Some contributions to the study of corollary discharges for saccadic eye movements in neurological patients

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Contents

List of figures

Figures

Chapter 3

Oculomotor control after hemidecortication: a single hemisphere encodes corollary discharges for bilateral saccades

Chapter 4

The classic double step saccade task is an imperfect tool for evaluating corollary discharge in parietal lesion patients

Supplementary figures

List of tables

Tables

Chapter 4

The classic double step saccade task is an imperfect tool for evaluating corollary discharge in parietal lesion patients

Chapter 5

Refuting the hypothesis that human parietal lesion impairs saccade corollary discharge

Supplementary tables

Chapter 3

Oculomotor control after hemidecortication: a single hemisphere encodes corollary discharges for bilateral saccades

Chapter 4

The classic double step saccade task is an imperfect tool for evaluating corollary discharge in parietal lesion patients

Chapter 5

Refuting the hypothesis that human parietal lesion impairs saccade corollary discharge

Abstract

High acuity vision in humans is only possible at the small, foveal region of the retina. In order to make sense of the world around us, we have developed a multi-functioning eye movement system that allows us to rapidly and accurately displace the fovea to areas of interest in the visual scene. The computational complexities that arise within this system provide a compelling challenge for systems neuroscientists: how does the system plan and generate eye movements? How do we maintain the perception of a stable visual world despite the near-constant movement of the eye, head and body? The prevailing and convincing theory that addresses these questions states that the eye movement system generates corollary discharges that encode each motor command (or efference copies), that are sent to sensory and motor planning areas. Sensory areas use this information for consolidation with sensory inputs and motor areas update the internal representation of the position of the fovea in space. The latter use of corollary discharges is frequently evaluated using the classic double step saccade task: while the subject fixates centrally, two targets are quickly flashed sequentially in the periphery. The subject is asked, upon extinction of the targets and the fixation point, to make a sequence of two saccades, in the dark, to the locations of the previously seen targets in the order they were presented. The success of the second saccade requires the use of corollary discharges informing the vector of the first saccade. The pathway that these corollary discharges take through the brain has not been fully mapped; conflicting findings between motor-based and sensory-based lesion studies has led to many questions concerning the brain areas involved in the processing of corollary discharge.

Previous work in our lab suggests that hemispherectomy subjects (who have had an entire hemisphere of cortex removed) have greater abilities than what would be expected based on smaller, isolated lesion studies. For example, they can generate accurate bilateral saccades despite the classic hypothesis that each cortical hemisphere only generates contralateral saccades. We hypothesized that their abilities may extend to generating corollary discharge for these bilateral saccadic eye movements as well. We designed two new versions of the classic double step task, engineered so that corollary discharge could

be assessed in hemianopic patients. Our findings in the first study of this thesis show that hemidecorticate patients have preserved the ability to monitor bilateral saccades, whether exogenously- or endogenously-driven, and use corollary discharges of previous saccades in the planning of subsequent saccades.

In light of these findings, we revisited the literature on corollary discharge systems in patients with smaller, isolated brain lesions. Clinical studies investigating saccade monitoring abilities in patients with parietal lesions have suggested that damage to this area (particularly of the right side) interrupts normal saccadic monitoring processes, and abolishes corollary discharges for contralesional saccades. Since hemispherectomy patients (who, by definition lack an entire hemisphere of cortex, including the parietal lobe) are capable of monitoring bilateral saccades, we thought that it was likely that patients with parietal lobe lesions should also retain this ability. We thought that attentional deficits that frequently result from lesions of the parietal lobe may contribute to their failure on the classic double step task used in previous studies, and that these results may not, in fact, indicate unambiguously a complete loss of corollary discharge for contralesional saccades.

In the second study of this thesis, we tested patients with parietal lobe lesions on a classic version of the double step task. When analyzed using previously-described techniques, we found results similar to those published previously. When the analysis techniques were changed slightly, however, by providing the patients sufficient time to complete the task and adequately evaluating corrective saccades to each target, we found that some patients were able to monitor saccades directed both ipsilesionally and contralesionally.

For the third study of this thesis, we then tested the same cohort of parietal lesion patients on two modified versions of the double step task, modeled from those used in the hemispherectomy study. When tested with our modified tasks, patients with parietal lesions of both the right and left hemisphere demonstrate the use of corollary discharge for bilateral saccades, whether exogenously- or endogenously-driven. This thesis thus shows

that the corollary discharge system is highly distributed, and is not destroyed with lesions of the parietal lobe, or indeed of an entire hemisphere of cortex.

Résumé

La vision à grande acuité chez les humains est uniquement possible à travers la région fovéale de la rétine. Afin d'interpréter son environnement, l'humain a développé un système oculomoteur qui lui permet de déplacer, rapidement et précisément, la fovéa vers les points d'intérêt de la scène visuelle. La complexité computationnelle de ce système présente le défi de comprendre: 1) comment le système planifie et génère les mouvements de l'œil et; 2) comment on maintient la perception d'un champ visuel stable malgré le mouvement constant de l'œil, de la tête et du corps. La théorie la plus acceptée postule que, pour chaque commande motrice, le système génère des décharges corollaires envoyées vers les régions sensorimotrices du cerveau. Cette information est intégrée avec les données visuelles dans les régions sensorielles, au moment où les régions motrices s'en servent pour mettre à jour la représentation interne de la position de la fovéa dans l'espace. Cette mise à jour est évaluée en utilisant la tâche classique de double-saccade: pendant que le sujet fixe son regard au centre de l'écran, deux stimuli visuels sont présentés de façon rapide et séquentielle en périphérie. La tâche requiert que le sujet fasse, suite à la disparition des stimuli, une séquence de deux saccades dans le noir, ciblant les positions originales des stimuli dans l'ordre dont ils furent présentés. La réussite de la deuxième saccade dépend de l'utilisation de l'information contenue dans les décharges corollaires de la première saccade. Les voies transmettant ces décharges corollaires ne sont pas complètement identifiées; les études de lésion évaluant les décharges corollaires dans le contexte des systèmes sensoriel et moteur présentent des résultats incompatibles, posant des questions sur les régions impliquées dans l'interprétation des décharges corollaires.

Des études précédemment effectuées dans notre laboratoire suggèrent que les patients hémi-décortiqués (chez lesquels un hémisphère du cortex est enlevé) possèdent de meilleures performances que les patients souffrant de lésions isolées et moins graves. Par exemple, ils sont capables de générer des saccades bilatérales précises, contrairement à l'hypothèse classique disant que chaque hémisphère cortical génère uniquement des saccades controlatérales. En se basant sur ces résultats, nous avons émis l'hypothèse que

les patients hémi-décortiqués seraient aussi capables de produire les décharges corollaires pour les saccades bilatérales. Nous avons développé deux nouvelles versions de la tâche classique de double-saccade, conçues pour évaluer la décharge corollaire chez les patients hémi-décortiqués. Les données de la première étude de cette thèse montrent que les patients hémi-décortiqués retiennent leur habileté de suivre les saccades bilatérales, générées de façon endogène ou exogène, et de se servir des décharges corollaires des saccades antérieures dans la planification des saccades suivantes.

Dans le cadre de ces résultats, nous avons remis en question la littérature scientifique concernant les systèmes de décharge corollaire chez les patients portant des lésions plus petites et définies. Des études cliniques investiguant la genèse des saccades bilatérales chez les patients à lésion pariétale ont suggéré que l'endommagement de cette région (particulièrement l'hémisphère droit) interrompt les processus normaux des saccades bilatérales et abolit les décharges corollaires des saccades du côté controlatéral à la lésion. Sachant que les patients hémi-décortiqués (dont la lésion inclut la région pariétale) retiennent la capacité de générer des double-saccades saccades bilatérales, nous avons formulé l'hypothèse que les patients souffrant d'une lésion pariétale uniquement, retiennent aussi cette capacité. Nous avons prédit que les déficiences attentionnelles causées souvent par les lésions pariétales auraient pu contribuer à la mauvaise performance de ces derniers dans la tâche classique de double-saccade et, que les résultats des études précédentes n'indiquent pas nécessairement une perte de décharges corollaires des saccades du côté controlatéral à la lésion chez ces patients.

Dans la deuxième étude de cette thèse, nous avons évalué la performance des patients à lésion pariétale dans une version classique de la tâche de double-saccade. En employant les méthodes d'analyses précédemment décrites dans la littérature, nos résultats étaient en accord avec ceux déjà publiés. Par contre, en introduisant à ces méthodes d'analyse de légères modifications consistant à fournir au sujet plus de temps à compléter la tâche et à évaluer les saccades correctives, nous avons trouvé que certains patients étaient capables de générer des décharges corollaire de saccades en directions ipsilatérale et controlatérale à la lésion.

Dans la troisième étude de cette thèse, nous avons évalué la performance de la même cohorte de patients à lésion pariétale dans deux versions modifiées de la tâche de double-saccade, adaptées de celles utilisées dans l'étude des patients hémi-décortiqués. En les examinant dans ces tâches, les patients à lésion pariétale (de l'hémisphère droit ou gauche) ont démontré la capacité de suivre, via décharges corollaires, les saccades bilatérales générées de façon endogène ou exogène. En conclusion, cette thèse montre que le système de décharge corollaire est considérablement distribué, et qu'il n'est détruit ni par une lésion pariétale, ni par une perte d'un hémisphère cortical au complet.

Acknowledgements

It is with great excitement that I submit this thesis for evaluation. It is the product of five years of reflection, investigation, and cafeteria-food. I owe its completion to a great number of people whom I'd like to acknowledge appropriately but, as I do not have the means to provide lifetime supplies of ice cream to so many (yet), these few paragraphs will have to suffice for the time being.

First and foremost, I must thank Dan for his unrelenting support, insight and commitment to excellence. It was in his long-running Systems Neuroscience class that my interest in research found its legs: I have joined the ranks of many others who pass through his class, our scholastic fates cemented by Dan's vibrant and infectious interest in the mysteries that underlie human brain function. While this contribution to my education alone merits space in this section, it pales in comparison to the vast toolkit of lessons Dan has imparted through five years of mentorship, instruction and dedication. His punctilious attention to detail and uncompromising rigor of the scientific process have informed my own scholastic methods and set an example to which I strive in all professional aspects of my life. He has been incredibly generous with his time and knowledge, and has shown a genuine and earnest interest in enabling my future endeavours; these qualities have made him an invaluable mentor. I will be forever grateful for the opportunities he has provided, the faith he has had in my abilities, and the rich personal relationship we have developed since we met, cultivated by endless hours of commiserating and debate (as are all the best ones). I hope he will acquiesce to continue to edit my writing (kidding!) and to impart his wisdom (this one's real!) for a long time to come.

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Preface & contribution of authors

Chapters 3, 4 and 5 are original research articles that represent distinct contributions to knowledge in the field of oculomotor control. Each of these chapters represents a study that was designed by me in conjunction with Dr. Daniel Guitton; I performed all experiments associated with each project, analyzed all of the data and wrote each chapter of this thesis under the supervision and guidance of Dan. Each of the original research studies is either published, or in a stage of the publication process. Chapter 3 entitled "Oculomotor control after hemidecortication: a single hemisphere encodes bilateral saccades" was published in *Cortex* (Rath-Wilson and Guitton, 2015). Chapter 4 entitled "The classic double step saccade task is an imperfect tool for evaluating corollary discharge in parietal lesion patients" is about to be submitted to *Cortex*. Finally, Chapter 5 entitled "Refuting the hypothesis that a unilateral human parietal lesion impairs saccade corollary discharge" is currently submitted to *Brain*. The introduction, literature review, and discussion were also written by me and edited by Dan.

List of abbreviations

CD – corollary discharge

TMS – transcranial magnetic stimulation

EBN – excitatory burst neurons

IBN – inhibitory burst neurons

PPRF – paramedian pontine reticular formation

LLBN – long lead burst neurons

OPN – omni-pause neurons

SC – superior colliculus

FEF – frontal eye fields

LIP – lateral intra-parietal area

PEF – parietal eye fields

SEF – Suppl. eye fields

dlPFC – dorsolateral prefrontal cortex

Cd – caudate

SNr – substantia nigra

SRT – saccade reaction time

MD – medio-doral neucleus of the thalamus

IOR – inhibition of return

FP – fixation point

T/T1/T2 – target/first target/second target

ΣS1/ΣS2 – sum of the vectors of all saccades towards T1/T2

FEP/FEP1/FEP2 – final eye position after saccades to T/T1/T2

DTI – diffusion tensor imaging

ipsiL – ipsilesional

contraL - contralesional

1 Introduction

The human visual system is a highly complex network in the human brain. It relies on many brain areas to function properly; information from the photosensitive cells of the retina is sent through thalamic structures to the occipital lobe, where it is processed to construct an understanding of visual space. This information is sent forward through the cortex where it is consolidated and processed, finally providing our conscious selves with a sensory representation of the visual scene. High acuity vision is only possible over a very small portion of the retina called the fovea. Acquiring accurate visual information requires the displacement of the fovea to observe relevant details in the scene. We rest our fovea on those areas that we decide require investigation through visual acuity; our eyes linger on faces in a crowd and on letters on a page so that we can gain information about these important features in the scene.

Eye movements are controlled by a highly developed motor system that can move our eyes at high speeds (up to 900 deg/sec, Kandel et al., 2000) and have them land with great precision on salient features (such as faces or words). The motor system has developed to such a level of sophistication that we can walk down the street, moving our bodies and our heads any way we please, while our eyes move around at our command, accurately taking in the scene around us. Throughout this process, we perceive a completely stable visual world; we can see that the car is moving by us and that the wind is moving the trees, while the images move across our retina. Amazingly, we can determine, unconsciously, how much of that perceived movement is due to reafference (our own actions: walking, moving our head and eyes) and how much is due to exafference (changes in the external world: the car's engine or the wind). One of the ways our saccadic motor and visual systems distinguishes between the motion due to reafference and the motion due to exafference is by tracking what we tell our eye muscles to do. This is accomplished by providing a copy of the motor command or a corollary discharge (CD) to appropriate brain areas for comparison and consolidation with visual inputs. If we are able to predict the movement across the retina of visual images due to eye movements with the

information provided by the CD signal, we can conclude that extraneous movements must have occurred due to other factors (like a car's engine or the wind). Tracking our movements in this way also enables us to keep an updated internal representation of where our fovea is pointed in space; this allows us to appreciate the spatial layout of our environment and to plan future movements to salient features in the scene.

Many studies have been done attempting to further investigate and describe these saccade CDs. The primary tool for investigating eye movement CD is an experiment called the classic double step task. It involves quickly (80-140ms) flashing two targets sequentially in the periphery while the subject fixates a central point. With the extinction of the fixation point and targets, the subject is asked to make a sequence of two saccades, in the dark, to the locations of the previously seen targets in the order they were presented. The success of the second saccade requires the use of CD informing the vector (amplitude and direction) of the first saccade. The saccadic eye movement system is an excellent model for other motor systems, since it is simple and has been so well characterized in the literature. Since the concept of a CD can be applied throughout the motor system for movement tracking of the entire body, gaining further understanding of saccade CD may provide insight into other systems that govern complex, multi-muscle movements that update in real time. Anatomical pathways have been proposed for the CD signal as it relates to eye movements. To our knowledge, however, no one has ever been able to fully disable the effects of CD with inactivation of these proposed pathways in monkeys and human studies have proven similarly inconclusive. We therefor believe that other pathways for this system or redundancies must exist. More details of the CD system will be provided in subsequent sections.

Hemispherectomy patients provide a unique case study for the abilities of a single hemisphere to perform certain tasks. They are remarkably adept considering the extent of their lesions; in addition to their rich careers and personal lives, our patients are surprisingly able to navigate the environment effectively, their hemianopia seeming to be the only obstacle to otherwise complete visual ability. Each cortical hemisphere is generally thought to generate contralateral saccades; previous studies in our lab have

shown that hemispherectomy patients, despite having only a single hemisphere of cortex, are able generate accurate bilateral saccades (i.e.: to the left and right) and track, via CD, bilateral smooth pursuit movements. We asked whether, since it is capable of generating accurate bilateral saccades, if this single hemisphere is also able to generate, transmit, and interpret an accurate CD for bilateral saccades. As outlined in Chapter 3, we developed two new versions of the classic double step task, designed to investigate CD for bilateral saccades despite our patients' hemianopia. We found that these patients can indeed generate CD for saccades to the left and right, and use this information to plan subsequent saccades. To our knowledge, this is the first evidence of CD for bilateral saccades in hemispherectomy patients.

Upon our finding that hemispherectomy patients, who have only a single hemisphere of cortex, can encode and use accurate CD for bilateral saccades, the next logical step was to revisit the literature on impairments in double step saccades in other neurological patients. It has been well established in the literature that patients with lesions of the parietal lobe, particularly of the right hemisphere, have a stereotyped deficit in generating an ipsilesional saccade (directed towards the side of the lesion) following a primary contralesional saccade (directed away from the side of the lesion) when attempting the classic double step task. These studies have thus concluded that lesions of the parietal lobe abolish CD for contralesional saccades. In light of our finding that hemidecorticate patients have the ability to monitor bilateral saccades, we hypothesized that patients with isolated unilateral parietal lesions may also still have this ability. We carefully evaluated the previous studies that conclude that patients with lesions of the parietal lobe do not have CD for contralesional saccades. We found that certain task parameters and analysis techniques employed in these studies were not appropriate for the patient population under investigation; attentional and visual processing deficits that frequently result from lesions of the parietal lobe may have been contributing to their failure on the classic double step task. This is explained in detail in Chapter 4. We then tested patients with parietal lesions using the task parameters and techniques used previously and, not surprisingly, found similar results to those of previous studies. When we changed our analysis methods slightly, however, in order to mitigate some common

attentional deficits associated with parietal lesions, we found strikingly different results, suggesting that these patients may, in fact, generate CD for bilateral saccades (Chapter 4). We then tested the same parietal patients on a series of tests similar to those used in the hemispherectomy study that we thought would be a better tool to evaluate the ability of patients with lesions of the parietal lobe to track, via CD, bilateral saccades generated in the dark. We show that this patient population, with isolated unilateral lesions of either the right or left parietal lobe, has CD for bilateral saccades, whether they are exogenously (aimed towards a previously-seen target) or endogenously (of self-determined amplitude) driven (Chapter 5). To our knowledge, this is the first time that patients with lesions of the parietal lobe have been shown to have CD for bilateral saccades.

2 Literature review

2.1 Introduction

As discussed above, the ability to displace the fovea quickly and accurately is essential in order to observe the visual scene. The brain controls foveal displacement with a variety of movement types, namely: smooth pursuit, gaze displacement, and saccadic eye movements. Smooth pursuit involves following a moving target through the visual scene with the fovea fixated upon it. Gaze displacement involves coordinated movements by the eyes and the head, resulting in a total displacement that brings the fovea onto the target. Saccades are rapid eye movements that displace the eye in the orbit with or without accompanying head movements. This thesis focuses on mechanisms related to saccades. Due to the simplicity of the eye plant, saccade generation, control and execution mechanisms have been well characterized in the literature and they are relatively well understood, making saccades a useful model for motor control systems.

