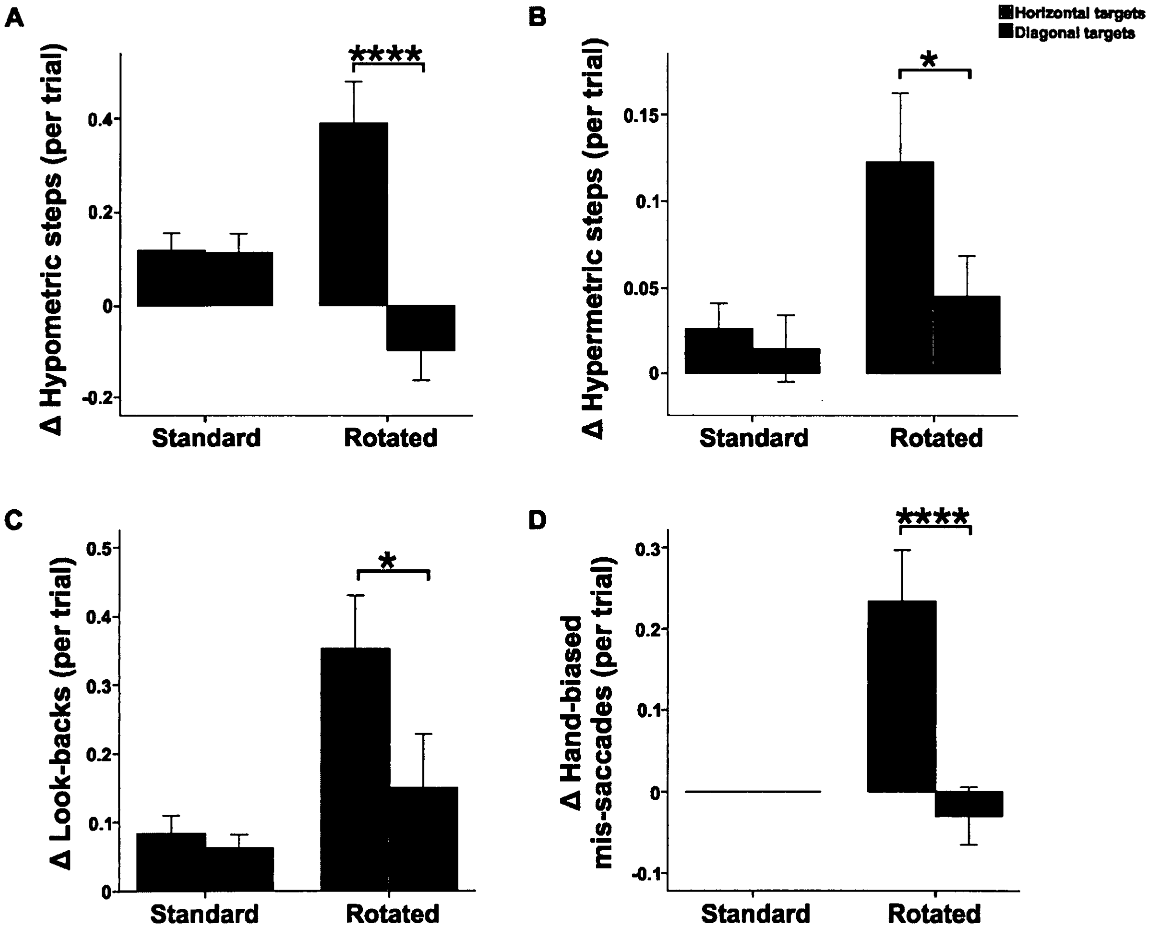

Figure 4.7. Eye movement errors. Change in hypometric (A) and hypermetric (B) steps (i.e. pauses in eye trajectory), look-backs towards the cursor (C) and hand-biased mis-saccades (D) for dual task conditions compared with control conditions to both horizontal (right and left; gray bars) and diagonal (top-right and top-left; black bars) targets. Asterisks represent significance (Bonferroni corrected) of post-hoc condition by target comparisons. Error bars denote SEM. *$p<0.05$; ****$p<0.0001$

Discussion

Our results demonstrate that the divided attention required during the dual task selectively impaired the implementation of a cognitive rule into a motor plan while sparing implicit sensorimotor control. As predicted, the most robust deficits were observed during the rotated condition towards the horizontal relative to the diagonal targets, implying alternate cortical control depending on target location. These deficits included slower eye and hand movement timing, hand-biased eye movements, as well as additional pauses in trajectory and 'look-backs' towards the cursor. We suggest that these additional eye movements are 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).

It has been suggested that participants exposed to different visuomotor rotations find those increasing up to 90° to become more challenging, while those increasing from 90° to 180° to become simpler (i.e. more of a quick inversion; Bock et al., 2003; see Bock, 2013). Thus, the 90° rotation represents the middle ground between gradual sensorimotor adaptation compared to quick rule-based transformation. Our previous work with a bilateral OA patient (Granek et al., 2013) revealed an impaired dorso-dorsal (Pisella et al., 2006; Pisella et al., 2009; Rizzolatti & Matelli, 2003) parieto-frontal network in implicit sensorimotor recalibration (see **Fig. 4.8A**), as performance in OA improved during situations relying on strategic control (e.g. 90° rotation, horizontal targets). In contrast, the dual task employed in the current study revealed impaired performance when guiding the rotated cursor towards the horizontal targets; thus, providing further evidence for alternate cortical control depending on target location.

