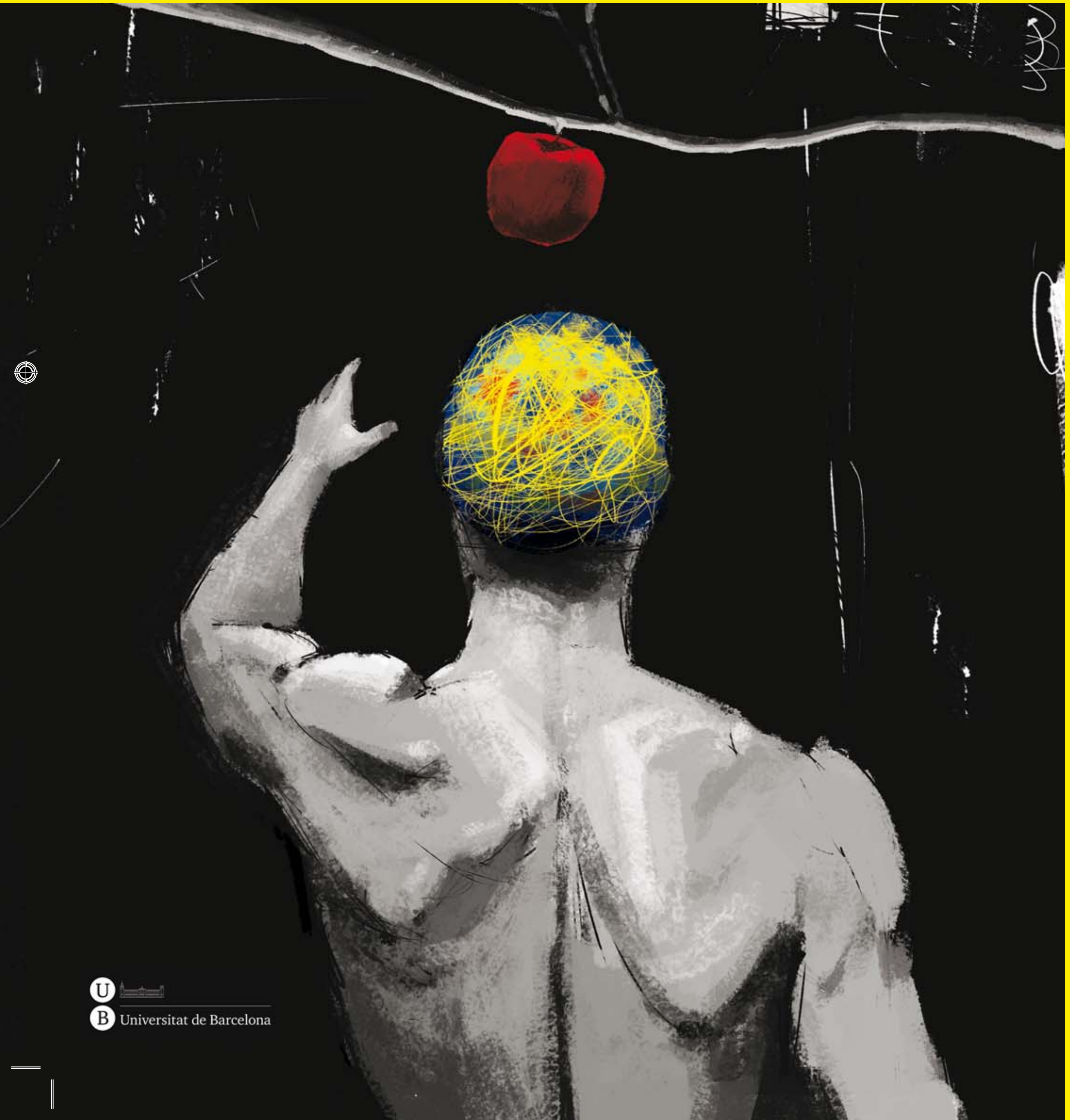
Spatio-temporal aspects in the control of the visuomotor system

Borja Rodríguez Herreros

“The great end of life is not knowledge but action”

T.H. Huxley (1825-1895); from A Technical Education (1877)



Universitat de Barcelona

PhD Thesis

2014

SPATIO-TEMPORAL ASPECTS IN THE CONTROL OF THE VISUOMOTOR SYSTEM

Borja Rodríguez Herreros

PhD Thesis

SPATIO-TEMPORAL ASPECTS IN THE CONTROL OF THE VISUOMOTOR SYSTEM

Borja Rodríguez Herreros

University of Barcelona

Spatio-temporal aspects in the control of the visuomotor system

Borja Rodríguez Herreros

Department of Basic Psychology
University of Barcelona

Spatio-temporal aspects in the control of the visuomotor system

This thesis is presented by
Borja Rodríguez Herreros

To obtain the degree of Doctor of Biomedicine from the University of Barcelona
In accordance with the requirements of the European PhD diploma

Supervisor
Prof. Joan López-Moliner

Tutor
Dr. Hans Supèr

Doctoral program in Biomedicine

A mis padres, a mis abuelos y a mi hermano

A Laia

Y a todo el que, de un modo u otro, ha contribuido a esta tesis.

Acknowledgements

Dicen que, en la vida, hay que hacer al menos tres cosas antes de morir: tener un hijo, plantar un árbol y escribir un libro. Esta tesis viene a llenar, en mi vida, el tercero de esos huecos. Ha sido un camino largo, muy largo, y no exento de dificultades. Pero parece que hemos llegado a buen puerto. Y digo *hemos*, porque sois muchas las personas que habéis contribuido de forma esencial a que el trabajo de tantos años haya por fin tomado forma. Sé de antemano que voy a olvidarme de muchos, pero espero que sepáis que no necesitáis ver aquí vuestro nombre para saber lo importantes que sois y el aprecio que os tengo.

En primer lugar, quiero dar las gracias al director de esta tesis, Joan. Te agradezco enormemente enseñarme qué es hacer ciencia. Desde los primeros días, me instruiste en cada paso a dar dentro de un estudio científico: conocer la bibliografía, plantear las hipótesis, registrar los datos, analizarlos e interpretarlos, para al final ponerlo todo por escrito. Cada uno de esos pasos, y por tanto toda esta tesis, no hubiera sido posible sin tu supervisión y tu ayuda. Muchas gracias por todo. También quiero hacer una mención especial a la imprescindible contribución del Dr. Antoni Rodríguez-Fornells. Hacia el ecuador de la tesis, surgió la posibilidad de poder complementar con electroencefalografía y técnicas de neuroimagen los estudios que veníamos haciendo. Toni, te agradezco enormemente haberme mostrado ese camino para conocer un poco mejor el cerebro. Valoro mucho el esfuerzo que me has dedicado y espero que estés orgulloso de los frutos cosechados y aún por cosechar.

También se merecen una gran parte del pastel de los agradecimientos todos los compañeros de laboratorio, tanto en Mundet como en Bellvitge. No sé por dónde ni por quién empezar. Bellido, si estás despierto, quiero agradecerte el compadreo constante y el buen rollo que me has transmitido codo con codo en Mundet. Ya te vaticino que no volveré a tener un tío tan de puta madre en la mesa de al lado. Recuerda que tenemos pendiente darle forma a la *dedete's illusion*. Cuni, mil gracias por todo el esfuerzo que pusiste en enseñarme qué son los ERPs. Cada trigger, cada condición y el ERPSS siempre estarán grabados en mi retina. Sabes que lo tengo que decir: Qué bueno eres, ¡hijo de p…! Ponseti, gracias por esos momentos de relax con un mando de PS3 en una mano y la otra en la bolsa de *llardons*. ¡Espero que la segona criatura et deixi temps per tornar a veure'ns les cares al FIFA! Cris, gracias por esas visitas al despacho para salir del ostracismo del R y del Matlab. ¡No sabes cuánto ayudan! Sobre mi afición por tirar el anzuelo para que Bellido pique, siempre negaré la mayor. Me limito a proporcionarle los mimbres para que no se desvíe del buen camino. Brendan, David, Eric, Javier y a todos los que no nombro pero qué sabéis quienes sois, gracias por toda vuestra ayuda en cada paso que di. Cogemos la Ronda para ir a Bellvitge. Amengual, te toca. Eh, vaya ciscal. Gracias por todos esos momentos en Lübeck, dónde nos lo pasamos bien no, lo siguiente. Y gracias por todas esas fructíferas discusiones científicas, estoy seguro que van a seguir por muchos años, Enate mediante. Pronto veremos culminada nuestra pequeña gran obra, y habrá que celebrarlo. Ane, no te alteres pero creo que la revisión del paper está a punto de llegar! Gracias por esas figuras de DTI, nunca el mundo vio unos clusters tan bellos. Josep, gracias por saberlo todo. Ernest, Cucu, Joan, Ruth, y a todos los que me dejo: gracias por acogerme como a uno más y gracias por esas calçotadas tan divertidas. No quiero olvidarme de los participantes en los experimentos. Sin vosotros y vuestro cerebro, esta tesis no se hubiera podido hacer. Finalmente, este capítulo lo cierro con un agradecimiento a Ignacio Serrano, el ilustrador de la portada.

Hay también dos etapas importantes de esta tesis que merecen una especial atención. Gracias a las estancias en centros europeos, he podido mirar más allá y entrar en la rueda de la ciencia al más alto nivel. La primera es la estancia que tuve la suerte de hacer en Amsterdam, en el grupo de Eli Brenner y Jeroen Smeets. Eli, Jeroen, your contribution to this thesis has been truly decisive. Thank you for opening me the doors of your group, for giving me the opportunity to be part of your team and for bringing me enthusiasm for research. It has been an honour to learn from you. I will always remember with joy the time I spent in your lab. I also want to thank all the help Denise gave me during those three months. En esta estancia, conocí a un chaval de Madrid con el que me he reído como pocas veces. Amsterdam da pie a ello. Marcos, esta tesis también es para ti, aunque suene a perogrullada. Y a Jorge, compañero de Marcos en Madrid. No conozco a nadie que sepa tanto de informática. Es una bestia. Y qué bien nos lo pasamos en nuestro primer congreso en Sant Feliu de Guíxols. ¡Gracias!

También quiero agradecer la posibilidad de poder trabajar bajo la supervisión de Thomas Münte, en Lübeck. Tom, thanks for making possible the fifth study of this thesis. Thanks for your unique welcome, and for giving me all the opportunities in such a professional and friendly way. En Lübeck conocí gente maravillosa que hizo que la estancia fuera todavía más rica. Gracias a Luis, Vicente, Laura, Sandra, Inma, Nuria y demás, pude disfrutar de seis meses inolvidables en los que aprendí muchas, muchas cosas. Pero no alemán. Lo dejaré para otra vida.

Si echo la vista atrás a mis etapas anteriores a la tesis, también encuentro mucha gente que me ha ayudado a ser quien ahora soy. No quiero olvidarme de todos los amigos que hice en el Máster de Neurociencias. Fue una etapa corta pero muy intensa dónde cuajó una amistad que estoy seguro que durará para siempre. Gracias a Cleo, Jordi, Rudy, Jorge, Nano, Júlia y a todos los que formamos esa invencible tropa. También quiero acordarme de los amigos de la carrera que, aunque diseminados por el mundo, intentamos siempre tenernos al día. Ellos me inocularon la idea de 'hacer una tesis'. Chema, Albert y Manolo gracias por esas fantásticas sesiones maratonianas en la ~~biblioteca~~ biofesta. Siempre siento nostalgia por aquellos años de *prietar vivo*. Por último, gracias a todos los amigos que me han acompañado durante más tiempo en mi corta existencia, los amigos de la escuela, *los de toda la vida*. Borraz, Labordeta, Maurel, Cuartero, Julitro, Otero, Chus, Escandell, Picó y otro puñado más que sabéis quienes sois. Después de una semana repleta de estrés y dificultades, no hay mejor premio que la llegada del viernes o el sábado para disfrutar como lo llevamos haciendo décadas. Y que siga, no pienso renunciar a ello. Como colofón, los amigos *del pueblo,* que llevan décadas estando ahí para hacerle a uno olvidarse de todas las penurias que pasa en la gran ciudad. Mención especial a los camaradas astures, que han proporcionado el soporte digital de esta tesis.

La parte final de los agradecimientos la he querido reservar para mi círculo más cercano. Desde que tengo uso de razón me he sentido un privilegiado por estar rodeado de las personas que forman mi familia. Mis padres siempre me han enseñado, desde bien pequeño, la cultura del esfuerzo, la generosidad, la perseverancia y la honestidad. Ellos me proporcionaron una infancia que solamente evoca momentos buenos, y un constante apoyo y mecenazgo en todo lo que he hecho después. Esta tesis es también vuestra. Si mis padres lo hicieron así de bien, estoy seguro que gran parte del mérito viene de cómo mis abuelos los educaron. Aunque dos de ellos ya no estén, los recuerdos que guardo del tiempo que compartí y comparto con ellos son imperecederos. Todos ellos tuvieron una vida mucho más dura de lo que nunca será la mía, y salieron adelante con fuerza. Podía y puedo escuchar sus historias de años pasados quedándome absorto, y siempre aprendo de ellos. Me enseñaron el valor de las pequeñas cosas, que a veces creemos prescindible. Por último, mi hermano es la persona con quien más tiempo he pasado en mi vida. La mayor parte de ese tiempo lo hemos pasado jugando, riendo, cantando…, en definitiva, ‘petando’. Y ya nos encargamos de recordarlo de vez en cuando. Esta tesis, la cual depositó él mismo, también es para él, dado que su mesita de noche no hace pie y necesita un buen taco.

El último párrafo lo quiero dedicar a Laia. Aquesta tesi també es teva. Tu millor que ningú saps l’esforç i les dificultats que envolten fer una tesi. I tu m’has acompanyat durant tot aquest camí, donant-me l’empenta necessària en els moments de més fatiga. Espero que siguis conscient de que aquesta tesi ha estat possible gràcies al teu suport constant, i a totes les coses que he après de tu. Gràcies per posar tota l’energia, l’entusiasme i la passió en les coses que fas. Intentaré insuflar-te tot el que tu m’has donat en el mateix camí que tu també has de recórrer ben aviat. Que no se m’oblidi: el teu sacrifici i la teva tenacitat et venen als gens. Admiro l’exemple de superació constant que veig en la teva mare i els teus avis. A ells també els hi dedico aquesta tesi. I al *jugón* que va aparéixer a les nostres vides ara fa casi dos anys i mig, una bestiola que només ens dóna bons moments i actua com a analgèsic constant. Amb aquesta tesi acaba una etapa, Laieta, quan vulguis comencem la següent.

Gracias.

BORJA

“Las cabezas deben juzgarse como los bolsillos. Al hacerlas sonar con las sacudidas de la conversación advertimos enseguida que unas contienen el oro de la sabiduría y del ingenio y otras la calderilla de la vulgaridad y de la rutina”

Santiago Ramón y Cajal

“Science is much more than a body of knowledge. It is a way of thinking”

Carl Sagan

SUMMARY

The complex voluntary motor behavior of higher primates is often regarded as a consequence of the development of sophisticated and adaptive perceptual and motor systems. Theoretical and behavioral investigations suggest that the control of motor acts involves a sequence of neural operations that select, plan and execute a movement. The visuomotor system integrates visual and proprioceptive signals to exert control on visually-guided actions, which generally allows to efficient localization of the stimuli and generation of the appropriate motor commands. Although the last two decades have witnessed a considerable progress on the understanding of the neural basis of visuomotor control, the shortage of the literature assessing directly this process boost the necessity of developing new spatio-temporal frameworks of how this process might work.

The present dissertation is focused on providing strong insights about the neural and behavioral aspects subserving the use of spatio-temporal information through vision and proprioception to accomplish accurate goal-directed actions. This dissertation encloses five different studies to shed some light on these issues, by combining neuroimaging and psychophysical tools. These empirical data are presented in Chapters 3 to 7, in the form of five articles. Two studies (Chapters 3 and 4) addressed object localization in reaching, by investigating the neural and behavioral mechanisms by which the integration of visual motion affects the execution of hand movements. We demonstrate that visual illusory percepts affect the hand trajectory toward a misperceived object, in a form that casts some doubts on the suitability of feedback circuits to sustain early motion-position interaction. Two other independent studies (Chapter 5 and 6) focused on the coding of hand location, by examining how the use of proprioception and the felt position of the arm influenced our temporal and spatial accuracy in interception. We uncover an increase in the weighting of proprioceptive signals when intercepting objects under poor visual conditions. In addition, the study of Chapter 6 reveals that proprioceptive cues of the hand location completely adapted to induced displacements of the visual input of the hand. The last study (Chapter 7) dealt with the online monitoring of a reaching movement. We have indentified a causal structure/function relationship between deficits in online motor control and the induction of inhibitory plastic changes over the medial intraparietal sulcus, suggesting this area as the neural locus in charge of the ability to update a motor command. We have found anatomical differences in white matter parietofrontal pathways responsible for the individual differences in the impairment of the online motor control.

Taken together, the research presented here strengthens the idea that our visuomotor system acts as a coordinated system that efficiently encodes relevant spatial and temporal features at different neural levels to ascertain a precise reaching behavior. Moreover, the combination of the sensory inputs that provide this information seems to depend on the reliability of the sensory source. I hope the work presented here will encourage the reader to explore deeper in the many aspects of this part of the brain still unrevealed.

RESUMEN

El complejo comportamiento motor voluntario de los primates superiores a menudo se considera como una consecuencia del desarrollo de complejos y adaptativos sistemas perceptuales y motores. Estudios teóricos y conductuales sugieren que el control de los actos motores implica una secuencia de operaciones neuronales que seleccionan, planifican y ejecutan un movimiento. El sistema visomotor integra señales visuales y propioceptivas para ejercer control sobre las acciones guiadas visualmente, permitiendo la localización eficiente de los estímulos y la generación de las órdenes motoras apropiadas. Aunque las dos últimas décadas fueron testigo de un progreso considerable en la comprensión de las bases neuronales del control visomotor, la escasez de bibliografía abordando directamente este proceso impulsa la necesidad de desarrollar nuevos marcos espacio-temporales de cómo podría funcionar el control visomotor.

Esta tesis se centra en proporcionar conocimientos robustos sobre los aspectos neurales y conductuales que promueven el uso de información espacio-temporal a través de la visión y la propiocepción, con el fin de realizar certeras acciones dirigidas a objetos. Esta tesis encierra cinco estudios diferentes para arrojar luz sobre estas cuestiones, mediante la combinación de psicofísica y técnicas de neuroimagen. Los datos empíricos se presentan en los capítulos 3 a 7, en forma de cinco artículos. Dos estudios (Capítulos 3 y 4) abordan la localización de objetos en acciones para alcanzarlos, mediante la investigación de los mecanismos neurales y conductuales por los que la integración de movimiento visual afecta la ejecución de movimientos manuales. Demostramos que las percepciones ilusorias visuales afectan la trayectoria de la mano hacia un objeto erróneamente percibido, y también cuestionan la idoneidad de los circuitos 'feedback' para explicar la temprana interacción movimiento-posición. Otros dos estudios independientes (Capítulos 5 y 6) se centran en la codificación de la posición de la mano, mediante el examen de como el uso de la propiocepción y la posición sentida del brazo influenciaron nuestra precisión temporal y espacial interceptando un objeto. Descubrimos un aumento en la ponderación de las señales propioceptivas al interceptar objetos bajo pobres condiciones visuales. Además, el estudio del Capítulo 6 revela que las señales propioceptivas de la ubicación de la mano se adaptaron completamente a desplazamientos inducidos de la información visual de la misma. El último estudio (Capítulo 7) se ocupó de la monitorización 'online' de un movimiento, mediante la identificación de una relación causal estructura/función entre los déficits en el control motor y la inhibición del surco intraparietal medial, lo que sugiere este área como la zona responsable de la capacidad de actualizar un comando motor. También identificamos diferencias anatómicas en los tractos parietofrontales de materia blanca causantes de las diferencias individuales en el deterioro del control motor.

En conjunto, la investigación presentada aquí refuerza la idea de que nuestro sistema visomotor actúa como un sistema coordinado que codifica de manera eficiente las características espaciales y temporales correspondientes a diferentes niveles neuronales para conseguir un preciso comportamiento motor. Además, la combinación de las vías sensoriales que proporcionan esta información parece depender de la fiabilidad de la fuente sensorial. Espero que el trabajo aquí presentado anime al lector a explorar más profundamente en los diversos aspectos de esta parte del cerebro todavía no revelados.

Table of contents

PREFACE XXIII

1. INTRODUCTION 1

1.1 VISUAL CODING OF OBJECT LOCATION 4

1.1.1 Low-level visual processing of object position 5

1.1.1.1 Position coding through non-primary visual inputs 6

1.1.1.2 The dorsal visual stream: action-relevant information of object position....8

1.1.2 Localizing stationary objects: a matter of space 10

1.1.2.1 Visual motion and the perceived position of stationary objects 10

1.1.3 Localizing moving objects: a matter of space and time 14

1.2 SPATIAL CODING WHEN REACHING AN OBJECT 15

1.2.1 Computing target location for action 17

1.2.1.1 The influence of visual motion in coding target's position for action 17

1.2.1.2 Neural mechanisms underlying motion's influence on action 20

1.2.2 Computing hand location in space 22

1.2.2.1 Aligning vision and proprioception 23

1.2.2.2 Encoding limb configuration in the peripersonal space 25

1.2.2.3 Plasticity of the peripersonal space: tool-use and shifted visual feedback 26

1.2.3 The control of reaching movements 28

1.2.3.1 Online computation of target-hand distance 30

1.2.3.2 Online motor control: Updating target location 31

1.2.3.3 The neural basis of online motor control 33

1.3 NEUROIMAGING OF THE VISUOMOTOR SYSTEM 35

1.3.1 Electroencephalography....36

1.3.2 Transcranial magnetic stimulation....38

1.3.3 Diffusion tensor imaging 40

1.3.4 Comparison of the methods 41

2. OUTLINE AND AIMS OF THE THESIS 45

3. STUDY I: THE INFLUENCE OF MOTION SIGNALS IN HAND MOVEMENTS 51

3.1 ABSTRACT 55

3.2 INTRODUCTION 55

3.3 GENERAL METHODS 56

3.3.1 Apparatus 56

3.3.2 Stimuli 56

3.3.3 Data acquisition and analysis 57

3.4 RESULTS 57

3.4.1 Experiment 1 57

3.4.2 Experiment 2 59

3.4.3 Experiment 3 61

3.5 DISCUSSION 61

3.6 ACKNOWLEDGEMENTS 62

3.7 REFERENCES 62

4. STUDY II: FEEDFORWARD CONNECTIONS THROUGH AREA MT DRIVE THE INFLUENCE OF MOTION IN POSITION CODING 65

4.1 ABSTRACT 69

4.2 INTRODUCTION 70

4.3 MATERIALS AND METHODS 71

4.3.1 Participants 71

4.3.2 Apparatus and behavioral acquisition 71

4.3.3 Stimulus design and procedure 72

4.3.4 Behavioral analysis 73

4.3.5 EEG acquisition and analysis 74

4.3.6 Current source density (CSD) analysis 75

4.3.7 Source localization analysis 76

4.3.8 Granger causality analysis 77

4.4 RESULTS 78

4.4.1 Behavioral results 78

4.4.2 ERP results 79

4.4.3 CSD estimates *81*
4.4.4 Source localization *84*
4.4.5 Granger causality estimates *84*

4.5 DISCUSSION 85
4.5.1 The motion-induced shift reflects a neural delay *86*
4.5.2 Motion-position interaction in MT *87*
4.5.3 Extrageniculate projections to MT *88*
4.5.4 Limitations of the study *89*

4.6 ACKNOWLEDGEMENTS 89

4.7 REFERENCES 90

5. STUDY III: PROPRIOCEPTION IMPROVES TEMPORAL ACCURACY IN A COINCIDENCE-TIMING TASK **95**

5.1 ABSTRACT 99

5.2 INTRODUCTION 99

5.3 METHODS 100
5.3.1 Subjects *100*
5.3.2 Stimuli *100*
5.3.3 Procedure *100*
5.3.4 Analysis *101*
5.3.5 Kinematics *101*
5.3.6 Statistical analysis *101*

5.4 RESULTS: EXPERIMENT 1 102
5.4.1 Systematic error *102*
5.4.2 Variable error *103*
5.4.3 Kinematics *103*

5.5 RESULTS: EXPERIMENT 2 104
5.5.1 Systematic error *104*
5.5.2 Variable error *105*

5.6 DISCUSSION 105

5.7 ACKNOWLEDGEMENTS 105

5.8 REFERENCES 105

6. STUDY IV: SHIFTED VISUAL FEEDBACK OF THE HAND AFFECTS REACHABILITY JUDGMENTS ON INTERCEPTION 109

6.1 ABSTRACT 113

6.2 INTRODUCTION 113

6.3 METHODS 114

6.3.1 Subjects 114

6.3.2 Apparatus 114

6.3.3 Stimuli 114

6.3.4 Procedure 114

6.3.5 Analysis 115

6.4 RESULTS 115

6.4.1 Reachability judgments 115

6.4.2 Hand movements 116

6.5 DISCUSSION 119

6.6 ACKNOWLEDGEMENTS 119

6.7 REFERENCES 119

7. STUDY V: WHITE MATTER INTEGRITY REGULATES THE INDUCED BREAKDOWN OF ONLINE MOTOR CONTROL 123

7.1 ABSTRACT 127

7.2 INTRODUCTION 128

7.3 MATERIALS AND METHODS 130

7.3.1 Participants 130

7.3.2 Apparatus and data acquisition 130

7.3.3 Stimuli and procedure 131

7.3.4 Experimental design 132

7.3.5 TMS protocol 133

7.3.6 Localization of stimulation sites 135

7.3.7 DTI acquisition and image processing 135

7.3.8 Behavioral analysis 136

7.3.9 Statistical analysis 138

7.3.10 DTI analysis 139

7.4 RESULTS 140

7.4.1 rTMS-induced deficits in online motor control 140

7.4.2 DTI results ...142
7.4.3 Fixed condition ...143
7.4.3 Kinematics ...144

7.5 DISCUSSION ...145

7.6 ACKNOWLEDGEMENTS ...149

7.7 SUPPLEMENTARY MATERIAL ...150
7.7.1 Supplementary figures and tables ...150
7.7.2 Supplementary video ...154

7.8 REFERENCES ...154

8. DISCUSSION 161

8.1 THE INFLUENCE OF VISUAL MOTION IN GOAL-DIRECTED REACHING ...163
8.1.1 Adaptation to visual motion affects hand movements ...163
8.1.1.1 Distortion of speed or of perceived position? ...164
8.1.1.2 Motion adaptation in static vs. moving objects ...165
8.1.2 The neural basis of motion-induced shifts in goal-directed reaching ...166
8.1.2.1 Motion processing through non-primary visual pathways ...167

8.2 COMBINING VISION AND PROPRIOCEPTION IN OBJECT'S INTERCEPTION ...170

8.3 VISUOMOTOR ADAPTATION INTERCEPTING MOVING OBJECTS ...171
8.3.1 Hand visual feedback determines reachable objects ...171
8.3.2 Hand visual feedback controls how to move to reachable objects ...173

8.4 THE ANATOMICAL BASIS OF AN ACCURATE ONLINE MOTOR CONTROL ...174
8.4.1 rTMS-induced deficits of online motor control ...174
8.4.1.1 Hemispheric specificity, saccadic deficits and kinematics ...175
8.4.2 Parietofrontal structural integrity predicts rTMS effects ...177

8.5 LIMITATIONS OF THE PRESENT DISSERTATION ...179

8.6 FUTURE DIRECTIONS ...180

9. CONCLUSIONS 183

10. SPANISH SUMMARY 189

REFERENCES 215

APPENDIX 237

PREFACE

The capacity for movement is a defining feature of animal life. As a result, one of the main functions of the brain is to direct the body's purposeful interactions with the environment. The understanding of how the brain fulfils this role is one of the great challenges in neural science. Sensory processing from visual and proprioceptive inputs generate in the brain an internal image of the external world and of the state of the body. Motor processing begins with an internal representation: the desired purpose of the movement. Crucially, however, this internal representation needs to be continuously updated by internal and external sensory information as the movement unfolds. The control of visually-guided movements has been a topic of tremendous interest in the neuroscience literature. Much of this work has followed from years of behavioral research aimed at investigating the processes underlying the relationship between movement speed and accuracy. Technical advancements in neuroimaging tools have led to a much better understanding of the neural foundation for goal-directed action. Neuroscientists and psychologists have taken their lead from movement scientists and have started to use 3D movement analysis techniques to try to understand the complex interactions between movement planning processes and the rapid online adjustments of goal-directed actions through the use of vision and other sources of feedback. It has become clear that the human visuomotor system is very flexible, and that it adapts fastly to the constraints and requirements of the action to execute an appropriate response.

In the present dissertation, my primary goal was to provide a comprehensive account of how the brain uses spatial and temporal information from visual and proprioceptive sensory inputs to accomplish accurate and voluntary visually-guided actions. Chapter 1 reviews the current state of affairs in vision and goal-directed movements. Chapter 2 traces the main objectives of this dissertation and the tested hypothesis in each study. In Chapter 3, I present a psychophysical study that examined the influence of illusory percepts caused by motion adaptation in the hand trajectory of a reach. Chapter 4 builds on Chapter 3 by identifying the neural mechanisms that subserve the effects of visual motion in the pattern of reaching paths. The next two chapters addressed the integration of visual and proprioceptive information during conflicting situations in object's interception. The study of Chapter 5 aimed to investigate the contribution of proprioceptive signals under empoverished visual conditions when intercepting a moving object. In Chapter 6, we introduce a study that showed how our proprioceptive inputs fully adjusted to a distorted visual information of the hand, and the effects it had on the judgment of the reaching boundary to intercept objects. Finally, Chapter 7 describes a multimodal neuroimaging study to explore the source of inter-individual differences after induced deficits in the online control of reaching.

Throughout this thesis, I document the central principle that the visuomotor system is not an unthinking passive cortical circuit controlled by more sophisticated parts of the brain. Instead, it is intimately involved in the many interrelated neural processes required to choose a plan of action and its execution.

1

INTRODUCTION

> “*Why do we have a brain? We have a brain for one reason and one reason only — that’s to produce adaptable and complex movements. Movement is the only way we have to affect the world around us*”
> Daniel M. Wolpert, Francis Crick Lecture (2004)

Imagine you want to turn a light off. First, you will need to visually localize the switch. To estimate the position of the switch, your visual system has to integrate different sources of sensory information, such as the object’s retinal location, the gaze direction relative to the head and, if you are moving, the background motion signals present in the scene. You will thus need to explicitly distinguish background motion from information about the object’s position. Whether the brain uses or ignores motion signals when localizing an object, and how they affect the actions directed to this object has been central to research in neuroscience, and several issues are still a matter of debate.

Secondly, you have to know where your hand is. People who cannot see the configuration of their arm or their hand location with either proprioceptive or visual signals cannot make accurate movements. Although vision usually predominates as the main source of sensory information to determine hand location, you will need access to the proprioceptive estimate, defined from limb’s joint angles. Whether the brain optimally weights and combines the ‘seen’ and the ‘felt’ position of the hand in order to achieve high spatial and temporal accuracy in reaching movements is still unresolved.

Finally, you will guide your hand to the switch. During the execution of the movement, your brain might compute continuously the difference between the position of the hand and the position of the target. Environmental unexpected changes such as displacements of the target or of your body may perturb this computation. In such situations, your visuomotor system has the ability to monitor the execution of the movement and perform a final voluntary correction to avoid an inaccurate response. However, it is not clear which are the neural foundations within the visuomotor system for the inter-individual differences in the ability to adjust an ongoing movement.

The apparent simplicity of these steps belies the abundant collection of neural processes that are involved in this action, including several hierarchical levels of the visual and the motor system (**Figure 1.1**). The present dissertation will try to shed some light on the abovementioned issues, by exposing the deep challenge the brain must tackle when integrating temporal and spatial information to achieve visuomotor goals.

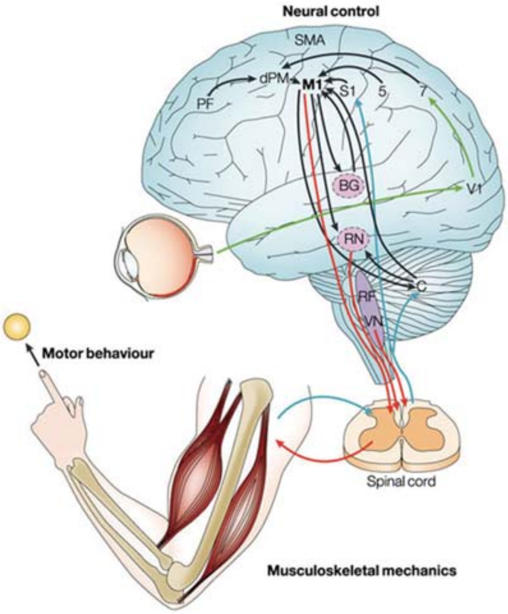


Figure 1.1. The diagram illustrates some of the key regions that are involved in goal-directed reaching movements. The central nervous system (CNS) has a hierarchical organization with three levels — the cortex, brainstem and spinal cord. The spinal cord is the lowest level, the final common pathway for all motor output, and integrates sensory feedback from the skin, muscle and joints with descending commands from higher centres. At the second level, brainstem regions enhance the spinal repertoire by improving postural control. The cortex is the highest level, and supports a large and adaptable visual and motor repertoire. The retina detects an object in the space, and the visual input travels through the thalamus to the primary visual cortex (V1). From V1, a dorsal stream projects to the parietal lobe, where takes place a series of sensorimotor transformations required to reach the object, from the retinal representations to specific spatial descriptions. Motor planning and visual feedback are provided through several parietal and premotor regions. The primary motor cortex (M1) neurons project to the corticospinal tract (CST) and receive input from other cortical regions that are predominantly involved in motor planning. The basal ganglia (BG) and cerebellum (C) are crucial for motor function through their connections with M1. *S1*, primary somatosensory cortex; *RF*, reticular formation; *VN*, vestibular nuclei; *RN*, red nucleus; *7*, Brodmann area 7; *dPM*, dorsal premotor cortex; *SMA*, supplementary motor area; *PF*, prefrontal cortex. [Extracted from Scott (2004)].

1.1 Visual coding of object location

To act upon an object one must perceive it. Among all the tasks that vision has to perform, it would seem that locating something should be one of the easiest. Last decades of modern neuroscience have become decisive to depict and understand the organizing principles of the visual system associated with position coding. As a result of these findings, we know that a network of interconnected cortical and subcortical structures mediates the visual coding of the location of a stimulus. In this section, I will outline a brief overview of the basic neural aspects underlying object localization. Subsequently, I will describe how our visual system integrates different sources of sensory information to judge the relative position of stationary and moving objects.

1.1.1 LOW-LEVEL VISUAL PROCESSING OF OBJECT POSITION

In a strict sense, vision consists in the coding of different patterns of light to neural impulses that finally result in a model of the world. The first stage to build the visual percept takes place in the retina, and starts what is known as low-level visual processing. This first neuronal computation includes the extraction of certain spatial and temporal features of the visual input, such as contrast, color or even motion (DeYoe & Van Essen, 1988; Wade & Wandell, 2002). For example, the firing rate of some retinal neurons is stronger when perceiving a moving object and lower with stimulus that have constant spatio-temporal features (Berry, Brivanlou, Jordan & Meister, 1999; Rodieck, 1965; Schwartz, Taylor, Fisher, Harris & Berry, 2007). This finding indicates that the extrapolation of the position of an object might begin early in the retina. In humans, the spatio-temporal selectivity of retinal processing has been proved using *grating stimuli*, contrast-defined patterns in which the intensity varies about the mean as a sinusoidal function of either space or time (**Figure 1.2**). Gratings at different spatial frequencies produced perceptual effects on the contrast sensitivity of retinal neurons (De Valois, Morgan & Snodderly, 1974). Similarly, constrast sensitivity of retinal ganglion cells was also affected when the intensity of the grating stimuli varied sinusoidally in time (Lee, Pokorny, Smith, Martin & Valberg, 1990). Hence, the neural image of the object that the eye transmits to the brain has already processed a substantial part of the spatio-temporal features present in the visual input.

It is likely that subsequent stages of the visual system continue this process, possibly by using similar mechanisms. For example, some of the hypothesis that tested this early differential responsivity proposed that specific retinal projections, the magnocellular pathway, were specially involved in transmitting information rapidly about the spatial location and the inherent motion of an object (Schiller, 1986). Retinal projections to the primary visual cortex (V1) diverge first to different subcortical visual centers in parallel,

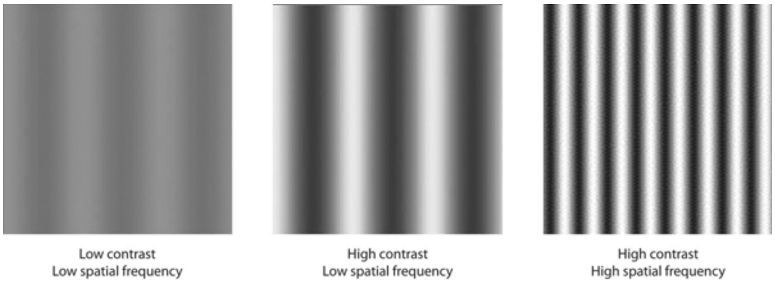


Figure 1.2. Sinusoid gratings used in psychophysical studies with human subjects and monkeys. These stimuli are employed in experiments testing spatial contrast sensitivity. [Extracted from De Valois et al. (1974)].

including —among others— the lateral geniculate nucleus (LGN), the superior colliculus (SC) and the pulvinar [see (Kaas & Huerta, 1988) for review] (**Figure 1.3A**). Of particular interest for the processing-time of location coding are the projections that, bypassing V1, terminate directly in extrastriate visual cortical regions (Leopold, 2012). In an influential article, Schneider (1969) postulated an anatomical separation between the visual coding of the location of a stimulus and the identification of that stimulus. He attributed the coding of the location to the extrageniculate pathway. However, the notion of 'localization' failed to distinguish between the many different patterns of behavior that vary with the spatial location of visual stimuli. Nevertheless, even though Schneider's original proposal is no longer generally accepted, it seems likely that extrageniculate visual inputs must be implicated in mediating fast acquisition of spatial and temporal properties necessary to localize a stationary or moving object in the space.

1.1.1.1 Position coding through non-primary visual inputs

The role of the SC and the pulvinar in vision is still not fully understood. In contrast with the LGN, which acts as a first-order relay of retinal signals to V1 (Guillery & Sherman, 2002), the widespread bidirectional connectivity of these two visual centers with nearly all visual areas indicates that they are not simply passive relays (Casanova, 2004). Whether and to what degree the human SC and pulvinar carry information about object position was recently addressed using neuroimaging tools. Fischer and Whitney (2009) demonstrated the existence of an accurate topographic encoding of visual stimuli in the human pulvinar, although less precise than that in early visual cortical areas. Similarly, the induced inhibition of the visual cortex unveiled a role of the SC in the discrimination of the spatial positions in foveally presented visual stimuli (Ro, Shelton, Lee & Chang, 2004). Notably, the strong input that extrastriate areas of the visual cortex receive from SC and pulvinar points to a prominent contribution of extrageniculate vision into the perceptual processes of visually-guided behaviors.

In this context, extrastriate areas interconnected with SC and pulvinar show response latencies that are almost as short as in V1, suggesting that they do not depend exclusively on V1 for visual input (Maunsell, 1987; Nowak & Bullier, 1997). In particular, when V1 is inactivated, certain dorsal extrastriate regions, as the middle temporal (MT) area, are capable of responding to visual information (Payne, Lomber, Villa & Bullier, 1996). MT is a motion selective area located in the junction of occipital, parietal and temporal lobes that responds to the direction and speed of moving stimuli (Snowden, Treue & Andersen, 1992; Watson et al., 1993). A standard view is

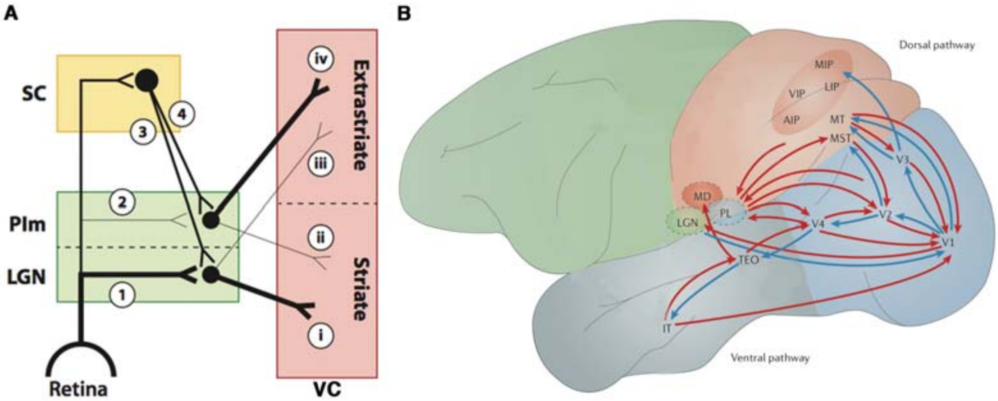


Figure 1.3. A. Schematic illustration of visual pathways to the cortex. There are two direct pathways from the retina to the dorsal thalamus, a retinogeniculate pathway (1) and a retinopulvinar pathway (2), as well as two indirect pathways that pass through the midbrain, the retinocolliculogeniculate pathway (3) and the retinocolliculopulvinar pathway (4). Both the LGN and the inferior pulvinar project to both V1 and the extrastriate visual cortex (i–iv), with the LGN projecting predominantly to V1 (i) and the inferior pulvinar projecting predominantly to the extrastriate cortex (iv). **B.** Feedback (red) and feedforward (blue) visual pathways. The visual cortical pathways begin in V1, which receives subcortical input from the LGN. The feedforward connections extend through a ventral pathway into the temporal lobe and through a dorsal pathway into the parietal cortex. Matching these feedforward connections are a series of reciprocal feedback circuits, which provide descending top-down influences that mediate re-entrant processing. Feedback is seen in direct corticocortical connections (those directed towards area V1), in projections from area V1 to the LGN and in interactions between cortical areas mediated by the pulvinar (PL). *PIm*, medial division of the inferior pulvinar; *VC*, visual cortex; *AIP*, anterior intraparietal area; *IT*, inferior temporal area; *LIP*, lateral intraparietal area; *MIP*, medial intraparietal area; *MST*, medial superior temporal area; *MT*, medial temporal area; *TEO*, tectum opticum; *MD*, medial dorsal nucleus of the thalamus. [Extracted and modified from Gilbert and Li (2013); Leopold (2012); Solomon and Lennie (2007)].

that V1 provides the "most important" input to MT (Felleman & Van Essen, 1991; Ungerleider & Desimone, 1986). Nonetheless, seminal neuroanatomical studies have revealed that MT inputs also include the LGN (Sincich, Park, Wohlgemuth & Horton, 2004), the SC and the inferior pulvinar (Standage & Benevento, 1983). The evidence for sensitivity to object position and movement in 'cortically-blind' patients is also well documented [for example, (Blythe, Bromley, Kennard & Ruddock, 1986; Blythe, Kennard & Ruddock, 1987; Bridgeman & Staggs, 1982)]. In fact, both motion perception (Barbur, Watson, Frackowiak & Zeki, 1993) and accurate pointing (Perenin & Jeannerod, 1975) persisted in patients with V1 lesions. Given the sheer number of projections to MT from each input, it appears that extrastriate-projecting neurons receive a direct retinal input and send it to the extrastriate cortex, establishing a putative pathway to relay motion-position information to MT rapidly. This view is supported by the abolishment of motion perception after ablation of SC and LGN in V1-lesioned patients (Maunsell, Nealey & DePriest, 1990; Rodman, Gross & Albright, 1990; Schmid et al., 2010). However, there is still much controversy over the exact form of the spatio-temporal computations carried out by this considerably direct circuit to MT. All in all, the precise functional role of the extrageniculate inputs in the visual coding of the position of objects remains to be elucidated.

In addition to the extrageniculate contribution to object localization, the Schneider's study also highlighted the distinction between object identification and spatial localization (between 'what' and 'where'), which has persisted in visual neuroscience.

1.1.1.2 The dorsal visual stream: action-relevant information of object position

Emanating from V1, Mishkin and Ungerleider (1982) distinguished two diverging feedforward visual streams to the extrastriate visual cortex: an occipitoparietal pathway or 'dorsal' stream, that progresses to the posterior parietal cortex (PPC); and an occipitotemporal pathway or 'ventral' stream, which projects to the inferior-temporal cortex (ITC) (**Figure 1.3B**). Based on the behavioral consequences after lesioning both tracts in monkeys, Mishkin and Ungerleider also proposed a functional segregation of these two pathways: whereas the dorsal stream is a key structure to locate the objects in the space and interact with them, the ventral stream carries visual information about features such as colour, shape or orientation of the object (Gross, Rocha-Miranda & Bender, 1972). However, more recent studies (Goodale & Milner, 1992; Milner &

Goodale, 1993) reinterpreted this distinction by focusing on the required transformations for the output purposes (vision for perception vs. vision for action) instead of the stimulus attributes. As a result, the dorsal stream would mediate the spatial perception and the organization of visually-guided actions towards an object (‘how’ to reach). The ventral stream, though, will be paramount for the formation of the cognitive and perceptual representations that embody the enduring characteristics of the object (‘what’ to reach).

Superimposed on the feedforward sweep, there are re-entrant or feedback pathways that convey higher-order information to antecedent cortical areas. Concretely, V1 receives feedback inputs from all extrastriate areas (Salin & Bullier, 1995). The organization of cortical visual processing thus consists on a feedforward sweep mostly paralleled by feedback connections going in the reverse direction (Felleman & Van Essen, 1991; Lamme & Roelfsema, 2000). For every feedforward connection, there is a reciprocal feedback connection conveying a rich amount of information to the areas from which it receives input. It facilitates the interpretation of the visual scene and that enables the visual system to build a stable representation of the object position (Gilbert & Li, 2013). Integrating information into a percept is a process that is largely under the control of these interactions. In the case of object localization, these circuits drive information to early visual areas that comes from differents sources of sensory inputs. These sources include the retinal location of the object (Bock, 1986), the position and movement of the eye (Deubel, Schneider & Bridgeman, 1996; Ross, Morrone & Burr, 1997), the nearby motion signals (De Valois & De Valois, 1991; Fröhlich, 1929; Matin, Boff & Pola, 1976) and vestibular or proprioceptive inputs (Schlag, Cai, Dorfman, Mohempour & Schlag-Rey, 2000). Our visual system integrates these sources of sensory information to judge the relative position of objects in the visual field. However, many psychophysical experiments tell us that visual localization is not that simple, and that systematic errors occur when the visual system assigns a position to a visual stimulus. It is unclear, however, whether these errors are mediated by feedforward or feedback processes, since very few studies have been performed to validate this directly. A challenge for future research will be to disentangle the relative contributions of these systems. Next, I will discuss how the visual system localize stationary and moving objects dealing with the spatio-temporal features of the diverse sensory inputs, and the underlying neural mechanism subserving these processes.

1.1.2 LOCALIZING STATIONARY OBJECTS: A MATTER OF SPACE

The ability to determine the spatial location of a static object allows observers to successfully engage in visually guided behaviors such as reaching and grasping. To localize a seen object, the visual system has to integrate the object's retinal location with the direction of the gaze (Helmholtz, 1925) (**Figure 1.4**). The process of localization, while efficient and usually accurate, involves, however, an accumulation of signals over space and time, in part because of noise in neural processing (Barlow, 1958). In particular, one of those signals is visual motion. In the next subsection, I will focus on the influence of motion signals in the position coding of stationary objects.

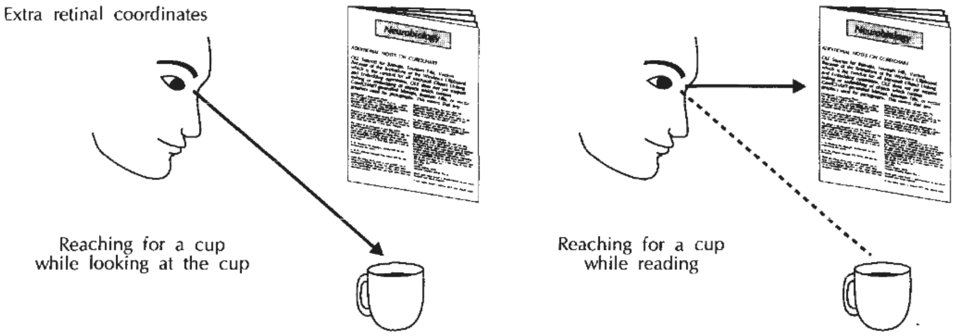


Figure 1.4. A. Extraretinal coordinates refer to the encoding of visual stimuli in higher level coordinate frames than simple retinal coordinates. In the left sketch, the person is fixating the cup, whereas on the right she/he is fixating the newspaper and the cup is imaged on a peripheral part of the retina. In both cases the subject is able to localize the cup with a reaching movement. As different parts of the retina are stimulated in the two conditions, information about eye position must also be available to accurately determine that the cup was at the same location in space. [Extracted and modified from Andersen, Snyder, Li, and Stricanne (1993)].

1.1.2.1 Visual motion and the perceived position of stationary objects

During last decades, a number of studies have demonstrated that motion in particular is an important source of information for the visual system. Visual motion is constantly produced as we move our eyes and head and as objects move in the world. During an eye movement, a stationary object's image moves across the retina. The visual system, therefore, faces a serious challenge in that it must register and discriminate target as well as background motion, and segment these different sources of motion in order to estimate the position of objects appropriately. The understanding of how the visual system processes motion information is thus crucial to ascertain the neural mechanisms underlying object localization and whether the assignment of an object's location is independent of its motion.

A considerable body of recent literature indicates that one is able to localize visual objects with great accuracy without regard to the specific characteristics of the object (Burbeck, 1988; Toet, van Eekhout, Simons & Koenderink, 1987). One of the most familiar tasks in which we judge the relative position of objects is known as Vernier acuity—named after Pierre Vernier. The smallest misalignment that we can reliably discern among two segments or gratings is known as our Vernier acuity. De Valois and De Valois (1991) showed that the movement within a grating leads to large misalignments (**Figure 1.5A**): If the stationary grating is drifting to the right, the whole patch appears to be displaced rightwards, and viceversa (Ramachandran & Anstis, 1990).

Similarly, after prolonged viewing of the same direction of motion (adaptation), a static pattern presented at the same location (test) is seen to move in the opposite direction (**Figure 1.5B**). This striking phenomenon, probably the best known in the study of visual illusions, is called the motion after-effect (MAE), and has attracted the attention of many studies that can be even traced back up to Aristotle (Anstis, Verstraten & Mather, 1998). MAE was described again by Addams (Addams, 1834), becoming also known as the waterfall illusion. Posteriorly, a landmark article on the MAE reported long-term storage of the after-effect (Wohlgemuth, 1911). It has been believed that the MAE is not accompanied by concomitant changes in position and spatial pattern. However, more recent studies have demonstrated that MAE can cause a stationary pattern to appear shifted in position in the direction of the after-effect (McGraw, Whitaker, Skillen & Chung, 2002; Nishida & Johnston, 1999; Snowden, 1998). The illusory motion of the MAE might therefore contribute to the coding of the location of the test pattern. However, motion and position of the object are still thought to be coded by distinct mechanisms, as the time-course of the perceived MAE and the position shift are slightly different (Nishida & Johnston, 1999). MAE illusion is consistent with the motion-induced misalignment in Vernier acuity abovementioned, as neither phenomenon requires a time marker or temporal reference. Since the stimulus test is stationary, there is no actual change in the position of the object, so no temporal mechanism could explain how the stimulus appears shifted in position.

The physiological substrate of aftereffects is still far from clear. The fatigue explanation was bolstered by physiological measures in the rabbit retina (Barlow & Hill, 1963). The

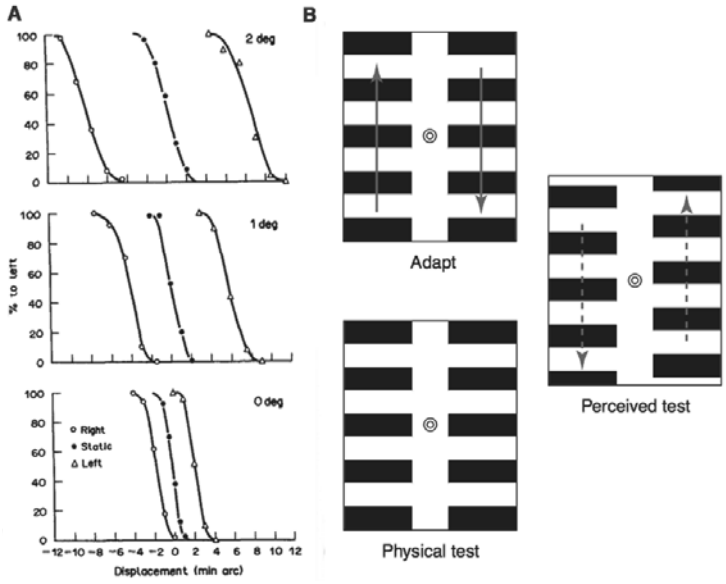


Figure 1.5. A. Psychometric functions for leftward-, rightward-drifting, and static patterns at three different eccentricities (0, 1, 2 deg), from bottom to top, respectively. The positional bias is reflected in the fact that a stationary Gabor with a rightward-moving grating appears to be shifted to the right and thus has to be positioned to the left to appear aligned with the comparison patterns. The movement-related bias increased with eccentricity. **B.** The motion after-effect, following motion adaptation, can be accompanied by a concurrent shift in the perceived position of the test pattern. [Extracted and modified from De Valois and De Valois (1991); Whitney (2002)].

authors explained the MAE in terms of the discharge decreasing of directionally selective neurons if a stimulus is continuously moved through the receptive field (RF) in the preferred direction; after the stimulation stops, the baseline firing rate remains suppressed for a short while. However, despite this early physiological support, it now seems clear that the fatigue of neuronal populations falls short as an explanation for after-effects. Culham et al. (1999), using functional imaging, revealed that area MT is not active during storage of the MAE, but reactivates after the presentation of a static test pattern. Given that both the spatial shift and the MAE increase did not occur over the storage phase, activity in MT and V1 would be a necessary condition for the spatial shift. Nishida and Johnston (1999) proposed that the MAE-induced spatial shift might reflect recurrent inputs from MT to V1. Subsequent neurophysiological studies showed that the shift was remarkably reduced after disrupting activity in area MT, but not after disrupting that in V1. These evidences strongly suggest that the spatial shift is a consequence of feedback connections from MT to V1.

In the motion-induced misalignment and MAE illusions described above, motion signals (whether due to physical motion or adaptation) in a local region of space were shown to influence the apparent position of an object in that same region. However, can the motion of one object affect the apparent position of a different object? Theoretically, the visual system could easily extract and link information about a particular object's motion and its location, and this could determine whether the object is displaced. It is known that when a stationary object is flashed near another moving stimulus, the flashed object appears displaced in the direction of the nearby motion (Durant & Johnston, 2004); this occurs even when the moving and flashed objects are separated by a substantial distance (Whitney & Cavanagh, 2000) (**Figure 1.6**). Note that in this case, as with previous mentioned displacements, the shift in the stationary object's position could not be due to a temporal mechanism.

Thus, it is well established that the representation of position, even in early visual cortical areas such as V1, depends on motion signals that are present in the scene (Whitney, Goltz, et al., 2003). Evidently, the perceived motion and location of any particular (even stationary) object is influenced by the predominant motion signals throughout large regions of visual space. These misalignments could certainly reflect a basic mechanism that underlies or contributes to many of the motion-based position displacement phenomena mentioned earlier. The issue, then, is whether the configuration of motion in the visual field influences the localization of not only stationary but also moving stimuli. Further, if the MT-V1 feedback connections underlying the motion-induced spatial shift applies to moving objects as well as to stationary ones, then it might shift the perceived position of moving stimuli by an even greater amount than the flashed stimuli.

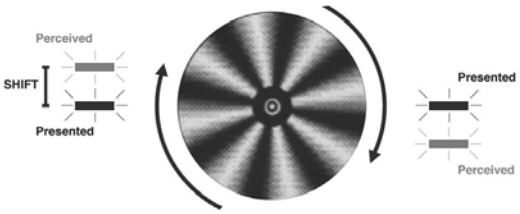


Figure 1.6. An illusory misalignment between two physically aligned flashes occurred when they were presented on either side of a rotating radial grating. The apparent misalignment was consistent with the direction of motion and occurred even when the flashed lines were distantly separated from the rotating grating. [Extracted from Whitney and Cavanagh (2000)].

1.1.3 LOCALIZING MOVING OBJECTS: A MATTER OF SPACE AND TIME

It takes on the order of 50-100 ms for striate neurons to respond to a visual stimulus (Schmolesky et al., 1998). There are non-trivial transmission delays of neural signals between the photoreceptors and the cortical areas devoted to analyze those signals. What we see, then, is not the world as is it now but as it was in the near past. In the case of a stationary object, this latency is unimportant, but one immediate consequence of these delays is that moving objects should appear significantly behind in their motion trajectory. The visual system must therefore take into account an object's motion when assigning its position. To catch a ball, for instance, one must intercept it at its true position at time t, even though at time t our visual system might be processing an image that occurred at time (t – 100) ms. Do we perceive the position of a moving object with a delay because of neuronal latencies? Or is there a brain mechanism that compensates for latencies such that we perceive the true position of a moving object in real time? The prevalent view is that the observed behavioral success is due to compensation at the higher motor cortical levels (Jordan & Wolpert, 1995). However, the motion-induced positional misalignments previously reported are in the correct direction to counteract the visual latency (De Valois & De Valois, 1991; Ramachandran & Anstis, 1990), which suggest that neural delays may also be compensated at sensory levels. This question has been intensely debated in the context of the visual illusions, specially the flash-lag effect (FLE).

Fröhlich (1923) was the first to report that, when a moving object appears abruptly from behind a static aperture, the object's initial position seems to be shifted forwards in the direction of motion. One of the earliest plausible explanations was that the Fröhlich effect is the result of differential perceptual delays for different parts of the moving object's trajectory (Metzger, 1932). Despite the lack of consensus about the mechanism responsible for the Fröhlich effect, the common theme among most models is that the timing of perception is important; the latency with which the initial position of the moving object is perceived determines where the object appears to be (Whitney, 2002). Several phenomena related to the Fröhlich effect were subsequently described (Mackay, 1958; Mateeff & Hohnsbein, 1988), until Romi Nijhawan reported a mislocalization effect which termed as the flash-lag effect (Nijhawan, 1994): When a flashed stimulus is presented physically aligned with a continuously moving object, the moving object seems to lead the flash [for review see (Krekelberg & Lappe, 2001)]. There has been much debate over whether this is an effect of motion on perceived position or a relative delay of flashed compared to moving objects.

Two important questions regarding object localization remain however. Does motion-aftereffects extend their influence to actions directed to the mislocalized objects? And which would be the nature of motion's influence in these actions depending on whether the object is moving or not? I will address these two issues in chapter 3 of the present dissertation.

1.2 Spatial coding when reaching an object

While all visually-guided actions take place in space, the spatial coding required will vary according to the action performed. In other words, there is no single representation of space like the retinotopic map in V1, but instead multiple effector-specific coordinate systems (Rizzolatti, Riggio & Sheliga, 1994). Evidence collected in recent years clearly support the view that there are many spatial maps, whose properties are tuned to the motor requirements. An example is *peripersonal* space, the space within our reach, which is encoded in areas different from those that represent *extrapersonal* space (Caggiano, Fogassi, Rizzolatti, Thier & Casile, 2009).

Reaching out and turning a light off, for example, is a complex act that demands sensorimotor transformations of different end-effectors such as the fingers, hands, upper limbs, torso, head and eyes. These sensorimotor transformations occur in the parietal lobe, the principal target of the dorsal visual stream. The dorsal stream projects from V1 through V2, V3 and the middle temporal area (MT) to posterior parietal regions. The most fine-grained parcellation of the posterior parietal cortex (PPC) in monkeys revealed several areas in the intraparietal sulcus (IPS), such as the lateral (LIP), ventral (VIP), medial (MIP) and anterior (AIP) portions, plus more posterior regions (Lewis & Van Essen, 2000). One of the most striking characteristics of many neurons in PPC was that they did not response exclusively to visual stimulation (Mountcastle, Lynch, Georgopoulos, Sakata & Acuna, 1975), but showed both sensory-related and motor-related activity (Andersen, 1987) (**Figure 1.7**). In agreement with this view, evidence

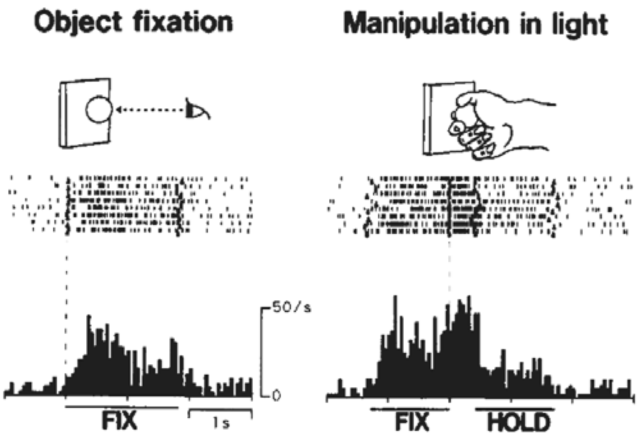


Figure 1.7. Example of object-type visuomotor neurons under manipulation and object fixation in the light. Raster and histograms were aligned with the moment at which the monkey released a key in the manipulation task and when the monkey pressed a key in the object-fixation task. The line below the histogram shows the mean duration of the "fixation" period (FIX) and "hold" period (HOLD). [Extracted from Murata, Gallese, Luppino, Kaseda, and Sakata (2000)].

collected during the last 20 years supports the idea that the coding of visuospatial information was computed in the PPC only when such spatial cues were required for acting on an object (Goodale & Milner, 1992). Since different groups of parietal neurons discharged during eye, arm or hand movements [for reviews, see (Andersen & Buneo, 2002; Lynch, 1980)], the transformation of the retinal representations into specific spatial descriptions varied depending on the body part controlled and its own motor requirements. This modular arrangement constitutes a functional distribution that transforms information from visually-based to motor-based coordinates (Stein, 1992). Many LIP neurons, for example, fire during the execution of a visually elicited saccade (Colby, Duhamel & Goldberg, 1996). The AIP has neurons that signal the size and orientation of objects that can be grasped (Taira, Mine, Georgopoulos, Murata & Sakata, 1990). Similarly, the MIP codes visuospatial information of targets prior and during the execution of reaching movements (Galletti, Fattori, Kutz & Battaglini, 1997).

Rapid aiming movements depend critically on spatial information obtained from the eyes. In fact, if eye or head movements are not allowed, reaching to eccentric targets is very inaccurate (Prablanc, Echallier, Komilis & Jeannerod, 1979). This introduces the question of the visual guidance of reaching. There are at least three aspects of this problem: (1) visual localization of the target in extrapersonal space and suitable coding of that information for use by the arm motor system; (2) visual localization of the hand before and during its movement through space; and (3) coordination of eye and hand responses to bring the hand to the object. The coding of absolute target position in space for action is a large subject that has been usually treated in the context of perception rather than movement. In the next section, I will introduce the sensorimotor computations that transform the retinal image of the target and the relevant sources of visual information that can affect this transformation.

1.2.1 COMPUTING TARGET LOCATION FOR ACTION

The only transducer that can detect a visual target is the retina, and it can relay the location of the target only in its own coordinate system. However, the retina sits on a rather complicated set of moving structures: Eyes rotate within the orbit, the head rotates on the shoulders, and the body can both rotate and translate. Therefore, the retinal location of the target does not provide our CNS with enough information to compute the target position in any coordinate frame other than that of the retina (Shadmehr, 2005). Because the PPC combines information from various sensory modalities, early studies on PPC proposed that its neurons transform the target location from retinotopic to body-centered coordinates.

In previous sections, we have confirmed that one of the main sources of visual information that influences object localization are the visual motion signals. It seems interesting to examine whether the computation of target location when we intend to reach the target will also be affected by the encoding of motion cues. The neural mechanisms previously hypothesized to subserve motion-position interactions predict that the retinal location of the target will be affected by the motion signals well before it reaches the PPC.

1.2.1.1 The influence of visual motion in coding target's position for action

We are constantly exposed to situations in which an object and the background move together, or even a target that remains stationary while the background moves. In both instances, there is background retinal motion that our visuomotor system has to separate from information about the position of the target in order to reach for the object accurately. During the last 20 years, several independent studies have found that, when reaching for a stationary object, nearby visual motion even when irrelevant to the object or task can shift the trajectory of the hand in the direction of motion (Brenner & Smeets, 1997; Mohrmann-Lendla & Fleischer, 1991; Proteau & Masson, 1997; Saijo, Murakami, Nishida & Gomi, 2005; Whitney, Westwood & Goodale, 2003; Yamagishi, Anderson & Ashida, 2001) (**Figure 1.8A-B**). Several singular features arise from this effect. First, even when the target is stationary and there are not latency issues, the retinal motion affects the reach. Secondly, the object can be remotely displayed with respect to the background motion, and the effect still takes place (Saijo et al., 2005; Whitney, Westwood, et al., 2003). Thirdly, the time that the reaching movement needs to be affected by the background motion is around 120-150 ms (Brenner & Smeets, 1997; Prablanc & Martin, 1992) (**Figure 1.8C**). Last but not least, perceptual processes coding target location were dissociated from the hand's trajectory, suggesting that the visuomotor system makes use of the visual motion signals to control the reach (Yamagishi et al., 2001) (**Figure 1.8D**).

To this day, there is not a general consensus about the underlying cause of the influence of visual motion on the hand's path and endpoint of visually-guided reaching. Is our movement biased because we perceive the target shifted? Or is the visual motion deviating directly our hand's trajectory? The distinction between *direct* or *indirect* influences of visual motion on visuomotor control has led to two possible explanations: An indirect influence in which background motion deviates the perceived object position (Whitney, Westwood, et al., 2003), and it is this shifted position coding which serves to guide the hand (Brenner & Smeets, 1997). Alternatively, a direct influence has been proposed where the visuomotor system could, independent of any target representation, encode and use visual motion to guide the hand (Gomi, Abekawa & Nishida, 2006; Saijo et al., 2005). Evidence supporting the indirect mechanism comes from several abovementioned studies that revealed the influence of visual motion in estimating the perceived location of both moving and stationary objects (De Valois & De Valois, 1991; McGraw et al., 2002; Nishida & Johnston, 1999; Ramachandran & Anstis, 1990; Whitney & Cavanagh, 2000). One possibility is that the hand's reach may simply be affected by the visual illusion and follow the perceived shift in target location. Although the directionality of the effect was comparable for perceptual and action-directed judgments (**Figure 1.8D**), (Yamagishi et al., 2001) found that the magnitudes differed. Kerzel and Gegenfurtner (2003) observed however similar values of the strength of the effect. The study of the time-course of the motion's influence on both perceptual and visumotor behavior provided different time scales for each system (Whitney, Westwood, et al., 2003). The authors found that when the target was presented just before a motion reversal, the hand initially deviated in the direction of the previous visual motion and then abruptly reversed its shift direction. When the perceived shift in the target position was measured, they observed that the moment at which a perceptual decision is reached lags behind the latency of motion's influence on reaching. Therefore, the visuomotor system may not depend upon a later perceptual awareness of target location, but modifies the hand's path online probably using representations of target position (Whitney, Murakami & Gomi, 2010) that do not necessarily reach awareness.

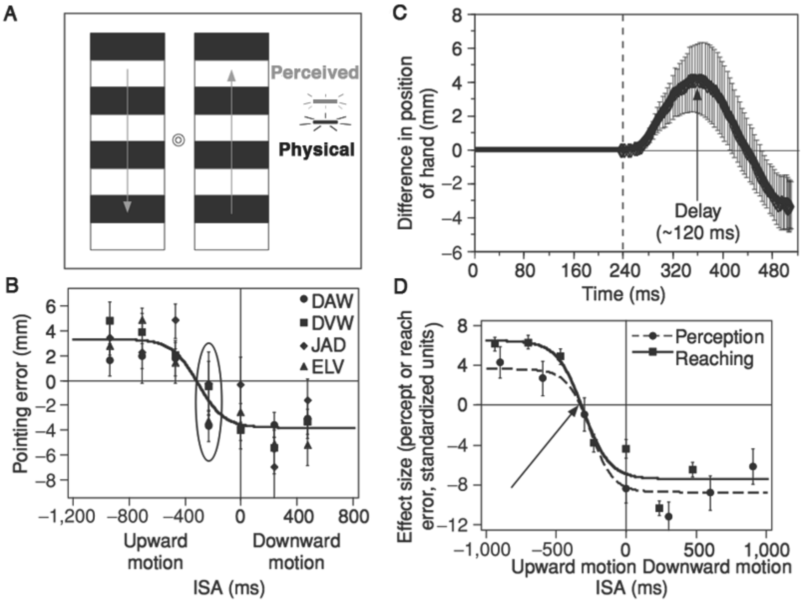


Figure 1.8. A. A static target was briefly flashed near a drifting grating. The nearby grating initially moved in one direction and then abruptly reversed direction. Subjects reached and hit the target with their index finger. **B.** Mean hand endpoints of reaching movements. The abscissa shows the interstimulus asynchrony (ISA) between the target presentation and the motion reversal. Data are presented in a manner such that initially the grating drifted upward and then reversed direction and drifted downward. Targets presented well before (after) the motion reversal produced systematic upward (downward) errors in the endpoint of the reach, always in the direction of the nearest moving grating. **C.** Difference in the trajectory of the hand as a function of the direction of visual motion. At an ISA of ~240 ms (**C**), the net effect of visual motion shows that the hand initially deviates upward, and then deviates back downward. The visuomotor delay was about 120 ms (arrow). **D**. Temporal dynamics of visual motion's influence on perceived position (dashed line, circles) and its influence on reaching (solid line, squares). Both the perceived position of the target and the endpoint position of the hand follow a similar time-course. [Extracted and modified from Whitney, Westwood, et al. (2003)].

Evidence of a direct influence of visual motion on the hand relies on the ability of the visuomotor system to access straight to visual motion, affecting the reaching independent of the position coding (Saijo et al., 2005). This hypothesis, termed as the manual following response (MFR), has been inspired in the ocular following response observed when eye position is affected by background retinal motion (Kawano & Miles, 1986). MFR is different from other reported visual illusions on action. When tracking a moving target with the hand, background motion affects the gain of the manual pursuit but in a direction opposite that of MFR (Masson, Proteau & Mestre, 1995; Soechting, Engel & Flanders, 2001). Directionality of MFR is also opposite to pointing error induced by gaze shifts (Henriques, Klier, Smith, Lowy & Crawford, 1998). These observations diminish the possibility that eye-hand coupling is in charge of MFR.

All together, the previous results point to a tight link between the processing of visual motion and motor control. To elucidate the potentially diverse functional mechanisms that allow for this visuomotor behavior, it is important to combine observations from both psychophysical and physiological techniques. The next subsection will discuss the possible neural basis of the motion's effect on reaching.

1.2.1.2 Neural mechanisms underlying motion's influence on action

Neurons in MT appear to play a role in visual motion perception. Neurophysiological studies examining neural activity in the visual cortex while tracking a moving target with the eyes revealed that many dorsal-stream neurons, most notably within the area MT, are tuned for the velocity and direction of the stimulus (Maunsell & Newsome, 1987; Maunsell & Van Essen, 1983). But, as well as providing information about the motion of individual objects in relation to the observer, it is likely that many directionally selective neurons participate in a direct visual monitoring of the reach.

There are several neurophysiologically plausible mechanisms that could serve to shift both the perceived representation of objects and the hand's trajectory in the direction of visual motion. The influence of visual motion in position coding has been explained with feedback connections from motion-related brain areas (MT) to retinotopic position coding in V1 (De Valois & De Valois, 1991; Nishida & Johnston, 1999). Notably, signals in V1 highly depend on feedback from area MT. Neurophysiological recordings in the area V1 of monkeys (Sundberg, Fallah & Reynolds, 2006) and cats (Fu, Shen, Gao & Dan, 2004) showed that the spatial RF properties of neurons can change and shift in response to moving stimuli. This suggests that feedback from MT may act on V1 neurons at the same time or even before information from the LGN reaches these cells. Other animal studies demonstrated that, even at the retina level, receptive fields shift toward a moving stimulus (Berry et al., 1999; Schwartz et al., 2007). Functional imaging evidence from humans support these findings, pointing to similar shifts of the retinotopic mapping of stationary objects in V1 and MT (Maus, Ward, Nijhawan & Whitney, 2013; Whitney, Goltz, et al., 2003). These results demonstrate that motion-induced position shifts are represented by population activity in MT. Using TMS, several studies have found that motion-induced mislocalizations are remarkably reduced after disrupting activity in area MT (McGraw, Walsh & Barrett, 2004; Whitney et al., 2007). These studies show the causal necessity of MT activity for perceptual and action-directed localization.