The current knowledge about the oculomotor system has been gained through experiments studying both humans and animals. Human experiments often involve patients who have sustained discrete lesions to various brain areas; by studying their behaviours, inferences can be drawn about the function of the brain areas that have been damaged. Imaging studies have revealed activation levels of discrete brain areas during specific tasks. Transcranial magnetic stimulation (TMS) studies (which involve temporarily altering the activity of controlled areas of cortex) have provided some insight into the localization of function. Animal studies have provided additional information through more invasive techniques, including single unit recordings, electrical microstimulation, as well as reversible activation or inhibition of specific brain areas using other microinjection techniques. Much insight has been gained by these experiments about how certain brain areas contribute to saccadic eye movement generation and control. It is important to note, however, that, like most complex neurological processes, the highly

distributed nature of these areas and functions make specific functional localization very difficult.

The kinematics of visually-guided saccades have been carefully studied and characterized in the literature, and can be described by two functions called the main sequence relationships. The first relationship states that the duration of saccades increases as a linear function of the saccadic amplitude (Bahill AT, 1975; Baloh et al., 1975; Fuchs, 1967; Robinson, 1964). The second relationship states that the peak velocity and mean velocity of a saccade increase as the amplitude of the saccade increases, saturating at large amplitudes (Bahill AT, 1975; Baloh et al., 1975; Boghen et al., 1974; Fuchs, 1967). The main sequence relationships have been useful when studying saccadic deficits in patients with lesions.

The classic conceptual framework for saccadic control involves the two hemispheres communicating synergistically via commissural pathways. Each hemisphere communicates with its ipsilateral midbrain and brainstem structures to control contralaterally-aimed saccades (and ipsilateral smooth pursuit). This traditional view is being modified in the wake of new studies that have found that a single hemisphere is capable of generating accurate, bidirectional saccades (Herter and Guitton, 2004; Hughes et al., 1992).

This chapter presents an overview of the literature related to saccade programming, the maintenance of visual stability through the use of corollary discharges, and the major lesion studies that led to the investigations contained within this thesis.

2.2 Generation and control of saccadic eye movements

2.2.1 Eye plant

Eye movements are controlled by six extra-ocular muscles: lateral and medial rectus, inferior and superior rectus, and inferior and superior oblique. The lateral and medial recti are engaged during horizontal saccades, while the superior and inferior oblique and recti muscles are engaged during vertical saccades. The cranial nerves III

(oculomotor), IV (trochlear) and VI (abducens) control the motor commands to these muscles (Kandel et al., 2000). Motor neurons in these nerves use a pulse-step discharge mechanism to innervate the extra-ocular muscles: a burst of action potentials to muscles that move the eyes in the saccade direction and lasts for the duration of the saccade, coinciding with a pause in discharge to muscles that would have the eyes move in the opposite direction (Hepp et al., 1989; Leigh and Zee, 1999; Moschovakis et al., 1996; Munoz, 2002; Scudder et al., 2002). The burst component of the discharge is generated by premotor activity in the brainstem reticular formation (Moschovakis et al., 1996; Munoz, 2002; Scudder et al., 2002). The number of spikes is correlated with the amplitude of the saccade and the frequency of the bursts is correlated with the velocity of the intended movement. The subsequent tonic discharge (the step component of the pulse-step mechanism) keeps the eyes in place with the fovea directed at the target, outside of the relaxed position in the orbit (Munoz, 2002).

2.2.2 Brainstem saccadic burst generator

The brainstem saccadic burst generator governs the neural activity that leads to the eye muscles generating a saccade. The excitatory burst neurons (EBN) and inhibitory burst neurons (IBN) of the brainstem saccadic burst generator discharge bursts of action potentials during saccade initiation, and are not active during fixation. EBNs monosynaptically excite motor neurons that engage muscles moving the eyes in the desired direction of the saccade, and simultaneously activate IBNs that will in turn silence motor neurons connected to antagonist muscles. EBNs and IBNs involved in horizontal saccade generation are located in the paramedian pontine reticular formation (PPRF) while EBNs and IBNs involved in vertical saccade generation are located in the rostral interstitial nucleus of the medial longitudinal fasciculus in the mesencephalon (Munoz, 2002). Long lead burst neurons (LLBN) in the reticular formation are believed to provide the burst input to the EBNs and IBNs, beginning with a low frequency buildup before reaching burst threshold for contralateral saccades. In order to ensure that this buildup of activity does not cause sporadic EBN/IBN activity, omnipause neurons (OPN) also located in the PPRF, fire tonically inhibiting EBN and IBN. They are active during fixation and pause during the

execution of saccades. In order for a saccade to take place, the OPNs must pause and the LLBNs must fire, causing the EBNs and IBNs to fire appropriately. Once the burst has taken place, the OPNs resume firing, allowing the step activity to maintain fixation at the target position of the saccade (Moschovakis et al., 1996; Munoz, 2002; Scudder et al., 2002).

The brainstem premotor circuitry is controlled largely by inputs from cortical and other subcortical areas (Gaymard et al., 1998; Leigh and Zee, 1999; Munoz, 2002; Pierrot-Deseilligny et al., 2002b). Important subcortical areas include the superior colliculus (SC), the cerebellum, the basal ganglia and the thalamus. Cortical areas that are important for saccade generation include the frontal eye fields (FEF), the lateral intraparietal area (LIP) in monkeys or the parietal eye fields (PEF) in humans, the supplementary eye fields (SEF) and the dorsolateral prefrontal cortex (dlPFC).

2.2.3 Subcortical areas

2.2.3.1 Superior colliculus

One critical area in guiding saccades is the SC, a complex multisensory integration area that also generates orienting movements of the head. The SC is anatomically divided into six layers and functionally divided into two layers: the superficial layer which exclusively mediates visual processing in the contralateral visual hemifield, and the deep layer which controls orienting behaviours (Moschovakis, 1996). The superficial layer receives inputs from the retina (Hubel et al., 1975; Moschovakis et al., 1996), striate and extrastriate cortex, as well as some brainstem structures, and is organized into a visual map of the contralateral hemifield (Moschovakis et al., 1996). The superficial layer is connected to the deep layer (Moschovakis et al., 1988b). The deep layers represent a retinotopically organized motor map that corresponds to the contralateral hemifield, co-extensive with the visual map of the superficial layer. Activity of the fixation neurons in the rostro-lateral pole (or foveal section) of the SC mediate fixation and are involved in encoding microsaccades. Activity of the saccadic neurons in the motor map encodes saccadic gaze shift vectors, specifying where (by its position on the retinotopic map) and when (by its level of activity relative to threshold) a saccade is to occur (Gandhi and

Katnani, 2011). These fixation and saccadic neurons project to the brainstem reticular formation principally via the predorsal bundle, influencing the premotor circuitry (Moschovakis et al., 1996). Auditory and tactile information also converge in the deeper layers of the SC, integrating sensory information to help guide behaviour based on the surroundings (Cuppini et al., 2010; Stein and Stanford, 2008). Other projections to the SC include saccade-related signals from the ipsilateral and contralateral FEFs, SEFs, and ipsilateral LIP and substantia nigra (Moschovakis et al., 1996). The deep SC in turn projects, via the thalamus, to the ipsilateral FEF, as well as to its contralateral counterpart via the tectal commissural pathway (Moschovakis et al., 1988a; Moschovakis et al., 1988b; Moschovakis et al., 1996). These bilateral efferent and afferent projections from and to the SC, respectively, are of special relevance to studies involving hemispherectomy patients.

2.2.3.2 Cerebellum

Another essential subcortical structure for the accurate and timely execution of saccades is the cerebellum. Recently shown to be related to planning saccade sequences (King et al., 2011), the cerebellum has long been implicated in the generation of accurate saccades. The flocculus/paraflocculus is involved in gaze holding and the dorsal oculomotor vermis and the fastigial oculomotor region have been implicated in the generation of saccades. Specifically, the cerebellum has been shown to have three major roles in saccade generation and execution: it provides an additional drive that allows the eyes to reach their maximum velocity during saccades; it monitors the saccade in real time and makes adjustments to motor commands to ensure the accuracy of the saccade trajectory; and it has been implicated in helping end the saccade at the right time by influencing the pulse drive (Kheradmand and Zee, 2011; King et al., 2011).

2.2.3.4 Basal ganglia

The basal ganglia are a combination of subcortical structures composed of the striatum (which is in turn composed of the caudate nucleus (Cd) and the putamen), the globus pallidus, the substantia nigra pars reticulata (SNr) and pars compacta, and the subthalamic nucleus. The basal ganglia often act as a mediating centre, regulating activity

in the brain to reach goals specific to the behavioural context (Watanabe and Munoz, 2011). The largest contributor of the basal ganglia to saccadic control is the SNr; its tonic activity continuously inhibits the SC and the thalamus, suppressing saccade initiation (Hikosaka and Wurtz, 1983a; Hikosaka and Wurtz, 1983b; Hikosaka and Wurtz, 1983c; Hikosaka and Wurtz, 1983d; Hikosaka and Wurtz, 1985a; Hikosaka and Wurtz, 1985b; Hikosaka et al., 2000). Modulating its activity by increasing or decreasing inhibition in these areas can either suppress or facilitate saccades (Basso and Wurtz, 2002; Handel and Glimcher, 1999; Sato and Hikosaka, 2002). SNr projects mainly to the ipsilateral SC and thalamus controlling contralateral saccades, but also has contralateral projections, suggesting it may modulate ipsilateral saccade generation as well (Cebrian et al., 2005; Jiang et al., 2003). The Cd, in turn, inhibits activity of the SNr, providing bursts of activity just prior to saccades; inhibiting the SNr, disinhibits the SC and thalamus, enabling the saccade to take place (Handel and Glimcher, 1999; Hikosaka and Wurtz, 1983a; Hikosaka and Wurtz, 1983b; Hikosaka and Wurtz, 1983c; Hikosaka and Wurtz, 1983d).

2.2.3.5 Thalamus

The thalamus has been shown to have neurons with saccade-related responses that have been identified as burst neurons, tonic eye position neurons, and pause neurons (Schlag-Rey and Schlag, 1984; Sommer and Wurtz, 2002). Neurons of the pulvinar nucleus have been associated with visual-, attention- and saccade-related information (Arend et al., 2008), even being implicated in the processing of CD (Robinson et al., 1986), although this viewpoint is controversial (Bender and Butter, 1987; Bender and Baizer, 1990). More recently and of particular importance in this study, it has been suggested that the medial dorsal nucleus of the thalamus is involved in conveying CD signals about contralateral eye movements from each SC up to the FEF of the ipsilateral hemisphere of cortex (Bellebaum et al., 2005a; Sommer and Wurtz, 2002).

2.2.4 Cortical areas

Cortical areas also control the brainstem premotor circuitry through direct and indirect connections. The FEF, LIP, SEF and dlPFC, together with the subcortical structures

indicated above, have been shown to form a vast oculomotor network that is responsible for eye movement. The network is extensive and complex; each of these cortical areas is connected reciprocally to every other, and is similarly reciprocally connected with the SC, the thalamus, and the basal ganglia. The basal ganglia and the thalamus similarly have reciprocal connections with the SC, as explained above. Each of these cortical areas sends inputs to the cerebellum as well (Pierrot-Deseilligny et al., 2002b; Sommer and Wurtz, 2004a; Sommer and Wurtz, 2004b).

2.2.4.1 Frontal eye fields

The FEF, located in the precentral gyrus and sulcus, are considered important in the generation and control of intentional eye movements such as visually-guided saccades, correct antisaccades, memory-guided saccades, endogenously-driven and predictive saccades (Pierrot-Deseilligny et al., 2002b). Lesion studies of this area show an increase in saccadic reaction time (SRT) as well as an inability to suppress saccades once a stimulus is presented contralateral to the lesion; studies performing electrical stimulation in FEF show that it plays an important role in saccade triggering (Gaymard et al., 1999; Guitton et al., 1985; Heide and Kompf, 1998; Lobel et al., 2001; Pierrot-Deseilligny et al., 1991a; Pierrot-Deseilligny et al., 1991b; Rivaud et al., 1994).

2.2.4.2 Parietal eye fields

The LIP in monkeys or PEF in humans, located in the polysensory association cortex of the parietal lobe, plays an important role in the generation of reflexive saccades, or saccades triggered by sensory stimuli (Barash et al., 1991a; Barash et al., 1991b). Lesions in this area can result in contralateral hemi-neglect (Corbetta and Shulman, 2011; Heide and Kompf, 1998). Of particular relevance to this study, however, is the severe disturbance that efference-guided saccades have been reported to undergo with lesions of PEF. It has been suggested that the PEF plays a particularly important role in the combining of CD with sensory information, informing the oculomotor system about saccadic movements aimed contralaterally, and maintaining accurate representations of visual space during and after these movements (Barash et al., 1991a; Barash et al., 1991b; Duhamel et al., 1992b).

Studies in area LIP of monkeys have shown, however, that remapping in this area occurs independently of saccade direction and location, suggesting that each area LIP has access to information about all saccades, regardless of direction (Heiser and Colby, 2006). Further studies investigating the link between CD and the parietal oculomotor areas found that updating in area LIP is not solely dependent on cortical-cortical transfer, and that some remapping is preserved following split-brain surgery (Berman et al., 2005; Berman et al., 2007; Heiser et al., 2005). This ability to remap despite a lack of inter-hemispheric transfer is especially relevant to this study. This is discussed further in the CD section.

2.2.4.3 Supplementary eye fields

The SEF, located anterior to the supplementary motor area in the upper part of the paracentral sulcus, appears to be involved in the initiation of motor programs that comprise saccades, including multiple-step saccadic programs (particularly on the left side) and saccades accompanied by head or trunk shifts (Gaymard et al., 1998; Heide and Kompf, 1998; Pierrot-Deseilligny et al., 1991a; Pierrot-Deseilligny et al., 1995; Schlag and Schlag-Rey, 1987). It has also been associated with encoding decision making features in complex saccade tasks involving choice and reward (So and Stuphorn, 2012).

2.2.4.4 Dorsolateral prefrontal cortex

The dlPFC is important for saccade inhibition, prediction, and spatial working memory. It is thus important in the generation of memory-guided saccades, and in the suppression of pro-saccades during the antisaccade task (Burke and Pierrot-Deseilligny, 2010; Guitton et al., 1985; Pierrot-Deseilligny et al., 2002a; Pierrot-Deseilligny et al., 2002b; Pierrot-Deseilligny et al., 2004; Tehovnik et al., 1999).

2.2.5 Exogenous and endogenous saccades

There are many studies showing differences in the encoding of endogenous and exogenous saccades. TMS over the superior prefrontal cortex increases SRT for endogenous saccades in the contralateral direction, but has no effect on exogenous saccades, indicating the importance of the human FEF in the generation of endogenous

saccades (Ro et al., 1997). Mechanism for reflexively (exogenous) and voluntarily (endogenous) orienting of visual attention are different (Berger et al., 2005).

The frontal lobe is more implicated in the direct movement planning and generation of cognitively-driven, voluntary saccades such as memory-guided and endogenous saccades (Dias and Segraves, 1999; Fernandes et al., 2014; Helminski and Segraves, 2003). Lesion and microstimulation studies have added to this story, suggesting that FEF is highly involved in the cognitive aspects of top-down saccadic behaviour (Dias et al., 1995; Mort et al., 2003). However, the activity of FEF neurons does not appear to be related to online features of the saccade such as motor error (Segraves and Park, 1993). This suggest that while the FEF is highly involved in the initiation and planning of endogenous saccades, it is unlikely the source of CD for these saccades.

The parietal areas encode information related to visual perception and saccade behaviour (Pare and Wurtz, 1997), and tend to be involved in the generation of more sensory-driven saccades (Li and Andersen, 2001; Mort et al., 2003). Area LIP has been attributed to be an earlier stage in the progressive evolution of neuronal processing for saccades (Pare and Wurtz, 2001). As area LIP in monkeys has been shown to carry updated information about impending and previous saccades, it is likely a recipient of CD signals, and is implicated in sensory remapping. Indeed, information about bilateral saccades has been observed in area LIP of a single hemisphere (Colby et al., 1993; Colby et al., 1995; Heiser and Colby, 2006). Voluntary saccades lead to increased activation in FEF and saccade–related areas of the inferior parietal lobule. By comparison, reflexive saccade behaviour is linked to activation in the angular gyrus of the inferior parietal lobule, particularly on the right side (Mort et al., 2003).

2.3 Corollary discharge

As described above, the human sensorimotor system has the ability to generate a perceptually stable world while interacting with the environment. Current views hold that the brain constructs multiple spatial representations of the environment in a variety of reference frames so that multiple systems can interpret and use the information effectively

(Colby and Duhamel, 1991; Colby et al., 1996; Colby, 1998; Rizzolatti et al., 1997). These spatial reference frames can be coded egocentrically (relative to the observer) or allocentrically (extrinsic to the observer). Patients with parietal lobe lesions present with dramatic impairments of spatial perception and action, indicating the importance of this brain region in computing or applying these reference frames. Various forms of neglect have been characterized that have illustrated a number of spatial reference frames that the brain uses, including studies that have indicated that some reference frames incorporate information about intended actions before they have occurred (Goodale and Milner, 1992; Goodale et al., 2004; Milner and Goodale, 2008; Pizzamiglio et al., 1989). In order to construct this reference frame, information pertaining to the intended motor output must be acquired. One such reference frame that has been relatively well-characterized is the eye-coded reference frame that allows real-time updates of space relative to the eyes, encoded by corollary discharge (CD). This thesis aims to shed light on this system by attempting to discern the ability of a single hemisphere to manage and employ the eye-centred spatial reference frame, as well as investigating the specific role of the parietal lobe in this process.

2.3.1 Role of corollary discharge in perception

Hermann Von Helmholtz originally postulated that the brain must be monitoring self-generated actions in some way. He determined that this must occur in order to allow us to distinguish which visual displacements across the retina are due to our own eye movements and which are due to movement in the environment. He described that an 'effort of will' must be monitored, perhaps by sending a copy of the motor command destined for the eye muscles to the brain areas that generate our internal image of the world and how we fit into it (Helmholtz and Southall, 1924). A simple experiment suggests that Helmholtz was correct; if you displace your retina without generating a concomitant motor command by pressing on the eye, the world appears to move (Colby, 1998). The concept of a motor command copy has since been well established. In 1950, two researchers working independently developed similar theories; an efference copy or CD signal is sent to the brain area that concocts spatial reference frames. These motor inputs

are used to perceptually 'cancel out' any motion that we perceive that is caused by our own movements (Sperry, 1950; Von Holst, 1950). This area would presumably compare a predicted retinal image flow based on the CD representing the upcoming movement with the actual retinal image flow; if the two signals are identical, cancelling each other out, we will not perceive any external motion flow (Crapse and Sommer, 2008). Any extra movement that cannot be explained by the eye movement will in turn be perceived as having been the result of movement in the environment. In humans and primates, areas PEF/LIP and FEF have been implicated in updating the internal image (Barash et al., 1991a; Barash et al., 1991b; Colby et al., 1996; Colby, 1998; Duhamel et al., 1992a; Heiser et al., 2005; Heiser and Colby, 2006), while the thalamus is believed to be responsible for transmitting the motor information up to the FEF from the SC (Bellebaum et al., 2005a; Sommer and Wurtz, 2004b).