Relying on quick coordination strategies can reduce larger performance errors during eye-hand decoupling (Redding & Wallace, 1993) and explicit knowledge of visuomotor rotations can improve the ability to adapt (Hegele & Heuer, 2010; Hinder, Woolley, Tresilian, Riek, & Carson, 2008), although only for initial hand end-point errors, not in the rate of adaptation (Mazzoni & Krakauer, 2006). In the current study, learning was quicker for the rotated condition towards the horizontal targets (see **Fig. 4.2**), since participants could align their arm-movement trajectory perpendicular to the border of the computer monitor. For the diagonal targets, participants could only estimate a rule (e.g. ~ top-left = ~bottom-right) since the required trajectory did not align directly with helpful allocentric cues (i.e. did not point exactly to the corner) and thus, a gradual recalibration between senses was required.

The current study employed a dual task paradigm in order to disrupt reaching tasks. Daily activities often require the simultaneous performance of two different tasks such as simultaneously walking and talking or singing while driving, however, dividing one's attention impairs even familiar tasks (Neider et al., 2011), potentially due to bottlenecking of neural resources (Pashler, 1990). In the laboratory setting, dual tasks have been utilized as a non-invasive means to causally impair a wide range of behaviors including active (Martin & Henriques, 2010) and passive (Martin, Deeghan, & Henriques, 2013) shape drawing, walking (Bock, 2008; Neider et al., 2011), and arithmetic (Lee & Kang, 2002). Tasks requiring explicit rules have been traditionally thought to require greater attention than implicit tasks which are predominantly unconscious (Jimenez et al., 2006), although implicit procedural learning can be impaired during a dual task (Shanks, Rowland, & Ranger, 2005). The dual task in the current study did in fact lead to a selective impairment of the conditions requiring the greatest strategic control.

It has been established that cognitive-motor integration involves a distributed parieto-frontal network (Connolly et al., 2000; Gorbet et al., 2004; Granek et al., 2010; Toni & Passingham, 1999). The addition of a cognitively-demanding secondary task such as sequential backwards counting has been shown to activate a similar network including the inferior parietal lobe (left AG; Dehaene & Cohen, 1997), a region activated for increase task complexity and the prefrontal cortex (DLPFC; Grabner et al., 2009), a region activated for initiation of a complex task (Menon et al., 2000). 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.

Deficits in calculations (acalculia; see Ardila & Rosselli, 2002) have provided insight for the crucial involvement of an intact parietal lobe for arithmetic. Specifically, the left AG has been implicated in sequential memorized mathematics (Lee, 2000; Menon et al., 2000) as it is linked with the verbal system (Dehaene & Cohen, 1997; Dehaene et al., 2003; Lee & Kang, 2002) and to recall of stored arithmetic facts (Grabner et al., 2009). Activations just inferior (Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002) and mesial (Simon et al., 2004) to the left AG, have been observed as a part of a parieto-frontal network involved for the linkage between and arithmetic and language (Simon et al., 2004). When participants have reported to utilize alternative procedural strategies than memory recall for verbal arithmetic, an even more distributed parieto-frontal network is observed (Grabner et al., 2009), which can be altered depending on which strategy is utilized (Rosenberg-Lee, Lovett, & Anderson, 2009).

Strategic control can rely on transformational rules (Wise et al., 1996) and has been suggested (Miller, 2000; Murray et al., 2000; Rougier, Noelle, Braver, Cohen, & O'Reilly, 2005) to be largely mediated by top-down control via connections from DLPFC into PMdr in non- human (Luppino et al., 2003; Matelli & 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 (Miyazaki et al., 2013). Ardila and Rosselli (2002) suggest that prefrontal patients with executive function acalculia 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 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. 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 employing a long delay between the cue and the movement (see Schenk, 2006), whereby a combination of compensatory temporal lobe and intact SPL activation is observed (Himmelbach et al., 2009). Hand endpoint performance has been shown to improve when OA patients had more time for processing the remembered representation of the movement goal (Blangero et al., 2008; 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 accurate allocentric cues (i.e. computer monitor boarder) was selectively impaired during the dual task. Utilizing allocentric cues for reaching is thought to take a longer (Thaler & Goodale, 2011) route along the ventral stream since a damaged lateral occipital cortex (as in visual agnosia; (James et al., 2003) has been shown to be impair allocentric reaching. Intact arithmetic performance seen in visual agnosia (Pesenti, Thioux, Samson, Bruyer, & Seron, 2000), however, provides evidence that ventral stream structures may have not been disrupted in the current study by our dual task.