The ability of the human brain to rapidly encode visual motion and object position seems therefore to be supported by a critical role of area MT (Schenk, Ellison, Rice & Milner, 2005). Although all these studies provide strong evidence for an involvement of MT in the coding of visual motion for perception and action, yet they do not resolve questions about the time-course of the neural mechanism by which visual motion affects reaching. The latency of the arm muscle activity in the MFR is comparable to that of the ocular following response (Saijo et al., 2005). The latency of the ocular following response is short because of a direct neural pathway between motion-related cortical areas and subcortical regions responsible for the generation of eye movements commands, such as the SC (Shidara, Kawano, Gomi & Kawato, 1993). These extrageniculate visual projections thus allow for a fast effect of motion in eye movements. An important question now arises: Which is the anatomical substrate by which motion affects our visuomotor control at a latency of ~120 ms? Apparently, feedback connections from MT to V1 would need more time to modulate the hand response (Nowak & Bullier, 1997). A possible alternative explanation is that MT may be activated by the input received from the SC or the pulvinar, which might be faster than input from V1. Up to now, whether extrageniculate projections to area MT can contribute to the rapid motion’s influence on visually-guided actions remains to be clarified. I will address this controversy in chapter 4 of this dissertation.

Parallely to the computation of the target location, the planning of a reaching movements concerns another crucial process: the coding of the end-effector (i.e., the hand) position. The sensors that transduce the arm's configuration (proprioceptors) have intrinsic joint-based coordinates that allow to compute hand location in the same coordinate system as the target. The next section will consider the coding of hand location in reaching.

1.2.2 COMPUTING HAND LOCATION IN SPACE

People who does not have visual access to the configuration of their arm or their hand location with either proprioceptive or visual signals cannot make accurate movements. The CNS thus needs to estimate hand location in space at the beginning and throughout the movement to move to a target precisely, and this computation requires sensory feedback (Shadmehr, 2005). It has been shown unequivocally that reaching is more accurate in the presence than in the absence of vision of the arm just before (Prablanc, Echallier, Jeannerod & Komilis, 1979) and during the movement (Conti & Beaubaton, 1976; Prablanc, Echallier, Jeannerod, et al., 1979; Prablanc, Echallier, Komilis, et al., 1979). Since this improvement was observed even for movements that were completed within 200 ms, it was proposed that visual cues from arm motion are processed at higher speeds than the times (190-260 ms) assumed necessary to use external visual feedback (Keele & Posner, 1968; Paillard, 1982). The other crucial sensory input required to the computation of hand position are proprioceptors, the sensors that measure the limb's joint angles or muscle lengths (Lackner & Shenker, 1985). Our visuomotor system must 'learn' to map joint angles to estimate current hand location and to change that mapping as your limb develops and controls different objects.

Hand location can be described within the peripersonal space in a variety of coordinate frames. For example, it might be coded depending on limb's joint angles. Nonetheless, coordinate frames based on vision can also compute hand location. It has been demonstrated that vision-based coordinate systems frequently predominate over other sensory modalities for the guidance of reaching and pointing (Todorov & Jordan, 2002). However, when you prepare to reach, you usually look at the target, not your hand. Hand location then usually falls outside central vision on a part of the retina with lower spatial resolution. Proprioceptive signals provide information to substitute low-quality visual input of the hand with high-quality information about joint angles. Also, what if you cannot see your hand, as when you reach in the dark? In that situation, information about limb's joint angles provided by proprioceptors plays a critical role aligning visual and proprioceptive inputs to estimate where you would see your hand. The next subsection will scrutinize the alignment of visual and proprioceptive information when reaching objects.

1.2.2.1 Aligning vision and proprioception

The visual estimate of the hand position is based on the retinal position of the hand's image and the orientation of the eyes. The proprioceptive estimate is defined as the ensemble of sensory information from receptors in the muscles, skin, and joints. When information is available in both modalities, the CNS uses proprioception and vision to obtain one coherent idea of where our hand is (Carrozzo, McIntyre, Zago & Lacquaniti, 1999; Ernst & Banks, 2002), as has been successfully modeled assuming an optimal combination of sensory information (Knill & Pouget, 2004; Smeets, van den Dobbelsteen, de Grave, van Beers & Brenner, 2006) (**Figure 1.9A-D**). When reaching to a visual target, we integrate visual input from target and hand positions with limb proprioceptive cues, to compute the motor error needed to produce a correct motor command (Jeannerod, 1988). An analysis of variable errors in tasks where a non-moving hand had to be localized revealed that the available proprioceptive and visual cues are combined efficiently (van Beers, Sittig & Denier van der Gon, 1996). The notion that both visual and proprioceptive modalities are integrated is also motivated by the intuition that we do not consciously perceive discrepancies between the felt and seen hand's position.

In this context, situations arise in which these sensory signals conflict (e.g., when looking through a microscope or in a mirror). Integration of vision and proprioception has been studied extensively in experiments in which subjects view their hand through optical prisms that displace the visual field and therefore induce a conflict between the visual and proprioceptive signals about hand position (Redding & Wallace, 1996; van Beers, Sittig & Gon, 1999; Warren & Pick, 1970). The picture that emerged from such studies is that the estimate of hand position relies more on vision than on proprioception. When reaching to a visual target, movements are adjusted in accordance

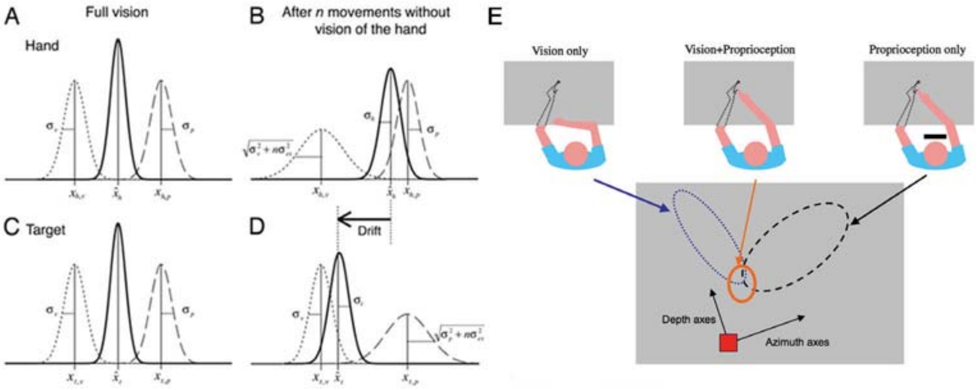


Figure 1.9. The Gaussian curves represent the hypothesized probability density functions of proprioceptive (dashed), visual (dotted), and combined (solid) estimates of position. When the hand is at the target with full vision, the positions of both the hand (**A**) and target (**C**) are based on the optimal combination of proprioceptive and visual cues. **B**. If the hand disappears from view, the visual estimate of its position gradually becomes less precise with each movement. The combined estimate of the hand location therefore relies less on vision, so that the combined estimate shifts toward the proprioceptive estimate, with a reduction in precision. **D**. The proprioceptive estimate of target location becomes less precise. The combined estimate of the target location will therefore rely less on proprioception, so that the combined estimate shifts toward the visual estimate, with a reduction in precision. To keep the perceived position of the hand on target, the hand will drift over a distance equal to the difference between the two combined estimates (black arrow). **E.** Bayesian integration of visual and proprioceptive cues. Top panels: Experimental setting for van Beers et al. experiments. Bottom panel: Schematic distribution of visual (dotted line), proprioceptive (dashed line) and bimodal (solid line) estimates of target position. The true position of the object is represented by the red circle. [Extracted from Deneve and Pouget (2004); Smeets et al. (2006)].

with the seen position and one learns a new visuomotor mapping (visuomotor adaptation) (Hay, Pick & Ikeda, 1965; Warren & Pick, 1970). There thus seems to be a weighting of the visual and the proprioceptive information, the greater weight usually being given to the visual information. The visual weights in most reports are between 0.6 and 0.8, and the proprioceptive weights are between 0.2 and 0.4 (Welch & Warren, 1986). The precise values depend on the experimental conditions: For instance, the proprioceptive weight is larger when the hand is moved actively than when it is moved passively, and also increases with decreasing availability of visual information (Mon-Williams, Wann, Jenkinson & Rushton, 1997). The visual-proprioceptive integration also varied with direction, as in the depth direction the estimate relies more on proprioception than on vision (van Beers, Wolpert & Haggard, 2002) (**Figure 1.9E**). This can be understood from the geometry of the arm. On the other hand, vision is more precise in the azimuthal direction with regard to the cyclopean eye.

Taken together all the abovementioned results, we are far from fully understand how the weighting of different sensory modalities takes place in reaching. They raise the intriguing question of whether our visuomotor system uses visual and proprioceptive information following similar weighting patterns when performing visually-guided movements in both depth and azimuthal directions. This gap in the literature constitutes the motivation of chapter 5 in the present dissertation.

1.2.2.2 Encoding limb configuration in the peripersonal space

We have seen how our brain estimates the position of the hand when we intend to reach an object. But, how do I know whether the target is reachable? Near space, also called peripersonal space (Làdavas, 2002), is defined by the extent that can be reached. In order to code visual peripersonal space, human and monkeys need an integrated system that controls both visual, tactile and proprioceptive inputs within reachable range, based on visual experience of body parts (di Pellegrino, Ladavas & Farne, 1997). Neurons in the putamen, and in parietal and frontal lobes have been reported to effectively discharge only when visual stimuli are located in spatial proximity to a particular body part (e.g., face or hand) (Ladavas, di Pellegrino, Farne & Zeloni, 1998). The evidence of the existence of a visual peripersonal space anchored to the hand is consistent with recent findings by Spence, Pavani, and Driver (1998), who reported in normal subjects that crossmodal tactile–visual congruency effects were significantly larger when lights were placed near the stimulated hand (rather than far away, near the other hand). These studies support the existence of an integrated system that controls both visual and tactile inputs within peripersonal space, and they show how this system is functionally separated from that which controls visual information in the extrapersonal space.

Hands are continuously moving in space, and the brain has to compute their location to update the visual mapping of space surrounding the hand. Recent studies have shown that visual information about hand, besides being necessary, can also be sufficient for mediating the integrated processing of visual–tactile input in peripersonal space. Watching a rubber hand being stroked synchronously with one's own unseen hand causes the rubber hand to be attributed to one's own body, to "feel like it's my hand". Attribution can be measured quantitatively as a drift of the perceived position of one's own hand toward the rubber hand. In an influential study, after 30 min of synchronous stimulation on the rubber hand and the participant's hand, participants mislocated the perceived position of their own hand (Botvinick & Cohen, 1998). Participants judged the position of their hand to be closer to the rubber hand, as if their hand had drifted toward the fake hand. Botvinick and Cohen suggested that rubber hand illusion, namely, a visual adaptation of proprioceptive position, is somewhat similar to the abovementioned prism adaptation: Vision captured touch, resulting in a mislocalization of the tactile percept toward the spatial location of the visual percept. An interesting question relating to peripersonal space is whether its spatial extension is fixed or, rather, whether it can be rapidly modified. This issue is addressed in the next subsection.

1.2.2.3 Plasticity of the peripersonal space: tool-use and shifted visual feedback

Although the length of our end-effectors (mainly the arms) limits our action space, we can use many different tools to extend our physical body structure and, consequently, our action space. For example, imaging holding a hammer and using it to pound a nail. In this situation, the nail head serves as the target and the hammer's head as the end-effector. Thus, the location of your hand, per se, matters only indirectly. Early intuitions (Head & Holmes, 1911) suggested that manipulated objects become 'incorporated into the body schema'. In recent years, there has been accumulative evidence showing that visual peripersonal space relating to the hand has important dynamic properties, for example, it can be expanded and contracted depending on tool use (Berti & Frassinetti, 2000; Witt, Proffitt & Epstein, 2005).

The experimental model used in many studies was to detect behavioral and neural changes in monkeys and humans following the use of simple tools to extend reaching space (Iriki, Tanaka & Iwamura, 1996). For instance, after two weeks of training, macaques skillfully used a rake in order to reach distant items of food (Ishibashi, Hihara & Iriki, 2000). Thus, monkeys effectively extended their reaching span by re-coding far visual stimuli as near stimuli. Iriki and colleagues recorded visuotactile neurons in the anterior bank of the IPS that had somatosensory RFs on the hand or arm and visual RFs nearby. Neuronal responses in these monkeys revealed an expansion of the visual RF of such neurons to include the entire length of the tool (**Figure 1.10**). Inspired by these experiments, several researchers have recently investigated the behavioral effects of tool-use in human observers, in order to ascertain whether similar neural mechanisms exist in the two species. These studies share a basic logic; that is, to identify whether tool-assisted reaching for stimuli presented beyond the hand's normal or unaided reach would produce similar behavioral effects as direct reaching for nearby stimuli (i.e. in reachable space) with the hands alone. Evidence that the human brain also codes space in terms of reachability was found in neuroimaging (Inoue et al., 2001) and clinical studies (Farne & Ladavas, 2000). In addition, psychophysical studies have demonstrated that people judge an object to be closer when they use a tool (Witt et al., 2005). This suggests that tool-use expands the representation of the participant's limb so that it encompasses the entire tool (Berti & Frassinetti, 2000), although it requires an active use of the tool (Farne, Bonifazi & Ladavas, 2005). To summarize, tools enable human beings, as well as other animals, to act on objects when they are not directly reachable by hands. Acting on distant objects by means of a tool requires sensory information that is mainly provided by vision and touch. An expansion of the peripersonal area whereby vision and touch are integrated allows the possibility of reaching and manipulating far objects as if they were near objects.

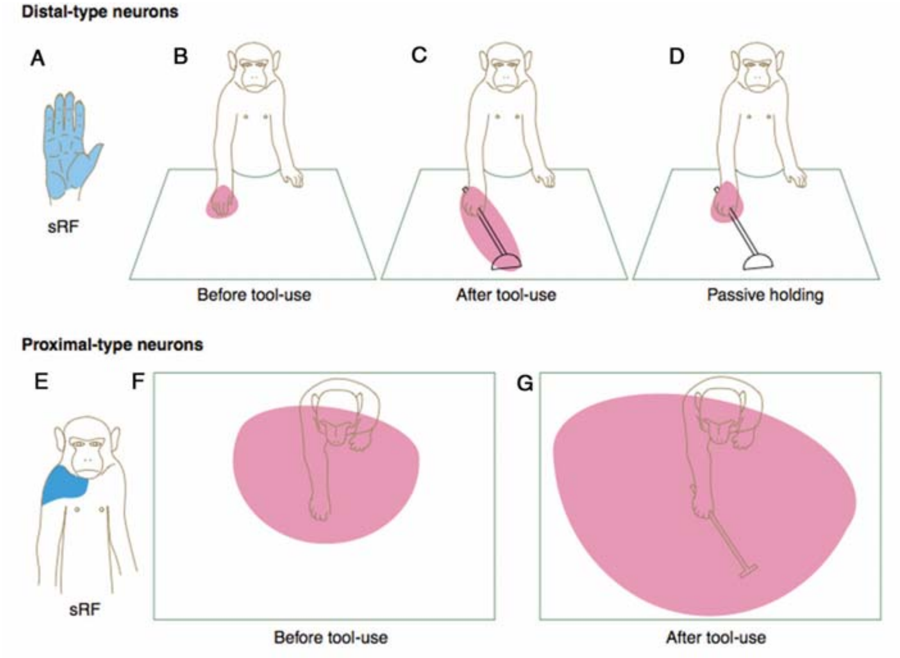


Figure 1.10. Changes in receptive field properties following tool-use. The somatosensory receptive fields (sRF) of neurons in this region were determined by light touches, passive manipulation of joints or active hand-use. The visual RF (vRF) was defined as the area in which cellular responses were evoked by visual probes. **A.** sRF (blue area) of the 'distal type' bimodal neurons and their vRF (pink areas) before tool-use (**B**), immediately after tool-use (**C**), and when just passively grabbing the tool (**D**). **E**. sRF of 'proximal type' bimodal neurons, and their vRF before (**F**) and immediately after tool-use (**G**), where visual RFs elongated to code the space now reachable with the rake. [Extracted from Maravita and Iriki (2004)].

However, the boundaries of the reachable range may also be modified by influencing where one judges one's own hand to be (Holmes & Spence, 2004). As seen in the rubber hand illusion, the fact that people combine the seen and felt positions of the hand to judge where their hand is in space suggests that shifting visual feedback about the position of the hand would alter judgments of reachability. In this context, de Grave, Brenner, and Smeets (2011) have recently showed to what extent shifts in the perceived position of one's hand can account for the shifts in the range of distances that are considered to be within reach. They found that perceptual reachability judgments can be changed by shifted visual feedback, but that this change is not correlated with the amount of visuomotor adaptation. Given that reachability estimations may have a critical importance in deciding to execute a reaching movement, one interesting question that remains to be clarified is whether these dynamics properties of visual peripersonal space would also apply for reaching movements towards the objects judged as reachable. Chapter 6 of this dissertation will try to shed light upon this issue.

Once our visuomotor system has decided to move from the initial hand position towards a target, how does it move from one location to another? The programming and on-line control of a particular action typically requires a unique set of transformations of the visual array, so that each component of the action can be correctly executed with respect to the goal object. As we have seen in previous sections, the CNS, while planning and executing a movement, simultaneously controls multiple subsystems that pursue individual and shared goals (locating the object, locating the hand, etc) in order to achieve the general aim of the task (reaching for the target). ‘Coordination’ can be understood as the organization of the cooperation among multiple subsystems involved in movement control, with different individual goals achieved such that certain common system constraints are met. The next section will describe the online computations that take place during the execution of a movement to successfully reach the object.

1.2.3 THE CONTROL OF REACHING MOVEMENTS

Much of the research on the control of hand movements has been addressed with the simple task of moving the hand from one initial position to the location of an object, generally as quickly and accurately as possible (**Figure 1.11A**). This task was first studied in the late nineteenth century (Woodworth, 1899), using procedures to constrain characteristics of movement (i.e., the movement time, MT) and measuring end-point variability (Keele & Posner, 1968). Woodworth proposed a two-component model of goal-directed aiming in which the movement is composed of an initial ballistic phase (initial impulse), followed by a ‘feedback-based’ phase. However, it was not until the advent of high-speed film (Langolf, Chaffin & Foulke, 1976) and optoelectric systems (Elliott, Garson, Goodman & Chua, 1991) that researchers began to take a detailed look at the spatial and temporal characteristics of individual movement trajectories. Typically, this is done by differentiating profiles of displacement or velocity versus time (**Figure 1.11B**). Reaction time (RT) and the early trajectory of the movement are taken to reflect the movement planning process, whereas later portions of the trajectory are more often associated with online control processes. The duration of the reaching movement tends to remain constant as the amplitude of the movement increases, because the speed of the movement increases as well (Georgopoulos, 1986). However, when accuracy constraints are present, there is a trade-off between the speed and the accuracy of the aimed movement: more accurate movements are performed more slowly, and conversely, faster movements are less accurate. This phenomenon, one of the most fundamental principles of movement behavior, was first reported by Paul M. Fitts (1954) and has been found to predict satisfactorily movement duration in reaching.

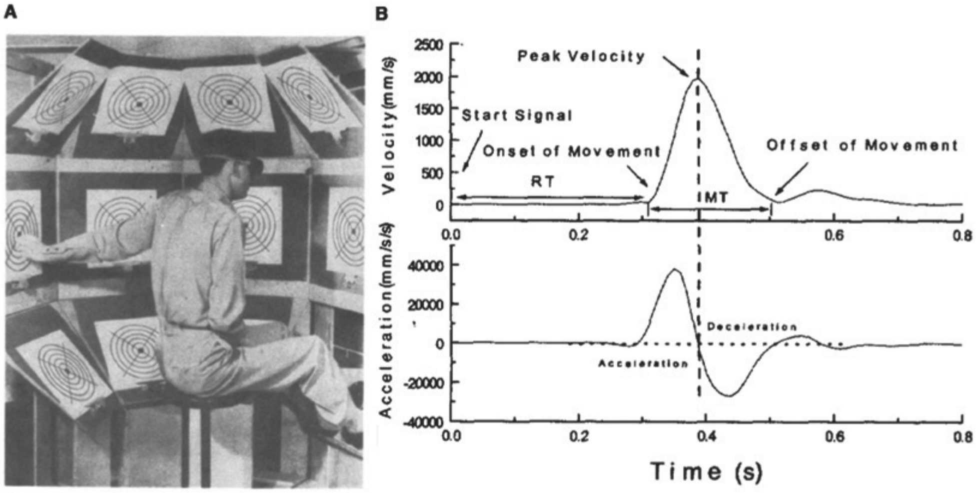


Figure 1.11. A. Experimental arrangement used to study the accuracy of blind reaching. Red goggles allowed the subject to look at a light straight ahead but prevented him from seeing the target areas. **B.** Profiles of movement velocity (top panel), acceleration, and deceleration (bottom panel) for a one-segment ballistic aiming arm movement. [Extracted from Fitts (1947); Yan, Thomas, Stelmach, and Thomas (2000)].

Motor control is the study of how organisms make accurate goal-directed movements. Our ability to produce a lifetime of precise movements lies in the fact that we are born with a nervous system that adapts to its own inherent neural limitations and continuously compensates for them. If left uncompensated, these limitations could give rise to systematic errors in our movements. When performing a simple reaching movement at a moderate speed under normal viewing conditions, our initial aim may be imperfect, or environmental changes such as movements of the target or of the body, may perturb our movement, which may result in an inaccurate response. In such situations, continuous control and a final voluntary correction are usually called for. Often, this type of motor control is called online motor control.

1.2.3.1 Online computation of target-hand distance

In order to control a reaching movement, the brain must compute the difference between the hand and the target position, which is called ‘motor error’. Hand and target location can each be defined in eye-centered coordinates, and a second possibility is that they were coded with respect to a fixed point in the trunk (body-centered coordinates), as we mentioned above. Both schemes will arrive at the same motor error (**Figure 1.12A**). Some PPC neurons in the IPS appear to encode hand and target location in eye-related coordinates (Crawford, Medendorp & Marotta, 2004), and others in body-related coordinates (Buneo, Jarvis, Batista & Andersen, 2002; McIntyre, Stratta & Lacquaniti, 1998). Additionally, some IPS neurons code spatial information of reach-related variables in both eye and hand coordinates, suggesting a role in transforming spatial cues between the two reference frames (Burnod et al., 1999).

A paradigm that allowed to isolate visual information from the target and from the hand was developed by Prablanc, Echallier, Jeannerod, et al. (1979) (**Figure 1.12B**). Inspired by the Held and Gottlieb (1958) device, a half reflecting mirror was used to prevent the vision of the hand while maintaining the vision of the stimulus. Through an electronic shutter controlling a light source in between the plane of the mirror and the plane of pointing, the visual reafferences from the whole limb were turned on or off within the range of milliseconds. This experimental apparatus was suitable to examine the eye-hand coordination during the execution of the movement. The next subsection introduces the ability to update a motor command after the initiation of the reaching.

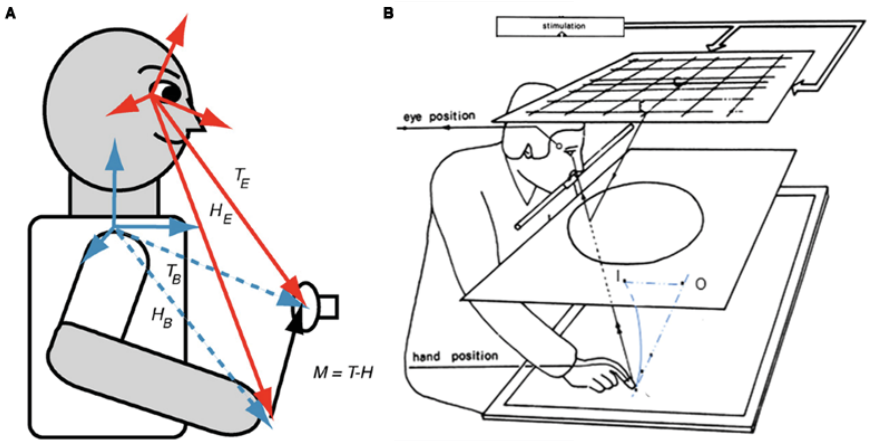


Figure 1.12. A. Schematic showing the reach-related variables described in the text. **B.** Initial apparatus used to implement real-time investigation of the eye-hand coordination. It includes a target presentation plane, a pointing plane and midway in between a half reflecting mirror allowing seeing both the target (or an object) on the pointing plane and the whole limb. However, the vision of the hand can be instantaneously occluded, triggered online by an eye- or hand-movement velocity threshold. Similarly, the initial stimulus can be independently and instantaneously interrupted, or its location perturbed, triggered by an eye or hand movement velocity threshold. *T*, target position; *H*, hand position; *M*, motor error; *B*, body-centered coordinates; *E*, eye-centered coordinates. [Extracted from Buneo and Andersen (2006); Prablanc, Echallier, Komilis, et al. (1979)].

1.2.3.2 Online motor control: Updating target location

When a close target appears within the peripheral visual field and a subject is required to look and point at it as accurately as possible, the natural sequence was always an eye saccade followed within 50 to 100 ms by a hand movement (Biguer, Jeannerod & Prablanc, 1982; Prablanc, Echallier, Jeannerod, et al., 1979; Rossetti, Stelmach, Desmurget, Prablanc & Jeannerod, 1994). The movement has long been considered as composed of two phases: an initial ballistic pre-planned phase, in which a predefined motor command is executed in a feedforward manner, and a later controlled phase, in which sensory feedback from the movement is used to correct for errors in the ballistic trajectory. Numerous studies have shown that, when the target is suddenly displaced, humans update their movement to take account of the jump, correcting their trajectory online to end the movement at the new target location [see (Prablanc, Desmurget & Grea, 2003) for review]. In fact, the ability to make an online correction is considerably robust against the effects of aging (Kadota & Gomi, 2010). Patients with Parkinson's disease and cerebral palsy also preserved online adjustments (Desmurget et al., 2004; Van Thiel, Meulenbroek, Smeets & Hulstijn, 2002). Moreover, people can adjust the movement extremely rapidly (~110 ms) in response to unexpected changes in the surroundings (Brenner & Smeets, 1997; Gielen, van den Heuvel & van Gisbergen, 1984; Soechting & Lacquaniti, 1983) or shifts in the perceived position of the body (Brenner & Smeets, 2003; Sarlegna et al., 2003). It is worth noting that the visuomotor delay for changes in target location is just as brief as the latency at which visual motion started to influence fast reaching movements (Brenner & Smeets, 1997; Whitney, Westwood, et al., 2003). This may indicate a possible link between visual motion and target-jump induced changes on hand's trajectory; that is, motion-generated position reassignment might be equivalent to a shift in the real position of the target. This is surprising, because it indicates that information unrelated to the target (extraneous visual motion) might be processed as fast as information specific to the target, such as actual target location.

Advances in optoelectronics have provided the opportunity to perturb the environmental context based on the participant's concurrent actions. In order to investigate how a planned movement is controlled naturally after its initiation, an adequate method called 'the double-step paradigm' resides in introducing a planning error unknown to the subject while preventing visual feedback of the movement. The double-step paradigm consisted of a peripheral target, both for pointing and gaze orienting, which could be maintained stationary or in a few cases slightly displaced in amplitude at the time of peak velocity of the orienting saccade. The results showed that pointing responses were shifted by the same amount as target jump. These rapid online corrections were obtained even when there was no visual feedback from the hand. Subjects were naive to the possible occurence of the perturbation as well as kinaesthetic sensation of correction. Corrective trajectories did not yield a different kinematic parameter (Goodale, Pelisson & Prablanc, 1986). These findings were taken as evidence that non-intentional fast corrections operate automatically, and the spatial updating of reaching has become known as the 'automatic pilot' (Pisella et al., 2000). This automatic process might be driven by an internal feedback loop comparing updated target location and kinesthetic feedback and/or efference copy (rather than visual feedback) of the hand.

Whether the unawareness of the change in target location was necessary for the occurrence of automatic corrections was further investigated (Castiello, Paulignan & Jeannerod, 1991; Komilis, Pelisson & Prablanc, 1993). In Castiello's study, the triggering signal that produced the random stimulus perturbation was not the saccade but the hand movement onset or the hand peak velocity. This way, subjects were aware of all perturbations and performed an online adjustment. Fast intentional corrections exhibited two velocity peaks and increased movement time (Diedrichsen, Hashambhoy, Rane & Shadmehr, 2005), consistent with the superposition of two motor commands, whereas automatic online corrections showed a single velocity peak, and no additional time (Prablanc & Martin, 1992). The results revealed that the non-conscious aspect of the perturbation was not a pre-requisite to perform the online adjustment. To determine whether, in response to a small aware target jump, the flexible automatic correction of the ongoing reaching overrides voluntary processes, Pisella et al. (2000) asked subjects to interrupt the reaching movement toward visual targets presented on a touch screen when a target jump occurred. Unexpectedly, subjects produced a significant number of inappropriate online corrections in the ‘stop’ condition. This failure to completely suppress corrective responses indicated that flexibility can be generated in an automatic mode that escapes conscious and voluntary processes.

The convergence of visuomotor psychophysics studies with neuroimaging tools have contributed to the understanding of the neural mechanisms in charge of those online correction processes. I will address this issue in the next subsection.

1.2.3.3 The neural basis of online motor control

The sharp contrast between brain activity in perturbed and unperturbed visuomotor responses revealed a network that included the contralateral PPC, the part of the motor cortex related to the upper arm and also the cerebellum (Desmurget et al., 2001). To further assess the involvement of PPC not only in planning but in online motor control, movement kinematics was studied in a patient with bilateral PPC lesions who did not exhibit spatial neglect. She could reach to objects normally if those objects fell near her fovea. The patient showed no deficits in planning, but was unable to amend her ongoing movement when the target suddenly jumped (Grea et al., 2002). Her arm completed the reach towards the initial location of the target, and then made a second movement toward the current location. The role of the cerebellum in online control was also highlighted by Liu, Ingram, Palace, and Miall (1999), as crucial for building-up a motor error signal and a forward model of the limb. Recent studies indicated the importance of subcortical structures, such as SC, in generating online corrections (Day & Brown, 2001; Himmelbach, Linzenbold & Ilg, 2013; Linzenbold & Himmelbach, 2012).

This network dovetails well with the network involved in the generation of externally-guided movements (Debaere, Wenderoth, Sunaert, Van Hecke & Swinnen, 2003). Electrophysiological evidence in monkeys suggest that the visuomotor transformations that orchestrate reaching are accomplished within a parietofrontal circuit interconnecting MIP and the dorsal premotor cortex (PMd) (Caminiti, Ferraina & Johnson, 1996; Johnson & Ferraina, 1996; Johnson, Ferraina & Caminiti, 1993). MIP neurons appear to represent the intention to move the arm along a specific trajectory in the space, whereas PMd also receives direct visual and proprioceptive inputs from the upper part of the PPC, the superior parietal lobule (SPL) (Lacquaniti, Guigon, Bianchi, Ferraina & Caminiti, 1995). In humans, neuroimaging techniques have revealed extensive activation of SPL, IPS and PMd during reaching, pointing and finger-tracking movements (Colebatch et al., 1991; Grafton, Mazziotta, Woods & Phelps, 1992; Kertzman, Schwarz, Zeffiro & Hallett, 1997). More recent studies with refined tasks have identified a putative homologue of MIP area, centered on the medial bank of the IPS and called medial intraparietal sulcus (mIPS) (Desmurget et al., 2001). The mIPS input that receive PMd neurons is thought to be transmitted through parietofrontal tracts, with a special relevance of the superior longitudinal fasciculus (SLF) as one of the main direct pathway that links the parietal and the frontal lobe (Boorman, O'Shea, Sebastian, Rushworth & Johansen-Berg, 2007). The activity of many mIPS neurons varies with the location of the target relative to the hand, the abovementioned ‘motor error’. They respond not only to passive sensory inputs but also before the movement onset and during the execution. This behavior permits the mIPS to integrate sensory input with efference copies of outgoing motor commands to compute a continuously updated estimate of the motor error.

Desmurget and colleagues used single-pulse TMS to disrupt mIPS function at the onset of the hand movement (Desmurget et al., 1999). On trials in which the target jumped, most of the participants performed hand movements that disregarded the shift in the target location (**Figure 1.13**). Subjects reached along a path much like that for a stationary target. Fast automatic corrections, however, remained normal in movements with the ipsilateral (left) hand; so did movements toward stationary targets. Thus, this study eliminated a global involvement of the PPC in the online control of motor responses, showing that the corrective deficits with the right hand were not caused by a visual impairment. Thus, it appears that PPC participates not only in the planning phase,

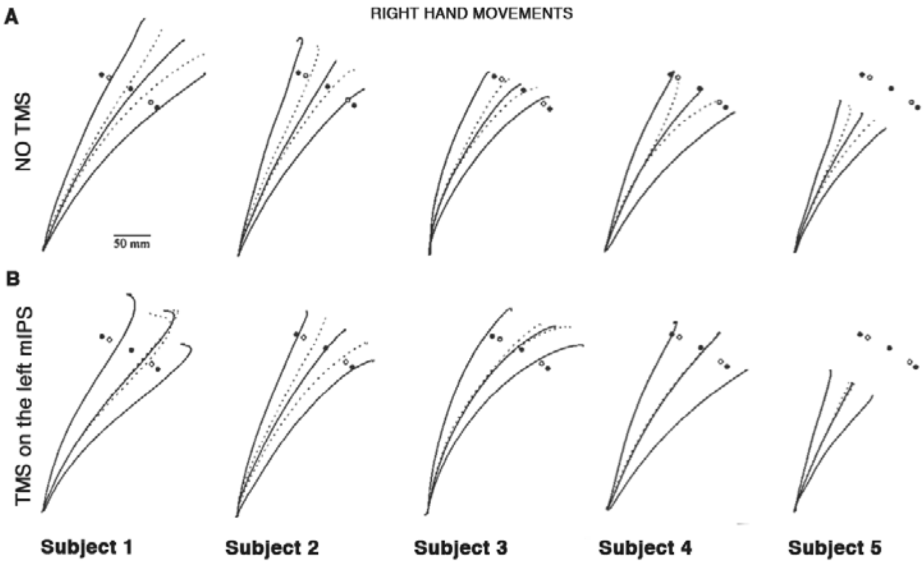


Figure 1.13. Mean hand paths produced by five subjects with the right, dominant hand after stimulated (lower row) -TMS single-pulse over the mIPS- and non-stimulated (upper row) conditions. The black solid curves represent the mean paths directed at stationary targets. The gray dashed curves represent the mean paths directed at jumping targets. Black circles indicate stationary target locations, whereas white circles represent jumping target locations. [Extracted and modified from Desmurget et al. (1999)].

but also in the online monitoring of target-hand location and the updating of motor error (Reichenbach, Bresciani, Peer, Bulthoff & Thielscher, 2011). It remains unknown, however, which neural mechanisms are behind inter-individual differences in online motor control. Looking at **Figure 1.13**, it is apparent that the impairment of the corrective trajectories induced by interfering mIPS function varied considerably over subjects. The understanding of the nature and extent of inter-subject variation is critical for understanding the neural basis of correction processes in normal and abnormal populations. The key question be to what extent anatomical differences within the parietofrontal ‘reaching’ circuit could explain the differential impact of TMS in online motor control. The overarching goal of chapter 7 is to provide new insights on this issue.

1.3 Neuroimaging of the visuomotor system

The ability to observe areas of the brain that are active during a specific neural process has helped to stimulate the current interest in the biological underpinnings of visual and motor functioning. It was not until well into the 20th century, however, that neuroimaging techniques became available. Previously, research on the biological basis of visual and motor functions was confined to post-mortem clinical studies of animals and patients with visuomotor disorders or direct cortical recordings using invasive methods (Adrian & Moruzzi, 1939; Penfield & Boldrey, 1937; Symonds & MacKenzie, 1957). From that time, the irruption of brain imaging has catalyzed the development of powerful non-invasive techniques to capture properties of the human brain in vivo. Specially, it has made possible to study human subjects, affording unprecedented views of the complexities of an intact working brain (Raichle & Mintun, 2006). Imaging of the living brain provide insights about normal brain function and structure, neural processing and neuroanatomic manifestations of neurological disorders. Several imaging modalities are widely used in the study of visual and motor system, including electroencephalography (EEG), transcranial magnetic stimulation (TMS), diffusion tensor imaging (DTI), magnetic resonance imaging (MRI), functional MRI (fMRI) and positron emission tomography (PET), among others. These modalities leverage different physiological characteristics to reflect properties of either brain structure or function. This dissertation largely focuses on EEG, TMS and DTI techniques, but some of the ideas presented can incorporate or extend to other modalities.

1.3.1 ELECTROENCEPHALOGRAPHY

Over 80 years ago, the EEG was first described as the measure of the electrical activity of the human brain by placing an electrode on the scalp, amplifying the signal, and plotting the changes in voltage over time (Berger, 1929) (**Figure 1.14A**). This electrical activity was provided by changes on the post-synaptic events of single neurons or a group of neurons located in superficial cortical layers (Caspers, Speckmann & Lehmenkuhler, 1980). Embedded within the EEG are the brain responses associated with specific visual and motor events. In its raw form, however, EEG signal is a very coarse measure of brain activity and it is difficult to assess these highly specific neural processes (Luck, 2005). Thus, it is needed to extract these responses from the overall EEG by means of a simple averaging method. These averaged responses are called event-related potentials (ERPs) to denote the fact that they represent neural activity associated with specific events, as a stimulus onset or a movement onset. After the time-locked averaging, the resulting ERP waveform consist of a sequence of positive and

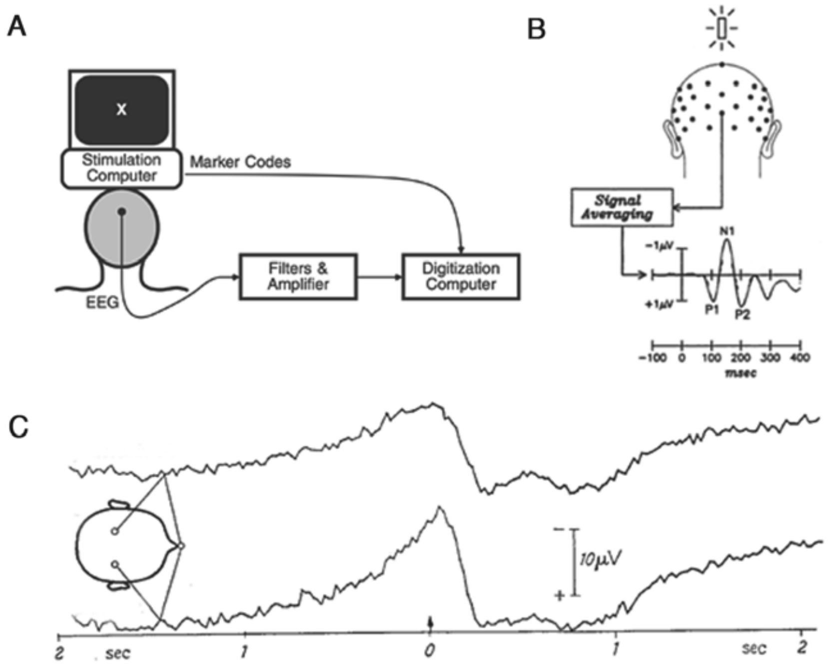


Figure 1.14. A. Example ERP experiment. The subject views a X presented on a computer monitor while the EEG is recorded from a midline parietal electrode site. This signal is filtered and amplified, making it possible to observe the EEG. **B.** Schematic representation of the visual ERP components in a typical spatial attention experiment. The ERP waveform consisted on a sequence of positive and negative deflections labeled P1, N1, P2 and N2. EEG signal averaging is required to obtain a reliable waveform. **C.** Averaged readiness potential evoked in a motor task with the left hand. Movement onset in all pictures at the arrow (0). Negative potential was higher in the contralateral hemisphere. [Extracted and modified from Kornhuber and Deecke (1965); Luck (2005); Mangun, Hillyard, and Luck (1993)].

negative voltage deflections, each called components and labeled by its polarity and position within the waveform (N1, P2,…). ERP components are defined by its exclusive polarity, latency, distribution across the scalp and its sensitivity to experimental manipulations.

In the study of vision, ERP components elicited after viewing different patterns of light were named visual-evoked potentials (VEPs) (**Figure 1.14B**). First human VEPs were described by Spehlmann (1965) by measuring occipital EEG signal when observing a flashed pattern on a screen. First major VEP component is a positive going potential that usually peaks around 80-130 ms, called P1 component (Mangun, 1995). Its amplitude is maximum over the occipital lobe and fMRI studies have located its source in the dorsal extrastriate cortex (Woldorff, Hillyard, Gallen, Hampson & Bloom, 1998). The P1 component is followed by the N1 wave. N1 deflection peaks at 150-200 ms, typically arising from parietal and lateral-occipital regions. Many studies have shown that spatial attention influences N1 component, suggesting its critical importance in the conscious perception and discrimination of visual stimuli (Hillyard, Vogel & Luck, 1998; Hopf, Vogel, Woodman, Heinze & Luck, 2002). Finally, a distinctive P2 component follows the N1 wave at anterior and central scalp locations. This component is larger for visual stimuli containing target features (Luck & Hillyard, 1994).

If subjects are instructed to make a voluntary movement towards a visual stimuli, the onset of the movement is preceded by a slow negative deflection at central and frontal sites that starts about one second before the actual response. This is called the *readiness potential* (RP) or *Bereitschaftspotential* (BP), and it reflects the cortical contribution to pre-motor planning of movements (Kornhuber & Deecke, 1965) (**Figure 1.14C**). BP has its peak in the pre-central motor regions over SMA, providing evidence that this brain region is involved in forming the intention to move (Libet, Gleason, Wright & Pearl, 1983). The lateralized portion of the RP is called the lateralized readiness potential (LRP), recorded over the motor cortex contralateral to the active limb about 200-250 ms before movement (Coles, 1989; Miller, Riehle & Requin, 1992). LRP is generally assumed to reflect the end of decision-making process and the onset of the formation of the motor command.

1.3.2 TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a non-invasive technique that stimulates the brain through the intact scalp. By applying one pulse using an stimulator coil, a rapidly changing magnetic field penetrates the scalp to induce electric currents in the area of the brain beneath the coil (Barker, Jalinous & Freeston, 1985; Wassermann, Epstein & Ziemann, 2008) (**Figure 1.15A**). The induced current pulse lasts for about 200 μs and is thought to activate cortical axons and subcortical white matter (Hallett, 2007). Depending on several parameters such as coil orientation and stimulus intensity, TMS activates a mixture of neurons; some are excitatory, others inhibitory, so it can be used to induce a transient interruption of normal brain activity in a relatively restricted area of the brain.

Single-pulse TMS produces complex but short responses. Repetitive TMS (rTMS) can have longer-lasting effects on the brain, which persist after the stimulation period. The nature and the duration of the after-effects depend on properties such as the frequency of application, the length of the train of pulses or the intensity (Huang, Rothwell, Chen, Lu & Chuang, 2011). For example, stimulation at frequencies lower than 1 Hz tends to decrease rather than increase cortical excitability (Chen et al., 1997). The mechanism underlying rTMS effects is not clear, though it is widely believed to reflect changes in synaptic efficacy similar to long-term potentiation (LTP) and long-term depression (LTD) processes (Fitzgerald, Fountain & Daskalakis, 2006). These properties have motivated the clinical interest to apply rTMS to promote plasticity in patients with movement disorders (Butler & Wolf, 2007; Siebner, Mentschel, Auer & Conrad, 1999) or motor recovery after stroke (Takeuchi, Chuma, Matsuo, Watanabe & Ikoma, 2005).

Most of our knowledge of the action of TMS on the human cortex comes from studies of the motor system. A single or paired TMS pulse over M1 causes depolarization and triggers an action potential. The induced current travels through the CST and finally produces muscle activity on the opposite side of the body, which can be measured using electromyographic (EMG) recordings. Two main features of EMG waveforms evoked

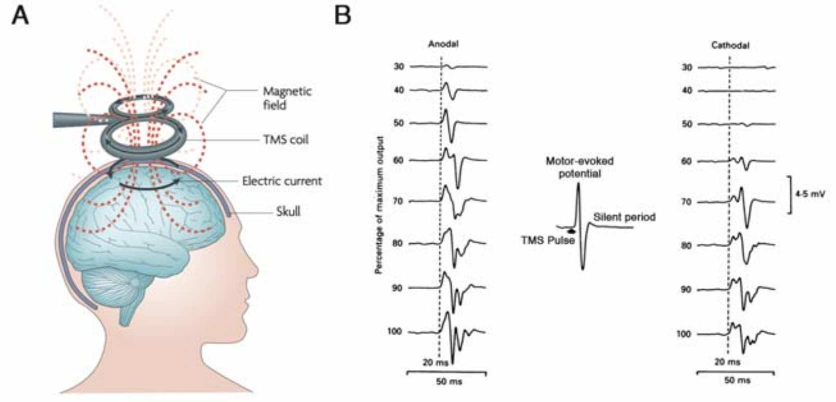


Figure 1.15. A. Each TMS pulse produces an electrical current in the brain. The magnetic field falls off rapidly with distance from the coil, so it is usually assumed, unless the stimulus intensity is very high at the surface of the brain, that the stimulus activates neural elements in the cortex or subcortical white matter. TMS of the cortex can potentially activate the axon of any neuron: recruitment depends on the threshold relative to the stimulus intensity. **B.** Comparison of surface EMG responses from the first dorsal interosseous (FDI) muscle following anodal (left column) and cathodal (right column) stimulation at different intensities. Intensities of cortical stimulation are given as a percentage of the maximum output of the stimulator. Dashed vertical line represents 20 ms elapsed time. [Extracted from Day et al. (1989); Ridding and Rothwell (2007)].

by a single TMS pulse can be observed. First, it produces a burst of activity that can last for 20 ms after the pulse, which is called motor-evoked potential (MEP) (Day et al., 1987) (**Figure 1.15B**). Second, the burst is followed by a longer refractory period (100-200 ms) in which activity is suppressed, the *cortical silent period* (CSP) (Fuhr, Agostino & Hallett, 1991). MEP amplitude is generally thought to be an index of the number of neurons activated by the pulse (Hallett & Chokroverty, 2005). By contrast, stimulation of most other parts of the cortex, at least with single pulses, has no obvious effects. The only exception is, in most individuals, the visual cortex, stimulation of which can elicit phosphenes (bright spots of light) that can be reported by subjects but cannot be quantified by observers (Amassian et al., 1989).

1.3.3 DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is an MRI application to visualize anatomical connections between different brain areas in vivo and non-invasively. The concept of DTI is to produce MRI-based quantitative maps based on how fast water diffuses within the brain. Because movement of water molecules is impeded by obstacles such as fibers or membranes, DTI is deeply rooted in the concept that water diffusion patterns can probe tissue structure and reveal microscopic details about the anatomical architecture and integrity of neural tissues (Le Bihan et al., 1986). DTI scans can be used to characterize the anisotropy of water diffusion (diffusion in different directions) (Basser, Mattiello & LeBihan, 1994). Given that the architecture of the axons facilitate the diffusion of water preferentially along their main direction, this anisotropy effect can be exploited to map the orientation in space of the white matter tracts (Douek, Turner, Pekar, Patronas & Le Bihan, 1991). Fractional anisotropy (FA) is a scalar value between zero and one that describes the degree of anisotropy. A value of one means that diffusion occurs only along one axis and is fully restricted along all other directions. Thus, FA is thought to reflect integrity and fiber density in white matter.

The most advanced application of DTI is fiber tracking. Tractography algorithms, based on the idea to follow the path of anisotropy, allow to trace a fiber along its whole length and infer the white-matter connectivity of the brain (e.g. the CST, through which the motor command transit from the M1 to the spinal cord) (**Figure 1.16**). The study of the motor system using DTI provided strong insights about the inter-individual differences

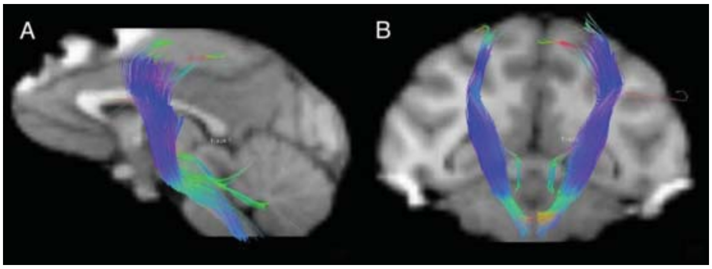


Figure 1.16. Examples of fiber tracking results. Tracks are overlaid on MRI anatomical images. (**A**) and (**B**) show the sagittal and coronal view of the corticospinal tract. [Extracted from Liu, Zhu, Gu, and Zhong (2009)].

in the performance of several motor tasks as a result of variations in the white matter structure, such as reaction time variability (Tuch et al., 2005). Some studies have also related the presence of specific motor skills to changes in brain morphology (Bengtsson et al., 2005; Gaser & Schlaug, 2003).

1.3.4 COMPARISON OF THE METHODS

Each of the neuroimaging approaches previously described present several limitations and advantages. Besides invasiveness, two more criteria are used to establish the suitability of a specific technique to measure a given neural process: the spatial resolution and the temporal resolution. Many studies have noted that EEG has complementary patterns of spatial and temporal resolution compared to hemodynamic measures such as MRI: EEG has a temporal resolution of 1 ms, whereas MRI is limited to a resolution of several seconds. However, hemodynamic measures have a spatial resolution in the millimeter range, which EEG cannot match. Given that most of the neural processes take place within the time-scale of milliseconds, EEG is a very useful tool to provide the temporal dynamics of any brain function. In contrast, the fact that ERPs are not easily localized provokes that voltage recorded at any moment from a single electrode reflects the summed contributions from many different ERP neural generators (Michel & Murray, 2012). Over the last years, sophisticated EEG source localization algorithms, such as BESA (Scherg, 1990) or LORETA (Pascual-Marqui, Michel & Lehmann, 1994), have further advanced the precision of source localization.

TMS has the distinctive feature that it is the unique technique capable of interfering brain function non-invasively. Similarly to ERPs, TMS has a high temporal resolution within the order of 1 ms, providing an accurate chronometry that allows to measure the exact timing of the contribution of the targeted brain region to a specific event (van den Wildenberg et al., 2010). TMS is thus a proper approach to establish causal relationships between a structure and a function of the brain. Nonetheless, TMS also has a poor spatial selectivity, since TMS pulses are administered within 1 cm^2. However, the distribution of the induced electric field can and has been modelled (Joy, Scott & Henkelman, 1989), and progress has been made in relating the induced currents to specific sites of activation with a resolution of a few millimeters. Some studies argue that rTMS is unlikely to restore function to specific synaptic connections that are affected by neurological disease because TMS is too non-specific in its action on neural population. However, it may be possible for rTMS to interact with the normal processes of brain plasticity that accompany damage or chronic disease. It might therefore be reasonable to harness these effects in a therapeutic setting, although it is already a remarkably unexplored field.

DTI measures have the paramount advantage of being the only non-invasive technique available to characterize anatomical connectivity in a living human brain. There are, however, important limitations to the accuracy and precision with which fiber tracking can be done with DTI. Specifically, only white matter bundles composed of a large number of axons are detectable. Also, there are specific white matter regions where different fiber bundles cross or bifurcate, leading to a confounding in the computation of difussion direction.

2

OUTLINE AND AIMS OF THE THESIS

Visuomotor control is essential in everyday life behavior and yet, its study has been mostly focused on indirect analysis of other neural processes. The scarcity of the literature addressing directly this process raises the necessity of developing a comprehensive framework, based on the coding of space and time, of how the visuomotor system takes charge of the control of voluntary movements. The overarching goal of the present dissertation is to provide solid data to advance in the understanding of how the brain optimally encodes spatial and temporal information to perform accurate reaching movements. By combining psychophysical and neuroimaging approaches, five studies are presented to deal with these unanswered issues through hypothesis derived from some of the questions raised in the introduction (Chapter 1). These empirical data are presented in Chapters 3 to 7, in the form of five articles. Below, I will briefly formulate the specific objectives of each study in relation to the global aim of this dissertation:

- In chapter 3, the aim was to explore, by means of psychophysical measures, whether visual illusions that shifted the perceived position of objects, such as the motion after-effect (MAE), also affected pointing and pursuit goal-directed actions towards these objects. Given that visual motion has been found to shift both the perceived position of objects and smooth eye movements, it is possible that illusory percepts caused by motion adaptation are also relevant for hand movements required to reach the object. We therefore tested the hypothesis that MAE can affect the reach by shifting the hand in the direction of the illusory after-effect motion. Nevertheless, it is not clear whether the mechanism by which MAE deviates the reach would act both in stationary and moving stimuli, and may therefore underlie a number of visual phenomena that involve the perceptual localization of a stimulus in the presence of motion (Whitney, 2002). We hypothesized that hand adaptation to MAE would require from a continuous update of the target position through time, being thus only present when reaching for moving objects.

- Chapter 4 sought to identify the neural basis of motion-induced shifts when performing reaching movements with background motion. Using EEG, we tracked the temporal course of neural activity in area MT to establish the contribution of feedforward and feedback circuits to the motion-induced deviation of hand movements. Common to most proposed mechanisms is that the integration of motion signals interacts with the perception of position (Eagleman & Sejnowski, 2007). A recent TMS study points to area MT as the possible neural site where the mechanism or likely combination of mechanisms that generate mislocalization of objects are implemented (Maus et al., 2013). Given the strong feedback connections from this area to V1, where retinotopic localization is very precise, it is possible that visual illusions reflect a re-entrant mechanism by which motion information influences position judgments. Nevertheless, the short latency at which mislocalization takes place casts some doubts on the suitability of feedback connections to sustain early motion-position interaction. The hypothesis was that feedforward inputs through direct extrageniculate inputs to MT can transmit highly processed motion information to shift the perceived position of an object.

- Chapter 5 addressed how the visuomotor system weights visual and proprioceptive cues to accomplish interceptive movements with optimal spatial and temporal accuracy. The main hypothesis to be tested is to ascertain whether, in case of poor visual resolution, the contribution of proprioceptive cues becomes paramount to reach an object with high spatial and temporal accuracy, and vice versa. We predict that the proprioceptive weight will increase when intercepting objects through the depth axis, where vision does not provide enough information to minimize spatial and temporal errors. However, visual-proprioceptive integration when hitting moving objects through the lateral axis would rely predominantly on the visual estimate of hand position.

- In chapter 6, the objective was to determine whether an unconscious adaptation to a shifted seen position of the hand affected the reachability judgments when we intercept moving objects within the peripersonal space. One possibility is that vision merely overrules the proprioceptive sense of the hand position during visuomotor adaptation. On the other hand, perhaps reaching with altered visual feedback of the hand causes proprioception to be readapted such that subjects begin to feel that their hand is at the same location at which they see it. We tested the hypothesis that our visuomotor system 'learns' to associate proprioceptive cues of arm's posture with visual information of the end-effector, even when that is not our hand. That is, the reachability estimations to decide the interception of a moving object will be adapted to whether or not the displaced hand position can reach the target.

- In Chapter 7, a multimodal approach combining repetitive TMS and DTI examined the neurophysiological and anatomical correlates within the parietofrontal 'reaching' circuit to give some insights on the inter-individual variability of deficits in online motor control. It is known that DTI studies have related the presence of specific motor skills to changes in brain morphology. However, pure behavioral measures may mask the integrated role of other brain areas. We applied 1 Hz repetitive TMS over the mIPS to induce a transient disruption of the neural processes underlying on-line motor adjustments. We hypothesize that the operational principles that govern a TMS-induced breakdown of online corrections are based on strength of white matter connectivity between the parietal and the frontal lobe. As a result, subjects with stronger behavioral consequences after rTMS application (that is, a higher reduction of online corrections) will exhibit higher white matter integrity in the parietofrontal tracts presumed to mediate the dynamic computation of the motor error from the mIPS to the motor cortex.

3

STUDY I

THE INFLUENCE OF MOTION SIGNALS IN HAND MOVEMENTS[†]

[†] This chapter correponds to:
Rodríguez-Herreros, B. & López-Moliner, J. (2008). The influence of motion signals in hand movements. **Experimental Brain Research**, 191(3):321-329.

RESUMEN

El estudio de la adaptación a señales visuales de movimiento ha demostrado que los post-efectos debidos al movimiento (motion after-effect, MAE), pueden afectar a la posición percibida de objetos en movimiento. Más recientemente, algunos estudios han presentado evidencias de que las señales MAE pueden también afectar a los movimientos oculares de rastreo. En el presente estudio, hemos investigado la relación entre las señales MAE y los movimientos manuales. El objetivo principal fue examinar si los movimientos manuales de persecución de un objeto en movimiento se vieron influenciados por la distorsionada percepción de la posición del objeto debido a las señales MAE. Además, también comprobamos si el efecto de las señales de movimiento en la posición percibida de un objeto móvil desaparece en la interceptación de un objeto estático. Los resultados muestran que la posición de la mano fue siguiendo el rastro del objeto a mucha menos distancia cuando las señales MAE coincidieron con la trayectoria del objeto. Sin embargo, cuando el efecto MAE se contrapuso a la dirección del objeto y de la mano que lo sigue, la velocidad de la mano se redujo causando distancias más grandes con el objeto. En los experimentos siguientes encontramos un efecto similar cuando se hizo una tarea de interceptación de un objeto en movimiento, pero no cuando el objeto se mantuvo estático. Podemos concluir que las señales MAE tienen una gran influencia en los movimientos de la mano, y ese efecto se manifiesta principalmente cuando el objeto está en movimiento. Por tanto, en base a estos resultados también se puede sugerir que el efecto del MAE es debido a su papel en la actualización de la posición dinámica de un objeto móvil.

RESUM

L'estudi de l'adaptació a senyals visuals de moviment ha demostrat que els post-efectes a causa del moviment (motion after-effect, MAE), poden afectar la posició percebuda d'objectes en moviment. Més recentment, alguns estudis han presentat evidències de que els senyals MAE poden també afectar als moviments oculars de rastreig. En el estudi que presentem, hem investigat la relació entre els senyals MAE i els moviments manuals. L'objectiu principal va ser examinar si els moviments manuals de persecució d'un objecte en moviment es van veure influenciats per la distorsionada percepció de la posició de l'objecte deguda als senyals MAE. A més, també vam comprovar si l'efecte dels senyals de moviment en la posició percebuda d'un objecte mòbil desapareix en la intercepció d'un objecte estàtic. Els resultats mostren que la posició de la mà va seguir el rastre de l'objecte a molta menys distància quan els senyals MAE van coincidir amb la trajectòria de l'objecte. No obstant això, quan l'efecte MAE es va contraposar a la direcció de l'objecte i de la mà que el segueix, la velocitat de la mà es va reduir causant distàncies més grans amb l'objecte. En els experiments següents vam trobar un efecte similar quan es va fer una tasca d'intercepció d'un objecte en moviment, però no quan l'objecte es va mantenir estàtic. Podem concloure que els senyals MAE tenen una gran influència en els moviments de la mà, i aquest efecte es manifesta principalment quan l'objecte està en moviment. Per tant, en base als resultats també es pot suggerir que l'efecte del MAE és degut al seu paper en l'actualització de la posició dinàmica d'un objecte mòbil.

Exp Brain Res (2008) 191:321–329
DOI 10.1007/s00221-008-1527-1

RESEARCH ARTICLE

The influence of motion signals in hand movements

Borja Rodríguez-Herreros · Joan López-Moliner

Received: 14 December 2007 / Accepted: 28 July 2008 / Published online: 14 August 2008

Abstract It has been shown that motion after-effects (MAE) may affect the perceived position of moving objects and, more recently, that MAE signals can also affect pursuit eye movements: smooth pursuit eye movements are favoured by the illusory motion percept that is caused by motion adaptation. Here we investigated the relationship between MAE and arm movements. The objective of our research was: (1) to analyze possible effects of MAE when the arm tracks the changing position of a moving object, and (2) to investigate the influence of MAE on pointing movements to both static and moving targets. Our results show that the (unseen) hand position was trailing the target much less when target and MAE direction was the same. At the end of manual pursuit, subjects caught up with the moving target. However, when target direction was opposite the MAE, subjects' hands moved more slowly, causing larger lags between the target and the hand position (Experiment 1). In Experiment 2, we found a similar effect of motion signals when subjects pointed to a moving target but found no effect of MAE when pointing to a static object (Experiment 3). We conclude that the effect of motion signals is only revealed when we need to update the changing position of a target.

Keywords Motion · Position · Arm movements · Motor control

B. Rodríguez-Herreros · J. López-Moliner
Grup d'Atenció, Acció i Percepció, GRNC,
Parc Científic de Barcelona, Faculty of Psychology,
Universitat de Barcelona, Barcelona, Spain

J. López-Moliner (✉)
Faculty of Psychology, P. Vall d'Hebron,
171, 08035 Barcelona, Catalonia, Spain
e-mail: j.lopezmoliner@ub.edu

Introduction

Localizing a moving object is not a trivial task for the visuo-motor system. The inherent delays in updating the changing position translate into spatial errors in many relative position judgements (Schlag and Schlag-Rey 2002). Different sources of information can be used (or combined) to update position of moving objects. Although motion and displacement are two physically related variables, the brain can deal with these two sources of information independently and use them separately in perception and action (Smeets and Brenner 1995). In a more recent study, Wilmer and Nakayama (2007) concluded that smooth pursuit eye movements are divided in two different level phases: a low-level motion signal, hence more related to motion information, would drive presaccadic acceleration, and a high-level motion signal in postsaccadic precision, closely linked to position signals.

One of the reasons that has led to the separation between motion signals and position comes from motion after-effect (MAE) studies that traditionally have maintained that MAE does not affect position (e.g. Gregory 1966; Nakayama 1985). However, many studies have reported evidence running counter to this view (e.g. Snowden 1998; Nishida and Johnston 1999; Whitaker et al. 1999; Whitney 2002) showing that judgements of spatial attributes are indeed affected by concomitant motion signals due to MAE. Sometimes adaptation is not even necessary. For example, Whitney and Cavanagh (2003) showed that the perceived position of a flash is shifted in the direction of motion and can occur even when the object is far from the moving object.

In a recent study, it has been shown that motion signals due to MAE affect the perceived position of moving objects (Linares et al. 2007) when they have to be compared relative to a flash. Furthermore, increasing the presentation time of the moving object before the flash made the perceived position of the moving object be progressively shifted in the direction of motion. As position seems to be one of the most relevant information to guide hand's trajectory it is worth asking whether pure motion signals may have an effect on hand movements as well.

Effects due to MAE have been studied in several types of action tasks. In eye movements, Braun et al. (2006) reported that smooth pursuit movements can be favoured by the illusory motion percept that is caused by motion adaptation, and the magnitude of the effect is about the same for perception and action. They concluded that the neural mechanisms that generate MAE for perception and pursuit are closely linked. Furthermore, Watamaniuk and Heinen (2007) in a recent study have provided more evidence of the influence of motion signals on the saccadic system.

Unlike eye movements, effects of motion signals on hand movements have been less studied. Previous studies have described the "manual following response" phenomenon, where retinal motion drags the hand in the direction of the motion (Whitney and Cavanagh 2003). This response increases with stimulus contrast and stimulus speed, both purely visual stimulus properties (Gomi et al. 2006). Some studies have shed light on its underlying mechanism (Saijo et al. 2005) by showing a parallel reflexive pathway where these visual motion signals are directly transformed into manual motor commands, independently of the cortical pathway for visual perception (Yamagishi et al. 2001). Finally, Whitney et al. (2007) have suggested that visual motion area MT+ plays an integral role in the process of generation this manual following response. Besides the study of this response, Whitney and Goodale (2005) found that background retinal motion is used by the visuomotor system in order to control a visually guided action. Links between eye and hand movements have not gone unnoticed either. A recent study (Maioli et al. 2007) have shown that tracking a moving object with the eyes inherently involves excitability changes in the motor control system of the arm, suggesting that both systems are driven by a common command signal. This possibility is also supported by the similarity in the response of the smooth pursuit and manual tracking movements to an abrupt change in the target motion (Engel et al. 2000).

The aim of this study is then to extend the knowledge of the effects of motion signals on hand movements by using two different manual tasks. A hand-pursuit task (Experiment 1) in which a sustained movement has to be performed for a relatively long period (about 2.5 s) and a pointing task that, in our case, is completed in a shorter period of time. This way we address the possible effects of MAE signals on hand movements characterized by different kinematic properties. The main hypothesis to be tested is whether hand movements are affected by the distorted perceived position of moving objects due to the MAE.

General methods

Apparatus

Figure 1a shows a sketch of the basic setup used in all experiments. Images were generated by a Macintosh G4 computer and displayed on a monitor HP LP2465 at a frame rate of 60 Hz with a resolution of 1,280×1,024 pixels (52 × 33 cm). The monitor was viewed through a mirror that was placed half way between a serial digitizing tablet (Calcomp DrawingBoard III 34240) and the monitor in order for the virtual image to be perceived on top of the tablet. Binocular information of the distance of the stimulus plane, thus, did not conflict with the proprioceptive distance cue of the unseen hand.

Stimuli

In all the experiments a sinusoidal grating was used to produce a MAE (Fig. 1b). The grating (40 × 18 cm) was

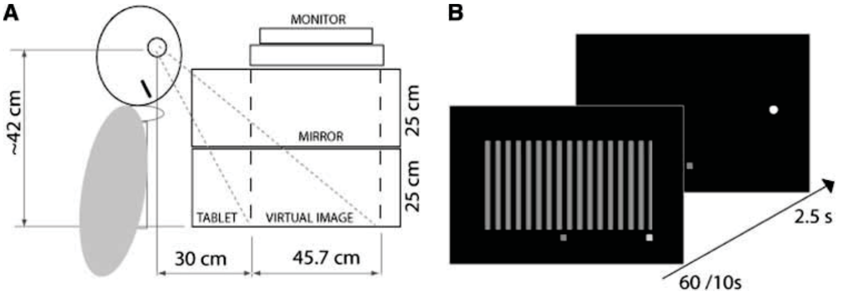


Fig. 1 **a** Side view of the experimental setup. The subjects looked at the mirror and saw the image projected on the surface of the graphic tablet. A chinrest was used to stabilise the head. They didn't have visual feedback of their hand position. **b** Adapting stimulus with the fixation point (*centred square*) used through all the experiments. After 60 s (or 10 s top-up adaptation), the lateral point cued the lateral position of the moving target

centred on the screen and the near and far edges subtended respectively 36.5 and 30 deg. As the grating moved laterally and therefore perpendicularly to the sagittal plane the average speed was 15.8 deg/s. The temporal frequency was 8 Hz and the spatial frequency was 0.56 and 0.46 c/deg for the near and far edges respectively. Subjects fixated a green dot situated below the grating through all the session keeping their head position fixed with the help of a chin-rest. After adaptation, a moving (Experiments 1 and 2) or a static (Experiment 3) target was presented and consisted of a white circle of 1.6 cm of diameter.

Data acquisition and analysis

The position of the pen on the tablet was recorded at a frame rate of 200 Hz. The individual position data time series were digitally low-pass filtered with a Butterworth filter (cutoff frequency of 5 Hz). First and second temporal derivatives of the position were computed from the smoothed data.

Experiment 1

In a first experiment we investigated the influence of MAE in pursuit arm movements by comparing the position of the (unseen) hand relative to the moving target across time when target and MAE moved in the same or opposite directions.

Subjects

Seven volunteers from our department participated in the experiment. Except for the authors, they were naive to the purpose of the experiment. Before the session, subjects gave their informed consent to participate in the study. The research in this study is part of an ongoing research program that has been approved by the local ethics committee.

Stimuli

Stimuli were ascribed to three different conditions: (1) Same and (2) opposite motion direction for moving target and MAE, and (3) a control condition, with no motion-adaptation. We tested these three different conditions both under eye-fixation and eye-pursuit conditions. In the former condition, subjects were instructed to maintain eye fixation during all the trial, whereas in the eye-pursuit condition, subjects tracked the moving target after foveal adaptation to motion. The direction of motion adaptation was blocked (4 blocks of 20 trials each, 80 trials in one session). In the first block the direction was chosen at random and the direction of motion was reversed with the beginning of a new block. Adaptation lasted for 60 s at every first trial of each block and a 10 s “top-up” re-adaptation was used in the following trials. Within a block the direction of the moving target was the same as the MAE in half of the trials and opposite in the other half. The two directions were presented randomly. Trials with no motion adaptation were presented in different sessions of 40 trials.

Procedure

At the beginning of each trial, while subjects brought their hand to a starting point (the same as fixation in the eye-fixation condition), we provided feedback of their hand position. Subjects were instructed to maintain fixation during the adaptation. In the eye-fixation condition, the fixation point was outside the moving grating (central point below the grating in Fig. 1b). In the eye-pursuit condition, the fixation point was exactly in the middle of the adapting grating. Once the adaptation (or re-adaptation) phase ended the grating disappeared and the manual pursuit period started. Feedback of the hand position was then removed. In the eye-fixation condition, subjects had to move the cursor (his/her hand) to an adapted position (previously occupied by the grating). A lateral point below the grating (see Fig. 1b), presented after the adaptation period, cued randomly the lateral direction (left or right) of the arm movement from the green fixation dot to the adapted zone. Subjects were instructed to move the hand to any point of their choice approximately aligned both with the yellow dot and with the vertical centre of the grating. At the end of this self-terminated hand movement, a moving target appeared at the final hand position and subjects had to track the moving target (10 cm/s) for 2.5 s while keeping fixating the central dot. In the eye pursuit condition, the same procedure was used except for the fact that subjects were instructed to follow the target with the eyes, therefore in both conditions the moving target was presented in an previously adapted retinal region. Subjects took one session with adaptation and one session without adaptation for each of the eye movement conditions and the order was randomize across subjects.

Results and discussion

The two upper panels of Fig. 2 show the average manual pursuit error as a function of time for the eye-fixation (left) and eye-pursuit (right) conditions split by MAE direction conditions: Same (solid line), Opposite (dashed line) and No adaptation (dotted line). We plotted this manual pursuit error as a signed error: positive values denote that hand position is ahead of the target position. The grey areas denote the 95% within-subject Confidence interval (CI) computed following the method described in Loftus and Masson (1994), so a direct comparison across time between adapting conditions can be easily made by inspecting

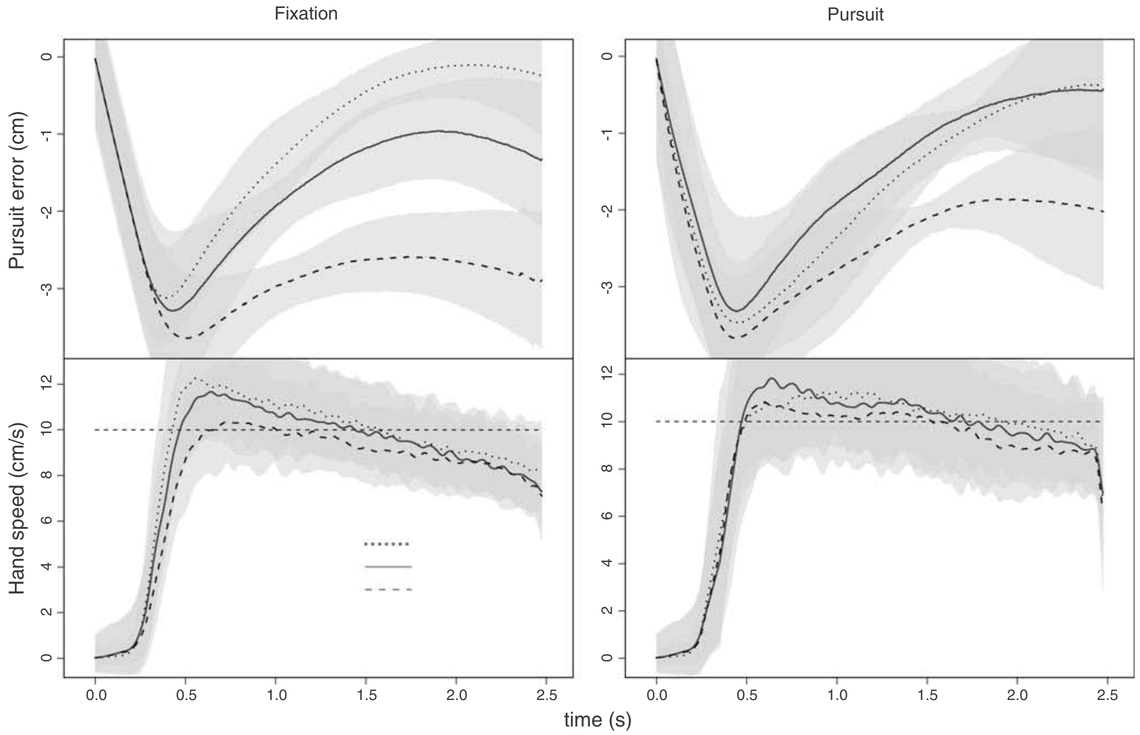


Fig. 2 *Upper panels* Effect of the motion after-effect on manual tracking error. The average pursuit signed error is shown as a function of time for the eye-fixation condition (*left panel*) and eye-pursuit (*right panel*). Data is shown for the three conditions: “Same” (same direction of the MAE and target motion), “Opposite” and a control condition with no motion adaptation. (*Bottom panels*) Hand speed as function of time for the eye-fixation condition (*left*) and eye-pursuit condition (*left*). The *horizontal dashed lines* denotes the target speed. All grey areas denote within-subject 95% Confidence intervals for the corresponding lines

whether there is some overlap of the CI. As can be seen, the error pattern is very similar for the fixation and pursuit conditions: overall, our results show that the hand position was trailing the target less when target and MAE direction was the same. In contrast, when target direction and MAE were opposite one another, subject’s hand moved more slowly, causing larger lags between the target and the hand position. There is a complete overlap between the no adaptation and the same as MAE condition along all the pursuing trajectory. However, considering the time course of the MAE, the effect of the adaptation seems to be larger in the fixation condition: the CI of the opposite MAE condition overlaps much less in the fixation condition than in the pursuit one. It is known that MAE is measured to be stronger in the periphery (like in our eye-fixation condition) when a nulling method with real motion is used to test the MAE (Wright 1986). This sort of interaction with real motion could explain the fact that the MAE turned out to be stronger in the fixation condition.