2.3.2 Remapping

The parietal and frontal extrastriate regions as well as the SC have been shown to update or 'remap' their activity in response to stimuli and eye movements, a phenomena that is believed to govern the visual perception of a stable world. These neurons have classical visual responses, firing when a stimulus is presented in their receptive field. They will also fire, however, when a saccade brings their receptive field onto a previously stimulated location. This updating must be the product of a transfer of visual information from neurons with a receptive field in the stimulated location, to neurons that will encode this same location after the saccade. The system must use a copy of the oculomotor command (i.e.: CD) in order to compute this transfer (Colby et al., 2005; Duhamel et al., 1992a; Goldberg and Bruce, 1990; Mays and Sparks, 1980b; Nakamura and Colby, 2002; Umeno and Goldberg, 1997; Umeno and Goldberg, 2001; Walker et al., 1995). Proprioceptive information was considered to be a possible contributor to remapping, but it has generally been accepted that a CD signal makes up the main signal from which remapping gains its information. Neurons have been shown to demonstrate remapping activities before the eye has moved and thus before proprioceptive information has changed, and direct tests of proprioception have shown that it is not necessary for

remapping to occur (Duhamel et al., 1992a; Guthrie et al., 1983; Heiser et al., 2005; Kusunoki and Goldberg, 2003; Nakamura and Colby, 2002; Wurtz, 2008). It has recently been postulated, however, that a combination of proprioceptive and CD information may underlie spatial updating in different proportions in different areas of the brain, and the debate is still active (Ziesche and Hamker, 2011).

2.3.3 Nature of corollary discharge signal

Recent double step studies have been conducted in order to investigate the nature of the information being conveyed within the CD signal. Multiple hypotheses exist as to exactly what information is being transferred between brain areas. A ballistic updating hypothesis suggests that the two targets are internalized, goal vectors are computed on the retinotopic neural maps of the brain, and the required motor vectors are calculated and then executed in sequence. In this hypothesis, the execution of the second saccade does not include any information about the success of the first saccade, being based entirely on the goal vectors calculated pre-saccadically (Bock et al., 1995; Ditterich et al., 1998; Dore-Mazars et al., 2006; Joiner et al., 2010; Munuera et al., 2009; Tanaka, 2003). It has been found that the updating motor system does not function this way, and that it uses real-time information about S1 to update the goal of S2 (Quaia et al., 2010).

The recent study by Quaia et al. (2010) attempted to characterize exactly what information is being used to update the saccade to T2. They presumed that the neural networks governing the saccadic execution will compute three sets of vectors: a set of visual vectors at the input level, a set of goal vectors at the level of retinotopic neural maps indicating the desired locations in space, and a set of motor vectors indicating the required motor transformations to bring the fovea from resting on the FP, to resting on each of the desired locations in space at T1 and T2. They presented two options for how we manipulate these vectors in the double step task: a goal updating hypothesis and a motor updating hypothesis. In the goal updating hypothesis, the T2 goal vector as described above is updated in real-time, reflecting the actual execution of the saccade to T1 and it is modified at the level of the retinotopic neural maps. Under this hypothesis, any error introduced in the motor execution of the first goal vector would be presumably corrected

in the new goal vector and a motor vector would then be calculated and a movement executed. Under the motor updating hypothesis, the motor vectors calculated to bring the fovea from the FP to T1 and from the FP to T2 are preplanned. The motor vector of FP to T1 is subtracted from the motor vector of FP to T2 and the S2 motor vector is the result; the goal vectors need not be updated. Under this system, saccade generation would rely only on the storage and updating of the motor vectors as opposed to goal vectors. The authors point out that from a theoretical point of view, this would seem to be the preferred method of motor updating. Since moving the eyes to the T2 location from anywhere in the visual scene (in the head fixed condition) results in the same final muscle innervation to keep the fovea fixated on the target (during the step phase), it would make sense to use this information, bypassing the need for further complex calculations in space. The authors designed a complex set of experiments that would have behavioural outcomes indicating which system is used in the normal brain. They found quite convincingly that the motor updating hypothesis is employed (Quaia et al., 2010).

Further qualification of efference copy signals have been studied by generating algorithms that attempt to model remapping activity that has been observed through primate unit recordings in different brain areas (Keith et al., 2010). It is important to note that remapping may employ various efference copy signals (visual, goal or motor) in different proportions at different levels in the brain, rendering comprehensive qualifications of these signals very complex.

2.3.4 Pathways for corollary discharge

A recently proposed pathway for CD in primates involves the intermediate layers of the SC sending CD information to the FEF via the mediodorsal (MD) nucleus of the thalamus (Lynch et al., 1994; Sommer and Wurtz, 2002; Sommer and Wurtz, 2004a; Sommer and Wurtz, 2004b; Sommer and Wurtz, 2006). An extensive study attempting to map this pathway selectively inhibited the MD thalamus, recorded from the various candidate areas, and observed the ability to generate saccade sequences that necessitate the use of CD. It was found that ipsilesional saccades, the CD of which uses machinery that was left in place, were tracked without a problem and the task was carried out effectively.

In contrast, contralesional saccades were not tracked as effectively, resulting in small errors in the second saccade of the double step sequence, suggesting that the CD flows from the contralateral SC, up the contralateral MD thalamus to the contralateral FEF (Wurtz and Sommer, 2004).

Specific pathways carrying CD signals to LIP/PEF have not been directly demonstrated, but as the area is central to remapping, it is likely that it has access to CD signals. It has been suggested that it may receive CD information via the FEF or from the SC via the pulvinar (Clower et al., 2001; Hall and Colby, 2011). Since inactivation of MD thalamus only causes a partial deficit in double step performance, additional pathways carrying CD are presumed to exist.

2.3.5 The double step paradigm

The double step task is often used to test whether a subject is able to generate and interpret CD. The task involves flashing two target stimuli (T1 and T2) very rapidly, sequentially in the periphery while the subject foveates a central fixation point (FP). Upon the extinction of the FP, the subject must make a series of saccades in the dark to the remembered location of each stimuli in the order in which they were presented. The first saccade (S1) is simply a retinotopically encoded memory-guided saccade; the second saccade (S2) begins at the final location of S1, and the subject must calculate where T2 was presented relative to this new location. This involves having access to and interpreting a CD or efference copy of S1. The double step task was first used to demonstrate that extra-retinal information is available to the oculomotor system, showing that it can track self-movements and integrate that information into the calculation of consequent saccades (Hallett and Lightstone, 1976a; Hallett and Lightstone, 1976b). While it is theoretically possible that the two visually encoded vectors from FP to T1 and T2 respectively may be used to calculate the vector of S2, careful studies have determined that it is indeed the motor vector of S1 that is used in the planning of S2 (Quaia et al., 2010). Humans and monkeys are both able to perform this task accurately (Baizer and Bender, 1989; Mays and Sparks, 1980a). This paradigm has since been used ubiquitously to test the ability of

patients and subjects to monitor their eye movements in different conditions and under different circumstances.

2.3.6 Corollary discharge between hemispheres

A series of experiments involving the ability of split-brain animals to complete the double step task has provided considerable insight into the possible pathways of remapping circuits. In one study that is of particular interest, Colby and others measured the ability of two monkeys to perform the double step task after sectioning of the forebrain commissures (Colby et al., 2005). They compared the abilities of these monkeys to carry out two double step paradigms. One involved an across-hemifield sequence in which T2 was updated from one visual hemifield to the other (saccades to T1 and T2 were in opposite directions but presented in the same hemifield, requiring the transfer of visual information about T2 to the contralateral hemisphere in order to generate a successful second saccade). The second paradigm involved a within-hemifield sequence in which T2 was updated within the same hemifield (T1 and T2 were presented in the same hemifield and required saccades in the same direction, only involving one hemisphere in the calculation and generation of the saccades). Initially, the monkeys were unable to complete the second saccade in the across-hemifield condition, as hypothesized by the authors (presuming that the corpus callosum represented the site for interhemispheric exchange of updating information). Performance remarkably improved very quickly, however, and further testing showed that the acquired updating ability was systemic, not just categorical as they were able to make trial-to-trial adjustments to the motor control of the second saccade as T2 moved slightly. This suggests that they had access to updating information across hemifields; it was further suggested that this information may be relayed through subcortical pathways. A follow up study on the same animals sought to discover the role of the cortex in this new found spatial updating ability; neurons in area LIP showed remapping signals for within-hemifield conditions as well as weaker and longer-latency remapping signals for across-hemifield tasks. In an attempt to characterize the transfer of visual information versus motor updating pathways for CD, another task that dissociated interhemispheric transfer of CD signals from visual information transfer was conducted.

T1 was presented in one visual hemifield and T2 was presented in the other; in this situation, information about the movement of the first saccade must be transferred to the other hemisphere to calculate the vector of the second saccade and no visual information transfer is required. On this task, the monkeys were not impaired at all, suggesting that subcortical structures that transfer CD signals interhemispherically do not rely on the forebrain commissures (Colby et al., 2005). This finding makes sense with the discovery that CD are sent from the SC to the FEF via the MD thalamus (Sommer and Wurtz, 2002). The SC projects both to the contralateral and ipsilateral FEF (Crapse and Sommer, 2009; Sommer and Wurtz, 2002; Vanegas and Centro Latino Americano de Ciencias Biológicas., 1984), and the contralateral and ipsilateral LIP (Clower et al., 2001). Importantly, this could represent the pathway for a CD that is bilaterally available to the cortical hemispheres. This thesis further probes whether a single hemisphere is able to track contraversive, as well as ipsiversive, movements and investigates the role of the parietal lobe in these calculations.

2.4 Patient studies

2.4.1 Hemidecorticate studies

Hemidecorticate subjects present a unique opportunity to observe the ability of a single hemisphere, along with brainstem structures, to perform a variety of tasks. Much has already been discerned on this topic by studying these patients, notably in oculomotor experiments designed to test tecto-cortical projections. It has already been found, using one of the same subjects participating in this study among others, that a single hemisphere along with the brainstem structures is capable of generating accurate bilateral saccades (Herter and Guitton, 2004). Evidence for the ability of a single hemisphere to trigger ipsiversive saccades had been gathered before (Hughes et al., 1992; Sharpe et al., 1979; Troost et al., 1972b), but studying further hemidecorticate patients allowed this to be confirmed and better characterized. Furthermore, in this same study, it was demonstrated that these subjects were able to use extra-retinal information in the planning and execution of a memory-guided saccade. The task involved fixating centrally, remembering a target location presented briefly in their seeing field, and then following via smooth pursuit the

fixation point as it brought them towards or away from the remembered location of the originally flashed saccade target. The fixation point would stop and disappear providing the go signal for the subjects to look to the remembered location of the saccade target. The subjects were able to complete this task accurately, implying that they had extra-retinal information available to help plan the vector of the saccadic movement. Remarkably, both subjects were able to perform the task accurately both when it involved contraversive and ipsiversive tracking, as well as when it involved contraversive and ipsiversive saccades to the target. Even more strikingly, corrective saccades on these tasks increased the accuracy of the final end point, suggesting that some internal monitoring was taking place. Corrective saccades in the contraversive direction increased accuracy more than corrective saccades in the ipsiversive direction, suggesting that internal monitoring may perhaps not be equal for both ipsiversive and contraversive saccades. Similarly, the SRTs of the patients were within the mean range of SRTs of the control, whole-brained subjects. These results aren't too surprising if we consider that hemidecorticate patients have been shown to track smoothly moving targets with saccades when the movement is contraversive to the remaining hemisphere and with smooth pursuit when the movement is ipsiversive (Troost et al., 1972a; Troost et al., 1972b). Each hemisphere ordinarily controls contraversive saccades and ipsiversive smooth pursuit (Leigh and Zee, 1999). It is clear from the results of this study that, unexpectedly, hemidecorticate patients can gain some ability to generate accurate ipsiversive saccades and to track contraversive smooth pursuit movements (Herter and Guitton, 2004). This latter observation suggests that some CD information is both generated by, and available to, the remaining brain structures in these patients. It is possible that this is due to the increased recruitment of sparse bilateral connections from cortex to brainstem oculomotor structures. Chapter 3 inspects the abilities of these patients to track ipsiversive saccades via CD, a capacity thought generally to be subserved by the missing contralateral hemisphere.

2.4.2 Why double step with hemidecorticate patients?

We decided to perform this study to determine whether a single hemisphere is capable of generating and making use of a CD signal for tracking eye movements. With the

unique opportunity to study the abilities of a single hemisphere, a logical experiment to build upon Herter and Guitton's paper would be to test whether hemispherectomy patients are able to monitor and use CD for bilateral saccades. The pathway for saccadic CD has still not been fully characterized, and the chance to test hemispherectomy patients on this ability would provide considerable new insight. It has been reported that the remaining FEF in these patients sends projections to the ipsilesional SC (Distel and Fries, 1982; Leichnetz et al., 1981; Shook et al., 1990). We wonder if this pathway could serve as the reciprocal connection for carrying CD information from the ipsilesional SC, up to the contralesional FEF (and subsequently to the PEF) for consolidation with other relevant oculomotor and visual information. The necessary real-time calculations that are believed to take place in the FEF/PEF during the double step task could then presumably occur in the FEF/PEF in the remaining hemisphere.

There are some important factors to keep in mind when studying hemispherectomy patients. First, these patients had intractable epilepsy for more than ten years. They were heavily medicated during this time as well. Each of our patients had their surgeries more than ten years ago; the incredible plasticity that their brains have performed can be assumed simply by observing their daily activities. They are all able to walk, an ability that technically should require two working motor cortices; there is no doubt that some wiring in the brain has been altered to make the best of their situations. However, for our purposes, testing these patients is incredibly useful. Based only on the fact that hemispherectomy patients observe a stable visual world (and, anecdotally, have since the day of their surgeries), we can assume that they must somehow be aware of self-generated movements that move images across the retina. Without some supervision of oculomotor commands, there would be no way of telling which image slips are due to exafference, and which are due to reafference. Further characterization of these abilities will give insight into the mechanisms and pathways underlying CD and remapping.

2.4.3 Frontal patient studies

Patients with frontal lobe lesions exhibit a specific pattern of difficulties in completing the double step task. They seem to be able to orient their saccades in the

correct direction of T2 suggesting their ability to update is intact, but their accuracy is generally impaired and they are slow (Heide et al., 1995). This finding is also consistent with findings from lesions of the frontal lobe in the monkey (Schiller and Sandell, 1983). Thus it appears that the frontal cortex plays a more prominent role in the motor component of the double step task (Hall and Colby, 2011), as opposed to spatial updating.

2.4.4 Parietal patient studies

Studies of patients with unilateral parietal lesions have determined that accurate updating in the double step task requires the use of the parietal cortex (Duhamel et al., 1992b; Heide et al., 1995). The first, a case study, found that a right fronto-parietal neglect patient would make erroneous second saccades if the first saccade was in the contralesional direction. The targets were never flashed more than 6° from the FP, and they were flashed very quickly. Furthermore, corrective saccades were not evaluated. The second study was much larger scale; they tested 19 patients (14 right and 5 left), and used a very similar task to the one used in the first study. These patients were found to be very slow at generating the double step sequence, and were only able to make accurate bilateral double step saccades when the two targets remained visible. If T1 was in the contralesional hemifield (requiring an S1 in the contralesional direction) and T2 was ipsilesional to T1's location (requiring an S2 in the ipsilesional direction), the patients appeared to be unable to successfully complete the task. Of particular importance, while they did evaluate corrective saccades, the authors only provided the patients with 1000ms to complete the task, which, as we'll see below, is not enough time. These studies both concluded that the patients were unable to either develop or interpret a CD signal for saccades directed contralesionally, implying the importance of the parietal lobe in monitoring contralateral eye movements. Importantly, this deficit was found to be specific to CD interpretation, since the motor planning abilities and retinotopic coding abilities for single saccades in this direction remained intact. Double step tasks that involved an ipsilesional S1 and a contralesional S2 were generally completed accurately by these patients. This is consistent with studies that found that inactivating LIP in monkeys leads to increased latency and decreased accuracy during saccades to an ipsilesional T2 when T1

is contralesional (Li and Andersen, 2001). It is also consistent with a study that found that TMS delivered to the right posterior parietal cortex at a critical interval during the double step task disrupts remapping, particularly for contralateral saccades (Morris et al., 2007; van Donkelaar and Muri, 2002). It stands in conflict, however, with many other studies that show a more ambiguous pattern of impairments in this population.

One study showed that, with a lesion of the right parietal lobe concomitant with a lesion of the corpus callosum, the patient is unable to generate an accurate second saccade when it is directed rightward, whether the first saccade was directed ipsilesionally or contralesionally (Pisella et al., 2011). This suggests a dominance of the right hemisphere in performing the calculations related to CD that are necessary when performing the double step task, whether the first saccade is directed to the right or to the left. This trend of higher influence of the right hemisphere's parietal lobe in CD calculations is found in many studies; as we describe below, however, we hypothesize that this has more to do with attentional impairments than it does with interruptions in the CD system.

Other studies investigating trans-saccadic perceptual remapping have proven to be similarly inconclusive and in contradiction with the previously-mentioned double step papers. Two studies found that, for patients with right parietal lobe lesions, remembering a target location in space after a saccade directed ipsilesionally is more impaired than after a saccade directed contralesionally (Russell et al., 2010; Vuilleumier et al., 2007). One would expect, if the CD system for contralesional saccades was impaired in these patients, to see the opposite result. Other studies investigating the remapping of the inhibition-of-return phenomenon (IOR) found that patients with a right parietal lesion (Sapir et al., 2004) or healthy subjects who underwent TMS of the right parietal lobe (van Koningsbruggen et al., 2010) are impaired in remapping IOR after a saccade in either direction. Moreover, TMS over the right parietal lobe was found to disrupt trans-saccadic memory for multiple objects after a saccade directed to the left or right in another study (Prime et al., 2008).

There is clearly not a consensus on the role of the parietal lobe in the CD system. Chapters 4 and 5 inspect the ability of patients with parietal lobe lesions to track bilateral saccades in the classic and two modified versions of the double step task.

2.4.5 Why double step with parietal patients?

Taken together, studies performed previously do not present a clear role for the parietal lobe in the processing of saccadic CD. Once we obtained the results of our hemispherectomy study (Chapter 3), we determined that it would be valuable to investigate more fully the role that the parietal lobe plays in successfully monitoring bilateral eye movements. Since patients with an entire hemisphere of cortex removed (including the parietal lobe) are able to monitor bilateral saccades and integrate this information into the planning of subsequent saccades, we hypothesized that it was likely that patients with unilateral parietal lesions also retain this ability. Chapters 4 and 5 outline these studies; we find that patients with lesions of the right or left parietal lobe have intact CD for saccades aimed contralesionally and ipsilesionally. The differences between the results of the previous studies described above and the results of our current studies may be explained by differences in paradigm, analysis and interpretation as outlined in detail in Chapters 4 and 5.

3 Oculomotor control after hemidecortication: a single hemisphere encodes corollary discharges for bilateral saccades (Rath-Wilson and Guitton, 2015)

3.1 Preface

This study was designed to evaluate the ability of hemidecorticate patients to monitor bilateral saccadic eye movements in the dark via corollary discharge (CD). While the literature on lesion studies using the double step saccade task implies the requirement of intact parietal lobes for contralateral saccade monitoring, our personal experiences with the hemidecorticate patients suggest that they retain this ability. They perceive a stable visual world and perform relatively normal navigation and visual exploration; we wanted to determine whether they would be successful at completing a modified double step task, engineered to evaluate CD for bilateral saccadic eye movements despite the patients' contralesional hemianopia.