Alternative connections for cognitive-motor integration could pass through IPL. Support of the IPL as an alternative pathway for slow cognitive visuomotor control (see Rossetti et al., 2005) comes from patients with IPL damage with impaired complex motor programming (e.g. Mattingley et al., 1998) and delayed reaching (Darling, Rizzo, & Butler, 2001). Interaction between the dorsal and ventral visual streams (v-d stream; Pisella et al., 2006; Pisella et al., 2009; Schenk & McIntosh, 2010) could potentially occur through area MT and its direct connections with IPL and the temporal cortex (Rozzi et al., 2006). Within IPL, the supramarginal gyrus (SMG/PFG) is connected with PMv (Rozzi et al., 2006; Rushworth et al., 2006; Tomassini et al., 2007), which in turn is connected to PMdc/F2 (Marconi et al., 2001). Alternatively, both AG and SMG are directly connected to the prefrontal cortex (for details, see **Fig. 4.8A**). Cross-talk between the dorsolateral and the dorsomedial parieto-frontal (Tanne-Gariepy et al., 2002) connections is also possible as seen from weak connections from the medial SPL to the anterior IPS observed in non-human primates (Borra et al., 2008; Gamberini et al., 2009).

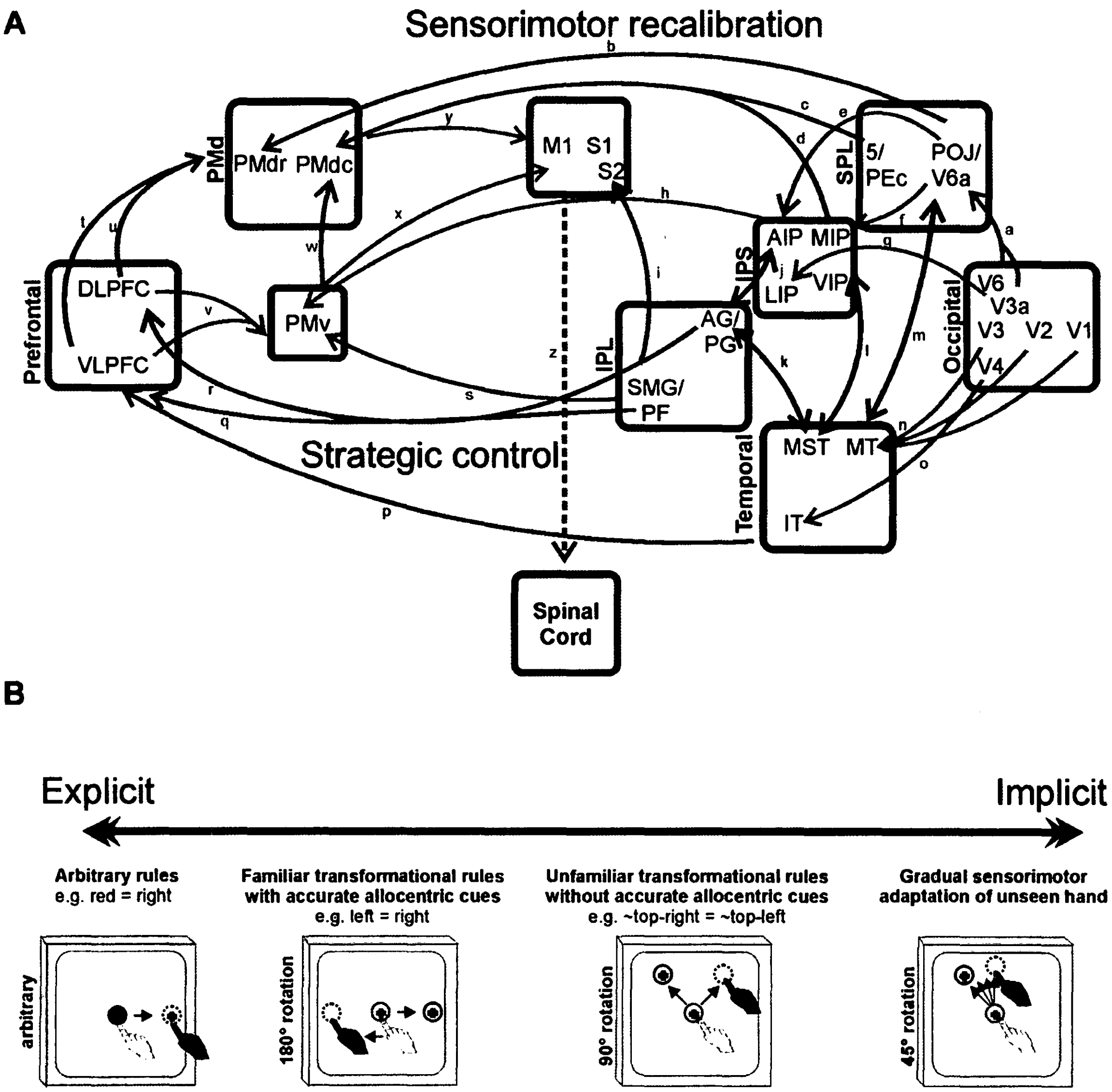

Figure 4.8. Putative cortical networks and example tasks requiring a relative contribution of strategic control and sensorimotor recalibration. (A) Schematic of the possible cortical connections based on a collaboration of human and macaque connection experiments (see lowercase letters below) involved in strategic control (red) sensorimotor recalibration (green), cross-talk between networks (black double arrows), and other intermediate connections (grey). Note that although most 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). **a**) (Galletti et al., 2001; Grol et al., 2007; Shipp, Blanton, & Zeki, 1998), **b**) (Caminiti et al., 1999; Marconi et al., 2001; Matelli, Govoni, Galletti, Kutz, & Luppino, 1998; Passarelli et al., 2011; Shipp et al., 1998; Tanne et al., 1995), **c**) (Bakola, Gamberini, Passarelli, Fattori, & Galletti, 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**) (Tanne et al., 1995), **g**) (Nakamura et al., 2001), **h**) (Matelli et al., 1986; Matelli & Luppino, 2001; Rozzi et al., 2006; Rushworth et al., 2006; Tanne-Gariepy et al., 2002), **i**) (Cavada & Goldman-Rakic, 1989a; Rozzi et al., 2006), **j**) (Borra et al., 2008), **k**) (Maunsell & van Essen, 1983), **l**) (Maunsell & van Essen, 1983), **m**) (Colby et al., 1988), **n**) (Maunsell & van Essen, 1983), **o**) (Maunsell & van Essen, 1983), **p**) (Petrides & Pandya, 2002; Tanne et al., 1995), **q**) (Petrides & Pandya, 2006; Petrides & Pandya, 2009; Rozzi et al., 2006; Tomassini et al., 2007), **r**) (Cavada & Goldman-Rakic, 1989b; Gamberini et al., 2009; Petrides & Pandya, 2009; Rozzi et al., 2006), **s**) (Petrides & Pandya, 2009; Rozzi et al., 2006; Rushworth et al., 2006; Tomassini et al., 2007) **t**) (Luppino et al., 2003; Tomassini et al., 2007), **u**) (Gamberini et al., 2009; Luppino et al., 2003; Matelli & Luppino, 2001; Tomassini et al., 2007), **v**) (Tomassini et al., 2007), **w**) (Dum & Strick, 2005; Marconi et al., 2001), **x**) (Rozzi et al., 2006), **y**) (Barbas & Pandya, 1987; Dum & Strick, 2005; Johnson et al., 1993; P. B. Johnson et al., 1996; Tanne et al., 1995), and **z**) (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.

In summary, we observed different performance declines during the implementation of the eye and hand motor plans during decoupled eye-hand coordination depending on target location. When simultaneously performing a 90° visuomotor rotation with a cognitively-demanding dual task, increased reliance on a cognitive rule (i.e. horizontal targets) was more susceptible to disruption, while reliance on sensorimotor recalibration (i.e. diagonal targets) was more preserved. These data suggest that suggest that independent neural pathways underlie the control of these different types of reach, since one class of movement was impaired to a greater extent than the other. Future imaging studies are required to further explore the details of these networks.