In addition, we conducted a 2-way repeated measure anova on the pursuit error with eye-movements (pursuit and fixation) and MAE condition (same, opposite and no adaptation) as within subjects variables. This analysis would help us test for differences between the critical conditions taking into account the average error. Only the MAE condition yielded a significant effect ($F(2,12) = 10.74$, $P = 0.002$). The means were -1.41, –1.6 and –2.5 cm for no-adaptation, same and opposite direction respectively. Neither eye movements ($F(2,12) < 1$, $P = 0.93$; means of –1.85 cm and –1.88 cm for fixation and pursuit respectively) nor the interaction between eye movements and MAE condition ($F(2,12) = 1.82$, $P = 0.20$) was significant. Post-hoc analysis revealed that the main effect of the MAE condition was due to the significant difference between the opposite direction and same ($t(6) = 5.22$, $P = 0.002$) and opposite and no-adaptation ($t(6) = 4.11$, $P = 0.006$). Importantly, no significant difference was observed between same direction and no-adaptation ($t = –1.52$, $P = 0.18$). The false discovery rate method (Benjamini and Hochberg 1995) was used to correct for type-I errors in the multiple t test comparisons.

One concern in the fixation condition is that subjects did not maintain fixation while tracking the target with the hand. The fact that we did not find evidence for a weaker effect of the MAE in the fixation condition runs counter to the possibility that subjects tried to pursue the target in this condition. Had the subjects tracked the target, we would have expected a smaller effect in the eye-fixation condition than in the eye-pursuit one because the target's image would then be projected on an unadapted retinal area. Although the MAE can be experienced in part of the visual field that were not stimulated at all (Snowden and Milne 1997), it is always weaker than the MAE at the stimulated locations which is consistent with adaptation at the local motion signal stage (López-Moliner et al. 2004).

The bottom panels of Fig. 2 show the average hand velocity for the same conditions. This average velocity reflects a typical trial in which the velocity of the hand reaches a maximum to catch up with the target and then becomes stable. Although there is a clear trend: the peak velocity is higher for the Same and No adapting conditions than for the opposite MAE one, the 95%-CI always overlapped.

At least two interpretations are consistent with this overall pattern of results. The first one would imply that the MAE does not affect the perceived position of the moving object but its speed. It is known that target speed affects the speed of the hand in interceptive tasks (Bairstow 1987), so that by moving the hand faster would result in smaller errors when MAE and target move in the same direction. Although we did not measure whether the speed was perceived faster in the "same-direction" condition, subjects reported so upon questioning after the experiment. This interpretation would also be consistent with that put forward in Smeets and Brenner (1995) using a hitting task. The second interpretation is that motion signals are actually affecting the perceived position of the moving object as reported in Linares et al. (2007) by using perceptual judgements. If the perceived position is shifted forward in the direction of motion then subjects will tend to minimize the discrepancy between the perceived (shifted) visual position and the felt position of the (unseen) hand. Linares et al. (2007) did not find differences on the perceived position between the condition with no adaptation and MAE in the same direction of target motion: with time the position of the moving object was equally shifted in the direction of motion. Our results support the second interpretation. In the next experiment we will systematically address whether MAE distinctly affects a pointing hand movement at different times since motion onset.

Experiment 2

Perceptual judgements in Linares et al. (2007) were made under eye-fixation conditions. So as to keep the experimental conditions as similar as possible we will only use the eye-fixation condition in this experiment. Although the target will be localized with less precision in this condition this will not undermine our potential conclusions as the loss in spatial resolution would affect both MAE directions to the same extent.

Subjects

Six people who participated in Experiment 1 served as subjects in Experiment 2. Except for the authors, participants were all unaware of the goal of the study.

Stimuli

In Experiment 2 we presented the same adaptation phase as in the previous experiment, a sinusoidal grating for 60 s. Subjects looked at the fixation point which was at the same position as the fixation point in the eye-fixation condition of Experiment 1. Once the grating disappeared, a target appeared at the left (right) of the grating and began to move rightwards (leftwards) towards the centre of the screen with a velocity of 10 cm/s during 2.5 s. The vertical position of the target was exactly at the vertical centre of the screen which corresponded with the vertical centre of the grating. The size of the target was the same as before (1.6 cm). A go-signal (a beep) was sounded at three different times (0.3, 0.8 and 1.6 s) from motion onset. As in the previous experiment, all trials were preceded by a 10 s "top-up" motion re-adaptation period. This period was 60 s for the first trial of each block.

Procedure

As before, subjects had to move their hand to the fixation point and once they reached this position visual feedback of their hand position was removed. Motion adaptation started for the designated period (60/10 s). After the adaptation phase, a target moving leftwards or rightwards appeared and subjects had to wait until they heard the beep in order to reach the target as soon as possible. We called "waiting-time" the time interval between the beginning of target movement and the go-signal or beep.

The experiment consisted of 96 trials, divided in 4 blocks of 24 trials. Target and MAE had the same direction in half of the trials and opposite in the other half. The three different waiting-times were randomly interleaved within every block. In addition, subjects were tested in a control condition in which there was no motion adaptation. The four blocks with adaptation were run within one session and each subject took part in one adaptation session. The control condition was run in a different session.

Results

Figure 3 shows the pointing error as a function of waiting-time. Bars are split by MAE direction condition: same

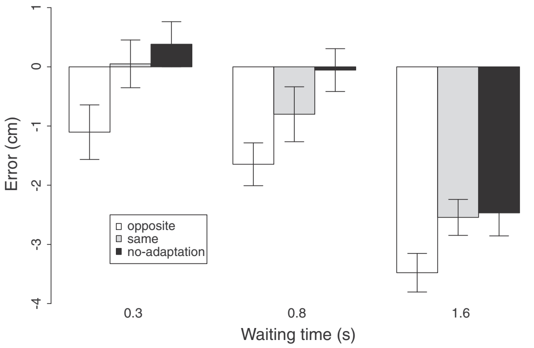


Fig. 3 *Bar plot* showing the effect of MAE on the pointing spatial error as a function of waiting time, split by "Same","Opposite" and "No-adaptation" MAE direction conditions. The height of the bars represents the error in the pointing task, and negative errors denote that hand positions ended behind the target. *Error bars* represent between-subject SEs

(grey), opposite (white) and no-adaptation (black). Negative error values indicate that subjects undershot the target (final position of the hand lagged the target). The results show a clear bias that increases with the target's travelled distance for all direction conditions: hand landed behind the moving target. Only in the first waiting-time, 0.3 s, we observed positive values: hand ended ahead of the moving target in the direction of motion. This point is resumed in the discussion.

A repeated-measure ANOVA was conducted on the pointing error with waiting-time and direction condition as within subject variables. Both factors yielded a significant effect (direction: $F(2,10) = 5.81$, $P = 0.021$; waiting time: $F(2,10) = 9.59$, $P = 0.004$). The interaction was not significant ($F(4,20) < 1$, $P = 0.92$).

Movement kinematics

We performed the same kind of ANOVA on reaction time, peak velocity and time to peak velocity.

Reaction time. We defined RT as the time interval between the beep and the start of hand movement. More specifically, beginning of hand movement was defined when the hand reached a speed of 0.5 cm/s. Only waiting-time yielded a significant main effect on RT ($F(2,10) = 38.45$, $P < 0.001$) with means of 280, 220 and 190 ms respectively for 0.3, 0.8 and 1.6 s waiting times. One possible explanation for the slower RT in the waiting time of 0.3 s could be the higher temporal uncertainty about the moment of the beep at the initial part of the target's motion. Another possibility, not incompatible though, is that subjects reach a maximum response preparation for longer time intervals (Bertelson and Boons 1960) resulting in the observed RT reduction. Direction did not affect RT significantly ($F(2,10) < 1$; $P = 0.61$) but the interaction between direction and waiting time was significant ($F(4,20) = 3.18$, $P = 0.035$) due to a smaller reaction time in the no adaptation condition (159 ms) than in the opposite (193 ms) and same direction (192 ms) conditions for the waiting time of 1.6 s.

Peak velocity and Time to peak velocity. As with reaction time, only waiting-time produced a significant main effect on both peak velocity ($F(2,10) = 12.89$, $P = 0.002$) and time to peak velocity ($F(2,10) = 33.56$, $P < 0.001$). Mean peak velocities were 36.4, 41.87 and 47.72 cm/s respectively for 0.3, 0.8 and 1.6 s waiting times. Time to peak velocities were 380, 365 and 325 ms for same waiting times. Therefore, peak velocity was faster for 1.6 s of waiting time and it took shorter than the other waiting times to reach the maximum velocity. Neither direction nor the interaction direction by waiting time produced any significant effect.

Discussion

MAE affected the final hand position in the same direction as in Experiment 1: the hand lagged most in the opposite condition (MAE and target had opposite directions). The effect of MAE on the final hand position was not due to any correction movement as the trajectories were virtually straight. Interestingly, direction condition did not have a significant effect on peak velocity. Unlike previous studies (e.g. Smeets and Brenner 1995) in which hand moved faster for faster targets, we did not find evidence for faster hand movements when the MAE signal was in the same direction as the moving target. Therefore the error difference between the direction condition (same/different) cannot be due to distinct velocity profiles. However, this pattern is consistent with the position of the moving target being further extrapolated for the "same direction" condition when compared to the "opposite" one. As mentioned above, we found a bias of the final hand position that increased with time (or travelled distance as we did not unconfound both variables). As this bias also appeared in the control condition and showed the same time course, we can conclude that this bias is not due to the MAE effect. A similar bias has been reported previously by van Beers et al. (1998).

So far our data suggest that motion signals are used to update position information of moving objects in a very similar way as reported for perceptual judgements (Linares et al. 2007). This interpretation leads us to predict that motion signals due to MAE would not be of any use if a target object is not moving and hence there is no need to update its position. We tested this hypothesis in the last experiment.

Experiment 3

Whitney and Cavanagh (2000) showed that motion information in one region of the visual field influences the perceived positions of flashed objects, even when they are located in distant areas of the stimulus scene. However, it is not clear whether a motion signal (MAE in our case) will affect the pointing to a static target. The difference between flashed and static objects is not trivial. (Mitrani and Dimitrov 1982; Van Beers et al. 2001) showed that subjects made larger localization errors with flashed stimuli when compared to static stimuli ahead of the fovea, but not behind it. Supposedly, the retinal slip caused by static objects may help localize their position especially when eye movements are involved. In this experiment we test the hypothesis that MAE will not affect pointing to static targets, as there is no need for the visual system to use motion information to update the position of a static object.

Subjects

The same six subjects that participated in Experiment 2 volunteered to take part in this experiment. They all had normal or corrected-to-normal vision.

Stimuli

We used the same adapting stimulus as in the previous experiments. Once the grating disappeared, a static target (diameter 1.6 cm) was shown for 2.5 s at a horizontal position chosen at random between 10 cm to the left and to the right of the centre of the screen.

Procedure

As in previous experiments, subjects were instructed to maintain fixation on the centred green point, and started the adaptation period. Once the adapting grating disappeared, a static target was shown and subjects had to point at it with the unseen hand. As before, grating direction was blocked. Each subject took part in one session that consisted of two blocks of 20 trials each.

Results and discussion

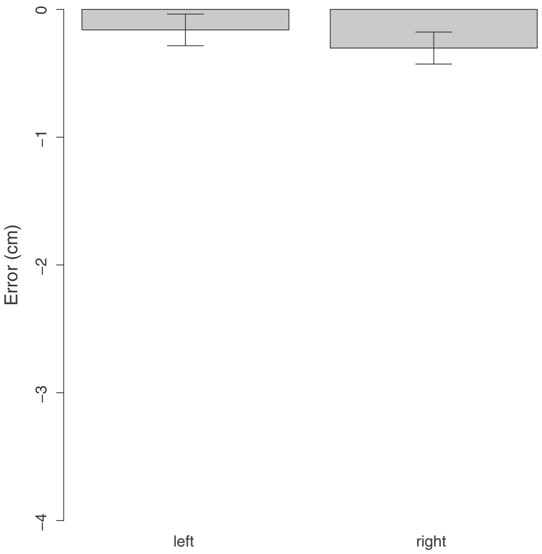


Fig. 4 Errors of the pointing task to the static target are shown for the two adaptation directions. *Error bars* represent between-subject SEs

Figure 4 shows a bar plot with the pointing error in each grating direction (left–right). Negative values indicate that subjects pointed to the left of the target. The absolute difference, averaged across subjects, between the two MAE directions was about 1.5 mm. This difference failed to be significant (paired *t* test, $t(5) = -0.98$, $P = 0.37$). Some previous studies have suggested that retinal background motion would have an effect on the initial part of the trajectory which would be corrected to hit the target accurately (Brenner and Smeets 1997; Whitney and Cavanagh 2003). The MAE signals could likewise have the same effect on our trajectories. Figure 5 shows the mean trajectories for the two MAE directions and both trajectories have the same shape with no evident initial correction for either MAE direction. Neither reaction time nor movement time were affected by the direction of the MAE. Mean reaction time was 571 ms and movement time was 871 ms. Previous studies have also reported a lack of effect of motion signals (i.e. background motion) on the final hand position when pointing to a static target (e.g. Bridgeman et al. 1981) in spite of the perceived target position being shifted in the direction of motion. Therefore, this result is compatible with the hypothesis that motion signals are used to update the position of moving objects but have no effect on static not-flashed objects.

Conclusions

We have shown in this study that motion signals are relevant for hand movements and have an effect when the target is moving. We conclude that the effect of motion signals is due to its role in updating the changing position of a moving object (Experiments 1 and 2) and that this effect dissipates when there are no new positions to update (Experiment 3). The effect we have found in hand movements parallels those previously reported in relative position judgements (Linares et al. 2007).

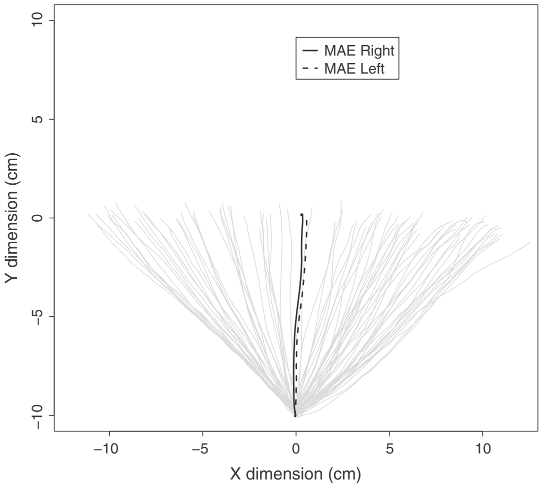


Fig. 5 Patterns of the mean trajectories in each grating direction: *Left* (*solid line*) and *Right* (*dotted line*). *Grey lines* denote individual trajectories for a representative subject

Our interpretation is consistent with the view that hand or arm trajectories are mainly determined by (changing) target position (e.g. Honda 1990; Smeets and Brenner 1995). However while Smeets and Brenner, for example, show a selective effect of (background) motion signals on some components of the motor action: reaction time and velocity but not final position, we here maintain that the effect of motion signals on hand movements is not restricted to such components.

Usually, as in Smeets and Brenner (1995), the target to be tracked is brought to the fovea in order to increase the spatial resolution and, furthermore, additional extra-retinal signals can be used to update its changing position. However, in our eye-pursuit condition in Experiment 1 we also observed a significant effect of the MAE signals. Therefore smooth pursuit eye movements cannot explain the difference between our findings and those of Smeets and Brenner. Two important differences between the two studies should be pointed out. First, in our study subjects did not have visual feedback of their hand position, so correction movements could only be made on the basis of comparing the visual target and the felt proprioceptive position of the hand. The lack of visual feedback would prevent subjects from integrating information from the different senses resulting in a possible inconsistent use of position and motion information (Smeets et al. 2006) If subjects had had feedback they would have integrated visual and proprioceptive position information to obtain the position of the hand relative to the target and correct their trajectory accordingly. Second, global background motion and MAE signals might have different sort of effects. Certainly MAE signals are more local and integrating motion signals with target motion might require signals to be locally defined in the area of the target. If target motion is used for position extrapolation (Nijhawan 1994) and such a mechanism has an adaptive role then it would imply that only those motion signals that are likely generated by the target are integrated. An interesting finding is that MAE effect could only be revealed when the direction of the MAE was opposite the target direction. If position is extrapolated, energy carried by real motion would suffice and MAE signals in the same direction would not contribute in a significant way.

Acknowledgments We would like to thank two anonymous reviewers for their comments and suggestions. This work has been supported by European Science Foundation, Eurocores 06-CNCC-FP-012 grant, and Grant SEJ2006-27544-E from the Spanish Government.

References

Bairstow PJ (1987) Analysis of hand movement to moving targets. Hum Mov Sci 6:205–231

Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 51:289–300

Bertelson P, Boons JP (1960) Time uncertainty and choice reaction time. Nature 187:531–532

Braun DI, Pracejus L, Gegenfurtner KR (2006) Motion aftereffect elicits smooth pursuit eye movements. J Vis 6:671–684

Brenner E, Smeets JB (1997) Fast responses of the human hand to changes in target position. J Motion Behav 29(4):297–310

Bridgeman B, Kirch M, Sperling A (1981) Segregation of cognitive and motor aspects of visual function using induced motion. Percept Psychophys 29:336–342

Engel KC, Anderson JH, Soechting F (2000) Similarity in the response of smooth pursuit and manual tracking to a change in the direction of target motion. J Neurophysiol 84:1149–1156

Gomi H, Abekawa N, Nishida S (2006) Spatiotemporal tuning of rapid interactions between visual-motion analysis and reaching movement. J Neurosci 26:5301–5308

Gregory RL (1966) Eye and Brain. McGraw-Hill, New York

Honda H (1990) The extraretinal signal from the pursuit-eye-movement system: its role in the perceptual and the egocentric localization systems. Percept Psychophys 48:509–515

Linares D, López-Moliner J, Johnston A (2007) Motion signal and the perceived positions of moving objects. J Vis 7(7):1–7

Loftus GR, Masson MEJ (1994) Using confidence intervals in within-subject designs. Psychon Bull Rev 1:476–490

López-Moliner J, Smeets JBJ, Brenner E (2004) Components of motion perception revealed: two different after-effects from a single moving object. Vis Res 44:2545–2549

Maioli C, Falciati L, Gianesini T (2007) Pursuit eye movements involve a covert motor plan for manual tracking. J Neurosci 27:7168–7173

Mitrani L, Dimitrov G (1982) Retinal location and visual localization during pursuit eye movement. Vis Res 22(8):1047–1051

Nakayama K (1985) Biological image motion processing: a review. Vis Res 25:625–660

Nijhawan R (1994) Motion extrapolation in catching. Nature 370:256–257

Nishida S, Johnston A (1999) Influence of motion signals on the perceived position of spatial pattern. Nature 397:610–612

Saijo N, Murakami I, Nishida S, Gomi H (2005) Large-field visual motion directly induces an involuntary rapid manual following response. J Neurosci 25:4941–4951

Schlag J, Schlag-Rey M (2002) Through the eye, slowly: Delays and localization errors in visual system. Nat Rev Neurosci 3:191–200

Smeets JBJ, Brenner E (1995) Perception and action are based on the same visual information: distinction between position and velocity. J Exp Psychol Hum Percept Perform 21:19–31

Smeets JBJ, van den Dobbelsteen JJ, de Grave DDJ, van Beers RJ, Brenner E (2006) Sensory integration does not lead to sensory calibration. Proc Natl Acad Sci 103:18781–18786

Snowden RJ (1998) Shifts in perceived position following adaptation to visual motion. Curr Biol 8:1343–1345

Snowden RJ, Milne AB (1997) Phantom motion aftereffects - evidence of detectors for the analysis of optic flow. Curr Biol 7:717–722

van Beers RJ, Sittig AC, van der Gon JJD (1998) The precision of proprioceptive position sense. Exp Brain Res 122:367–377

van Beers RJ, Wolpert DM, Haggard P (2001) Sensorimotor integration compensates for visual localization errors during smooth pursuit eye movements. J Neurophysiol 85:1914–1922

Watamaniuk SNJ, Heinen SJ (2007) Storage of an oculomotor motion aftereffect. Vis Res 47:466–473

Whitaker D, McGraw PV, Pearson S (1999) Non-veridical size perception of expanding and contracting ob jects. Vis Res 39:2999–3009

Whitney D (2002) The influence of visual motion on perceived position. Trends Cogn Sci 6(5):211–216

Whitney D, Cavanagh P (2000) Motion distorts visual space: shitfting the perceived position of remote stationary objects. Nat Neurosci 3:954–959

Whitney D, Cavanagh P (2003) Motion adaptation shifts apparent position without the motion aftereffect. Percept Psychophys 65:1011–1018

Whitney D, Goodale M (2005) Visual motion due to eye movements helps guide the hand. J Vis 162:394–400

Whitney D, Ellison A, Rice NJ, Arnold D, Goodale M, Walsh V, Milner D (2007) Visually guided reaching depends on motion area MT+. Cereb Cortex 17:2644–2649

Wilmer JB, Nakayama K (2007) Two distinct visual motion mechanisms for smooth pursuit: Evidence form individual differences. Neuron 54:987–1000

Wright MJ (1986) Apparent velocity of motion aftereffects in central and peripheral vision. Perception 15:603–612

Yamagishi N, Anderson SJ, Ashida H (2001) Evidence for dissociation between the perceptual and visuomotor systems in humans. Proc R Soc Lond 268:973–977

4

STUDY II
FEEDFORWARD CONNECTIONS THROUGH AREA MT DRIVE THE INFLUENCE OF MOTION IN POSITION CODING[‡]

[‡] This chapter corresponds to:
Rodríguez-Herreros, B., Rodríguez-Fornells, A., López-Moliner, J. (2014). Fast feedforward connections through area MT+ drive the influence of motion in position coding. ***Under review***

RESUMEN

Una percepción y acción exitosa y competente en el mundo real requiere una codificación precisa y rápida de la posición de los objetos. En particular, las señales de movimiento pueden ejercer una influencia poderosa sobre la localización de objetos en el entorno. Dado el papel crítico del área visual primaria (V1) en la codificación de la posición de objetos, algunos estudios han propuesto tradicionalmente las vías de retroalimentación ‘feedback’ desde el área temporal media (MT) a V1 como una explicación de los efectos del movimiento en la asignación de la posición. Sin embargo, la evidencia concreta de respuestas neuronales relativas a este postulado aún no ha sido probada. Usando potenciales evocados relacionados con eventos (ERPs), medimos la latencia de las respuestas evocadas visuales (VEPs) en la corteza visual para desentrañar el circuito cerebral que transmite las ilusiones de movimiento que afectan a la posición. Por primera vez, proporcionamos evidencia neurofisiológica de que las señales de movimiento cercanas a un objeto retrasan la detección del mismo, y que el procesamiento sensorial más lento correlaciona con el desplazamiento espacial del objeto inducido por el movimiento. Por otra parte, hemos identificado un procesamiento muy temprano del movimiento en el área MT, independiente de la conexión con V1, como el contribuyente causal de este retraso neuronal. Nuestros resultados tienen importantes implicaciones en nuestra comprensión de las bases neuronales de codificación de posición. Creemos que estos resultados representan un fuerte avance más allá del trabajo existente en aspectos globales de procesamiento visual, ya que describen una estrategia de predicción, en consonancia con los mecanismos de compensación, para extender el uso beneficioso del movimiento a través de los rápidos circuitos de alimentación directa ‘feedforward’ por vías visuales no primarias.

RESUM

Una percepció i acció exitosa i competent en el món real requereix una codificació acurada i ràpida de la posició dels objectes. En concret, les senyals de moviment poden exercir una poderosa influència sobre la localització d'objectes en l'entorn. Atès el paper crític de l'àrea visual primària (V1) en la codificació de la posició d'objectes, alguns estudis han proposat tradicionalment les vies de retroalimentació ‘feedback’ des de l'àrea MT a V1 com una explicació dels efectes del moviment en l'assignació de la posició. No obstant això, l'evidència concreta de respostes neuronals relatives a aquest postulat encara no ha estat provada. Utilitzant potencials evocats relacionats amb esdeveniments (ERPs), vam mesurar la latència de les respostes evocades visuals (VEPs) en l'escorça visual per a desentranyar el circuit cerebral que transmet les il·lusions de moviment que afecten a la posició. Per primera vegada, proporcionem evidència neurofisiològica de que les senyals de moviment properes a un objecte retarden la detecció del mateix, i que el processament sensorial més lent correlaciona amb el desplaçament espacial de l'objecte induït pel moviment. Per altra banda, hem identificat un processament molt ràpid del moviment en l'àrea MT, independent de la connexió amb V1, com el contribuent causal d’aquest retard neuronal. Els nostres resultats tenen importants implicacions en la comprensió de les bases neuronals de la codificació de la posició. Creiem que aquests resultats representen un fort avanç més enllà del treball existent en aspectes globals de processament visual, ja que descriuen una estratègia de predicció, d'acord amb els mecanismes de compensació, per estendre l’ús beneficiós del moviment a través de ràpids circuits d’alimentació directa 'feedforward' per vies visuals no primàries.

4.1 Abstract

A basic function of the visual system is the location of objects. Psychophysical evidence has shown that motion signals can shift the perceived position of stationary objects. The neural mechanisms that sustain this effect are generally assumed to be mediated by feedback connections from the middle temporal area (MT) to the primary visual cortex (V1). However, evidence from neural responses is lacking. We used event-related potentials (ERPs) and Granger Causality Analysis (GCA) —a tool to predict the causal connectivity of two brain responses— to unravel the circuit by which motion influences position coding. We found that the motion-induced shift is related to a neural delay with larger shifts of perceived position being correlated with slower sensory processing. We identified early activity in MT as the cause of this delay which likely reflects the early use of motion in coding the position. These results suggest rapid feedforward circuits, rather than feedback pathways, as the main neural substrate in charge of the motion-induced mislocalization.

4.2 Introduction

Object localization is a challenging task for the visual system. Numerous psychophysical findings indicate that position coding depends not only on the retinal location (Bock, 1986) and eye movements (Cai, Pouget, Schlag-Rey & Schlag, 1997), but also on nearby motion (Snowden, 1998). A particularly compelling example occurs when a stationary object is flashed in the vicinity of a moving pattern: the perceived position of and the reaching towards the object are biased in the direction of motion (Brenner & Smeets, 1997; De Valois & De Valois, 1991; Whitney & Cavanagh, 2000). These shifts indicate that motion-related brain areas, such as MT, are crucial in spatial coding (McGraw, Walsh & Barrett, 2004). Little is known, however, about the neural mechanisms that serve to induce the bias. Animal single-cell recordings described motion-induced shifts in the receptive field properties of retinal, V1 and V4 neurons (Berry, Brivanlou, Jordan & Meister, 1999; Fu, Shen, Gao & Dan, 2004; Sundberg, Fallah & Reynolds, 2006). Neuroimaging studies revealed similar changes in the retinotopic representation of stationary flashes in V1 and MT (Maus, Fischer & Whitney, 2013; Whitney, Goltz, et al., 2003). As V1 is involved in position coding, motion's influence have been traditionally associated with MT-V1 recurrent circuits (De Valois & De Valois, 1991; Nishida & Johnston, 1999). Structurally, a rich network of reciprocal projections exist between these two regions, conveying feedback connections to V1 (Shipp & Zeki, 1989). This is done, however, at the cost of adding neural delays that compromise fast recovering of spatial codes, especially in rapid goal-directed actions, early affected by motion (~120 ms) (Brenner & Smeets, 1997; Whitney, Westwood & Goodale, 2003).

We investigated the time-course of the neural correlates associated with motion-induced shifts. We explored the possibility that the bias may be fastly subserved by feedforward connections, before resorting to the MT-V1 re-entrant circuit. MT neurons responding to visual stimuli fire almost simultaneously to V1 (~40-75 ms) (Maunsell, 1987; Nowak & Bullier, 1997). It is difficult to assume, therefore, that earliest MT responses depend on V1 input. Instead, thalamocortical projections seem to sustain MT short latency (Sincich, Park, Wohlgemuth & Horton, 2004; Standage & Benevento, 1983), carrying visual signals to V1 and MT in parallel (ffytche, Guy & Zeki, 1995). Both motion discrimination (Barbur, Watson, Frackowiak & Zeki, 1993) and accurate pointing

(Perenin & Jeannerod, 1975) persisted in patients with V1 lesions, reflecting the importance of thalamic pathways in perception and action processing streams. Consequently, fast motion-reaching interactions (Gomi, Abekawa & Nishida, 2006; Saijo, Murakami, Nishida & Gomi, 2005) might not hinge on feedback connections to V1, but through MT affecting spatial codes earlier (Whitney et al., 2007).

We determined the motion-induced shift by quantifying hand's deviation when reaching a stationary flash in the presence of motion. Visual-evoked potentials (VEPs) were used as a measure of electrophysiological activity in the visual cortex. We found that motion delayed the detection of the flash, and that this delay predicted the size of the shift. Early activity in MT was the causal contributor to this delay, suggesting a predictive strategy to extend the beneficial use of motion through feedforward circuits.

4.3 Materials and Methods

4.3.1 PARTICIPANTS

Twenty right-handed naïve volunteers (10 women; 23.6 ± 2.6 years) participated in the experiment. Prior to the experiment, participants provided written informed consent. Uncorrected deficits in visual acuity or neuromuscular disorders were not reported. The study was approved by the local ethics committee in accord with the declaration of Helsinki.

4.3.2 APPARATUS AND BEHAVIORAL ACQUISITION

Participants sat in front of a digital tablet (Calcomp DrawingBoard III 34240) which was (vertical distance) 48-50 cm below the eyes. Virtual stimuli were generated by an Apple MacPro 2.6GHz Quad-Core and displayed by a Mitsubishi SD220U projector (72 Hz, 800x600 pixels). The stimuli was viewed through a half-silvered mirror between the projected image and a digital tablet in order to perceive the image on the tablet where the movements were executed. Participants used a stylus (which we will refer as the hand position) to perform the task underneath the half-silvered mirror. Its position on the tablet was recorded at 200 Hz with a 0.01mm spatial resolution.

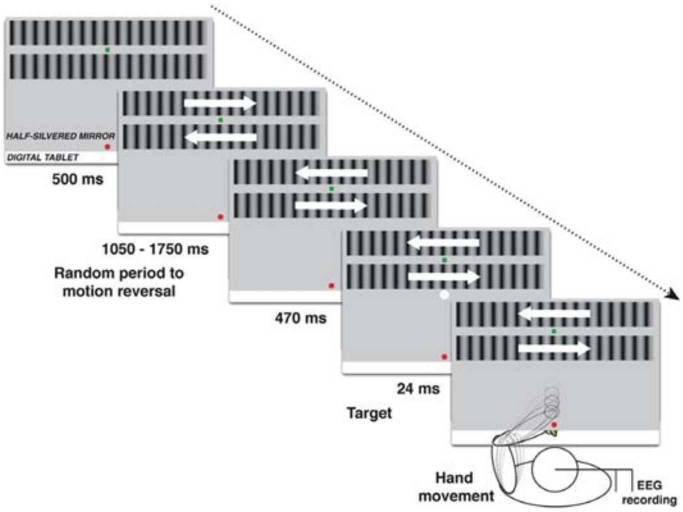


Figure 4.1. Task design and experimental setup. Schematic illustration of a standard 470 ISA trial. White arrows indicate the direction of motion. Participants fixated on a green square between the two gratings. The initial position of the hand was depicted with a red dot. We measured hand's endpoint deviation at each ISA and compared it to an identical condition but with a static pattern. When the grating was initially moving to the right, the influence of the motion signals was calculated by subtracting averaged hand endpoint position for initially rightward motion trials minus initially leftwards motion trials, and vice versa (Whitney, Westwood, et al., 2003). Vision of the hand was occluded to ensure that the influence of motion on reaching was not due to visual information of the hand, and to exclude any effect of motion other than that caused by the stimulus.

4.3.3 STIMULUS DESIGN AND PROCEDURE

Two sinusoidal gratings (contrast of 100%) moved horizontally in opposite directions (speed 12.8° s^{-1} and TF of 10 Hz) with vertical and horizontal visual angles of 5.7° x 26.7° (Whitney, Westwood, et al., 2003). This speed of motion, lower than 16o s-1, allowed the visual system to similarly integrate local luminance of stationary and moving objects (Burr, 1981). Participants fixated their gaze on a green square located between the gratings. In each trial, the position of the fixation point varied laterally within a range of 3 cm (1.16° approx.). The gratings remained static during the first 500 ms of the trial and then began to drift for a period between 1050 and 1750 ms. After this time they reversed their direction and continued moving for an equivalent period of time in the opposite direction. The initial direction of the gratings was randomized in each trial. An additional condition with a static grating was added to the experiment as a control condition. Either before or after the reversal, a target (flash) of 2 cm in diameter was presented for 24 ms. The target was randomly presented at five different times (ISA, interstimulus asynchrony from -720 ms before to 470 ms after the motion reversal: -720, -235, 0, 275 or 470 ms) (**Figure 4.1**). In the static condition, the fixed timing of the flash onset was identical to the moving condition, even though there was no motion reversal. The lateral (*x*) coordinate of the target location also varied randomly from trial to trial (-3, 0 +3 cm), to prevent subjects from using stereotyped movements to memorized positions. Participants were instructed to reach as fast as possible the target's position as accurately as possible. The distance between the starting position and the target was approximately 20 cm. We encouraged participants to refrain from doing excessive body, head and eye movements, although they were not physically restrained to prevent subject's behaviour from being different than in natural conditions (Steinman, Kowler & Collewijn, 1990). Each participant completed 27 blocks of 100 trials distributed in two different days (18 moving, 9 static). One minute of rest was given between each block. Half of the blocks were performed with the right hand and the other half were executed with the left hand, ensuring the control of possible motor asymmetries in the EEG data. Consequently, there were 90 trials for each hand, motion, and ISA. All conditions were counterbalanced across participants. the location of a flashed stationary object using a stylus pen through a digital tablet (Whitney, Westwood, et al., 2003).

4.3.4 BEHAVIORAL ANALYSIS

Data recording began 200 ms before the onset of the stimulus and ended 500 ms after the end of the movement. We registered the *x* (lateral) and *y* (depth) tablet coordinates of the hand trajectory for each trial. The relevant error (e.g. induced by gratings motion) was that observed along the lateral dimension, defined as the distance between the target and the hand endpoint position in the abscissa. A negative pointing bias indicated that the hand movement ended at the left of the target, and vice versa. The motion-induced mislocalization was determined by the absolute value of the difference between the spatial error in the static condition minus the spatial error in the moving condition. A velocity threshold of 50 mm s^{-1} was used to detect the beginning and the end of the hand movement. Reaction times that were out of the 200-800 ms range were discarded from the analysis. Left and right hand movements were collapsed in the analysis since the used hand did not yield any significant main effects or interaction ($p > 0.18$ for all comparisons). We conducted a 2 x 5 repeated measures analysis of variance (ANOVA) with factors Motion (static, moving) and ISA (-720, -235, 0, 275, 470) to determine their influence on the hand endpoint position. ISA with the most biased averaged endpoint position was considered as 'high' mislocalization, whereas ISA with the minimum misalignment was defined as 'low' mislocalization. We tested differences between the two (moving vs. static) average values of spatial error for each ISA's value using paired t-tests with Bonferroni's correction.

4.3.5 EEG ACQUISITION AND ANALYSIS

Continuous EEG signal was acquired to register early VEPs for all experimental conditions. EEG was recorded from 27 scalp electrodes mounted in an elastic electrocap (Electro-Cap) referenced against the right mastoid electrode and re-referenced off-line against the half mean of the left mastoid. The electrodes were located at standard 10/20 positions: F3/4, C3/4, P3/4, O1/2, F7/8, T3/4, T5/6, FC1/2, FC5/6, CP1/2, CP5/6, PO1/2, Fz, Cz, Pz. We monitored eye movements by electrodes placed above and below the right eye, and on the outer canthi of the left and right eyes, respectively. Electrode impedances were kept below 5kΩ. The electrophysiological signals were sampled at 250 Hz and filtered on-line with a bandpass of 0.01-50 Hz (half-amplitude cutoffs). Trials with base-to-peak electrooculogram (EOG) amplitude of more than 50 μV, amplifier saturation, or a baseline shift exceeding 200 μV s^{-1} were automatically rejected (Cunillera, Gomila & Rodriguez-Fornells, 2008).

Stimulus-locked ERPs for artifact-free trials were averaged over epochs of 400 ms, including a 100 ms pre-stimulus baseline. Only participants with at least 75 artifact-free trials for each response hand, motion direction and ISA were included in the analysis ($n = 18$). The hand (left or right) was not considered as a factor, since preliminary analyses revealed a lack of statistical main effects and interactions ($P > 0.31$ for all comparisons). For an easier visualization, we therefore collapsed hand factor with the right-left flip of the hemispheres in trials performed with left hand to align ipsilateral and contralateral channels (Stevens, Calhoun & Kiehl, 2005). After averaging, epochs were low-pass filtered with a cut-off frequency of 30 Hz in order to facilitate the peak measurement of the VEPs along the epoch for all conditions (Rodionov, Goodman, Fisher, Rosenstein & Sohmer, 2002). We specifically measured the peak-latencies of the visual N1 component, the primary VEP elicited by the perception of an object. The peak of the N1 was defined as the most negative peak within the 0–270 ms time-window (Cunillera et al., 2008). We submitted N1 latency values to an ANOVA that included two within-subjects factors for the topographical study of N1: Motion (static vs. moving) and Electrode (19 levels Fz, T3, CP5, C3, CP1, Cz, CP2, C4, CP6, T4, T5, P3, Pz, P4, T6, PO1, PO2, O1, O2). Motion x Electrode interaction was decomposed by selecting twelve of these 19 electrodes for a topographical analysis according to three factors (Cunillera, Toro, Sebastian-Galles & Rodriguez-Fornells, 2006): Hemisphere [2 levels: contralateral (T3, T5, O1, C3, P3, PO1), ipsilateral (T4, T6, O2, C4, P4, PO2)], Laterality [2 levels: lateral (T3, T5, O1, T4, T6, O2), central (C3, P3, PO1, C4, P4, PO2)] and Anterior-posterior [3 levels: anterior (T3, C3, T4, C4), medial (T5, P3, T6, P4), posterior (O1, PO1, O2, PO2)]. This analysis was carried on data corrected using the vector normalization procedure (McCarthy & Wood, 1985). We performed a subsequent analysis of N1 latency in static and moving conditions as a function of the within-subject ISA factor confined to the region that showed a maximum effect (parieto-central, Pz). Post-hoc analyses using paired t-tests were performed when appropriate. Finally, we conducted Pearson bivariate correlations to analyze the relationship between behavioral and electrophysiological data using a linear regression analysis. Two ISA values were not considered. First, -235 ISA was discarded since hand position was affected by online corrections during reaching, distorting the motion-induced shift (Whitney, Westwood, et al., 2003). Second, preliminary analysis of 275 ISA showed that motion-reversal VEPs modulated both the N1 amplitude and latency (Kuba, Toyonaga & Kubova, 1992).

4.3.6 CURRENT SOURCE DENSITY (CSD) ANALYSIS

CSD is a reference-free technique that computes the second spatial derivative (Laplacian) of the scalp electric potential. Laplacian provides the location, direction (entering (*sinks*) and leaving (*sources*) the scalp (Nunez, 2006)) and intensity of the radial current flow that determine an ERP topography (Mitzdorf, 1985; Perrin, Pernier, Bertrand & Echallier, 1989). Using CSD, we aimed to study the possible neural substrate of the motion-induced mislocalization. CSD estimates permitted to refine the voltage source localizations of the earliest VEPs at the initial stages that succeed the target onset. We therefore transformed all the averaged ERP waveforms into reference-free current source density estimates (µV cm^{-2} units, head radius=10 cm). We used the spherical spline surface Laplacian (Perrin et al., 1989) with computation parameters (50 iterations; spline flexibility $m = 4$; smoothing constant $\lambda = 10^{-5}$) previously established for our 27-channel recording montage). Hand factor was collapsed ($P > 0.4$ for all comparisons) and hemispheres were swapped. Preliminary analyses of CSD estimates discarded the hemisphere (contralateral or ipsilateral) as a relevant factor, as they revealed a lack of statistical main effect and interactions ($P > 0.2$ for all comparisons).

As ERP data, separate stimulus-locked CSD waveforms for artifact-free trials were averaged over epochs of -100 ms to 400 ms for each condition. CSD estimates of high (0 ISA) and low (470 ISA) mislocalization at temporal, occipital and parieto-occipital subsets (homologous electrodes for both hemispheres) were submitted to a repeated measures ANOVA which included four within-subjects factors: Mislocalization (high, low) Motion (static, moving), Electrode (T5, T6, PO1, PO2, O1, O2) and Time (0-20, 20-40, 40-60, 60-80, 80-100 ms). We systematically assessed the source of interactions by calculating pairwise comparisons using paired t-tests. T-tests were also applied specifically to the peak of the sink/source component (48-72 ms). We conducted Pearson correlations to analyze the relationship between the N1 latency and the amplitude of the early VEPs. Time windows for the measurement of early VEPs mean amplitudes were defined on the basis of the peak of the sink/source activity (60 ms). Next, mean amplitudes were determined within a ±12 ms time window centered on this latency (48-72 ms). Both in ERP and CSD analysis, Bonferroni's and Greenhouse-Geisser epsilon correction were applied (Jennings & Wood, 1976).

4.3.7 SOURCE LOCALIZATION ANALYSIS

Brain Electric Source Analysis (BESA 2000 version 5.3 (Scherg, 1990)) was used to estimate the cortical areas in which the early VEP generators were located. BESA algorithm computes the location and the orientation of multiple equivalent dipolar sources by calculating the voltage scalp distribution that would be produced for a given dipole model (forward solution) and comparing it with the original scalp distribution. Interactive changes in the location and orientation of the dipole sources lead to a minimization of the residual variance (RV) between the model and the spatio-temporal distributions observed.

We modeled the anatomical sources of the motion-induced neural changes at 0 ISA The difference waveform obtained subtracting static minus motion condition was analyzed. Following previous descriptions of the neural sources of early VEPs (Clark, Fan & Hillyard, 1994), we fitted one single dipole and two symmetrical dipoles within intervals that encompassed the distinctive VEP components in the waveform (40-100 ms). A single dipole was fit to the N1 onset based on its occipital topography. The symmetrical dipoles were subsequently fitted near the temporo-occipital region based on the location of MT. The final locations of each dipole were projected on mean structural T1 MRI image of 24 individuals and converted into Talairach coordinates (Talairach & Tournoux, 1988). The latencies of major peaks in the dipole source waveforms were taken as indices of neural response timing. Each dipole pair was constrained to be mirror-image in location only.

4.3.8 GRANGER CAUSALITY ANALYSIS

We employed GCA to estimate the directionality of the neural interactions underlying the pattern of the scalp potential. GCA has become a useful tool to statistically predict the amount of variance in signal X that can be determined by the past of signal Y better than relying on the past of X alone (Granger, 1969). Granger causality is implemented by vector autoregressive (MVAR) modeling, in which a set of time series is modeled as weighted sums of past values. We adapted the Granger Causal Connectivity Analysis (GCCA) toolbox (Seth, 2010), widely accredited in electrophysiological studies (Hesse, Moller, Arnold & Schack, 2003; Zhang & Ding, 2010).

Unfiltered time-domain CSD data for each participant were computed to estimate the direction of the synaptic transmission between the early VEPs elicited in the temporo-occipital region and the representative region where the delay of the visual N1 was sharply observed (Pz). In particular, the two time series pooled for the analysis were: (i) T5, O1 and PO1 electrodes at 60 ms; and (ii) Pz electrode at 200 ms (peak of the visual N1), both within a ±50 ms time-window to ensure sufficient number of observations (Seth, 2010). Ipsilateral hemisphere was not added to the analysis since none of the temporo-occipital electrodes (T6, O2, PO2) reached statistical significance in the Pearson correlation. For each participant, we preprocessed data from targeted electrodes by calculating and subtracting the ensemble mean from each single trial, to provide a zero-mean status required for MVAR model fitting. All mean-corrected data was checked for covariance stationarity. We defined the optimal number of past observations to incorporate in the regression model by the Akaike Information (Akaike, 1974), setting the VAR model order at 10. We applied conditional G-causality for preprocessed data and Granger F-tests were conducted on model residuals to probe a putative causal influence of electrode Y in electrode X. Statistically significant set of G-causality interactions were defined below a p-value of 0.01 and Bonferroni corrected for multiple comparisons. The strength of the MVAR model was determined by a model consistency higher than 80% (Seth, 2010).

Time-variant GCA (Hesse et al., 2003) was applied to significant causal interactions to detect when the maximum values of G-causality peaked. Finally, time-domain causal flow (outgoing connections minus incoming connections) of each electrode was inferred from significant G-causalities. Static condition did not show a source/sink temporo-occipital activity at 60 ms and its model consistency was consequently under 80% (66.1 %), being discarded from the G-causality analysis.

4.4 Results

4.4.1 BEHAVIORAL RESULTS

Hand deviation was different across ISAs (F[4,68] = 10.44, *p* < 0.001, ε = .66; **Figure 4.2A**) and, more importantly, the endpoint position at each ISA was modulated by the visual motion (Motion x ISA: F[4,68] = 17.11, *p* < 0.001, ε = .64). Endpoint position was not biased when there was no visual motion. Further pairwise comparisons between moving and static conditions at each ISA confirmed that the motion-induced shift was significantly higher when the target was presented at the same exact moment of the motion reversal (t[17] = -3.08, *p* = 0.02). In contrast, the lowest spatial misalignment was found at 470 ISA. The other moving vs. static comparisons were not significant (*p*

> 0.07 for all comparisons). These results suggest that the hand position deviated either rightwards or leftwards consistent with the direction of the nearby motion, corroborating the influence of the motion signals in previous studies (Whitney, Westwood, et al., 2003).

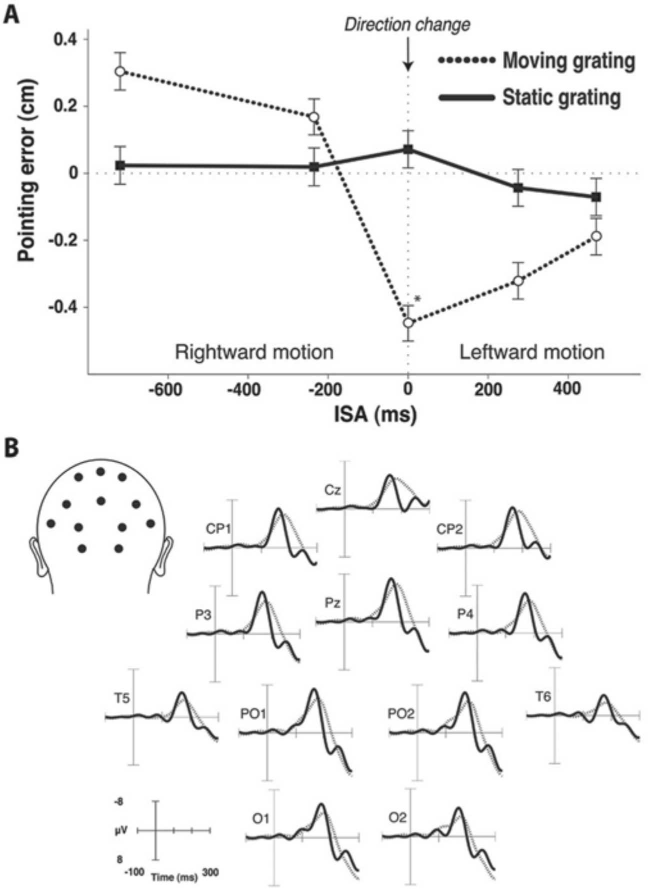


Figure 4.2. Behavioral and electrophysiological effects after adaptation to visual motion. **(A)** Averaged spatial error, in the abscissa axis, for each ISA. Data have been merged so that the nearest horizontal grating to the target was rightwards (inverse pattern when the initial direction of the grating was left). Positive values of pointing error thus reflected that the hand ended at the right of the target, and vice versa. The motion reversal is depicted by the horizontal dotted line at 0 *y*-axis. Error bars show s.e.m. **(B)** Grand-average (N = 18) stimulus-locked ERP waveforms from 12 representative scalp locations in response to static and moving patterns.

4.4.2 ERP RESULTS

We compared static and moving grand average ERPs waves from -100 ms pre-stimulus to 300 ms post-stimulus of the occipital, temporal, parietal and centroparietal electrodes

(**Figure 4.2B**). Latency values of the visual N1 component were longer in the presence of visual motion than with no motion (F[1,17] = 51.3, $p < 0.001$). The topographical analysis showed a significant effect of Electrode (F[18,306] = 2.71, $p = 0.037$) and Motion x Electrode interaction (F[18,306] = 2.64, $p = 0.029$), indicating differences in the topographical distribution of the Motion main effect. Decomposition of the interaction revealed that the slower sensory processing with visual motion had a parieto-central (Pz) maximum (Motion x Laterality, F[1,17] = 10.72, $p = 0.004$), although no significant effects were found in Motion x Hemisphere (F[1,17] = 0.234, $p = 0.63$) nor in Motion x Anterior-posterior (F[1,17] = 0.34, $p = 0.71$). We subsequently examined how the N1 peak-latency at Pz varied as a function of the ISA (**Figure 4.3A**). The analysis revealed a marginal main effect of ISA factor (F[4,68] = 2.4, $p = 0.058$) and, more importantly, we found that the delay of the N1 peak-latency in the moving condition was not exclusively enhanced by the exposure to visual motion and was different across ISAs (F[4,68] = 2.71, $p = 0.03$), Pairwise-comparisons showed that the lag of N1 latency at 0 ISA (t[17] = 3.1, $p = 0.025$) and at 275 ISA (t[17] = 3.04, $p = 0.03$) was significantly longer when comparing to 470 ISA. The rest of comparisons were not significant ($p > 0.19$ for all comparisons). Thus, we observed different latency delays depending on the size of the motion-induced shift. These results indicate that motion effects in position coding affected the N1 morphology, causing a slower sensory processing.

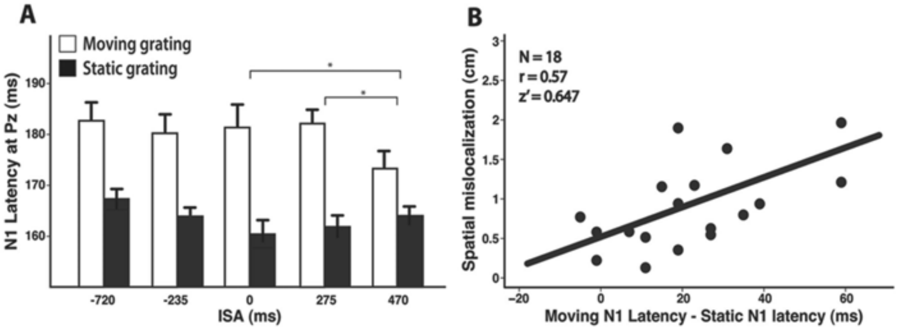


Figure 4.3. Peak-latency analysis of visual N1 component. (**A**) N1 latency (mean ± SEM) at Pz electrode with moving (white) and static (black) gratings for each of the five ISAs. *$p < 0.05$. (**B**) Link between the observed latency of N1 and the goal-directed accuracy in judging the position of the object at 0 ISA. The scatter plot shows, for each participant (N = 18), the correlation between the motion-induced mislocalization and the delay when subtracting the peak-latency for the static gratings from that for the moving.

We correlated the behavioural differences observed between static and moving conditions with their electrophysiological outcome. Pearson correlations between the size of the mislocalization and the difference in the N1 peak-latency were performed at each ISA (two values were excluded, see **Materials and Methods**). Participants with higher biases of the perceived position presented longer temporal shifts between the N1 latencies at 0 ISA ($r = 0.57$, $p = 0.013$; **Figure 4.3B**). It is also worth noting that previous pairwise comparisons confirmed that the 0 ISA condition yielded the strongest effect on both the biased perceived position and the delay of N1 peak. The rest of ISAs showed weaker or non-significant correlations, in consonance with the size of the motion effect (-720 ISA, $p = 0.26$; 470 ISA, $p = 0.76$). Hence, the strength of the correlation apparently decreased when both behavioral and electrophysiological differences diminished.

4.4.3 CSD ESTIMATES

CSD analysis evaluated the topographical distribution of current sources and sinks on the scalp. We found that motion signals induced a different morphology of the early modulations at temporo-occipital sides between 40-80 ms after the target onset (**Figure 4.4C** for 0 ISA; **Figure 4.4D** for 470 ISA).

A significant four-way interaction (Mislocalization x Motion x Time x Electrode, $F[20,340] = 2.64$, $p < 0.001$). revealed that differences between Moving and Static CSD estimates in each electrode through time were differently modulated depending on the size of the motion-induced shift. At 0 ISA (high mislocalization), motion elicited a positive current flow (source) in temporal areas of both hemispheres (T5/T6) around 60 ms after the target onset (**Figure 4.4A**, dotted line). Also, occipital (O1, O2) and partially parieto-occipital (PO1, PO2) regions exhibited a concurrent negative peak (sink). In the corresponding difference waveform (**Figure 4.4B**), we observed a negative component at T5 in between 40-60 ms, which shows inverted polarity at parieto-occipital sides (PO1 or O1). The scalp distribution of this CSD component reflects a temporo-occipital source/sink activity starting at 40-60 ms until 60-80 ms (**Figure 4.4C**), which was more active when participants committed a higher bias localizing the object.

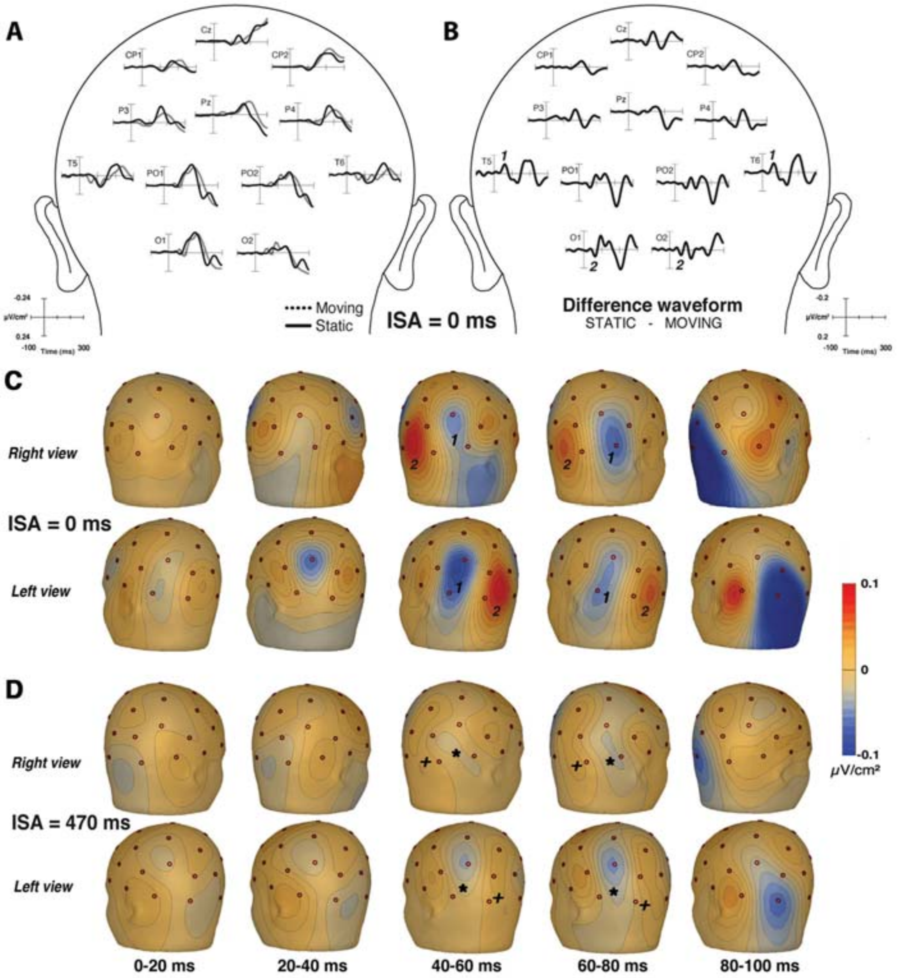


Figure 4.4. CSD waveforms. (A) Grand-average (N = 18) stimulus-locked CSDs waveforms at 0 ISA for each Motion condition and their respective different waveform **(B)**. **(C)** 3D isovoltage topographical mapping illustrates the scalp distribution of the CSD difference waveform from 0 to 100 ms for each hemispheric view. Post-hoc comparisons between Moving and Static CSD estimates reported higher activity with the presence of visual motion at 40-60 ms (T5, $p < 0.001$; O1, $p = 0.03$; PO1, $p = 0.047$; O2, $p = 0.043$), at 60-80 ms (negativity [*1*] in T5, $p = 0.005$; and T6, $p < 0.001$) and at 80-100 ms (positivity [*2*] in O1, $p < 0.001$; PO1, $p = 0.001$; and O2, $p = 0.009$). In contrast, 470 ISA (**D**) only showed higher activity at 60-80 ms in T6 ($p = 0.01$) and at 80-100 ms (O1, $p = 0.001$; PO1, $p = 0.014$). Note the lack of different morphology of temporoccipital (negativity[*] in T5, T6), parietooccipital (PO1,PO2) and occipital (positivity[+] in O1, O2) scalp locations around 60 ms after the target onset. We also compared Moving and Static CSD estimates at specifically 60±12 (48-72 ms): 0 ISA (high mislocalization) unfolded significant higher neural activity in all electrodes when visual motion was present (T5, $p < 0.001$; T6, $p < 0.001$; O1, $p = 0.004$; O2, $p = 0.036$; PO1, $p = 0.008$; PO2, $p = 0.006$), whereas in 470 ISA condition only T6 ($p = 0.005$) and PO2 ($p = 0.04$) were significant.

We correlated the mean CSD amplitude of the difference waveform with the delay in the latency of the N1 CSD estimates, to test whether the source/sink activity modulated not only the behavioral outcome but also the speed of sensory processing. The shift in N1 latency highly correlated with the amplitude of T5 (r = 0.63, p = 0.005; **Figure 4.5A**) and O1 (r = 0.52, p = 0.02), but not with PO1 (p = 0.4). The ipsilateral hemisphere yielded marginal correlation in all electrodes: T6 (r = 0.44, p = 0.069), O2 (r = 0.44, p = 0.065) and PO2 (r = 0.43, p = 0.071). These results may suggest that participants with longer N1 delays also presented higher temporo-occipital activation 60 ms after the target onset.

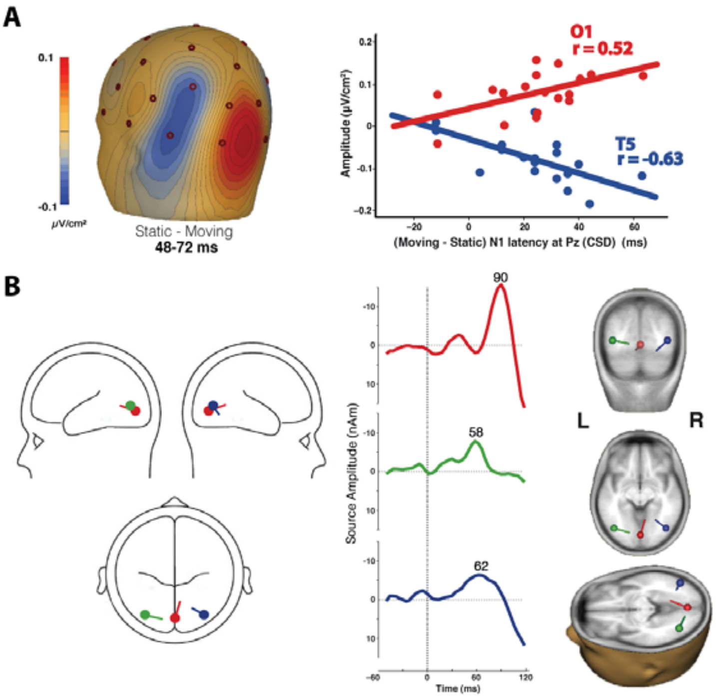


Figure 4.5. Source/sink correlations and the correspondent source localization analysis at 0 ISA. (A) Pearson correlations between the CSD estimates of the difference waveform at the temporo-occipital scalp locations (T5 in blue, O1 in red) and the delay of the visual N1 peak at the parieto-central region (Pz). For each participant (N = 18), the scatter plot depicts the delay in the N1 peak-latency as a function of the mean amplitude at the source/sink locations. (B) Dipole model for the neural sources of the (static – moving) ERP difference waveform. Both dipole 1 (red; x = -0.1, y = -78.9, z = -3.0) and symmetric dipoles 2 (green) and 3 (blue) (x = ±37.4, y = -70.4, z = 4.9) were fit over the 40–100 ms interval. Time-course of each computed dipole is represented in the source waveform. Images on the right side show the anatomical location of each dipole.

4.4.4 SOURCE LOCALIZATION

We identified the possible neural generators of the early VEPs in a high motion-induced bias. Early VEPs were explained by a three-source model with one single dipole located in V1 and two symmetrical sources situated in the left/right posterior bank of MT (**Figure 4.5B,** Talairach coordinates in figure caption). This three-source model accounted for up to 90% of the variance in the scalp distribution over the 40-100 ms time window, with a residual variance (RV) of 9.3%. Source waveforms of symmetric dipoles showed nearly identical peak-latency at approximately 60 ms, whereas the time-course of V1 source had a later peak at 90 ms. These data support the hypothesis that a fast V1-independent mechanism through MT is the first to convey the influence of motion in position coding.

4.4.5 GRANGER CAUSALITY ESTIMATES

The results extracted from the GCA denoted significant direct causal influence from O1 → Pz ($p = 0.006$; **Figure 4.6A**) and from PO1 → Pz ($p < 0.001$). At the same time, T5 → PO1 was also significant ($p < 0.001$), suggesting an indirect causal interaction from T5 to Pz. Model consistency (part of data that fitted the model) was higher than 80% (83.31%). Granger causality estimates of each significant interaction were also analyzed as a function of time (**Figure 4.6B**). We observed that maximum instantaneous G-values peaked between 60 and 70 ms —around 80 ms in the PO1 → Pz interaction—, indicating that their highest contributions to the Pz signal coincided with the peak-latency of the temporo-occipital component. The analysis of the causal flow (**Figure 4.6C**) shed light on the configuration of the causal network underlying the dominant CSD topographies. Noteworthy, network analysis on the causal flow revealed T5 and O1 locations as 'sources' nodes with a significant outflow towards parietal areas (**Figure 4.6D**). In contrast, parietal lobe (Pz) had the highest number of incoming connections (causal 'sink'). Based on the descriptive GCA results presented here above, the parietal region -were the delay of the N1 was sharply observed- might act as an inflow hub of temporo-occipital connections. MT activity at 60 ms would therefore crucially contributed to the posterior N1 delay observed in higher motion-induced mislocalizations.

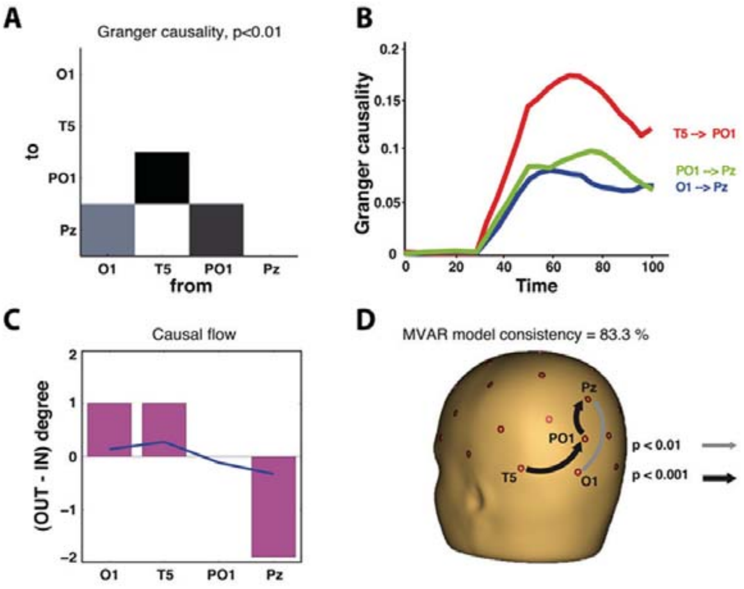


Figure 4.6. GCA analysis at 0 ISA moving condition for the contralateral hemisphere. **(A)** G-causality significant network interactions between each temporoccipital scalp location, representing the level of significance as a function of color darkness (black, $p < 0.001$). **(B)** G-values of significant interactions across time. **(C)** Bar plot of the net Granger causal outflow for each scalp location. Positive causal flow values corresponded to 'causal source' regions with higher outgoing causal connections, whereas negative causal flow were inflow hubs. **(D)** Network of significant causal connectivity with a dominant directional influence (Bonferroni corrected).

4.5 Discussion

We demonstrate that the shift in the hand endpoint induced by motion correlates with a temporal delay of the visual N1, a primary VEP elicited by the flash onset (**Figures 4.2 and 4.3**). Moreover, we provide evidence for early neural activity in MT that causes the effects on N1 (**Figures 4.4, 4.5 and 4.6**). These findings contradict the feedback account (De Valois & De Valois, 1991; Nishida & Johnston, 1999; Whitney & Cavanagh, 2000) as the putative neural mechanism that subserves the effects of motion in position coding. Instead, they imply a faster mechanism through MT presumably channeled by non-primary visual pathways. The speed of sensory processing under exposure to visual motion also reveals a predictive strategy invoked to maximize the use of motion signals in order to improve reaching accuracy, serving as a compensatory mechanism for neural delays when localizing objects in a dynamic scene.

4.5.1 THE MOTION-INDUCED SHIFT REFLECTS A NEURAL DELAY

Previous studies supported the effect of background motion signals on reaching, which induce hand endpoint shifts in the direction of the neighboring motion (Brenner & Smeets, 1997; Mohrmann-Lendla & Fleischer, 1991; Rodriguez-Herreros & Lopez-Moliner, 2008; Saijo et al., 2005; Whitney, Westwood, et al., 2003). Our data also concur that the strongest mislocalization took place at the exact moment of the motion reversal (Whitney & Cavanagh, 2000). However, the nature of this spatial offset is still debated, prompting a variety of potential explanations. It has been argued that the position coding of a stationary object is processed differently than that of a moving object (Purushothaman, Patel, Bedell & Ogmen, 1998), but the alternative idea of a common mechanism by which motion signals affect position's assignment of both stationary and moving objects has gained validity (Durant & Johnston, 2004; Whitney & Cavanagh, 2000). A timing error has been postulated to explain the spatial offset of motion-dependent phenomena with moving stimuli, such as the flash-lag effect (FLE) (Murakami, 2001; Wojtach, Sung, Truong & Purves, 2008). It is still to be determined, however, whether the cause of errors when estimating the location of a stationary flash could be related to temporal mechanisms. The correlation observed in the present study between the spatial bias and the temporal delay of the VEPs (**Figure 4.3B**) points to a close link between spatial and timing errors. These results are in agreement with the idea that the temporal coding of a flashed object is crucial when estimating its position, in such a way that the timing of the perception would determine the error in the perceived position (Durant & Johnston, 2004). Arguably, motion signals might delay the perceptual localization process of a stationary stimulus, by allowing extra time to use visual motion in order to update and recode the object location. In our study, the temporal dynamics of sensory processing dovetail nicely with an anticipatory sensory strategy also observed in FLE, based on longer neural latencies to flashed objects in comparison with responses to motion (Jancke, Erlhagen, Schoner & Dinse, 2004). Additional time to process the perception of the flash might thus act as a compensatory change to improve visually-guided behavior in dynamic environments. The observed time-course is also consistent with oculomotor evidence of long-latency saccades showing a gradually built-up bias of saccade endpoints in the direction of motion (de'Sperati & Baud-Bovy, 2008). Indeed, perceptual delays related to saccades with longer latencies could depend on the recruitment of higher-order visual areas such as MT (Nishida & Johnston, 1999). Recent neurophysiological evidence points to the crucial role of MT in predictive coding framework (Vetter, Grosbras & Muckli, 2013).

4.5.2 MOTION-POSITION INTERACTION IN MT

An extensive body of literature has validated MT as a key player in the discrimination and detection of visual motion. However, only recent neurophysiological evidence has shown that MT integrity is also critical when reaching stationary objects in the presence of nearby motion (Whitney et al., 2007). Our CSD and source localization analysis exhibited increased neural activity in MT when reaching was performed in the presence of motion. This activity was higher with the maximum spatial shift, which occurred when the object was presented at the moment of the motion reversal (**Figure 4.4**) (Whitney & Cavanagh, 2000). In contrast, MT activity decreased for the lowest spatial mislocalization (**Figure 4.4D**). These findings lend credence to the hypothesis that motion processing in MT might modulate the earliest stages of position coding (De Valois & De Valois, 1991), likely affecting the temporal coding of the perceived object location.

Anatomically, MT efferent backprojections to V1 were postulated as the neural pathways by which motion information altered the estimation of a position (Whitney & Cavanagh, 2000). According to this view, these feedback connections would continuously update the early representation of target position hinging on motion information previously coded in MT (Whitney, Westwood, et al., 2003). Thus, one possibility is that visual motion is processed more rapidly than the encoding of position. Psychophysical evidence reflects that the motion's influence may act at various levels of the visual system (Fukiage, Whitney & Murakami, 2011), with even non-human physiological findings revealing to motion-induced coding of position in the retina (Berry et al., 1999). In this regard, our data offer new electrophysiological insights about the timing of the early visual process that assigns stationary positions under the presence of visual motion. Source analysis demonstrated that prior MT activity, peaking approximately at 60 ms, is in line with electrophysiological studies that described very short latencies of visual responses in MT (Schmolesky et al., 1998), occasionally showing VEP components in MT before V1 (Buchner et al., 1997). Notably, CSD and source waveforms (**Figures 4.4 and 4.5**) did not show an earlier onset of the VEPs surrounding V1 previous to that observed in MT. In agreement with these results, GCA and CSD correlations strengthen the idea that MT activity at 60 ms affected both spatial coding and the VEPs latency. First, the intensity of the preceding VEP component in MT correlated with the longer N1 latency later detected (**Figure 4.5**). Secondly, we identified a causal influence of MT activity in the lag of VEPs peak-latency (**Figure 4.6**). Such evidence indicates that the neural underpinnings by which motion exerts powerful influences on object localization may affect the initial phases of position coding (De Valois & De Valois, 1991), nearly parallel to the arrival of visual input to V1 (ffytche et al., 1995).

4.5.3 EXTRAGENICULATE PROJECTIONS TO MT

The hierarchical levels of the visual cortex have been shown to require around 100 ms to launch the cascade of feedforward connections from V1 and reach the higher-level areas, including MT (Nowak & Bullier, 1997). It is therefore conceivable that MT recurrent connections to V1 would take at least 100 ms. Given that hierarchical models of the visual system cannot explain such small timing differences here reported between V1 and MT, it is likely that the fastest responses that we observed in MT are not dependent on the input from V1. Rather, we propose a V1-bypassing circuit which sustains early motion perception responsible for the shift when coding the position of objects. In this sense, the fast visual inputs that MT receives from the superior colliculus (SC) through the pulvinar, as well as the direct route from the lateral geniculate nucleus (LGN), might arise as better candidates to be the anatomical basis of the first stages of this phenomenon. Although there is some controversy about the latency of SC-pulvinar inputs to MT (from 40 ms (ffytche et al., 1995) to 90 ms (Schoenfeld et al., 2002)), this secondary visual pathway has continuously generated interest as a potential source of visual motion inputs to MT. Recent clinical and neuroanatomical studies have sought evidence that retinocollicular pathways to high order dorsal stream areas, such as those to MT, may explain motion discrimination in the absence of V1 (Azzopardi & Hock, 2011; Lyon, Nassi & Callaway, 2010). Since a reliable group of retinal projections terminates directly in the pulvinar (O'Brien, Abel & Olavarria, 2001), the functional significance of this considerably direct pathway to MT might mediate the fast transmission of feedforward retinal inputs directly to higher-order areas of the dorsal stream. However, a recent study has cast doubts on the view of the pulvinar as a powerful source of motion inputs to MT (Berman & Wurtz, 2011), proposing instead the direct path from LGN to MT as the most straightforward explanation for motion perception when V1 is impaired. This account is based in the suppression of MT activity during LGN blockade (Maunsell, Nealey & DePriest, 1990; Schmid et al., 2010). All in all, the functional role of MT motion inputs from LGN and SC-pulvinar pathways remains to be elucidated.

4.5.4 LIMITATIONS OF THE STUDY

Some issues have to be addressed in future studies. First, our study is blind as to which secondary visual pathway conveys the motion signals that posteriorly cause the shift. This question can be tackled with neuroanatomical recordings in conjunction with effective comparisons of the deficits in motion perception caused by the independent disruption of LGN and pulvinar. A second limitation concerns the low spatial resolution that EEG entails for source localization. It is likely, however, that further imaging studies help to clarify the specific locus that actively contributes to the motion-induced mislocalization of objects.