3.2 Abstract

Patients who have had a cerebral hemisphere surgically removed as adults can generate accurate leftward and rightward saccadic eye movements, a task classically thought to require two hemispheres each controlling contralateral saccades. Here, we asked whether one hemisphere can generate sequences of saccades, the success of which requires the use of corollary discharges. Using a double step saccade paradigm, we tested two hemidecorticate subjects who, by definition, are contralesionally hemianopic. In experiment 1, two targets, T1 and T2, were flashed in their seeing hemifield and subjects had to look in the dark to T1, then T2. In experiment 2, only one target was flashed; before looking at it, the subject had first to saccade voluntarily elsewhere. Both subjects were able to complete the tasks, independent of first and second saccade direction and whether the saccades were voluntarily or visually triggered. Both subjects displayed a strategy, typical in hemianopia, of making multiple-step saccades and placing, at overall movement-end, the

recalled locations of T1 and T2 on off-foveal locations in their seeing hemifield, in a retinal area typically spanning a 5-15° window, depending on the subject, trial type and target eccentricity. In summary, a single hemisphere monitored the amplitude and direction of the first multiple-step saccade sequence bilaterally, and combined this information with the recalled initial retinotopic location of T2 (no longer visible) to generate a correct target-directed second saccade sequence in the dark. Unexpectedly, our hemidecorticate subjects performed better on the double step task than subjects with isolated unilateral parietal lesions, reported in the literature to have marked deficiencies in monitoring contralesional saccadic eye movements. Thus, plasticity-dependent mechanisms that lead to recovery of function after hemidecortication are different than those deployed after smaller lesions. This implies a reconsideration of the classical links between behavioural deficits and discrete cortical lesions.

3.3 Introduction

Saccadic eye movements are used to scan a visual scene by displacing rapidly the fovea from one point of interest to another. Saccades are generated via a complex bilateral network involving many cortical and subcortical areas within one hemisphere and interactive links between the two hemispheres. Electrical stimulation of major areas controlling saccades in one hemisphere such as the cortical frontal eye fields (FEF) and midbrain's superior colliculus (SC) evokes contralaterally-directed saccades. Neurons in these areas have contralateral movement fields and their deactivation severely impairs contralateral saccades. These observations have led to the generally accepted proposition that each hemisphere controls saccades directed contralateral to itself (reviewed in Leigh and Zee, 1999; Pierrot-Deseilligny et al., 2002b).

There is considerable evidence, however, against this strict left brain - right saccade, and vice versa, view of the saccadic system's organization. For example, microstimulation of the supplementary eye field (SEF) in one hemisphere can evoke either contralateral or ipsilateral saccades (Penfield and Jasper, 1954; Schlag and Schlag-Rey, 1987). Neurons in the FEF of each hemisphere project to both the contralateral and ipsilateral SC (Distel and

Fries, 1982; Leichnetz et al., 1981). At the behavioural level, callosotomy patients can direct their saccades either to the left or right depending on the colour of a cue presented to the same single hemisphere (Hughes et al., 1992). Finally, and particularly relevant to the present study is that hemidecorticate subjects – who have had an entire cortical hemisphere surgically removed – are able to generate accurate bilateral saccades (humans: Herter and Guitton, 2004; monkeys: Tusa et al., 1986).

If one hemisphere contains circuits for bilateral saccade control, an important question is whether, in this hemisphere, the circuits that drive leftward and rightward saccades can communicate with each other and with the visual system. The classical model postulates that information about the vector of a saccade is communicated to various brain areas, including the opposite hemisphere, by a copy of the motor command called the "corollary discharge" (CD) or efference copy (Sperry, 1950; von Holst and Mittelstaedt, 1950). This mechanism is critical for vision because it contributes to our abilities to maintain: 1) a perceptually stable visual world by combining visual information from the retina with motor information about saccades to determine whether an image movement on the retina is due to movement of our own eyes or that of the environment (von Helmholtz, 1925); and 2) an updated internal representation of the position of our eyes in the orbit and where they are pointing in space during scanning eye movements consisting of multiple saccade steps (Guthrie et al., 1983). Point 2 is the subject of this paper.

A common tool used to study the encoding of multiple saccades is the double step paradigm (Hallett and Lightstone, 1976a) wherein a subject, in the dark, typically fixates centrally while two targets (T1 and T2) are briefly flashed sequentially in the periphery. The subject must make two saccades (S1 and S2) in complete darkness to the remembered locations of the targets in the order in which they were presented. The visual information about T1 and T2 is available in retinal coordinates. Therefore, the subject must use CD information about S1 – called CD_{S1} – in order to make an accurate S2, according to the simple vector equation: $S2 = T2 - CD_{S1}$. It is known that normal humans and monkeys can perform the double step task successfully (Baizer and Bender, 1989; Becker and Jurgens, 1979; Gellman and Carl, 1991; Gnadt and Andersen, 1988; Goldberg and Bruce, 1990;

Hallett and Lightstone, 1976a; Li and Andersen, 2001; Mays and Sparks, 1980b; Medendorp et al., 2006; Ray et al., 2004), by monitoring ongoing motor output and appropriately adjusting the motor plan for subsequent eye movements (Quaia et al., 2010).

Patients with parietal lobe lesions present with a stereotyped deficit in the double step task: they are unable to complete an ipsilesionally-directed saccade if it follows a contralesionally-directed saccade (Duhamel et al., 1992b; Heide et al., 1995). The latter authors have also shown a left-right asymmetry in hemispheric control. Other studies have found that transient inactivation of the human posterior parietal cortex in healthy control subjects can cause errors in saccades that follow a contralesionally-directed saccade (Morris et al., 2007; van Donkelaar and Muri, 2002). All these authors suggest that the CD of the contralesional saccade, S1, executed by the lesioned hemisphere, is not transmitted to the planning areas of S2 either within the lesioned hemisphere or in the other, intact hemisphere, thereby implicating the parietal lobe in the processing of CD. Imaging studies in healthy control subjects have also implicated the parietal lobes in the processing of CD information (Bellebaum et al., 2005b). These studies do not reveal, however, whether the CD is generated by the parietal lobe itself or whether a lack of the intact parietal region prevents the contralateral transmission of the CD generated somewhere else in the hemisphere. They also do not show by which pathways and mechanisms a CD, generated by one hemisphere, can be made available to the other. This is a complicated topic considered further in the Discussion.

One sure way to avoid concern about the involvement of commissural pathways is to study hemidecorticate patients which we do here. No study to date has demonstrated convincingly whether a single hemisphere can control bilateral saccades when information about the bilateral CD for these saccades is required. Our investigation probes whether a single hemisphere is able to track contraversive and ipsiversive saccades. Previous studies in hemidecorticate subjects have showed that they are able to generate accurate bilateral saccades following intervening pursuit movements (Herter and Guitton, 2004). Here we determine if this ability extends to saccadic eye movement monitoring.

Previous results have been presented as an abstract in the Journal of Eye Movement Research 'Book of Abstracts from the European Conference on Eye Movements (2013)'.

3.4 Materials and methods

3.4.1 Participants

Two hemidecorticate subjects and two age, gender and handedness-matched control subjects participated in this study, which was approved by the Montreal Neurological Institute and Hospital Research Ethics Committee. The participants gave informed and voluntary consent before participating, in accordance with the Declaration of Helsinki.

The case histories of the hemidecorticate subjects have been described elsewhere (Leh et al., 2006a; Leh et al., 2006b; Tomaiuolo et al., 1997) and will only briefly be summarized here.

DR is a right-handed woman – 39 at the time of testing – who underwent a complete right functional hemidecortication at the age of 17 to relieve intractable epilepsy caused by Rasmussen's Chronic Encephalitis. (A functional hemidecortication is a procedure which involves the removal of the critical part of a hemicortex, a corpus callosotomy, and the assurance that any remaining tissue left on the operated side – often to mechanically stabilize the remaining brain tissue – is disconnected from the rest of the brain.) Note that DR was an active child who did not display any cognitive, motor or visual impairment until the age of 11, when her health declined rapidly. Her intellectual functions, as measured using standard tests, remains in the average range, and she displays partial contralateral hemiplegia and complete contralateral hemianopia without macular sparing. Despite these handicaps she demonstrates, in interpersonal relationships, remarkable intelligence, analytical and social skills, and served a term as president of a provincial lobby group. MRI images of her brain are shown in Fig. 3.1A and 3.1B; more detailed scans can be found in previous studies (Leh et al., 2006a; Ptito et al., 2001).

JB is a left-handed man (with language lateralized to the right cortical hemisphere) who underwent a two-step left functional hemidecortication at the age of 20 to relieve intractable epilepsy due to a porencephalic cyst. His left frontal and parietal poles were left in place, but surgically disconnected from the remaining hemisphere. He was 46 at the time of testing. His intellectual functioning is in the average range, and he displays partial contralateral hemiplegia and contralateral hemianopia with 3.5° of residual vision along the entire vertical meridian. He holds a full-time job. MRI images of his brain are shown in Fig. 3.1C and 3.1D. A map of his visual field deficits (Wessinger et al., 1996) and more detailed MRI images can be found in previous studies (Leh et al., 2006a; Ptito et al., 2001).

Interestingly, differences have been reported in the remaining cortical networks of these two subjects using the Diffusion Tensor Imaging (DTI) technique for identifying axon tracts, specifically the existence of a novel ascending tract from the ipsilesional SC to the remaining hemisphere, present in DR but not in JB (Leh et al., 2006a). We will consider the implications of the latter study on our results in the Discussion section.

3.4.2 Experimental procedure and design

Our objective for the present study was to determine whether hemidecorticate subjects are able to generate and use CD – or efference copy – information about their saccadic eye movements for the subsequent generation of accurate future saccades. We were unable to use the classical version of the double step task as described in the introduction with these subjects because they are hemianopic in the contralesional visual hemifield, i.e.: unable to see a target presented in their blind hemifield contralateral to the lesioned hemisphere. We developed a novel version of the double step task that would allow us to determine if our subjects had access to efference copy information for eye movements in either direction.

In all experiments, participants were seated in a dark room with their heads restrained by a bite bar. The experiments consisted of blocks of 60 trials in which several conditions were interleaved. Between each trial, a room light came on for 1000ms to prevent dark adaptation.

In a simple orienting task, hemianopic subjects generate saccades that typically undershoot targets in their seeing field (Herter and Guitton, 2007; Troost et al., 1972b). This behaviour assures that, after the saccade, a target of interest will remain in their seeing hemifield. Conversely if a target is in their blind hemifield, they tend to overshoot it, again with the objective of placing the target in their seeing hemifield. We wanted to quantify this behaviour and determine if it resulted in a fixed 'default' off-foveal circumscribed retinal area into which a hemidecorticate subject placed a target's location each time they were required to look to a remembered target location. We therefore performed a series of control experiments (Fig. 3.2A, 3.2B and 3.2E) that required a simple orienting saccade to a target in their seeing hemifield and which allowed us to quantify their undershooting behaviour. This provided important information for analyses of the double step experiments. In the *simple* control saccade task, subjects fixated a central fixation point (FP) for 750ms after which, while FP stayed on, a peripheral target in the seeing field was presented for 800ms, 1000ms or 1200ms on the horizontal meridian at either 5°, 10°, 20° or 25° (Fig. 3.2A). Upon the simultaneous extinction of the target and the FP, subjects made a saccade in the dark to the remembered location of the target. In different blocks, the FP remained on an extra 300ms after the peripheral target was extinguished, and subjects were not allowed to look away until the FP was extinguished (Fig. 3.2B). In this latter *delay* control task, we determined whether there was any degradation in their ability to be accurate over the 300ms time period which, in the double step paradigm, corresponded to approximately the time between the extinction of T2 (the first seen target, see below) and the GO signal (the extinction of FP).

In addition to the control experiments, there were two main types of double-saccade experiments dubbed *exogenous* and *endogenous*, as described in Fig. 3.2C, 3.2D and 3.2E. Each trial began with the presentation of the FP for 750ms.

The *exogenous* series of experiments involved flashing two peripheral targets (T1, green; T2, white) at different positions along the horizontal meridian in the seeing hemifield of the hemidecorticate subjects while they fixated the central FP (Fig. 3.2C). Subjects were required, upon extinction of the FP, to look to the remembered location of

first the green target, T1, presented *second*, and then to the white target, T2, presented *first*. We presented the targets in the reverse order at which they were to be looked in order to increase the accuracy of the first saccade (S1 to T1). This approach has been used for studying the effects of lateral intraparietal area (LIP) inactivation in monkeys (Li and Andersen, 2001) as well as spatial updating in humans (Morris et al., 2007). T2 was presented for 800ms, 1000ms or 1200ms, while FP remained illuminated. When T2 was extinguished, T1 was presented for 350ms; after the first 200ms of T1 being illuminated, the FP was extinguished, leaving T1 on alone an additional 150ms. This arrangement aimed to maximize the accuracy of S1. Three trial types were interleaved within these blocks: *same*, *ipsiL-contraL*, and *ipsiL-ipsiL* (Fig. 3.2E shows the expected eye movements for DR with a right hemisphere lesion). (The 'L' in the appellation signifies that the direction of a saccade is with reference to the lesioned hemisphere; thus, *ipsiL* signifies an ipsilesional saccade and *contraL* signifies a contralesional saccade.) In the *same* condition, the targets appeared sequentially in the same location, acting as a 'catch' trial. In the *ipsiL-contraL* condition, T1 was presented more eccentric than T2 in the *seeing* hemifield thereby requiring S1 to be ipsilateral to the lesioned hemisphere (*ipsiL*: into the seeing field) and the second saccade (S2) to be contralateral to the lesioned hemisphere (*contraL*: into the blind field). In the *ipsiL-ipsiL* condition, both T1 and T2 required saccades S1 and S2 to be in the same direction: both ipsilateral to the lesioned hemisphere into the seeing field. Targets could appear at 5°, 10°, 20° or 25°.

The *endogenous* series of experiments involved flashing a single green target (T) in the seeing hemifield for 800ms, 1000ms or 1200ms while the subject fixated the central FP (Fig. 3.2D). To assure congruency with the exogenous experiments, we will rename T2 = T, noting that there was no T1. Three trial types were performed in different blocks, depending on the instructions: *contraL-ipsiL*, *ipsiL-contraL*, and *ipsiL-ipsiL* (Fig. 3.2E). In the *contraL-ipsiL* condition, upon extinction of the FP, subjects were required to make an S1 of self-determined amplitude in the direction contralateral to the lesioned hemisphere (into their blind field), and then an S2 to the remembered location of the previously seen T in their seeing field, i.e.: in the ipsilateral direction relative to the lesioned hemisphere. In the endogenous *ipsiL-contraL* condition, upon extinction of the FP the subjects were

required to make an S1 of self-determined amplitude in the direction ipsilateral to the lesioned hemisphere (into their seeing field) that would place their fovea beyond the location of the previously seen T, therefore requiring an S2 directed contralateral to the lesioned hemisphere (into their blind field), to the remembered location of the previously seen T. In the endogenous *ipsiL-ipsiL* condition, upon extinction of the FP the subjects were required to make an S1 of self-determined amplitude in the direction ipsilateral to the lesioned hemisphere (into their seeing field) that would place their fovea on a location between the FP and the location of the previously seen T, and would require an S2 to the remembered location of the previously seen T in the direction ipsilateral to the lesioned hemisphere (into the seeing field). Depending on the trial type, targets could appear at 5°, 10°, 20°, 25° or 30°.

3.4.3 Stimuli and apparatus

Visual stimuli were generated in MATLAB using the Psychophysics Toolbox. They were back-projected at 85Hz with an Electrohome Marquee 8000 projector (projection resolution, 1024 X 768 pixels) onto a screen located at a distance of 57cm from the participant. We patched one eye of each subject to avoid possible compensatory tactics by the patients, for example, by aligning each eye differently to increase their angle of vision. We allowed them to choose which eye they wanted patched; they both chose the contralesional eye. Monocular eye position of the non-patched eye was recorded by a video eye-tracker (EyeLink 1000, SR research) at a sampling rate of 1000Hz for all subjects.

The visual stimuli for the task consisted of a circular 1° light spot; the FP and different colour targets were isoluminant and flashed on a black background. The FP was located at the centre of the screen and was red. The targets were either green (T1, T) or white (T2). Different colours were used to help the subjects distinguish the order in which targets were to be foveated. Targets were presented on the horizontal meridian in the seeing field at 5°, 10°, 20°, 25° or 30°. In all tasks, the saccades were made in complete darkness.

3.4.4 Data analysis

For each trial, the target locations, target onsets, target offsets, FP onsets, FP offsets and the X and Y eye position signals were stored online for further offline analysis.

Data from all trials were inspected visually and all trials were included in the main analysis except those we deemed unacceptable, specifically: 1) trials in which there was only one saccade except for the *control* and *same* conditions which did not require double step saccade responses; 2) the first saccade was in the wrong direction; 3) the S1 latencies were less than 100ms or larger than 1000ms; 4) the initial eye position deviated more than 2.5° from the FP; and 5) there were significant blink artefacts or noise in the eye position signal. Suppl. Table 3.1 shows the breakdown of the number of trials deemed to be acceptable in each trial type.

Since DR and JB have the right and left hemispheres removed, respectively, a saccade to the seeing hemifield would be directed to the right for DR and to the left for JB. Thus, JB and his control subject MO actually performed all the experiments in the reverse direction to those performed by DR and her control subject SR. For ease and clarity in presenting the data, all horizontal direction values in JB and MO have been reversed to match the experiments performed by DR and SR.

Eye velocity was obtained by digitally differentiating the time trace of the eye position signal. Saccades were deemed acceptable if they were of amplitude greater than 1°, reached a velocity greater than 80°/s, and lasted less than 500ms. Saccade onset was determined as the point at which eye velocity exceeded 30°/s.

In all trial types, the hemidecorticate patients usually generated multiple saccades – as many as 5 – to reach a single target, either T1 or T2. Each saccade's onset and offset times and initial and final eye positions were recorded. The number of trials that included five saccades to reach a single target comprised less than 1% of all trials and we have omitted these trials from the analysis. Here, we have only included trials in which up to two saccades were generated to reach the first target location and up to four saccades were

generated to reach the second target location. This restriction eliminated 11% of the trials accepted for analysis as defined above. We define ΣS1 and ΣS2 to mean the sum, in a single trial, of all the amplitudes of all saccades used to reach T1 and T2 respectively. ΣS1 could include up to two saccades (dubbed S1.1 and S1.2) and ΣS2 could include from one to four saccades (dubbed S2.1 – S2.4). Suppl. Table 3.2 shows the percentage of trials that had the various numbers of saccades by trial type. Saccades were categorized as being part of ΣS1 or part of ΣS2 based on a combination of their horizontal direction and the time intervals between saccades, depending on the trial type. We will show in the Results section (3.5.2) that this is a valid method for determining the end of the ΣS1 sequence and the beginning of the ΣS2 sequence. We will also show that analyzing multiple saccades for a single saccade target is a valid method to observe the ability of these subjects to internally monitor eye position. In each trial, the eye position at the end of the last saccade in the sequence has been dubbed FEP1 and FEP2, respectively.

Saccade reaction time (SRT) was calculated as the time between the GO signal (the extinguishing of the FP) and the beginning of the first saccade. Saccadic time intervals were calculated as the time between the end of one saccade and the beginning of the next (Fig. 3.2F and Fig. 3.3).