Chapter Five

General Discussion

5.1. General discussion and conclusions

Although our everyday movements typically involve a direct ("standard") interaction with the object that we are viewing, we have also evolved an ability to interact with objects via tools ("non-standard"). In tool-use (such as using a computer mouse) the direction of our gaze and the object we are manipulating can be in different depths or spatial planes. In such situations, the correspondence between what one sees and what one does must be learned and calibrated. Although imaging research has provided evidence for vast cortical regions involved in rule-based visually-guided reaching, the particular nodes within the interconnected networks responsible for cognitive-motor integration have yet to be fully characterized. As such, the current dissertation explored the effects of brain damage or divided attention on different nodes within the proposed networks (see **Fig. 4.8A**).

Each of the three studies in this dissertation provided additional insight into the crucial nodes within the cortical networks responsible for non-standard eye-hand coordination. Since all participants were free to foveate the visual targets, but their limbs were required to move in a direction which was spatially decoupled from the direction of gaze, we were able to be the first group to explore the "natural" scan path behavior during decoupled eye-hand coordination. As a result, we observed a number of eye-hand strategies which were employed by participants in order to compensate for either their damaged cortex or for the increased divided attention required to successfully incorporate a cognitive rule into a motor action.

In chapter two, my **first goal** was to decipher the role of one of the cortical nodes, the caudal SPL, in different non-standard situations. To address the role of the caudal SPL in non-standard reaching, we tested two unilateral OA patients who were missing their right caudal SPL on a series of non-standard tasks and compared them to age-matched controls. We examined the eye and hand performance of two unilateral optic ataxic patients (CF and MFL), and healthy age-matched controls in reaching tasks which involved different levels of dissociation (spatial plane changes, rotated visual feedback, arbitrary associations). OA patients have previously shown deficits in reaching accuracy when guiding a decoupled limb towards **extra-foveal** targets, with the contralateral arm and contralateral visual field. Here, we showed that these deficits extended to guiding a decoupled limb with peripheral vision towards **foveal** targets, with spared direct reaching and strategic control involved in arbitrary mappings. In both patients, we observed a gaze-direction dependent reaching bias when the visual feedback of hand location was rotated. Analysis of the eye data revealed that both of the chronic patients developed alternate eye-movement strategies in order to interact with the external world. The patients would either move their hand before the eyes, saccade towards the direction of the hand movement prior to the hand movement, or they would glance back and forth between the target and their hand during the rotated tasks. Despite the additional eye movement errors, hand movement performance was still compromised in OA patients when their eyes and hand moved in opposite directions. In addition, even though the patients were instructed to foveate the target, they appeared unable to successfully decouple eye and hand movements. Thus, an intact caudal SPL appears to be necessary for successful initiation and guidance of reaches with this type of dissociated visuomotor compatibility.