4.6 Acknowledgements

The authors thank T. Cunillera, J. Marco-Pallarés and J. L. Amengual for helpful discussions and advice on data collection/analysis. Thanks also to D. Linares, E. Johnson, E. Brenner and M. A. Schoenfeld for comments on the manuscript. This work was supported by an AGAUR B.E. grant from the Catalan government to BRH, Spanish government grants to ARF (PSI2012-29219) and JLM (PSI2010-15867) and a grant from the Generalitat de Catalunya (SGR2005-00831). JLM was also supported by an ICREA Academia Distinguished Professorship award.

4.7 References

Akaike, Hirotugu. (1974). A new look at the statistical model identification. *Automatic Control, IEEE Transactions on, 19*(6), 716-723.

Azzopardi, P., & Hock, H. S. (2011). Illusory motion perception in blindsight. *Proceedings of the National Academy of Sciences of the United States of America, 108*(2), 876-881.

Barbur, J. L., Watson, J. D., Frackowiak, R. S., & Zeki, S. (1993). Conscious visual perception without V1. *Brain, 116 (Pt 6)*, 1293-1302.

Berman, R. A., & Wurtz, R. H. (2011). Signals conveyed in the pulvinar pathway from superior colliculus to cortical area MT. *Journal of Neuroscience, 31*(2), 373-384.

Berry, M. J., 2nd, Brivanlou, I. H., Jordan, T. A., & Meister, M. (1999). Anticipation of moving stimuli by the retina. *Nature, 398*(6725), 334-338.

Bock, O. (1986). Contribution of retinal versus extraretinal signals towards visual localization in goal-directed movements. *Experimental Brain Research, 64*(3), 476-482.

Brenner, E., & Smeets, J. B. (1997). Fast Responses of the Human Hand to Changes in Target Position. *J Mot Behav, 29*(4), 297-310.

Buchner, H., Gobbele, R., Wagner, M., Fuchs, M., Waberski, T. D., & Beckmann, R. (1997). Fast visual evoked potential input into human area V5. *Neuroreport, 8*(11), 2419-2422.

Burr, D. C. (1981). Temporal summation of moving images by the human visual system. *Proceedings of the Royal Society of London. Series B: Biological Sciences, 211*(1184), 321-339.

Cai, R. H., Pouget, A., Schlag-Rey, M., & Schlag, J. (1997). Perceived geometrical relationships affected by eye-movement signals. *Nature, 386*(6625), 601-604.

Clark, Vincent P, Fan, Silu, & Hillyard, Steven A. (1994). Identification of early visual evoked potential generators by retinotopic and topographic analyses. *Human Brain Mapping, 2*(3), 170-187.

Cunillera, T., Gomila, A., & Rodriguez-Fornells, A. (2008). Beneficial effects of word final stress in segmenting a new language: evidence from ERPs. *BMC Neuroscience, 9*, 23.

Cunillera, T., Toro, J. M., Sebastian-Galles, N., & Rodriguez-Fornells, A. (2006). The effects of stress and statistical cues on continuous speech segmentation: an event-related brain potential study. *Brain Research, 1123*(1), 168-178.

De Valois, R. L., & De Valois, K. K. (1991). Vernier acuity with stationary moving Gabors. *Vision Research, 31*(9), 1619-1626.

de'Sperati, C., & Baud-Bovy, G. (2008). Blind saccades: an asynchrony between seeing and looking. *Journal of Neuroscience, 28*(17), 4317-4321.

Durant, S., & Johnston, A. (2004). Temporal dependence of local motion induced shifts in perceived position. *Vision Research, 44*(4), 357-366.

ffytche, D. H., Guy, C. N., & Zeki, S. (1995). The parallel visual motion inputs into areas V1 and V5 of human cerebral cortex. *Brain, 118 (Pt 6)*, 1375-1394.

Fu, Y. X., Shen, Y., Gao, H., & Dan, Y. (2004). Asymmetry in visual cortical circuits underlying motion-induced perceptual mislocalization. *Journal of Neuroscience, 24*(9), 2165-2171.

Fukiage, T., Whitney, D., & Murakami, I. (2011). A flash-drag effect in random motion reveals involvement of preattentive motion processing. *J Vis, 11*(13).

Gomi, H., Abekawa, N., & Nishida, S. (2006). Spatiotemporal tuning of rapid interactions between visual-motion analysis and reaching movement. *Journal of Neuroscience, 26*(20), 5301-5308.

Granger, Clive WJ. (1969). Investigating causal relations by econometric models and cross-spectral methods. *Econometrica: Journal of the Econometric Society*, 424-438.

Hesse, W., Moller, E., Arnold, M., & Schack, B. (2003). The use of time-variant EEG Granger causality for inspecting directed interdependencies of neural assemblies. *Journal of Neuroscience Methods, 124*(1), 27-44.

Jancke, D., Erlhagen, W., Schoner, G., & Dinse, H. R. (2004). Shorter latencies for motion trajectories than for flashes in population responses of cat primary visual cortex. *Journal of Physiology, 556*(Pt 3), 971-982.

Jennings, J. R., & Wood, C. C. (1976). Letter: The epsilon-adjustment procedure for repeated-measures analyses of variance. *Psychophysiology, 13*(3), 277-278.

Kuba, M., Toyonaga, N., & Kubova, Z. (1992). Motion-reversal visual evoked responses. *Physiological Research, 41*(5), 369-373.

Lyon, D. C., Nassi, J. J., & Callaway, E. M. (2010). A disynaptic relay from superior colliculus to dorsal stream visual cortex in macaque monkey. *Neuron, 65*(2), 270-279.

Maunsell, J. H., Nealey, T. A., & DePriest, D. D. (1990). Magnocellular and parvocellular contributions to responses in the middle temporal visual area (MT) of the macaque monkey. *Journal of Neuroscience, 10*(10), 3323-3334.

Maunsell, John HR. (1987). Physiological evidence for two visual subsystems *Matters of intelligence* (pp. 59-87): Springer.

Maus, G. W., Fischer, J., & Whitney, D. (2013). Motion-dependent representation of space in area MT+. *Neuron, 78*(3), 554-562.

McCarthy, G., & Wood, C. C. (1985). Scalp distributions of event-related potentials: an ambiguity associated with analysis of variance models. *Electroencephalography and Clinical Neurophysiology, 62*(3), 203-208.

McGraw, P. V., Walsh, V., & Barrett, B. T. (2004). Motion-sensitive neurones in V5/MT modulate perceived spatial position. *Current Biology, 14*(12), 1090-1093.

Mitzdorf, U. (1985). Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Physiological Reviews, 65*(1), 37-100.

Mohrmann-Lendla, H., & Fleischer, A. G. (1991). The effect of a moving background on aimed hand movements. *Ergonomics, 34*(3), 353-364.

Murakami, I. (2001). The flash-lag effect as a spatiotemporal correlation structure. *J Vis, 1*(2), 126-136.

Nishida, S., & Johnston, A. (1999). Influence of motion signals on the perceived position of spatial pattern. *Nature, 397*(6720), 610-612.

Nowak, Lionel G, & Bullier, Jean. (1997). The timing of information transfer in the visual system. *Cerebral Cortex – New York Plenium press-*, 205-242.

Nunez, Paul L. (2006). *Electric fields of the brain: the neurophysics of EEG*: Oxford University Press.

O'Brien, B. J., Abel, P. L., & Olavarria, J. F. (2001). The retinal input to calbindin-D28k-defined subdivisions in macaque inferior pulvinar. *Neuroscience Letters, 312*(3), 145-148.

Perenin, MT, & Jeannerod, Marc. (1975). Residual vision in cortically blind hemiphields. *Neuropsychologia, 13*(1), 1-7.

Perrin, F., Pernier, J., Bertrand, O., & Echallier, J. F. (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalography and Clinical Neurophysiology, 72*(2), 184-187.

Purushothaman, G., Patel, S. S., Bedell, H. E., & Ogmen, H. (1998). Moving ahead through differential visual latency. *Nature, 396*(6710), 424.

Rodionov, V., Goodman, C., Fisher, L., Rosenstein, G. Z., & Sohmer, H. (2002). A new technique for the analysis of background and evoked EEG activity: time and amplitude distributions of the EEG deflections. *Clinical Neurophysiology, 113*(9), 1412-1422.

Rodriguez-Herreros, B., & Lopez-Moliner, J. (2008). The influence of motion signals in hand movements. *Experimental Brain Research, 191*(3), 321-329.

Saijo, N., Murakami, I., Nishida, S., & Gomi, H. (2005). Large-field visual motion directly induces an involuntary rapid manual following response. *Journal of Neuroscience, 25*(20), 4941-4951.

Scherg, Michael. (1990). Fundamentals of dipole source potential analysis. *Auditory evoked magnetic fields and electric potentials. Advances in audiology, 6*, 40-69.

Schmid, M. C., Mrowka, S. W., Turchi, J., Saunders, R. C., Wilke, M., Peters, A. J., . . . Leopold, D. A. (2010). Blindsight depends on the lateral geniculate nucleus. *Nature, 466*(7304), 373-377

Schmolesky, M. T., Wang, Y., Hanes, D. P., Thompson, K. G., Leutgeb, S., Schall, J. D., & Leventhal, A. G. (1998). Signal timing across the macaque visual system. *Journal of Neurophysiology, 79*(6), 3272-3278.

Schoenfeld, M. A., Noesselt, T., Poggel, D., Tempelmann, C., Hopf, J. M., Woldorff, M. G., . . . Hillyard, S. A. (2002). Analysis of pathways mediating preserved vision after striate cortex lesions. *Annals of Neurology, 52*(6), 814-824.

Seth, Anil K. (2010). A MATLAB toolbox for Granger causal connectivity analysis. *Journal of Neuroscience Methods, 186*(2), 262-273.

Shipp, S., & Zeki, S. (1989). The Organization of Connections between Areas V5 and V1 in Macaque Monkey Visual Cortex. *European Journal of Neuroscience, 1*(4), 309-332.

Sincich, L. C., Park, K. F., Wohlgemuth, M. J., & Horton, J. C. (2004). Bypassing V1: a direct geniculate input to area MT. *Nature Neuroscience, 7*(10), 1123-1128.

Snowden, R. J. (1998). Shifts in perceived position following adaptation to visual motion. *Current Biology, 8*(24), 1343-1345.

Standage, G. P., & Benevento, L. A. (1983). The organization of connections between the pulvinar and visual area MT in the macaque monkey. *Brain Research, 262*(2), 288-294.

Steinman, R. M., Kowler, E., & Collewijn, H. (1990). New directions for oculomotor research. *Vision Research, 30*(11), 1845-1864.

Stevens, M. C., Calhoun, V. D., & Kiehl, K. A. (2005). Hemispheric differences in hemodynamics elicited by auditory oddball stimuli. *Neuroimage, 26*(3), 782-792.

Sundberg, K. A., Fallah, M., & Reynolds, J. H. (2006). A motion-dependent distortion of retinotopy in area V4. *Neuron, 49*(3), 447-457.

Talairach, Jean, & Tournoux, Pierre. (1988). Co-planar stereotaxic atlas of the human brain. 3-Dimensional proportional system: an approach to cerebral imaging.

Vetter, P., Grosbras, M. H., & Muckli, L. (2013). TMS Over V5 Disrupts Motion Prediction. *Cerebral Cortex*.

Whitney, D., & Cavanagh, P. (2000). Motion distorts visual space: shifting the perceived position of remote stationary objects. *Nature Neuroscience, 3*(9), 954-959.

Whitney, D., Ellison, A., Rice, N. J., Arnold, D., Goodale, M., Walsh, V., & Milner, D. (2007). Visually guided reaching depends on motion area MT+. *Cerebral Cortex, 17*(11), 2644-2649.

Whitney, D., Goltz, H. C., Thomas, C. G., Gati, J. S., Menon, R. S., & Goodale, M. A. (2003). Flexible retinotopy: motion-dependent position coding in the visual cortex. *Science, 302*(5646), 878-881.

Whitney, D., Westwood, D. A., & Goodale, M. A. (2003). The influence of visual motion on fast reaching movements to a stationary object. *Nature, 423*(6942), 869-873.

Wojtach, W. T., Sung, K., Truong, S., & Purves, D. (2008). An empirical explanation of the flash-lag effect. *Proceedings of the National Academy of Sciences of the United States of America, 105*(42), 16338-16343.

Zhang, Y., & Ding, M. (2010). Detection of a weak somatosensory stimulus: role of the prestimulus mu rhythm and its top-down modulation. *J Cogn Neurosci, 22*(2), 307-322.

5

STUDY III

PROPRIOCEPTION IMPROVES TEMPORAL ACCURACY IN A COINCIDENCE-TIMING TASK[§]

[§] This chapter corresponds to:
Rodríguez-Herreros, B. & López-Moliner J. (2011). Proprioception improves temporal accuracy in a coincidence- timing task. **Experimental Brain Research**, 210(2):251-258.

RESUMEN

La información espacial y temporal es crucial cuando intentamos interceptar un objeto en movimiento en una zona específica. Para integrar esa información de forma óptima, nos basamos en la aportación del sistema visual y del sistema propioceptivo a la posición de la mano y del objeto a alcanzar. Estas dos fuentes de información sensorial se combinan dando más peso a una u otra en función de las condiciones y la certidumbre de cada una de ellas. En este estudio, hemos intentado dilucidar el patrón de utilización de la información visual y propioceptiva en la interceptación de un objeto en movimiento. Para ello, hemos investigado si existe una mejora de la resolución temporal en situaciones en las que la resolución visual es pobre y la información propioceptiva ejerce un papel esencial. La tarea consistió en alcanzar con el dedo la zona y el momento de la colisión de dos objetos en movimiento uno hacia el otro, de los que se mostró la parte inicial de la trayectoria. Los resultados mostraron mayor precisión temporal cuando la trayectoria de la mano se hizo en el mismo eje que la trayectoria del objeto (en el eje sagital, de profundidad). Esta mejora desapareció cuando los participantes en el estudio tuvieron simplemente que estimar el momento de la colisión apretando un botón, sin tener que ejecutar un movimiento. Estos hallazgos indican una contribución especial de la información propioceptiva de la trayectoria de la mano, que ayuda a reducir la incertidumbre temporal.

RESUM

La informació espacial i temporal és crucial quan intentem interceptar un objecte en moviment en una zona específica. Per integrar aquesta informació de forma òptima, ens basem en l'aportació del sistema visual i del sistema propioceptiu a la posició de la mà i de l'objecte a interceptar. Aquestes dues fonts d'informació sensorial es combinen donant més pes a una o l'altra en funció de les condicions i la certesa de cadascuna d'elles. En aquest estudi, hem intentat dilucidar el patró d'utilització de la informació visual i la propioceptiva en la intercepció d'un objecte en moviment. Per a això, hem investigat si hi ha una millora de la resolució temporal en situacions en que la resolució visual és pobre i la informació propioceptiva exerceix un paper essencial. La tasca va consistir a interceptar amb el dit la zona i el moment de la col·lisió de dos objectes en moviment un cap a l'altre, dels quals es va mostrar la part inicial de la seva trajectòria. Els resultats van mostrar major precisió temporal quan la trajectòria de la mà es va fer en el mateix sentit que la trajectòria de l'objecte (en l'eix sagital, de profunditat). Aquesta millora va desaparèixer quan els participants en l'estudi van simplement estimar el moment de la col·lisió prement un botó, sense haver d'executar cap moviment. Aquestes troballes indiquen una contribució especial de la informació propioceptiva de la trajectòria de la mà, que ajuda a reduir la incertesa temporal.

Exp Brain Res (2011) 210:251–258
DOI 10.1007/s00221-011-2627-x

RESEARCH ARTICLE

Proprioception improves temporal accuracy in a coincidence-timing task

Borja Rodríguez-Herreros · Joan López-Moliner

Received: 30 September 2009 / Accepted: 7 March 2011 / Published online: 23 March 2011

Abstract Temporal and spatial information are necessary when pointing to touch moving objects at a specific location. Here, we introduce an interception paradigm that allows us to uncorrelate spatial and temporal errors so that subjects did not have to trade one for the other. We showed the initial trajectories of two objects that moved (laterally or sagittally) with random presentation times and speeds along a collision path. Subjects had to point manually to the collision place at the correct time. We found better temporal accuracy when hand movements matched the motion target direction (e.g., the hand sagittally pointed to a collision point defined along a sagittal trajectory). This temporal selectivity disappeared when subjects had to judge the collision time responding with a single press. The results point to a contribution of proprioceptive information of hand velocity in reducing the temporal uncertainty in a temporal coincidence task.

Keywords Interception · Arm movement · Visuomotor control · Timing

Introduction

The ability to intercept a moving object requires one to be at the right place at the right time. The visuomotor system requires, therefore, both spatial and temporal information to perform optimally. One way to exert control in interception tasks is the online modulation of spatial and temporal properties of our effector's movements (Caljouw et al. 2006; Tresilian and Plooy 2006). As this is limited by the tradeoff between the speed of our movement and the achieved spatial accuracy (Fitts 1954; Fitts and Peterson 1964; Hancock and Newell 1985), one has to find a compromise between reducing either type of error.

Concerning spatial and temporal errors, Brenner and Smeets (2009) have recently suggested that visual resolution is the limiting factor in people's ability to intercept moving targets. They show that both temporal and spatial accuracy could be explained in terms of visual resolution. However, the fact that interception obviously occurs in our peripersonal space (we need to be able to reach the object in order to intercept it) implies that information from our sensed arm/hand movement (proprioceptive) might come into play in the task. Although visual information has been shown to dominate other modalities when determining the spatial mapping of a static object in the peripersonal space (Ladavas et al. 2000), the contribution of modalities other than visual in the timing of our actions when intercepting objects has remained less explored. Tresilian (1994) demonstrated that proprioceptive perceptual systems contributed to the extraction of time-to-contact information. In fact, this contribution could be especially decisive in situations where the visual resolution is somehow undermined. For example, Mon-Williams et al. (1997) pointed out the contribution of proprioception in perceiving a limb position, especially when vision was absent. In the same way, the use of visual and proprioceptive information in the spatial localization of one's hand with respect to the body is distinctly weighted (van Beers et al. 1996, 1999) depending on the axis (lateral or sagittal). The question

---

B. Rodríguez-Herreros · J. López-Moliner (✉)
Departament de Psicologia Bàsica, Faculty of Psychology,
Universitat de Barcelona, P. Vall d'Hebron, 171,
08035 Barcelona, Catalonia, Sapin
e-mail: j.lopezmoliner@ub.edu

J. López-Moliner
Institute for Brain, Cognition and Behaviour (IR3C),
Universitat de Barcelona, Barcelona, Spain

now is how much we can benefit from using proprioceptive information in timing our responses to moving objects.

To answer this question, we modified a previously reported interception paradigm (Bootsma and Oudejans 1993) with two moving targets. The modification allowed us to examine temporal and spatial errors independently. Most interceptive tasks used up to now imply a compromise between spatial and temporal accuracy, so one is often forced to favor either type of accuracy. This may lead us to conclude that people's accuracy in localizing moving objects at an indicated moment is severely limited by their poor temporal resolution (Brenner et al. 2006). As a consequence, the spatial uncertainty increases with target speed, and the relevance of timing errors relative to spatial ones increases with the target velocity (Brenner et al. 2002; Brouwer et al. 2005; Tresilian and Lonergan 2002; Tresilian et al. 2003). The interdependency between spatial and temporal accuracy has been revealed even when both types of accuracy are promoted (i.e., Tresilian et al. 2009). To play down this dependency, we made people intercept two objects that moved along a collision path so that they could opt for reducing one type of error without compromising the other (i.e., reducing the temporal error while leaving the spatial error intact). In our case, we have the same speed-accuracy tradeoff as when intercepting a single object: spatial accuracy with respect to the aimed position will decrease with hand velocity. However, as we determine an actual point in space where interception occurs, the spatial error defined as the difference between the actual collision point and the point where the hand landed is not correlated with the temporal error in our interception paradigm. This has the advantage that we can compare temporal errors across two directions (lateral and sagittal) without these measurements being distorted by side effects due to different spatial resolutions for these directions.

Experiment 1: coincidence timing in lateral and sagittal dimensions

Methods

Subjects

Seven volunteers took part in the experiments, and all participants were unaware of the purpose of the study. All subjects had normal or corrected-to-normal vision and no one had any history of neuromuscular disorders. Previously, all the subjects gave their informed consent to participate in the study. The research in this study is part of an ongoing research program that has been approved by the local ethics committee.

Apparatus and data acquisition

Figure 1a shows a schematic top view of the basic setup used in all the experiments. Subjects faced a table whose horizontal surface was (vertical distance) between 48 and 50 cm below the eyes depending on the subject. Computer-generated displays were projected on the table by a Mitsubishi SD220U ceiling projector at a frame rate of 72 Hz with a resolution of 800 × 600 pixels (52 × 33 cm) and controlled by a Macintosh Pro 2.6 Ghz Quad-core computer. This arrangement made the impression that the visual items were displayed in the same horizontal plane in which the movements were performed.

Interceptive movements were recorded using a digitizing tablet (Calcomp DrawingBoard III 34240). The displayed image was viewed through a half-silvered mirror that was placed face-up midway between the digital graphic tablet and the monitor (see Fig. 1b) in order for the visual image to be perceived on top of the tablet (see Rodriguez-Herreros and Lopez-Moliner 2008 for a detailed description of the setup). Subjects looked at the mirror and saw the image projected on the surface of the digital graphic tablet (60 × 45 cm). The position of the pen on the tablet was recorded at a frame rate of 200 Hz. Data recording started before targets onset and ended 200 ms after the hand stopped. The individual position data time series were digitally low-pass filtered with a Butterworth filter (cutoff frequency of 6 Hz) for further analysis. First and second temporal derivatives of the position were computed from the smoothed data.

Stimuli

Stimuli were projected in a dimly lit room and consisted of the initial trajectory of two objects that moved opposite one another along one dimension: either lateral or sagittal. The targets' collision was never shown and the time between target onset and the moment of collision was randomly selected within a range from 1,000 to 2,000 ms. The objects were visible for a random period uniformly distributed in the range from 40 to 70% of the collision time. Speeds were independently set for each target and uniformly chosen between 5 cm/s and 15 cm/s. The initial positions of each target were also set randomly. Assuming that a zero origin is the center of the table, physical collision points were uniformly distributed from -10 to $+10$ cm in the abcissa (x-axis) for the lateral dimension and from -10 to $+10$ cm in the ordinate (y-axis) for the sagittal dimension.

Procedure

We instructed participants to reach the location at which the two targets collided and at the exact time of collision as accurately as possible. The objects could move along the

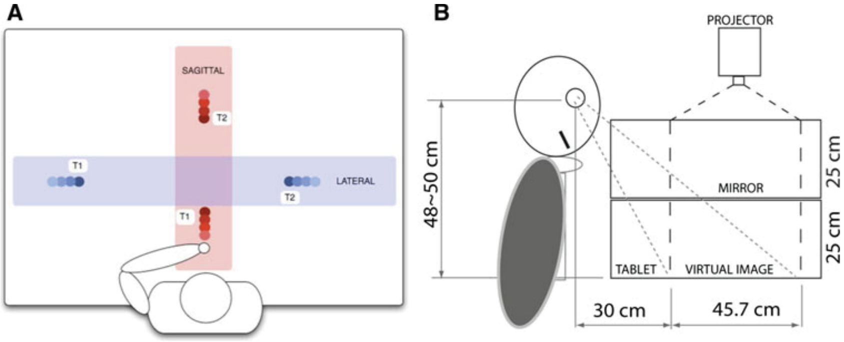


Fig. 1 Sketch of the setup of experiments 1 and 2. **a**. The objects moved in two different directions (laterally and sagittally) at random velocities. The objects and the starting position were displayed in the table from a ceiling projector. In each trial, two objects moved along the same axis with opposite directions. **b**. Side view of the experimental setup. The subjects looked at the mirror and saw the image projected on the surface of the graphic tablet. A chinrest was used to stabilize the head

lateral or sagittal directions (target motion). Before the actual experiment started, subjects performed 20 practice trials in each condition to get used to the task. There were two different hand movement conditions depending on the location of the starting hand position: (a) a manual interception movement performed along the sagittal plane in which the initial position was close to the body at the centre of the screen (0 value in *x*-axis, see Fig. 1a), and (b) an interception movement executed along the lateral direction with the starting point located at the right of the screen and origin of the *y*-axis. Each session started by moving the tip of the stylus to the initial position. Once the pen's tip was held there, the trial was launched and the two targets appeared. Participants executed the interceptive movement reaching the collision point at the collision time. The hand remained in the final position until the starting point reappeared and participants brought their hand back to the starting position to launch the next trial. Participants were instructed not to move their trunk with respect to the chair during the entire session. In contrast, head movements were allowed. We did not immobilize any body part due to the possibility of subjects' behavior could be different than in natural conditions (Steinman et al. 1990). Lateral and sagittal target motions were interleaved randomly within a block of 100 trials. Each participant completed four sessions of 100 trials for each hand movement direction condition in random order. There was a break between blocks. In two of these sessions (chosen at random) visual feedback of the hand's position was provided by turning on a light below the half-silvered mirror.

Analysis

Spatial and temporal errors

We were interested in both bias (systematic error) and variability in our subject's performance. The temporal systematic error was defined as the signed difference between the moment at which the hand movement ended and the physical collision time. The end of the hand movement was defined using a velocity threshold (see below). Positive values denoted early responses. Spatial systematic errors were defined as the distance between the final hand position and the physical collision point along the axis of the targets' motion. The sign of the bias denoted undershooting (negative spatial error) or overshooting (positive error). When necessary, we also analyzed the bias in the orthogonal direction. For the two directions, we averaged the data in two steps. The individual systematic error for a given condition was the individual means of the temporal and spatial biases as defined above. Individual variability was defined as the standard deviation of the individual data points within a particular condition.

Kinematics

We also measured reaction time (RT), movement time (MT), peak velocity and time to peak velocity. A velocity threshold of 1.5 cm/s was used to detect the beginning and the end of the hand movement. Reaction time was defined as the time between targets' onset and the beginning of that hand's movement. Movement time was the interval between movement initiation and the time that the hand stopped. Time to peak velocity was the interval between the hand movement onset and the time at which hand velocity reached its maximum.

Statistical analysis

We conducted a repeated measure ANOVA in order to determine effects on the magnitude of the temporal and spatial systematic error (absolute values), temporal and spatial variability and kinematics. Target motion direction (sagittal, lateral), hand movement direction (sagittal, lateral), visual feedback (feedback, no-feedback) and presentation time (short, long) were the within-subject factors of the ANOVA. The median of the distribution of presentation times (825 ms) was used as the boundary value between both short and long categories.

Results and discussion

Figure 2 shows the spatial and the temporal biases when hand movements are executed sagittally. Data is split by target motion direction (sagittal-lateral) and feedback condition. Likewise, Figure 3 represents these spatial and temporal biases in lateral hand movements.

Systematic error

The observed pattern reveals a dissociation on the temporal error between the two directions of the visual stimuli and the two directions of the hand movements (Figs. 2b and 3b). Participants committed larger temporal systematic errors when the targets moved along the lateral dimension than when they did in the sagittal one in the condition when the hand moved sagittally. This pattern was reversed when the hand movement was in the lateral plane. This dissociation resulted in a significant interaction between target motion direction and direction of the hand movements ($F_{(1,6)} = 15.83$, $p = 0.007$; sagittal-hand lateral-target = 207 ms, sagittal-hand sagittal-target = 181 ms, lateral-hand lateral-target = 163 ms, lateral-hand sagittal-target = 210 ms).

A different pattern was observed in the spatial systematic bias. Subjects tended to overshoot the collision position both in the lateral and sagittal direction, but the magnitude of this bias in the sagittal direction was higher when the hand moved sagittally (Fig. 2a). In contrast, the analysis of the systematic spatial error when interception was performed laterally (Fig. 3a) denoted higher biases with lateral trajectories (sagittal-hand lateral-target = 1.62 cm, sagittal-hand sagittal-target = 2.93 cm, lateral-hand lateral-target = 1.89 cm, lateral-hand sagittal-target = 1.78 cm; $F_{(1,6)} = 8.35$, $p = 0.02$).

Providing visual feedback of the hand obviously help reduce the spatial bias (feedback = 1.65 cm, no-feedback = 2.45 cm; $F_{(1,6)} = 19.12$, $p = 0.004$). However, it failed to reach a significant effect on the temporal systematic error (feedback = 180 ms, no-feedback = 201 ms; $F_{(1,6)} = 4.68$, $p = 0.07$).

Presentation time had a significant effect on the temporal systematic error (long = 239 ms, short = 142 ms; $F_{(1,6)} = 10.4$, $p = 0.01$), and spatial systematic error (long = 2.11 cm, short = 2.00 cm; $F_{(1,6)} = 6.01$, $p = 0.049$). More importantly, the interaction between presentation time, hand movement direction and motion target direction was significant (long presentation time: sagittal-hand lateral-target = 264 ms, sagittal-hand sagittal-target = 223 ms, lateral-hand lateral-target = 203 ms, lateral-hand sagittal-target = 2 65 ms; short presentation time (sagittal-hand lateral-traj = 148 ms, sagittal-hand sagittal-target = 140 ms, lateral-hand lateral-target = 123 ms, lateral-hand sagittal-target = 154 ms; $F_{(1,6)} = 10.09$, p = 0.02). Therefore, longer viewing time undermined somehow the temporal accuracy when the hand sagittally reached targets moving laterally.

In addition, we examined the bias of some subjects toward negative temporal values, mainly subject two (see Fig. 2b). One possibility could be that this participant tried to obtain optimal visual information before the execution of the hand movement. We would expect higher reaction

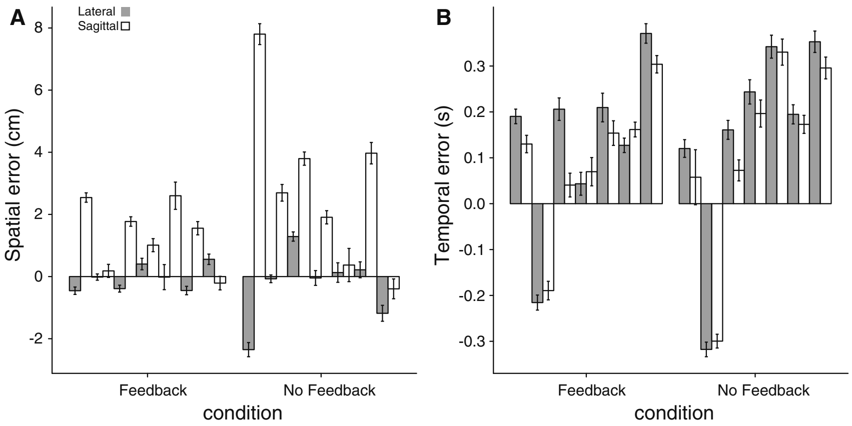


Fig. 2 Sagittal hand movements: Average temporal and spatial systematic error (bias) of individual subjects split by target motion direction (*gray bars* for lateral and *white bars* for sagittal) and the two visual feedback conditions (presence or absence of feedback). *Error bars* represent the SEM

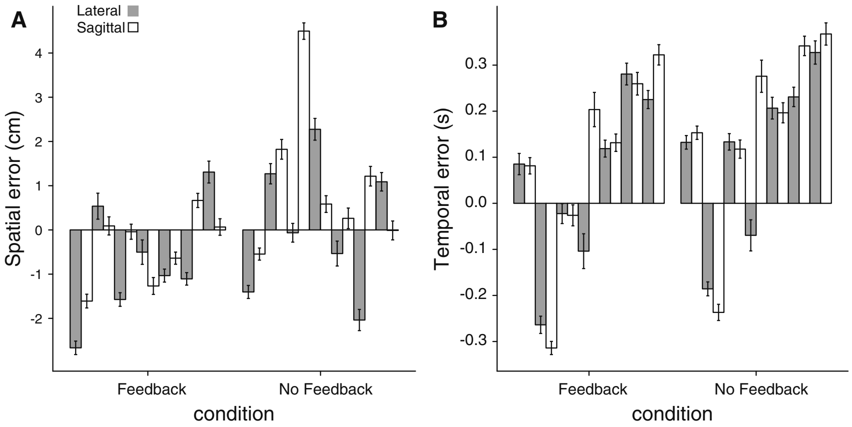


Fig. 3 The same information of Figure 2 is shown here for lateral hand movements. Average temporal and spatial systematic error of individual subjects split by target motion direction (*gray bars* for lateral and *white bars* for sagittal) and the two visual feedback conditions (presence or absence of feedback). *Error bars* represent the SEM

time values and a clear correlation of reaction time as a function of presentation time. The kinematic analysis was consistent with this interpretation (data not shown).

Variable error

Both temporal and spatial variable error showed a significant main effect of presentation time (long = 210 ms, short = 171 ms; $F_{(1,6)} = 55.23$, $p < 0.001$) (long = 2.08 cm, short = 1.89 cm; $F_{(1,6)} = 13.43$, $p < 0.01$). However, we found higher spatial variability in the sagittal target motion than in the lateral one (lateral = 1.89 cm, sagittal = 2.18 cm; $F_{(1,6)} = 5.90$, $p < 0.05$). On the temporal side, the difference was not significant (lateral = 182 ms, sagittal = 199 cm; $F_{(1,6)} = 3.43$, $p < 0.11$). Again, the interaction between presentation time, hand movement direction and trajectory's direction was significant for both temporal ($F_{1,6)} = 9.8$, $p = 0.02$) and spatial variability ($F_{1,6)} = 7.02$, $p = 0.03$).

Finally, the visual feedback of the hand did not have any effect on the temporal variability (feedback = 195 ms, no-feedback = 185 ms; $F_{(1,6)} = 2.20$, $p = 0.18$). As expected, it did on the spatial variable error (feedback = 1.79 cm, no-feedback = 2.17 cm; $F_{(1,6)} = 11.72$, $p = 0.01$). None of the other interactions were significant.

Kinematics

Reaction time Only presentation time had a significant effect on reaction time. We observed shorter reaction times when there was a short period of viewed time (long = 565 ms, short = 459 ms; $F_{(1,6)} = 13.59$, $p < 0.01$) These results can be regarded as subjects trying to use all the available visual information before the execution of the interception movement. This trend is particularly noticeable when the targets move sagittally. No interactions were significant.

Time to peak velocity Time to peak velocity was not significantly different between lateral and sagittal target motion (lateral = 386 ms, sagittal = 390 ms; $F_{(1,8)} = 0.08$, $p = 0.78$) or for the feedback condition (feedback = 396 ms, no-feedback = 381 ms; $F_{(1,6)} = 1.16$, $p = 0.32$). Significance was reached when we analyzed the time to peak depending on presentation time (long = 403 ms, short = 374 ms; $F_{(1,6)} = 30.35$, $p < 0.001$). All interactions were not significant.

Peak velocity Hand movement, feedback and target motion direction conditions failed to give significant differences for peak velocity: (lateral hand movement = 62.08 cm/s, sagittal = 47.18 cm/s; $F_{(1,6)} = 5.08$, $p = 0.065$), (feedback = 53.4 cm/s, no-feedback = 56.68 cm/s; $F_{(1,6)} = 1.33$, $p = 0.29$) and (target motion lateral = 54.99 cm/s, target motion sagittal = 55.09 cm/s; $F_{(1,6)} = 0.007, p = 0.93$). However, we found faster movements with short presentation times (long = 52.07 cm/s, short = 58.01 cm/s; $F_{(1,6)} = 29.31$, $p =$ 0.001). Only the interaction between feedback and hand movement condition was significant (feedback lateral hand = 63.4 cm/s, no-feedback lateral-hand = 62.5 cm/s, feedback sagittal hand = 43.34 cm/s, no-feedback lateral-hand = 50.86 cm/s; $F_{(1,6)} = 10.86, p = 0.01$).

Movement time Finally, movement time was affected by presentation time only (long = 842 ms, short = 749 ms;

$F_{(1,6)} = 72.19$, $p < 0.001$). Interactions between presentation time and feedback condition ($F_{(1,6)} = 7.86$, $p < 0.03$) and presentation time and direction of target motion ($F_{(1,6)} = 11.14$, $p < 0.01$) were significant. This result suggests the crucial influence of the viewing time on the temporal constraints of the hand movement. It seems that participants tried to obtain as much visual information of the hand position as possible (larger movement times with the presence of feedback). Finally, the smaller movement times with shorter viewing times denote that, once the objects disappeared, they are focused on the execution phase of the hand movement.

In sum, the temporal performance was more accurate when the objects and the hand moved along the same direction. Subjects performed the task with higher temporal accuracy, but not necessarily combined with a better spatial performance. In addition, no significant differences were observed between sagittal and lateral kinematic variables. Therefore, these differences in timing performance cannot be accounted for by different speed-accuracy tradeoffs. However, at this point we cannot tell whether the improvement was only caused by proprioceptive information due to the motor action or by visually comparing the hand changing position with the moving targets. Vision of the hand does not seem to have any critical effect. One possible explanation is that subjects could obtain a better estimate of target velocity, because it could compare the speeds of the target and the hand along the same direction. To further support the conclusion that the motor action combined with the target motion contributed to the observed pattern, we conducted an experiment based on perceptual judgments.

Experiment 2: perceived coincidence timing task

Previous research has shown better temporal accuracy of perceptual processes when they promote actions, compared to coincidence anticipation timing (Bootsma 1989). In order to factor out the contribution of the motor action to the observed pattern in Experiment 1, we presented the same visual stimulus and participants had to indicate when the two targets would collide by pressing a button of an external device without making any interception movement. The stimuli parameters and conditions were the same as in Experiment 1. The same seven subjects that took part in the Experiment 1 participated in this second experiment. Like in the previous experiment, they were not given any feedback of their performance and were tested in the same number of trials per condition. If the felt velocity of the hand movement was indeed responsible for the double dissociation in the time estimates between target motion direction (lateral and sagittal) and hand movement direction, the difference between lateral and sagittal directions should not be significant in the perceptual task.

Results and discussion

In the perceptual coincidence-timing task, the temporal systematic error was defined as the difference in time between when the button was pressed and the physical collision time. Note that there is no spatial error associated with a goal-directed response in this task; therefore, we will only analyze the temporal bias.

Figure 4 shows the individual signed temporal bias obtained for lateral and sagittal directions in the perceptual task (left). For the sake of comparison, we show the temporal bias obtained in the sagittal and lateral hand movement conditions from Experiment 1. As the visual feedback of the hand did not affect temporal accuracy in Experiment 1, the data shown in Fig. 4 for the hand movement conditions were pooled across feedback conditions.

Systematic error

In order to compare the temporal error of the perceptual and manual conditions, we conducted a repeated-measure ANOVA with target motion direction (lateral, sagittal), task (perceived, sagittal hand movement, lateral hand movement) and presentation time (short, long) as the within-subject factors. We specifically analyzed the interaction between task and target motion direction condition and we found a significant interaction (perceptual-lateral = 252 ms, sagittal-hand lateral = 202 ms, lateral-hand lateral = 165 ms; perceptual-sagittal = 251 ms, sagittal-hand sagittal = 175 ms, lateral-hand sagittal = 210 ms;

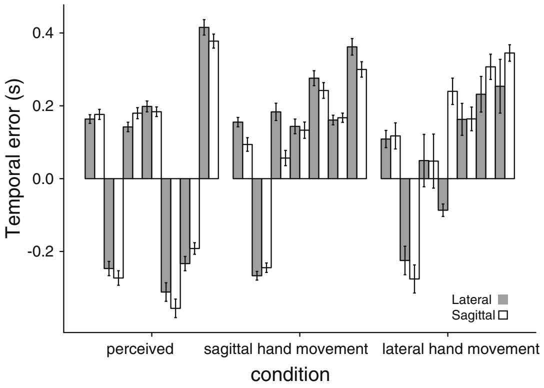


Fig. 4 Temporal error in the perceptual task split by target motion direction (*right*). For the sake of comparison the temporal error measured in the manual conditions (Experiment 1) is shown in the *central panel* (sagittal hand movement) and *right panel* (lateral hand movement). *Error bars* represent SEM

$F_{(2,12)} = 5.34$, $p = 0.02$). Most importantly, a paired comparison revealed a non-significant difference between the motion target directions in the perceptual task [$t(6) = 0.33$, $p = 0.75$]. This result is consistent with the hypothesis that suggests a benefit from using the proprioceptive motion cues available when the targets and hand movements are coupled up.

Interestingly, the interaction between task type and presentation time was significant (perceptual-long = 247 ms, sagittal-hand long = 244 ms, lateral-hand long = 239 ms; perceptual-short = 256 ms, sagittal-hand short = 132 ms, lateral-hand short = 135 ms; $F_{(2,12)} = 4.23$, $p = 0.04$). Therefore, only the perceptual task benefit from having more viewing time denoting that people relied more on visual information as they did not have any chance to increase accuracy via the motor execution (Battaglia and Schrater 2007). No other interaction was significant.

Variable error

The variable error was not significantly different between the interceptive tasks and the perceptual one (sagittal-hand = 199 ms; lateral-hand = 191 ms, perceptual = 172 ms; $F_{(2,12)} = 1.49$, $p = 0.26$), but the interaction between task and presentation time was (perceptual-long = 173 ms; perceptual-short = 201 ms; sagittal-hand long = 204 ms; sagittal-hand short = 186 ms, lateral-hand long = 181 ms; lateral-hand short = 174 ms; $F_{(2,12)} = 6.22$, $p = 0.04$). Again, temporal variability was significantly reduced when subjects had more viewing time in the perceptual task. No other interaction was significant.

Conclusion

The present study sought to examine spatial and temporal biases in a temporal coincidence-timing task when subjects did not have to trade off one type of error for the other. For example, subjects could be very accurate temporally irrespective of the spatial accuracy.

Although our task permitted independent control of the spatial and temporal accuracies, we found some interdependencies between spatial and temporal biases that are similar to those reported in the previous studies with independent manipulation of both accuracies too (Tresilian et al. 2009). We obtained a double dissociation of the spatial and temporal systematic errors between directions. While the temporal accuracy was smaller when the hand and targets moved along the same direction, the pattern for the spatial systematic error was reversed. This result can be regarded as subjects trading off time requirements over spatial ones. Our task requires people to control where the interception takes place as well as when. This introduces the possibility to analyze both spatial and temporal accuracy in a way that one would never be subordinate to the other. Consistent with this pattern, it has been reported that subjects adapt their interception movements to changes in temporal accuracy demands, but not to changes in spatial requirements (Tresilian et al. 2004).

Our results show a benefit on the time estimates from using proprioceptive cues in specific combinations with target motion. One possible explanation for this synergy could be that subjects used the felt velocity of the hand as an additional reference to compare the speed of the targets when the targets and the hand moved along the same axis. In addition, the lack of effect of the visual feedback of the hand on the temporal performance is consistent with this hypothesis. We cannot rule out attentional effects driven by the action itself. In this sense, our results would be consistent with Tipper et al. (1992) proposal of an action-centered attention in reaching. Therefore, performing a sagittal movement could enhance perceptual processing in the same axis. In sum, we believe that these results add some new aspects to the existing literature, which has mainly emphasized the use of visual information in interceptive timing (see Zago et al. 2009 for a recent review). By pointing out the contribution of proprioceptive information, which is internally generated, in reducing temporal uncertainty our work adds to existing models that promote the use of internal models in interception (Indovina et al. 2005; Lopez-Moliner et al. 2007).

Acknowledgments We would like to thank two anonymous reviewers for their comments and suggestions. This work has been supported by European Science Foundation, Eurocores 06-CNCC-FP-012 grant, and Grant SEJ2006-27544-E from the Spanish Government.

References

Battaglia PW, Schrater PR (2007) Humans trade off viewing time and movement duration to improve visuomotor accuracy in a fast reaching task. J Neurosci 27(26):6984–6994. doi:10.1523/JNEUROSCI.1309-07.2007

Bootsma RJ (1989) Accuracy of perceptual processes subserving different perception-action systems. Q J Exp Psychol A 41(3): 489–500. doi:10.1080/14640748908402378

Bootsma RJ, Oudejans RR (1993) Visual information about time-to-collision between two objects. J Exp Psychol Hum Percept Perform 19(5):1041–1052. doi:10.1037/0096-1523.19.5.1041

Brenner E, Smeets JB (2009) Sources of variability in interceptive movements. Exp Brain Res 195(1):117–133. doi:10.1007/s00221-009-1757-x

Brenner E, de Lussanet MH, Smeets JB (2002) Independent control of acceleration and direction of the hand when hitting moving targets. Spat Vis 15(2):129–140. doi:10.1163/15685680252875129

Brenner E, van Beers RJ, Rotman G, Smeets JB (2006) The role of uncertainty in the systematic spatial mislocalization of moving objects. J Exp Psychol Hum Percept Perform 32(4):811–825. doi:10.1037/0096-1523.32.4.811

Brouwer AM, Smeets JB, Brenner E (2005) Hitting moving targets: effects of target speed and dimensions on movement time. Exp Brain Res 165(1):28–36. doi:10.1007/s00221-005-2277-y

Caljouw SR, van der Kamp J, Savelsbergh GJ (2006) The impact of task-constraints on the planning and control of interceptive hitting movements. Neurosci Lett 392(1–2):84–89. doi:10.1016/j.neulet.2005.08.067

Fitts PM (1954) The information capacity of the human motor system in controlling the amplitude of movement. J Exp Psychol 47(6):381–391. doi:10.1037/h0055392

Fitts PM, Peterson JR (1964) Information capacity of discrete motor responses. J Exp Psychol 67:103–112. doi:10.1037/h0045689

Hancock PA, Newell KM (1985) The movement speed-accuracy relationship in space-time. In: Heuer H, Kleinbeck U, Schmidt KH (eds) Motor behavior: programming, control and acquisition. Springer, Berlin, pp 153–185

Indovina I, Maffei V, Bosco G, Zago M, Macaluso E, Lacquaniti F (2005) Representation of visual gravitational motion in the human vestibular cortex. Science 308(5720):416–419. doi:10.1126/science.1107961

Ladavas E, Farne A, Zeloni G, di Pellegrino G (2000) Seeing or not seeing where your hands are. Exp Brain Res 131(4):458–467. doi:10.1007/s002219900264

Lopez-Moliner J, Field DT, Wann JP (2007) Interceptive timing: prior knowledge matters. J Vis 7(13):11–18. doi:10.1167/7.13.11

Mon-Williams M, Wann JP, Jenkinson M, Rushton K (1997) Synaesthesia in the normal limb. Proc R Soc Lond B 264(1384):1007–1010. doi:10.1098/rspb.1997.0139

Rodriguez-Herreros B, Lopez-Moliner J (2008) The influence of motion signals in hand movements. Exp Brain Res 191(3):321–329. doi:10.1007/s00221-008-1527-1

Steinman RM, Kowler E, Collewijn H (1990) New directions for oculomotor research. Vis Res 30(11):1845–1864. doi:0042-6989(90)90163-F

Tipper SP, Lortie C, Baylis GC (1992) Selective reaching: evidence for action-centered attention. J Exp Psychol Hum Percept Perform 18(4):891–905. doi:10.1037/0096-1523.18.4.891

Tresilian JR (1994) Approximate information sources and perceptual variables in interceptive timing. J Exp Psychol Hum Percept Perform 20(1):154–173

Tresilian JR, Lonergan A (2002) Intercepting a moving target: effects of temporal precision constraints and movement amplitude. Exp Brain Res 142(2):193–207. doi:10.1007/s00221-001-0920-9

Tresilian JR, Plooy A (2006) Systematic changes in the duration and precision of interception in response to variation of amplitude and effector size. Exp Brain Res 171(4):421–435. doi:10.1007/s00221-005-0286-5

Tresilian R, Oliver J, Carroll J (2003) Temporal precision of interceptive action: differential effects of target size and speed. Exp Brain Res 148(4):425–438. doi:10.1007/s00221-002-1309-0

Tresilian JR, Plooy A, Carroll TJ (2004) Constraints on the spatiotemporal accuracy of interceptive action: effects of target size on hitting a moving target. Exp Brain Res 155(4):509–526. doi:10.1007/s00221-003-1793-x

Tresilian JR, Plooy AM, Marinovic W (2009) Manual interception of moving targets in two dimensions: performance and space-time accuracy. Brain Res 1250:202–217. doi:10.1016/j.brainres.2008.11.001

van Beers RJ, Sittig AC, Denier van der Gon JJ (1996) How humans combine simultaneous proprioceptive and visual position information. Exp Brain Res 111(2):253–261. doi:10.1007/BF00227302

van Beers RJ, Sittig AC, Denier van der Gon JJ (1999) Localization of a seen finger is based exclusively on proprioception and on vision of the finger. Exp Brain Res 125(1):43–49. doi:10.1007/s002210050656

Zago M, McIntyre J, Senot P, Lacquaniti F (2009) Visuo-motor coordination and internal models for object interception. Exp Brain Res 192(4):571–604. doi:10.1007/s00221-008-1691-3

6

STUDY IV
SHIFTED VISUAL FEEDBACK OF THE HAND AFFECTS REACHABILITY JUDGMENTS ON INTERCEPTION[**]

[**] This chapter corresponds to:
Rodríguez-Herreros, B., de Grave, D., López-Moliner, J., Brenner, E. & Smeets J.B.J. (2013). Shifted visual feedback of the hand affects reachability judgments in interception. **Vision Research,** 88C:30-37.

RESUMEN

La estimación de si un objeto es alcanzable es importante si tenemos la intención de interaccionar con el objeto. Estudios recientes han demostrado que el uso de herramientas o que la distorsión de la información visual de la mano pueden afectar los juicios perceptivos de si un objeto estático es alcanzable o no. En este estudio, hemos tratado de determinar si una adaptación inconsciente al desplazamiento de la posición percibida de la mano puede influenciar los juicios de alcanzabilidad para interceptar un objeto en movimiento. Además de analizar si hubo diferencias respecto a la dirección de la trayectoria de los objetos (objetos que se acercan o se alejan del participante), también examinamos si la distorsión de la información visual sobre donde está la mano alteró los movimientos manuales. Los resultados arrojaron claras diferencias en el juicio de alcanzabilidad según el tipo de distorsión de la mano: cuando esa distorsión era hacia adelante, 5 cm alejada de la mano, los participantes juzgaron como alcanzables objetos que, a la misma distancia, fueron inalcanzables cuando la distorsión fue 5 cm hacia el cuerpo del participante. En segundo lugar, los datos mostraron que los juicios de alcanzabilidad no fueron significativamente distintos según si el objeto se acercaba o se alejaba del sujeto. Finalmente, los análisis demuestran que los movimientos, al igual que los juicios de alcanzabilidad, se adaptaron completamente a la distorsión implementada. Podemos concluir que el sistema visomotor adaptó la información propioceptiva de la mano a la información visual distorsionada, lo que sugiere una gran dominancia de la modalidad sensorial visual.

RESUM

L'estimació de si es pot arribar a interceptar un objecte és important si tenim la intenció d'interaccionar amb l'objecte. Estudis recents han demostrat que l'ús d'eines o que la distorsió de la informació visual de la mà poden afectar els judicis perceptius de si un objecte estàtic es pot arribar a interceptar. En aquest estudi, hem tractat de determinar si una adaptació inconscient al desplaçament de la posició percebuda de la mà pot influenciar els judicis de si es pot arribar a interceptar un objecte en moviment. A més d'analitzar si va haver diferències respecte a la direcció de la trajectòria dels objectes (objectes que s'apropen o s'allunyen del participant), també vam examinar si la distorsió de la informació visual sobre on està la mà va alterar els moviments manuals. Els resultats van demostrar clares diferències en el judici de si es pot arribar a l'objecte segons el tipus de distorsió de la mà: quan aquesta distorsió era cap endavant, 5 cm allunyada de la mà, els participants van jutjar com abastables objectes que, a la mateixa distància, van ser inabastables quan la distorsió va ser 5 cm cap al cos del participant. En segon lloc, les dades van mostrar que els judicis d'abastabilitat no van ser significativament diferents segons si l'objecte s'acostava o s'allunyava del subjecte. Finalment, les anàlisis van demostrar que els moviments, igual que els judicis d'abastabilitat, es van adaptar completament a la distorsió implementada. Podem concloure que el sistema visomotor va adaptar la informació propioceptiva de la mà a la informació visual distorsionada, suggerint una gran dominància de la modalitat sensorial visual.

Vision Research 88 (2013) 30–37

Contents lists available at SciVerse ScienceDirect

Vision Research

journal homepage: www.elsevier.com/locate/visres

Shifted visual feedback of the hand affects reachability judgments in interception

Borja Rodríguez-Herreros [a,b,*], Denise D.J. de Grave [c], Joan López-Moliner [a,b], Eli Brenner [c], Jeroen B.J. Smeets [c]

[a] *Vision & Control of Action (VISCA) Group, Departament de Psicologia Bàsica, Facultat de Psicologia, Universitat de Barcelona, Spain*
[b] *Institute for Brain, Cognition and Behaviour (IR3C), Universitat de Barcelona, Spain*
[c] *Research Institute MOVE, Faculty of Human Movement Sciences, VU University, Amsterdam, The Netherlands*

ARTICLE INFO

Article history:
Received 30 October 2012
Received in revised form 13 June 2013
Available online 27 June 2013

Keywords:
Hand movement
Feedback
Reachability
Visuomotor control

ABSTRACT

Estimating whether an object is reachable is important if one intends to interact with the object. If an object is moving, it will be reachable only within a certain time-window. In such situations, motion of the object relative to the body has to be taken into account to judge the moment at which the target becomes reachable. We know that judgments of reachability are influenced by displaced visual feedback about the position of the hand when objects are static. Here we examine whether displaced feedback of the hand also influences reachability judgments when reachability is temporally constrained because the object is moving. The task for the subjects was to intercept a virtual cube with their unseen index finger as soon as the cube was considered to be reachable. Subjects received visual feedback about the position of their index finger, but this feedback was shifted in depth by 5 cm, either away from or closer to their body. The region that was judged to be reachable was larger when feedback of the hand was shifted away from the body than when the feedback was shifted closer to the body. This effect was correlated with the spatial error committed at the interception point. We conclude that all judgments about the surrounding space are adjusted in relation to the shifted visual feedback of the hand.

1. Introduction

One of the most common motor tasks in daily life is to reach out to manipulate an object. In order to decide whether it is worthwile starting to do so, the visuomotor system requires a judgment about whether the object is reachable, based on variables like body posture and the length of the arm. Studies of reachability examine the range of positions that one judges to be reachable. In spite of the apparent simplicity with which one estimates the reachability of an object, numerous studies have demonstrated that doing so is not trivial. Indeed, previous literature has reported that visual judgments of reachability can be influenced by various factors. Carello et al. (1989) proposed that misjudging the stability of one's posture while reaching out to an object is one of the factors that cause people to think that they can reach a static object that they cannot (Bootsma et al., 1992; Gabbard, Ammar, & Lee, 2006; Heft, 1993; Mark et al., 1997). This explanation is known as the postural stability account. As the risk of falling over is lower in a seated position, participants are more confident of reaching out further when seated, leading to overestimations of reachability (Robinovitch, 1998). Another explanation for overestimating reachability is the "whole body engagement" hypothesis (Rochat & Wraga, 1997). This states that participants are not able to account for the constraints of the experimental set-up when performing the task (e.g. participants fail to consider the restriction of their range of motion when the trunk is strapped to the chair). Yet another explanation is that the circumstances could affect our visual judgments of distance (Sousa, Brenner, & Smeets, 2010). Coello (2005) showed that reachability judgments are overestimated in impoverished visual conditions (Coello & Iwanow, 2006). Witt, Proffitt, and Epstein (2005) showed that objects that are beyond reach without a tool look closer and reachable when holding a tool. According to Berti and Frassinetti (2000), the tool was assimilated to the hand like an artificial extension of the body, causing one to believe that one could reach further. Subsequent studies demonstrated specific kinematic changes because of tool-use that suggested an update of the somatosensory representation congruent with an increased length of the arm (Cardinali et al., 2009). They also demonstrated that this gradual elongation from the hand towards the tip of the tool needed an active physical connection between them (Longo & Lourenco, 2006; Gamberini et al., 2008). In fact, the re-size of the near space seems to require a clear intention to use the tool

---

[*] Corresponding author. Address: Faculty of Psychology, P. Vall d'Hebron, 171, 08035 Barcelona, Catalonia, Spain.

E-mail address: borja.rodriguez@ub.edu (B. Rodríguez-Herreros).

0042-6989/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.visres.2013.06.005

(active use), since the mere presence of a long stick resting near the hand (Maravita et al., 2001) or passively held (Farnè, Bonifazi, & Làdavas, 2005; Witt, Proffitt, & Epstein, 2005) produced no such effect. Nevertheless, the use of a tool is not strictly necessary. The extension of reachable space can also be modified by displacing the felt from the seen position of the hand (Holmes & Spence, 2004). de Grave, Brenner, and Smeets (2011b) recently reported that such modifications are not correlated with the amount of visuomotor adaptation, although some other studies supported the idea that reachability judgments are closely linked to changes in visuomotor variability (Bourgeois & Coello, 2012).

A common aspect of all these studies is that subjects performed a perceptual judgment about the reachability of either a static (Denise et al., 2011) or a moving object (Fischer et al., 2003; Delevoye-Turrell, Vienne, & Coello, 2011; de Grave, Brenner, and Smeets (2011a)), each demanding different information. However, as reachability judgments are thought to form the basis of decisions to make a movement, we sought to examine whether the influence of displaced visual feedback on estimating reachability is also evident when making such decisions about moving objects. Specifically, we investigated whether displacing the feedback affected the actions towards moving objects, imposing a time constraint to the reachability judgment. We chose an interceptive hand movement towards a moving object, since the temporal cues needed to hit the target cannot be recruited merely from the visual information of the target motion (Brouwer, Brenner, & Smeets, 2003), demanding an estimation of the reachability. This required estimation in order to judge when to start the movement is based on two evidences: first, if reachability judgments were uniquely sustained on visual cues, feedback displacement would have no effect on them. Second, the resolution of the on-line control when making temporal adjustments is lower comparing to spatial ones (Brenner & Smeets, 1997; Brenner, Smeets, & de Lussanet, 1998). Thus, when one reaches out to interact with a moving object one must estimate when the object will be reachable. Consequently, motion of the object relative to the body has to be taken into account, and a continuous update of the reachability judgment has to be made. The complexity of this task consists of taking into account the velocity of the object and the velocity and duration of the planned arm movement. In this context, our experimental design allowed us to test whether visual information presented a strong dominance when localizing the hand in the interceptive task, or whether proprioceptive information assists the vision of our hand crucially when the location coding implied body parts involved in the action (Rodriguez-Herreros & Lopez-Moliner, 2011; Rossetti, Desmurget, & Prablanc, 1995).

2. Methods

2.1. Subjects

Six right-handed volunteers (4 women; mean age 31.5 ± 11.4 years) participated in the experiments, including two of the authors. Except for them, all subjects were naive with respect to the experimental hypothesis. Participants had normal or corrected-to-normal visual acuity and no one had any history of neuromuscular disorders. Prior to their inclusion in the study, participants gave their informed consent. The local ethics committee approved this study.

2.2. Apparatus

We used the same set-up as (de Grave, Brenner, & Smeets, 2011a, see Fig. 1) to present virtual stimuli. In a dark room, subjects sat on a height-adjustable stool in front of two mirrors in which each eye saw a seperate CRT monitors (1096×686 pixels, 47.3×30.0 cm, 160 Hz). A three-dimensional virtual environment was created by presenting different images to the left and the right eye using this combination of mirrors and monitors. The imaginary line that protruded from a position between the eyes and was tilted 30° downward from eye-height will be referred to as the *z*-axis. Infrared markers were attached to the index finger tip of the subjects' dominant right arm to register hand movements. These movements were recorded at 250 Hz with a 0.01 mm spatial resolution using the Optotrak 3020 motion analysis system (Northern Digital, Inc.). The individual position data time series were processed with a low-pass Butterworth filter (cutoff frequency of 6 Hz) for further analysis. Velocity and acceleration data were derived from the smoothed position data.

2.3. Stimuli

At the start of each trial, a start position for the finger was presented (a $1 \times 1 \times 1$ cm pink cube located 15 cm to the right of the *z*-axis ($x = 15$)) (see Fig. 1). A yellow cube (also $1 \times 1 \times 1$ cm) provided visual feedback about the position of the index finger. Stimuli consisted of a $5 \times 5 \times 5$ cm blue target cube that moved along one of several paths at a constant speed of 15 cm/s for a fixed duration of 1.5 s. On each trial the trajectory of the target was chosen at random from twelve interleaved staircases. For six staircases, the starting position of the target was such that the target passed the subject's body 10 cm closer than the maximal distance that the participant could reach along the *z*-axis. For the other six staircases the starting position of the target was 10 cm further than the participant's maximal reach distance. The six pairs of staircases (one starting near and one far) differed with respect to motion direction of the target (from left to right or from right to left) and trajectory of the target (approaching, departing or frontal). On one third of the trials the target moved parallel to the lateral axis (x) (frontal trials). The other two thirds of trials were trajectories with an angle of 20° with respect to the x axis: one third for departing trials (moving away for the body), and the other for approaching (moving closer to the body).

2.4. Procedure

The first step was to determine the furthest position that the participant could reach (true reachability). To do so, the participant moved his or her outstretched right arm from left to right, crossing the sagittal plane. The position of the marker on his/her finger was tracked with the Optotrak. This procedure was performed in total darkness (without visual feedback about the position of the index finger). The finger's path was used to determine the starting positions of the target's trajectories, in a way that the target's initial positions of the first trial of each staircase were determined by the minimum and maximum Z coordinates of the finger's path. For instance, initial position of trial 1 in staircase 1 (departing target from left to right) was the X min and Z min coordinates. As the stool was positioned in such a way that the participant held his or her nose against the edges of the mirrors (Fig. 1), participants could hardly move their trunk forward, but they were not physically restrained in any other way.

Each participant performed two blocks of trials, with a break between them. The blocks differed with respect to the visual feedback about the position of the hand. In one block of trials the visual feedback was shifted 5 cm in depth away from the participant's body, and in the other block the feedback was shifted 5 cm towards his or her body. The authors knew about the manipulation of the visual feedback, although they could not distinguish the specific displacement (away, closer) of each block. The four naïve participants were not informed about the feedback manipulation and none of them reported any difference between the seen and the felt position of their finger. Each block contained 12 staircases. At the

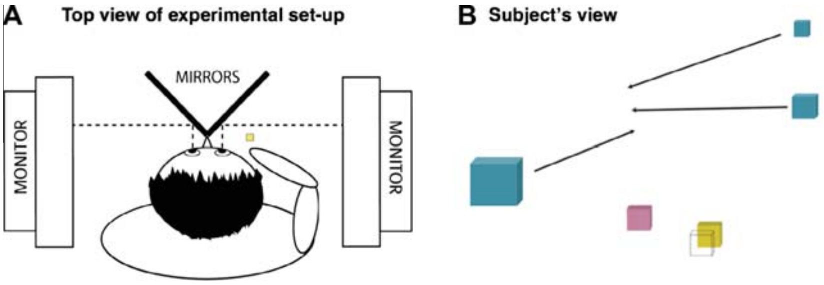


Fig. 1. Top view (A) and participant's view (B) of the experimental setup (not to scale). The blue cubes indicate the moving targets that participants had to reach (only one cube appeared in each trial). The yellow cube represents the visual feedback about the position of the index finger. Indicated is the situation in which the visual feedback was 5 cm further away than the real finger position (dotted cube). The pink cube represents the starting position. The yellow cube had to be moved to the pink one in order to start the trial. The task was then to intercept the blue cube, if doing so was deemed possible. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

start of each block participants performed 20 practice trials to get familiar with the task. The two feedback shifts were separated in two different blocks in order to avoid the participants to be aware of the distortion. After the experimental sessions, participants were asked about the feedback displacement and none of them reported awareness of the distortion.

The starting position (pink cube) was presented at the beginning of each trial. Participants had to move the virtual image of the index finger (yellow cube) to the start position in order to start the trial. The index finger was considered to be at the start position when the virtual image of the index finger was raised higher than 10 cm below the start position and its velocity was lower than 1.5 cm/s for 400 ms. As soon as the index finger was at the starting position, the moving target cube was presented for 1.5 s. The task was to intercept the cube with the index finger as soon as it was judged to be reachable. If the target was judged to be unreachable along its entire path, the subject had to remain at the starting position and wait for the next trial. If the target was judged to be reachable, the stimulus on the next trial of that staircase was shifted 2 cm away from the body. If the target was judged to be unreachable (i.e. the subject did not move), the stimulus was shifted 2 cm closer to the body on the next trial for that staircase. On trials that were judged to be reachable, subjects had to bring their hand back to the starting position in order to start the next trial. Visual feedback about the position of the hand was provided throughout a block, except when the index finger tip was within 10 cm of the target. The order of the blocks was counterbalanced across participants. A block of trials ended when all staircases contained 10 switches between trials in which subjects moved the hand and trials in which they did not. The average number of trials was 651 and each block took about one hour.

2.5. Analysis

In all analysis, the knowledge of the experimental manipulation was not considered as a factor, since preliminary analyses had revealed a lack of statistical main effects and interactions ($p > .6$ for all comparisons). We know the z (depth) and x (lateral) coordinates of the entire target path for each trial. The minimal distance between the target trajectory and the starting position of the hand (real position of the finger marker) was used to determine the participant's performance on judging the reachability of the object. The proportion of "unreachable" answers (trials in which participants did not move their finger because they judged the target as not reachable throughout the path) was the subjects' response that we calculated for each distance to the path. This was done for every direction of the stimulus (departing, approaching, frontal), combining data from the ascending and descending staircases. Psychometric functions (cumulative normal distributions) were fitted for each participant and each block using the R statistic software, which implements the maximum-likelihood method described by Wichmann and Hill (2001). We performed a 2×3 repeated measures ANOVA to evaluate the fitted parameters for the standard deviation (sigma) and the judged reachability threshold with the within-subject factors feedback (forward or backward shift), and direction of the stimulus (departing, approaching, frontal). Post-hoc tests were conducted to see which levels of a factor differed. Additionally, a subsequent analysis was performed to determine whether approaching and departing objects were judged reachable and intercepted at different distances. We measured the target position in trials in which participants moved the hand towards the target. Specifically, we compared the location of the target at the onset and at the offset of the hand movement for both approaching and departing paths. We conducted a $2 \times 2 \times 2$ repeated measures analysis of variance (ANOVA) with factors feedback (forward or backward shift), direction of the stimulus (departing, approaching) and time (onset, offset).

Finally, hand movement trajectories were determined from the three-dimensional spatial coordinates of the position of the index finger. The beginning and end of each hand movement were defined as the moments the hand reached a velocity that was higher and lower than 1.5 cm/s respectively. Spatial errors in depth were defined as the difference between the z position of the hand and the z position of the target at the moment the hand movement ended (positive errors indicate that the hand was further than the target). The individual systematic error for a given condition was the mean of the spatial errors defined in this manner. The euclidian distance between the starting and endpoint position of the finger was also calculated for every hand movement. To check the magnitude of the adaptation to the feedback displacement, a repeated measures ANOVA with factors feedback and direction of the object's path was performed on the individual systematic errors and on the movement distances. For all the analysis, trials in which the reaction time (time interval from the target onset until the movement onset) was shorter than 700 ms (most of them departing) were removed from the sample, since the position at which the target was intercepted is likely to have been limited by the reaction time rather than by judgments of when the target came within reach. Threshold for statistical significance was set at $p < .05$. Post-hoc comparisons were performed using paired sample t-tests.

3. Results

3.1. Reachability judgments

Each panel of Fig. 2 represents the psychometric curves of all subjects. Panel A shows that the reachability judgments followed the shift of the hand's visual feedback: the grey curves (feedback shifted closer) are positioned at smaller distances than the black curves (feedback shifted away). Panel B shows no clear effect of the direction of the stimulus.

The ANOVA on the reachability thresholds (50% values of psychometric curves) showed a main effect of visual feedback displacement (away = 68.4 cm, closer = 55.6 cm, $F_{(1,5)} = 46.4$, $p < .01$). On average, participant's reachability boundary was about 13 cm further away when the feedback was shifted 5 cm away from the body compared to when the feedback was shifted 5 cm closer to the body. This value is slightly more than the sum of the two feedback shifts (10 cm). No significant effect of stimulus direction was found ($F_{(2,10)} = 2.27$, $p = .15$), and the interaction was also not significant ($F_{(2,10)} = 1.45$, $p = .28$). The analysis of the variability (the standard deviation of the fitted function, corresponding to the slopes of the psychometric curves) yielded no significant effects of feedback conditions ($F_{(1,5)} = 3.8$, $p = .11$), stimulus direction ($F_{(2,10)} = 1.84$, $p = .21$) or interaction between these factors ($F_{(2,10)} = 0.82$, $p = .47$). On average, the standard deviation was 13.8 cm.

To test whether participants estimate the reachable position of the object taking into consideration the time employed to intercept the target at this position, we measured where the target was when participants decided to move and when they ended the movement. Fig. 3 depicts a top view of the target locations of a representative subject for both closer (3A–3B) and away (3C–3D) feedback displacements. Target locations at the onset of the movement corresponded to A and C panels, whereas B and D were for target positions at the end of the hand movement. The pattern of data for the rest of the subjects is very similar (not shown). The black rectangle in the lower part of both panels indicates where the visual feedback of the index finger was required to be in order to start the trial. The real position of the index finger at that time (purple dots) was not centered on the black rectangle because of the shift in the feedback. Thus the starting position of the finger differed between the feedback conditions.

We observed a significant main effect of the feedback distortion both at the beginning (away = −41.42 cm, closer = −34.76 cm, $F_{(1,5)} = 12.47$, $p = .016$) and at the end of the movement (away = −41.45 cm, closer = −34.6 cm, $F_{(1,5)} = 13.05$, $p = .015$), showing that the target was judged reachable further when the displacement of the feedback was away from the body, in both cases. In contrast, for the direction of the movement, we found significant differences only at the onset (approaching = −43.4 cm, departing = −36.1 cm, $F_{(1,5)} = 19.1$, $p = .007$), whereas the location of departing and approaching objects did not differ when the hand movement ended (approaching = −38.5 cm, departing = −37.5 cm, $F_{(1,5)} = 1.2$, $p = .32$). Neither of the interactions was found to be significant.

3.2. Hand movements

Fig. 4 shows that the spatial error in depth (difference between z-coordinates of the target and the real hand) at the end of the movement varied considerably between subjects and visual feedback conditions.

We found a significant effect of feedback condition (away: −13.99 cm, closer: −2.6 cm, $F_{(1,5)} = 54.2$, $p < .001$) but not of the direction of the stimulus ($F_{(2,10)} = 3.15$, $p = .09$), and the interaction was not significant ($F_{(2,10)} = 0.66$, $p = .53$). Neither the movement

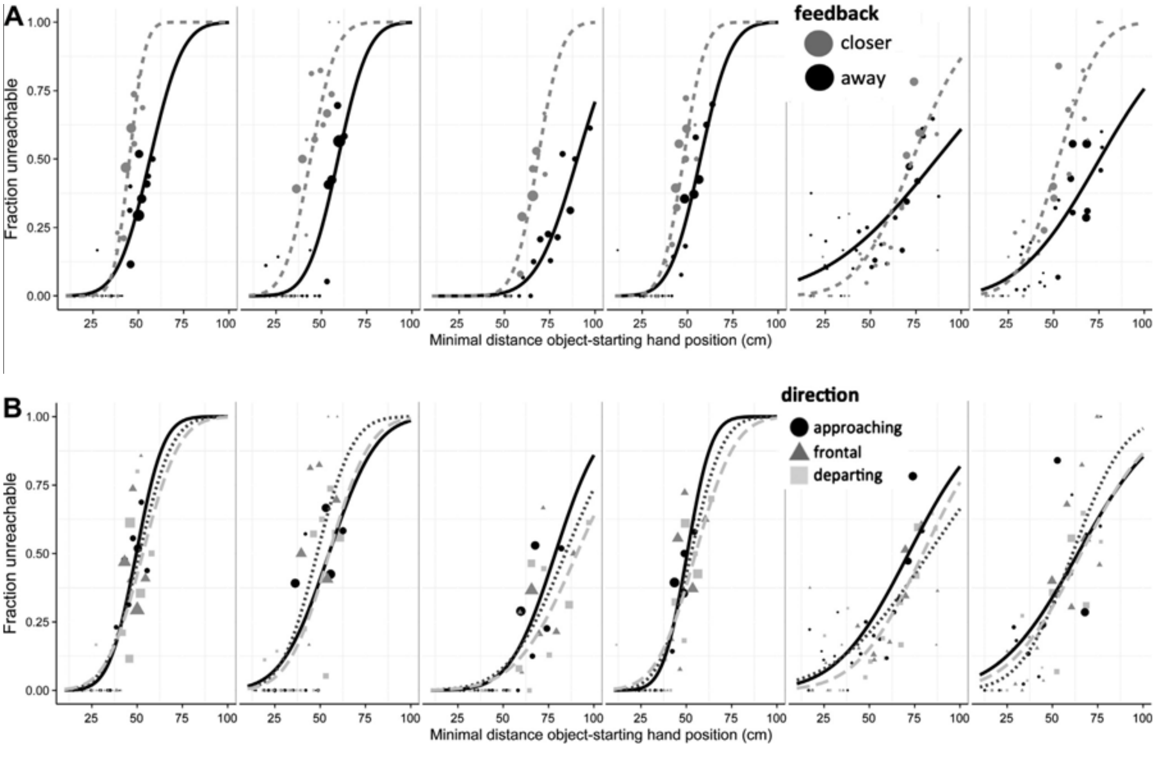


Fig. 2. (A) Psychometric curves for each subject for the two feedback conditions. Black (continuous line) represents trials in which feedback was shifted away from the body and grey (dashed line) ones in which feedback was shifted closer to the body. (B) Psychometric curves for each subject for the three directions of target motion. Solid black line (disks) represents approaching targets, dashed light grey line (squares) represents departing targets, and dotted dark grey line (triangles) represents frontal trials. Size of the dots represent the number of trials: big dots (>20 trials), medium dots (5–20 trials) and small dots (<5 trials).