The results are best depicted by the scatterplots in Fig. 3.4-3.8. To determine the accuracy of our subjects across trial types, we performed a combination of ANOVA and regression analyses. In order to determine accuracy in the control trials and in ΣS1 of the exogenous experiments, we compared final eye position (FEP) using two factor ANOVAs with paradigm type as the first factor and target position as the second factor for each subject. In assessing accuracy in the control conditions, this was straightforward: three paradigm types were included (*simple*, *delay* and *catch*) and the four target eccentricities were included (5°, 10°, 20° and 25°) as illustrated in Fig. 3.4. In assessing the accuracy of S1s in the exogenous experiments, we included the *simple*, *delay* and *catch* paradigms of the control conditions, plus the *ipsiL-contraL* and *ipsiL-ipsiL* paradigms of the exogenous double step condition. Only the 10° and 20° targets were included in this analysis, since they were the only target locations common across all trial types (Fig. 3.5). (In the

exogenous *ipsiL-contraL* condition, the T1 locations were 25°, 20° or 10° and in the exogenous *ipsiL-ipsiL* condition, the T1 locations were 5°, 10° or 20° and therefore, across both exogenous conditions, the target offsets common to T1 were 10° and 20°).

In order to determine the accuracy of the second step of the double step tasks (both exogenous and endogenous), we performed regression analyses on the data illustrated in Fig. 3.6-3.8. First, we found the line of best fit through the data for each subject and determined if the regression lines were significant. Second (for the data illustrated in Fig. 3.6 and Fig. 3.8), we compared the slopes of the regressions lines of each of the paradigm types with the slopes of the regression lines for the subjects' control data using the Student's t test. This allowed us to determine whether the subjects were as accurate in achieving the second target location in a double step task as they were at foveating a single target in a control task. We then assessed whether the slope of the hemidecorticate subjects' lines of best fit were significantly different than those of their respective control subjects in each condition. This allowed us to observe how well the hemidecorticate subjects were able to tailor the amplitude of their second saccade based on the amplitude of their first saccade, without necessarily including the confounding factor of their ever-present undershoot and off-foveal range (which, for the latter, is represented in this analysis by the intercept of each line).

Similar to previous studies of double step saccades in monkeys (McKenzie and Lisberger, 1986; Schlag et al., 1990) and humans (Herter and Guitton, 1998; Herter and Guitton, 2004; Ohtsuka, 1994; Zivotofsky et al., 1996), we performed quantitative comparisons between correlations of overall gaze shift amplitude to T2 with two diametrically opposed potential behavioural outcomes: the encoding of the second step sequence to T2 was in spatiotopic or in retinotopic coordinates. The overall gaze shift amplitude of the second step was calculated as the difference between the horizontal eye position (FEP2) at the end of ΣS2 and the horizontal eye position (FEP1) at the end of ΣS1. Spatiotopic compensation in each condition is suggested if (FEP2 – FEP1) is better correlated to (T2 – FEP1) than to (T2 – initial eye fixation position), the latter being the retinotopic location of T2 which is provided to the subject during the initial fixation period

(Fig. 3.2C). Put another way, spatiotopic encoding implies that the initial retinotopic error between the fixating eye and T2 has been updated to account for the intervening ΣS1.

It is most straight-forward to compare spatiotopic and retinotopic encoding in the exogenous and endogenous *ipsiL-contraL* condition since, for compensation to occur, the second saccade should be in the opposite direction to the initial, retinotopic presentation of T2 during fixation (Suppl. Table 3.3). This means that, should our subjects be using exclusively retinotopic coordinates to plan their saccades in the exogenous and endogenous *ipsiL-contraL* conditions, we would expect their second saccade in the sequence to be an ipsilesionally directed saccade (incorrectly into the seeing field), of the same amplitude as FP – T2. As we will see, this was not the case (Suppl. Table 3.3, Fig. 3.6A and 3.8B).

3.5 Results

3.5.1 Breakdown of accepted trials for analysis

A breakdown of the accepted trials for analysis of each subject on each task including the main reasons for rejection, as defined in Methods and Data Analysis sections, is available in the Suppl. Materials (Suppl. Table 3.1). For each of the control subjects (SR and MO), more than 90% of trials were considered acceptable across all tasks combined. By comparison, across all experiments, the number of acceptable trials was considerably lower in the hemidecorticate patients: DR (51% of all trials) and JB (46% of all trials). In the *simple* control experiment, both patients had difficulty suppressing reflexive saccades to the target in the seeing hemifield during the 800ms, 1000ms or 1200ms wait period before both FP and T were extinguished simultaneously, thereby providing the GO signal (DR: 46% acceptance, JB: 57% acceptance). In the *delay* control experiment, JB had only a 27% acceptance rate due to false starts before FP was extinguished and was much worse than DR (68% acceptance) whose errors were due primarily to blinks. DR showed considerable difficulty suppressing reflexive saccades during the exogenous tasks, achieving only 27% and 24% acceptance rates for the exogenous *ipsiL-contraL* task and the exogenous *ipsiL-ipsiL* task respectively. (Recall that the terms *contraL* and *ipsiL* are with

respect to the lesioned hemisphere in our patients.) On all other tasks, the hemidecorticate subjects' acceptance rates were higher than 40%.

It is known from the studies of Duhamel et al., (1992) and Heide et al., (1995) that patients with isolated unilateral parietal lesions often fail to generate an S2, or make an erroneous S2, when tested on an analogous version of the endogenous *contraL-ipsiL* task. Therefore, we were surprised that the hemidecorticate subjects were able to generate the requisite two saccade sequences as well as they did on this task, as we shall show below. Indeed, DR even had the highest acceptance rate on this particular saccade sequence with 68% (Suppl. Table 3.1).

3.5.2 SRT and number of saccades

Fig. 3.3A shows the mean SRT for the first saccade in each task for DR and JB, as well as the control subjects. Error bars represent the standard error of the mean. Note that the hemidecorticate subjects' mean SRT's on each task were similar to those of their control subjects.

Hemidecorticate subjects frequently make more saccades than control subjects to reach a target location (Herter and Guitton, 2004). For the present experiments, Suppl. Table 3.2 gives the number of saccades generated by each subject to reach the target location expressed as a percentage of each trial type. In the hemidecorticate subjects, most trials showed only one or two saccades in each of ΣS1 and ΣS2 (S1: 89%; S2:89%). Fig. 3.3B illustrates the time interval between the end of the ΣS1 and the beginning of ΣS2 for all trials in which a single saccade was generated to reach the first target location. For each of the tasks, the hemidecorticate subjects were slower at initiating ΣS2 than their control subjects, which is not surprising as hemidecorticate subjects have been shown to have task-dependent differences in SRT (Herter and Guitton, 2007)

Figure 2F shows an example eye position trace of the endogenous *contraL-ipsiL* task (Fig. 3.2E) performed by DR (trace was filtered with a 20Hz low pass band filter). Here, DR made two *contraL* saccades (ΣS1) to attain the endogenous T1 location and two *ipsiL*

saccades (ΣS2) towards T2, which was undershot. To ascertain consistency in our analyses, it was important to determine reliably the end of ΣS1 and the beginning of ΣS2. We found consistently that the interval between ΣS1 and ΣS2 was much longer than that between S1.1 and S1.2 and between S2.1 and S2.2. This characteristic is illustrated in Fig. 3.2F. Figure 3C shows quantitatively the time intervals between S1.1 and S1.2 (Interval 1) and between S1.2 and S2.1 (Interval 2) for all those trials in which two saccades were generated to reach the first target. Stars with error bars (depicting the standard error of the mean) show Interval 1 of ΣS1 for DR (blue), JB (red) and MO (grey with dashed line). Squares with error bars show Interval 2 for the same subjects. (Note that control subject SR did not make two saccades to reach the first target often enough to obtain a reliable mean for all trial types.) We were able to discern the end of the ΣS1 and the beginning of ΣS2 based on the length of the time intervals between saccades. As shown in Fig. 3.3C, Interval 2 was consistently significantly longer than Interval 1 on every trial type for every subject, in particular for DR and JB. S1.2 was most often a corrective saccade performed very shortly after the first saccade.

We performed the same analysis on saccadic time intervals in ΣS2 (not shown). The last saccade in the series was followed by the longest time interval of fixation; for every trial type and for each subject, the time interval after the last saccade in the series was significantly longer ($P<0.05$) than the time intervals of the previous fixations.

In summary, we used the longest time intervals or fixation periods to determine FEP1 and FEP2, which we believe to be a reliable method to classify saccades, as there were consistently two significantly longer time intervals in each trial type. This is further illustrated by the histogram in the inset at the top-left of each panel of Fig. 3.4, which show the FEP for all control trials (*simple* and *delay* combined) in which a subject oriented to a target at 20°. From top to bottom, the histograms show the FEP in those control trials for which a subject made one, two, three and four saccades, respectively, to reach the target location. The mean and scatter of FEP in each histogram is similar and the number of saccades that the subjects performed in each control trial did not affect their accuracy in

orienting to the target location. These results are shown to validate, in conjunction with Fig. 3.3C, our acceptance of multiple-step saccades for a single target location.

3.5.3 Control experiments and catch trials

Figure 3.4 shows the distribution of FEP to the various target locations after we included all saccades in any given trial – there could be 1, 2, 3 or 4 saccades – in the *simple* control (triangles) and *delay* control (circles) tasks. (Eye position at initial fixation is defined as 0). The crosses show FEP for the *catch* trials that were interleaved in the exogenous condition blocks. Recall that in the *catch* trials, both T1 and T2 appeared at the same location thereby requiring no S2, or one of zero amplitude. Statistical analysis revealed that FEP did not vary significantly across the three tasks within the same subject (DR [$F(2,332)=1.3$, $P=0.27$], JB [$F(2,290)=0.81$, $P=0.45$], SR [$F(2,191)=1.6$, $P=0.20$]) except in the case of MO, JB's control subject (MO [$F(2,274)=4.44$, $P=0.01$]). In his case, the *delay* control task FEPs were significantly different than the FEPs of the *simple* control and the *catch* trials as revealed by the Tukey test; the *catch* trials and *simple* control FEPs were not significantly different from each other. These results in our hemidecorticate patients have several important implications for our study: 1) our measure of FEP is consistent across tasks; 2) the accuracy of the sum of saccades was not significantly different in the *delay* and *simple* control conditions, which suggests that the accuracy of ΣS2 in double step experiments should not suffer due to a deterioration in working memory of the position of T2 during the intervals in which T1 was presented (except perhaps in the case of MO); and 3) because the undershoot profiles of our patients in the control and interleaved *catch* trials were similar, it is likely that they were using the same motor strategies throughout the double step experiments as during the control trials.

Comparing the FEP of patients (Fig. 3.4A and 3.4B) with that of the controls (Fig. 3.4C and 3.4D) shows that the mean FEP of both hemidecorticate subjects was consistently less than the control subjects; i.e., the patients had larger undershoot errors to the flashed targets. This behaviour has been described before in hemianopic subjects and is believed to be adaptive, with the goal of keeping target locations in the seeing hemifield after a saccade (Herter and Guitton, 2007; Troost et al., 1972b).

Note that across experimental conditions, for each subject there was a significant increase of FEP with target eccentricity thereby implying that every subject in every experiment was tailoring eye movement amplitudes based on the eccentricity of the presented target ($P<0.001$ for each subject in each paradigm type). Visual inspection of Fig. 3.4A and 3.4B suggest that the mean error increased with target eccentricity implying therefore that there was not a small 'offset fovea' to which our hemidecorticate subjects aimed the eye but perhaps an 'offset foveal range' of 5-15° in which the subjects would place the target location. Hemidecorticate subjects also showed less precision on this task, with slightly larger error distributions than their respective control subjects (especially DR – see Fig. 3.4A), lending more credence to the concept of a less precise 'offset foveal range'.

Another point of interest was that there was a significant interaction effect, on our measure of final eye position, between the target position and the paradigm type for DR [$F(6,332)=2.15$, $P=0.05$)] and for SR [$F(6, 191)=3.24$, $P<0.005$], but not for JB [$F(6,290)=0.8$, $P=0.57$] or MO [$F(6,274)=0.85$, $P=0.53$]. This result for DR and SR may be explained by a few outliers in the control data for each subject that only occurred in a single paradigm type in a single target location (20° in the *delay* condition for DR and 20° in the *simple* condition for SR).

3.5.4 Exogenous series: saccade accuracy to T1

We now proceed with an analysis of the double step responses, concentrating first on the saccades to the first target, T1. Figure 3.5 compares the final eye position (FEP1) at the end of the first series of saccades, ΣS1, to T1 in three conditions: the combined control conditions (*simple*, *delay* and *catch*), the exogenous *ipsiL-contraL* condition, and the exogenous *ipsiL-ipsiL* condition. Note that for this analysis, we have only included those trials in the various control conditions that involved either one or two saccades to reach the visual target. We have removed trials with three or four saccadic steps to reach T1 in the control conditions to avoid any possible confounding effects of a greater number of saccades. Since we have only included trials in the exogenous conditions with one or two saccadic steps to reach T1, we wanted to ensure that we were using the same restrictions for our control data in this particular analysis. Note that restricting our analysis of ΣS1 to

trials having one or two saccades does not force us to eliminate the majority of trials and still leaves us with 85%, 81.5% and 97% of all accepted trials of the hemidecorticate subjects for the combined control, exogenous *ipsiL-contraL*, and the exogenous *ipsiL-ipsiL* conditions respectively

Visual inspection of Fig. 3.5 suggests the patients performed similarly in all three tasks (DR: Fig. 3.5A and JB: Fig. 3.5B). The FEP1s in the exogenous condition could be compared quantitatively with the single target control experiments for the target locations 10° and 20°, since these were the only two T1 target locations available for a comparative analysis across the *simple*, *delay*, *catch*, *ipsiL-contraL* and *ipsiL-ipsiL* experimental conditions (Methods). The FEP1 for ΣS1 was calculated for each of these conditions as described in the Methods, Data Analysis section, and each was compared independently with the FEP recorded in the control conditions.

For DR (Fig. 3.5A), a significant difference was found between paradigm types when the initial ANOVA was performed (DR [$F(4, 239)=4.33$, $P=<0.005$]). There was a significant effect of target location ($P<0.001$) and there was not a significant effect of interaction ($P=0.22$). The Tukey test determined that, while the *ipsiL-ipsiL* FEP1s were not significantly different than the control conditions, the *ipsiL-contraL* FEP1s were significantly different ($P<0.05$). Further testing revealed that, in the *ipsiL-contraL* condition DR's FEP1 to T1 was significantly more accurate than in the control condition; i.e., the mean FEP1 was closer to T1 (DR [$F(3,201)=5.12$, $P<0.01$]). DR's increase in accuracy to T1 in the *ipsiL-contraL* condition was associated with overshoots of T1 on some trials which resulted in a much larger variance around the mean FEP1. This behaviour was not observed in any other condition. The reduction of mean error with a concurrent increase in the variance of FEP1 was not related to changes in SRT of ΣS1 which, in DR, were similar in the exogenous *ipsiL-contraL* and *ipsiL-ipsiL* conditions (Fig. 3.3A). For DR's control subject SR (not shown) no significant difference was found between the FEP in the control conditions and her FEP1 to T1 in either of the exogenous conditions where T1 = 10° or 20° (SR [$F(4,156)=2.60$, $P=0.19$]). In the case of SR, there was a significant effect of target location ($P<0.001$) and there was not a significant effect of interaction ($P=0.25$).

A significant difference was found for patient JB between paradigm types for T1=10° and 20° (JB [$F(4,370)=50.47$, $P<0.001$], Fig. 3.5B). There was a significant effect of target location ($P<0.001$) but not a significant effect of interaction ($P=0.24$). This was also the case for JB's control subject (not shown) who showed a significant difference between paradigm types (MO [$F(4,221)=19.48$, $P<0.001$]) and a significant difference between target locations ($P<0.001$) but no significant effect of interaction ($P=0.72$). Note that the Tukey test revealed that each of the exogenous conditions were significantly different than the control conditions, but not significantly different than each other for both JB and MO ($P<0.05$). Both JB and MO landed closer to the target on average in the exogenous tasks than in the control tasks. This could be an effect of practise, as both subjects completed the control tasks before the exogenous tasks. It is also important to note that there was no statistical difference in FEP1 for JB or MO between the exogenous *ipsiL-contraL* and *ipsiL-ipsiL* conditions (JB [$F(1,223)=0.34$, $P=0.56$], MO [$F(1,86)=0.32$, $P=0.57$]).

In summary for both patients, the sum of their saccades, ΣS1, for all trials in which there were one or two saccades, to T1 were more accurate in the exogenous *ipsiL-contraL* condition than in the control condition. By comparison, for the *ipsiL-ipsiL* condition the results were split: DR did as well in the exogenous and control conditions whereas JB did better in the former.

3.5.5 Endogenous series: amplitudes of first (self-generated) saccade

Note that by definition, the FEP1s of the endogenous series cannot be checked for accuracy since ΣS1s are self-generated without an external target. We wanted to ensure, however, that the distributions of FEP1 for the endogenous condition trials were at least as varied along the horizontal meridian as the distribution of FEP1 in the exogenous condition trials, to avoid a motor memory or practice effect that might result if the subjects always looked to the same first location. The subjects were told to vary the amplitude of this ΣS1, and for each subject in each condition, the distribution of FEP1 in the endogenous condition was at least as varied as the distributions of FEP1 in the exogenous conditions (see insets of Fig. 3.8B and Fig. 3.8C respectively).

3.5.6 Exogenous series: saccades to T2 compensate for variability of saccades to T1

Figure 3.6 illustrates the ΣS2 (incorporating up to four saccadic steps) made by each subject in each exogenous condition. Each diamond represents a single trial. Each graph shows the actual overall displacement due to ΣS2 plotted against the expected ΣS2 displacement required to land directly on T2 from FEP1. Coloured diamonds are the data from the patients (blue for DR and red for JB) and a specific subset of these points are shown as darker circles, to be considered below. The grey outline white diamonds are the results of the control subject matched to the specific hemidecorticate subject; SR for DR and MO for JB. The unity lines represent a perfect performance. Recall that the sign of the direction of saccades made by JB and MO have been reversed in these figures for ease and clarity in comparing all subjects.

The control subjects performed well in all tasks, falling on or near the unity line across trial types. This indicates the effective use of a CD by the control subjects and is evident by visual inspection of the grey outlined diamonds of Fig. 3.6. Especially convincing of this fact is the results presented in Fig. 3.6A, those of the exogenous *ipsiL-contraL* condition: the very fact that they made these saccades in the correct direction suggests that they are using extra-retinal information to calculate the S2 vector. If they had access exclusively to retinotopic coordinates, these ΣS2 saccades would be in the ipsilesional direction (i.e.: the diamonds would be grouped in the second quadrant). The regression lines for control subjects in each of the exogenous conditions were highly significant ($P<0.001$ for both SR and MO). For SR, the slope of each line of best fit through the exogenous *ipsiL-contraL* and the exogenous *ipsiL-ipsiL* data were significantly different than the slope of the regression line through her control data (exogenous *ipsiL-contraL*: $t(253)=11.01$, $P<0.001$, exogenous *ipsiL-ipsiL*: $t(230)=8.04$, $P<0.001$). Thus, she was not quite as accurate in foveating the second target in the exogenous double step tasks as she was in foveating a single target in the control tasks. The same can be said for control subject MO (exogenous *ipsiL-contraL*: $t(359)=5.06$, $P<0.001$, exogenous *ipsiL-ipsiL*: $t(348)=-2.64$, $P<0.01$). This decrease in accuracy was slight as can be determined through visual inspection of Fig. 3.6, but was significant nonetheless.