In chapter three, my **second goal** was to further expand the role of the caudal SPL in non-standard reaching in situations where explicit strategic rules could be utilized versus situations relying on more implicit realignment between senses such as proprioception and vision (i.e. sensorimotor recalibration). Here we tested a bilateral patient (IG) renowned for her deficits in automatic online updating and compared her performance to age-matched controls. We tested all participants on a series of decoupled eye-hand coordination tasks again, but this time in some less familiar orientations. We controlled for familiarity based on previous experience with a computer mouse by testing all participants in an additional spatial plane (para-sagittal plane). In addition, we controlled for strategic control during a visuomotor rotation by adding a less familiar 90° rotation, which is known to be more difficult to learn via gradual sensorimotor recalibration. Finally, to decrease the reliance on strategic control, we tested all participants towards both canonical well-categorized orientations in space (along the horizontal axis) and towards non-canonical, less-categorized orientations in space (along the diagonal axis). IG was the most impaired during the unfamiliar situations towards non-canonical orientations in space, whereby she could not rely on strategic rules nor relevant allocentric cues to guide her decoupled limb in peripheral space. Thus, these data provide further evidence that the OA deficit is during the sensorimotor recalibration between the felt hand position and the visual information with preserved strategic control. These results suggest that an intact SPL is required for non-standard situations when implicit sensorimotor recalibration is required. These deficits were markedly smaller for mappings involving explicit rule integration, suggesting an independent pathway for processing strategic control in non-standard visually-guided reaching.

In chapter four, my **third goal** utilized a dual-task paradigm to further differentiate the neural pathways involved for these two classes of movement control (sensorimotor recalibration versus strategic control), by increasing the neural load associated with explicit rule integration, but not implicit visual-proprioceptive alignment. Here, we trained healthy adults on visually-guided reaching with both veridical and 90° rotated cursor feedback, while simultaneously performing an attentionally-demanding task (backwards counting by different amounts). Again, participants oriented a cursor towards both horizontal (on-axis) involving an explicit rule (up = right) and diagonal (off-axis) targets involving a learned mental rotation between gaze and hand position. The dual task was successful in selectively impairing movements which were learned via strategic control to a greater extent than those which were implicitly incorporated as a part of the motor plan via sensorimotor recalibration. The fact that one type of movement was interfered with to a greater extent than the other provides further evidence for alternative parieto-frontal communication during strategic control of rule-based eye-hand coordination.

Taken together, these projects provide novel insight to the alternative cortical networks involved in decoupled eye-hand coordination. We propose that an intact caudal SPL is crucial for accurate guidance of a limb in peripheral vision not just as previously shown towards extra-foveal targets during central fixation (Blangero et al., 2008; Perenin & Vighetto, 1988), but also during decoupled visuomotor control towards foveated targets. We have shown that eye and hand movement performance during decoupled visuomotor control **improves** in OA and **declines** during a dual task in situations relying on strategic control. As such, we propose that the caudal SPL is responsible for accurate sensorimotor recalibration during decoupled visuomotor control, while dorsolateral and ventral inputs into frontal regions are responsible for the strategic control during decoupled visuomotor control (for details, see **Fig. 4.8A**).

5.2. Limitations and future considerations

The patient data presented in chapters two and three come from three rare patients all of whom have experienced neuroplasticity as compensation from their lesions. In addition, in exception of patient MFL who has focal damage to her caudal SPL, the other two patients have lesions which expand beyond the caudal SPL including the white matter tracts connecting the parieto-frontal networks which are damaged in patient CF, as well as part of the AG which is damaged in patient IG. In addition, aside from patient MFL, the other two patients have plenty of experience in the laboratory setting which could alter their behavior. As well, the statistical analysis of case studies offers additional limitations. Since we employed the Crawford technique (Crawford et al., 2010), which is implemented to control for the small sample sizes, we conducted a series of corrected t-tests which do not correct for multiple comparisons. As such, the multiple comparisons required for the analyses presented in the tables (particularly for chapter two) should be considered when interpreting the data. As such, we have provided additional tables for chapters two and three which outline the significant results which have been corrected for multiple comparisons (Holm-Bonferroni corrected; see **Appendices 1 & 2**).

Although the studies outlined within this dissertation infer deficits along suggested brain connections, further examination is required using imaging techniques to fully characterize the overlapping, yet potentially distinct networks involved in the strategic versus the sensorimotor recalibration of rule-based motor control. It would be of interest to examine the neural correlates of reaching using fMRI during a 90° visuomotor rotation towards both canonical (aligned by accurate allocentric cues along the ordinal axes) and non-canonical (not aligned with accurate allocentric cues along the oblique axis) orientations in space. Finally, to further causally decipher the role of each node within the network, additional patient studies (e.g. visual agnosia, ideomotor apraxia, etc.) and TMS studies are required to provide causal links for the role of specific nodes within this network. Specifically, administration of continuous theta-burst stimulation (cTBS) over different cortical would provide a window to test the deficits during decoupled visuomotor control. Regions within the IPL (AG and anterior SMG) – potentially providing alternative spatial information during cognitive-motor integration – as well as prefrontal regions (DLPFC) – potentially providing the top-down cortical in order to incorporate a rule into a motor action – would be important targets regions for cTBS administration. Similar to the proposed fMRI experiment, the 90° rotation towards both canonical and non-canonical orientations in space would provide further evidence for a relative weighting between sensorimotor recalibration and strategic control of decoupled eye-hand coordination (see **Fig. 4.8B**).