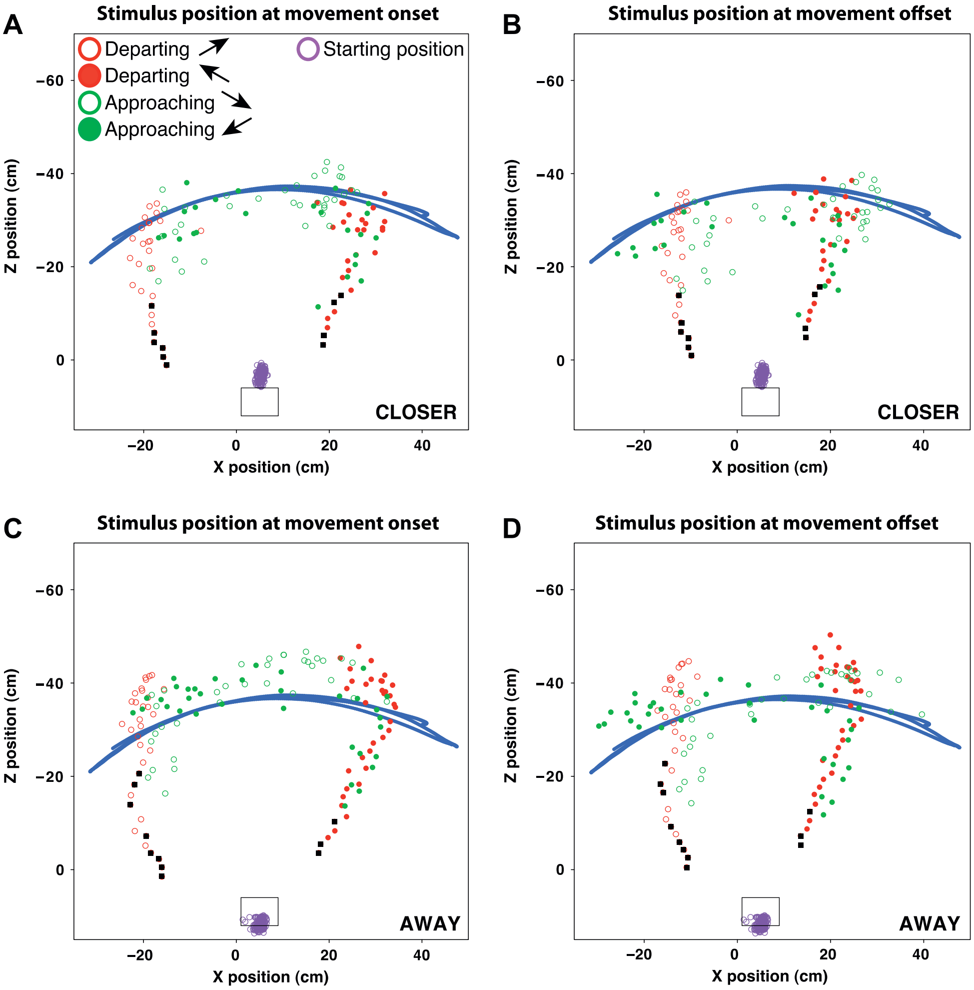


Fig. 3. Top view of the target locations at the onset (A–C) and at the offset (B–D) of the hand movement for a representative subject. A and B panels corresponded to the feedback distortion 5 cm closer than the real finger position and C–D for 5 cm away. The reaching range of the arm is represented by the blue line. Purple dots are the starting positions of the finger. Other symbols indicate the target position. Colors indicate the direction of the target's path (see Legend). Trials in which the reaction time was shorter than 700 ms are shown as black squares (removed from the analysis). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

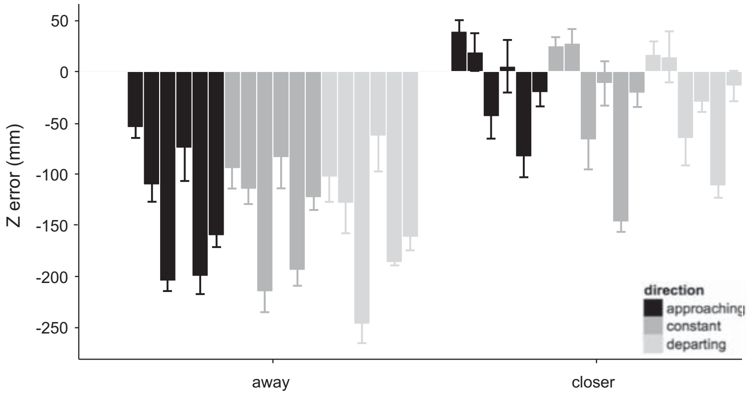


Fig. 4. The average systematic error at the end of the movement of each subject for both feedback conditions (away, closer) and the three directions of motion: approaching (black), frontal (dark grey) and departing (light grey). Error bars show the SEM.

direction ($F_{(2,10)} = 0.12$, $p = .88$) nor the feedback condition ($F_{(1,5)} = 0.18$, $p = .69$) influenced the spatial variability significantly, and the interaction between them was also not significant ($F_{(2,10)} = 1.82$, $p = .21$). Both the influence of the feedback condition on judged reachability and its effect on the spatial error in depth are about 10 cm, which is the distance between the two feedback distortions.

To illustrate this we present a top view of the performance of a representative subject, both when feedback was shifted away (Fig. 5A) and when it was shifted closer to the body (Fig. 5B). The lines indicate the target's paths on trials in which the subject did not move. Here we see the difference in judged reachability (the lines are nearer in panel B) and in the spatial errors (the endpoints in panel B overlap considerably with the lines that represent paths that were judged to be unreachable). The fact that the finger often ended beyond the blue curve indicates that this subject leaned further forward for intercepting the targets than when initially indicating how far he/she could reach. Comparing the locations at which the finger movements ended (dots in Fig. 5) with the blue curves indicating the true limits of reachability shows that the central endpoints when the feedback was close to the body were clearly nearer to the blue line (some of them even overlap with

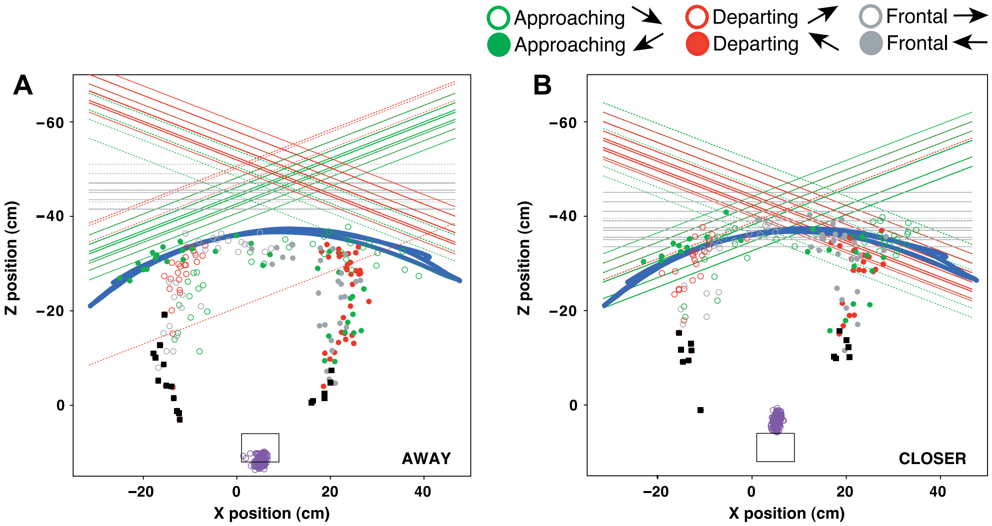


Fig. 5. Overview of various values for a representative subject. The reaching range of the arm is represented by the blue line. Purple dots are the starting positions of the finger. Other symbols indicate the final position of the finger. Colors indicate the direction of the target's path (see Legend). Trials in which the reaction time was shorter than 700 ms are shown as black squares (removed from the analysis) to indicate that the position at which the target was intercepted is likely to have been limited by the reaction time rather than by judgments of when the target came within reach. Lines indicate target trajectories on trials in which the hand did not move. (A) Condition in which the feedback was 5 cm further away than the finger. (B) Condition in which the feedback was 5 cm closer than the finger. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

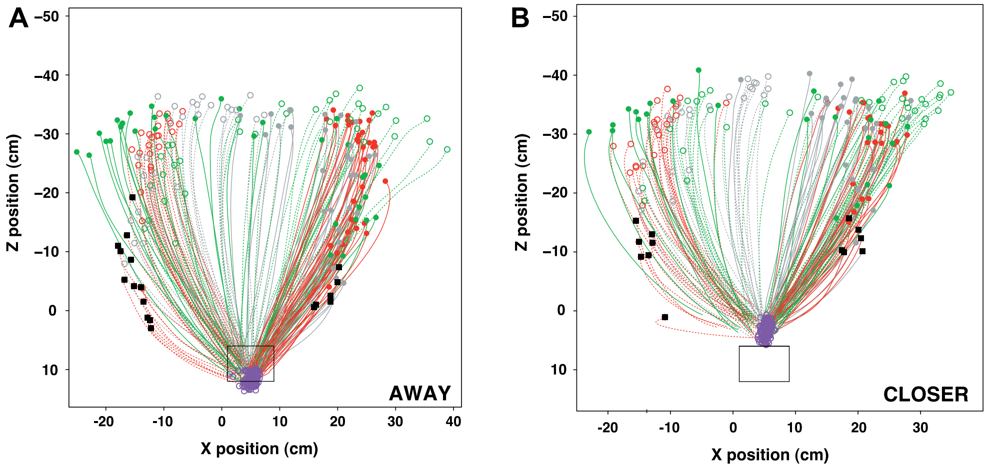


Fig. 6. Top view of the hand trajectories of a representative subject for the feedback distortion 5 cm away from the finger (A) and for 5 cm closer to the body (B). Green lines correspond to hand movements performed towards approaching objects, red lines for departing and grey lines for objects moving in the frontal plane. Open dots and dotted lines represent targets moving from left to right and solid dots and lines represent targets moving from right to left. Black squares were the trials removed from the sample, as in the previous analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

it), whereas the endpoints when the distortion was away were well below the true reachability indicating a shorter extension of the hand movement because of the adaptation to the away feedback distortion.

Fig. 6 shows the corresponding hand trajectories of the final hand endpoints represented in Fig. 5. Moving to the same endpoints means that the subject had to move his or her hand further when the feedback was shifted further from the body than when the feedback was shifted closer. However, the Z coordinate of the final hand position was found to be 5 cm further when the shift of the feedback was close to the body (away: −29.1 cm, closer: −33.7 cm, $F_{(1,5)} = 16.94$, $p < .01$). Given the fact that the gap between the starting positions of the two feedback distortions was 10 cm, the amplitude of the hand movement was then 5 cm larger when the feedback distortion was away from the body (away: 43.7 cm, closer: 38.8 cm, $F_{(1,5)} = 16.1$, $p = .01$). Neither the Z value of the hand endpoint ($F_{(2,10)} = 0.15$, $p = .86$) nor the euclidian distance of the hand movement ($F_{(2,10)} = 1.4$, $p = .29$) differed significantly as a function of the direction of the movement. Interactions were not significant.

4. Discussion

In this study, we wanted to investigate the influence of shifting the visual feedback of the hand's position on reachability estimates during movements towards a moving object. Our task required continuous visual estimation of the object's motion relative to the observer's body in order to judge where and when the object will be at a reachable position, as well as motor planning and execution of the hand movement. These aspects introduced temporal restrictions that were absent in studies that only involved perceptual judgments (de Grave, Brenner, & Smeets, 2011a).

From the results of our experiment, it is clear that a forward shift of the visual feedback of the hand resulted in an increase of the judged reachability. Quantitatively, the magnitude of the effect was approximately the distance between the two feedback shifts (10 cm). Hence, we replicated the effect on reachability estimations that de Grave, Brenner, and Smeets (2011a) found for static objects with a temporally restricted reaching movement towards a moving target. Data are also consistent with studies that reported moving objects to be judged as reachable when they are more distant than if they are static (Rochat & Wraga, 1997), since the magnitude of our feedback effect was higher than in de Grave's study. In contrast, our findings are not in agreement with different reachability judgments for different directions of stimulus motion, such as objects to be reachable at larger distances when the object moved towards the observer (Delevoye-Turrell, Vienne, & Coello, 2011; Fischer, 2000). The difference may lie in the way the data are analyzed, in that we consider the inevitable delays during motor planning and execution of the movement. These delays imply that the hand must start moving towards an approaching object when the object is still unreachable in order to intercept the object as soon as it becomes reachable. Interception of departing objects must occur before they become unreachable. In studies based on perceptual judgments of rechability, the task did not involve moving but participants were instructed to say 'stop' when they thought they could reach the object that was moved by the experimenter (Fischer, 2000). Thus the difference may be that our participants had to take into account the time they themselves spent performing the hand movement, rather than accounting for the experimenter's reaction time and movement. This view is endorsed by the lack of differences between approaching and departing objects looking at the target position at the end of the hand movement, whereas approaching objects were considerably further at the onset. Consequently, we suggest that participants estimated an 'interception region' independent of the stimulus direction, relying on the time needed to perform a reaching movement to the object at this region.

Our results also confirm that hand movements are fairly fully adjusted to feedback distortion (Bourgeois & Coello, 2012). In fact, in this study the change in judged reachability was even slightly larger than the imposed shifts. This is not as strange as it may seem because the change in judged distance with simulated distance is probably underestimated (Sousa, Brenner, & Smeets, 2011; Sousa, Brenner, & Smeets, 2010). As a result of this complete adaptation to the distortion, the spatial accuracy when intercepting the target was conditioned to the amplitude of the movement in a way that participants with longer movements committed higher spatial errors, as reported in previous studies (Sarlegna & Blouin, 2010). Also, the shorter extension of the arm when the feedback distortion was away from the body resulted in higher spatial errors in the depth axis, suggesting that the hand visual feedback takes part in the control of the movement amplitude together with the visual information of the target (Brenner & Smeets, 2003) and the proprioceptive feedback mechanisms (Bagesteiro, Sarlegna, & Sainburg, 2006).

In sum, these results suggest that participants' judgments are completely adapted to the shifts in feedback that we imposed. The critical influence of the hand visual feedback on the reachability estimates and on their underlying actions also states the importance of the visual information as the prominent sensory input (Desmurget et al., 1995). Participants judged targets to be reachable in accordance with whether the feedback cube could reach the target rather than whether the finger could reach the target. This is consistent with earlier reports that tools can affect judgments of reachability. Our task expands on previous studies of judged reachability in showing that the adjustments to what is judged to be reachable are reflected in many aspects of our actions.

Acknowledgments

The author (J.L.M.) was supported by Grant PSI2010-15867 from the Ministry of Science and Innovation of the Spanish government and an ICREA Academia Distinguished Professorship award.

References

Bagesteiro, L. B., Sarlegna, F. R., & Sainburg, R. L. (2006). Differential influence of vision and proprioception on control of movement distance. *Experimental Brain Research, 171*, 358–370.

Berti, A., & Frassinetti, F. (2000). When far becomes near: Remapping of space by tool use. *Journal of Cognitive Neuroscience, 12*(3), 415–420.

Bootsma, R. J., Bakker, F. C., Van Snippenberg, F. J., & Tdlohreg, C. W. (1992). The effects of anxiety on perceiving the reachability of passing objects. *Ecological Psychology, 4*(1), 1–16.

Bourgeois, J., & Coello, Y. (2012). Effect of visuomotor calibration and uncertainty on the perception of peripersonal space. *Attention, Perception and Psychophysics, 74*(6), 1268–1283.

Brenner, E., & Smeets, J. B. J. (1997). Fast responses of the human hand to changes in target position. *Journal of Motor Behavior, 29*(4), 297–310.

Brenner, E., & Smeets, J. B. J. (2003). Fast corrections of movements with a computer mouse. *Spatial Vision, 16*, 365–376.

Brenner, E., Smeets, J. B. J., & de Lussanet, M. H. E. (1998). Hitting moving targets – Continuous control of the acceleration of the hand on the basis of the target's velocity. *Experimental Brain Research, 122*(4), 467–474.

Brouwer, A. M., Brenner, E., & Smeets, J. B. J. (2003). When is behavioral data evidence for a control theory? Tau-coupling revisited. *Motor Control, 7*(2), 103–110.

Cardinali, L., Frassinetti, F., Brozzoli, C., Urquizar, C., Roy, A. C., & Farne, A. (2009). Tool-use induces morphological updating of the body schema. *Current Biology, 19*(12), R478–R479.

Carello, C., Grosofsky, A., Reichel, F. D., Solomon, H. Y., & Turvey, M. T. (1989). Visually perceiving what is reachable. *Ecological Psychology, 1*(1), 27–54.

Coello, Y. (2005). Spatial context and visual perception for action. *Psicologica, 26*, 39–59.

Coello, Y., & Iwanow, O. (2006). Effect of structuring the workspace on cognitive and Sensorimotor distance estimation: no dissociation between perception and action. *Perception & Psychophysics, 68*(2), 278–289.

de Grave, D. D. J., Brenner, E., & Smeets, J. B. J. (2011a). Judgments of reachability are independent of visuomotor adaptation. *Perception, 40*, 962–974.

de Grave, D. D. J., Brenner, E., & Smeets, J. B. J. (2011b). Using a stick does not necessarily alter judged distances or reachability. *PLoS One, 6*(2), e16697.

Delevoye-Turrell, Y., Vienne, C., & Coello, Y. (2011). Space boundaries in schizophrenia: Voluntary action for improved judgments of social distances. *Journal of Social Psychology, 42*(193), 204.

Desmurget, M., Rossetti, Y., Prablanc, C., Stelmach, G., & Jeannerod, M. (1995). Integration of sensroy cues about hand position used for a goal directed movement. *Canadian Journal of Psychology and Pharmacology, 73*, 262–272.

Farnè, A., Bonifazi, S., & Làdavas, E. (2005). The role played by tool-use and tool-length on the plastic elongation of peri-hand space: A single case study'. *Cognitive Neuropsychology, 22*, 408–418.

Fischer, M. H. (2000). Estimating reachability: Whole body engagement or postural stability? *Human Movement Science, 19*, 297–318.

Fischer, M. H. (2003). Can we correctly perceive the reaching range of others? *British Journal of Psychology, 94*(Pt 4), 487–500.

Gabbard, C., Ammar, D., & Lee, S. (2006). Perceived reachability in single-and-multiple-degree-of-freedom workspaces. *Journal of Motor Behavior, 38*(6), 423–429.

Gamberini, L., Seraglia, B., & Priftis, K. (2008). Processing of peripersonal and extrapersonal space using tools: Evidence from visual line bisection in real and virtual environments. *Neuropsychologia, 46*(5), 1298–1304.

Heft, H. (1993). A methodological note on overestimates of reaching distance: Distinguishing between perceptual and analytical judgments. *Ecological Psychology, 5*(3), 255–271.

Holmes, N. P., & Spence, C. (2004). The body schema and the multisensory representation(s) of peripersonal space. *Cognitive Processes, 5*(2), 94–105.

Longo, M. R., & Lourenco, S. F. (2006). On the nature of near space: Effects of tool use and the transition to far space. *Neuropsychologia, 44*(6), 977–981.

Maravita, A., Husain, M., Clarke, K., & Driver, J. (2001). Reaching with a tool extends visual-tactile interactions into far space: Evidence from cross-modal extinction. *Neuropsychologia, 39*, 580–585.

Mark, L. S., Nemeth, K., Gardner, D., Dainoff, M. J., Paasche, J., Duffy, M., et al. (1997). Postural dynamics and the preferred critical boundary for visually guided reaching. *Journal of Experimental Psychology: Human Perception and Performance, 23*(5), 1365–1379.

Robinovitch, S. N. (1998). Perception of postural limits during reaching. *Journal of Motor Behavior, 30*, 352–358.

Rochat, P., & Wraga, M. (1997). An account of the systematic error in judging what is reachable. *Journal of Experimental Psychology: Human Perception and Performance, 23*(1), 199–212.

Rodriguez-Herreros, B., & Lopez-Moliner, J. (2011). Proprioception improves temporal accuracy in a coincidence-timing task. *Experimental Brain Research, 210*, 251–258.

Rossetti, Y., Desmurget, M., & Prablanc, C. (1995). Vectorial coding of movement: Vision, proprioception, or both? *Journal of Neurophusiology, 74*(1), 457–463.

Sarlegna, F. R., & Blouin, J. (2010). Visual guidance of arm reaching: Online adjustments of movement direction are impaired by amplitude control. *Journal of Vision, 10*(5), 1–12.

Sousa, R., Brenner, E., & Smeets, J. B. J. (2010). A new binocular cue for absolute distance: Disparity relative to the most distant structure. *Vision Research, 50*(18), 1786–1792.

Sousa, R., Brenner, E., & Smeets, J. B. J. (2011). Judging an unfamiliar object's distance from its retinal image size. *Journal of Vision, 11*(19), 1–6.

Wichmann, F. A., & Hill, N. J. (2001). The psychometric function: I. Fitting, sampling and goodness of fit. *Perception & Psychophysics, 63*, 1293–1313.

Witt, J. K., Proffitt, D. R., & Epstein, W. (2005). Tool use affects perceived distance, but only when you intend to use it. *Journal of Experimental Psychology: Human Perception and Performance, 31*(5), 880–888.

DATA OF THE REST OF PARTICIPANTS ARE INCLUDED AT THE APPENDIX

7

STUDY V
WHITE MATTER INTEGRITY REGULATES THE INDUCED BREAKDOWN OF ONLINE MOTOR CONTROL[††]

[††] This chapter corresponds to:
Rodríguez-Herreros, B., Amengual, J. L., Richter, L., Jauer, P., Erdmann, C., Schweikard, A., López-Moliner, J., Rodríguez-Fornells, A. and Münte, T. F. (2014) White matter integrity regulates the induced breakdown of online motor control. ***Under review***

RESUMEN

Fundamental para la investigación en neurociencia es la exploración de la relación entre la función y la estructura en el cerebro humano. Se ha propuesto que las diferencias interindividuales en el rendimiento de varias tareas motoras pueden deberse a variaciones en la estructura de la materia blanca. El objetivo del presente estudio fue determinar si las consecuencias conductuales de interferir la funcionalidad del área encargada del control motor de un movimiento se podrían explicar en base a las características microestructurales de los tractos de sustancia blanca que presuntamente transmiten esta función. Hemos combinado la técnica de resonancia magnética con tensores de difusión (DTI) con la estimulación magnética transcraneal (TMS) para encontrar evidencias de que la integridad de la materia blanca rige el deterioro de la capacidad de actualizar un comando motor. Se aplicó un protocolo inhibidor de 1-Hz de TMS repetitiva sobre el surco intraparietal medial izquierdo (mIPS), con el objetivo de inducir una 'lesión virtual' que alterara el control motor en el contexto de un cambio inesperado de la posición de un objeto a alcanzar. Las repercusiones conductuales observadas implicaron una reducción de correcciones motoras. La variabilidad interindividual en esa reducción respondió a diferencias anatómicas en las conexiones directas entre las zonas parietal y frontal. Específicamente, se encontró que los participantes con menor deterioro del control motor mostraron los valores más altos de integridad de la materia blanca en la segunda rama del fascículo longitudinal superior (SLF II). Estos resultados sugieren que la cohesión estructural de la materia blanca puede utilizarse como un predictor sólido para caracterizar la magnitud de las deficiencias motoras inducidas por TMS.

RESUM

Fonamental per a la investigació en neurociència és l'exploració de la relació entre la funció i l'estructura en el cervell humà. S'ha proposat que les diferències interindividuals en el rendiment de diverses tasques motores poden ser degudes a variacions en l'estructura de la matèria blanca. L'objectiu d'aquest estudi va ser determinar si les conseqüències conductuals d'interferir la funcionalitat de l'àrea encarregada del control motor d'un moviment es podrien explicar en base a les característiques microestructurals dels tractes de substància blanca que presumptament transmeten aquesta funció. Hem combinat la tècnica de ressonància magnètica amb tensors de difusió (DTI) amb l'estimulació magnètica transcranial (TMS) per trobar evidències de que la integritat de la matèria blanca regeix el deteriorament de la capacitat d'actualitzar una ordre motora. Es va aplicar un protocol inhibidor de 1-Hz de TMS repetitiva sobre el solc intraparietal medial esquerre (mIPS), amb l'objectiu d'induir una 'lesió virtual' que alterés el control motor en el context d'un canvi inesperat de la posició d'un objecte a interceptar. Les repercussions conductuals observades van implicar una reducció de correccions motores. La variabilitat interindividual d'aquesta reducció va respondre a diferències anatòmiques en les connexions directes entre les zones parietal i frontal. Específicament, es va trobar que els participants amb menor deteriorament del control motor van mostrar els valors més alts d'integritat de la matèria blanca a la segona branca del fascicle longitudinal superior (SLF II). Aquests resultats suggereixen que la cohesió estructural de la matèria blanca pot utilitzar-se com un predictor sòlid per caracteritzar la magnitud de les deficiències motores induïdes per TMS.

7.1 Abstract

An ever enlarging arsenal of techniques has probed the structure/function relationship in the brain. In this context, neuroimaging studies using diffusion tensor imaging (DTI) have related the presence of specific motor skills to changes in brain morphology. However, pure behavioral measures may mask the integrated role of other brain areas. In the current study, we present a multimodal approach to test whether the strength of structural connectivity between two key regions in motor control was associated with variations in the ability to update a movement. We applied 1 Hz repetitive transcranial magnetic stimulation (rTMS) over the medial intraparietal sulcus (mIPS) to induce a transient disruption of the neural processes underlying on-line motor adjustments. After the stimulation protocol, participants generally showed a reduction of corrective trajectories during a reaching task that included unexpected visual perturbations. A whole-brain analysis of the fractional anisotropy (FA) revealed that the participants that exhibited higher white matter integrity in the second branch of the superior longitudinal fasciculus (SLF II) suffered less rTMS-induced behavioral impact in the motor performance. These results indicate that individual differences in white matter structure are a sensitive index of functional deficits in online motor control.

7.2 Introduction

During the last decades, the dichotomy between brain structure and function has become a pivotal issue in neuroscience. Using diffusion tensor imaging (DTI), recent neuroimaging studies indicate a robust relationship between brain anatomy and the existence of certain motor abilities (Gaser and Schlaug 2003; Bengtsson et al. 2005). A particularly compelling example is the correlation between the interindividual variability in reaction time (RT) and the fractional anisotropy (FA), a measure which is thought to reflect integrity and fiber density in white matter (WM), of the visuospatial WM pathways and the corpus callosum (Tuch et al. 2005; Westerhausen et al. 2006). With regard to more sophisticated motor computations, differences in bimanual coordination across individuals have been attributed to the integrity of the part of the corpus callosum that links supplementary motor areas (SMA) (Johansen-Berg et al. 2007). Moreover, the grey matter density of the pre-SMA region appears to be linked to the ability to select appropiate actions in situations of response conflict (van Gaal et al. 2011). Therefore, inter-individual variations in both the initiation and the cognitive control processes of simple and complex motor tasks are reflected in the structural anatomy of the brain. There are also important individual differences in how healthy adults perform goal-directed reaching movements that require an on-line control to adjust their performance in case of unexpected visual perturbations (Reichenbach et al. 2008; Boy et al. 2010). The main goal of the present study was to examine whether induced individual differences in on-line motor control might be related to differences in brain anatomy.

Numerous studies implicate the posterior parietal cortex (PPC) in the on-line control of a movement after its initiation. The role of the intraparietal sulcus (IPS), a specific subregion of the PPC, in monitoring visually-guided grasping (Tunik et al. 2007) and reaching movements (Clower et al. 1996) has been widely supported by neurophysiological (Sakata et al. 1995) and brain imaging studies (Culham et al. 2003; Frey et al. 2005). Furthermore, within the IPS, there appears to be a functional separation for the neural control of grasping and reaching (Johnson and Grafton 2003; Grefkes and Fink 2005): Seminal studies in monkeys suggest that parieto-frontal circuits that link the medial intraparietal sulcus (MIP) and the dorsal premotor cortex (PMd) are thought to sustain the visuomotor transformations for the online control of reaching (Johnson et al. 1993; Caminiti et al. 1996; Johnson and Ferraina 1996), whereas more anterior regions of the IPS (AIP) might be involved in grasping (Jeannerod et al. 1995). The superior longitudinal fasciculus (SLF) has been postulated as an important neural tract within the premotor-parietal network that connects the IPS and the PMd (Boorman et al. 2007; Thiebaut de Schotten et al. 2012). In humans, neuroimaging techniques have detected extensive activation of a putative homologue of MIP area, called medial intraparietal sulcus (mIPS), and the dorsal premotor cortex (PMd) during reaching and pointing movements (Colebatch et al. 1991; Kertzman et al. 1997; Desmurget et al. 2001). Many mIPS neurons discharge with changes in the location of the target relative to the hand, which is called ‘motor error’ (Andersen and Buneo 2002). They respond not only before the movement onset and during the execution, which allows the mIPS to integrate sensory input with efference copies of outgoing motor commands to compute a continuously updated estimate of the motor error. A brief burst of TMS pulses over the medial intraparietal sulcus (mIPS) has been shown to inducing short-lived disruptions of the capacity to correct reaching movements (Desmurget et al. 1999; Della-Maggiore et al. 2004). Subsequent studies confirmed that interfering mIPS function disturbed visuomotor transformation processes (Grefkes et al. 2004; Prado et al. 2005) and direction vectors (Davare et al. 2012) that are essential for the control of visually-guided reaching.

By using high-resolution DTI in combination with TMS, we present a multimodal approach to test whether the integrity of WM parietofrontal pathways governed the degree of rTMS-affectation in the ability to update a movement. Purely baseline behavioral measures may reflect the integrated function of multiple brain regions. Rather, the specific impact of TMS application in online motor control could be a more informative and isolated measure of this brain function with which to compare structural parameters (Boorman et al. 2007). We applied an inhibitory protocol of 1 Hz repetitive TMS over the mIPS to induce a transient disruption of on-line motor control in the context of shifting task goals. FA values indexed microstructural integrity. Individual differences in TMS-induced alteration of the online motor control showed specific correlations with FA in localized regions of WM parietofrontal tracts, specifically the second branch of the superior longitudinal fasciculus (SLF II), and also in the cerebellum. These results shed some light into the structural/functional correlates that are altered with deficits in online motor control, and support the idea of microstructural features of white matter tracts as a sensitive index of the consequences of rTMS effects.

7.3 Materials and Methods

7.3.1 PARTICIPANTS

Twenty-four healthy right-handed volunteers (12 women; mean age 26.6 ± 4.9 years) participated in this study. All subjects were naïve with respect to the experimental procedures and the hypothesis of the study. Participants had normal or corrected-to-normal visual acuity and reported neither previous nor current neuropsychiatric disorders. Prior to their inclusion in the study, participants provided written informed consent. The study was performed according with the declaration of Helsinki and was approved by the ethics committee of the University of Lübeck. All participants were screened for MRI and TMS compatibility (Machii, Cohen, Ramos-Estebanez & Pascual-Leone, 2006). The Edinburgh handedness inventory was required to assess right-handedness (Oldfield, 1971). All participants were paid for their participation.

7.3.2 APPARATUS AND DATA ACQUISITION

An overview of the experimental setup is shown in **Figure 7.1**. Subjects sat at a table that was 45-50 cm below the eyes. Visual stimuli were generated by an Apple MacBook 2.2 GHz Quad-Core and displayed on a 17” LCD monitor with a refresh rate of 120 Hz and a resolution of 1280 x 1024 pixels (43.3 cm of diagonal viewing size). A 3D marker with infrared LEDs was attached to the index finger tip of the hand to track the finger’s spatial position during reaching movements. The marker was connected to and tracked by a high-speed optical tracking system (Atracsys accuTrack compact, Atracsys LLC, Inc). The spatial resolution was 0.01 mm in each spatial axis. The sampling rate of the recording was set to 200 Hz. For each movement, finger coordinates were recorded from 200 ms before the stimulus was presented on the screen (see below for a full description of the stimuli) and ended 300 ms after the end of the movement. Missing samples in recorded coordinates due to erratic orientations of the infrared marker were interpolated off-line (Tunik, Frey & Grafton, 2005) using spline functions (Liu & McMillan, 2006). Time series of the recorded individual position coordinates were processed with a low-pass Butterworth filter (cutoff frequency of 6 Hz) for further analysis (Mason, Gomez & Ebner, 2001; Rodriguez-Herreros & Lopez-Moliner, 2011). Velocity was derived from the smoothed time series of the position of the marker by first numerical differentiation.

7.3.3 STIMULI AND PROCEDURE

The experimental task (Adjusting Condition, AC) consisted in performing a reaching movement towards a visual target located on the screen. Prior to the initiation of the trial, participants were required to move the index finger to a red bulge situated 30 cm in front of a screen and localizable by sensory tactile feedback. After 1000 ms with the finger placed at this starting point, a small white fixation point was automatically shown as a warning signal in the centre of the screen (**Figure 7.1A**). Subjects were asked to fixate the point until a target appeared in the centre of the screen (30 mm in diameter green dot), 30 cm above the surface of the table. In order to avoid participants from predicting the target onset, a variable foreperiod (300 or 800 ms) between the appearance of fixation point and the target onset was used. Trials without (66%) and with displacement (34%) were presented in pseudorandom order. In undisplaced trials, the target remained static in the centre of the screen. In contrast, displaced trials showed an unexpected lateral displacement of the target position at the time of the movement onset, 10 cm lateral of the initial position. The displacement was timed at the movement onset to assure that participants did not have relevant information about the final position of the target during the initial planning of the movement. To this aim, the movement onset was detected by a specific velocity threshold (see Behavioral analysis section) obtained from the infrared data. To discard trials with long reaction times, a warning sound was provided if the velocity threshold was not exceeded within 500 ms after the target onset. Participants were instructed to hit the target with the index finger. When a target was displaced they had to modify their trajectories to the final target location. They were instructed to start and perform the movement as fast as possible. The target was presented for 1000 ms. At the end of the reaching movement, participants brought their hand back to the starting point.

An additional condition (Fixed Condition, FC) was introduced to check whether rTMS stimulation affected the ability to process the visual target information (**Figure 7.1B**).

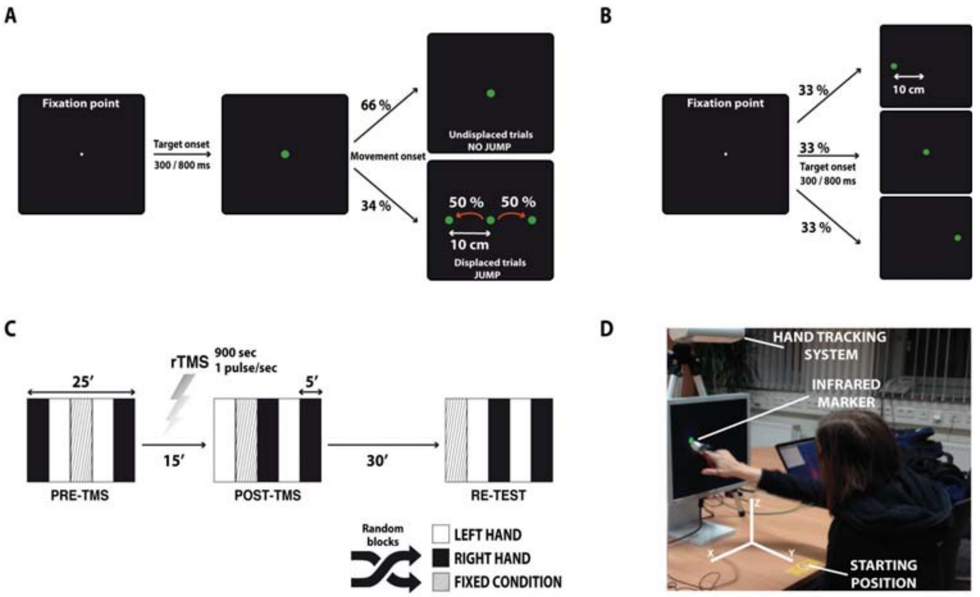


Figure 7.1. Visual display of the adjusting condition (AC) **(A)** and the fixed condition (FC) **(B). C.** Time course of the experimental events. Each block lasted around 5 minutes, so an entire session was approximately 25 minutes. Blocks were randomly distributed within each session. **D.** Illustration of an on-line adjustment after a displaced trial in the adjusting condition. A three-dimensional reference coordinates system was established with the centre of the lateral axis ($x = 0$) determined by the centre of the screen, and the zero value of the longitudinal axis ($y = 0$) defined by the hand starting point. Origin of the vertical axis (z) was the surface of the table. As a result, the origin of coordinates was settled as the hand starting position. The distance between the virtual target and the hand initial position was approximately 42 cm.

FC differed from AC in that the target directly appeared either in the centre or in one of the two laterally displaced locations with no displacement at the movement onset. Hence, participants had the information about the final position of the target during the planning phase of the movement. In FC, central and lateral target locations appeared in pseudorandom order with equal probability for the three locations.

7.3.4 EXPERIMENTAL DESIGN

The experimental design comprised three different sessions (**Figure 7.1C**): a baseline measurement (Pre-rTMS); immediately after the application of the rTMS (Post-rTMS) and 30 minutes after the end of the Post-rTMS measurement (Re-Test). Each session was composed of four blocks of the AC and one block of the FC with 100 trials each. Two blocks of AC were performed with the right hand and the other two with the left hand. The single block of the FC was only performed with the right hand. The order of blocks was counterbalanced across subjects for each session. Therefore, each participant completed 1500 trials in the whole experiment: 1200 trials of the AC and 300 trials of the FC. Before the experiment started, subjects performed 40-50 practice trials to get familiar with the task. Participants were instructed not to move their trunk with respect to the chair during the entire block. Head movements were allowed to avoid that subject's behavior could be different than in natural conditions (Steinman, Kowler & Collewijn, 1990) (**Figure 7.1D**). Between each block, one minute of rest was given.

7.3.5 TMS PROTOCOL

A robotized TMS system with active motion compensation was used for accurate and consistent stimulation (Matthaus, 2008; Richter, 2013). Stimulation pulses were applied using a MCF-B65 figure-of-eight coil (9 cm each wing) designed for focal stimulation. The coil was connected to a MagPro X100 MagOption stimulator (MagVenture A/S, Farum, Denmark) for biphasic stimulation and was attached to the end effector of the articulated arm of an Adept Viper s850 serial six joint robot (Adept Technology, Inc., Livermoore, CA, USA), ensuring an accurate placement of the coil (**Figure 7.2A**). The robot was driven by a standard PC with an image-guided robot-control software. A Polaris stereo-optic infrared tracking system (Northern Digital Inc., Waterloo, Ontario, Canada) recorded the head movements by tracking a marker consisting of five reflective spheres that was placed at subject's forehead with a headband. The headband position was continuously tracked during the stimulation for head navigation. Likewise, a pointer with identical passive reflective marker spheres was utilized to acquire an individual 3D digital outline of the participant's head by recording approximately 500 surface points and three standard landmarks (lateral orbital rims and tip of the nose). We calibrated the tracking system setting the robot position as a reference of coordinates (Richter, Ernst, Schlaefer & Schweikard, 2011). As a result, real-time robotic motion compensation of the head movements was rendered by its respective coil motion. This methodological advantage assures an accurate location of the stimulation region throughout the entire TMS protocol. In contrast to hand-held approaches, this montage guaranteed to keep the initial orientation and strength throughout the entire experiment by adapting the coil motion to unrestrained head movements (Richter, Trillenberg, Schweikard & Schlaefer, 2013).

Prior to the rTMS procedures, motor evoked potentials (MEPs) were recorded attaching surface Ag/Cl electrodes to the skin over the right first dorsal interosseous (FDI) muscle in a belly-tendon setting. Electromyographic (EMG) data was recorded by a 2 channel DanTec Keypoint Portable system (Alpine Biomed Aps, Skovlunde, Denmark) at a sampling rate of 50 kHz. The EMG signal was processed with a (10 Hz – 10 kHz) band-pass filter. First, resting (rMT) and active (aMT) motor thresholds were measured for each participant. For this, the coil was positioned over the hand area of the left primary motor cortex. The rMT was defined as the minimum stimulator intensity at which 50% of pulses induced a MEP of at least 0.05mV of amplitude in the relaxed FDI muscle (Rossini et al., 1994). The aMT was defined as the minimum stimulation intensity at which 50 % of pulses induced a MEP of at least 0.2 mV during a voluntary contraction of the FDI (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). The rTMS protocol consisted on a train of 900 pulses delivered in a frequency of 1 Hz (15 min). During the application of pulses, subjects maintained a relaxed posture and kept their eyes closed. The intensity of the magnetic stimulation was fixed to 60% of the maximum stimulator output (MSO), following several TMS studies on PPC (Buelte et al., 2008; Machii et al., 2006; Vesia, Prime, Yan, Sergio & Crawford, 2010). After the stimulation, only three subjects reported neck pain, which they all attributed to postural reasons.

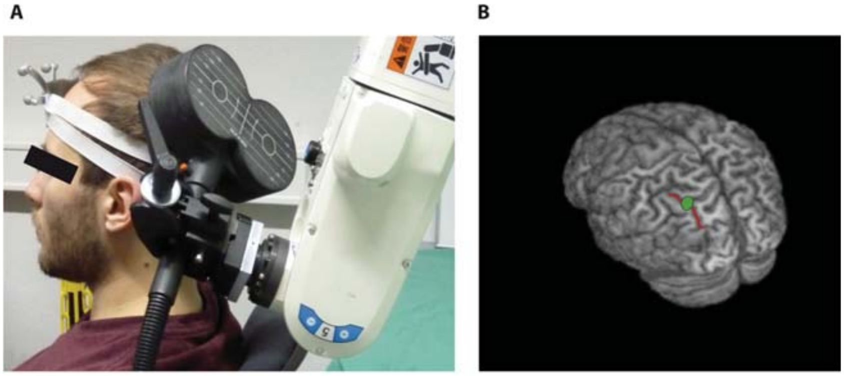


Figure 7.2. **(A)** Setup of the robotized TMS system, with the coil attached to the robot during a TMS session. Reflexive spheres in the forehead were the markers to track the head movements. **(B).** Mean localization of the exact stimulated region (left mIPS) after normalization into MNI coordinates. Intraparietal sulcus is marked in red. Mean MNI coordinates are represented at the center of the green ellipse. Ellipse area corresponds to the 95% confidence interval of all Talairach coordinates.

7.3.6 LOCALIZATION OF STIMULATION SITES

The medial intraparietal sulcus (mIPS) of the left hemisphere was chosen for stimulation, located over the midposterior junction of the IPS, caudal to the aIPS (Desmurget et al., 1999; Glover, Miall & Rushworth, 2005; Prado et al., 2005; Vesia et al., 2010). A T1-weighted high-resolution 3D structural MRI (3T Philips Achieva whole-body scanner) was obtained for each participant. **Figure 7.2B** shows a rendered 3D image of the stimulated region. For all participants, average normalized coordinates for the targeted area were reported according to standardized stereotaxic space (Rey, Dellatolas, Bancaud & Talairach, 1988). In particular, the left mIPS was determined by the medial bank of the intraparietal sulcus over the midposterior junction [group mean ± SD: Talairach coordinates (TCs), $x = -27.8 \pm 3.2$, $y = -55.4 \pm 6.8$, $z = 50.8 \pm 7.1$). The coordinates were concurrent with other TMS (Davare et al., 2012; Vesia et al., 2010) and brain imaging (Blangero, Menz, McNamara & Binkofski, 2009; Grefkes, Ritzl, Zilles & Fink, 2004; Prado et al., 2005) studies. The coordinates were translated to the robotic software for localization of the appropriate stimulation region on the subject's scalp. The orientation of the coil was tangentially to the cortical surface and positioned 45^{o} with respect to the sagittal plane of the cranial MRI data. Direction of the current in the coil was anteroposterior.

7.3.7 DTI ACQUISITION AND IMAGE PROCESSING

Whole-brain diffusion magnetic resonance imaging (dMRI) using a diffusion tensor spin-echo planar imaging sequence was acquired with the following scanning parameters: voxel size of 2 x 2 x 2 mm, matrix of 112 x 112, 55 slices with 2 mm-thick and no gap, TE = 60 ms, TR = 7582 ms, EPI factor = 59, field of view = 224 mm, bandwidth = 2743.6 Hz, b-value = 800 s/mm2. One single run of 32 diffusion-weighted directions with one non-diffusion-weighted volume was acquired.

Motion and eddy-current correction were performed using FMRIB's Diffusion Toolbox (FDT), part of the FMRIB Software Library (FSL www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004; Woolrich et al., 2009). The gradient matrix was then rotated and the structural image was fully-stripped using FSL's Brain Extraction Tool (Smith et al., 2002). Diffusion tensors were reconstructed using the linear least-squares method provided in Diffusion Toolkit (Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for

Biomedical Imaging, Massachusetts General Hospital). The tensor was spectrally decomposed in order to obtain its eigenvalues and eigenvectors. The fiber direction was assumed to correspond to the principal eigenvector (the eigenvector with the largest eigenvalue). Fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) values were generated from the eigenvalues. FA maps from all participants were registered to a MNI FA template (FMRIB58_FA, MNI152 space) using FNIRT (Andersson, Jenkinson & Smith, 2007a, 2007b). FA quantifies the anisotropy in each voxel, with values ranging from 0 (fully isotropic) to 1 (diffusion is favored in one axis and hindered in the remaining two). In degenerated tracts, water diffusion is more isotropic, thus, FA decreases substantially compared to normal fiber tracts.

White matter structural analysis was carried out using Voxel Based Analysis (VBA) (Camara, Bodammer, Rodriguez-Fornells & Tempelmann, 2007; Fuentemilla et al., 2009). FA maps were processed using MATLAB 7.8.0 (The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM8; The Welcome Department of Imaging Neuroscience, London). Normalized images were smoothed by using an isotropic spatial filter (FHWN = 6 mm) to reduce residual inter-individual variability.

7.3.8 BEHAVIORAL ANALYSIS

For each trial, we obtained three-dimensional spatial coordinates of the position of the index finger. Two types of trajectories were established for displaced trials: erroneous trajectories and corrective trajectories. The rationale to establish whether a trajectory was corrective or erroneous was as follows (**Figure 7.3**): (1) we first obtained the distribution of all the finger endpoints for the undisplaced trials by calculating the accuracy 95% confidence interval ellipses-shaped (Granek, Pisella, Blangero, Rossetti & Sergio, 2012; Messier & Kalaska, 1999). Trajectories of displaced trials in which the index-finger endpoint position was within this confidence interval were considered as erroneous trajectories (Pisella et al., 2000). (2) Additionally, since the main instruction provided to participants was to hit the target, trajectories that ended out of the 95 % confidence interval ellipses-shaped formed by the endpoints of the displaced trials were also considered as erroneous trajectories. All the confidence intervals were independently calculated for each session, hand and side of the displacement (right, left) in each participant. In all subjects, no overlapping was observed between confidences ellipses of undisplaced (1) and displaced (2) trials for a given hand within a session. Finally, (3) trajectories that did not pass a velocity threshold of 100 mm/s in its lateral component of the trajectory (Neggers & Bekkering, 2002) during the 85% of the movement time were also considered as erroneous trajectories. The rest of trajectories were considered as corrective trajectories.

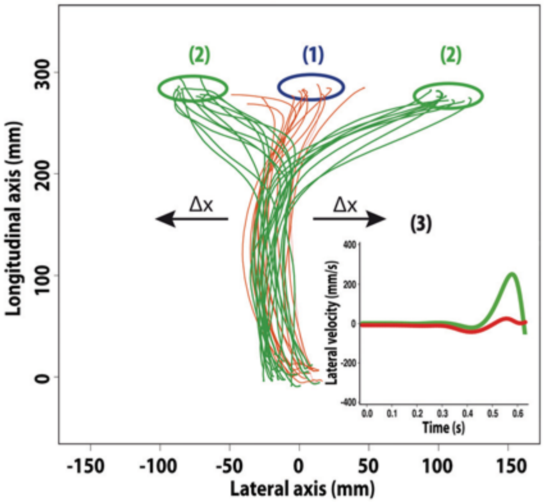


Figure 7.3. Requirements in order to distinguish erroneous (red lines) and corrective trajectories (green lines). (1) A corrective trajectory must end out of the 95% CI of the undisplaced hand endpoint positions (blue ellipse). (2) The endpoint position has to be within the 95% CI of the displaced trials (green ellipse). (3) inset: Lateral component (*x*) of the speed ought to reach a threshold of 100 mm/s during the 85% of the movement trajectory in order to consider the trajectory as corrective. Zero value of the abcissa axis corresponds to target onset.

Kinematic values were inferred from the 3D position of the index finger obtained from the attached infrared markers. We measured the reaction time (RT), movement time (MT), peak velocity (PV) and time to peak velocity (TPV), deceleration time (DT) and correction time (CT) as parameters for posterior analysis in both FC and AC. A velocity threshold of 50 mm/s in the longitudinal axis was used to detect the onset and the offset of the movement (Neggers & Bekkering, 2002; van Beers, Haggard & Wolpert, 2004). Reaction time was defined as the time passed between target onset and the movement onset. Movement time was obtained by subtracting the movement onset value from the corresponding movement offset. Peak velocity was defined as the maximum speed value achieved within the movement time, and time to peak velocity was defined as the time passed between the movement onset and the moment when the peak velocity was reached. Deceleration time was obtained by subtracting TPV to MT. CT was detected with the abovementioned threshold of lateral velocity used as a criteria to detect a corrective movement. The CT was also expressed as a percentage of MT. Finally, we measured the spatial error in the FC as the euclidian distance between the position of the target and the end-position of the index-finger. The systematic error for a given condition was the mean of the spatial errors.

7.3.9 STATISTICAL ANALYSIS

In all analyses, the direction of the displacement (left or right) was not considered as a factor, since preliminary analyses had revealed a lack of statistical main effects and interactions ($P > 0.34$ for all comparisons). Trajectories with more than five consecutive missing recording-samples were removed from the analysis. One participant was discarded due to a high number of missing samples in many trajectories. Prior to analysis, all trials with reaction times faster than 170 ms and slower than 500 ms were removed. Concerning the movement time, we delimited a valid range from 200 ms to 600 ms (Pisella et al., 2000). Participants with a rejection rate higher than 30% were excluded from the analysis.

In AC, we analyzed the effect of the rTMS on the ability to correct in displaced trials using the error rate (as the percentage of erroneous trajectories) for left and right hand in each session serving as dependent variables. We conducted a 2 x 3 repeated measures analysis of variance (ANOVA) with factors session (Pre-rTMS, Post-rTMS, Re-test) and hand (right, left). We also tested for correlations between the error rate of each hand and the rMT and AMT, independently. To ensure that the behavioral aftereffects of the rTMS on the error rate were not attributable to changes in kinematic patterns of the global motor output, differences in MT, PV and TPV were tested using a 3 x 2 x 2 repeated measures ANOVA including session, hand and type of trial (displaced, undisplaced), only considering displaced trials with a corrective trajectory (Boulinguez, Nougier & Velay, 2001). An analogue analysis was carried out for the RT but omitting the ‘trial’ factor since the visual perturbation in AC always occurred at the movement onset. In FC, we analyzed differences in the spatial error and in the spatial variability with a repeated measures ANOVA with a single factor session, as only right hand movements were performed.

Post-hoc comparisons were performed using paired sample t-tests. When reported, the nomenclature for the post-hoc comparisons is 'Session-hand' (*e.g.* Pre-right). Threshold for statistical significance was set at $P < 0.05$ and Bonferroni corrected for multiple comparisons. For all statistical effects involving two or more degrees of freedom, the Greenhouse-Geisser epsilon was used to correct for possible violations of the sphericity assumption (Jennings & Wood, 1976). We report Greenhouse-Geisser epsilon, corrected *p*-values of the ANOVA and the original degrees of freedom.

7.3.10 DTI ANALYSIS

All normalized and smoothed FA images were entered into a voxel-based whole brain linear regression analysis using a one-sample t-test employing a random effects analysis within the general linear model and were correlated with the increase of the error rate (Post-rTMS erroneous trajectories minus Pre-TMS erroneous trajectories) of the right and left hand, respectively. Pearson's correlation coefficients were calculated from the main significant clusters (*P*-value threshold = 0.005) by averaging the FA values across the whole cluster and correlating it with the increase of erroneous movements.

The clusters were superimposed on the MNI152 template supplied by FSL. FSLview and its atlas tools (International Consortium of Brain Mapping DTI-81 white matter labels atlas) in addition to general neuroanatomical and cerebellar atlases (Catani & de Schotten, 2012; Schmahmann et al., 1999) were used to anatomically label the location of significant clusters in MNI152 space. In parenthesis adjacent to the cerebellum, we see the equivalent anatomical label of Schmahmann et al. (1999), based on Larsell and Jansen (1970). Additionally, a region of interest (ROI) analysis in the SLF II was performed to confirm the whole brain voxel-based findings, using a probabilistic SLF atlas at a 80% probability threshold, kindly provided by M.T. de Schotten (Thiebaut de Schotten et al., 2011). In the ROI analysis, we assessed the size of each cluster exceeding this primary threshold and highlighted all clusters whose size exceeded a cluster-size threshold that controlled the familywise error rate at $P < 0.05$, thus correcting for multiple tests.

7.4 Results

7.4.1 RTMS-INDUCED DEFICITS IN ONLINE MOTOR CONTROL

Figure 7.4 compares the error rate in displaced trials for the three sessions and for each hand. The ANOVA showed significant differences in error rate as a function of the session [Session, $F_{2,44} = 16.08$, $P < 0.001$]. A significant session x hand interaction was found [$F_{2,44} = 7.03$, $P < 0.01$, $\varepsilon = 0.76$], showing that differences in error rate depended on the hand that performed the movement. Post-hoc comparisons revealed that the error rate increased after rTMS in both left [Post-left vs. Pre-left, $t_{(22)} = 2.43$, $P < 0.05$] and right [Post-right vs. Pre-right, $t_{(22)} = 4.7$, $P < 0.001$] hand movements. Relative to the Post-rTMS session, a decrease of the error rate was found for the Retest session [Post-left vs. Retest-left, $t_{(22)} = 5.1$, $P < 0.001$; Post-right vs. Retest-right, $t_{(22)} = 5.07$, $P < 0.001$]. The error rate of Pre-rTMS and Retest-rTMS did not differ significantly ($P > 0.37$ in both comparisons). Additionally, error rate was higher in the Post-rTMS session for right compared to left movements [$t_{(22)} = 2.13$, $P < 0.05$; $P > 0.05$ for all other comparisons]. The increase in error rate from the Pre-rTMS to the Post-rTMS session with the left hand was about 28%, whereas it was almost 90% for the right hand (**Figure 7.4**).

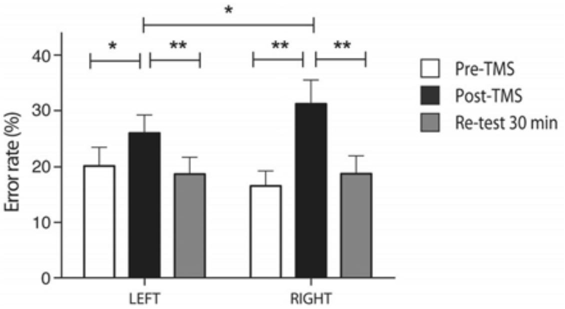


Figure 7.4. Behavioral results: Bar plot with the mean (± s.e.m.) of the percentage of 'erroneous' responses (non corrective movements when the target jumps) as a function of the session and the hand. *$P < 0.05$; ** $P < 0.01$

No significant differences were found between right and left hand in the other two sessions. Error rates are reported in **Table 7.1**. Also, the increase of erroneous movements did not correlate neither with the rMT (right hand, $P = 0.26$; left hand, $P = 0.11$) nor with the aMT (right hand, $P = 0.27$; left hand, $P = 0.19$).

Adjusting condition

	PRE-rTMS		POST-rTMS		RE-TEST	
Error rate (%)	Left **20.2** (15.7)	Right **16.6** (13)	Left **25.6** (15.7)	Right **31.2** (20.9)	Left **18.7** (13.9)	Right **18.9** (14.6)

Fixed condition

	PRE-rTMS	POST-rTMS	RE-TEST
Spatial error (mm)	**21.1** (7.8)	**20.5** (9.1)	**18.9** (8.3)

Table 7.1. Summary of mean values for the error rate (%) in displaced trials of AC and spatial error (mm) in FC. Table reports mean (SD) for each dependent measure.

Figure 7.5 illustrates the top view of trajectories of a representative subject. The increase of erroneous trajectories (coloured in red) after rTMS is more pronounced for the right hand.

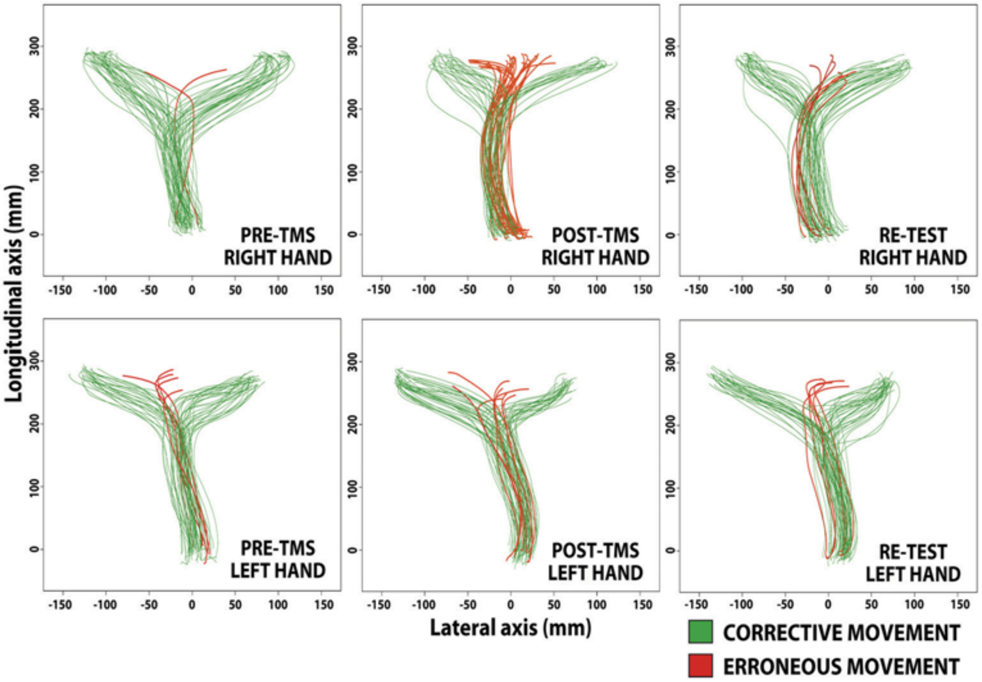


Figure 7.5. Top view of the hand trajectories of a representative subject for displaced trials, for each session and for the right (top) and the left (down) hand. Green lines correspond to hand trajectories that were considered as corrective, whereas the red ones were non-corrective (erroneous).

7.4.2 DTI RESULTS

The VBA whole brain analysis revealed a significant negative correlation between the rTMS behavioral impact on the right hand and a cluster in the left SLF II (53% probability) ($t_{(22)} = 5.45$, $P < 0.001$), such that the increase of erroneous trajectories after rTMS application was lower in subjects with higher FA values in that region ($r_{\text{Pearson}} = -0.77$, $P < 0.001$) (**Figure 7.6**). In addition, two ipsilateral clusters in the pons ($t_{(22)} = 5.69$, $P < 0.001$) and the vermis of the cerebellum ($t_{(22)} = 4.27$, $P < 0.001$) were also found to correlate negatively with the rTMS-induced effect on movements with the right hand. SLF cluster was family-wise error corrected ($t_{(22)} = 5.45$, $P = 0.039$) (**Table 7.2**). For the errors committed with the left hand (**Supplementary Figure 7.1**), negative correlations between the error increases of the left hand and clusters in the left putamen ($t_{(22)} = 6.06$, $P < 0.001$), bilateral SLF I (left SLF I: $t_{(22)} = 4.89$, $P < 0.001$ and right SLF I: $t_{(22)} = 4.89$, $P < 0.001$), and left SLFII ($t_{(22)} = 3.54$, $P = 0.001$) were found (**Supplementary Table 7.1**).

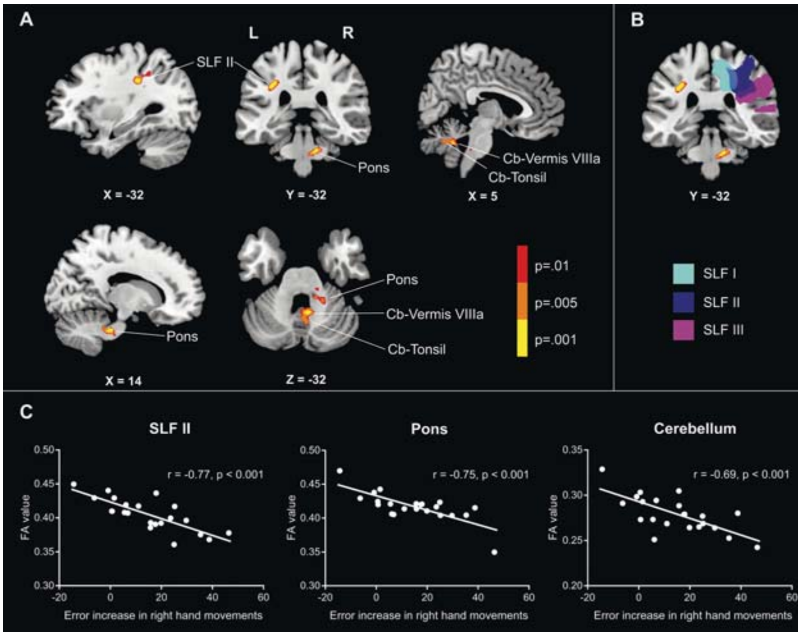


Figure 7.6. **A.** Areas which structural integrity negatively correlated with the error increase of the right hand movements at uncorrected $P = 0.001$ (red), $P = 0.005$ (orange) and $P = 0.01$ (yellow) thresholds. **B.** Cluster located at the contralateral SLF II and probabilistic SLF masks divided by subregions, at 50% probability threshold. SLF I mask is shown in cyan, SLF II in blue and SLF III at violet. **C.** Scatter plots of each area of panel A (SLFII, pons and cerebellum) showing the correlations between mean FA values and the error increase in right hand movements immediately after rTMS protocol. The index of correlation and the p-value are provided on each plot box.

Area-Tract	Hemisphere	Cluster size (mm^3)	T-value	Peak coordinates x	y	z
P = 0.001 uncorrected (min cluster size= 70 mm^3)						
Pons	R	162	5.69	12	-34	-35
SLF *	L	190	5.45	-32	32	34
Cb-Tonsil (IX)	R	74	4.27	8	-53	-31
P = 0.005 uncorrected (min cluster size= 250 mm^3)						
Pons	R	479	5.69	12	-34	-35
SLF *	L	443	5.45	-32	32	34
Cb-Vermis (VIIIa)	R	491	4.43	3	-61	-30
P = 0.01 uncorrected (min cluster size= 600 mm^3)						
Pons	R	793	5.69	12	-34	-35
SLF *	L	724	5.45	-32	32	34
Cb-Vermis (VIIIa)	R	754	4.43	3	-61	-30

* $P < 0.05$ Family-Wise Error corrected at cluster level in ROI analysis

Table 7.2. Correlation between rTMS-induced deficits in online motor control with the right hand and FA maps. Table shows areas that negatively correlate at uncorrected $P = 0.001$ threshold and 70 voxels, $P = 0.005$ and 250 voxels and $P = 0.01$ and 600 voxels of spatial extent, respectively. Adjacent to the cerebellum, we added the equivalent anatomical label of Schmahmann et al. (1999), based on Larsell and Jansen (1970). Peak coordinates are given following the MNI system. Cb: cerebellum; SLF: superior longitudinal fasciculus. L, left hemisphere; R, right hemisphere.

7.4.3 FIXED CONDITION

Figure 7.7A depicts the hand trajectories of the FC which are clearly different from AC. Here, the trajectory of the hand did not have to be adjusted to target displacement. The spatial error associated with the goal-directed movement is depicted in **Figure 7.7B**. This condition served as a control to rule out that the impairments seen in AC could be attributed to unspecific effects of rTMS rather than a specific impairment of the capacity to correct the hand trajectory. The analysis revealed that spatial error was not different across session [$F_{2,44} = 1.02$, $P = 0.37$]. Also, the dispersion of the hand endpoint position was not affected by the session [$F_{2,44} = 1.54$, $P = 0.23$]. Mean spatial errors are reported in **Table 7.1**. **Figure 7.7B** summarizes the distribution of the final mean endpoint positions.

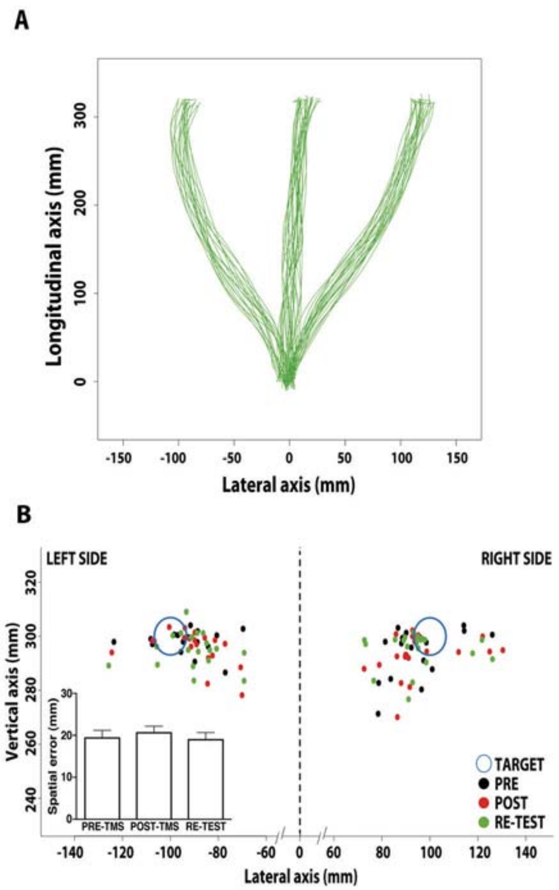


Figure 7.7. **(A)** Top view of the hand trajectories of some trials of a representative subject in the Fixed Condition. **(B)** Two dimensional distribution of the spatial error in each side depending on the session. Each dot represents the mean spatial error of one participant in a specific session. **Inset:** Barplot of the mean (± s.e.m.) of the spatial error committed for each session in the Fixed condition.

7.4.3 KINEMATICS

Supplementary Table 7.2 compiles the kinematic parameters of AC and FC movements. AC RTs differed between sessions [$F_{2,44} = 17.13$, $P < 0.001$, $\varepsilon = 0.72$] with higher RTs in the Pre-rTMS session compared with either the Post-rTMS ($p < .001$) or the Retest session ($P < 0.001$) (**Supplementary Figure 7.2A**). We neither found a hand effect ($F_{1,22} = 0.92$, $P = 0.35$) nor a session x hand interaction ($F_{2,44} = 0.46$, $P = 0.63$). With regard to MT again a main effect of session was obtained [$F_{2,44} = 19.93$, $P < 0.001$, $\varepsilon = 0.73$] (**Supplementary Figure 7.2B**). Post-hoc comparisons revealed slower movements in the Pre-rTMS session compared with either the Post-rTMS ($P < 0.001$) or the Retest session ($P < 0.001$). Longer MTs were found for the left hand [$F_{1,22} = 4.55$, P

< 0.05] and displaced trials [$F_{1,22} = 72.3$, $P < 0.001$]. None of the interactions was significant. For PV a significant main effect emerged for session [$F_{2,44} = 10.3$, $P < 0.001$], with lower PVs in the Pre-rTMS with respect to either the Post-rTMS ($P < 0.001$) or the Re-test session ($P < 0.01$), but all other factors and interactions were non-significant. The analysis of the TPV for corrective (**Supplementary Figure 7.2C**) and undisplaced (**Supplementary Figure 7.2D**) trials revealed a significant effect of hand [$F_{1,22} = 8.15$, $P < 0.01$], reflecting the fact that right hand movements reached the peak velocity earlier. All the other factors and interactions were not significant for TPV. DT was different across sessions [$F_{2,44} = 13.4$, $P < 0.001$] and was higher for corrective than for undisplaced trials [$F_{1,22} = 69.4$, $P < 0.001$] (**Supplementary Figure 7.2E and 7.2F**). Lastly, CT was only modulated as a function of the session [$F_{2,44} = 4.52$, $P = 0.016$], with longer times for the slower movements performed in the Pre-rTMS session. As a result, normalized CT dissipated session effect [$F_{2,44} = 0.04$, $P = 0.96$], but revealed that CT was a higher percentage of MT in left hand movements [$F_{1,22} = 9.9$, $P < 0.004$] (**Supplementary Figure 7.2G and 7.2H**).

In FC, we observed that movements in Pre-rTMS were slower, with longer MTs [$F_{2,44} = 9.49$, $P < 0.001$], mainly caused by higher DTs [$F_{2,44} = 5.37$, $P = 0.008$]. We found lower PV values in Pre-rTMS session [$F_{2,44} = 3.32$, $P < 0.04$], but TPV was similar across sessions [$F_{2,44} = 1.23$, $P < 0.3$]. Last but not least, the comparison between FC and undisplaced AC trials of the same hand revealed similar RTs [$F_{1,22} = 0.19$, $P < 0.67$], MTs [$F_{1,22} = 2.4$, $P < 0.13$], TPVs [$F_{1,22} = 2.5$, $P < 0.12$] and DTs [$F_{1,22} = 3.6$, $P < 0.07$]. Only PV was found higher in FC trials [$F_{1,22} = 14.3$, $P < 0.001$].

7.5 Discussion

In the present study, a multimodal approach combining repetitive TMS and DTI examined the neurophysiological and anatomical correlates within the parietofrontal ‘reaching’ circuit to give some insights on the inter-individual variability of rTMS-induced deficits in online motor control. We applied a 15-minutes long period of 1-Hz rTMS over the mIPS that produced, as we predicted, a clear reduction of the ability to correct reaching movements in response to target perturbations. Furthermore, we found that the individual differences observed in the behavioral impact after rTMS, measured as the increase of the error rate as a function of the pre-rTMS baseline, were predicted by the individual microstructural properties in the white matter fibers of the second branch of the contralateral SLF, which links the rTMS-targeted region with specific pre-frontal motor regions that are implicated in action re-programming. These results suggest that the behavioral consequences of the modulation of the synaptic efficacy produced by the rTMS interventions depend, partially but consistently, on the structural characteristics of the anatomical pathways of the brain networks hosting the target regions implicated in such behavior. We believe that these results provide suggestive evidence on the mechanisms underlying causal connectivity within visuomotor brain networks, and they indicate that the structural alignment and cohesion of the white matter may be used as a solid predictor to characterize the extent of rTMS motor impairments.

Previous studies have broadly supported the contribution of the mIPS to the on-line control of visually-guided reaching movements (Davare et al., 2012; Desmurget et al., 1999; Grafton, Mazziotta, Woods & Phelps, 1992). Also, our data is compatible with prior fMRI evidence suggesting an involvement of mIPS in later stages of the sensorimotor transformation by coding visual information into a sensorimotor reference (Grefkes et al., 2004; Prado et al., 2005). Previous TMS studies administered a single or a short burst of magnetic pulses in order to momentarily disrupt the mIPS activity at specific stages of the task (Desmurget et al., 1999; Vesia et al., 2010). This method provides also a very good chronometry, being a reliable tool to measure the time-course of the activity of the stimulated area (Amengual et al., 2013; van den Wildenberg et al., 2010). However, it has been demonstrated that high-frequency bursts, as well as the application of single pulses, might induce facilitatory behavioral effects rather than the desired disruption of a given function due to the high intensity at which they must be applied (Rossi et al., 2006). In contrast, off-line rTMS allowed to execute the task separately to its application, removing non-specific effects of the “on-line” TMS (Bolognini & Ro, 2010). There is an overwhelming number of studies supporting that the application of rTMS can either potentiate or decrease the cortical excitability of the targeted region depending on the stimulation conditions, and consequently affect the behavioral counterpart of these brain areas [see (Siebner, Hartwigsen, Kassuba & Rothwell, 2009) for review]. Importantly, we induced a long-lasting inhibition by using

1-Hz rTMS, instigating an enduring weakening of the synaptic efficacy. The clear advantage of the rTMS technique is that these induced neuroplastic changes allow to establish a causal relationship between the stimulated brain region, here the mIPS, and its function in healthy population. In addition, we used a robotized arm which used a motion compensation system that adjusted the coil's position automatically in response to spurious head movements (Richter, 2013), increasing the reliability of the outcome of the rTMS application.