The hemidecorticate subjects' regression lines through the exogenous data in Fig. 3.6 were also all highly significant ($P<0.001$). The slopes of the lines of best fit through the exogenous *ipsiL-contraL* data were significantly different than the slopes through the control data for each subject (DR: $t(412)=2.98$, $P<0.005$ and JB: $t(501)=46.09$, $P<0.001$). Like the control subjects, the hemidecorticate subjects were slightly less accurate in the exogenous *ipsiL-contraL* trials than they were on the control trials. Interestingly, however, both hemidecorticate subjects were as accurate in the exogenous *ipsiL-ipsiL* paradigm as they were in their control paradigms. The slopes through the lines of best fit for these trials compared to the control data were not significantly different (DR: $t(389)=1.74$, $P=0.08$ and JB: $t(445)=-1.48$, $P=0.14$). This phenomenon can be attributed to the much larger confidence intervals around the means in the case of the hemidecorticate subjects' data.

Another interesting finding came to light when comparing the slopes of the lines of best fit between the data of the hemidecorticate subjects and their respective control subjects. While the slopes of the lines of best fit between JB and MO were significantly different in both exogenous *ipsiL-contraL* ($t(302)=-31.38$, $P<0.001$) and exogenous *ipsiL-ipsiL* ($t(235)=-4.57$, $P<0.001$) conditions, the same was not true of DR and SR. The slopes of the lines of best fit were not significantly different in either the *ipsiL-contraL* data ($t(148)=0.25$, $P=0.80$) or the *ipsiL-ipsiL* data ($t(102)=0.20$, $P=0.79$), suggesting that DR was as good at tailoring the amplitude of her second saccade in these paradigms as her control subject.

The dark circles in each of Fig. 3.6A and 3.6B are a subset of the coloured diamonds and represent trials in which the distance between T1 and T2 was 15°; that is, for the *ipsiL-contraL* trials T1=20° with T2=5° and for the *ipsiL-ipsiL* trials T1=10° with T2=25°. Plotting a series of trials of the exact same type (same T1 location and same T2 location) in this fashion allowed us to determine how the oculomotor system dealt with variability in the accuracy of ΣS1 over individual trials of the same type. We wanted to determine whether slight overshoots or slight undershoots would be corrected for within individual trials with the amplitude of ΣS2. This would indicate that our subjects have access to motor efference

information and are not simply performing visual vector manipulations. If vector manipulations were being employed, subjects could determine the amplitude of the saccade to T2 based on the subtraction of two visual vectors to T1 and T2 respectively. We would not see any compensation in the ΣS2 amplitude for minor variations in ΣS1 amplitude. We focussed specifically on this subset of data because we had enough data points for one set of targets to illustrate how the summed amplitude, ΣS2, of the saccades to T2 compensated for the variability in the summed amplitude, ΣS1, of saccades to T1. Panels A and B of Fig. 3.7 show, respectively, the data from DR and JB in the 20°-5° trials of the *ipsiL-contraL* condition and 10°-25° trials of the *ipsiL-ipsiL* condition, plotted as the amplitude of ΣS2 versus the amplitude of ΣS1.

Let us consider first the 20°-5° *ipsiL-contraL* exogenous condition (Fig. 3.7A) in which the inter-target distance was 15°. If ΣS1= 20° in all trials, then perfect compensation would be ΣS2 = -15°. However, in reality ΣS1 varied; the ideal compensation is indicated by the grey line with negative slope. If simple visual vector manipulations were being used by our subjects to calculate ΣS2, all the points in Fig. 3.7A would line up on y=-15°. Note first the broad distribution of ΣS1 amplitudes (or FEP1) and the frequent undershoot of T1 and the overshoot of T2, in both DR and JB. This was considered in previous sections that considered Fig. 3.4-3.6. Importantly, the amplitude of ΣS2 compensated, at least partially, for variability in the amplitude of ΣS1 as indicated by the negative slope of the best-fit regression line ($P<0.05$) for each subject. This means that in the *ipsiL-contraL* condition, smaller ΣS1 amplitudes resulted in smaller ΣS2 amplitudes and larger ΣS1 amplitudes resulted in larger ΣS2 amplitudes (note negative signs on ordinate because *contraL* saccades in both subjects are normalized to leftward).

Similarly, in the 10°-25° exogenous *ipsiL-ipsiL* condition (Fig. 3.7B), smaller ΣS1 amplitudes resulted in larger ΣS2 amplitudes and larger ΣS1 amplitudes resulted in smaller ΣS2 amplitudes (note here the positive signs on ordinate because *ipsiL* saccades in both subjects are normalized to rightward). If simple visual vector manipulations were being used by our subjects to calculate ΣS2, all the points in Fig. 3.7B would line up on y=15°. In

both conditions, errors established in ΣS1 were corrected by the amplitude of ΣS2. This is a highly persuasive argument for the presence and use of a CD signal when calculating ΣS2.

3.5.7 Endogenous series: saccades to T2 compensate for variability of S1

The control subjects, SR and MO, performed well in all endogenous tasks, falling on or near the unity line across trial types. This is evident by visual inspection of Fig. 3.8 and indicates the effective use of a CD by the control subjects. The regression lines for the control subjects in each of the endogenous conditions were highly significant ($P<0.001$). Furthermore, for each control subject, the slope of the line of best fit through all three endogenous conditions' data was significantly different that the slope of the regression line through their respective control data: endogenous *contraL-ipsiL* (SR: $t(330)=2.07$, $P<0.05$, MO: $t(433)=-11.64$, $P<0.001$), endogenous *ipsiL-contraL* (SR: $t(311)=10.46$, $P<0.001$, MO: $t(428)=-1.99$, $P<0.05$), and endogenous *ipsiL-ipsiL* (SR: $t(326)=5.68$, $P<0.001$, MO: $t(428)=-9.14$, $P<0.001$).

Figure 3.8A shows the interesting result that the hemidecorticate subjects performed very well on the endogenous *contraL-ipsiL* task which involved a self-generated saccade sequence, ΣS1, into their *blind* hemifield (no T1 presented), and a ΣS2 in the dark to a T flashed into their seeing field. The actual ΣS2 of the hemidecorticate subjects undershot the expected ΣS2 – i.e., the diagonal unity line (especially in the case of JB) – but was clearly tailored to the appropriate amplitude and direction of ΣS2 based on the amplitude of their first ΣS1. Indeed, the regression lines of both DR and JB were highly significant for this data set ($P<0.001$ for both subjects). The slopes of the lines of best fit through this dataset for both hemidecorticate subjects were also significantly closer to 1 than the slopes of the lines of best fit through their respective control data: endogenous *contraL-ipsiL* (DR: $t(609)=-7.41$, $P<0.001$, JB: $t(473)=-5.44$, $P<0.001$). They were more accurate in the endogenous *contraL-ipsiL* double step task than they were on the control tasks. In fact, as in the exogenous datasets, the slope of the line of best fit through DR's data in Fig. 3.8A was not significantly different than that through SR's data ($t(422)=1.08$, $P=0.28$), suggesting again that DR performed as well on this task as her control subject. By

comparison, the slopes of the lines of best fit through the data of JB and MO were significantly different ($t(348)=-21.82$, $P<0.001$).

Figure 3.8B shows that the patients had considerable difficulty with the endogenous version of the *ipsiL-contraL* task in which they had first to generate a saccade in the dark that voluntarily *overshot* the target (that we call T) that had been flashed into their seeing hemifield (recall that no T1 was shown in the endogenous conditions, Fig. 3.2D). For DR (Fig 3.8B in blue), the closed blue diamonds are tightly grouped around the ordinate below the abscissa, and represent the many trials in which this subject's ΣS1 ended close (about ±5°) to the previously seen T. The closed diamonds in the fourth quadrant were the result of ΣS1 being not large enough to overshoot the remembered location of T (as required by the task), thereby requiring a rightward (positive) ΣS2 to foveate T's location, a response she only made in one trial (single point in first quadrant). While the regression line through her data is highly significant ($P<0.001$) due to a minority of points in the third quadrant (note that these trials represent those in which DR successfully overshot the T location with her first saccade), the slope of this line was significantly different than the slope through her control data ($t(532)=9.21$, $P<0.001$) and was also significantly different than the slope through her control subjects' data for this same paradigm type ($t(326)=-9.53$, $P<0.001$). For JB (Fig. 3.8B in red), the failure to overshoot T occurred in the majority of trials, with no correctly-directed ΣS2. The regression line through his data was not significant ($P=0.38$). Possible reasons for this result are considered in the Discussion section.

Figure 3.8C shows the results of the endogenous *ipsiL-ipsiL* trials in which the subjects had to voluntarily *undershoot* T, flashed in their seeing hemifield, with their ΣS1. The regression lines of both JB and SR were highly significant for this dataset ($P<0.001$). As in the case of both control subjects, the hemidecorticate subjects were slightly less accurate in the endogenous *ipsiL-ipsiL* trials than they were in the control trails (DR: $t(612)=4.05$, $P<0.001$, JB: $t(430)=2.28$, $P<0.05$). The slopes of the lines of best fit through each hemidecorticate subject was also significantly different than the slopes of the lines of best

fit through their respective control subjects' data (DR: $t(421)=-4.32$, $P<0.001$, JB: $t(300)=-16.86$, $P<0.001$).

3.5.8 Overview of compensation by second step: retinotopic versus spatiotopic encoding

Suppl. Table 3.3 compares the linear regression relationships between the gaze shift amplitude that a subject actually generated and two possible encoding schemes: the spatiotopic amplitude in which a subject kept track of her/his ΣS1 displacement and a retinotopic amplitude in which a subject did not take account of her/his ΣS1 and calculated ΣS2 solely from the initial retinal position of T2, during initial fixation before ΣS1 (see Methods, Data Analysis). Suppl. Table 3.3 clearly shows that the gaze shift amplitude was consistently better correlated with spatiotopic than retinotopic amplitude, implying the consistent monitoring of ΣS1.

3.6 Discussion

3.6.1 Evidence for a bilateral corollary discharge signal by the remaining hemisphere

Here, we tested two hemidecorticate subjects DR (right ablation) and JB (left ablation), in a double step saccade task executed in the dark. As is typical in hemianopia, these subjects frequently generated multiple-step saccades to reach a target and the number of saccades in each sequence (Suppl. Table 3.2) was comparable to their performance in our previous experiments (Herter and Guitton, 2004; Herter and Guitton, 2007). In the *exogenous* condition, the first saccade sequence (ΣS1) was always directed ipsilateral to the lesioned hemisphere in response to a flashed, but no longer visible target (T1) in their seeing hemifield. In the *endogenous* condition, ΣS1 was 'internally' or voluntarily generated in either direction; no T1 was presented. The second saccade sequence in the *endogenous* condition (ΣS2) was made to a target (T) flashed in the seeing hemifield before ΣS1, ensuring that only the retinotopic position of T was available to the motor circuits that generated ΣS2. In both the *exogenous* and *endogenous* conditions, for

ΣS2 to be accurate, the subject had not only to compensate for the multiple-step spatial displacement of the eye in ΣS1, but also for the multiple steps of the saccade sequence ΣS2.

Both patients were accurate in all tasks except the endogenous *ipsiL-contraL* series, independent of the direction of ΣS1, thereby showing that a single hemisphere can not only generate saccades in any direction, it can also generate corollary discharges (CD) encoding the vectors of these ΣS1saccades and can combine these CDs with the retinotopic location of T2 to calculate ΣS2. This result stands in sharp contrast with observation in the literature on subjects with isolated unilateral lesions of the fronto-parietal cortical region, or posterior parietal cortex, which show that such patients are highly deficient in monitoring contralesional saccades in a *contraL-ipsiL* task (Duhamel et al., 1992b; Heide et al., 1995). Our patients with much larger lesions were not. Indeed, DR performed as well as her control subject in the endogenous *contraL-ipsiL* task.

It is interesting that both DR and JB had great difficulty with the endogenous *ipsiL-contraL* task in which they had to *overshoot*, with a voluntary saccade made in the dark in the absence of a T1, the position of previously flashed T. This internally generated ΣS1 for both subjects frequently undershot T, despite the instructions to forcibly overshoot this target which, if accomplished, would require contralesionally-directed saccades to reach T. Despite the fact that they clearly understood the task, the subjects repeatedly and independently were unable to overshoot T on the majority of trials in the endogenous *ipsiL-contraL* task. Recall that DR and JB were able to perform the exogenous *ipsiL-contraL* task when T1 was flashed. Therefore, the particular difficulty in eliciting an endogenously-driven S1 that placed the T location into their blind hemifield underlies differences in generating voluntarily-driven versus visually-triggered (or reactive) saccades. This hypothesis is supported by each subject's attitude towards the former trial type. Both DR and JB strongly expressed their dislike for the endogenous *ipsiL-contraL* task and became irate during testing. A probable reason for this result is the adapted behaviour that these hemianopic subjects had developed to always keep relevant targets in their seeing hemifield; i.e., to overshoot targets in their blind field and undershoot targets in their seeing field (Herter and Guitton, 2004; Herter and Guitton, 2007; Troost et al., 1972a;

Troost et al., 1972b). It is not surprising that they had difficulty with a task that required them to override their adapted behaviour to place a target into their blind hemifield.

The behaviour of the hemidecorticate patients was also striking given that they regulated the overall amplitude of their saccade sequences so as to keep the final post-saccade eye position of the previously-flashed target in their seeing hemifield. This meant, for example, that in the exogenous *ipsiL-contraL* task, they undershot with ΣS1 the remembered location of T1 (Fig. 3.5A and 3.5B). In some trials this would bring the remembered location of T2 into their blind field which, with a *contraL* ΣS2, they then overshot so as to bring the virtual T2 into their seeing hemifield.

Recent studies have suggested that lesions of the parietal lobe, in conjunction with diagnoses of visuospatial neglect and/or constructional apraxia, cause a particular remapping impairment when a specific location in space must be remapped into the contralesional field with an ipsilesional eye movement (Russell et al., 2010; Vuilleumier et al., 2007). Note that these studies did not require saccadic remapping to occur; the subjects were not asked to make multiple saccades but were simply required to report if they detected changes in the location of a target after a single saccade – no second saccade was necessary. By comparison, our subjects were able to perform the exogenous *ipsiL-contraL* tasks accurately in those trials where they were able to overcome their adaptive strategies of keeping the target locations in the seeing field (i.e., trials in the exogenous condition where they did not undershoot T2) (Fig. 3.6A). This shows further that they were able to not only remap the location of T2 in the contralesional direction as they generated their first ipsilesionally-directed saccade to T1, but also to use this information to encode and generate an appropriate ΣS2 towards T2.

DR and JB performed well on the endogenous *ipsiL-ipsiL* task. To generate these saccades, both aimed ipsilateral to the lesioned hemisphere, the subjects were presumably using the classical saccade generation and CD monitoring pathways normally available to the intact hemisphere when driving saccades contralateral to itself. Their error, after the multiple saccades to reach T, was not greater than that in their control task suggesting that

they were monitoring their motor output with each saccade and accounting for this in the generation of subsequent saccades.

Additional convincing evidence for the presence and use of a bilateral CD signal by the single hemisphere in hemidecorticate subjects in all tasks is presented in Suppl. Table 3.3. We show for each subject, and for each task, that the ΣS2 amplitude was consistently better correlated with the spatiotopic amplitude rather than with the retinotopic amplitude of T2. In summary, DR and JB compensated for intervening saccadic eye movements rather than basing their responses on the initial retinal position of a target.

3.6.2 Relationship to double step saccade deficits reported in literature

In Heide et al., (1995) patients with lesions of the *right* posterior parietal cortex (14 months post lesion) were impaired in generating the second of two saccades in a double step task in two conditions: one wherein the two saccades spanned the two visual hemifields, and one wherein the task was confined within a single hemifield. The two targets in the first task were flashed successively in the left (T1, contralesional) and right (T2, ipsilesional) hemifields respectively (an across the two visual hemifield task analogous to our endogenous *contraL-ipsiL* condition, Fig. 3.2D and 3.2E). In the second task of Heide et al., (1995) (which we could not use due to the contralesional hemianopia of our patients) the first target was presented more peripherally in the contralesional left hemifield and the second target was presented closer to the fixation point but in the same hemifield, requiring a similar sequence of saccades as in the first experiment, but confined within a hemifield. The parietal patients were impaired in generating the second rightward ipsilesional saccade in both tasks. This study of parietal patients complemented and confirmed the single–patient report (30 years post lesion) by Duhamel et al., (1992) but also extended it by testing right lesioned patients with double-saccades made across visual hemifields.

It is interesting that Heide et al., (1995) revealed a right hemisphere advantage: patients with *left* parietal lesions were *not* impaired in the across hemifield condition for a sequence of contralesional (right) to ipsilesional (left) double step saccades, but *were*

impaired in the within-hemifield condition for the same saccade sequence. It is important to note that such deficits in their parietal patients were not present when saccades were made to visual targets that remained illuminated throughout the task. We found no evidence of hemispheric specialization by comparing our two patients each with either the right (DR) or left (JB) hemisphere missing; both performed our task well. It is important to note, however, that in both of our patients, it was the non-language or non-dominant hemisphere that was removed.

Heide et al., (1995) also studied patients with frontal lesions (3-5 months post lesion) and found that they had impaired temporal control and triggering abilities to both flashed and visible targets: for example, inverting the order of their saccades, or aborting the second saccade when it had to cross the vertical meridian. The only "across the visual field" task we were able to do in our patients was the endogenous *contraL-ipsiL* condition, in which both subjects performed very well (Fig. 3.8A). Our patients did, however, have trouble preventing false starts (Suppl. Table 3.1) which may relate to their missing frontal lobe.

3.6.3 Neurophysiological mechanisms

There may be several explanations for why DR and JB performed better than subjects with isolated unilateral parietal lesions. We will consider first the bilateral motor command and then the corollary discharge.

BILATERAL MOTOR COMMAND: Because our subjects could make accurate bidirectional saccades with only a single hemisphere, it is implied that they have functional bilateral connections from their single remaining hemisphere to bilaterally-conserved subcortical areas that control saccades (considered also in Herter and Guitton, 2004). Innate bilateral connections exist from the superior colliculus to the frontal lobe (Distel and Fries, 1982; Leichnetz et al., 1981; Shook et al., 1990), the nucleus reticularis tegmenti pontis (Huerta et al., 1986; Leichnetz et al., 1981; Stanton et al., 1988) and the paramedian pontine reticular formation (Huerta et al., 1986; Leichnetz et al., 1981; Shook et al., 1990; Stanton et al., 1988). Furthermore, an increased number of crossed connections from cortex to the

superior colliculus have been observed following experimental hemidecortication in cats (Adelson et al., 1995). This may explain why the superior colliculus remains anatomically intact on the decorticate side following experimental hemidecortication in monkeys (Theoret et al., 2001). Bilateral involvement of the superior colliculus is supported further by another observation showing that our hemidecorticate patients could generate short-latency *express* saccades to auditory targets ipsilateral to their intact hemicortex (Reuter-Lorenz et al., 2011). The generation of express saccades requires the superior colliculus (Schiller et al., 1987).