The fundamental research conducted in these series of studies can provide a basis for a myriad of clinical applications, such as being used as an assessment tool for cases of mild brain dysfunction. Preliminary research has demonstrated that mild brain dysfunction can impair performance when the goal of the eye and the hand has been decoupled. Specifically, this assessment tool could be used to detect early stages of Alzheimer's disease, as well as function assessment as a part of the return-to-play protocols following a concussion. Preliminary evidence in our lab (Hawkins, Thayaparan, Bida & Sergio, 2011) suggests that decoupled eye-hand coordination can detect deficits in individuals with just a family history of Alzheimer's disease, without the actual diagnosis itself and even detect deficits in athletes with a history of concussion, but without any current symptoms (Brown, Hughes, & Sergio, 2011). Currently the assessment tools available involve testing the ability to move and to think independently, while our tasks test the ability to think and to move simultaneously.

In summary, these studies have provided novel information about the contribution of brain areas (summarized in **Fig. 4.8**) to one of our most fundamental human behaviors, the ability to combine thought and action in order to interact with our environment in a meaningful and skilled way.

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Appendix A

Appendix A. Corrected hand movement timing significant differences separated by hand and visual target between MFL and CF compared with the control group

Patient	Dependent variable	Condition	Hand	Target	t-value	Effect size	Adjusted p-value
MFL	RT	VR	R	T	17.4	18.5	0.00004
		HR	L	L	12.5	13.3	0.00004
		HR	L	T	10	10.6	0.0008
		HR	R	L	10.2	10.8	0.0007
		HR	R	T	8.5	9	0.002
		HR	L	R	7.5	7.9	0.004
		HR	R	R	7.5	7.9	0.003
		VR	L	B	5.9	6.3	0.02
		VR	R	B	5.8	6.1	0.02
		VR	R	L	5.6	6	0.02
		H	R	T	5.1	5.4	0.03
	MT	VR	R	T	5.9	6.3	0.02
	CMT	VR	R	T	11.2	11.9	0.0004
		H	L	R	5.9	6.2	0.04
	VE	HR	R	B	10	10.7	0.0006
		HR	R	T	7.4	7.8	0.005
		H	L	R	7.2	7.6	0.005
		HR	R	L	10.8	6.7	0.01
		VR	R	L	5.8	6.2	0.03
		HR	R	R	7.1	7.5	0.03
	DR180	HR	R	L	9	9.5	0.001
CF	MT	VR	L	R	5.7	6	0.03
		VR	R	R	5.5	5.8	0.04
	VE	VR	L	R	5.6	6	0.03
	DR 180°	HR	L	R	7	7.4	0.006

Appendix A note: Dependent variables (RT = reaction time; MT = ballistic movement time; CMT = corrective movement time; VE = variable error; DR 180° = direction reversal) were tested with separate modified t-tests ($p' < 0.05$) for each condition (V = vertical; VR = vertical rotated; H = horizontal; HR = horizontal rotated) for each hand and each visual target (R = right; T = top; L = left; B = bottom) and corrected for multiple comparisons (Holm-Bonferroni).

Appendix B

Appendix B. Corrected eye movement errors significant differences separated by hand and visual target between MFL and CF compared with the control group

Patient	Dependent variable	Condition	Hand	Target	t-value	Effect size	Adjusted p-value
MFL	DE	HR	R	R	+	+	+
		HR	R	T	+	+	+
	Look-backs	HR	R	R	16.8	17.8	0.00003
		HR	R	B	15.2	16.1	0.00003
		VR	R	R	11.3	12	0.0003
		VR	L	B	11	11.7	0.0003
		HR	L	T	9.8	10.4	0.0006
		VR	R	T	9.1	9.7	0.001
		HR	L	L	9.4	10	0.008
		H	R	B	5.7	6.1	0.02
		VR	L	R	4.9	5.2	0.04
		VR	R	L	4.9	5.2	0.04
	Hypometric	HR	L	R	33.5	35.5	0.00003
		HR	R	T	6.1	6.5	0.02
	Hypermetric	H	R	R	40	42.7	0.00003
		HR	R	R	26.2	27.8	0.00003
		VR	R	L	22.7	24.1	0.00003
		V	R	T	18.8	20	0.00003
		H	L	L	15.8	16.7	0.00003
		HR	R	L	14.3	15.2	0.00003
		VR	L	L	14.2	15	0.00003
		HR	R	B	13.2	14	0.00002
		HR	L	B	11.6	12.3	0.0002
		VR	R	T	7.9	8.4	0.002
		H	R	L	7.7	8.1	0.003
		H	L	B	7.6	8.1	0.002
		HR	L	T	7.1	7.6	0.004
		VR	R	R	5	5.3	0.03

Appendix B continued.