The behavioral counterpart of the application of the rTMS in the left mIPS was predominantly observed in contralateral (right) hand movements. However, smaller but significant effect was also observed in hand movements ipsilateral to the stimulated hemisphere. Conflicting conclusions have been reported regarding the hemispheric specificity of on-line adjustments (Desmurget et al., 1999; Vesia et al., 2010). Our results concur with imaging studies showing bilateral frontoparietal activations with contralateral predominance (Medendorp, Goltz, Vilis & Crawford, 2003). Noteworthy, movements with the non-dominant hand showed higher error rates than those performed with the dominant hand during the baseline session. This is consistent with previous studies reporting manual asymmetries and a superior ability of the dominant hemisphere to correct movements (Boulinguez et al., 2001; Sainburg & Kalakanis, 2000). Importantly, we controlled the possibility that the offline effect of 1-Hz rTMS resulted in an impairment of the visual processes that coded the location of the target. The lack of differences in the FC condition led us to conclude that the target location was processed properly. Hence, the increase of the error rate in later stages of sensorimotor integration should response to the inhibition of the mIPS (Davare et al., 2012). A remaining issue is whether the increase in error rate after rTMS is due to a more general effect on the motor output rather than a specific effect on movement correction. Koch et al. (2007) modulated the excitability of the primary motor areas delivering rTMS over other remote but functionally connected areas. Such modulation of activity in primary motor regions should be reflected by changes in kinematic parameters such as movement time and time-to-peak velocity. Although these parameters both were slightly shorter for right than for left movements, this effect was present in all sessions and showed no interaction with stimulation, probably reflecting a handedness effect. Reaction times and movement times were higher in the Pre-rTMS session compared to both Post-rTMS and the Re-test, likely due to a practice effect (Georgopoulos, Kalaska

& Massey, 1981; Krakauer, Ghilardi & Ghez, 1999). Additionally, the lack of kinematic differences between Post-rTMS and Re-test sessions of the AC and FC allowed us to conclude that kinematics cannot explain the impairment of the ability to correct after the rTMS application.

One major concern when interpreting the behavioral and neurophysiological after-effects of the application of rTMS relies on the high inter-individual variability that is generally observed. Many factors contribute to this variability, including gender, time of day, age and neuromodulators [see (Ridding & Ziemann, 2010) for review]. In this line, although our data revealed a clear and global decrease of the capacity to correct movements after the application of the rTMS (that is, a clear rTMS effect), we found strong inter-individual differences in these effects. Indeed, we found that two participants showed an increase in their capacities to correct trajectories towards the new position of the target when it was demanded, suggesting a certain facilitation produced by the rTMS which could be, however, spurious but in this case suggest a wide spectrum in our results in terms of the rTMS effect. Other studies devoted to impair the normal function of the mIPS found such variability between participants (Desmurguet et al. 1999). However, little is known about the implication of the anatomical substrate in this variability. In order to seek for anatomical markers that would explain such variability in the affected capacity to adjust on-line motor movements, we calculated the correlation between the increase of the error rate produced by the rTMS and the whole-brain FA as a marker of microstructural properties of white matter. Importantly, this analysis unveiled that subjects with stronger contralateral rTMS-behavioral consequences exhibited higher FA values specifically in the parietofrontal tracts of the second branch of the SLF (SLF II) in the stimulated hemisphere. Therefore, these results suggest that these tracts might have an active role in mediating the dynamic computation of the motor error from the mIPS to the PMd and, in a more general level, the operational principles that govern rTMS behavioral effects have causal consequences as a function of the microstructural properties of connections that sustain brain networks. The microstructural integrity of the white matter in the cerebellum and ipsilateral pons also explained the differential impact of TMS in online motor control. Specifically, the cerebellum has been found to coordinate a motor error signal and a forward model of the limb response (Miall, Weir et al. 1993; Liu, Ingram et al. 1999).

To note, the sign of the correlation shows that the behavioral repercussion of the TMS was weaker when these tracts presented higher anisotropy. Keeping in mind the 'virtual-lesion' model, in which inhibitory rTMS might act as a breakdown of the cognitive function associated to the targeted area, these results are in line with studies in traumatic brain injury (TBI) (Strangman, O'Neil-Pirozzi et al. 2012) and stroke patients (Qiu, Darling et al. 2011). In these studies, FA predicts their prognosis, that is to say, FA could be seen as a biomarker that may predict which of these patients will recover their cognitive loss and which not. In our context, the effects of the application of inhibitory rTMS over the mIPS, causing a virtual partial lesion in terms of decrease of excitability in this area, might be predicted by the microstructural properties of the white matter that compose the affected network. Indeed, affecting the functional counterpart of one node of this network (as mIPS is from the fronto-parietal network) might be compensated by the structural substrate of parietofrontal connections, such as the SLF. With respect to the lower TMS effect in the ipsilateral hand, DTI also showed the importance of the white matter integrity in the parietofrontal tracts when adjusting movements with the left hand. Interestingly, ipsilateral SLF also correlated with the behavioral effect of the rTMS.

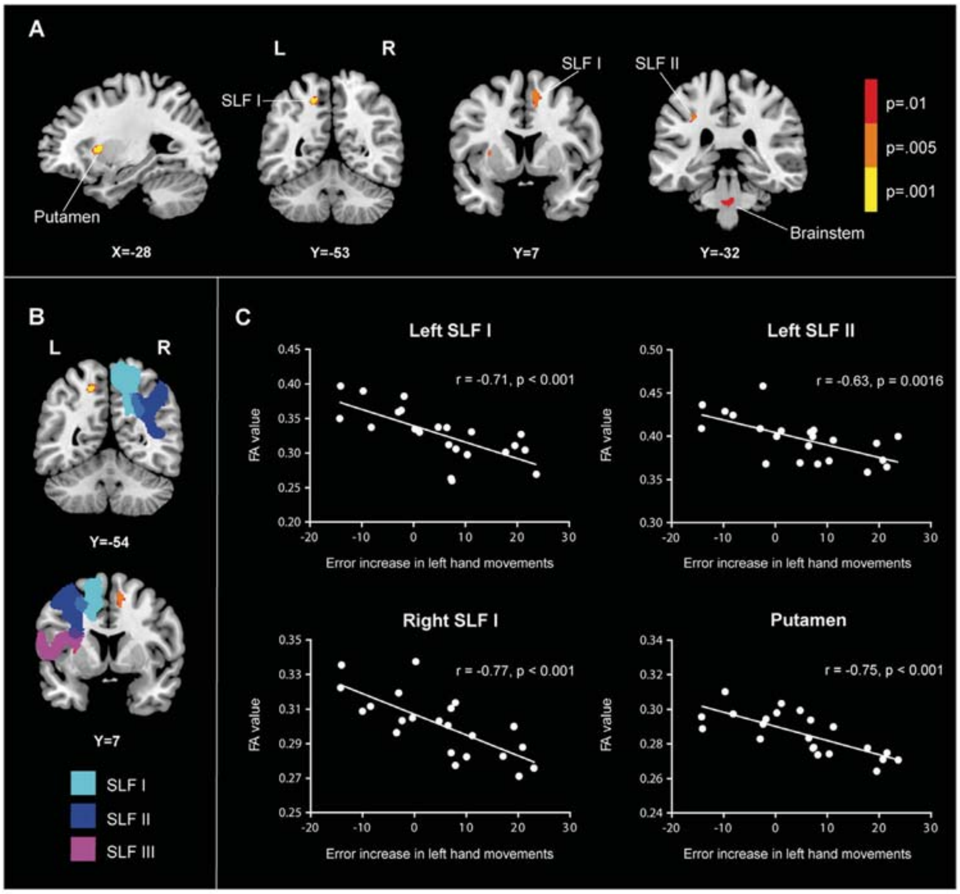
Despite of the clarity of its results, the current study has several limitations. First, the effect of interfering mIPS function on the correction of reaching movements cannot rule out that other movements, such as grasping, might also be affected, even though previous studies have implicated more anterior areas within the IPS for grasping (Tunik et al., 2005). A second limitation is that the study is blind to the directionality of the flow of information within the dorsal stream between premotor and medial parietal areas (Culham et al., 2003). This question should be tackled by additional experiments involving hemodynamic or electroencephalographic recordings in conjunction with effective connectivity measures (Fox et al., 2012).

7.6 Acknowledgements

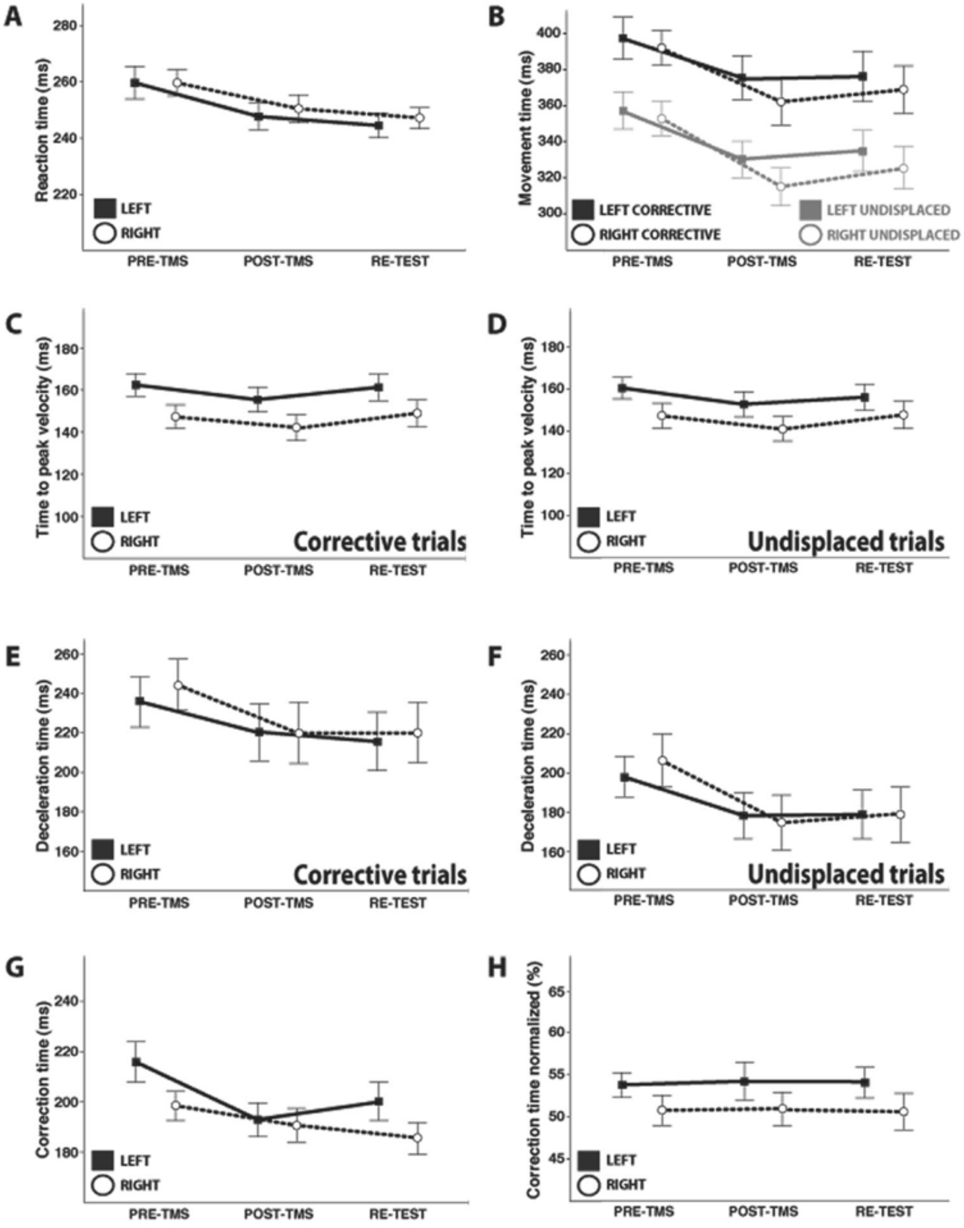
This work was supported by an AGAUR B.E. grant from the Catalan government to BRH, a Spanish goverment grant to ARF (PSI2012-29219) and a grant from the Generalitat de Catalunya (SGR2005-00831). TFM is supported by DFG and the BMBF.

7.7 Supplementary material

7.7.1 SUPPLEMENTARY FIGURES AND TABLES



Supplementary Figure 7.1. FA correlation with rTMS-induced deficit in left hand movements. A. Areas which structural integrity negatively correlated with the error increase of the left hand movements, at uncorrected *P* = 0.001 (red), *P* = 0.005 (orange) and *P* = 0.01 (yellow) thresholds. **B.** Cluster located at the contralateral SLF II and probabilistic SLF masks divided by subregions, at 50% probability threshold. SLF I mask is shown in cyan, SLF II in blue and SLF III at violet. **C.** Scatter plots of significant regions of panel A at uncorrected *P* = 0.005 threshold and 150 voxels of cluster extent, showing the correlations between mean FA values and the error increase in left hand movements immediately after rTMS protocol. The index of correlation and the p-value are provided on each plot box.



Supplementary Figure 7.2. Kinematic analysis. Mean (± s.e.m.) for the kinematics of the adjusting condition. Right and left conditions are indicated by white circle and black square, respectively. **(A)** Differences in reaction time splitted by session and hand, including all trials of the AC. **B.** Movement time results for each session and hand comparing undisplaced (grey) and corrective (black) trials. Time to peak velocity values for corrective **(C)** and undisplaced **(D)** trials. Deceleration time for corrective **(E)** and undisplaced **(F)** trials. **G.** Differences in the time needed to initiate an online correction, for each session and hand. **H.** Analysis of correction time normalized with respecto to MT.

Area-Tract	**Hemisphere**	**Cluster size (mm^3)**	**T-value**	**Peak coordinates**		
				x	**y**	**z**
***P* = 0.001 uncorrected (min cluster size= 70 mm^3)**						
Putamen	L	193	6.06	-28	10	7
SLF I	L	110	4.89	-16	-53	50
***P* = 0.005 uncorrected (min cluster size= 150 mm^3)**						
Putamen	L	354	6.06	-28	10	7
SLF I	L	236	4.89	-16	-53	50
SLF I	R	180	4.54	11	7	55
SLF II	L	228	3.54	-30	32	41
***P* = 0.01 uncorrected (min cluster size= 230 mm^3)**						
Putamen	L	354	6.06	-28	10	7
SLF I	L	236	4.89	-16	-53	50
SLF I	R	180	4.54	11	7	55
Brainstem	R	235	3.84	3	-33	-37
CST	L	237	3.55	-3	-23	-31
SLF II	L	228	3.54	-30	32	41

Supplementary Table 7.1. Correlation between rTMS-induced deficits in online motor control with the left hand and FA maps. Table shows areas that negatively correlate at uncorrected $P = 0.001$ threshold and 70 voxels, $P = 0.005$ and 150 voxels and $P = 0.01$ and 230 voxels of spatial extent, respectively. Peak coordinates are given following the MNI system. No clusters resisted FWE correction. CST corticospinal tract; SLF superior longitudinal fasciculus. L, left hemisphere; R, right hemisphere.

Adjusting condition

	PRE-rTMS		POST-rTMS		RE-TEST	
RT (ms)	Left	Right	Left	Right	Left	Right
	259 (28)	**259** (22)	**248** (23)	**250** (24)	**244** (21)	**247** (17)

Adjusting condition – Undisplaced trials

	PRE-rTMS		POST-rTMS		RE-TEST	
MT (ms)	Left	Right	Left	Right	Left	Right
	357 (48)	**352** (45)	**330** (49)	**315** (50)	**335** (54)	**325** (55)
PV (mm/s)	Left	Right	Left	Right	Left	Right
	2648 (573)	**2652** (587)	**2929** (651)	**2992** (663)	**2851** (656)	**2851** (751)
TPV (ms)	Left	Right	Left	Right	Left	Right
	163 (25)	**150** (29)	**155** (29)	**143** (29)	**159** (32)	**150** (30)
DT (ms)	Left	Right	Left	Right	Left	Right
	194 (48)	**202** (63)	**175** (55)	**171** (66)	**176** (59)	**175** (66)

Adjusting condition – Corrective trials

	PRE-rTMS		POST-rTMS		RE-TEST	
MT (ms)	Left	Right	Left	Right	Left	Right
	397 (55)	**391** (46)	**376** (58)	**362** (60)	**377** (65)	**369** (62)
PV (mm/s)	Left	Right	Left	Right	Left	Right
	2594 (596)	**2654** (564)	**2896** (612)	**2910** (658)	**2931** (703)	**2797** (699)
TPV (ms)	Left	Right	Left	Right	Left	Right
	162 (26)	**147** (26)	**155** (28)	**142** (29)	**161** (30)	**149** (30)
DT (ms)	Left	Right	Left	Right	Left	Right
	235 (61)	**244** (63)	**220** (69)	**220** (74)	**215** (71)	**220** (73)
CT (ms)	Left	Right	Left	Right	Left	Right
	215 (38)	**198** (27)	**192** (32)	**190** (31)	**199** (36)	**185** (30)

Fixed condition

	PRE-rTMS	POST-rTMS	RE-TEST
RT (ms)	**257** (22)	**252** (22)	**250** (21)
MT (ms)	**343** (44)	**315** (42)	**319** (51)
PV (mm/s)	**2991** (632)	**3193** (727)	**3127** (736)
TPV (ms)	**160** (36)	**151** (39)	**157** (32)
DT (ms)	**183** (58)	**164** (52)	**162** (53)

Supplementary Table 7.2. Summary of mean values for kinematic parameters in AC (undisplaced and corrective trials) and in FC. Table reports mean (SD) for each dependent measure. RT reaction time; MT movement time; PV peak velocity; TPV time to peak velocity; DT deceleration time; CT correction time.

7.7.2 SUPPLEMENTARY VIDEO

Supplementary Video 7.1. Experimental setup.

7.8 References

Amengual, J. L., Marco-Pallares, J., Richter, L., Oung, S., Schweikard, A., Mohammadi, B., . . . Munte, T. F. (2013). Tracking post-error adaptation in the motor system by transcranial magnetic stimulation. *Neuroscience, 250*, 342-351.

Andersen, R. A., & Buneo, C. A. (2002). Intentional maps in posterior parietal cortex. *Annual Review of Neuroscience, 25*(1), 189-220.

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007a). Non-linear optimisation FMRIB Technical report TR07JA1: Oxford: University of Oxford FMRIB Centre.

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007b). Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2. *FMRIB Analysis Group of the University of Oxford*.

Bengtsson, S. L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H., & Ullen, F. (2005). Extensive piano practicing has regionally specific effects on white matter development. *Nature Neuroscience, 8*(9), 1148-1150.

Blangero, A., Menz, M. M., McNamara, A., & Binkofski, F. (2009). Parietal modules for reaching. *Neuropsychologia, 47*(6), 1500-1507.

Bolognini, N., & Ro, T. (2010). Transcranial magnetic stimulation: disrupting neural activity to alter and assess brain function. *Journal of Neuroscience, 30*(29), 9647-9650.

Boorman, E. D., O'Shea, J., Sebastian, C., Rushworth, M. F., & Johansen-Berg, H. (2007). Individual differences in white-matter microstructure reflect variation in functional connectivity during choice. *Current Biology, 17*(16), 1426-1431.

Boulinguez, P., Nougier, V., & Velay, J. L. (2001). Manual asymmetries in reaching movement control. I: Study of right-handers. *Cortex, 37*(1), 101-122.

Boy, F., Evans, C. J., Edden, R. A., Singh, K. D., Husain, M., & Sumner, P. (2010). Individual differences in subconscious motor control predicted by GABA concentration in SMA. *Current Biology, 20*(19), 1779-1785.

Buelte, D., Meister, I. G., Staedtgen, M., Dambeck, N., Sparing, R., Grefkes, C., & Boroojerdi, B. (2008). The role of the anterior intraparietal sulcus in crossmodal processing of object features in humans: an rTMS study. *Brain Research, 1217*, 110-118.

Camara, E., Bodammer, N., Rodriguez-Fornells, A., & Tempelmann, C. (2007). Age-related water diffusion changes in human brain: a voxel-based approach. *Neuroimage, 34*(4), 1588-1599.

Caminiti, R., Ferraina, S., & Johnson, P. B. (1996). The sources of visual information to the primate frontal lobe: a novel role for the superior parietal lobule. *Cerebral Cortex, 6*(3), 319-328.

Catani, Marco, & de Schotten, Michel Thiebaut. (2012). *Atlas of human brain connections*: Oxford University Press.

Clower, D. M., Hoffman, J. M., Votaw, J. R., Faber, T. L., Woods, R. P., & Alexander, G. E. (1996). Role of posterior parietal cortex in the recalibration of visually guided reaching. *Nature, 383*(6601), 618-621.

Colebatch, J. G., Deiber, M. P., Passingham, R. E., Friston, K. J., & Frackowiak, R. S. (1991). Regional cerebral blood flow during voluntary arm and hand movements in human subjects. *Journal of Neurophysiology, 65*(6), 1392-1401.

Culham, J. C., Danckert, S. L., DeSouza, J. F., Gati, J. S., Menon, R. S., & Goodale, M. A. (2003). Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. *Experimental Brain Research, 153*(2), 180-189.

Davare, M., Zenon, A., Pourtois, G., Desmurget, M., & Olivier, E. (2012). Role of the medial part of the intraparietal sulcus in implementing movement direction. *Cerebral Cortex, 22*(6), 1382-1394.

Della-Maggiore, V., Malfait, N., Ostry, D. J., & Paus, T. (2004). Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. *Journal of Neuroscience, 24*(44), 9971-9976.

Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature Neuroscience, 2*(6), 563-567.

Desmurget, M., Grea, H., Grethe, J. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (2001). Functional anatomy of nonvisual feedback loops during reaching: a positron emission tomography study. *Journal of Neuroscience, 21*(8), 2919-2928.

Frey, S. H., Vinton, D., Norlund, R., & Grafton, S. T. (2005). Cortical topography of human anterior intraparietal cortex active during visually guided grasping. *Brain Research: Cognitive Brain Research, 23*(2-3), 397-405.

Fox, M. D., Halko, M. A., Eldaief, M. C., & Pascual-Leone, A. (2012). Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). *Neuroimage, 62*(4), 2232-2243.

Fuentemilla, L., Camara, E., Munte, T. F., Kramer, U. M., Cunillera, T., Marco-Pallares, J., . . . Rodriguez-Fornells, A. (2009). Individual differences in true and false memory retrieval are related to white matter brain microstructure. *Journal of Neuroscience, 29*(27), 8698-8703.

Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *Journal of Neuroscience, 23*(27), 9240-9245

Georgopoulos, A. P., Kalaska, J. F., & Massey, J. T. (1981). Spatial trajectories and reaction times of aimed movements: effects of practice, uncertainty, and change in target location. *Journal of Neurophysiology, 46*(4), 725-743.

Glover, S., Miall, R. C., & Rushworth, M. F. (2005). Parietal rTMS disrupts the initiation but not the execution of on-line adjustments to a perturbation of object size. *Journal of Cognitive Neuroscience, 17*(1), 124-136.

Grafton, S. T., Mazziotta, J. C., Woods, R. P., & Phelps, M. E. (1992). Human functional anatomy of visually guided finger movements. *Brain, 115 (Pt 2)*, 565-587.

Granek, J. A., Pisella, L., Blangero, A., Rossetti, Y., & Sergio, L. E. (2012). The role of the caudal superior parietal lobule in updating hand location in peripheral vision: further evidence from optic ataxia. *PloS One, 7*(10), e46619.

Grefkes, C., & Fink, G. R. (2005). The functional organization of the intraparietal sulcus in humans and monkeys. *Journal of Anatomy, 207*(1), 3-17.

Grefkes, C., Ritzl, A., Zilles, K., & Fink, G. R. (2004). Human medial intraparietal cortex subserves visuomotor coordinate transformation. *Neuroimage, 23*(4), 1494-1506.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201-206.

Jeannerod, M., Arbib, M. A., Rizzolatti, G., & Sakata, H. (1995). Grasping objects: the cortical mechanisms of visuomotor transformation. *Trends in Neurosciences, 18*(7), 314-320.

Jennings, J. R., & Wood, C. C. (1976). Letter: The epsilon-adjustment procedure for repeated-measures analyses of variance. *Psychophysiology, 13*(3), 277-278.

Johansen-Berg, H., Della-Maggiore, V., Behrens, T. E., Smith, S. M., & Paus, T. (2007). Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage, 36 Suppl 2*, T16-21.

Johnson, P. B., & Ferraina, S. (1996). Cortical networks for visual reaching: intrinsic frontal lobe connectivity. *European Journal of Neuroscience, 8*(7), 1358-1362.

Johnson, P. B., Ferraina, S., & Caminiti, R. (1993). Cortical networks for visual reaching. *Experimental Brain Research, 97*(2), 361-365.

Johnson, S. H., & Grafton, S. T. (2003). From 'acting on' to 'acting with': the functional anatomy of object-oriented action schemata. *Progress in Brain Research, 142*, 127-139.

Kertzman, C., Schwarz, U., Zeffiro, T. A., & Hallett, M. (1997). The role of posterior parietal cortex in visually guided reaching movements in humans. *Experimental Brain Research, 114*(1), 170-183.

Koch, G., Oliveri, M., Torriero, S., Salerno, S., Lo Gerfo, E., & Caltagirone, C. (2007). Repetitive TMS of cerebellum interferes with millisecond time processing. *Experimental Brain Research, 179*(2), 291-299.

Krakauer, J. W., Ghilardi, M. F., & Ghez, C. (1999). Independent learning of internal models for kinematic and dynamic control of reaching. *Nature Neuroscience, 2*(11), 1026-1031.

Larsell, Olof, & Jansen, Jan. (1970). *The Comparative Anatomy and Histology of the Cerebellum: From Monotremes Through Apes* (Vol. 2): Univ Of Minnesota Press.

Liu, G. , & McMillan, L. (2006). Estimation of missing markers in human motion capture. *The Visual Computer, 22*(9), 721-728.

Liu, X., Ingram, H. A., Palace, J. A., & Miall, R. C. (1999). Dissociation of 'on-line' and 'off-line' visuomotor control of the arm by focal lesions in the cerebellum and brainstem. *Neuroscience Letters, 264*(1-3), 121-124.

Machii, K., Cohen, D., Ramos-Estebanez, C., & Pascual-Leone, A. (2006). Safety of rTMS to non-motor cortical areas in healthy participants and patients. *Clinical Neurophysiology, 117*(2), 455-471.

Mason, C. R., Gomez, J. E., & Ebner, T. J. (2001). Hand synergies during reach-to-grasp. *Journal of Neurophysiology, 86*(6), 2896-2910.

Matthaus, L. (2008). *A robotic assistance system for transcranial magnetic stimulation and its application to motor cortex mapping*. (Dissertation), University of Lübeck., University of Lübeck. Retrieved from http://www.rob.uni-luebeck.de/node/131?pub=76

Medendorp, W. P., Goltz, H. C., Vilis, T., & Crawford, J. D. (2003). Gaze-centered updating of visual space in human parietal cortex. *Journal of Neuroscience, 23*(15), 6209-6214.

Messier, J., & Kalaska, J. F. (1999). Comparison of variability of initial kinematics and endpoints of reaching movements. *Experimental Brain Research, 125*(2), 139-152.

Miall, R. C., Weir, D. J., Wolpert, D. M., & Stein, J. F. (1993). Is the cerebellum a smith predictor? *J Mot Behav, 25*(3), 203-216.

Neggers, S. F., & Bekkering, H. (2002). Coordinated control of eye and hand movements in dynamic reaching. *Hum Mov Sci, 21*(3), 349-376.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Pisella, L., Grea, H., Tilikete, C., Vighetto, A., Desmurget, M., Rode, G., . . . Rossetti, Y. (2000). An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. *Nature Neuroscience, 3*(7), 729-736.

Prado, J., Clavagnier, S., Otzenberger, H., Scheiber, C., Kennedy, H., & Perenin, M. T. (2005). Two cortical systems for reaching in central and peripheral vision. *Neuron, 48*(5), 849-858.

Qiu, M., W. G. Darling, et al. (2011). White Matter Integrity Is a Stronger Predictor of Motor Function Than BOLD Response in Patients With Stroke. *Neurorehabilitation and Neural Repair,* **25**(3): 275-284.

Reichenbach, A, Bresciani, J-P, Peer, A, Bülthoff, HH, & Thielscher, A. (2008). Inter-individual spatial diversity in motor control processes within the posterior parietal cortex assessed with transcranial magnetic stimulation. *Brain Stimul, 1*(3), 283-284.

Rey, M., Dellatolas, G., Bancaud, J., & Talairach, J. (1988). Hemispheric lateralization of motor and speech functions after early brain lesion: study of 73 epileptic patients with intracarotid amytal test. *Neuropsychologia, 26*(1), 167-172.

Richter, L. (2013). *Robotized Transcranial Magnetic Stimulation* (1st ed.). New York: Springer New York.

Richter, L., Ernst, F., Schlaefer, A., & Schweikard, A. (2011). Robust real-time robot-world calibration for robotized transcranial magnetic stimulation. *International Journal of Medical Robotics + Computer Assisted Surgery, 7*(4), 414-422.

Richter, L., Trillenberg, P., Schweikard, A., & Schlaefer, A. (2013). Stimulus intensity for hand held and robotic transcranial magnetic stimulation. *Brain Stimul, 6*(3), 315-321.

Ridding, M. C., & Ziemann, U. (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *The Journal of Physiology, 588*(13), 2291-2304.

Rodriguez-Herreros, B., & Lopez-Moliner, J. (2011). Proprioception improves temporal accuracy in a coincidence-timing task. *Experimental Brain Research, 210*(2), 251-258.

Rossi, S., Pasqualetti, P., Zito, G., Vecchio, F., Cappa, S. F., Miniussi, C., . . . Rossini, P. M. (2006). Prefrontal and parietal cortex in human episodic memory: an interference study by repetitive transcranial magnetic stimulation. *European Journal of Neuroscience, 23*(3), 793-800.

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., . . . et al. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology, 91*(2), 79-92.

Sainburg, R. L., & Kalakanis, D. (2000). Differences in control of limb dynamics during dominant and nondominant arm reaching. *Journal of Neurophysiology, 83*(5), 2661-2675.

Sakata, H., Taira, M., Murata, A., & Mine, S. (1995). Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cerebral Cortex, 5*(5), 429-438.

Schmahmann, J. D., Doyon, J., McDonald, D., Holmes, C., Lavoie, K., Hurwitz, A. S., . . . Petrides, M. (1999). Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. *Neuroimage, 10*(3 Pt 1), 233-260.

Siebner, Hartwig R., Hartwigsen, Gesa, Kassuba, Tanja, & Rothwell, John C. (2009). How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex, 45*(9), 1035-1042.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23 Suppl 1*, S208-219.

Smith, S. M., Zhang, Y., Jenkinson, M., Chen, J., Matthews, P. M., Federico, A., & De Stefano, N. (2002). Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage, 17*(1), 479-489.

Steinman, R. M., Kowler, E., & Collewijn, H. (1990). New directions for oculomotor research. *Vision Research, 30*(11), 1845-1864.

Strangman, G. E., O'Neil-Pirozzi, T. M., Supelana, C., Goldstein, R., Katz, D. I., & Glenn, M. B. (2012). Fractional anisotropy helps predicts memory rehabilitation outcome after traumatic brain injury. *NeuroRehabilitation, 31*(3), 295-310.

Thiebaut de Schotten, M., Ffytche, D. H., Bizzi, A., Dell'Acqua, F., Allin, M., Walshe, M., . . . Catani, M. (2011). Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *Neuroimage, 54*(1), 49-59.

Thiebaut de Schotten, Michel, Dell'Acqua, Flavio, Valabregue, Romain, & Catani, Marco. (2012). Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex, 48*(1), 82-96.

Tuch, D. S., Salat, D. H., Wisco, J. J., Zaleta, A. K., Hevelone, N. D., & Rosas, H. D. (2005). Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proceedings of the National Academy of Sciences of the United States of America, 102*(34), 12212-12217.

Tunik, E., Frey, S. H., & Grafton, S. T. (2005). Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. *Nature Neuroscience, 8*(4), 505-511.

Tunik, E., Rice, N. J., Hamilton, A., & Grafton, S. T. (2007). Beyond grasping: representation of action in human anterior intraparietal sulcus. *Neuroimage, 36 Suppl 2*, T77-86.

van Beers, R. J., Haggard, P., & Wolpert, D. M. (2004). The role of execution noise in movement variability. *Journal of Neurophysiology, 91*(2), 1050-1063.

van den Wildenberg, W. P., Burle, B., Vidal, F., van der Molen, M. W., Ridderinkhof, K. R., & Hasbroucq, T. (2010). Mechanisms and dynamics of cortical motor inhibition in the stop-signal paradigm: a TMS study. *Journal of Cognitive Neuroscience, 22*(2), 225-239.

van Gaal, S., Scholte, H. S., Lamme, V. A., Fahrenfort, J. J., & Ridderinkhof, K. R. (2011). Pre-SMA graymatter density predicts individual differences in action selection in the face of conscious and unconscious response conflict. *Journal of Cognitive Neuroscience, 23*(2), 382-390.

Vesia, M., Prime, S. L., Yan, X., Sergio, L. E., & Crawford, J. D. (2010). Specificity of human parietal saccade and reach regions during transcranial magnetic stimulation. *Journal of Neuroscience, 30*(39), 13053-13065.

Westerhausen, R., Kreuder, F., Woerner, W., Huster, R. J., Smit, C. M., Schweiger, E., & Wittling, W. (2006). Interhemispheric transfer time and structural properties of the corpus callosum. *Neuroscience Letters, 409*(2), 140-145.

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., . . . Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *Neuroimage, 45*(1 Suppl), S173-186.

8

DISCUSSION

Throughout the last 20 years, there has been an upsurge of interest in the role that vision plays in the control of goal-directed movements. This interest has been driven in part by the new prominence that the study of action has found in the contemporary psychophysical and physiological literature. From a biological standpoint, humans must code and store complex spatiotemporal information and then translate it into the appropriate motor commands needed to achieve the task goal. Given that perception is not instantaneous, logic dictates that real-time action must cope with and overcome inherent delays in the nervous system. However, the requisite computations of space and time for accurate actions and their underlying neural mechanisms are still under debate. The aim of the present dissertation has been to characterize the process that subserves the integration of spatial and temporal information in the visuomotor control of reaching. The lack of sufficient knowledge about these fundamental questions and the intention to provide a broad an inclusive framework of the visuospatial coding devoted to action motivated this attempt. This aim was addressed through the extensive use of psychophysical and neuroimaging tools to experimentally test specific hypothesis built on previous work on particular aspects of the visuomotor system.

Some of the implications extracted from the findings of each study have been discussed in full in each of the individual chapters. Nonetheless, the paragraphs below relate the interpretation of the findings of each study in light of the examined behavioral and neurophysiological parameters. Thereby, in this chapter I will build up the discussions of the previous chapters in order to accomodate the insights of the present dissertation within a more global perspective of visuomotor control.

8.1 The influence of visual motion in goal-directed reaching

8.1.1 ADAPTATION TO VISUAL MOTION AFFECTS HAND MOVEMENTS

Adaptation has traditionally been used to investigate the mechanisms of sensory coding (Clifford, 2005). In the three experiments carried out in Chapter 3 we capitalize on the motion aftereffect (MAE) to investigate whether the illusory motion of a stationary object can elicit changes in the hand trajectory committed to reach this object. The motion after-effect (MAE) is a result of prolonged viewing of a pattern in constant motion: Following exposure to a stimulus moving in one direction, a subsequently presented stationary pattern appears to move in the opposite direction. We used two visuomotor tasks after the adaptation period that differed in their intrinsic kinematic properties: a manual pursuit movement, in which participants were instructed to track a target for a relatively long interval time; and a goal-directed pointing task, where a ballistic fast movement toward the perceived position of a stationary target was required. Critically, the direction of the MAE modulated the lag between the hand and the target position during the manual pursuit. Experiment 1 showed that the hand trailed the target at a shorter distance when the MAE direction was congruent with the target motion. However, opposite directions produced larger hand-target misalignments. This effect expressed in full when the subjects fixated their gaze on a specific dot in the centre of the screen while performing the manual pursuit of the target. The pattern of these results is consistent with a long body of literature suggesting that the strength of the MAE hinged on the gaze fixation during the adaptation period (Wohlgemuth, 1911) and on the distance to the gaze center, being higher in peripheral vision (Anstis & Moulden, 1970; Brandt, Dichgans & Koenig, 1973; Wright, 1986).

8.1.1.1 Distortion of speed or of perceived position?

The subsequent analysis of the hand velocity profiles during the manual pursuit revealed that MAE direction altered the kinematic pattern of the manual tracking. The hand movement as a function of time was slower in the condition where the direction of the MAE and the target trajectory differed. Thus, this experiment demonstrated that motion adaptation unrelated to the object was capable of modifying the movement characteristics when reaching the object. One plausible explanation for this effect relies upon the possibility that MAE distorted the perceived speed of the tracked object. Visual information can be utilized to modulate different aspects of the intercepting movement. Many studies investigating goal-directed reaching to moving objects have shown that our visuomotor system monitors target motion and uses this information to guide the hand (Brenner, Smeets & de Lussanet, 1998; Schenk, Mair & Zihl, 2004). The target's speed has a very consistent effect on the speed of the hand movement: one moves quicker to faster targets (Bairstow, 1987; Savelsbergh, Whiting, Burden & Bartlett, 1992; van Donkelaar, Lee & Gellman, 1992). Constrained by the speed accuracy trade-off (Fitts, 1954), one explanation is based on the fact that getting the timing right is more important with a fast object, because the spatial error is directly proportional to the target's speed. Thus, the benefit of moving fast increases as the velocity of the target increases (Brouwer, Brenner & Smeets, 2000). Surprisingly, making the object appear to move faster by moving the background in the opposite direction does not make people aim further ahead, and making it appear to move more slowly does not make them aim less far ahead (Brouwer, Brenner & Smeets, 2002; Smeets & Brenner, 1995). This could indicate that the movement time and the hand's path are planned separately on the basis of different information. A second interpretation is based on the fact that visual motion might be affecting the perceived position of the moving object (Brenner & Smeets, 2000; Linares, Lopez-Moliner & Johnston, 2007; Whitney, 2002; Whitney & Cavanagh, 2000; Whitney & Murakami, 1998). According to this view, motion signals would mediate the MAE-induced misalignment between the hand and the target position. Given that MAE influence was restricted to the condition with opposite directions, the lack of differences in the hand velocity profile between the condition with congruent directions and the no-adaptation condition is consistent with this second account.

8.1.1.2 Motion adaptation in static vs. moving objects

Under the premise that MAE signals are integrated to update position coding of a moving object (Linares et al., 2007), Experiments 2 and 3 investigated the influence of MAE in interceptive movements. As expected, MAE-opposite direction to the object produced higher shifts between the hand endpoint position and the target location. The MAE-induced bias also increased as a function of the length of the adaptation period, which is consistent with previous studies that propose a dynamic system that integrates motion information over time (Nishida & Johnston, 1999). Assuming that MAE signals would only be encoded when estimating the position of an object that changes over time, we examined the MAE influence on the reaching behavior towards stationary objects. The data showed no effect of motion adaptation in the hand trajectories directed to stationary objects. Given that stationary objects in the presence of background visual motion are indeed perceived shifted in the direction of motion (De Valois & De Valois, 1991; Durant & Johnston, 2004; Whitney & Cavanagh, 2000), these results suggest that global background motion signals and motion adaptation may be processed differently when estimating the position of stationary objects. In all the background motion-based phenomena, the perceived position of an static object is shifted in the direction of its apparent motion, which suggests that the locations assigned to stimuli interact with their motion signals. In motion adaptation paradigms, the shift occurs in the direction the shift occurs in the direction opposite to that of the adaptation period. Apparently, MAE direction is able to alter dynamic position coding over time, based on the continuous updating of position information. In this sense, motion extrapolation hypothesis as a compensating mechanism for neural delays would imply that only target-related motion cues are integrated (Nijhawan, 1994; Snowden, 1998). According to this view, our visual system makes use of the motion signals to extrapolate the position of the moving object, thus shifting its apparent position in the direction of motion. Extrapolation would not occur, however, for flashed or stationary objects. The lack of MAE-induced misalignment in stationary objects could thus reflect a more complex neural mechanism that contributes to the motion-based position displacement. Overall, the issue, then, might not be the dissociation between the coding of stationary and moving stimuli, but how the configuration of both motion and motion aftereffects influences the localization of both moving and stationary stimuli.

8.1.2 THE NEURAL BASIS OF MOTION-INDUCED SHIFTS IN GOAL-DIRECTED REACHING

There is not consensus about the underlying cause of the influence of visual motion on the trajectory and endpoint of goal-directed reaching movements. Previous research has postulated backprojections from area MT to V1 as the neural mechanism that implements motion-induced shifts (McGraw et al., 2004; Nishida & Johnston, 1999; Whitney & Cavanagh, 2000). These re-entrant circuits have been proposed to support visual awareness of motion (Pascual-Leone & Walsh, 2001; Silvanto, Cowey, Lavie & Walsh, 2005).

In Chapter 4, we addressed the possibility that early motion processing in MT has a direct access to displace position coding in V1 well before feedback connections take place. Based on the short latencies of the influence of background motion in visually-guided reaching, we propose feedforward circuits independent from V1 input to MT as the physiological explanation of the hand deviation in the direction of motion signals. To that end, we used the well-known visuomotor paradigm introduced by Whitney, Westwood, et al. (2003), in which participants hit the position of a flashed stationary object in the presence of distant motion signals that could reverse their direction before or after target onset. Using ERPs, we recorded visual-evoked potentials to examine the temporal dynamics of the visuomotor response. What this experiment showed was a change in the hand trajectory depending on the direction of the background motion. In particular, the condition where the target appeared at the same exact moment of the motion reversal yielded the strongest deviation in the reaching path, consistently with previous reports (Whitney & Cavanagh, 2000; Whitney, Westwood, et al., 2003), perhaps owing in part to an easier assimilation of the new motion direction following the reversal (Tse, Whitney, Anstis & Cavanagh, 2011). A further result reported in Chapter 4 is the close relationship between the magnitude of the motion-induced shift and the latency of the perceptual processes related to the shifted target. The fact that the reached object is not moving might led to think that the nature of the misperception could not be linked to temporal mechanisms, as occurs with moving objects (Mateeff & Hohnsbein, 1988; Murakami, 2001; Whitney & Murakami, 1998). However, running counter to this conclusion is the finding that participants with a higher shift in the hand trajectory also showed slower sensory processing of the target, with longer latencies of the VEPs concerned with object's perception. These results concur with the suggestive idea that perceptual timing is critical when encoding the position of an object (Durant & Johnston, 2004; Maij, Brenner & Smeets, 2009). It is possible that the delay in the perception of the object could be and adaptive and beneficial response that the visuomotor system employs to guide the reaching, by maximizing the motion-processing time to refine position coding (Whitney et al., 2010). We suggest that this neural delay of the perceptual processes and the posterior hand shift may support the hypothesis of an 'indirect' mechanism to explain motion's influence on reaching. According to this view, the shifted representation of the target, reflected in the delayed latency of the neural correlates, would subsequently modulate the visuomotor response (Brenner & Smeets, 1997; Whitney, Westwood, et al., 2003). As we shall see in the next section, motion-related area MT appears to play an important role in this modulation (Maus et al., 2013; Schenk et al., 2005).

8.1.2.1 Motion processing through non-primary visual pathways

One of the principal results observed in Chapter 4 and the one leading to hypothesize about the neural mechanism that subserves motion's effect on reaching is the time-course of the neural activity in extrastriate cortex. We found very early activity near area MT responsible for the mislocalization of the object. CSD estimates in temporoccipital regions revealed patterns of activity that correlated with the length of the abovementioned sensory slowing down. Participants with higher MT activity showed longer VEPs delays. Interestingly, the source localization analysis indicated that peak activity occurred around 60 ms after target onset, which points to a very early motion processing as the cause of the deviation of the hand. The strong feedback projections from MT to V1 (Zeki & Blakemore, 1990), where retinotopic localization is very precise (Daniel & Whitteridge, 1961; De Valois & De Valois, 1991), make plausible that the motion-induced shift reflects a re-entrant mechanism by which motion information influences position (Nishida & Johnston, 1999; Zeki & Blakemore, 1990). In accordance with this account, feedback inputs to V1 would constantly update the target location depending on visual motion cues previously coded in MT (Whitney, Goltz, et al., 2003). Feedforward projections from V1 can transmit information to extrastriate areas very quickly (Bullier, Hupe, James & Girard, 1996; Nowak & Bullier, 1997). Nonetheless, research by Semir Zeki and collaborators has suggested that certain types of visual information may reach MT before it even reaches V1 (ffytche, Guy & Zeki, 1995). In the same line, physiological evidence reflects that motion's influence may act at as early stages of the visual system as the retinal level (Berry et al., 1999), which points to the possibility that visual motion may be processed before the encoding of object position. It is therefore conceivable that the short latency of MT area in our study, which precedes feedback inputs, apparently rules out the possibility that the shift-related activity comes from MT backprojections feedback inputs to V1. In this context, the role of non-primary visual pathways to MT may be of paramount importance to describe the mechanisms that sustain reaching behavior owing to the exposure of background motion.

Of considerable neuropsychological interest to address the role of thalamic visual conduits have been the many reports that patients with cortical (V1-lesioned) blindness in one visual hemifield ('hemianopia') can discriminate and use motion information to guide their actions within the blind field (Barbur et al., 1993; Weiskrantz, 1986). The first of these studies showed this by asking three incredulous patients to move their eyes toward a light that they insisted they could not see (Poppel, Held & Frost, 1973). Their eye movements were inaccurate, but nonetheless bore a statistically significant relationship to the location of the light, and went on to show much higher spatial accuracy when were instructed to make pointing movements with his arm. Confirmatory support was soon provided by Perenin and Jeannerod (1975), who reported evidence for accurate pointing within the blind fields of six hemianopic patients. In any case, it is clear that considerable visual control of the direction and amplitude of both eye and arm movements can be developed in cortically blind patients. If one accepts the fact that patients with cortical blindness can indeed move their eyes and hands accurately towards visual stimuli that they cannot ‘see’, the question remains as to what pathways underlie this residual ability. Weiskrantz, Warrington, Sanders, and Marshall (1974) and others have attributed the residual visuomotor ability in their cortically blind patients to the 10 per cent or so of the optic fibers that terminate in the superior colliculus (Perry & Cowey, 1984). Direct pathways from the thalamus to the MT have been extensively investigated using retrograde tracers injected into the extrastriate cortex, revealing that some of the retrogradely labeled pulvinar neurons, and all the labeled LGN neurons, are candidates for relaying motion information from either the SC or the retina to the MT (Sincich et al., 2004). It is challenging to speculate that a putative pathway through LGN relays motion information to MT. Establishing visual pathways through the SC is even more difficult, because two synapses must act as relays. However, one study found that the laminar pattern of disynaptic labeling in the SC following extrastriate injections in area MT was more consistent with the pulvinar route than with the LGN route, suggesting that the colliculopulvinar pathway is more promi- nent than the colliculogeniculate pathway (Lyon, Nassi & Callaway, 2010). Noteworthy, there is fragmentary evidence to support the idea that the superior colliculus can play a crucial role in the control of reaching. For example, a study by Solomon, Pasik, and Pasik (1981) showed directly that the superior colliculus was involved in mediating reaching towards a visual target following V1 lesions in monkeys: although the animals retained this ability after V1 lesions alone, they then lost it after an additional lesion of the SC. And yet more recent evidence for a role of the colliculus in visually guided reaching comes from a study which describes cells in the deep collicular layers in monkeys that fire in close association with such movements (Werner, 1993).

There is still much controversy over the exact form of the computations carried out in area MT, and some research suggests that feature motion is in fact already available at lower levels of the visual system such as V1 (Wilson, Ferrera & Yo, 1992). It is clear from our results, however, that we do not consider motion-induced shifts to be well characterized as feedback connections from MT to V1. We believe that, bypassing V1, the visual system is able to complete a substantial deal of motion processing in less than

100 ms, enough to trigger shift-related responses in extrastriate and striate cortex. Taken together, we think we provide convincing evidence to suggest that extrageniculate pathways may be able to provide the necessary visual information about background motion, without the mediation of V1, to compensate and modulate actions directed to objects.

8.2 Combining vision and proprioception in object's interception

A pervasive feature of manual control is the stark stereotypy of eye-hand coordination: the eye and the hand appear tethered in a highly adaptive fashion to optimize task success. The differential role of visual and proprioceptive inputs has been found to modulate the judgment of hand location (Hay et al., 1965; Mon-Williams et al., 1997; Welch & Warren, 1986). Also, the integration of both inputs diverges as a function of the task constraints (van Beers et al., 2002). For example, the precision of visual and proprioceptive localization in a horizontal plane is non-uniform, with vision being more precise in lateral (orthogonal to the obsever) than in sagittal (radial direction relative to the observer); and proprioception being more precise in depth than in azimuth (van Beers, Sittig & van der Gon, 1998). Based on these observations, we explored in Chapter 5 the alignment and weighting of visual and proprioceptive information when reaching objects. To achieve that goal, we investigated the contribution of visual and proprioceptive information in a task in which subjects had to indicate with a hand movement the predicted point of collision between two visual objects. We used a novel interception paradigm that allowed to separate the spatial component of the reach (endpoint position) from the temporal component of the reach (endpoint timing). The overarching structure of the interceptive task required participants to view the initial trajectory of two dots moving (Bootsma & Oudejans, 1993), in either the sagittal or lateral plane, towards each other on a collision course and predict the time at which the dots would contact each other. Participants were asked to match both the timing of the dots' collision and the spatial location of the collision.

We observed less temporal bias and variability when the objects moved along the subject's sagittal axis than when they moved perpendicular to it. When participants were asked to judge collision time without making interceptive movements towards the collision point, they significantly reduced their accuracy in the sagittal direction. In addition, temporal accuracy and movement characteristics were not affected by the presence or the absence of visual feedback of the hand. These results support that, when multiple sources of sensory information are encoded to minimize the uncertainty in the final estimate, the theoretically optimal way to combine the information is to weight each source by its precision, which is the inverse of its variance (Ghahramani & Wolpert, 1997; Jacobs, 1999; van Beers et al., 1999). Reducing the visual information will lead to less precise visual localization and therefore to a reduction of the visual weight. Our study expands such considerations to the guidance of reaching during a coincidence-timing task, and uncover the privileged use of proprioceptive information to guide the endpoint timing component in depth.

8.3 Visuomotor adaptation intercepting moving objects

One question that stands out here is whether vision prevails over the proprioceptive inputs of the hand position when reaching an object during a process of visuomotor adaptation. One possibility is that perhaps reaching with a distorted visual feedback of the hand induced proprioception to be readapted such that the hand is felt at the same misaligned location at which is seen. As it was outlined in the introduction section (Chapter 1), several studies have demonstrated that the boundaries of reachable space can be modified by influencing where one judges one's own hand to be (Holmes & Spence, 2004). A compelling example of the displacement in the perceived position of the hand, the rubber hand illusion, illustrates that people combines the seen and felt positions of the hand to judge where their hand is in space. The research provided in Chapter 6 provides evidence that shifting visual feedback about the position of the hand will also displace judgments of reachability when intercepting moving objects.

8.3.1 HAND VISUAL FEEDBACK DETERMINES REACHABLE OBJECTS

Our experimental paradigm instructed subjects to intercept a moving virtual cube when they judged the object to be reachable (de Grave et al., 2011; Delevoye-Turrell, Vienne & Coello, 2011; Fischer, 2003). Otherwise they should inhibit a motor response. Visual feedback of the subject's hand position was varied in two directions resulting in a displacement of the hand closer to the body or further away from the body. The results revealed that targets at the same distance were more frequently judged to be reachable when hand position was shifted away from the body. The effects observed in the reachability estimation were independent of the movement direction of the object, either approaching or departing from the observer. On the basis of these results, reachability judgments about the surrounding space are based on the seen hand position.

Our study complements previous findings that changing the visual location of the hand affects (1) the spatial accuracy of reaching movement (Sarlegna & Blouin, 2010) and (2) reachability judgments (Bourgeois & Coello, 2012; de Grave et al., 2011). De Grave's study reported no correlation between the visuomotor adaptation and the change in the reachability judgments. Our view is that the visuomotor adaptation reported by introducing shifted endpoint positions when the hand movements are performed (Bourgeois & Coello, 2012), implies different sensorimotor transformations than an all-time feedback displacement. More general, the finding of the influence of visual feedack in judgments of reachability of moving objects when there is a intended action to hit them clearly points to a visual dominance in hand location in the context of this interceptive task. Based on previous studies (Brouwer, Middelburg, Smeets & Brenner, 2003), however, we argue that the judgment of when a moving object becomes reachable cannot be exclusively determined by optical variables like tau-gap, but requires from a reachability estimation. This assumption is supported by many studies that reported the velocity of the hand movement to be dependent on the target's speed (Brouwer et al., 2003; Lee, Georgopoulos, Clark, Craig & Port, 2001), leading to an online adjustment during the execution of the movement. As a result, the online control cannot be exclusively modulated by tau-coupling, but also the pairment between target and hand velocities might play an essential role (Brouwer et al., 2000).

Some further considerations regarding the similarities of the reachability judgments for approaching and departing objects need to be discussed. The study tackles this issue and reveals a lack of directional effect. This result seems to contradict previous studies that claimed the observation of larger reachability estimates when objects moved toward the participant, compared to conditions when objects moved away from the participant (Fischer, 2000). Noteworthy, we believe this difference may be related to the way the data was collected and analyzed. A directional effect might be interpreted to imply the presence of a predictive planning of the movement. Clearly, the implementation of a motor plan takes time (Rosenbaum, 1980; Rosenbaum, Hindorff & Munro, 1987), as does the execution of the movement itself (Fitts, 1954). Therefore, it makes sense that estimates of reachability devoted to intercept dynamic objects take into consideration the time that elapses during motor implementation and movement completion for reaches toward the object, as well as changes in object position during this time.

8.3.2 HAND VISUAL FEEDBACK CONTROLS HOW TO MOVE TO REACHABLE OBJECTS

The present study demonstrated how we fully adapt our actions to a visual feedback when doing reachability judgements. The feedback effect on the reachability estimations was correlated with the spatial error committed at the interception point. The distance in depth between our final hand position and the object (spatial error) does not seem to be affected by the movement direction, although the marginal effect points to higher errors in departing objects. We think the first result is the one that contradicts Fischer's study, since we did not observed that the approaching objects were judged reachable at further distances. Our view is that participants took into account their movement time in order to intercept the object in a common 'interception zone' for both departing and approaching objects. We added a specific data analysis to test if participants took into account their movement time when judging reachability. The analysis to test this hypothesis consisted on the measurement of the target position at the onset and offset of the hand movement in reachable trials (the ones where the subject moved). If participants included the movement time in their judgment, we should find differences between approaching and departing objects at the beginning of the movement but not at the end, showing that targets are intercepted in a common zone independently of the direction of the movement. The fact that approaching targets were judged reachable further only at the onset of the movement, but they were at similar distances when the movement ended, supports the assumption that participants considered a common area to intercept the targets irrespective of their direction.

Given the above, we believe these results demonstrate how perceived reachable space was larger when the location of the hand was shifted, and how one consider his/her planned hand movement toward a moving object when estimating their potential reachability.

8.4 The anatomical basis of an accurate online motor control

A reach must frequently be modified in some way either just before or during execution, as the reached for object moves or there are signs that it might be inappropriate to touch. Therefore, reaching must be a flexible form of motor behavior that requires planning and on-line control in order to modify or suppress the original motor plan or the ongoing hand movement, when needed. Online corrections are a crucial part of our ability to interact with the world and unraveling the neural substrates of these corrections adds to our understanding of how we reach objects in dynamic surroundings. As we have seen before, numerous studies implicate the PPC in the on-line control of a movement after its initiation. Next, in monkeys cortico-cortical connections relay visual information from PPC to motor and premotor areas, and there exist both feedforward and feedback connections in the parieto-frontal system (Averbeck, Crowe, Chafee & Georgopoulos, 2009; Caminiti et al., 1996). In chapter 7, we combined neuroimaging tools and kinematic recording and analysis in order to identify the neurophysiological and anatomical underpinnings of this parietofrontal circuit underlying the inter-individual variation of deficits in online motor control.

8.4.1 rTMS-INDUCED DEFICITS OF ONLINE MOTOR CONTROL

In humans, the cortical network involved in on-line control of hand movements has been studied using both Transcranial Magnetic Stimulation (TMS) and Functional Magnetic Resonance Imaging (fMRI). Neurophysiological and neuroimaging studies have depicted a network that proposed the medial intraparietal sulcus (mIPS), the PMd and the cerebellum to sustain the visuomotor transformations for the online control of reaching (Colebatch et al., 1991; Desmurget et al., 2001; Kertzman et al., 1997). When parietal mIPS activity is temporarily disrupted through TMS delivered at the onset of hand movement, normal subjects are able to make direct reaches, but fail to make on-line corrections when the target moves in space (Della-Maggiore, Malfait, Ostry & Paus, 2004; Desmurget et al., 1999). Within this framework, our results nicely fit previous studies and expand the knowledge of the effects after interfering mIPS function, as we developed a novel offline intervention through the application of a prolonged train of inhibitory rTMS. After the rTMS protocol over the left mIPS, participants showed a clear reduction of their ability to voluntarily correct reaching movements in response to a target displacement, which was reverted to baseline values 60 minutes after the stimulation. Repeated stimulation has been widely adopted as a tool to purposively modulate the activity in local cortical areas in order to establish their functional roles (Rollnik et al., 2004; Siebner & Rothwell, 2003). It can exert effects on the efficiency of the synaptic transmission (Muellbacher, Ziemann, Boroojerdi & Hallett, 2000), either enhancing (long-term potentiation, LTP) or decreasing (long-term depression, LTD) excitability of cortical circuits (Pascual-Leone, Valls-Sole, Wassermann & Hallett, 1994). However, the conditioning effects of the cortical plasticity promoted by the rTMS are not limited to the targeted region but also modulate excitability of remote interconnected areas (Gerschlager, Siebner & Rothwell, 2001; Siebner et al., 2000; Wassermann, Wedegaertner, Ziemann, George & Chen, 1998), providing a measure of connectivity between these regions (Fox, Halko, Eldaief & Pascual-Leone, 2012). Therefore, offline interference seems to rely on different neurophysiological mechanisms as online interference.

One view about movement correction is that the motor command signals are updated continuously based on sensory feedback of the target and limb state (Day & Lyon, 2000; Desmurget et al., 1999; Goodale et al., 1986; Gritsenko, Yakovenko & Kalaska, 2009; Pelisson, Prablanc, Goodale & Jeannerod, 1986; Prablanc & Martin, 1992; Saunders & Knill, 2003). Apparently, mIPS might be crucial in the dynamic computation of the distance between the target and the hand during the execution of the reach, called the motor error. Since inactivation or lesioning of parietal cortex can result in impaired estimates of limb position (Wolpert, Goodbody & Husain, 1998), it has been speculated that the defective online correction is a consequence of an erroneous computation of the motor error.

8.4.1.1 Hemispheric specificity, saccadic deficits and kinematics

The rTMS effect on the ability to update an ongoing movement was more prominent for the hand contralateral to the stimulated hemisphere. The majority of functional neuroimaging studies have reported bilateral activation in response to pointing and reaching movements of either arm or hand, but that the modulation is stronger for contralateral movements (Astafiev et al., 2003; Beurze, de Lange, Toni & Medendorp, 2007; Connolly, Andersen & Goodale, 2003; Medendorp, Goltz, Vilis & Crawford, 2003; Merriam, Genovese & Colby, 2003; Sereno, Pitzalis & Martinez, 2001).

However, TMS in humans has also revealed lateralized deficits in mIPS and online control for reaching (Desmurget et al., 1999; van Donkelaar & Adams, 2005; Vesia, Prime, Yan, Sergio & Crawford, 2010). Recent studies suggest that there appears to be a rostro-caudal gradient of upper-limb specificity within parietal cortex: Both fMRI and lesion data are consistent with the notion that there is a greater lateralization for contralateral hand movements in more anterior–lateral than medial–posterior foci (Blangero, Menz, McNamara & Binkofski, 2009). Consistent with this, our TMS effects support a certain degree of lateralization of the mIPS, as the rTMS effect is greater in the contralateral hand but also significant in the ipsilateral limb.

The spatial variability in the hand endpoint position was analyzed to discard the possibility that saccadic deficits explain the results, rather than hand control deficits. The effect of rTMS is present for both the right and left hand, but even if the effect is smaller for the left hand, the possibility cannot be ruled out as saccadic control is partially lateralized in eye-hand coordinated movements. The analysis demonstrated that, after rTMS, a reach towards a target in one of the two sides was not less accurate than that at the centre of the screen. Therefore, the reduction of online corrections was not due to an alteration of saccadic response. Importantly, we controlled the possibility that the induction of the virtual lesion implied an impairment of the visual processing that encoded the target location. The lack of differences in the FC condition after rTMS led us to conclude that the target location was processed properly. Hence, the increase of the error rate in later stages of sensorimotor integration should response to the inhibition of the mIPS (Davare, Zenon, Pourtois, Desmurget & Olivier, 2012). Although endpoint accuracy in reaching strongly depends on online motor control (Desmurget et al., 2005; Todorov & Jordan, 2002), the functional integrity of the mIPS would only become crucial with high spatial incongruencies between the target and hand locations during the movement (displaced trials). Smaller conflicts would not require a decisive contribution. These results also dovetail nicely with previous studies suggesting that spatial location of a target might be coded at more posterior occipitoparietal areas (Ciavarro et al., 2013; Filimon, Nelson, Huang & Sereno, 2009). A detailed analysis of movement characteristics eliminated the possibility of an overall alteration of the motor command, as the structure of the movement was similar before and after the application of rTMS. In conclusion, we demonstrated that an enduring virtual lesion of the mIPS interferes with the on-line motor control of a reaching movement for the contralateral and less so for the ipsilateral hand. The mIPS thus is a key-player within the parieto-frontal network involved in encoding new sensorimotor information and updating a motor command.

8.4.2 PARIETOFRONTAL STRUCTURAL INTEGRITY PREDICTS RTMS EFFECTS

In light of the transient impairment of the online corrections induced by the administration of an inhibitory rTMS protocol, which was controlled for the abovementioned confoundings, we explored the source of the inter-individual variability in the degree of affectation after the mIPS disruption. There are important individual differences in how healthy adults perform goal-directed reaching movements that require an on-line control to adjust their performance in case of unexpected visual perturbations (Boy et al., 2010; Reichenbach, Bresciani, Peer, Bülthoff & Thielscher, 2008). Similarly, the rTMS-induced impairment of the online motor control by interfering mIPS function also varied considerably over subjects (Desmurget et al., 1999). The understanding of the nature and extent of inter-subject variation is critical for understanding the neural basis of correction processes in normal and abnormal populations.

Seminal studies revealed activity in the ventral aspect of the mIPS as well as the rostral part of PMd when updating a pre-specified motor instruction, suggesting a cortico-cortical parieto-frontal pathway between these areas (Johnson & Ferraina, 1996; Wise, Boussaoud, Johnson & Caminiti, 1997). A homologue circuit was identified in humans, emphasizing the concomitant contribution of dorsal premotor areas and the mIPS (Chouinard, Van Der Werf, Leonard & Paus, 2003) and stating the importance of PMd in action reprogramming (Hartwigsen et al., 2012). In general, the PMd system is held to be required when a new motor plan is initiated or its goal changed in a discrete/intermittent fashion (Archambault, Caminiti & Battaglia-Mayer, 2009). Therefore, the modulation of the excitability of the mIPS induced by the application of the rTMS might affect its inputs into the rostral PMd (Caminiti et al., 1996), affecting its capacity to reprogram the movement towards the new location of the target. Specially, the SLF has been postulated as an important neural tract within the premotor-parietal network that connects the IPS and the PMd (Boorman et al., 2007; Thiebaut de Schotten, Dell'Acqua, Valabregue & Catani, 2012). The DTI analysis unveiled that subjects with stronger contralateral behavioral consequences after rTMS application (that is, a higher reduction of online corrections with the right hand) exhibited higher white matter integrity in the parietofrontal tracts presumed to mediate the dynamic computation of the motor error from the mIPS to the PMd. A whole-brain analysis of the FA showed that participants that exhibited higher white matter integrity in the contralateral SLF II, cerebellum and the pons suffered less rTMS-induced behavioral impact in the motor performance. If our reasoning is correct, then our study shows that the structural alignment and cohesion of the white matter may be used as a solid predictor to characterize the extent of motor impairments. Therefore, one might assume that the operational principles that govern a TMS-induced breakdown of online corrections are based on strength of white matter connectivity between the parietal and the frontal lobe. Specifically, the sign of the correlation suggest that the behavioral repercussion of the TMS was weaker when tracts presented higher cohesion. The microstructural features of the white matter in cerebellum and ipsilateral pons also explained the differential impact of TMS in online motor control. These results nicely dovetail with PET studies in which the sharp contrast between brain activity in perturbed and unperturbed visuomotor responses revealed a network that included the contralateral PPC, the part of the motor cortex related to the upper arm and the cerebellum (Desmurget et al., 2001). The role of the cerebellum in online motor control has been widely highlighted, as crucial for building-up a motor error signal and a forward model of the limb response (Liu et al., 1999; Miall, Weir, Wolpert & Stein, 1993). In its turn, the cerebellum receives a large input from fibres descending from the motor cortex, via the pons, and it is thought that these represent the efferent copy of outgoing motor commands (Wolpert & Miall, 1996).

A final interesting question concerns to the physiological meaning of these findings. What we know from previous studies is that rTMS interventions, as the one used in this work, cause local changes in excitability of the target area that have a compound of cognitive consequences associated to the stimulated structure and its networked regions (Fox, Ingham et al. 1997; Fox, Halko et al. 2012). Therefore, it seems reasonable that the structural properties of the white matter bundles linking these regions might have a direct repercussion in these processes. Specifically, FA values give insight about a variety of qualitative physiological characteristics of these fibers, such as directionality and integrity (Stinear, Barber et al. 2007; Klöppel, Bäumer et al. 2008; Strangman, O'Neil-Pirozzi et al. 2012). This is based on diffusion anisotropy in WM, which is likely influenced by a number of factors, including the degree of myelination, the density, diameter distribution, and orientational coherence of axons (Beaulieu, 2002). Therefore, the physiological mechanisms for the observed TMS effect–FA correlation require substantial further investigation. The correlation may be due to the influence of myelin thickness on both water self-diffusion (Beaulieu, 2002) and nerve conduction velocity (Jack et al., 1983). The myelin hypothesis would predict a negative correlation between TMS effect and FA because increased myelin thickness would cause increased FA and faster nerve conduction velocity, which would in turn result in faster action reprogramming. However, more evidence will be required to make strong claims about the underlying physiological mechanism that links the motor impairment caused by the rTMS and the anatomical correlates of the 'reaching' circuit.

8.5 Limitations of the present dissertation

Certain inherent limitations can be observed in the set of studies presented in this thesis. All the studies were tested on right-handed participants. Investigating a left-dominant population would be required to verify whether the left-right asymmetry effects are genuinely due to differences in the relative proprioceptive/visual feedback processing capabilities of the two systems or are just incidental due to one hand having been used more extensively in the subject's lifetime and hence operating with better internal models and reduced motor noise.

Concerning the experiments described in Chapter 3, an important limitation was the lack of monitoring of the eye movements, as a robust control to avoid unintentional saccades during the manual pursuit of the peripheral target that moved for 2.5 s. In Chapter 4, the evidence of causality only involves the activity in area MT and the timing of N1 component, but there is not a causal inference on behavioral data. Moreover, given the limited spatial resolution of ERPs, it is doubtfully possible to distinguish activity within adjacent areas in the extrastriate cortex. The addition of a neuroimaging technique might provide strong insights about the exact neural locus of the motion's effect on reaching and about the contribution of thalamic pathways.

In Chapter 5, the subjects were instructed to focus only strictly on the spatio-temporal accuracy and no emphasis was laid on performance speed. Constraining the task accuracy and/or speed of performance may validate the assumptions about the increased weight of proprioception as the primary sensory input when intercepting targets under poor visual conditions.

While the visual demand in the reachability study (Chapter 6) was manipulated using a shifted visual feedback of the hand position, the proprioception was not manipulated in this study. Either using differential demands on proprioception or working with sections of the population with proprioceptive disabilities would produce interesting behaviors, which would help us to understand and develop the role of the feedback component.

Finally, the design of the TMS-DTI study might benefit from including a control stimulation site or control stimulation protocol, or both. These controls are not performed but often regarded essential in TMS intervention studies. Also, the exclusive use of the double-step paradigm somewhat limited the generalization of the findings. As explained in Chapter 1, there are many ways in which spatial errors can be artificially introduced into an ongoing trajectory in order to study the motor system’s corrective response, for instance, by applying a force to the moving arm (Wolpert, Ghahramani & Jordan, 1995), or by using optically-displacing prisms to perturb vision of the target, so that the initial movement is inaccurate (Jakobson & Goodale, 1989). It is therefore important to acknowledge the influence that the choice of paradigm may have had upon the results and conclusions of the present experiments.

8.6 Future directions

This dissertation addresses a number of interesting questions on the nature of planning, control and execution of reaching movements. However, it has also opened up a wide range of equally interesting questions yet to be answered and several lines of thoughts worth exploring. Some of these may help prove/disprove the empirical findings, while others might clarify some key assumptions and yet others might help extending the observations and to be applied to a more general class of movements. Clinical studies could be benefited from the experiments exposed in Chapter 4, as the experimental setup might allow the identification of the neural markers associated with visual neurophysiological disorders. To that end, the join of behavioral and neuroimaging disciplines to compare brain activity while processing visual motion between 'cortically blind' patients and healthy participants could be an interesting scientific framework. This method may be used to identify specific location and timing of abnormal visual-evoked potentials.

The multimodal approach of Chapter 7 raises some questions. For instance, a new procedure might explore whether the effect of a virtual lesion in the mIPS could affect other movements, such as grasping, and which parietofrontal tracts would govern the impact of the rTMS on the grip aperture. That being said, although the use of a single reaching movement is restricting in one sense, this limitation of the present work should not be overstated. Indeed, it is arguably a great strength of the present thesis that such a simple task design has served, with a range of minor variations, to illuminate such a range of issues in online control, and the use of a consistent task and analysis strategy has allowed for maximum comparability of the findings across studies.

In taking the research of this dissertation forward, it will be important to consider more specific aspects of task design that might have important implications for experimental outcomes. Two key elements to be considered in future application of the reaching task are the number of potential target locations, and the clear difference in movement characteristics when using the two hands.

9

CONCLUSIONS

The research of this thesis provides critical insights to the literature about the control that the visuomotor system exerts on manual aiming movements. It is a wide-ranging work of a number of aspects that compose reaching behavior. Amongst other things, this thesis presents robust findings that are evident in small sample sizes, with noticeable individual variability in performance. There are of course, theoretical and methodological limitations within the thesis, and issues that have not been addressed. Although there is still a long road ahead, the conclusions drawn from this body of work significantly advance our understanding of how our brain encodes spatial and temporal cues to direct accurate actions to objects.

Based on the aims outlined in the Chapter 2, the conclusions of the present dissertation can be formulated as follows:

- Motion adaptation signals, such as MAE, remarkably affected the trajectory and accuracy of goal-directed actions towards misperceived objects. The modulation of this effect occurs eminently in moving objects, where the position dynamically changes over time and needs to be updated.
- The shift in the perceived position of a stationary object in the presence of background motion signals correlates with slower perceptual correlates of the object, suggesting a temporal component to explain at least part of the nature of the spatial offset. The short latency of the neural activity in area MT that causally generates the delay in the perceptual timing challenge the feedback account as the neural substrate in charge of motion effects on reaching. Instead, non-primary visual pathways might integrate a substantial amount of motion cues to induce an early mislocalization of the object.
- Our temporal accuracy when intercepting moving objects with impoverished visual information makes a preferential use of precise proprioceptive signals, supporting the weighting model of visual and proprioceptive integration within the spatio-temporal framework of interceptive actions.
- An unconscious visuomotor adaptation to a displaced visual feedback of the hand position altered the reachability estimations to decide the ‘when and where’ of a interceptive action towards a moving object. The hand trajectories

performed to hit reachable objects fully adapted to the feedback displacement, denoting the dominance of visual inputs of hand location.

- A transient impairment, induced by rTMS, of the medial intraparietal sulcus disturbed the neural processes that subserve online motor corrections in reaching behavior. The inter-individual differences of this induced visuomotor deficit were explained by the strength of the microstructural properties in the parietofrontal tracts that connect the medial intraparietal sulcus with the motor cortex.

To revisit the example of the reaching movement to turn a light off: You localize the switch precisely by processing and integrating the motion signals that arise from your eye, head and body movements, and the inherent motion that may come from the scene. You then weight the visual input of the target and hand location depending on their reliability to guide your limb towards the switch. How the movement is successfully accomplished depends on the integrity and functionality of the parietofrontal 'reaching' circuit, that drives the continuous computation of the hand-switch distance.