BILATERAL COROLLARY DISCHARGE IN ONE HEMISPHERE: Our patients may have recruited a novel contralateral connection between the ipsilesional SC and the remaining hemisphere, as suggested by a Diffusion Tensor Imaging (DTI) study performed on these subjects (Leh et al., 2006a). This pathway, together with the normal ascending ipsilateral pathway from the contralesional SC are possible ascending routes to the remaining hemisphere for efference copy information for saccades in either direction. Given that patients with parietal lesions still have remaining cortical networks on the lesioned side that likely still take part in contralateral saccade generation, it is possible that the new pathways identified in the hemidecorticate subjects by Leh et al., (2006a) and Adelson et al. (1995) for a bilateral CD signal did not develop in the parietal-lesion patients. This concept of increased recruitment of new pathways based on the extent of the cortical lesion may have important clinical implications, and should be further studied.

3.7 Conclusions

Brain reorganization following hemidecortication occurs optimally when surgery is performed in early life (reviewed in Burke et al., 2012). However, there is evidence that cerebral reorganization can take place even when a hemidecortication is performed beyond infancy, in a 15 year old subject (Chiricozzi et al., 2005). The present study of hemidecorticate subjects who were operated beyond infancy as young adults – and studied here more than 20 years post-surgery – also supports considerable brain plasticity. Indeed, their much larger lesion led to a better performance in the double step saccade task

compared to patients with much smaller discrete parietal lesions that occurred in adulthood (for example, Duhamel et al., 1992; patient 30 years post-operative). It can be argued for our patients that a putative presurgical plasticity repaired their bilateral saccade abilities. However, it remains unexplained why this plasticity did not extend to 'repairing' their dense hemianopia and hemiparesis of their contralesional arm and fingers.

4 The classic double step saccade task is an imperfect tool for evaluating corollary discharge in parietal lesion patients

4.1 Preface

Since our hemidecorticate study revealed their preserved ability to monitor bilateral saccadic eye movements in the dark via corollary discharge (CD), we decided to revisit the literature concerning the failure of patients with parietal lesions to perform the double step saccade task. We hypothesized that the perceived failure of these patients on this task may not be due simply to a lack of CD for contralateral saccades; patients with parietal lesion have a vast array of attentional deficits that are difficult to characterize and even harder to stereotype. We thus had a cohort of patients with parietal lesions perform the classic double step task; when analyzed using classic techniques, we found much the same results as have been published in the literature. When we changed the analysis technique slightly, however, by allowing the patients sufficient time to complete the task, and by carefully evaluating their corrective saccades to each target, we actually find that some of the patients display the ability to monitor bilateral saccades via CD.

4.2 Abstract

This paper questions the current dominant theory about the existence of saccade-related corollary discharge (CD) in patients with parietal lesions. A CD is an efferent copy of the saccade motor command which is distributed to various sensorimotor areas to update perceptual and motor systems about self-generated movements. In the classic double step saccade task, used to investigate saccade-related CD, two targets (T1 and T2) are quickly (80-140ms) flashed sequentially in the periphery. With the extinction of the fixation point and targets, subjects are asked to make two saccades, in the dark, to the remembered locations of the targets in the order they appeared (S1 to T1, S2 to T2). The success of S2 requires the use of CD informing the vector of S1. The current literature

indicates that patients with parietal lobe lesions, tested on the classic double step task, fail to generate S2 more frequently when S1 is directed contralesionally than ipsilesionally. If an S2 is generated, it is less accurate after an S1 generated contralesionally than ipsilesionally. These two findings have led to the conclusion that parietal lesions, particularly on the right, abolish CDs for contralesional saccades. Here, we tested five patients with parietal lesions on the classic double step task; when analyzed using previously-described methods, the data reveals the expected results, described above. However, when analysis methods were altered slightly by providing patients with sufficient time to complete each trial and by evaluating corrective saccades to each target, most of the patients show evidence of CD for contralesional S1s (4/5) and some for ipsilesional S1s (2/5). We hypothesize that well-known attentional and visual processing impairments in patients with parietal lesions confound investigations into CD using the classic double step saccade task and, furthermore, that these deficits explain the continued difficulty of some patients to complete the task. In summary, we propose that the failure of patients with parietal lesions on the classic double step task is not due to a lack of contralesional CD; rather the classic double step task is an inappropriate tool for investigating saccade-related CD in patients with parietal lesions.

4.3 Introduction

Fast eye movements called saccades are generated several times per second to move the high resolution fovea to different locations in a visual scene. 'Corollary discharges' (CD) or 'efference copies' of the motor command for these saccadic eye movements (Sperry, 1950; Von Holst, 1950) are sent to various sensorimotor areas and used, for example to: distinguish between self- and externally-generated visual events on the retina; maintain a stable representation of space across saccades; and update the internal representation of where the fovea is located in space (Guthrie et al., 1983).

The classic double step saccade task is a primary tool for investigating saccade-related CD (Becker and Jurgens, 1979; Goldberg and Bruce, 1990; Hallett and Lightstone, 1976b; Mays and Sparks, 1980a). It involves flashing two targets (T1 and T2) sequentially,

very briefly (80-140ms) in the periphery while the subject fixates a central light spot (FP). With the extinction of the FP and the two targets, the subject is required to make a sequence of two saccades (S1 and S2) in the dark to the remembered locations of the previously-seen targets in the order they were presented. The first saccade in the sequence (S1: FP to T1) is simply a memory-guided saccade. In order to generate S2 accurately, however, the location of T2 relative to the new position of the fovea must be updated after S1. This could theoretically be accomplished by manipulating purely retinotopic vectors (from FP to T1, and FP to T2, respectively). We know, however, that variations in S1 amplitude are integrated into the planning and generation of S2, suggesting that CDs informing the vector of S1 and the retinotopic visual vector of the FP to T2 are used together to calculate the vector of S2 (Quaia et al., 2010).

Two influential studies investigating CD in patients with parietal lesions (Duhamel et al., 1992b; Heide et al., 1995) showed that these patients have significant difficulty completing an ipsilesionally-directed S2 if it follows a contralesionally-directed S1. These authors postulate that the CD of S1, generated by the lesioned hemisphere, is not available to the intact hemisphere to plan S2, thereby implicating the parietal lobe – particularly on the right side – in the processing of contralesional CD. These studies used a classic version of the double step saccade task described above: T1 and T2 were presented very briefly (80-140ms) either within the same hemifield (within-hemifield version) or in different hemifields (across-hemifield version) and the targets were presented within 10° of the FP.

A recent study conducted by our lab investigated the ability of hemispherectomy patients to track bilateral eye movements via CD (Rath-Wilson and Guitton, 2015). We found that these patients, who by definition lack all cortex in one hemisphere including the parietal lobe, are able to monitor bilateral S1s via CD, and generate accurate S2s. This led us to question the conclusions of previous studies investigating CD in patients with parietal lobe lesions: how could hemispherectomy patients have preserved bilateral CD, while patients with unilateral lesions of the parietal lobe lack contralesional CD? Evidence from neurophysiological and lesion experiments in monkey (Colby et al., 2005; Heiser and Colby, 2006), as well as imaging studies in human (Medendorp et al., 2003; Medendorp et al.,

2006) support the hypothesis that CD of bilateral saccades is available to each cortical hemisphere. We hypothesized that patients with parietal lesions may thus retain the ability to monitor bilateral saccades via CD.

We critically evaluated the previously mentioned studies that have used the classic double step task to investigate CD in parietal patients, and found that several methods of analysis employed in each were problematic. First, Duhamel et al. (1992) did not evaluate multiple-step saccades to each target – thereby omitting potential corrective saccades – which underestimates accuracy since patients with parietal lesions tend to generate several saccades to reach a single target location. Heide et al. (1995) did evaluate corrective saccades to each target, but only provided their subjects with 1000ms to complete a trial, which is insufficient: we found here that patients frequently started S2 more than 1000ms after the FP was extinguished.

We also found that each study used a potentially ambiguous method of evaluating saccade CD. Duhamel et al. (1992) considered the mean S2 amplitude in relation to the expected S2 amplitude of T2-T1 in order to determine the presence or absence of CD. Heide et al. (1995) considered the mean absolute error after S2 in relation to T2 in a given trial type. These methods do not show whether S2 compensates for variations in S1 for a given T2 and many oculomotor impairments can influence the accuracy of S2. We believe that a more appropriate method for investigating CD specifically is to evaluate the relationship between the S1 and S2 amplitudes in each trial within a given task type; i.e., if S2 compensates for variations in S1 when both are generated in the dark, the planning areas of S2 must have access to CD about S1.

As we show below, when multiple-step saccades are evaluated and subjects are given enough time to complete a task, there arises evidence that patients with lesions of the parietal lobe have a CD for bilateral saccades. We propose that the difficulties that patients demonstrate in completing the classic double step saccade task are the result of visual-processing and attentional deficits that commonly result from lesions of the parietal lobe that are unrelated to the CD system. This suggests that the classic double step task is an imperfect tool for evaluating saccade CDs.

4.4 Materials and methods

4.4.1 Participants

Five patients with parietal lobe lesions (four left, one right) participated in this study, which was approved by the Montreal Neurological Institute and Hospital Research Ethics Committee. Participants gave informed and voluntary consent before participating, in accordance with the Declaration of Helsinki. A neurologist experienced in neuroimaging (LK Fellows) and blind to task performance, traced individual lesions from the most recent clinical MRI images directly onto the standard Montreal Neurological Institute (MNI) brain, using MRIcro software (www.mricro.com; Rorden and Brett, 2000). This standard method combines registration and segmentation into a single step requiring no additional transformations (Kimberg et al., 2007). We used MRIcro software to generate lesion images. Figure 4.1A shows the reconstructed outline of each lesion in representative axial slices in standard space for all patients tested in this study. In 4/5 cases, the boundaries of the lesions were easily identified. However, PL1 had a very chronic ischemic event in the middle cerebral artery territory, the boundaries of which were more difficult to demarcate. The definite areas of injury are shown in Fig. 4.1A (PL1), mainly affecting white matter underlying the parietal lobe. However, there was evidence of a much more distributed chronic injury in the territory of the posterior branch of the middle cerebral artery as a whole, with parieto-temporal cortical atrophy, atrophy of the posterior insula, widening of the Sylvian fissure, and ex vacuo dilatation of the posterior horn of the left lateral ventricle. The raw MRI of PL1 is available in Suppl. Fig. 4.1.

Figure 4.1B provides further details about each patient. We performed a classic Posner task to evaluate neglect; the mean reaction time for valid trials was subtracted from the mean reaction time for uncued trials separately for ipsilesional (ipsiL) and contralesional (contraL) targets (Posner, 1980). A Posner effect score was then evaluated by subtracting this ipsiL value from the contraL value. The Posner reaction time test has been shown to be the most sensitive test to evaluate neglect at both the acute and chronic stages (Rengachary et al., 2009). The Posner effect revealed neglect in all patients (a score of zero indicates no neglect); the score was highest in PL4 and lowest in PL1.

4.4.2 Stimuli and apparatus

Visual stimuli were generated in MATLAB using the Psychophysics Toolbox. They were back-projected at 85Hz with an Electrohome Marquee 8000 projector (projection resolution: 1024 x 768 pixels) onto a screen located 57cm from the participant. Monocular eye position (patient chose patched eye) was recorded by a video eye-tracker (EyeLink 1000, SR research) at a sampling rate of 1000Hz for all subjects.

The visual stimuli for the tasks consisted of 0.6° circular light spots. The FP, located at the centre of the screen, and the targets were white, isoluminant, and flashed on a black background.

4.4.3 Experimental design

During the experiment, the participant was seated in a dark room with the head restrained by a bite bar. Experiments consisted of blocks of 60 trials. Before each block, the camera was calibrated. Between each trial, the screen was briefly illuminated to prevent dark adaptation. Importantly, subjects were always given 2500ms in the dark to complete the task.

Patients participated in two oculomotor tasks, similar to those in Duhamel et al. (1992): a visually-guided (Fig. 4.2A) and a flashed (Fig. 4.2B) version of the classic double step paradigm, performed in different blocks. In the flashed task, after the fixation point (FP) was extinguished, we flashed two targets (T1 and T2) in sequence (Fig. 4.2A-B). A patient was required to look, in the dark, to the locations T1 and then T2, where the targets had been presented. In the visually-guided version of this task, the targets were kept visible for 500ms each (Fig. 4.2A). Fig. 4.2C shows the expected saccadic eye movement sequences for each trial type in the two tasks. The different combinations of target positions are given in Fig. 4.2D. Note that *ipsiL* and *contraL* refer to saccades in the ipsilesional and contralesional directions.

4.4.4 Data analysis

For each trial, the target location, target onset, target offset, FP onset, FP offset and the horizontal and vertical eye position signals were stored online for further offline analysis. The data were analyzed using the methods described below, similar to those of Rath-Wilson and Guitton (2015), as well using methods outlined in previous studies (Duhamel et al., 1992b; Heide et al., 1995).

4.4.4.1 Accepted use of multiple-saccade sequences

Eye velocity was obtained by digitally differentiating the time trace of the eye position signal. Saccades were deemed acceptable if the amplitude was greater than 1° and a velocity greater than 80°/sec was attained. Saccade onset was determined as the point at which eye velocity exceeded 30°/sec. The first saccades to T1 and T2 in the multiple-step sequences are called S1.1 and S2.1, respectively. The S1.1 start time and S2.1 start time were calculated as the time between the GO signal (FP-off) and the indicated saccade's onset.

In all trial types, the parietal patients tended to generate multiple saccades to reach a single target. Each saccade's onset and offset times and initial and final eye positions were recorded. We defined ΣS1 and ΣS2 to mean the sum, in a single trial, of the vectors of all saccades used to reach T1 and T2, respectively. ΣS1 could include up to three saccades (dubbed S1.1, S1.2, S1.3) and ΣS2 could include up to four saccades (dubbed S2.1-S2.4). For every trial, the eye position at the end of the last saccade in each sequence (ΣS1 and ΣS2) was dubbed FEP1 and FEP2 respectively. To ensure consistency, it was important to determine reliably the end of ΣS1 and the beginning of ΣS2. To do this, we used a combination of direction and intersaccadic time interval to determine which saccades were aimed at which targets, as in Rath-Wilson and Guitton (2015). Suppl. Tables 4.1 and 4.2 give the number of saccades generated by each patient to reach a target location in each trial type. Most patients on most tasks performed an average of between one and two saccades in ΣS1 and ΣS2 to reach T1 and T2, respectively. In the analysis of our data we allowed multistep saccades as did Heide et al. (1995). To analyze our data using the

Duhamel et al. (1992) method, we did not evaluate corrective saccades; only the first two saccades of each trial were retained and called S1 and S2.

4.4.4.2 Accepted trials

All trials were inspected visually by the experimenter, and all trials were included in the main analysis except those deemed unacceptable because 1) there were significant blink artefacts or noise in the eye position signal; 2) the initial eye position deviated more than 2° from the FP; 3) the S1 latencies were less than 100ms or more than 2000ms from the GO signal; 4) the first saccade was in the wrong direction; or 5) there was only a single saccade in the trial. Suppl. Tables 4.3 and 4.4 show the breakdown of the number of trials deemed to be acceptable in each trial type using our new analysis methods.

We have opted to present in the Results section, not here in Methods, a detailed treatment of accepted versus rejected trials. This is because our patients' behaviour in rejected trials is an important result. For example, if a patient makes a first saccade, S1, to T1 without a second saccade to T2, then this trial will be rejected in our analysis of double step behaviour. However this failure to generate S2 does not necessarily mean that the patient lacked a CD, as would have claimed Duhamel et al. (1992) and Heide et al. (1995) in their analyses. Many mechanisms may have resulted in a lack of a second saccade: e.g., attentional deficits. What counts in our analysis is that there were trials in which a patient could make S2 and we could evaluate its accuracy in order to determine whether CD was being used by adjusting S2 to variations in S1.

It is also important to note that we rejected additional trials, within our 'accepted trials' pool, when we performed the Heide et al. (1995) analysis. To emulate their analysis methods, we only looked at the first 1000ms of each trial. If ΣS2's onset was after 1000ms, we rejected this trial in our Heide et al. (1995) method of analyzing our data. This is described in detail in Results and the breakdown of the additional rejected trials (beyond our own rejected trials) can be found in Suppl. Table 4.5.

4.4.4.3 Corollary discharge

Our main results using our new analysis are best depicted by the scatterplots in Fig. 4.4 and in Table 4.1. To determine the performance of subjects across trial types, we performed a series of regression analyses. We evaluated the amplitude of ΣS2 as a function of the amplitude of ΣS1; a significant regression coefficient for the dataset relating to a particular trial type indicated that patients were monitoring the vector of ΣS1 and using this information to plan ΣS2. Since these saccades took place in the dark, once the targets were extinguished, the only way they could access the vector of ΣS1 would be to use a CD. This method allows for different levels of inaccuracy of the first and second saccade and assesses more directly whether the patient is actually monitoring, via CD, the ΣS1 movement. It is also a rigorous and conservative method; by requiring a significant regression coefficient to determine whether a CD is used, we are ensuring that the phenomenon is real and consistent. Note that we only performed regression analyses when there were more than six data values available in a given condition.

It was imperative to assess the patients' other oculomotor abilities as well; the visually-guided version of the task allowed this. Inaccuracies on the visually-guided version of the task suggest that failure on the flashed task is not due solely to CD; the evaluation of their success on the flashed task is analyzed below in relation to their performance on the visually-guided task.

4.5 Results

Here, we studied the ability of patients with parietal lobe lesions to look, in the dark, to the respective locations of two targets previously flashed, briefly and sequentially. This classic 'double step' saccade task requires the use of a corollary discharge (CD) that encodes the first saccade's vector. The main literature on this topic (Duhamel et al., 1992b; Heide et al., 1995) indicates that parietal patients lack a contralesional CD, and when our data were analyzed using these previously-described methods, we corroborated their observations. Indeed, as shown in a subsequent section, our patient population is

comparable to those studied in the past. However, when we modified our analysis methods, by including the contribution of multiple-step saccades and allowing patients sufficient time to complete the task, we found that some of the patients who appeared 'unsuccessful' on the classic double step task using the previously-described methods, appeared 'successful' using our analysis methods and were able to use a CD for saccades in both directions. The following sections consider the same patient population and the same dataset analysed using different methods. First we show the results using our analysis methods. Next, we show that using the analysis methods of the Duhamel and Heide studies, respectively, we obtain results very similar to what they presented.

4.5.1 Results using our modified analysis methods

4.5.1.1 Accepted versus rejected trials

We analyzed our data using methods first employed in Rath-Wilson and Guitton (2015), in which corrective saccades were evaluated and the patients were given 2500ms to complete each trial. Overall, using this method, the patients completed – i.e., made both ΣS1 and ΣS2 (Methods) – a total of 237 trials out of 794; a success rate of only 30% of total trials accepted (Suppl. Tables 4.3 and 4.4). More specifically, we see from these Tables that of the 376 trials in which ΣS1 was directed ipsilesionally, 92 trials were accepted or 24%. Of the 418 trials in which ΣS1 was directed contralesionally, 151 were accepted or 35%. In the Discussion, the reasons for rejecting trials are evaluated and we speculate on why the task was difficult for these patients.