Patient	Dependent variable	Condition	Hand	Target	t-value	Effect size	Adjusted p-value
CF	DE	HR	R	T	+	+	+
	Hypermetric	H	R	T	32.1	34	0.00003
		VR	R	B	30.6	32.5	0.00003
		V	R	L	25.5	25	0.00003
		VR	L	T	25.5	27.1	0.00003
		V	L	L	25.1	26.7	0.00003
		VR	L	L	25.1	26.7	0.00003
		H	R	L	19.9	21.1	0.00003
		HR	L	R	19.3	20.5	0.00002
		V	L	R	18.6	19.7	0.00002
		VR	L	R	18.6	19.7	0.00002
		VR	L	B	17.8	18.9	0.00002
		V	L	B	15.6	16.5	0.00002
		H	L	L	13.1	13.9	0.00002
		HR	R	L	12.6	13.3	0.00002
		H	L	R	9.7	10.3	0.0005
		H	R	B	9.7	10.3	0.0005
		HR	L	B	16.8	18.4	0.001
		VR	R	R	7.9	8.4	0.001
		H	R	R	7.6	8.1	0.001
		V	L	T	7.4	7.9	0.002
		HR	R	R	7.1	7.6	0.002
		VR	R	L	6.5	6.9	0.003
		HR	L	L	5.8	6.1	0.006
		V	R	R	5.8	6.2	0.006
		HR	R	B	5.3	5.6	0.007

Appendix B note: Dependent variables (DE = initial eye movement direction error; Hypermetric = hypermetric steps; Look-backs; Hypermetric = hypermetric steps) were tested with separate modified t-tests ($p' < 0.05$) for each condition (V = vertical; VR = vertical rotated; H = horizontal; HR = horizontal rotated) for each hand and each visual target (R = right; T = top; L = left; B = bottom) and were corrected for multiple comparisons (Holm-Bonferroni). + No statistical comparison between the case and the control group could be performed because the control group had a mean and standard deviation of zero.

Appendix C

Appendix C. Corrected hand movement significant differences separated by visual target type IG and the control group

Target type	Dependent Variable	Condition	IG: mean Δ in performance	Controls: mean Δ in performance (± 95%) CI)	t-value	Effect size	Adj. p-value
Diagonal	HRT	C180°	354.4 ms	99.5 ± 31.9 ms	5	5.4	0.03
		C90°	733.5 ms	253.0 ± 57.0 ms	5.6	6.1	0.02
	HCMT	C180°	447.2 ms	46.6 ± 24.4 ms	10.8	11.7	0.0008
		C90°	2487.8 ms	309.1 ± 126.0 ms	15.4	16.6	0.0002
	Peak velocity	C90°	-69.0 ms/s	-4.5 ± 8.3 mm/s	-6.8	-7.4	0.008
	On-axis CE	C180°	-12.1 mm	0.3 ± 1.0 mm	-10.2	-11	0.001
	Off-axis CE	S	6.5 mm	0.8 ± 0.9 mm	4.7	5.1	0.04
		C180°	6.2 mm	-1.0 ± 1.1 mm	6.3	6.9	0.04
	Path length	C180°	32.6 mm	14.6 ± 6.6 mm	10.6	11.4	0.001
	Angle	C180°	11.6°	2.4 ± 1.4°	5.5	5.9	0.02
		S	12.2°	2.6 ± 1.1°	6.2	6.7	0.01
		C90°	25.9°	3.1 ± 1.4°	17.1	18.5	0.00008
	TTR	C90°	2613.5 ms	410.5 ± 112.4 ms	18.1	19.6	0.00008
Horizontal	HMT	C90°	316.6 ms	73.0 ± 77.0	4.6	5	0.04
		C180°	408.3 ms	52.6 ± 62.1 ms	5.1	5.5	0.03
	HCMT	C90°	702.7 ms	220.0 ± 85.7 ms	4.5	4.8	0.03
		H	98.7 ms	26.2 ± 10.4 ms	4.8	5.2	0.03
	Peak velocity	C90°	-57.0 ms/s	-21.5 ± 9.3 mm/s	-4.4	-4.8	0.05
	Path length	C180°	24.0 mm	7.2 ± 3.7 mm	5.2	5.6	0.03
	TTR	C180°	1622.0 ms	439.5 ± 0 mm	4.2	4.5	0.05

Appendix C note: Dependent variables (HRT = hand reaction time; HMT = ballistic hand movement time; HCMT = corrective hand movement time; peak velocity; on/off-axis CE = constant error; Angle = angle at peak velocity; path length; TTR = time to recovery from a direction reversal) were tested with separate modified t-tests ($p' < 0.05$) for each condition (C = coronal 180°/90°; H = horizontal; S = para-sagittal) for each visual target type (diagonal/horizontal) and were corrected for multiple comparisons (Holm-Bonferroni).