10

SPANISH SUMMARY

10.1 Introducción

Si queremos realizar un movimiento como el de, por ejemplo, apagar una luz, en primer lugar tendremos que localizar visualmente el interruptor. Para estimar la posición del interruptor, nuestro sistema visual tiene que integrar diferentes fuentes de información sensorial, como la ubicación del objeto en la retina, la dirección de la mirada respecto a la cabeza y, si nos estamos moviendo, las señales de movimiento de fondo presentes en la escena. Si el cerebro utiliza o ignora las señales de movimiento cuando localiza un objeto, y cómo afectan a las acciones dirigidas a este objeto, son cuestiones que siguen siendo un tema de debate. En segundo lugar, tenemos que saber dónde está nuestra mano. Aunque la visión por lo general predomina como principal fuente de información sensorial para determinar la ubicación de mano, nuestro cerebro requerirá de la estimación propioceptiva definida a partir de los ángulos de las articulaciones de las extremidades. Si el cerebro pondera o no de manera óptima los pesos de la posición ‘vista’ y ‘sentida’ de la mano con el fin de lograr una alta precisión espacial y temporal en los movimientos sigue siendo un tema sin resolver. Por último, tendremos que guiar la mano al interruptor. Durante la ejecución del movimiento, el cerebro podría calcular continuamente la diferencia entre la posición de la mano y la posición del objeto. Cambios inesperados tales como desplazamientos del objeto o de nuestro cuerpo pueden perturbar este cálculo. En tales situaciones, el sistema visomotor tiene la capacidad de supervisar la ejecución del movimiento y realizar una corrección voluntaria final para evitar una respuesta inexacta. Sin embargo, no está claro cuales son las bases neuronales dentro del sistema visomotor que explican las diferencias interindividuales en la capacidad de ajustar un movimiento en curso.

Esta tesis va a tratar de arrojar algo de luz sobre las cuestiones antes mencionadas, mediante la exposición del profundo reto al cual nuestro cerebro tiene que hacer frente a la hora de integrar la información temporal y espacial para lograr alcanzar los objetivos en tareas visomotoras.

10.1.1 CODIFICACIÓN VISUAL DE LA POSICIÓN DE UN OBJETO

Para actuar sobre un objeto hay que percibirlo. La primera etapa de la construcción de la percepción visual se desarrolla en la retina, y comienza lo que se conoce como el procesamiento visual de bajo nivel. Este primer cálculo neuronal incluye la extracción de ciertas características espaciales y temporales de la información visual (Deyoe & Van Essen, 1988; Wade & Wandell, 2002). En humanos, la selectividad espacio-temporal del procesamiento de la retina se ha demostrado utilizando estímulos de rejilla 'grating'. Rejillas en diferentes frecuencias espaciales (De Valois, Morgan & Snodderly, 1974) y temporales (Lee, Pokorny, Smith, Martin & Valberg, 1990) producen efectos de sensibilidad al contraste en las neuronas de la retina. Por lo tanto, la imagen neuronal del objeto que sale del ojo ya ha procesado una parte sustancial de las características espaciotemporales presentes. Es probable que las etapas posteriores del sistema visual sigan un proceso similar. Las proyecciones de la retina a la corteza visual primaria (V1) divergen paralelamente a diferentes centros visuales subcorticales, incluyendo -entre otros- el núcleo lateral geniculado (LGN), el colículo superior (SC) y el pulvinar (Kaas & Huerta, 1988). Las conexiones que proyectan directamente desde estos centros talámicos a zonas de la corteza visual extraestriada, sin pasar por V1, son de particular interés para estudiar el tiempo de procesamiento de la posición de un objeto (Leopold, 2012). Parece probable que las proyecciones extrageniculadas estén implicadas en la rápida adquisición de propiedades espaciales y temporales necesaria para localizar un objeto estático o en movimiento en el espacio. En qué grado el SC y el pulvinar llevan información acerca de la posición del objeto se abordó recientemente con el uso de herramientas de neuroimagen. Fischer y Whitney (2009) demostraron la existencia de una codificación topográfica precisa de estímulos visuales en el pulvinar, aunque menos precisa que en V1. Del mismo modo, la inhibición inducida de la corteza visual dio a conocer un papel del SC en la discriminación de las posiciones espaciales de estímulos visuales en la fóvea (Ro et al., 2004). Las áreas extraestriadas interconectadas con SC y pulvinar han mostrado latencias casi tan cortas como V1, lo que sugiere que no dependen exclusivamente de V1 (Maunsell, 1987; Nowak & Bullier, 1997). Particularmente, cuando V1 se inactiva, ciertas regiones extraestriadas dorsales como el área temporal media (MT), son capaces de responder a información visual (Payne et al., 1996). MT es un área sensible a movimiento situada en el cruce de los lóbulos occipital, parietal y temporal (Snowden et al., 1992; Watson et al., 1993). Las conexiones entrantes a MT también incluyen el LGN (Sincich et al., 2004), el SC y el pulvinar inferior (Standage & Benevento, 1983). Hay evidencias documentadas de la sensibilidad a la posición y al movimiento de los objetos en los pacientes con lesiones en V1 (Blythe et al., 1986; Blythe et al., 1987; Bridgeman & Staggs, 1982) tanto en percepción del movimiento (Barbur et al., 1993) como en movimiento manual (Perenin

& Jeannerod, 1975). Sin embargo, todavía hay mucha controversia sobre los cálculos espaciales y temporales realizados por este circuito directo a MT.

La organización del procesamiento visual cortical desde V1 consiste en un barrido de conexiones 'feedforward' en paralelo con conexiones 'feedback' que van en la dirección inversa (Felleman & Van Essen, 1991; Lamme & Roelfsema, 2000). Para cada conexión de 'feedforward', hay una conexión 'feedback' recíproca que transmite una rica cantidad de información a las áreas de las que recibe entrada, lo cual permite que el sistema visual construya una representación estable de la posición del objeto (Gilbert & Li, 2013). Estas conexiones incluyen información que proviene de diferentes fuentes de información sensorial: la ubicación del objeto en la retina (Bock, 1986), la posición y el movimiento del ojo (Deubel, Schneider & Bridgeman, 1996; Ross, Morrone & Burr, 1997) o las señales de movimiento cercanas (De Valois & De Valois, 1991; Fröhlich, 1929; Matin, Boff & Pola, 1976). Nuestro sistema visual integra todas estas fuentes de información sensorial para juzgar la posición relativa de los objetos en el campo visual. Sin embargo, muchos experimentos psicofísicos nos dicen que la localización visual no es tan sencilla, y que los errores sistemáticos ocurren con frecuencia. No está claro, sin embargo, si estos errores son mediados por procesos 'feedback' o 'feedforward', ya que se han realizado muy pocos estudios para validar esta cuestión.

10.1.1.1 Localizar un objeto estático: una cuestión espacial

La capacidad de determinar la ubicación espacial de un objeto estático permite alcanzarlo o agarrarlo de forma precisa. El proceso de localización, por lo general eficiente y preciso, puede sufrir una acumulación excesiva de señales espacio-temporales debido a ruido en el procesamiento neuronal (Barlow, 1958). En particular, una de esas señales es el movimiento visual. Un gran número de estudios han demostrado que el movimiento es una importante fuente de información para el sistema visual. Movimiento visual se produce constantemente a medida que movemos nuestros ojos y la cabeza, o los objetos se mueven en el mundo. El sistema visual, por lo tanto, se enfrenta a un serio desafío en el que debe registrar y discriminar lo que es el objeto de lo que es movimiento visual de fondo, con el fin de estimar la posición del objeto apropiadamente. De Valois & De Valois (1991) mostraron que el movimiento dentro de un 'grating' conduce a grandes errores de alineación: si el movimiento dentro del ‘grating’ estático es a la derecha, todo el ‘grating’ parece ser desplazado hacia la derecha, y viceversa (Ramachandran & Anstis, 1990). Del mismo modo, la prolongada visualización de una misma dirección de movimiento (adaptación), produce que un patrón estático presentado en esa misma ubicación se vea moverse en la dirección opuesta. Este fenómeno se llama ‘motion after-effect’ (MAE), y ha atraído la atención de muchos estudios que se remontan hasta Aristóteles (Mather, Verstraten & Anstis, 1998). Se ha creído que el MAE no se acompaña de cambios concomitantes en la posición y patrón espacial. Sin embargo, estudios más recientes han demostrado que el MAE puede causar desviación de la percepción de un patrón estático en la dirección del post-efecto (McGraw, Whitaker, Skillen & Chung, 2002; Nishida & Johnston, 1999; Snowden, 1998). Su sustrato fisiológico todavía está lejos de ser claro. Culham et al. (1999), usando fMRI, encontraron que el área MT no está activa durante el almacenamiento del MAE, pero se reactiva tras la presentación del patrón estático. Nishida y Johnston (1999) propusieron que el desplazamiento espacial inducido por el MAE podría reflejar conexiones ‘feedback’ de MT a V1. Estudios neurofisiológicos posteriores mostraron que la ilusión se redujo notablemente después de interrumpir la actividad en el área MT, pero no después de interrumpirla en V1. Estas evidencias sugieren fuertemente que el desplazamiento espacial es una consecuencia de fuertes interacciones entre MT y V1 .

En la ilusión inducida por el MAE, las señales de movimiento en una región del espacio influyeron en la posición de un objeto estático en la misma región. Sin embargo, ¿puede el movimiento de un objeto afectar a la posición de un objeto distinto? En teoría, el sistema visual puede extraer fácilmente y vincular la información sobre el movimiento de un objeto en particular y su ubicación, y esto podría determinar si el objeto se desplaza. Se sabe que cuando un objeto estático aparece brevemente cerca de otro estímulo en movimiento, el objeto aparece desplazado en la dirección del movimiento (Durant & Johnston , 2004; Whitney & Cavanagh, 2000). Tanto en este caso como en la ilusión del MAE, el desvío en la posición del objeto no puede ser debido a un mecanismo temporal, dado que el objeto está estático. Estos desajustes podrían ciertamente reflejar un mecanismo básico que subyace o contribuye a muchos de los fenómenos de desplazamiento de la posición. La cuestión, entonces, es si la configuración del movimiento en el campo visual influye en la localización de no sólo estímulos estáticos, sino también móviles.

10.1.1.2 Localizar un objeto en movimiento: una cuestión espacial y temporal

Se tarda del orden de 50-100 ms para que las neuronas de la corteza visual respondan a un estímulo (Schmolesky et al., 1998). Lo que vemos, entonces, no es el mundo tal como es ahora, sino como fue en el pasado cercano. En el caso de un objeto estático esta latencia no es importante, pero una consecuencia inmediata de estos retrasos es que los objetos en movimiento se perciben significativamente detrás en su trayectoria de movimiento. Por tanto, el sistema visual debe tener en cuenta el movimiento de un objeto en la asignación de su posición: ¿Percibimos la posición de un objeto en movimiento con un retraso debido a las latencias neuronales? ¿O hay un mecanismo cerebral que compensa las latencias de tal manera que percibimos la verdadera posición de un objeto en movimiento en tiempo real? La opinión predominante es que el éxito del comportamiento observado es debido a la compensación a los más altos niveles corticales motores (Jordan & Wolpert , 1995). De hecho, los desajustes posicionales descritos en la sección anterior están en la dirección correcta para contrarrestar la latencia visual (De Valois & De Valois, 1991). Esta cuestión ha sido objeto de intensos debates en el contexto de las ilusiones visuales, especialmente el efecto del flash-lag (FLE). Romi Nijhawan reportó que cuando un breve estímulo se presenta físicamente alineado con un objeto que se mueve de forma continua, el objeto en movimiento se percibe adelantado (Nijhawan, 1994). Ha habido mucho debate sobre si el FLE es un efecto de movimiento en la posición percibida o un retraso neuronal procesando el estímulo breve. Dos preguntas importantes con respecto a la localización de objetos permanecen sin respuesta: ¿Se extiende esta influencia del movimiento a las acciones dirigidas a los objetos mal localizados? ¿Y cuál sería la naturaleza de la influencia del movimiento en estas acciones en función de si el objeto se mueve o no? Me referiré a estas dos cuestiones en el capítulo 3 de la tesis.

10.1.2 CODIFICACIÓN ESPACIAL PARA ALCANZAR UN OBJETO

La codificación del espacio cuando se hace para dirigir movimientos variará de acuerdo con la acción realizada. Alcanzar el interruptor y apagar la luz, por ejemplo, es un acto complejo que exige la transformación sensoriomotora de diferentes efectores terminales como los dedos, las manos o los ojos. Estas transformaciones sensoriomotoras ocurren en el lóbulo parietal, el destino principal de las vías visuales dorsales. Una de las características más sorprendentes de muchas neuronas parietales fue que no se activan exclusivamente en respuesta a la estimulación visual, sino también con actividad motora

(Mountcastle, Lynch, Georgopoulos, Sakata & Acuña, 1975; Andersen, 1987). De acuerdo con este punto de vista, la evidencia recogida durante los últimos 20 años apoya la idea de que la codificación de la información visoespacial fue calculada en el PPC sólo cuando se requerían tales señales espaciales para actuar sobre un objeto (Goodale & Milner, 1992). El AIP, por ejemplo, tiene neuronas que indican el tamaño y la orientación de los objetos que pueden ser agarrados (Taira, Mina, Georgopoulos, Murata & Sakata, 1990), mientras que el MIP proporciona información visoespacial para alcanzar un objeto (Galletti, Fattori, Kutz & Battaglini, 1997). Hay al menos tres aspectos importantes para realizar bien estos movimientos: (1) la localización visual del objeto en el espacio y la codificación adecuada de dicha información para su uso en el sistema motor; (2) la localización visual de la mano antes y durante su movimiento a través del espacio; y (3) la coordinación de las respuestas de los ojos y de la mano para llevar la mano correctamente al objeto.

10.1.2.1 Computar la localización del objeto a alcanzar

La única estructura que puede detectar un objeto es la retina, y puede transmitir la ubicación de ese objeto sólo en su propio sistema de coordenadas. Sin embargo, la retina se encuentra dentro de una serie compleja de sistemas que se mueven: los ojos giran dentro de la órbita, y la cabeza gira sobre los hombros. Por lo tanto, la ubicación retiniana no proporciona suficiente información para calcular la posición del objeto (Shadmehr, 2005). Los primeros estudios sobre el PPC proponen que sus neuronas transforman la ubicación retiniana del objeto a coordenadas centradas en el cuerpo. En las secciones anteriores hemos confirmado que una de las principales fuentes de información visual que afecta la localización de objetos son las señales visuales de movimiento. Parece interesante examinar si el cómputo de la ubicación del objeto cuando se pretende alcanzarlo también se verá afectado por la codificación de señales de movimiento.

Estamos constantemente expuestos a situaciones en las que un objeto y el fondo se mueven juntos, o incluso un objeto que permanece estático mientras que el fondo se mueve. En ambos casos, nuestro sistema visomotor tendrá que discriminar y separar el movimiento de fondo de la información acerca de la posición del objeto con el fin de alcanzarlo con precisión. Varios estudios independientes han encontrado que, al alcanzar un objeto estático, el movimiento de fondo cercano puede alterar la trayectoria de la mano en la dirección de ese movimiento de fondo (Brenner & Smeets, 1997; Saijo, Murakami, Nishida & Gomi, 2005; Whitney, Westwood & Goodale, 2003). El tiempo que el movimiento de fondo necesita para comenzar a afectar a la trayectoria manual es de alrededor de 120-150 ms (Brenner & Smeets, 1997; Prablanc & Martin, 1992). Estos hallazgos apuntan a un vínculo estrecho entre el procesamiento de movimiento visual y el control motor. A día de hoy, no hay un consenso general acerca del mecanismo neuronal subyacente de la influencia de las señales visuales de movimiento en el patrón y la precisión de la acción manual. Hay varios mecanismos neurofisiológicamente plausibles que podrían servir para cambiar tanto la representación percibida de objetos como la trayectoria de la mano en la dirección del movimiento de fondo. Las neuronas en MT parecen desempeñar un papel en la percepción del movimiento visual (Maunsell & Newsome, 1987). Una de las hipótesis con más peso propone conexiones ‘feedback’ desde áreas sensibles a movimiento (MT) hacia la codificación de posición en V1 (De Valois & de Valois, 1991; Nishida & Johnston, 1999). Estudios de neuroimagen en humanos sugieren cambios en los campos receptivos de V1 y MT (Maus et al., 2013; Whitney, Goltz, et al., 2003). La disrupción del area MT con TMS ha mostrado que el efecto se reduce notablemente (McGraw, Walsh & Barrett, 2004 ; Whitney et al, 2007). Estos estudios muestran la contribución causal de MT para la localización perceptual y de acción de un objeto. Aunque todos estos estudios proporcionan una fuerte evidencia de una intervención de MT en la codificación de movimiento visual para la percepción y la acción, no resuelven cuestiones sobre el curso temporal de ese mecanismo. ¿Cuál es el sustrato anatómico por el que el movimiento de fondo afecta a nuestro control visomotor a una latencia de ~120 ms? Al parecer, las conexiones ‘feedback’ de MT a V1 necesitarían más tiempo para modular la respuesta de la mano (Nowak & Bullier, 1997). Una posible explicación alternativa es que MT pueda ser activado por las proyecciones que recibe desde el SC o el pulvinar, más rápidamente que la conexión desde V1. Hasta el momento, el papel de las conexiones extrageniculadas del área MT no está claro. Me referiré a esta controversia en el capítulo 4 de esta tesis.

10.1.2.2 Computar la localización de la mano

Las personas que no tienen acceso a la configuración de su brazo o a la ubicación de la mano, ya sea propioceptiva o visualmente, no pueden realizar movimientos precisos. Aparte de la visión, la otra entrada sensorial esencial requerida para el cálculo de la posición de la mano son los propioceptores, los sensores que miden los ángulos de las articulaciones de la extremidad o longitudes musculares (Lackner & Shenker, 1985). En situaciones en las que no podemos ver nuestra mano, la información propioceptiva desempeña un papel fundamental para estimar donde veríamos la mano, alineando visión y propiocepción. Cuando la información está disponible en ambas modalidades, el sistema nervioso central utiliza las dos fuentes para obtener una idea coherente de donde está nuestra mano (Carrozzo, McIntyre, Zago & Lacquaniti, 1999; Ernst & Banks, 2002), mediante una óptima combinación de la información sensorial (Knill & Pouget, 2004; Smeets, van den Dobbelsteen, de Grave, van Beers & Brenner, 2006). En este contexto, se pueden presentar situaciones conflictivas (e.g., cuando se mira a través de un microscopio o un espejo). La conclusión que surgió de los estudios que investigaron conflictos entre visión y propiocepción es que la estimación visual domina a la propioceptiva, ya que los movimientos se ajustan de acuerdo con la posición vista, y uno aprende una nueva asignación (adaptación) visomotora (Hay, Pick & Ikeda, 1965; Warren & Pick, 1970). El peso propioceptivo es mayor con la disminución de la disponibilidad de la información visual (Mon-Williams, Wann, Jenkinson & Rushton, 1997). La integración también varió con la dirección, ya que en el eje de profundidad también se da más peso a la propiocepción (van Beers, Wolpert & Haggard, 2002). Esto se puede entender a partir de la geometría del brazo. Por otro lado, la visión es más precisa en el eje lateral. Aún así, estamos lejos de entender completamente cómo la ponderación de diferentes modalidades sensoriales se lleva a cabo para ejecutar movimientos de intercepción. Una posibilidad es que nuestro sistema visomotor utilice la información visual y propioceptiva siguiendo patrones similares de ponderación en los ejes laterales y de profundidad al interceptar objetos. Este vacío en la bibliografía constituye la motivación del capítulo 5 de esta tesis.

Hemos visto cómo nuestro cerebro calcula la posición de la mano cuando tenemos la intención de alcanzar un objeto. Pero, ¿cómo podemos saber si el objeto es alcanzable? El espacio peripersonal (Làdavas, 2002), se define por la medida en que se puede abarcar. Las manos se mueven continuamente en el espacio, y el cerebro tiene que calcular su localización para actualizar el mapa visual del espacio que rodea a la mano. Estudios recientes han demostrado que la información visual sobre la mano, además de ser necesaria, puede también ser suficiente para mediar en el procesamiento del espacio peripersonal. Ver como se acarician sincronizadamente una mano de goma y la propia mano de la persona (ocultada) hace que la mano de goma se atribuya a nuestro propio cuerpo. Esta atribución puede medirse cuantitativamente como una deriva de la posición percibida de la propia mano hacia la mano de goma (Botvinick & Cohen, 1998). Botvinick y Cohen sugirieron que la ilusión de la mano de goma resulta en un error en la percepción táctil hacia la ubicación espacial de la percepción visual. Una cuestión interesante en relación con el espacio peripersonal es si estas ilusiones pueden modificar la extensión espacial del mismo. Aunque la longitud de nuestros brazos limita nuestro espacio de acción, podemos utilizar diferentes herramientas para ampliar nuestro espacio de acción. Las primeras intuiciones (Head & Holmes, 1911) sugirieron que los objetos manipulados se incorporan en el esquema corporal. En los últimos años, se han acumulado evidencias que muestran que el espacio peripersonal visual en relación con la mano tiene importantes propiedades dinámicas, y puede ser expandido o contraído en función del uso de una herramienta (Berti & Frassinetti, 2000; Witt, Proffitt & Epstein, 2005). Por ejemplo, después de dos semanas de entrenamiento, los macacos utilizan hábilmente un rastrillo con el fin de alcanzar alimentos distantes (Ishibashi, Hihara & Iriki, 2000). Estudios psicofísicos en humanos han demostrado que la gente juzga un objeto más cerca cuando utilizan una herramienta (Witt, Proffitt & Epstein, 2005). Esto sugiere que el uso de herramientas expande la representación de la extremidad del sujeto (Berti & Frassinetti, 2000). Sin embargo, los límites de la frontera abarcable también pueden ser modificados por influir en la estimación de la posición de la mano (Holmes & Spence, 2004). Como se ve en la ilusión de la mano de goma, el hecho de que las personas combinen la posición de la mano 'vista' y 'sentida' sugiere que el cambio de información visual acerca de la posición de la mano desplazaría juicios de alcanzabilidad. En este contexto, de Grave, Brenner y Smeets (2011) han mostrado recientemente en qué medida los cambios en la posición percibida de la mano pueden dar cuenta de los cambios en el rango de distancias que se consideran dentro del alcance. Teniendo en cuenta que las estimaciones de alcanzabilidad pueden tener una importancia crucial en la decisión de ejecutar un movimiento de intercepción, una pregunta interesante que queda por aclarar es si estas propiedades dinámicas del espacio peripersonal visual también se aplicarían para hacer los movimientos hacia los objetos juzgados como alcanzables. El Capítulo 6 de esta tesis tratará de arrojar luz sobre esta cuestión.

10.1.2.3 El control de los movimientos

Una vez que nuestro sistema visomotor ha decidido pasar de la posición inicial de la mano hacia el objeto, ¿cómo se mueve de un lugar a otro? El control motor es el estudio de cómo los organismos hacen movimientos dirigidos a un objetivo preciso. Al realizar un simple movimiento a una velocidad moderada en condiciones de visión normales, nuestro objetivo inicial puede ser alterado por cambios imperfectos, o ambientales, tales como movimientos del objeto o de nuestro cuerpo, lo cual puede perturbar nuestro movimiento y resultar en una respuesta inexacta. En tales situaciones, se require el control continuo y una corrección voluntaria final. Con el fin de controlar un movimiento, el cerebro debe calcular la diferencia entre la mano y la posición de destino, distancia denominada 'error motor'. Desde los primeros estudios a finales del siglo XIX, el movimiento ha sido considerado compuesto por dos fases: una fase inicial balística preplanificada, y una fase posterior controlada, en la que el ‘feedback’ sensorial del movimiento se utiliza para corregir errores en la trayectoria balística (Woodworth, 1899). Numerosos estudios han demostrado que, cuando el objetivo se mueve repentinamente, somos capaces de actualizar el movimiento para tener en cuenta el salto y corregir la trayectoria (Prablanc, Desmurget & Gréa, 2003). Parece que el ajuste del movimiento es extremadamente rápido (110 ms) en respuesta a los cambios inesperados en el entorno (Brenner & Smeets, 1997; Gielen, van den Heuvel & van Gisbergen, 1984; Soechting & Lacquaniti, 1983). Vale la pena señalar que el retraso visomotor para cambios en la ubicación del objeto es tan breve como la latencia en la que movimiento visual de fondo comenzó a influir en los movimientos manuales (Brenner & Smeets, 1997; Whitney, Westwood, et al., 2003). Esto puede indicar que los cambios de la posición generados por el movimiento de fondo podrían ser equivalentes a un cambio en la posición real del objeto.

Con el fin de investigar cómo un movimiento previsto es controlado de forma natural después de su iniciación, un método adecuado, llamado el paradigma del ‘doble paso’, consiste en desplazar la posición de un objeto durante la sácada que se hace al mismo, de forma que no se percibe el cambio. Los resultados mostraron que los movimientos se desplazaron en la dirección del salto, aún cuando los participantes no eran conscientes de la perturbación. Estos hallazgos se han tomado como evidencia de que las correcciones rápidas no intencionadas operan automáticamente, en lo que se conoce como el ‘piloto automático’ (Pisella et al., 2000). Otros estudios introdujeron la perturbación al inicio del movimiento de la mano. De esta manera, los sujetos eran conscientes de las perturbaciones y realizaron un ajuste durante la ejecución. Las correcciones intencionadas mostraron dos picos de velocidad y un aumento de tiempo de movimiento (Diedrichsen, Hashambhoy, Rane & Shadmehr, 2005), consistente con la superposición de dos órdenes motoras, mientras que las correcciones automáticas mostraron un único pico de velocidad sin tiempo adicional (Prablanc & Martin, 1992). La convergencia de los estudios psicofísicos visomotores con herramientas de neuroimagen ha contribuido a la comprensión de los mecanismos neuronales a cargo de los procesos de corrección. El fuerte contraste entre la actividad cerebral en las respuestas visomotoras perturbadas y no perturbadas reveló una red que incluye el PPC contralateral, la parte de la corteza motora relacionada con el brazo superior y el cerebelo (Desmurget et al., 2001). Pruebas electrofisiológicas en monos sugieren que las transformaciones visomotoras que orquestan la corrección se realizan en un circuito de interconexión parietofrontal entre el MIP y la corteza premotora dorsal (PMd) (Caminiti, Ferraina & Johnson, 1996; Johnson & Ferraina, 1996). En humanos, las técnicas de neuroimagen han revelado una activación de SPL, mIPS y PMd durante los movimientos (Colebatch et al., 1991). La conexión del mIPS que reciben las neuronas del área PMd se cree que se transmite a través de tractos parietofrontales, con especial relevancia del fascículo longitudinal superior (SLF) como una de las principales vías que une el lóbulo parietal con el frontal (Boorman, O'Shea, Sebastian, Rushworth & Johansen-Berg, 2007). La interrupción de la función en el área mIPS usando TMS provocó una drástica reducción del número de correcciones (Desmurget et al., 1999). Así, parece que el PPC participa no sólo en la fase de planificación, sino también en el seguimiento en línea y la actualización del error motor (Reichenbach, Bresciani, Peer, Bulthoff & Thielscher, 2011). Se desconoce, sin embargo, cuáles son los mecanismos neuronales que están detrás de las diferencias interindividuales en el control motor. La comprensión de la naturaleza y la magnitud de la variación interindividual es fundamental para entender las bases neuronales de los procesos de corrección. La pregunta clave podría ser en qué medida las diferencias anatómicas en los tractos parietofrontales explican el impacto diferencial de la TMS en el control motor. El objetivo general del capítulo 7 es proporcionar nuevos conocimientos sobre este tema.

10.2 Objetivos de la tesis

El objetivo general de esta tesis doctoral es proporcionar datos sólidos para avanzar en la comprensión de cómo el cerebro codifica de manera óptima la información espacial y temporal para realizar movimientos precisos. Se presentan cinco estudios para hacer frente a estas cuestiones:

- En el estudio I, el objetivo fue explorar, a través de medidas psicofísicas, si las ilusiones visuales que alteran la posición percibida de los objetos, tales como el ‘motion after-effect’ (MAE), también afectaron las acciones dirigidas a esos objetos. La hipótesis de que la adaptación de la mano al MAE requeriría de una actualización continua de la posición del objeto, estando por tanto sólo presente cuando se intercepten objetos en movimiento, también se testeó.

- El estudio II trató de identificar la base neuronal de los errores inducidos por movimiento visual al interceptar objetos. El uso de EEG permitió rastrear el curso temporal de la actividad en el área MT para establecer la contribución de los circuitos ‘feedback’ y ‘feedforward’ a la desviación de la mano inducida por el movimiento.

- El estudio III aborda cómo el sistema visomotor pondera visión y propiocepción para llevar a cabo movimientos de intercepción con óptima precisión espacial y temporal. La principal hipótesis a comprobar es saber si, con pobre resolución visual, la contribución de las claves propioceptivas es fundamental para llegar a un objeto con alta precisión.

- El objetivo del estudio IV fue determinar si una adaptación inconsciente a una posición visual desplazada de la mano afectó los juicios de alcanzabilidad cuando interceptamos objetos en el espacio peripersonal. Una posibilidad es que la visión anule el sentido propioceptivo de la posición de la mano durante la adaptación visomotora.

- En el estudio V, un enfoque multimodal que combinó TMS con DTI examinó los correlatos neurofisiológicos y anatómicos de los tractos parietofrontales para estudiar la variabilidad interindividual en los déficits de control motor. Se hipotetizó que los principios que rigen una disrupción de correcciones inducida por TMS se basan en la integridad de la conectividad entre el lóbulo parietal y frontal.

10.3 Resultados y Discusión

10.3.1 ESTUDIO I: LA ADAPTACIÓN AL MOVIMIENTO VISUAL EN INTERCEPCIÓN

En los tres experimentos llevados a cabo en el estudio I nos centramos en la repercusión del efecto MAE para investigar si el movimiento ilusorio de un objeto estático puede provocar cambios en la trayectoria para alcanzar ese objeto. Después del período de adaptación, se utilizaron dos tareas visomotoras que diferían en sus propiedades intrínsecas cinemáticas: un movimiento de seguimiento manual, en el que los participantes fueron instruidos para realizar una persecución de un objeto durante un intervalo de tiempo relativamente largo; y una tarea de alcanzar un objeto, donde se requiere un movimiento rápido hacia la posición percibida de un objeto estático. Los resultados muestran que la dirección del MAE modula el retraso entre la mano y la posición del objeto durante el seguimiento manual. El experimento 1 mostró que la mano siguió al objeto a una distancia más corta cuando la dirección MAE era congruente con la de la trayectoria de la mano. Sin embargo, las direcciones opuestas producen mayores desajustes mano-objeto. Este efecto se expresa en su totalidad cuando los sujetos fijaron su mirada en un punto específico en el centro de la pantalla mientras se realiza el seguimiento manual del objeto. El patrón de estos resultados es consistente con la bibliografía que sugiere que la fuerza del MAE depende de la fijación de la mirada durante el periodo de adaptación (Wohlgemuth, 1911) y de la distancia al punto donde se mira, siendo mayor en la visión periférica (Anstis & Moulden, 1970; Brandt, Dichgans & Koenig, 1973; Wright, 1986). El posterior análisis de los perfiles de velocidad de la mano durante el seguimiento manual reveló que la dirección del MAE alteró el patrón cinemático: el movimiento de la mano fue más lento en la condición en la que la dirección del MAE y la trayectoria de la mano fueron opuestas. Estos datos demuestran que la adaptación al movimiento visual es capaz de modificar las características del movimiento manual cuando intenta alcanzar el objeto.

Bajo la premisa de que las señales del MAE se integran para actualizar la posición de un objeto en movimiento (Linares et al., 2007), los experimentos 2 y 3 investigaron la influencia del MAE en los movimientos de intercepción. Como era de esperar, la dirección del MAE opuesta al objeto produjo desviaciones mayores entre la posición final de la mano y la ubicación del objeto. El sesgo inducido por el MAE también aumentó en función de la duración del período de adaptación, lo cual concuerda con estudios anteriores que proponen un sistema dinámico que integra información de movimiento a lo largo del tiempo (Nishida & Johnston, 1999). Asumiendo que las señales MAE sólo se codifican en la estimación de la posición de un objeto en movimiento, se analizó la influencia del MAE sobre los movimientos hacia objetos estáticos. Los datos no mostraron ningún efecto de adaptación de movimiento en las trayectorias de la mano. Dado que los objetos fijos sí se perciben desplazados en presencia de movimiento visual de fondo (De Valois & De Valois, 1991; Durant & Johnston, 2004; Whitney & Cavanagh, 2000), estos resultados sugieren que las señales de movimiento de fondo y la adaptación de movimiento puede ser procesadas de forma diferente cuando se estima la posición de un objeto estático. Una diferencia es que en los paradigmas de adaptación a movimiento, como el MAE, el desplazamiento se produce en la dirección opuesta a la del período de adaptación. La falta de desalineación inducida por MAE en objetos estáticos podría por lo tanto reflejar un mecanismo neuronal más complejo para explicar el desplazamiento de la posición debido al movimiento visual.

10.3.2 ESTUDIO II: MECANISMOS NEURONALES DEL EFECTO DEL MOVIMIENTO VISUAL EN LA CODIFICACIÓN DE LA POSICIÓN

En el estudio II, se abordó la posibilidad de que un temprano procesamiento del movimiento visual en MT sea capaz de desplazar la codificación de la posición en V1 mucho antes de que tengan lugar las conexiones ‘feedback’. Basado en las cortas latencias de la influencia del movimiento visual en las acciones dirigidas a objetos estáticos, proponemos circuitos ‘feedforward’, independientes de la conexión que va de V1 a MT, como la explicación fisiológica de la desviación de la mano. Para ello, utilizamos el paradigma visomotor introducido por Whitney, Westwood, y Goodale (2003), en el que los participantes alcanzaron la posición de un objeto estático en presencia de señales de movimiento que podían revertir su dirección antes o después de aparecer el objeto. Con el uso de ERPs, registramos los potenciales evocados visuales para examinar la dinámica temporal de la respuesta visomotora. Este experimento replicó el cambio en la trayectoria de mano dependiendo de la dirección del movimiento de fondo. En particular, la condición en la que el objeto apareció en el mismo momento exacto de la inversión del movimiento produjo la desviación más fuerte en el movimiento manual, lo cual es consistente con estudios anteriores (Whitney & Cavanagh, 2000; Whitney, Westwood, et al., 2003). Un resultado aún más interesante reportado en este estudio es la estrecha relación entre la magnitud del desplazamiento inducida por el movimiento y la latencia de los procesos perceptivos relacionados con el objeto desplazado. El hecho de que el objeto alcanzado no se mueva lleva a pensar que la naturaleza de la percepción errónea de su posición no puede estar vinculada a mecanismos temporales, como ocurre con los objetos en movimiento (Mateeff & Hohnsbein, 1988; Murakami, 2001; Whitney & Murakami, 1998). Sin embargo, el hallazgo de que los participantes que mostraron un cambio mayor en la trayectoria de la mano también mostraron un procesamiento sensorial del objeto más lento va en contra de ese postulado. Estos resultados concuerdan con la idea de que el tiempo de percepción es fundamental cuando se codifica la posición de un objeto (Durant & Johnston, 2004; Maij, Brenner & Smeets, 2009). Es posible que el retraso en la percepción del objeto pueda indicar una respuesta adaptativa que el sistema visomotor emplea para guiar el movimiento manual, maximizando el tiempo de procesamiento de movimiento visual para refinar la codificación de la posición del objeto (Whitney, Murakami & Gomi, 2010).

Uno de los principales resultados observados en el estudio II, y el que conduce a la hipótesis sobre el mecanismo neuronal que sustenta el efecto del movimiento visual, es la evolución temporal de la actividad neuronal en el área MT. Hemos encontrado actividad muy temprana en la zona cercana a MT responsable de la desalineación del objeto. Los valores de CSD en regiones temporoccipitales revelaron patrones de actividad que correlacionaron con la magnitud del enlentecimiento sensorial anteriormente mencionado. Los participantes con mayor actividad en MT mostraron latencias más largas en sus VEPs. Curiosamente, el análisis de localización del área generadora de esa actividad indicó que la actividad máxima de MT se produjo alrededor de 60 ms después de la aparición del objeto, lo que apunta a un procesamiento del movimiento visual muy temprano como la causa de la desviación de la mano. Hay evidencia neurofisiológica que refleja que la influencia del movimiento podría actuar en las primeras etapas del sistema visual, incluso a nivel de retina (Berry et al., 1999), lo que apunta a la posibilidad de que el movimiento visual puede ser procesado antes que la codificación de la posición del objeto. Por tanto, es concebible que la corta latencia de área MT en nuestro estudio, que precede a las conexiones ‘feedback’, descarte la posibilidad de que el mecanismo que regule el efecto del movimiento en la posición provenga de circuitos ‘feedback’ de MT a V1. En este contexto, el papel de las vías visuales no primarias a MT puede ser de suma importancia para describir los mecanismos que sustentan este fenómeno. Se ha demostrado que los pacientes con una ceguera cortical (lesión en V1) pueden discriminar y utilizar la información de movimiento para guiar sus acciones (Barbur, Watson, Frackowiak & Zeki, 1993, Weiskrantz, 1986). Si se acepta el hecho de que los pacientes con ceguera cortical pueden mover sus ojos y sus manos con precisión hacia los estímulos visuales que no pueden 'ver', la cuestión sigue siendo qué vías sustentan esta capacidad residual. Weiskrantz et al. (1974) y otros han atribuido la capacidad visomotora residual en sus pacientes al 10% de las fibras ópticas que terminan en el SC (Perry & Cowey 1984). Es un reto especular que conexiones directas LGN-MT pudieran también transmitir información de movimiento. Establecer vías visuales a través del SC es aún más difícil, debido a que dos sinapsis deben actuar como intermediarias. Hay evidencia fragmentaria para apoyar la idea de que el SC pueda desempeñar un papel crucial en el control de movimientos. Por ejemplo, un estudio realizado por Solomon et al. (1981) demostró directamente que el SC estuvo implicado en la mediación para llegar a un objeto visual tras lesionar V1 en monos: aunque los animales conservaban esta habilidad después de la lesión, la perdieron después de una lesión adicional en el SC. Todavía hay mucha controversia sobre la forma exacta de los cálculos que se realizan en el área de MT. Se desprende de nuestros resultados, sin embargo, que el sistema visual es capaz de completar una parte sustancial de procesamiento de movimiento visual en menos de 100 ms, suficiente para desencadenar respuestas relacionadas con el error en movimientos manuales. En conjunto, creemos que este estudio nos proporciona pruebas convincentes para sugerir que las vías extrageniculadas pueden ser capaces de proporcionar la información visual necesaria sobre movimiento de fondo, sin la mediación de V1, para compensar y modular las acciones dirigidas a los objetos.

10.3.3 ESTUDIO III: COMBINACIÓN VISO-PROPIOCEPTIVA INTERCEPTANDO OBJETOS

El ojo y la mano aparecen conectados de una manera altamente adaptativa para optimizar el éxito de tareas motoras. Se ha encontrado el papel diferencial de fuentes visuales y propioceptivas para modular la estimación de la ubicación mano (Hay, Pick & Ikeda, 1965; Mon-Williams, Wann, Jenkinson & Rushton, 1997; Welch & Warren, 1986). En el capítulo 5 hemos explorado la alineación y ponderación de la información visual y propioceptiva al interceptar objetos. Para lograr ese objetivo, se determinó la contribución de la información visual y propioceptiva en una tarea en la que los sujetos debían indicar con un movimiento manual el punto de colisión entre dos objetos. Se utilizó un paradigma nuevo de intercepción que permitió separar el componente espacial de movimiento (posición de final de la mano) del componente temporal (tiempo de colisión). La estructura de la tarea requirió a los participantes observar la parte inicial de la trayectoria de los dos objetos (Bootsma & Oudejans, 1993), ya sea en el plano sagital o lateral, en un curso de colisión y predecir el momento en que chocarían. Se pidió a los participantes que ejecutaran un movimiento en el que coincidiera tanto el momento de la colisión como la ubicación espacial de la colisión. En los resultados, observamos un error y variabilidad temporal menores cuando los objetos se movían a lo largo del eje sagital del sujeto, que cuando se movían perpendicularmente al mismo. Cuando se pidió a los participantes juzgar el tiempo de colisión sin hacer movimientos de intercepción, redujeron significativamente su precisión en la dirección sagital. Además, la precisión temporal del movimiento no se vio afectada significativamente por la presencia o ausencia de información visual de la mano. Estos resultados apoyan la idea de que cuando múltiples fuentes de información sensorial se codifican para reducir al mínimo la incertidumbre en la estimación final, la forma teóricamente óptima para combinar la información es ponderar cada fuente por su precisión, que es la inversa de su varianza (Ghahramani & Wolpert, 1997; Jacobs, 1999; van Beers, Sittig & Gon, 1999). La reducción de la información visual da lugar a una localización visual menos precisa y, por lo tanto, a una reducción del peso visual en la estimación total. Nuestro estudio amplía estas consideraciones a una tarea de intercepción con coincidencia temporal, y descubre el uso privilegiado de la información propioceptiva para guiar la precisión temporal del movimiento en el eje de profundidad.

10.3.4 ESTUDIO IV: ADAPTACIÓN VISOMOTORA EN LA INTERCEPCIÓN DE OBJETOS

Como se describe en la introducción, varios estudios han demostrado que los límites del espacio accesible pueden ser modificados influyendo en la estimación de la posición de la propia mano (Holmes & Spence 2004). La investigación del estudio IV proporciona evidencias de que la alteración visual de la posición de la mano también desplazará juicios de alcanzabilidad al interceptar objetos en movimiento. El paradigma experimental instruyó a los sujetos a interceptar un cubo virtual en movimiento cuando juzgaran el objeto como alcanzable (de Grave, Brenner & Smeets, 2011). De lo contrario, debían inhibir la respuesta motora. La información visual de la posición de la mano del sujeto se distorsionó en dos direcciones, resultantes en un desplazamiento de la mano más cerca del cuerpo o más lejos del cuerpo. Los resultados revelaron que objetos a una misma distancia fueron juzgados con más frecuencia alcanzables cuando la posición de la mano se desplazó lejos del cuerpo. Los efectos observados en la estimación de alcanzabilidad fueron independientes de la dirección de movimiento del objeto, ya fuera acercándose o alejándose del observador. Sobre la base de estos resultados, los juicios de alcanzabilidad en el espacio circundante se basan en la posición 'vista' de la mano. Nuestro estudio complementa los hallazgos previos de que el cambio de ubicación visual de la mano afecta a (1) la exactitud espacial de los movimientos (Sarlegna & Blouin, 2010) y (2) los juicios de alcanzabilidad (de Grave et al., 2011, Bourgeois & Coello, 2012). El hallazgo de la influencia de la información visual en juicios de alcanzabilidad de los objetos en movimiento cuando hay una acción prevista para interceptarlos apunta claramente a una dominancia visual en el marco de esta tarea de intercepción.

Algunas consideraciones adicionales con respecto a las similitudes de los juicios de alcanzabilidad para objetos que se alejan o se acercan deben ser discutidas. El estudio aborda este tema y revela una falta de efecto direccional. Este resultado parece contradecir estudios anteriores que aseguraban la observación de estimaciones de alcanzabilidad más grandes cuando los objetos se acercan al participante, en comparación con cuando los objetos se alejaron (Fischer, 2000). Creemos que esta diferencia puede estar relacionada con la forma en que los datos fueron recogidos y analizados. Un efecto direccional puede ser interpretado para implicar la presencia de una planificación de predicción del movimiento. Claramente, la implementación de un plan motor lleva tiempo (Rosenbaum, 1980; Rosenbaum et al., 1987), al igual que la ejecución del movimiento en sí mismo (Fitts, 1954). Por lo tanto, tiene sentido que las estimaciones de alcanzabilidad destinadas a interceptar objetos dinámicos tengan en cuenta el tiempo que transcurre durante la implementación del plan y la terminación del movimiento hacia el objeto, así como los cambios en la posición del objeto durante este tiempo. La distancia entre la posición final de la mano y el objeto (error espacial) no parece verse afectada por la dirección del movimiento. Nuestra opinión es que los participantes tomaron en cuenta su tiempo de movimiento con el fin de interceptar el objeto en una zona de intercepción común tanto para objetos que se acercan como con los que se alejan. Añadimos un nuevo análisis de datos para probar que los participantes tuvieron en cuenta su tiempo de movimiento cuando juzgaron la alcanzabilidad. El análisis para probar esta hipótesis consistió en la medición de la posición del objeto en el inicio y el final del movimiento de la mano en los objetos alcanzables. Si los participantes incluyen el tiempo de movimiento en su juicio, deberíamos encontrar diferencias entre el comienzo del movimiento entre objetos que se acercan y se alejan, pero no en el final del movimiento manual, lo que muestra que los objetos son interceptados en una zona común independientemente de la dirección del movimiento. El hecho de que los objetos que se acercan fueran juzgados alcanzables más lejos sólo en el inicio del movimiento, pero a distancias similares cuando terminó el movimiento, apoya la hipótesis de que los participantes consideraron un área común para interceptar los objetivos independientemente de su dirección. Teniendo en cuenta todo lo anterior, creemos que este estudio demuestra que el espacio percibido como alcanzable fue mayor cuando se alteró la ubicación de la mano, y como adaptamos totalmente nuestras acciones a la información visual de la mano cuando hacemos juicios de alcanzabilidad.

10.3.5 ESTUDIO V: LAS BASES ANATÓMICAS DE UN CONTROL MOTOR PRECISO

Con frecuencia hemos de modificar, ya sea justo antes o durante la ejecución, el movimiento hacia un objeto. Las correcciones 'online' son una parte crucial de nuestra capacidad para interactuar con el mundo, y desentrañar los sustratos neuronales de estas correcciones se suma a nuestra comprensión de cómo se alcanzan objetos en un entorno dinámico. Como hemos visto antes, numerosos estudios han involucrado el PPC en el control motor de un movimiento después de su inicio. En el capítulo 7, se combinaron herramientas de neuroimagen y el registro cinemático con el fin de identificar los fundamentos neurofisiológicos y anatómicos de la variación interindividual de los déficits en el control motor. En nuestro estudio, hemos encontrado una reducción del número de correcciones motoras después de interrumpir temporalmente, a través de TMS, la funcionalidad del mIPS. Los resultados encajan muy bien con estudios anteriores (Della-Maggiore et al., 2004; Desmurget et al., 1999), y amplían el conocimiento de los efectos después de interferir la función de mIPS, ya que hemos desarrollado una novedosa intervención a través de la aplicación de un protocolo prolongado de rTMS inhibitoria. Los valores normales de control motor se volvieron a recuperar 60 minutos después de la estimulación. La estimulación repetitiva ha sido ampliamente adoptada como una herramienta para modular deliberadamente la actividad en las áreas corticales locales con el fin de establecer sus roles funcionales (Siebner & Rothwell, 2003; Rollnik et al, 2004). Se pueden ejercer efectos sobre la eficiencia de la transmisión sináptica (Muellbacher et al., 2000), o bien potenciando (potenciación a largo plazo, LTP) o disminuyendo (depresión a largo plazo, LTD) la excitabilidad de los circuitos corticales (Pascual-Leone et al., 1994). Sin embargo, los efectos de condicionamiento de la plasticidad cortical promovidos por la rTMS no se limitan a la región 'diana', sino que también modulan la excitabilidad de las zonas interconectadas a distancia (Gerschlager et al., 2001; Siebner et al., 2000; Wassermann et al., 1998), proporcionando una medida de la conectividad entre estas regiones (Fox et al., 2012). Por lo tanto, la interferencia 'offline' parece basarse en diferentes mecanismos neurofisiológicos en comparación con la interferencia 'online'.

El efecto de la rTMS en la capacidad de actualizar un movimiento fue más prominente para la mano contralateral al hemisferio estimulado. La mayoría de los estudios de neuroimagen funcional han informado de activación bilateral en respuesta a los movimientos de cualquiera de los brazos o de la mano, pero que la modulación es más fuerte para los movimientos contralaterales (Astafiev et al., 2003; Beurze et al., 2007; Connolly et al., 2003; Medendorp et al., 2003; Merriam et al., 2003; Sereno et al., 2001). Sin embargo, la TMS en humanos también ha puesto de manifiesto los déficits lateralizados en mIPS y control motor (Desmurget et al., 1999; van Donkelaar & Adams, 2005; Vesia et al., 2010). Estudios recientes sugieren que parece haber un gradiente rostro-caudal de la especificidad de las extremidades superiores en la corteza parietal. En general, los datos son consistentes con la noción de que hay una mayor lateralización para movimientos de la mano contralateral en zonas antero-laterales que en medial-posterior (Blangero et al., 2009). De acuerdo con esto, nuestros efectos TMS soportan un cierto grado de lateralización del mIPS, aún siendo también significativa en el miembro ipsilateral. La variabilidad espacial en la posición final de la mano fue analizada para descartar la posibilidad de que los déficits sacádicos explicaran los resultados, en lugar de los déficits en control motor. El análisis demostró que, después de la rTMS, los movimientos a cualquiera de los dos lados no fueron menos precisos que al centro de la pantalla. Es importante destacar que también controlamos la posibilidad de que la inducción de la lesión virtual implicara un deterioro del procesamiento visual que codifica la ubicación del objeto. La falta de diferencias en la condición control después de la rTMS nos llevó a la conclusión de que la codificación de la posición se procesó correctamente. Aunque la precisión final depende en gran medida del control motor (Desmurget et al., 2005; Todorov & Jordan, 2002), la integridad funcional del mIPS sólo sería crucial con grandes incongruencias espaciales entre el objeto y la posición de la mano durante el movimiento (saltos del objeto). Conflictos más pequeños no requerirían una contribución decisiva del mIPS. Finalmente, un análisis detallado de las características del movimiento eliminó la posibilidad de una alteración general del comando motor.

A la luz del deterioro transitorio de las correcciones por culpa de la rTMS, exploramos el origen de la variabilidad interindividual en el grado de afectación después de la interrupción del mIPS. Existen importantes diferencias individuales en cómo los adultos realizan movimientos que dirigidos a objetos que requieren un control motor para ajustar su actuación en caso de perturbaciones inesperadas (Boy et al., 2010; Reichenbach et al., 2008). Del mismo modo, el deterioro inducido por rTMS del control motor al interferir la función del mIPS también varió considerablemente en los sujetos (Desmurget et al., 1999). El análisis DTI dio a conocer que los sujetos con un fuerte impacto en el control motor contralateral después de la aplicación de rTMS mostraron una menor integridad de la materia blanca en los tractos parietofrontales que presuntamente conducen el cómputo dinámico del error motor desde mIPS a PMd. Un análisis de todo el cerebro de la FA mostró que los participantes que tenían una mayor integridad de la materia blanca en el SLF II contralateral, cerebelo y pons sufrieron menos repercusiones conductuales por culpa de la rTMS en el rendimiento motor. Si nuestro razonamiento es correcto, entonces el estudio muestra que la cohesión estructural de la materia blanca pueden utilizarse como un índice sólido para caracterizar la extensión de las deficiencias motoras. Por lo tanto, se podría suponer que los principios de funcionamiento que rigen la disrupción inducida por TMS de correcciones motoras se basan en la fortaleza de la conectividad parietofrontal. En concreto, el signo de la correlación sugiere que la repercusión de la TMS es más débil cuando los tractos presentaron mayor cohesión. Las características microestructurales de la sustancia blanca en el cerebelo y pons también explicaron el impacto diferencial de la TMS en el control motor. El papel del cerebelo ha sido ampliamente destacado, y crucial para la construcción de una señal de error motor (Liu et al., 1999; Miall et al., 1993). A su vez, el cerebelo recibe un gran aporte de fibras que descienden de la corteza motora, a través del pons, y se piensa que éstas representan la copia eferente de órdenes motoras salientes (Wolpert & Miall, 1996). A pesar del efecto TMS inferior en el lado ipsilateral, los análisis de DTI también mostraron la importancia de la integridad de la materia blanca en los tractos parietofrontales al ajustar los movimientos con la mano izquierda.

Se ha propuesto que las diferencias interindividuales en el rendimiento de varias tareas motoras pueden deberse a variaciones en la estructura de la materia blanca (Madden et al, 2004; Tuch et al, 2005). Un ejemplo especialmente convincente es la correlación entre la variabilidad interindividual en el tiempo de reacción y la FA de las vías visoespaciales de materia blanca y el cuerpo calloso (Tuch et al, 2005; Westerhausen et al, 2006). Con respecto a tareas motoras más sofisticadas, las diferencias en la coordinación bimanual entre los individuos se han atribuido a la integridad de la parte del cuerpo calloso que une las áreas motoras suplementarias (SMA) (Johansen-Berg, Della-Maggiore, Behrens, Smith & Paus, 2007). Por otra parte, la densidad de la materia gris de la región pre-SMA parece estar vinculada a la capacidad de seleccionar las acciones apropiadas en situaciones de conflicto (van Gaal, Scholte, Lamme, Fahrenfort & Ridderinkhof, 2011). Por lo tanto, las variaciones interindividuales en los procesos de control cognitivo de tareas motoras simples y complejas se reflejan en la anatomía estructural del cerebro. Medidas de comportamiento puras como referencia, sin embargo, corren el riesgo de reflejar la función integrada de múltiples regiones del cerebro. Más bien, el impacto específico de la aplicación TMS podría ser una medida más informativa y aislada de esta función del cerebro con la cual comparar los parámetros estructurales (Boorman et al., 2007). En este contexto, estos autores encontraron una relación entre el MEP, una medida fisiológica de la conectividad funcional, y los valores de FA, una medida de la conectividad estructural. En nuestro estudio, en cambio, utilizamos el impacto conductual de la TMS en la función cerebral específica.

10.4 Conclusiones finales

Esta tesis presenta conclusiones valiosas sobre el control que el sistema visomotor ejerce en los movimientos manuales. Aunque todavía queda un largo camino por delante, las conclusiones extraídas de este conjunto de trabajos mejoran significativamente nuestra comprensión de cómo el cerebro codifica las claves espaciales y temporales para dirigir acciones precisas a objetos. Por un lado, esta tesis destaca que las señales de adaptación al movimiento afectan notablemente la trayectoria y la precisión de acciones dirigidas a objetos móviles percibidos desalineados. Además, se ha observado que el cambio en la posición percibida de un objeto puede acarrear un procesamiento sensorial más lento, lo que sugiere un componente temporal para explicar al menos parte de la naturaleza del desalineamiento espacial. Estos correlatos neuronales, junto con un patrón de activación temprano en MT, desafían las teorías establecidas sobre los mecanismos neuronales que explican los efectos del movimiento visual en la codificación de la posición. Esta tesis también arroja luz sobre el modelo de ponderación de la integración visual y propioceptiva en el marco espacio-temporal de las acciones de intercepción. Además, también ofrece claves sobre cómo una adaptación visomotora de la posición de la mano altera nuestras estimaciones para decidir el ‘cuándo’ y el ‘dónde’ de una intercepción de un objeto móvil. Finalmente, demuestra que las diferencias entre individuos en los déficits a la hora de actualizar un comando motor se explican por las propiedades microestructurales de ciertos tractos parietofrontales.

REFERENCES

Addams, R. (1834). An account of a peculiar optical phenomenon seen after having looked at a moving body. *London and Edinburgh Philosophical Magazine and Journal of Science, 5*, 373–374.

Adrian, E. D., & Moruzzi, G. (1939). Impulses in the pyramidal tract. *The Journal of Physiology, 97*(2), 153.

Amassian, V. E., Cracco, R. Q., Maccabee, P. J., Cracco, J. B., Rudell, A., & Eberle, L. (1989). Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroencephalography and Clinical Neurophysiology, 74*(6), 458-462.

Andersen, R. A. (1987). Inferior parietal lobule function in spatial perception and visuomotor integration. *Comprehensive Physiology*.

Andersen, R. A, & Buneo, C. A. (2002). Intentional maps in posterior parietal cortex. *Annual Review of Neuroscience, 25*(1), 189-220.

Andersen, R. A., Snyder, L. H., Li, C. S., & Stricanne, B. (1993). Coordinate transformations in the representation of spatial information. *Current Opinion in Neurobiology, 3*(2), 171-176.

Anstis, S. M., & Moulden, B. P. (1970). After effect of seen movement: Evidence for peripheral and central components. *The Quarterly Journal of Experimental Psychology, 22*(2), 222-229.

Anstis, S., Verstraten, F. A., & Mather, G. (1998). The motion aftereffect. *Trends Cogn Sci, 2*(3), 111-117.

Archambault, P. S., Caminiti, R., & Battaglia-Mayer, A. (2009). Cortical mechanisms for online control of hand movement trajectory: the role of the posterior parietal cortex. *Cerebral Cortex, 19*(12), 2848-2864.

Astafiev, S. V., Shulman, G. L., Stanley, C. M., Snyder, A. Z., Van Essen, D. C., & Corbetta, M. (2003). Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *Journal of Neuroscience, 23*(11), 4689-4699.

Averbeck, B. B., Crowe, D. A., Chafee, M. V., & Georgopoulos, A. P. (2009). Differential contribution of superior parietal and dorsal-lateral prefrontal cortices in copying. *Cortex, 45*(3), 432-441.

Bairstow, P. J. (1987). Analysis of hand movement to moving targets. *Hum Mov Sci, 6*(3), 205-231.

Barbur, J. L., Watson, J. D., Frackowiak, R. S., & Zeki, S. (1993). Conscious visual perception without V1. *Brain, 116 (Pt 6)*, 1293-1302.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *The Lancet, 325*(8437), 1106-1107.

Barlow, H. B. (1958). Temporal and spatial summation in human vision at different background intensities. *Journal of Physiology, 141*(2), 337-350.

Barlow, H. B., & Hill, R. M. (1963). Evidence for a Physiological Explanation of the Waterfall Phenomenon and Figural after-Effects. *Nature, 200*, 1345-1347.

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal, 66*(1), 259-267.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system–a technical review. *NMR in Biomedicine*, *15*(7-8), 435-455.

Bengtsson, S. L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H., & Ullen, F. (2005). Extensive piano practicing has regionally specific effects on white matter development. *Nature Neuroscience, 8*(9), 1148-1150.

Berger, H. (1929). Über das elektrenkephalogramm des menschen. *European Archives of Psychiatry and Clinical Neuroscience, 87*(1), 527-570.

Berry, M. J., Brivanlou, I. H., Jordan, T. A., & Meister, M. (1999). Anticipation of moving stimuli by the retina. *Nature, 398*(6725), 334-338.

Berti, A., & Frassinetti, F. (2000). When far becomes near: remapping of space by tool use. *Journal of Cognitive Neuroscience, 12*(3), 415-420.

Beurze, S. M., de Lange, F. P., Toni, I., & Medendorp, W. P. (2007). Integration of target and effector information in the human brain during reach planning. *Journal of Neurophysiology, 97*(1), 188-199.

Biguer, B., Jeannerod, M., & Prablanc, C. (1982). The coordination of eye, head, and arm movements during reaching at a single visual target. *Experimental Brain Research, 46*(2), 301-304.

Blangero, A., Menz, M. M., McNamara, A., & Binkofski, F. (2009). Parietal modules for reaching. *Neuropsychologia, 47*(6), 1500-1507.

Blythe, I. M., Bromley, J. M., Kennard, C., & Ruddock, K. H. (1986). Visual discrimination of target displacement remains after damage to the striate cortex in humans. *Nature, 320*(6063), 619-621.

Blythe, I. M., Kennard, C., & Ruddock, K. H. (1987). Residual vision in patients with retrogeniculate lesions of the visual pathways. *Brain, 110 (Pt 4)*, 887-905.

Bock, O. (1986). Contribution of retinal versus extraretinal signals towards visual localization in goal-directed movements. *Experimental Brain Research, 64*(3), 476-482.

Boorman, E. D., O'Shea, J., Sebastian, C., Rushworth, M. F., & Johansen-Berg, H. (2007). Individual differences in white-matter microstructure reflect variation in functional connectivity during choice. *Current Biology, 17*(16), 1426-1431.

Bootsma, R. J., & Oudejans, R. R. (1993). Visual information about time-to-collision between two objects. *Journal of Experimental Psychology: Human Perception and Performance, 19*(5), 1041-1052.

Botvinick, M., & Cohen, J. (1998). Rubber hands 'feel' touch that eyes see. *Nature, 391*(6669), 756.

Bourgeois, J., & Coello, Y. (2012). Effect of visuomotor calibration and uncertainty on the perception of peripersonal space. *Atten Percept Psychophys, 74*(6), 1268-1283.

Boy, F., Evans, C. J., Edden, R. A., Singh, K. D., Husain, M., & Sumner, P. (2010). Individual differences in subconscious motor control predicted by GABA concentration in SMA. *Current Biology, 20*(19), 1779-1785.

Brandt, T., Dichgans, J., & Koenig, E. (1973). Differential effects of central versus peripheral vision on egocentric and exocentric motion perception. *Experimental Brain Research, 16*(5), 476-491.

Brenner, E., & Smeets, J. B. (1997). Fast Responses of the Human Hand to Changes in Target Position. *J Mot Behav, 29*(4), 297-310.

Brenner, E., & Smeets, J. B. (2000). Motion extrapolation is not responsible for the flash-lag effect. *Vision Research, 40*(13), 1645-1648.

Brenner, E., & Smeets, J. B. (2003). Fast corrections of movements with a computer mouse. *Spatial Vision, 16*(3-4), 365-376.

Brenner, E., Smeets, J. B., & de Lussanet, M. H. (1998). Hitting moving targets. Continuous control of the acceleration of the hand on the basis of the target's velocity. *Experimental Brain Research, 122*(4), 467-474.

Bridgeman, B., & Staggs, D. (1982). Plasticity in human blindsight. *Vision Research, 22*(9), 1199-1203.

Brouwer, A. M., Brenner, E., & Smeets, J. B. (2000). Hitting moving objects. The dependency of hand velocity on the speed of the target. *Experimental Brain Research, 133*(2), 242-248.

Brouwer, A. M., Brenner, E., & Smeets, J. B. (2002). Hitting moving objects: is target speed used in guiding the hand? *Experimental Brain Research, 143*(2), 198-211.

Brouwer, A. M., Middelburg, T., Smeets, J. B., & Brenner, E. (2003). Hitting moving targets: a dissociation between the use of the target's speed and direction of motion. *Experimental Brain Research, 152*(3), 368-375.

Bullier, J., Hupe, J. M., James, A., & Girard, P. (1996). Functional interactions between areas V1 and V2 in the monkey. *Journal of Physiology, Paris, 90*(3-4), 217-220.

Buneo, C. A., & Andersen, R. A. (2006). The posterior parietal cortex: sensorimotor interface for the planning and online control of visually guided movements. *Neuropsychologia, 44*(13), 2594-2606.

Buneo, C. A., Jarvis, M. R., Batista, A. P., & Andersen, R. A. (2002). Direct visuomotor transformations for reaching. *Nature, 416*(6881), 632-636.

Burbeck, C. A. (1988). Large-scale relative localization across spatial frequency channels. *Vision Research, 28*(7), 857-859.

Burnod, Y., Baraduc, P., Battaglia-Mayer, A., Guigon, E., Koechlin, E., Ferraina, S., . . . Caminiti, R. (1999). Parieto-frontal coding of reaching: an integrated framework. *Experimental Brain Research, 129*(3), 325-346.

Butler, A. J., & Wolf, S. L. (2007). Putting the brain on the map: use of transcranial magnetic stimulation to assess and induce cortical plasticity of upper-extremity movement. *Physical Therapy, 87*(6), 719-736.

Caggiano, V., Fogassi, L., Rizzolatti, G., Thier, P., & Casile, A. (2009). Mirror neurons differentially encode the peripersonal and extrapersonal space of monkeys. *Science, 324*(5925), 403-406.

Caminiti, R., Ferraina, S., & Johnson, P. B. (1996). The sources of visual information to the primate frontal lobe: a novel role for the superior parietal lobule. *Cerebral Cortex, 6*(3), 319-328.

Carrozzo, M., McIntyre, J., Zago, M., & Lacquaniti, F. (1999). Viewer-centered and body-centered frames of reference in direct visuomotor transformations. *Experimental Brain Research, 129*(2), 201-210.

Casanova, C. (2004). The visual functions of the pulvinar. *The visual neurosciences, 1*, 592-608.

Caspers, H., Speckmann, E. J., & Lehmenkuhler, A. (1980). Electrogenesis of cortical DC potentials. *Progress in Brain Research, 54*, 3-15.

Castiello, U., Paulignan, Y., & Jeannerod, M. (1991). Temporal dissociation of motor responses and subjective awareness. A study in normal subjects. *Brain, 114 (Pt 6)*, 2639-2655.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., & Cohen, L. G. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology, 48*(5), 1398-1403.

Chouinard, P. A., Van Der Werf, Y. D., Leonard, G., & Paus, T. (2003). Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. *Journal of Neurophysiology, 90*(2), 1071-1083.

Ciavarro, M., Ambrosini, E., Tosoni, A., Committeri, G., Fattori, P., & Galletti, C. (2013). rTMS of Medial Parieto-occipital Cortex Interferes with Attentional Reorienting during Attention and Reaching Tasks. *Journal of Cognitive Neuroscience*.

Clifford, C. W. (2005). Functional ideas about adaptation applied to spatial and motion vision. *Fitting the mind to the world: Adaptation and after-effects in high-level vision*, 47-82.

Colby, C. L., Duhamel, J. R., & Goldberg, M. E. (1996). Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *Journal of Neurophysiology, 76*(5), 2841-2852.

Colebatch, J. G., Adams, L., Murphy, K., Martin, A. J., Lammertsma, A. A., Tochon-Danguy, H. J., . . . Guz, A. (1991). Regional cerebral blood flow during volitional breathing in man. *Journal of Physiology, 443*, 91-103.

Coles, M. G. (1989). Modern mind-brain reading: psychophysiology, physiology, and cognition. *Psychophysiology, 26*(3), 251-269.

Connolly, J. D., Andersen, R. A., & Goodale, M. A. (2003). FMRI evidence for a 'parietal reach region' in the human brain. *Experimental Brain Research, 153*(2), 140-145.

Conti, P, & Beaubaton, D. (1976). Utilisation des informations visuelles dans le contrôle du mouvement: étude de la précision des pointages chez l'homme. *Le Travail Humain*, 19-32.

Crawford, J. D., Medendorp, W. P., & Marotta, J. J. (2004). Spatial transformations for eye-hand coordination. *Journal of Neurophysiology, 92*(1), 10-19.

Culham, J. C., Dukelow, S. P., Vilis, T., Hassard, F. A., Gati, J. S., Menon, R. S., & Goodale, M. A. (1999). Recovery of fMRI activation in motion area MT following storage of the motion aftereffect. *Journal of Neurophysiology, 81*(1), 388-393.

Daniel, P. M., & Whitteridge, D. (1961). The representation of the visual field on the cerebral cortex in monkeys. *Journal of Physiology, 159*, 203-221.

Davare, M., Zenon, A., Pourtois, G., Desmurget, M., & Olivier, E. (2012). Role of the medial part of the intraparietal sulcus in implementing movement direction. *Cerebral Cortex, 22*(6), 1382-1394.

Day, B. L., & Brown, P. (2001). Evidence for subcortical involvement in the visual control of human reaching. *Brain, 124*(Pt 9), 1832-1840.

Day, B. L., Dressler, D., Maertens de Noordhout, A., Marsden, C. D., Nakashima, K., Rothwell, J. C., & Thompson, P. D. (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology, 412*, 449-473.

Day, B. L., & Lyon, I. N. (2000). Voluntary modification of automatic arm movements evoked by motion of a visual target. *Experimental Brain Research, 130*(2), 159-168.

Day, B. L., Rothwell, J. C., Thompson, P. D., Dick, J. P., Cowan, J. M., Berardelli, A., & Marsden, C. D. (1987). Motor cortex stimulation in intact man. 2. Multiple descending volleys. *Brain, 110 (Pt 5)*, 1191-1209.

de Grave, D. D., Brenner, E., & Smeets, J. B. (2011). Judgments of reachability are independent of visuomotor adaptation. *Perception, 40*(8), 962-974.

De Valois, R. L., & De Valois, K. K. (1991). Vernier acuity with stationary moving Gabors. *Vision Research, 31*(9), 1619-1626.

De Valois, R. L., Morgan, H., & Snodderly, D. M. (1974). Psychophysical studies of monkey vision. 3. Spatial luminance contrast sensitivity tests of macaque and human observers. *Vision Research, 14*(1), 75-81.

Debaere, F., Wenderoth, N., Sunaert, S., Van Hecke, P., & Swinnen, S. P. (2003). Internal vs external generation of movements: differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. *Neuroimage, 19*(3), 764-776.

Delevoye-Turrell, Y., Vienne, C., & Coello, Y. (2011). Space Boundaries in Schizophrenia. *Social Psychology, 42*(3), 193-204.

Della-Maggiore, V., Malfait, N., Ostry, D. J., & Paus, T. (2004). Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. *Journal of Neuroscience, 24*(44), 9971-9976.

Deneve, S., & Pouget, A. (2004). Bayesian multisensory integration and cross-modal spatial links. *Journal of Physiology, Paris, 98*(1-3), 249-258.

Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature Neuroscience, 2*(6), 563-567.

Desmurget, M., Gaveau, V., Vindras, P., Turner, R. S., Broussolle, E., & Thobois, S. (2004). On-line motor control in patients with Parkinson's disease. *Brain, 127*(Pt 8), 1755-1773.

Desmurget, M., Grea, H., Grethe, J. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (2001). Functional anatomy of nonvisual feedback loops during reaching: a positron emission tomography study. *Journal of Neuroscience, 21*(8), 2919-2928.

Desmurget, M., Turner, R. S., Prablanc, C., Russo, G. S., Alexander, G. E., & Grafton, S. T. (2005). Updating target location at the end of an orienting saccade affects the characteristics of simple point-to-point movements. *Journal of Experimental Psychology: Human Perception and Performance, 31*(6), 1510-1536.

Deubel, H., Schneider, W. X., & Bridgeman, B. (1996). Postsaccadic target blanking prevents saccadic suppression of image displacement. *Vision Research, 36*(7), 985-996.

DeYoe, E. A., & Van Essen, D. C. (1988). Concurrent processing streams in monkey visual cortex. *Trends in Neurosciences, 11*(5), 219-226.

di Pellegrino, G., Ladavas, E., & Farne, A. (1997). Seeing where your hands are. *Nature, 388*(6644), 730.

Diedrichsen, J., Hashambhoy, Y., Rane, T., & Shadmehr, R. (2005). Neural correlates of reach errors. *Journal of Neuroscience, 25*(43), 9919-9931.

Douek, P., Turner, R., Pekar, J., Patronas, N., & Le Bihan, D. (1991). MR color mapping of myelin fiber orientation. *Journal of Computer Assisted Tomography, 15*(6), 923-929.

Durant, S., & Johnston, A. (2004). Temporal dependence of local motion induced shifts in perceived position. *Vision Research, 44*(4), 357-366.

Eagleman, D. M., & Sejnowski, T. J. (2007). Motion signals bias localization judgments: a unified explanation for the flash-lag, flash-drag, flash-jump, and Frohlich illusions. *J Vis, 7*(4), 3.

Elliott, D., Garson, R. G, Goodman, D. G., & Chua, R. (1991). Discrete vs. continuous visual control of manual aiming. *Hum Mov Sci, 10*(4), 393-418.

Ernst, M. O., & Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature, 415*(6870), 429-433.

Farne, A., Bonifazi, S., & Ladavas, E. (2005). The role played by tool-use and tool-length on the Plastic Elongation of peri-hand space: a single case study. *Cognitive Neuropsychology, 22*(3), 408-418.

Farne, A., & Ladavas, E. (2000). Dynamic size-change of hand peripersonal space following tool use. *Neuroreport, 11*(8), 1645-1649.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex, 1*(1), 1-47.

ffytche, D. H., Guy, C. N., & Zeki, S. (1995). The parallel visual motion inputs into areas V1 and V5 of human cerebral cortex. *Brain, 118 (Pt 6)*, 1375-1394.

Filimon, F., Nelson, J. D., Huang, R. S., & Sereno, M. I. (2009). Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. *Journal of Neuroscience, 29*(9), 2961-2971.

Fischer, J., & Whitney, D. (2009). Precise discrimination of object position in the human pulvinar. *Human Brain Mapping, 30*(1), 101-111.

Fischer, M. H. (2000). Estimating reachability: Whole body engagement or postural stability? *Hum Mov Sci, 19*(3), 297-318.

Fischer, M. H. (2003). Can we correctly perceive the reaching range of others? *British Journal of Psychology, 94*(4), 487-500.

Fitts, P. M. (1947). A study of location discrimination ability. *Psychological research on equipment design*, 207-217.

Fitts, P. M. (1954). The information capacity of the human motor system in controlling the amplitude of movement. *Journal of Experimental Psychology, 47*(6), 381-391.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology, 117*(12), 2584-2596.

Fox, P., Ingham, R., George, M. S., Mayberg, H., Ingham, J., Roby, J., . . . Jerabek, P. (1997). Imaging human intra-cerebral connectivity by PET during TMS. *Neuroreport, 8*(12), 2787-2791.

Fox, M. D., Halko, M. A., Eldaief, M. C., & Pascual-Leone, A. (2012). Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). *Neuroimage, 62*(4), 2232-2243.

Fröhlich, F. W. (1923). Uber die Messung der Empfindungszeit [Measuring the time of sensation]. *Z Sinnesphysiol, 54*, 58-78.

Fröhlich, F. W. (1929). *Die empfindungszeit*: G. Fischer.

Fu, Y. X., Shen, Y., Gao, H., & Dan, Y. (2004). Asymmetry in visual cortical circuits underlying motion-induced perceptual mislocalization. *Journal of Neuroscience, 24*(9), 2165-2171.

Fuhr, P., Agostino, R., & Hallett, M. (1991). Spinal motor neuron excitability during the silent period after cortical stimulation. *Electroencephalography and Clinical Neurophysiology, 81*(4), 257-262.

Galletti, C., Fattori, P., Kutz, D. F., & Battaglini, P. P. (1997). Arm movement-related neurons in the visual area V6A of the macaque superior parietal lobule. *European Journal of Neuroscience, 9*(2), 410-413.

Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *Journal of Neuroscience, 23*(27), 9240-9245.

Georgopoulos, A. P. (1986). On reaching. *Annual Review of Neuroscience, 9*(1), 147-170.

Gerschlager, W., Siebner, H. R., & Rothwell, J. C. (2001). Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. *Neurology, 57*(3), 449-455.

Ghahramani, Z., & Wolpert, D. M. (1997). Modular decomposition in visuomotor learning. *Nature, 386*(6623), 392-395.

Gielen, C. C., van den Heuvel, P. J., & van Gisbergen, J. A. (1984). Coordination of fast eye and arm movements in a tracking task. *Experimental Brain Research, 56*(1), 154-161.

Gilbert, C. D., & Li, W. (2013). Top-down influences on visual processing. *Nature Reviews: Neuroscience, 14*(5), 350-363.

Gomi, H., Abekawa, N., & Nishida, S. (2006). Spatiotemporal tuning of rapid interactions between visual-motion analysis and reaching movement. *Journal of Neuroscience, 26*(20), 5301-5308.

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences, 15*(1), 20-25.

Goodale, M. A., Pelisson, D., & Prablanc, C. (1986). Large adjustments in visually guided reaching do not depend on vision of the hand or perception of target displacement. *Nature, 320*(6064), 748-750.

Grafton, S. T., Mazziotta, J. C., Woods, R. P., & Phelps, M. E. (1992). Human functional anatomy of visually guided finger movements. *Brain, 115 (Pt 2)*, 565-587.

Grea, H., Pisella, L., Rossetti, Y., Desmurget, M., Tilikete, C., Grafton, S., . . . Vighetto, A. (2002). A lesion of the posterior parietal cortex disrupts on-line adjustments during aiming movements. *Neuropsychologia, 40*(13), 2471-2480.

Gritsenko, V., Yakovenko, S., & Kalaska, J. F. (2009). Integration of predictive feedforward and sensory feedback signals for online control of visually guided movement. *Journal of Neurophysiology, 102*(2), 914-930.

Gross, C. G., Rocha-Miranda, C. E., & Bender, D. B. (1972). Visual properties of neurons in inferotemporal cortex of the Macaque. *Journal of Neurophysiology, 35*(1), 96-111.

Guillery, R. W., & Sherman, S. M. (2002). Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. *Neuron, 33*(2), 163-175.

Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron, 55*(2), 187-199.

Hallett, M., & Chokroverty, S. (2005). *Magnetic stimulation in clinical neurophysiology*: Elsevier Health Sciences.

Hartwigsen, G., Bestmann, S., Ward, N. S., Woerbel, S., Mastroeni, C., Granert, O., & Siebner, H. R. (2012). Left dorsal premotor cortex and supramarginal gyrus complement each other during rapid action reprogramming. *Journal of Neuroscience, 32*(46), 16162-16171.

Hay, J. C, Pick, H. L, & Ikeda, K. (1965). Visual capture produced by prism spectacles. *Psychonomic science*.

Head, H., & Holmes, G. M. (1911). Sensory disturbances from cerebral lesions. *Brain, 34*(2-3), 102-254.

Held, R., & Gottlieb, N. (1958). Technique for studying adaptation to disarranged hand-eye coordination. *Perceptual and Motor Skills, 8*(3), 83-86.

Helmholtz, H. V. (1925). Treatise on psychological optics. *Optical Society of America, 3*, 482.

Henriques, D. Y., Klier, E. M., Smith, M. A., Lowy, D., & Crawford, J. D. (1998). Gaze-centered remapping of remembered visual space in an open-loop pointing task. *Journal of Neuroscience, 18*(4), 1583-1594.

Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 353*(1373), 1257-1270.

Himmelbach, M., Linzenbold, W., & Ilg, U. J. (2013). Dissociation of reach-related and visual signals in the human superior colliculus. *Neuroimage, 82*, 61-67.

Holmes, N. P., & Spence, C. (2004). The body schema and the multisensory representation(s) of peripersonal space. *Cogn Process, 5*(2), 94-105.

Hopf, J. M., Vogel, E., Woodman, G., Heinze, H. J., & Luck, S. J. (2002). Localizing visual discrimination processes in time and space. *Journal of Neurophysiology, 88*(4), 2088-2095.

Huang, Y. Z., Rothwell, J. C., Chen, R. S., Lu, C. S., & Chuang, W. L. (2011). The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. *Clinical Neurophysiology, 122*(5), 1011-1018.

Inoue, K., Kawashima, R., Sugiura, M., Ogawa, A., Schormann, T., Zilles, K., & Fukuda, H. (2001). Activation in the ipsilateral posterior parietal cortex during tool use: a PET study. *Neuroimage, 14*(6), 1469-1475.

Iriki, A., Tanaka, M., & Iwamura, Y. (1996). Coding of modified body schema during tool use by macaque postcentral neurones. *Neuroreport, 7*(14), 2325-2330.

Ishibashi, H., Hihara, S., & Iriki, A. (2000). Acquisition and development of monkey tool-use: behavioral and kinematic analyses. *Canadian Journal of Physiology and Pharmacology, 78*(11), 958-966.

Jacobs, R. A. (1999). Optimal integration of texture and motion cues to depth. *Vision Research, 39*(21), 3621-3629.

Jack, J. J. B., Noble, D., & Tsien, R. W. (1983). Electric Current Flow in Excitable Cells: Oxford University Press, New York.

Jakobson, L. S., & Goodale, M. A. (1989). Trajectories of reaches to prismatically-displaced targets: evidence for "automatic" visuomotor recalibration. *Experimental Brain Research, 78*(3), 575-587.

Jeannerod, M. (1988). *The neural and behavioural organization of goal-directed movements*: Clarendon Press/Oxford University Press.

Johansen-Berg, H., Della-Maggiore, V., Behrens, T. E., Smith, S. M., & Paus, T. (2007). Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage, 36 Suppl 2*, T16-21.

Johnson, P. B., & Ferraina, S. (1996). Cortical networks for visual reaching: intrinsic frontal lobe connectivity. *European Journal of Neuroscience, 8*(7), 1358-1362.

Johnson, P. B., Ferraina, S., & Caminiti, R. (1993). Cortical networks for visual reaching. *Experimental Brain Research, 97*(2), 361-365.

Jordan, M. I., & Wolpert, D. M. (1995). Computational motor control. The Cognitive Neurosciences.: MIT Press, Cambridge.

Joy, M., Scott, G., & Henkelman, M. (1989). In vivo detection of applied electric currents by magnetic resonance imaging. *Magnetic Resonance Imaging, 7*(1), 89-94.

Kaas, J. H., & Huerta, M. F. (1988). The subcortical visual system of primates. *Comparative primate biology, 4*, 327-391.

Kadota, K., & Gomi, H. (2010). Implicit visuomotor processing for quick online reactions is robust against aging. *Journal of Neuroscience, 30*(1), 205-209.

Kawano, K., & Miles, F. A. (1986). Short-latency ocular following responses of monkey. II. Dependence on a prior saccadic eye movement. *Journal of Neurophysiology, 56*(5), 1355-1380.

Keele, S. W., & Posner, M. I. (1968). Processing of visual feedback in rapid movements. *Journal of Experimental Psychology, 77*(1), 155-158.

Kertzman, C., Schwarz, U., Zeffiro, T. A., & Hallett, M. (1997). The role of posterior parietal cortex in visually guided reaching movements in humans. *Experimental Brain Research, 114*(1), 170-183.

Kerzel, D., & Gegenfurtner, K. R. (2003). Neuronal processing delays are compensated in the sensorimotor branch of the visual system. *Current Biology, 13*(22), 1975-1978.

Kloppel, S., Baumer, T., Kroeger, J., Koch, M. A., Buchel, C., Munchau, A., & Siebner, H. R. (2008). The cortical motor threshold reflects microstructural properties of cerebral white matter. *Neuroimage, 40*(4), 1782-1791.

Knill, D. C., & Pouget, A. (2004). The Bayesian brain: the role of uncertainty in neural coding and computation. *Trends in Neurosciences, 27*(12), 712-719.

Komilis, E., Pelisson, D., & Prablanc, C. (1993). Error processing in pointing at randomly feedback-induced double-step stimuli. *J Mot Behav, 25*(4), 299-308.

Kornhuber, H. H, & Deecke, L. (1965). Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere, 284*(1), 1-17.

Krekelberg, B., & Lappe, M. (2001). Neuronal latencies and the position of moving objects. *Trends in Neurosciences, 24*(6), 335-339.

Lackner, J. R., & Shenker, B. (1985). Proprioceptive influences on auditory and visual spatial localization. *Journal of Neuroscience, 5*(3), 579-583.

Lacquaniti, F., Guigon, E., Bianchi, L., Ferraina, S., & Caminiti, R. (1995). Representing spatial information for limb movement: role of area 5 in the monkey. *Cerebral Cortex, 5*(5), 391-409.

Làdavas, E. (2002). Functional and dynamic properties of visual peripersonal space. *Trends Cogn Sci, 6*(1), 17-22.

Ladavas, E., di Pellegrino, G., Farne, A., & Zeloni, G. (1998). Neuropsychological evidence of an integrated visuotactile representation of peripersonal space in humans. *Journal of Cognitive Neuroscience, 10*(5), 581-589.

Lamme, V. A., & Roelfsema, P. R. (2000). The distinct modes of vision offered by feedforward and recurrent processing. *Trends in Neurosciences, 23*(11), 571-579.

Langolf, G. D, Chaffin, D. B, & Foulke, J. A. (1976). An investigation of Fitts' law using a wide range of movement amplitudes. *J Mot Behav, 8*(2), 113-128.

Le Bihan, D., Breton, E., Lallemand, D., Grenier, P., Cabanis, E., & Laval-Jeantet, M. (1986). MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology, 161*(2), 401-407.

Lee, B. B., Pokorny, J., Smith, V. C., Martin, P. R., & Valberg, A. (1990). Luminance and chromatic modulation sensitivity of macaque ganglion cells and human observers. *Journal of the Optical Society of America A: Optics and Image Science, 7*(12), 2223-2236.

Lee, D. N., Georgopoulos, A. P., Clark, M. J., Craig, C. M., & Port, N. (2001). Guiding contact by coupling the taus of gaps. *Experimental Brain Research, 139*(2), 151-159.

Leopold, D. A. (2012). Primary visual cortex: awareness and blindsight. *Annual Review of Neuroscience, 35*, 91-109.

Lewis, J. W., & Van Essen, D. C. (2000). Mapping of architectonic subdivisions in the macaque monkey, with emphasis on parieto-occipital cortex. *Journal of Comparative Neurology, 428*(1), 79-111.

Libet, B., Gleason, C. A., Wright, E. W., & Pearl, D. K. (1983). Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential) The unconscious initiation of a freely voluntary act. *Brain, 106*(3), 623-642.

Linares, D., Lopez-Moliner, J., & Johnston, A. (2007). Motion signal and the perceived positions of moving objects. *J Vis, 7*(7), 1 1-7.

Linzenbold, W., & Himmelbach, M. (2012). Signals from the deep: reach-related activity in the human superior colliculus. *Journal of Neuroscience, 32*(40), 13881-13888.

Liu, X., Ingram, H. A., Palace, J. A., & Miall, R. C. (1999). Dissociation of 'on-line' and 'off-line' visuomotor control of the arm by focal lesions in the cerebellum and brainstem. *Neuroscience Letters, 264*(1-3), 121-124.

Liu, X., Zhu, T., Gu, T., & Zhong, J. (2009). A practical approach to in vivo high-resolution diffusion tensor imaging of rhesus monkeys on a 3-T human scanner. *Magnetic Resonance Imaging, 27*(3), 335-346.

Luck, S. J. (2005). *An introduction to the event-related potential technique*: MIT press Cambridge, MA.

Luck, S. J., & Hillyard, S. A. (1994). Electrophysiological correlates of feature analysis during visual search. *Psychophysiology, 31*(3), 291-308.

Lynch, J. C. (1980). The functional organization of posterior parietal association cortex. *Behavioral and Brain Sciences, 3*(04), 485-499.

Lyon, D. C., Nassi, J. J., & Callaway, E. M. (2010). A disynaptic relay from superior colliculus to dorsal stream visual cortex in macaque monkey. *Neuron, 65*(2), 270-279.

Mackay, D. M. (1958). Perceptual stability of a stroboscopically lit visual field containing self-luminous objects. *Nature, 181*(4607), 507-508.

Madden, D. J., Whiting, W. L., Huettel, S. A., White, L. E., MacFall, J. R., & Provenzale, J. M. (2004). Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *Neuroimage, 21*(3), 1174-1181.

Maij, F., Brenner, E., & Smeets, J. B. (2009). Temporal information can influence spatial localization. *Journal of Neurophysiology, 102*(1), 490-495.

Mangun, G. R. (1995). Neural mechanisms of visual selective attention. *Psychophysiology, 32*(1), 4-18.

Mangun, G. R., Hillyard, S. A., & Luck, S. J. (1993). IQ Electrocortical Substrates of Visual Selective Attention. *Attention and performance XIV: Synergies in experimental psychology, artificial intelligence, and cognitive neuroscience, 14*, 219.

Maravita, A., & Iriki, A. (2004). Tools for the body (schema). *Trends Cogn Sci, 8*(2), 79-86.

Masson, G., Proteau, L., & Mestre, D. R. (1995). Effects of stationary and moving textured backgrounds on the visuo-oculo-manual tracking in humans. *Vision Research, 35*(6), 837-852.

Mateeff, S., & Hohnsbein, J. (1988). Perceptual latencies are shorter for motion towards the fovea than for motion away. *Vision Research, 28*(6), 711-719.

Matin, L., Boff, K. R., & Pola, J. (1976). Vernier offset produced by rotary target motion. *Attention, Perception, & Psychophysics, 20*(2), 138-142.

Maunsell, J. H., Nealey, T. A., & DePriest, D. D. (1990). Magnocellular and parvocellular contributions to responses in the middle temporal visual area (MT) of the macaque monkey. *Journal of Neuroscience, 10*(10), 3323-3334.

Maunsell, J. H., & Newsome, W. T. (1987). Visual processing in monkey extrastriate cortex. *Annual Review of Neuroscience, 10*, 363-401.

Maunsell, J. H., & Van Essen, D. C. (1983). Functional properties of neurons in middle temporal visual area of the macaque monkey. I. Selectivity for stimulus direction, speed, and orientation. *Journal of Neurophysiology, 49*(5), 1127-1147.

Maunsell, John HR. (1987). Physiological evidence for two visual subsystems *Matters of intelligence* (pp. 59-87): Springer.

Maus, G. W., Ward, J., Nijhawan, R., & Whitney, D. (2013). The perceived position of moving objects: transcranial magnetic stimulation of area MT+ reduces the flash-lag effect. *Cerebral Cortex, 23*(1), 241-247.

McGraw, P. V., Walsh, V., & Barrett, B. T. (2004). Motion-sensitive neurones in V5/MT modulate perceived spatial position. *Current Biology, 14*(12), 1090-1093.

McGraw, P. V., Whitaker, D., Skillen, J., & Chung, S. T. (2002). Motion adaptation distorts perceived visual position. *Current Biology, 12*(23), 2042-2047.

McIntyre, J., Stratta, F., & Lacquaniti, F. (1998). Short-term memory for reaching to visual targets: psychophysical evidence for body-centered reference frames. *Journal of Neuroscience, 18*(20), 8423-8435.

Medendorp, W. P., Goltz, H. C., Vilis, T., & Crawford, J. D. (2003). Gaze-centered updating of visual space in human parietal cortex. *Journal of Neuroscience, 23*(15), 6209-6214.

Merriam, E. P., Genovese, C. R., & Colby, C. L. (2003). Spatial updating in human parietal cortex. *Neuron, 39*(2), 361-373.

Metzger, W. (1932). Versuch einer gemeinsamen theorie der phänomene fröhlichs und hazelhoffs und kritik ihrer verfahren zur messung der empfindungszeit. *Psychologische Forschung, 16*(1), 176-200.

Miall, R. C., Weir, D. J., Wolpert, D. M., & Stein, J. F. (1993). Is the cerebellum a smith predictor? *J Mot Behav, 25*(3), 203-216.

Michel, C. M., & Murray, M. M. (2012). Towards the utilization of EEG as a brain imaging tool. *Neuroimage, 61*(2), 371-385.

Miller, J., Riehle, A., & Requin, J. (1992). Effects of preliminary perceptual output on neuronal activity of the primary motor cortex. *Journal of Experimental Psychology: Human Perception and Performance, 18*(4), 1121-1138.

Milner, A. D., & Goodale, M. A. (1993). Visual pathways to perception and action. *Progress in Brain Research, 95*, 317-337.

Mishkin, M., & Ungerleider, L. G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behavioural Brain Research, 6*(1), 57-77.

Mohrmann-Lendla, H., & Fleischer, A. G. (1991). The effect of a moving background on aimed hand movements. *Ergonomics, 34*(3), 353-364.

Mon-Williams, M., Wann, J. P., Jenkinson, M., & Rushton, K. (1997). Synaesthesia in the normal limb. *Proceedings: Biological Sciences, 264*(1384), 1007-1010.

Mountcastle, V. B., Lynch, J. C., Georgopoulos, A., Sakata, H., & Acuna, C. (1975). Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *Journal of Neurophysiology, 38*(4), 871-908.

Muellbacher, W., Ziemann, U., Boroojerdi, B., & Hallett, M. (2000). Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. *Clinical Neurophysiology, 111*(6), 1002-1007.

Murakami, I. (2001). The flash-lag effect as a spatiotemporal correlation structure. *J Vis, 1*(2), 126-136.

Murata, A., Gallese, V., Luppino, G., Kaseda, M., & Sakata, H. (2000). Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. *Journal of Neurophysiology, 83*(5), 2580-2601.

Nijhawan, R. (1994). Motion extrapolation in catching. *Nature, 370*(6487), 256-257.

Nishida, S., & Johnston, A. (1999). Influence of motion signals on the perceived position of spatial pattern. *Nature, 397*(6720), 610-612.

Nowak, L. G., & Bullier, J. (1997). The timing of information transfer in the visual system *Extrastriate cortex in primates* (pp. 205-241): Springer.

Paillard, J. (1982). Apraxia and the neurophysiology of motor control. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 298*(1089), 111-134.

Pascual-Leone, A., Valls-Sole, J., Wassermann, E. M., & Hallett, M. (1994). Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain, 117 (Pt 4)*, 847-858.

Pascual-Leone, A., & Walsh, V. (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science, 292*(5516), 510-512.

Pascual-Marqui, R. D., Michel, C. M., & Lehmann, D. (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *International Journal of Psychophysiology, 18*(1), 49-65.

Payne, B. R., Lomber, S. G., Villa, A. E., & Bullier, J. (1996). Reversible deactivation of cerebral network components. *Trends in Neurosciences, 19*(12), 535-542.

Pelisson, D., Prablanc, C., Goodale, M. A., & Jeannerod, M. (1986). Visual control of reaching movements without vision of the limb. II. Evidence of fast unconscious processes correcting the trajectory of the hand to the final position of a double-step stimulus. *Experimental Brain Research, 62*(2), 303-311.

Penfield, W., & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain: A journal of neurology, 60*(4), 389-443.

Perenin, M. T., & Jeannerod, M. (1975). Residual vision in cortically blind hemiphields. *Neuropsychologia, 13*(1), 1-7.

Perry, V. H., & Cowey, A. (1984). Retinal ganglion cells that project to the superior colliculus and pretectum in the macaque monkey. *Neuroscience, 12*(4), 1125-1137.

Pisella, L., Grea, H., Tilikete, C., Vighetto, A., Desmurget, M., Rode, G., . . . Rossetti, Y. (2000). An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. *Nature Neuroscience, 3*(7), 729-736.

Poppel, E., Held, R., & Frost, D. (1973). Leter: Residual visual function after brain wounds involving the central visual pathways in man. *Nature, 243*(5405), 295-296.

Prablanc, C., Desmurget, M., & Grea, H. (2003). Neural control of on-line guidance of hand reaching movements. *Progress in Brain Research, 142*, 155-170.

Prablanc, C., Echallier, J. E., Jeannerod, M., & Komilis, E. (1979). Optimal response of eye and hand motor systems in pointing at a visual target. II. Static and dynamic visual cues in the control of hand movement. *Biological Cybernetics, 35*(3), 183-187.

Prablanc, C., Echallier, J. F., Komilis, E., & Jeannerod, M. (1979). Optimal response of eye and hand motor systems in pointing at a visual target. I. Spatio-temporal characteristics of eye and hand movements and their relationships when varying the amount of visual information. *Biological Cybernetics, 35*(2), 113-124.

Prablanc, C., & Martin, O. (1992). Automatic control during hand reaching at undetected two-dimensional target displacements. *Journal of Neurophysiology, 67*(2), 455-469.

Proteau, L., & Masson, G. (1997). Visual perception modifies goal-directed movement control: supporting evidence from a visual perturbation paradigm. *Quarterly Journal of Experimental Psychology. A: Human Experimental Psychology, 50*(4), 726-741.

Raichle, M. E., & Mintun, M. A. (2006). Brain work and brain imaging. *Annual Review of Neuroscience, 29*, 449-476.

Ramachandran, V. S., & Anstis, S. M. (1990). Illusory displacement of equiluminous kinetic edges. *Perception, 19*(5), 611-616.

Redding, G. M., & Wallace, B. (1996). Adaptive spatial alignment and strategic perceptual-motor control. *Journal of Experimental Psychology: Human Perception and Performance, 22*(2), 379-394.

Reichenbach, A, Bresciani, J-P, Peer, A, Bülthoff, HH, & Thielscher, A. (2008). Inter-individual spatial diversity in motor control processes within the posterior parietal cortex assessed with transcranial magnetic stimulation. *Brain Stimul, 1*(3), 283-284.

Reichenbach, A., Bresciani, J. P., Peer, A., Bulthoff, H. H., & Thielscher, A. (2011). Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS. *Cerebral Cortex, 21*(7), 1602-1612.

Ridding, M. C., & Rothwell, J. C. (2007). Is there a future for therapeutic use of transcranial magnetic stimulation? *Nature Reviews: Neuroscience, 8*(7), 559-567.

Rizzolatti, G., Riggio, L., & Sheliga, B. M. (1994). Space and selective attention. *Attention and performance XV, 15*, 231-265.

Ro, T., Shelton, D., Lee, O. L., & Chang, E. (2004). Extrageniculate mediation of unconscious vision in transcranial magnetic stimulation-induced blindsight. *Proceedings of the National Academy of Sciences of the United States of America, 101*(26), 9933-9935.

Rodieck, R. W. (1965). Quantitative analysis of cat retinal ganglion cell response to visual stimuli. *Vision Research, 5*(11), 583-601.

Rodman, H. R., Gross, C. G., & Albright, T. D. (1990). Afferent basis of visual response properties in area MT of the macaque. II. Effects of superior colliculus removal. *Journal of Neuroscience, 10*(4), 1154-1164.

Rollnik, J. D., Schroder, C., Rodriguez-Fornells, A., Kurzbuch, A. R., Dauper, J., Moller, J., & Munte, T. F. (2004). Functional lesions and human action monitoring: combining repetitive transcranial magnetic stimulation and event-related brain potentials. *Clinical Neurophysiology, 115*(1), 145-153.

Rosenbaum, D. A. (1980). Human movement initiation: specification of arm, direction, and extent. *Journal of Experimental Psychology: General, 109*(4), 444-474.

Rosenbaum, D. A., Hindorff, V., & Munro, E. M. (1987). Scheduling and programming of rapid finger sequences: tests and elaborations of the hierarchical editor model. *Journal of Experimental Psychology: Human Perception and Performance, 13*(2), 193-203.

Ross, J., Morrone, M. C., & Burr, D. C. (1997). Compression of visual space before saccades. *Nature, 386*(6625), 598-601.

Rossetti, Y., Stelmach, G., Desmurget, M., Prablanc, C., & Jeannerod, M. (1994). The effect of viewing the static hand prior to movement onset on pointing kinematics and variability. *Experimental Brain Research, 101*(2), 323-330.

Saijo, N., Murakami, I., Nishida, S., & Gomi, H. (2005). Large-field visual motion directly induces an involuntary rapid manual following response. *Journal of Neuroscience, 25*(20), 4941-4951.

Salin, P. A., & Bullier, J. (1995). Corticocortical connections in the visual system: structure and function. *Physiological Reviews, 75*(1), 107-154.

Sarlegna, F., Blouin, J., Bresciani, J. P., Bourdin, C., Vercher, J. L., & Gauthier, G. M. (2003). Target and hand position information in the online control of goal-directed arm movements. *Experimental Brain Research, 151*(4), 524-535.

Sarlegna, F. R., & Blouin, J. (2010). Visual guidance of arm reaching: online adjustments of movement direction are impaired by amplitude control. *J Vis, 10*(5), 24.

Saunders, J. A., & Knill, D. C. (2003). Humans use continuous visual feedback from the hand to control fast reaching movements. *Experimental Brain Research, 152*(3), 341-352.

Savelsbergh, G. J., Whiting, H. T., Burden, A. M., & Bartlett, R. M. (1992). The role of predictive visual temporal information in the coordination of muscle activity in catching. *Experimental Brain Research, 89*(1), 223-228.

Schenk, T., Ellison, A., Rice, N., & Milner, A. D. (2005). The role of V5/MT+ in the control of catching movements: an rTMS study. *Neuropsychologia, 43*(2), 189-198.

Schenk, T., Mair, B., & Zihl, J. (2004). The use of visual feedback and on-line target information in catching and grasping. *Experimental Brain Research, 154*(1), 85-96.

Scherg, M. (1990). Fundamentals of dipole source potential analysis. *Auditory evoked magnetic fields and electric potentials. Advances in audiology, 6*, 40-69.

Schiller, P. H. (1986). The central visual system. *Vision Research, 26*(9), 1351-1386.

Schlag, J., Cai, R. H., Dorfman, A., Mohempour, A., & Schlag-Rey, M. (2000). Extrapolating movement without retinal motion. *Nature, 403*(6765), 38-39.

Schmid, M. C., Mrowka, S. W., Turchi, J., Saunders, R. C., Wilke, M., Peters, A. J., . . . Leopold, D. A. (2010). Blindsight depends on the lateral geniculate nucleus. *Nature, 466*(7304), 373-377.

Schmolesky, M. T., Wang, Y., Hanes, D. P., Thompson, K. G., Leutgeb, S., Schall, J. D., & Leventhal, A. G. (1998). Signal timing across the macaque visual system. *Journal of Neurophysiology, 79*(6), 3272-3278.

Schneider, G. E. (1969). Two visual systems. *Science, 163*(3870), 895-902.

Schwartz, G., Taylor, S., Fisher, C., Harris, R., & Berry, M. J., 2nd. (2007). Synchronized firing among retinal ganglion cells signals motion reversal. *Neuron, 55*(6), 958-969.

Scott, S. H. (2004). Optimal feedback control and the neural basis of volitional motor control. *Nature Reviews: Neuroscience, 5*(7), 532-546.

Sereno, M. I., Pitzalis, S., & Martinez, A. (2001). Mapping of contralateral space in retinotopic coordinates by a parietal cortical area in humans. *Science, 294*(5545), 1350-1354.

Shadmehr, R. (2005). *The computational neurobiology of reaching and pointing: a foundation for motor learning*: MIT press.

Shidara, M., Kawano, K., Gomi, H., & Kawato, M. (1993). Inverse-dynamics model eye movement control by Purkinje cells in the cerebellum. *Nature, 365*(6441), 50-52.

Siebner, H. R., Mentschel, C., Auer, C., & Conrad, B. (1999). Repetitive transcranial magnetic stimulation has a beneficial effect on bradykinesia in Parkinson's disease. *Neuroreport, 10*(3), 589-594.

Siebner, H. R., Peller, M., Willoch, F., Minoshima, S., Boecker, H., Auer, C., . . . Bartenstein, P. (2000). Lasting cortical activation after repetitive TMS of the motor cortex: a glucose metabolic study. *Neurology, 54*(4), 956-963.

Siebner, H. R., & Rothwell, J. (2003). Transcranial magnetic stimulation: new insights into representational cortical plasticity. *Experimental Brain Research, 148*(1), 1-16.

Silvanto, J., Cowey, A., Lavie, N., & Walsh, V. (2005). Striate cortex (V1) activity gates awareness of motion. *Nature Neuroscience, 8*(2), 143-144.

Sincich, L. C., Park, K. F., Wohlgemuth, M. J., & Horton, J. C. (2004). Bypassing V1: a direct geniculate input to area MT. *Nature Neuroscience, 7*(10), 1123-1128.

Smeets, J. B., & Brenner, E. (1995). Perception and action are based on the same visual information: distinction between position and velocity. *Journal of Experimental Psychology: Human Perception and Performance, 21*(1), 19-31.

Smeets, J. B., van den Dobbelsteen, J. J., de Grave, D. D., van Beers, R. J., & Brenner, E. (2006). Sensory integration does not lead to sensory calibration. *Proceedings of the National Academy of Sciences of the United States of America, 103*(49), 18781-18786.

Snowden, R. J. (1998). Shifts in perceived position following adaptation to visual motion. *Current Biology, 8*(24), 1343-1345.

Snowden, R. J., Treue, S., & Andersen, R. A. (1992). The response of neurons in areas V1 and MT of the alert rhesus monkey to moving random dot patterns. *Experimental Brain Research, 88*(2), 389-400.

Soechting, J. F., Engel, K. C., & Flanders, M. (2001). The Duncker illusion and eye-hand coordination. *Journal of Neurophysiology, 85*(2), 843-854.

Soechting, J. F., & Lacquaniti, F. (1983). Modification of trajectory of a pointing movement in response to a change in target location. *Journal of Neurophysiology, 49*(2), 548-564.

Solomon, S. G., & Lennie, P. (2007). The machinery of colour vision. *Nature Reviews: Neuroscience, 8*(4), 276-286.

Solomon, S. J., Pasik, T., & Pasik, P. (1981). Extrageniculostriate vision in the monkey. VIII. Critical structures for spatial localization. *Experimental Brain Research, 44*(3), 259-270.

Spehlmann, R. (1965). The averaged electrical responses to diffuse and to patterned light in the human. *Electroencephalography and Clinical Neurophysiology, 19*(6), 560-569.

Spence, C, Pavani, F, & Driver, J. (1998). What crossing the hands can reveal about crossmodal links in spatial attention. *Psychonomic Society, 3*, 13.

Standage, G. P., & Benevento, L. A. (1983). The organization of connections between the pulvinar and visual area MT in the macaque monkey. *Brain Research, 262*(2), 288-294.

Stein, J. F. (1992). The representation of egocentric space in the posterior parietal cortex. *Behavioral and Brain Sciences, 15 Spec No 4*, 691-700.

Stinear, C. M., Barber, P. A., Smale, P. R., Coxon, J. P., Fleming, M. K., & Byblow, W. D. (2007). Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain, 130*(Pt 1), 170-180.

Strangman, G. E., O'Neil-Pirozzi, T. M., Supelana, C., Goldstein, R., Katz, D. I., & Glenn, M. B. (2012). Fractional anisotropy helps predicts memory rehabilitation outcome after traumatic brain injury. *NeuroRehabilitation, 31*(3), 295-310.

Sundberg, K. A., Fallah, M., & Reynolds, J. H. (2006). A motion-dependent distortion of retinotopy in area V4. *Neuron, 49*(3), 447-457.

Symonds, C., & MacKenzie, I. (1957). Bilateral loss of vision from cerebral infarction. *Brain, 80*(4), 415-455.

Taira, M., Mine, S., Georgopoulos, A. P., Murata, A., & Sakata, H. (1990). Parietal cortex neurons of the monkey related to the visual guidance of hand movement. *Experimental Brain Research, 83*(1), 29-36.

Takeuchi, N., Chuma, T., Matsuo, Y., Watanabe, I., & Ikoma, K. (2005). Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke, 36*(12), 2681-2686.

Thiebaut de Schotten, Michel, Dell'Acqua, Flavio, Valabregue, Romain, & Catani, Marco. (2012). Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex, 48*(1), 82-96.

Todorov, E., & Jordan, M. I. (2002). Optimal feedback control as a theory of motor coordination. *Nature Neuroscience, 5*(11), 1226-1235.

Toet, A., van Eekhout, M. P., Simons, H. L., & Koenderink, J. J. (1987). Scale invariant features of differential spatial displacement discrimination. *Vision Research, 27*(3), 441-451.

Tse, P. U., Whitney, D., Anstis, S., & Cavanagh, P. (2011). Voluntary attention modulates motion-induced mislocalization. *J Vis, 11*(3), 12.

Tuch, D. S., Salat, D. H., Wisco, J. J., Zaleta, A. K., Hevelone, N. D., & Rosas, H. D. (2005). Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proceedings of the National Academy of Sciences of the United States of America, 102*(34), 12212-12217.

Ungerleider, L. G., & Desimone, R. (1986). Cortical connections of visual area MT in the macaque. *Journal of Comparative Neurology, 248*(2), 190-222.

van Beers, R. J., Sittig, A. C., & Denier van der Gon, J. J. (1996). How humans combine simultaneous proprioceptive and visual position information. *Experimental Brain Research, 111*(2), 253-261.

van Beers, R. J., Sittig, A. C., & Gon, J. J. (1999). Integration of proprioceptive and visual position-information: An experimentally supported model. *Journal of Neurophysiology, 81*(3), 1355-1364.

van Beers, R. J., Sittig, A. C., & van der Gon, J. J. D. (1998). The precision of proprioceptive position sense. *Experimental Brain Research, 122*(4), 367-377.

van Beers, R. J., Wolpert, D. M., & Haggard, P. (2002). When feeling is more important than seeing in sensorimotor adaptation. *Current Biology, 12*(10), 834-837.

van den Wildenberg, W. P., Burle, B., Vidal, F., van der Molen, M. W., Ridderinkhof, K. R., & Hasbroucq, T. (2010). Mechanisms and dynamics of cortical motor inhibition in the stop-signal paradigm: a TMS study. *Journal of Cognitive Neuroscience, 22*(2), 225-239.

van Donkelaar, P., & Adams, J. (2005). Gaze-dependent deviation in pointing induced by transcranial magnetic stimulation over the human posterior parietal cortex. *J Mot Behav, 37*(2), 157-163.

van Donkelaar, P., Lee, R. G., & Gellman, R. S. (1992). Control strategies in directing the hand to moving targets. *Experimental Brain Research, 91*(1), 151-161.

van Gaal, S., Scholte, H. S., Lamme, V. A., Fahrenfort, J. J., & Ridderinkhof, K. R. (2011). Pre-SMA graymatter density predicts individual differences in action selection in the face of conscious and unconscious response conflict. *Journal of Cognitive Neuroscience, 23*(2), 382-390.

Van Thiel, E., Meulenbroek, R., Smeets, J. B., & Hulstijn, W. (2002). Fast adjustments of ongoing movements in hemiparetic cerebral palsy. *Neuropsychologia, 40*(1), 16-27.

Vesia, M., Prime, S. L., Yan, X., Sergio, L. E., & Crawford, J. D. (2010). Specificity of human parietal saccade and reach regions during transcranial magnetic stimulation. *Journal of Neuroscience, 30*(39), 13053-13065.

Wade, A. R., & Wandell, B. A. (2002). Chromatic light adaptation measured using functional magnetic resonance imaging. *Journal of Neuroscience, 22*(18), 8148-8157.

Warren, D. H, & Pick, H. L. (1970). Intermodality relations in localization in blind and sighted people. *Perception and Psychophysics, 8*(6), 430-432.

Wassermann, E., Epstein, C. M., & Ziemann, U. (2008). *Oxford handbook of transcranial stimulation*: Oxford University Press.

Wassermann, E. M., Wedegaertner, F. R., Ziemann, U., George, M. S., & Chen, R. (1998). Crossed reduction of human motor cortex excitability by 1-Hz transcranial magnetic stimulation. *Neuroscience Letters, 250*(3), 141-144.

Watson, J. D., Myers, R., Frackowiak, R. S., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., . . . Zeki, S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cerebral Cortex, 3*(2), 79-94.

Weiskrantz, L. (1986). Some aspects of memory functions and the temporal lobes. *Acta Neurologica Scandinavica. Supplementum, 109*, 69-74.

Weiskrantz, L., Warrington, E. K., Sanders, M. D., & Marshall, J. (1974). Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain, 97*(4), 709-728.

Welch, R. B., & Warren, D. H. (1986). Intersensory interactions. *Handbook of perception and human performance., 1*, 25-21.

Werner, W. (1993). Neurons in the primate superior colliculus are active before and during arm movements to visual targets. *European Journal of Neuroscience, 5*(4), 335-340.

Westerhausen, R., Kreuder, F., Woerner, W., Huster, R. J., Smit, C. M., Schweiger, E., & Wittling, W. (2006). Interhemispheric transfer time and structural properties of the corpus callosum. *Neuroscience Letters, 409*(2), 140-145.

Whitney, D. (2002). The influence of visual motion on perceived position. *Trends Cogn Sci, 6*(5), 211-216.

Whitney, D., & Cavanagh, P. (2000). Motion distorts visual space: shifting the perceived position of remote stationary objects. *Nature Neuroscience, 3*(9), 954-959.

Whitney, D., Ellison, A., Rice, N. J., Arnold, D., Goodale, M., Walsh, V., & Milner, D. (2007). Visually guided reaching depends on motion area MT+. *Cerebral Cortex, 17*(11), 2644-2649.

Whitney, D., Goltz, H. C., Thomas, C. G., Gati, J. S., Menon, R. S., & Goodale, M. A. (2003). Flexible retinotopy: motion-dependent position coding in the visual cortex. *Science, 302*(5646), 878-881.

Whitney, D., & Murakami, I. (1998). Latency difference, not spatial extrapolation. *Nature Neuroscience, 1*(8), 656-657.

Whitney, D., Murakami, I., & Gomi, H. (2010). The utility of visual motion for goal directed reaching. *Space and time in perception and action*, 121-145.

Whitney, D., Westwood, D. A., & Goodale, M. A. (2003). The influence of visual motion on fast reaching movements to a stationary object. *Nature, 423*(6942), 869-873.

Wilson, H. R., Ferrera, V. P., & Yo, C. (1992). A psychophysically motivated model for two-dimensional motion perception. *Visual Neuroscience, 9*(1), 79-97.

Wise, S. P., Boussaoud, D., Johnson, P. B., & Caminiti, R. (1997). Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. *Annual Review of Neuroscience, 20*, 25-42.

Witt, J. K., Proffitt, D. R., & Epstein, W. (2005). Tool use affects perceived distance, but only when you intend to use it. *Journal of Experimental Psychology: Human Perception and Performance, 31*(5), 880-888.

Wohlgemuth, A. (1911). *On the after-effect of seen movement*: University Press.

Woldorff, M. G., Hillyard, S. A., Gallen, C. C., Hampson, S. R., & Bloom, F. E. (1998). Magnetoencephalographic recordings demonstrate attentional modulation of mismatch-related neural activity in human auditory cortex. *Psychophysiology, 35*(3), 283-292.

Wolpert, D. M., Ghahramani, Z., & Jordan, M. I. (1995). Are arm trajectories planned in kinematic or dynamic coordinates? An adaptation study. *Experimental Brain Research, 103*(3), 460-470.

Wolpert, D. M., Goodbody, S. J., & Husain, M. (1998). Maintaining internal representations: the role of the human superior parietal lobe. *Nature Neuroscience, 1*(6), 529-533.

Wolpert, D. M., & Miall, R. C. (1996). Forward Models for Physiological Motor Control. *Neural Netw, 9*(8), 1265-1279.

Woodworth, R. (1899). Accuracy of voluntary movement. *The Psychological Review: Monograph Supplements, 3*(3).

Wright, M. J. (1986). Apparent velocity of motion aftereffects in central and peripheral vision. *Perception, 15*(5), 603-612.

Yamagishi, N., Anderson, S. J., & Ashida, H. (2001). Evidence for dissociation between the perceptual and visuomotor systems in humans. *Proceedings: Biological Sciences, 268*(1470), 973-977.

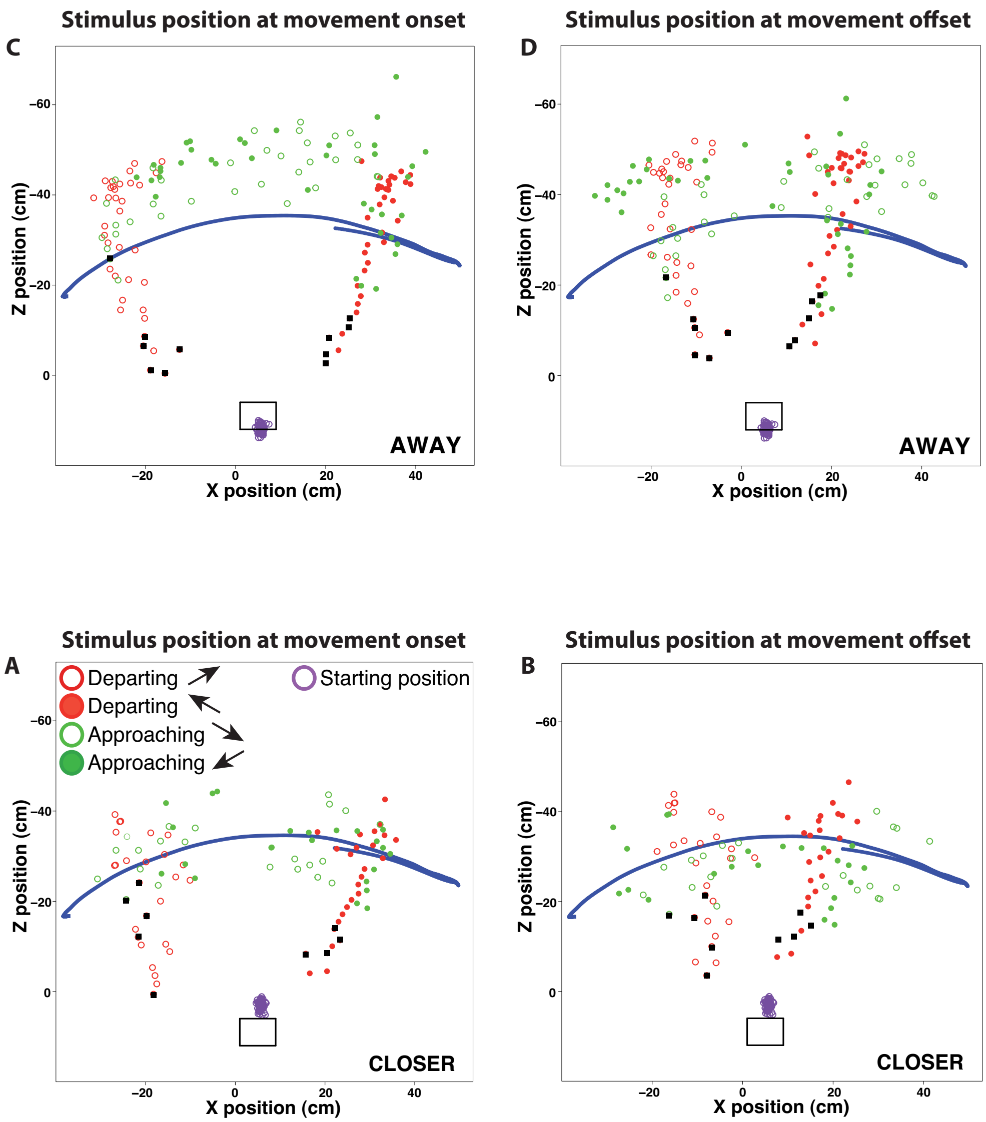
Yan, J. H., Thomas, J. R., Stelmach, G. E., & Thomas, K. T. (2000). Developmental features of rapid aiming arm movements across the lifespan. *J Mot Behav, 32*(2), 121-140.

Zeki, S., & Blakemore, C. (1990). The motion pathways of the visual cortex. *Vision: Coding and efficiency*, 321-345.

APPENDIX

Figure 3 of Chapter 6

SUBJECT 2



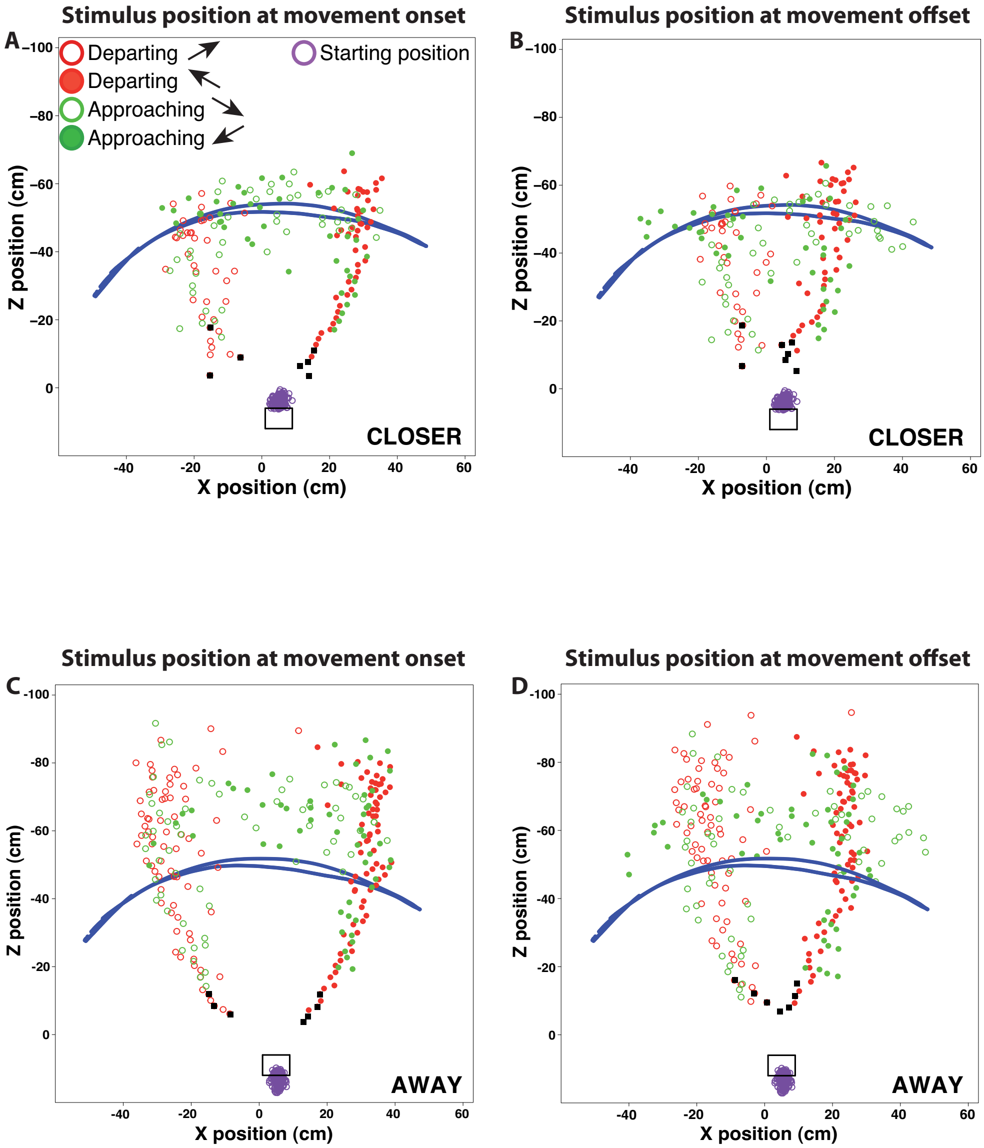
Stimulus position at movement onset

Stimulus position at movement offset

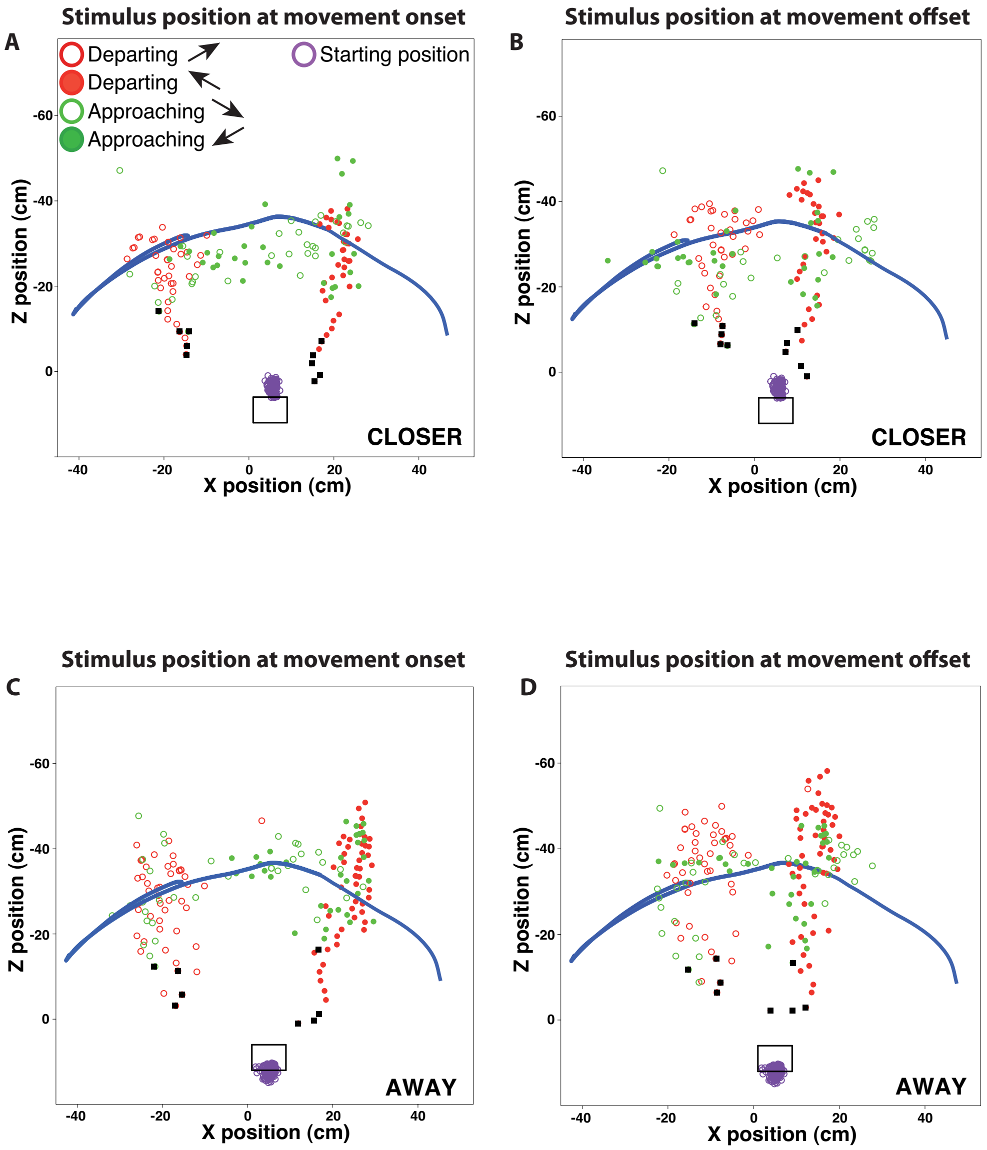
Stimulus position at movement onset

Stimulus position at movement offset

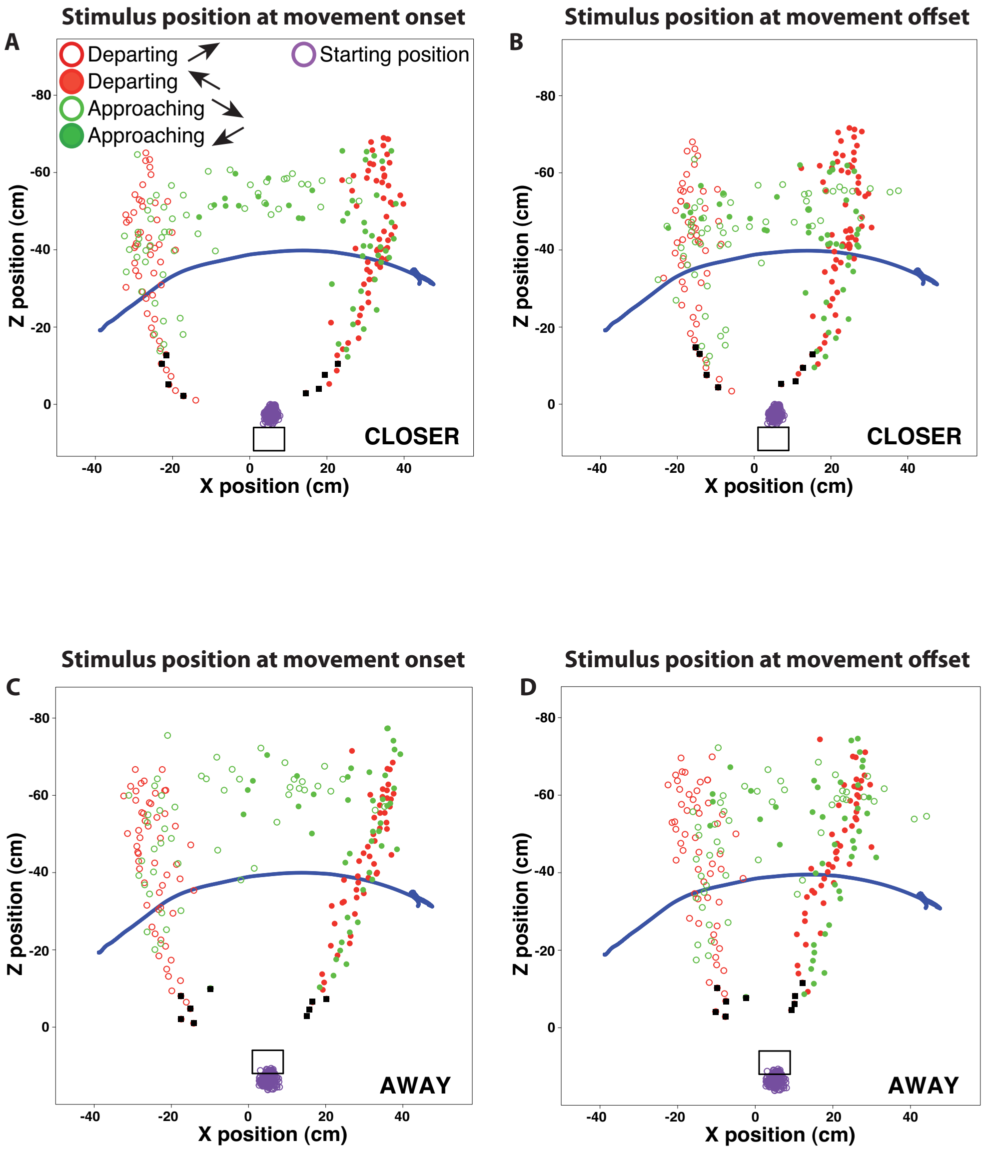
SUBJECT 3


Stimulus position at movement onset
Stimulus position at movement offset
A
B
C
D
Departing
Departing
Approaching
Approaching
Starting position
CLOSER
CLOSER
AWAY
AWAY
Z position (cm)
X position (cm)
-100
-80
-60
-40
-20
0
-40
-20
0
20
40
60

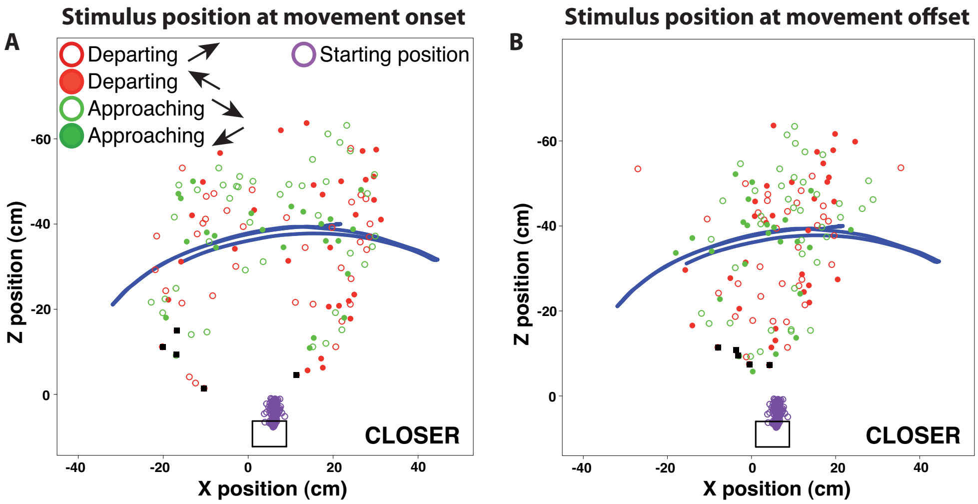
SUBJECT 4


Stimulus position at movement onset
A
Departing ↗
Departing ↖
Approaching ↘
Approaching ↙
Starting position
Z position (cm)
-60
-40
-20
0
-40
-20
0
20
40
X position (cm)
CLOSER
Stimulus position at movement offset
B
CLOSER
Stimulus position at movement onset
C
AWAY
Stimulus position at movement offset
D
AWAY

Subject 5


Stimulus position at movement onset
A
Departing ↗
Departing ↖
Approaching ↘
Approaching ↙
Starting position
Z position (cm)
X position (cm)
CLOSER
Stimulus position at movement offset
B
CLOSER
Stimulus position at movement onset
C
AWAY
Stimulus position at movement offset
D
AWAY
-80
-60
-40
-20
0
-40
-20
0
20
40

SUBJECT 6


Stimulus position at movement onset
A
Departing ↗
Departing ↖
Approaching ↘
Approaching ↙
Starting position
CLOSER
Z position (cm)
-60
-40
-20
0
X position (cm)
-40
-20
0
20
40
Stimulus position at movement offset
B
CLOSER
Z position (cm)
X position (cm)

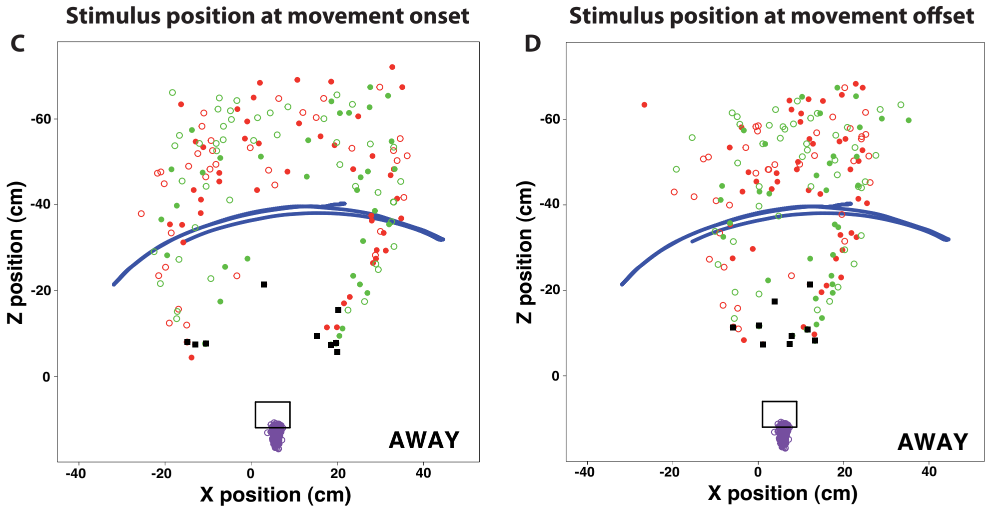
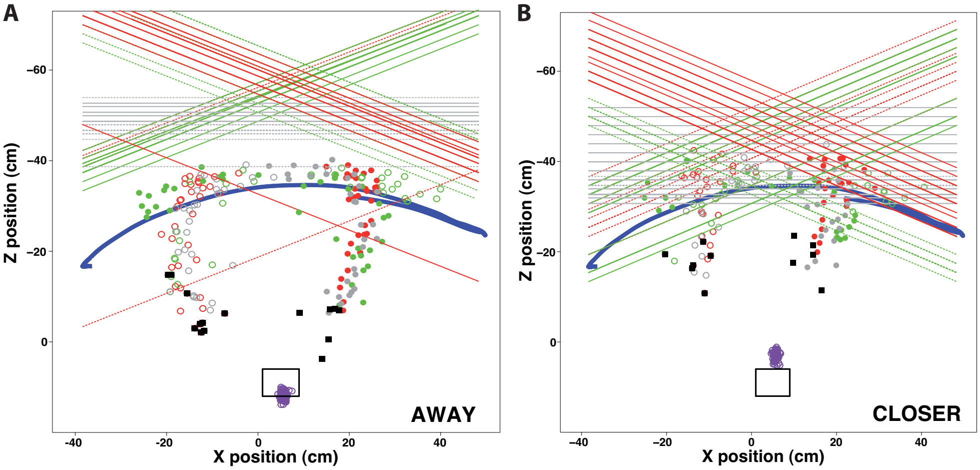
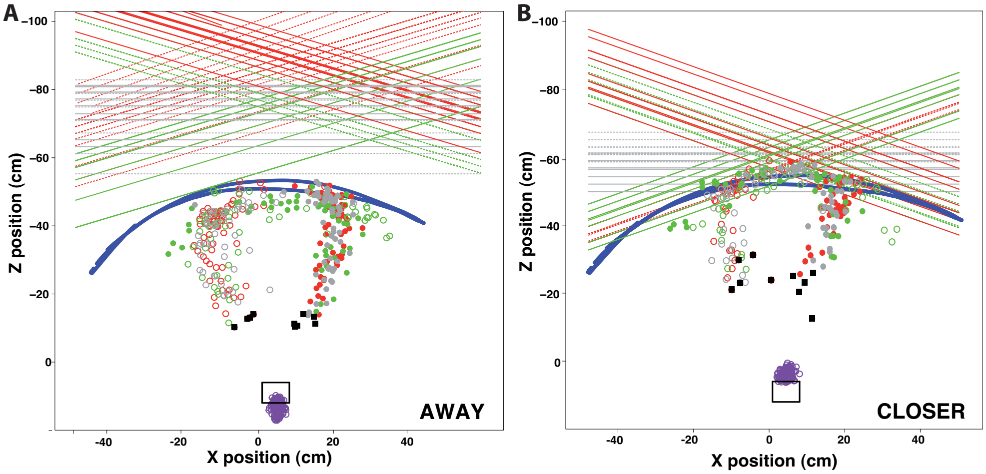

Stimulus position at movement onset
C
AWAY
Z position (cm)
-60
-40
-20
0
X position (cm)
-40
-20
0
20
40
Stimulus position at movement offset
D
AWAY
Z position (cm)
X position (cm)

Figure 5 of Chapter 6

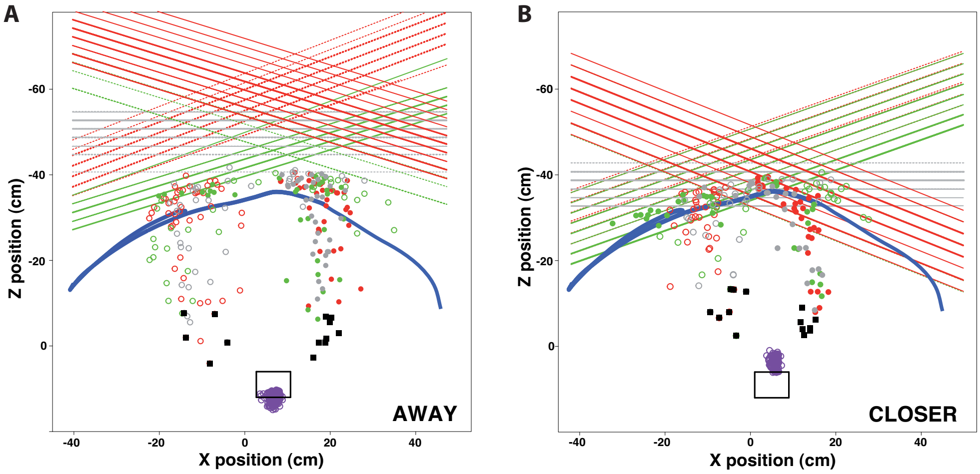
SUBJECT 2



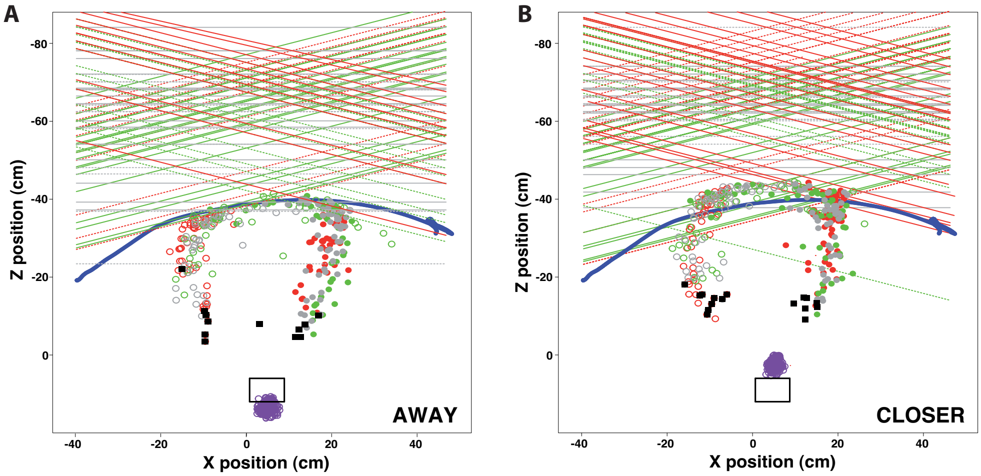
SUBJECT 3



Subject 4



Subject 5



SUBJECT 6

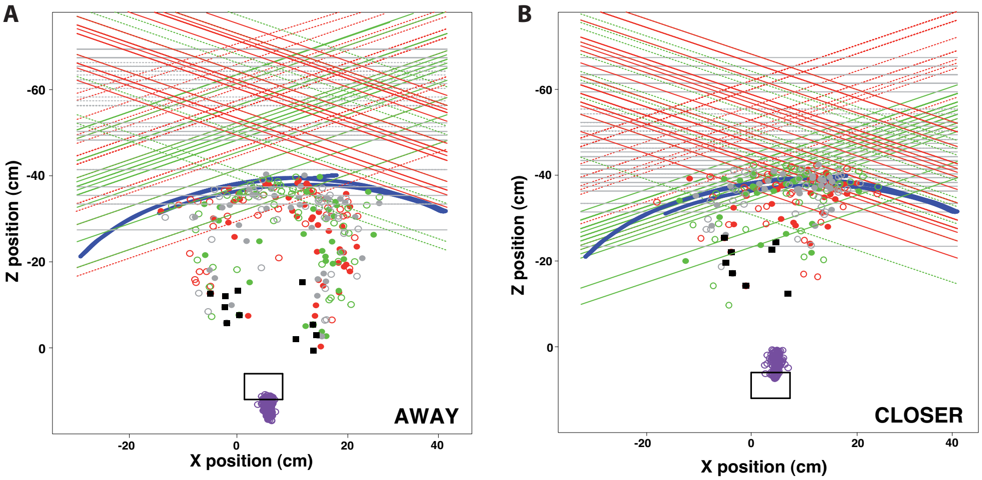
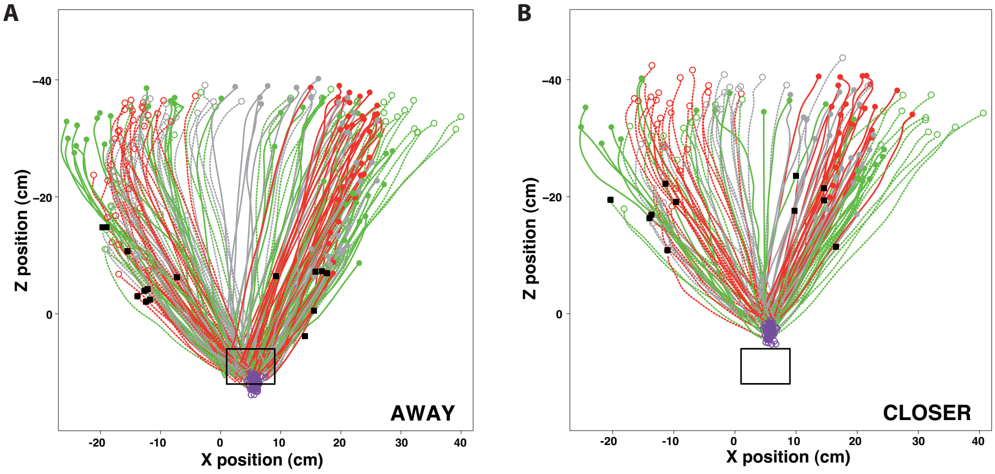
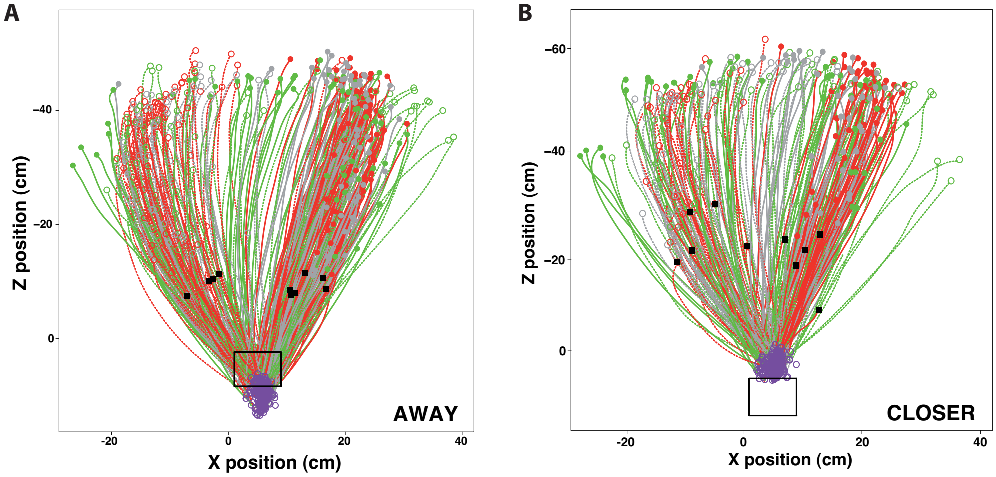


Figure 6 of Chapter 6

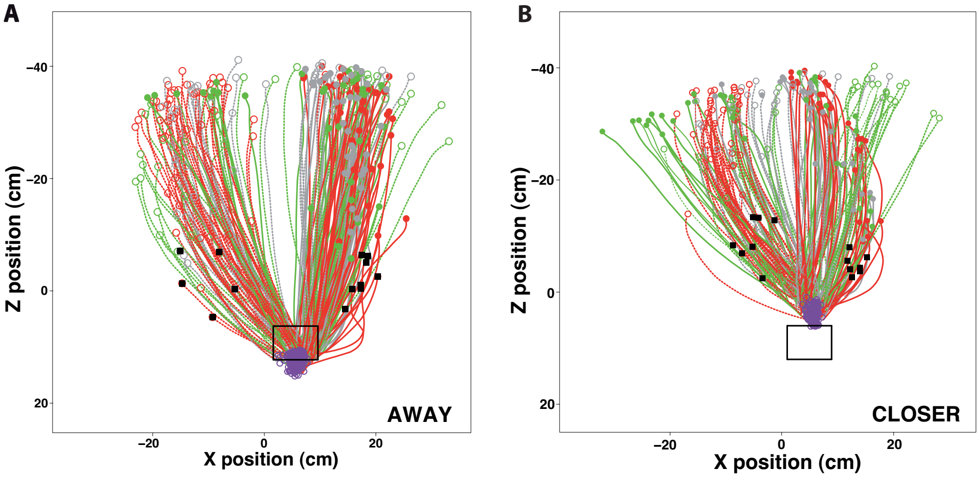
SUBJECT 2



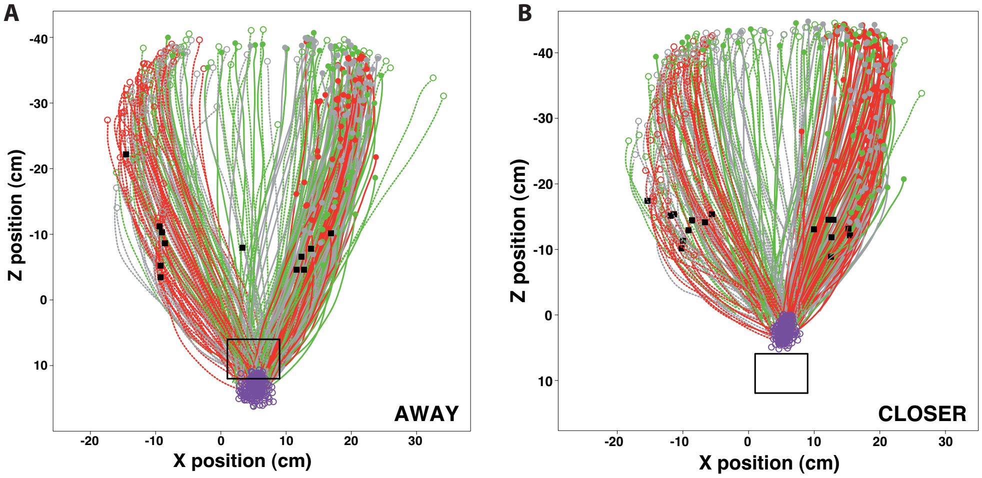
SUBJECT 3



SUBJECT 4



SUBJECT 5



SUBJECT 6