Appendix D

Appendix D. Corrected eye movement significant differences separated by visual target type IG and the control group

Target type	**Dependent Variable**	**Condition**	**IG: mean Δ in performance**	**Controls: mean Δ in performance (± 95% CI)**	**t-Value**	**Effect size**	**Adj. p-value**
Diagonal	ERT	C90°	429.9 ms	82.8 ± 39.1	7.3***	7.9	0.005
	EMT	H	59.1 ms	9.0 ± 8.3 ms	7.2***	7.8	0.006
		C90°	225.2 ms	45.5 ± 8.2 ms	15.6****	16.8	0.0002
		C90°	429.9 ms	82.8 ± 39.1 ms	7.3***	7.9	0.005
	Look-backs	C180°	0.2/trial	0.01 ± 0.07/trial	6.1**	6.6	0.01
		C90°	1.5/trial	0.06 ± 0.03/trial	10.4***	11.2	0.001
		S	0.25/trial	0 ± 0/trial	+	+	+
	HBMS	C90°	0.28/trial	0.02 ± 0.03/trial	7.1***	7.7	0.007
Horizontal	ERT	C90°	577.5 ms	104.6 ± 37.7	11.8***	12.8	0.0006
	EMT	C90°	224.9 ms	32.9 ± 27.4 ms	6.2**	6.7	0.01
		C180°	100.7 ms	2.8 ± 12.9 ms	5.5**	5.9	0.02
		H	-49.2 ms	2.4 ± 8.3 ms	-5.2**	-7.4	0.02
	Hypermetric steps	C180°	0.25/trial	-0.02 ± 0.03/trial	4.5**	4.9	0.008
	Look-backs	S	0.28/trial	0.0008 ± 0.03/trial	7.7***	8.3	0.004
	HBMS	S	0.17/trial	0.02 ± 0.03/trial	4.2**	4.6	0.04

Appendix D note: Dependent variables (ERT = eye reaction time; EMT = eye movement time; hypermetric eye movement steps; look-backs to cursor; HBMS = hand-biased mis-saccades) were tested with separate modified t-tests ($p' < 0.05$) for each condition (C = coronal 180°/90°; H = horizontal; S = para-sagittal) for each visual target type (diagonal/horizontal) and were corrected for multiple comparisons (Holm-Bonferroni). + No statistical comparison between the case and the control group could be performed because the control group had a mean and standard deviation of zero.

THE ROLE OF THE POSTERIOR PARIETAL CORTEX IN COGNITIVE-MOTOR INTEGRATION

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ABSTRACT

When interacting with an object within the environment, one must combine visual information with the felt limb position (i.e. proprioception) in order compute an appropriate coordinated muscle plan for accurate motor control. Amongst the vast reciprocally connected parieto-frontal connections responsible for guiding a limb throughout space, the posterior parietal cortex (PPC) remains a front-runner as a crucial node within this network. Our brain is primed to reach directly towards a viewed object, a situation that has been termed "standard". Such direct eye-hand coordination is common across species and is crucial for basic survival. Humans, however, have developed the capacity for tool-use and thus have learned to interact indirectly with an object. In such "non-standard" situations, the directions of gaze and arm movement are spatially decoupled and rely on both the implementation of a cognitive rule and online feedback of the decoupled limb.

The studies included within this dissertation were designed to further characterize the role of the PPC in different types of visually-guided reaching which require one to think and to act simultaneously (i.e. cognitive-motor integration). To address the relative contribution of different cortical networks responsible for cognitive-motor integration, we tested three patients with optic ataxia (OA; two unilateral – first study, and one bilateral – second study) as well as healthy participants during a cognitively-demanding dual task (third study) on a series of visually-guided reaching tasks each requiring a relative weighting between explicit cognitive control and implicit online control of the spatially decoupled limb. We found that the eye and hand movement performance during decoupled reaching was the most compromised in OA during situations relying on sensorimotor recalibration, and the most compromised in healthy participants during a dual task relying on strategic control. Taken together, these data presented in this dissertation provide further evidence for the existence of alternate task-dependent neural pathways for cognitive-motor integration.

To my inspirations to succeed,

Jaden and Patricia

Keep on being yourselves…

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Glossary of Abbreviations

Abbreviation	Non-Abbreviated Term
aMT	Hand movement time acceleration phase
AD	Alzheimer's Disease
AE	Hand absolute error
ARB	Arbitrary condition
BG	Basal ganglia
BOLD	Blood oxygenated level dependent
C	Coronal condition
C180°	Coronal 180° rotated condition
C90°	Coronal 90° rotated condition
CE	Hand movement constant error
CES	Cumulative effect size
CMT	Hand corrective movement time
dMT	Hand movement time deceleration phase
DE/DR	Direction error
DLPFC	Dorsal lateral prefrontal cortex
EMT	Eye movement time
ERT	Eye reaction time
fMRI	Functional magnetic resonance imaging
H	Horizontal condition
HMT/MT	Hand ballistic movement time
MT	Middle temporal cortex
MST	Medial superior temporal cortex
HR	Horizontal rotated condition
HRT/RT	Hand reaction time
ID	Index of difficulty
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
IPS	Intraparietal sulcus
M1	Primary motor cortex
OA	Optic ataxia
PFv+o	Ventral and orbital prefrontal cortex
PMd	Dorsal premotor region
PMdc	Caudal dorsal premotor region
PMdr	Rostral dorsal premotor region
PMv	Ventral premotor region
POJ	Parieto-occipital junction
PPC	Posterior parietal cortex

S	Para-sagittal condition
S1	Primary sensory cortex
S2	Secondary somatosensory cortex
SFG	Superior frontal gyrus
SMG	Supramarginal gyrus
SPL	Superior parietal lobule
TMT	Total hand movement time
TTR	Time to recovery from a hand direction error
V	Vertical condition
VE	Hand movement variable error
VLPFC	Ventrolateral prefrontal cortex
VR	Vertical rotated condition