4.5.1.2 Saccade latencies

We restricted the following SRT analyses to trial types in which more than six trials were accepted for a given subject. This permitted some statistical analyses. We show (Fig. 4.3A), for each subject and task, the mean start time of S1.1 (directed towards T1) relative to the GO signal (FP-off). Note that in a given task (e.g., ipsiL-contraL) and for a specific subject, there may have been fewer than six accepted trials (which is why several bars are missing from the bar graph; see Suppl. Tables 4.3 and 4.4). The inter-subject variability

was large; mean S1.1 start time ranged between 300ms and 950ms, depending on the patient and trial type. The mean start time of the first saccade (S2.1) in the multiple-step saccade sequence, Σ2, to T2, relative to the GO signal (FP-off), is given in Fig. 4.3B for each trial type and each patient. The mean S2.1 start time varied between 650ms and 1600ms. This finding is important because in the Heide et al. (1995) study, subjects were only given 1000ms to complete a task, which would have eliminated many trials, as indicated in Fig. 4.3B. By comparison, our patients were given 2500ms to complete each trial.

4.5.1.3 Accuracy in visually-guided double step task

As explained above, we tested each patient on a *visually-guided* version of the classic double step task in which targets were on for 500ms each. This served as a control. Indeed, before evaluating CD for each condition, it was imperative to determine if patients could generate accurate and correct saccade sequences when the targets were visible, thus eliminating some of the possible confounding factors that could explain failure on the classic task besides a lack of CD, for example, not being able to initiate an appropriate ΣS2 from various foveal starting positions (FEP1). Most patients – e.g. PR1 considered below – were able to complete the visually-guided versions of the tasks quite well. Only PL1 and PL3 had significant difficulty and are also considered below.

Figure 4.4 shows the Σ2 amplitude of each trial as a function of its respective ΣS1 amplitude for two example subjects, left-lesion PL1 (Fig. 4A and B) and right lesion PR1 (Fig. 4.4C and D). PL1's performance for the visually-guided contraL-ipsiL and ipsiL-contraL-X trial types was notably impaired (Fig. 4.4A, fourth quadrant open black triangles; and Fig. 4.4B, second quadrant open black circles, respectively). The large black circular dot for each trial type indicates where the data points would cluster for a perfect performance on the task: i.e., the goal. This dot represents the actual target size (0.6° in diameter) using the axes' coordinates. In the contraL-ipsiL trial type for PL1 (Fig. 4.4A, fourth quadrant), the visually-guided contralesional saccades (ΣS1) to T1 were inaccurate; the subject most often undershot T1 situated at +6° (Fig. 4.4A: open black triangles are to the left of the black dot). However, the second saccades (ΣS2) to T2 (also visually-guided) in the

ipsilesional direction were quite accurate, as illustrated by the open triangles lying close to the unity line. In the trials of the ipsiL-contraL-X trial type, the first visually-guided ipsilesionally directed ΣS1 to T1 at -3° was quite accurate; the second, ΣS2, contralesionally-directed visually-guided saccade to T2 at +6° undershot the goal (Fig. 4.4B, second quadrant: open black circles are below the large black circle). This indicates that PL1 had difficulty encoding *contralesional* target locations, even for a visually-guided saccade, since she made severely *hypometric* saccades to targets in that direction.

PL3's performance (not illustrated) for the ipsiL-contraL and contraL-ipsiL-X trials was also impaired, but differently from PL1; the contralesional visually-guided saccades tended to *overshoot* the target locations. By comparison, visually-guided ipsilesional saccades were quite accurate. Finally, as noted above, PR1 did well in the visually-guided saccade task (Fig. 4.4C and D).

4.5.1.4 Corollary discharge in the classic flashed double step task

Recall that our classic double step flashed task was similar to that in Duhamel et al. (1992), and used only a single combination of two target locations for each trial type (Fig. 4.2C and D). To analyse our data (for accepted trials) we plotted, for each trial type, the ΣS2 amplitude in each trial against its respective ΣS1 amplitude (*ΣS2vsΣS1*). The data from the two example subjects, PL1 and PR1, are shown using coloured symbols in Figs. 4.4A-D (Table 4.1 considers all patients). As explained in the Methods section 2.4.3, above, since all saccades took place in the dark when all visual stimuli had been eliminated, any variations in ΣS1 amplitude that were compensated by variations in ΣS2 amplitude could only be explained by the subject's internal monitoring of ΣS1 amplitude via a CD and using this information to generate ΣS2 (Eq. 1: ΣS2=T2-FEP1). This phenomenon would be seen in Fig. 4.4 as coloured points aligning on or near the respective unity line for that trial type, as seen, for example, for PR1 in Fig. 4.4C, second quadrant. An alternative explanation could be that subjects were employing visually-determined vector calculations, using the retinotopic positions of T1 and T2, to determine ΣS2. This strategy would produce

horizontally aligned points as seen arguably for PL1 in Fig. 4.4A, second quadrant, blue diamonds.

To evaluate the relationship between the variations in ΣS1 and ΣS2 amplitudes, we analyzed blocks of data in which six or more trials were available and did a linear regression analysis on these data (*ΣS2vsΣS1* in Table 4.1). The results are described below.

4.5.1.5 Ipsilesional CD

The blue points in Fig. 4.4 show the results of our two example patients, PL1 and PR1, in all accepted flashed trials in which their ΣS1 was directed ipsilesionally. Fig. 4.4A, blue diamonds, second quadrant, shows the results of the ipsiL-contraL flashed task for PL1 which can be compared to the results of the visually-guided experiments shown by the open diamonds. The ΣS2 amplitude in the flashed task did not depend on the ΣS1 amplitude; PL1 tended to generate a fixed contralesional ΣS2 amplitude of ~2°, independent of the amplitude of ΣS1. The clearly non-significant regression equation for this dataset (Table 4.1) indicates that PL1 was *not* using a CD of ipsilesional ΣS1 when generating a contralesional ΣS2 in ipsiL-contraL task.

In the ipsiL-contraL-X flashed task (Fig. 4.4B, second quadrant) PL1 did not complete sufficient trials to evaluate her performance (n=1, Suppl. Table 4.3, main reason for rejecting trials was no movement). Interestingly, as explained above, this subject was hypometric on contralesional saccades in the visually-guided version of this task (open circles in Fig. 4.4B, second quadrant). Thus, failure on the flashed task cannot be attributed unambiguously to a lack of CD; there was clearly an impairment in visually-guided contralesional saccades.

PR1, like PL1, did not show evidence of a CD for ipsilesional ΣS1on the ipsiL-contraL task (Fig. 4.4C, fourth quadrant, blue diamonds, non-significant regression) or on the ipsiL-contraL-X task (Fig. 4.4D, fourth quadrant, blue circles; non-significant regression). These data are summarized in Table 4.1. However, in contrast to PL1 who made *hypometric* contralesional ΣS2 (in say, ipsiL-contraL tasks) PR1 made *hypermetric* ones: the blue

diamonds in Fig. 4.4C and the blue circles in Fig. 4.4D are frequently below the blue unity line. Note again that PR1, contrary to PL1, did well on all visually-guided trial types for these conditions; the black dot indicating perfect performance for PR1 is hidden behind the data points; the star around the dot is intended as a visual aid.

Patient PL2 (not illustrated) showed evidence of using a CD of the ipsilesional ΣS1 in the generation of ΣS2: Table 4.1 shows that on both the ipsiL-contraL and ipsiL-contraL-X task, this patient had a significant regression coefficient (she was also quite accurate on the visually-guided version of both trial types).

Patient PL3 had difficulty with the visually-guided version of the ipsiL-contraL task (hypermetric contralesional saccades, unlike PL1 who was hypometric). However, despite this hypermetria, there was a significant covariation between his ΣS1 and ΣS2 amplitudes on the flashed version of this task. This is strong evidence for CD for ipsilesional saccades, despite impaired (hypermetric) contralesional saccades. PL3 did not complete enough flashed trials on the ipsiL-contraL-X task to adequately evaluate his performance.

Patient, PL4, had only five accepted trials in the ipsiL-contraL task condition (Table 4.1) and so we could not adequately evaluate his performance. For the ipsiL-contraL-X condition, the regression equation for PL4 did not have a significant regression coefficient, thereby suggesting that he was not using a CD of the ipsilesional ΣS1 in the generation of ΣS2. Note that PL4 was quite accurate in the visually-guided version of both the ipsiL-contraL and ipsiL-contraL-X trial types.

In summary, two of our five patients, PL2 and PL3, out of the five provided evidence of using an ipsilesional CD, by virtue of the significant slopes of the regression line through their respective data (Table 4.1). However, one may ask regarding the other, 'unsuccessful', patients whether their failure to provide evidence for an ipsilesional CD on the flashed task could have resulted, not from a failure of CD, but from a different problem related to the encoding of visual targets in the visually-guided version of the task. Our data could not resolve this question. Subject PL1 did not show evidence of an ipsilesional CD of ΣS1 and also did not perform well on the visually-guided version of the task. PL2 used an

ipsilesional CD of ΣS1 to correctly generate a contralesional ΣS2 in the classic double step flashed task and also performed well on the visually-guided version of the task. Subject PL3, despite poor performance on the visually-guided version of the task, did show evidence of an ipsilesional CD of ΣS1 on the flashed task. Subjects PL4 and PR1 did not show evidence of an ipsilesional CD on the flashed version of the tasks, but had a good performance on the visually-guided version of the tasks. We discuss below and in the Discussion why the failure of three of the five patients tested on flashed tasks, with ipsilesional first saccades, cannot be unambiguously attributed to a lack of CD for ipsilesional saccades.

4.5.1.6 Contralesional CD

For the contraL-ipsiL visually-guided task, we considered above that PL1 undershot T1 (Fig. 4.4A, fourth quadrant, black outlined open triangles) with the contralesional ΣS1s but the ipsilesional ΣS2s to the visible T2 were quite accurate. For the flashed contraL-ipsiL task, (Fig. 4.4A, fourth quadrant, orange triangles), PL1's regression equation had a significant slope but it was incorrectly inversely correlated (due to three outlier points) relative to what should be a correct response (Table 4.1); i.e., she failed. In the contraL-ipsiL-X task, we see in Fig. 4.4B (fourth quadrant, orange squares) that PL1 could not tailor the amplitude of ΣS2 to account for variations in the expected ΣS2 amplitude, despite a good performance on the visually-guided version of the task. Indeed, this subject's regression equation had a significant slope in this dataset but it was also incorrectly inversely correlated (Table 4.1) to what should be a correct response in this task. This suggests that PL1 was not using a CD of the contralesional ΣS1 to generate ΣS2; in addition, as we showed above, to the impaired CD for ipsilaesional saccades. Possible reasons for this failure are outlined in the Discussion.

By comparison, PR1 – who recall was successful in all our visually-guided tasks, but not in the flashed double step task when the first saccade was ipsilesionally-directed – was successful in both the contraL-ipsiL and contraL-ipsiL-X flashed tasks. This is shown by the significant co-variation between ΣS1 and ΣS2 in the expected direction (second quadrant,

orange triangles and squares in Fig. 4.4C and 4.4D, respectively). Patients PL2, PL3 and PL4 were also successful in the contraL-ipsiL task, but not PL1, as we saw above. Only PR1 was successful in the contraL-ipsiL-X task (Table 4.1).

In summary (Table 4.1) all subjects except PL1 showed evidence of using a CD of the contralesional ΣS1 to generate an ipsilesional ΣS2 in the classic double step flashed contraL-ipsiL task. This success of three of our four left parietal patients and, in particular, PR1's success in this contraL-ipsiL task, is contrary to the classically accepted impairment of contralesional CD in parietal subjects, particularly with right-side lesions. Interestingly, all patients except PR1 were unsuccessful in the contraL-ipsiL-X task when the ipsilesional ΣS2 had to cross hemifields. Thus, PR1 was our most successful patient in terms of showing a consistent CD for contralesional saccades across both 'contraL' paradigms in Table 4.1.

As we will show in the following two sections, we suggest that the results of our study differ from those in the literature, not because of differences in our patients' lesion size or location (see the extent of PR1's lesion in Fig. 4.1), but instead because of: 1) our acceptance of multiple-step saccades to each target; 2) the amount of time provided to the subjects to complete each trial and; 3) our method of evaluating CD by investigating the correlation between ΣS1 and ΣS2 amplitudes. These points will be further elucidated below and in Discussion where we will argue that PL1's failure on the tasks requiring a first contralesional ΣS1 cannot be unambiguously attributed to a lack of CD.

4.5.2 Results using previously employed analysis methods

We show here that when our data are analyzed using the previously-described methods of Duhamel et al. (1992) and Heide et al. (1995) our results are similar to theirs, thereby showing that our patient population is representative and behaves similarly to that tested by others in the past.

4.5.2.1 Duhamel et al. (1992)

In our experience testing hemispherectomy patients on a double step task, we observed that multiple-step saccades were often generated towards both T1 and T2 (Rath-Wilson and Guitton, 2015). We saw here that this was also true for parietal patients. In the Duhamel et al. (1992) study, however, such multiple-step saccades to individual targets were not evaluated. According to their text, this means that any trial, in which a multiple-step sequence was directed towards T1, would have been categorized as failed. In the following text, we standardized the data such that a positive amplitude indicated the contralesional direction and a negative amplitude indicated the ipsilesional direction, thereby enabling us to compare across left and right lesioned subjects.

Recall that we used a task almost identical to that of Duhamel et al. (1992) and this permitted us to re-analyze our own raw data using their methods. Accordingly, we evaluated only the first two saccades of each trial, that we called S1 and S2, respectively. Then, as described in the Duhamel study, we evaluated the mean S2 amplitude (S2amp) for each trial type (Table 4.2) and compared it with the expected S2amp, defined as T2-T1, identified at the top of the table. As seen in Table 4.2, we calculated these values for each patient individually. Since we had four patients with left lesions, we determined for them a weighted average of the S2amps for each trial type. The circled values in Table 4.2, are the mean S2amp results obtained by Duhamel et al. (1992) on the identified trial types for their patient.

IPSILESIONAL S1: According to this analysis method our left patients generated a mean S2amp that was hypometric on all tasks. For example, in the ipsiL-contraL task their mean S2amp = 2.8° compared to the T2-T1 = 4° objective. This undershoot was especially evident in the across-hemifield ipsiL-contraL-X task, where their T2-T1 = 6°, but mean S2amp = 1.4°.

We next consider our right-lesioned patient, PR1, of importance because the Duhamel et al. (1992) study was of a single right lesioned patient. Referring to Table 4.2, we found for PR1, that mean S2s that followed an ipsilesional S1, were close to the

expected S2 amplitude (=T2-T1). For example, in the ipsiL-contraL task PR1 produced a mean S2amp = 5.2° which was reasonably close to the goal value of 4°, a result surprisingly close to thee 3.5° of Duhamel et al (1992).

CONTRALESIONAL S1: Our left patients generated a mean S2amp that was hypometric on all tasks. For example, in the contraL-ipsiL task, the mean S2amp = -2.1° compared to the T2-T1 = -4° objective. This undershoot was also more pronounced in the across-hemifield contraL-ipsiL-X task, where T2-T1 = -6°, but mean S2amp = -1.9°.

For PR1, the mean S2 amp after a contralesional S1 was severely hypometric. For example, in the contraL-ipsiL task, PR1 produced a mean S2amp = 0.3° which was much smaller than the goal of -4°. This result and the result of our contraL-ipsiL-X task were also close to those of Duhamel et al. (1992). Thus using the Duhamel analysis method, PR1 would have been classified as having an impaired CD for contralesional saccades. However, when our method of analyzing the same data set was used (Table 4.1) we found that PR1 was not impaired.

INTERPRETATION: When PR1's first saccade was directed in the ipsilesional direction, a single saccade was generated in ΣS1 on 74% of accepted trials. In contrast, when the first saccade was directed contralesionally, a single saccade was generated in ΣS1 on only 46% of accepted trials (Suppl. Tables 4.1 and 4.2). This would explain Duhamel et al. (1992) results, wherein only the first two saccades of a trial were accepted: they would have miscategorised more trials as 'failed' in the contraL-ipsiL and contraL-ipsiL-X trial types because more correctives saccades in ΣS1 were generated on these trial types than in the ipsiL-contraL and ipsiL-contraL-X trial types.

The problem of miscategorising saccades was exacerbated by the fact that PR1 also tended to generate more saccades in ΣS2 on contraL-ipsiL and contral-ipsiL-X trials (ΣS2 contained a single saccade on only 25% of trials). By comparison, in ipsiL-contraL and ipsiL-contraL-X trials, ΣS2 contained a single saccade on 43% of accepted trials. Therefore, in Duhamel et al. (1992) the conclusion would have been drawn mistakenly that an ipsilesional S2 is less accurate more frequently after a contralesional S1 than after an

ipsilesional S1 because only the first saccade in a series of saccades generated by the patient was analyzed.

The observations summarized above – essentially based on the fact that patients with parietal lesions generate more multiple-step saccades to contralesional target locations – are what led Duhamel et al. (1992) to the general hypothesis that parietal patients lack a CD for contralesional first saccades. We argue here that this is not strong evidence of a lack of CD for contralesional saccades.

Interestingly, when we performed regression analyses of S2vsS1 (as in Fig. 4.4 and Table 4.1) on the data processed using the Duhamel et al. (1992) approach – i.e., considering only the first two saccades in a trial – we found (not shown) evidence of a CD for *ipsilesional* first saccades in the same two patients (PL2, PL3) who showed evidence of this ability using our own analysis method that accounted for multiple-step saccades (Table 4.1 and Suppl. Table 4.6). This was because these patients generated only a single saccade to T1 and a single saccade to T2 on a sufficient proportion of trials to still observe the relationship between the amplitudes of S1 and S2. The same explanation – sufficient proportion of single saccades generated to T1 and T2 – held for three (PL3, PL4, PR1) of the four patients that originally showed evidence in our own analysis of CD for *contralesional* first saccades (Table 4.1, Suppl. Table 4.6). Therefore we suggest that if Duhamel et al (1992) had performed a regression analysis of their data for their patient they might have found a CD.

4.5.2.2 Heide et al. (1995)

While corrective saccades were evaluated in the Heide et al. (1995) study, their double step paradigm accorded only 1000ms for a patient to complete the task, which our results suggest is inadequate. In our experience with hemispherectomy patients (Rath-Wilson and Guitton, 2015) and the present parietal patients, S2.1 often started after 1000ms following the GO signal (Fig. 4.3B).

Across the five patients tested in this study, when the first saccade was directed in the ipsilesional direction, of all our accepted trials, 46% had a ΣS2 that began after 1000ms (Suppl. Table 4.5). In contrast, when the first saccade was directed in the contralesional direction, ΣS2 began after 1000ms in 66% of our accepted trials. These would result in many rejected trials in the Heide et al. (1995) approach compared to ours, as seen in Suppl. Table 4.5. Put another way, if we only consider our trials in which ΣS2 began before 1000ms, there would have been, had we used the Heide et al. (1995) 1000ms time criterion, a larger percentage of rejected trials when the first saccade sequence, ΣS1, was in the contralesional compared with the ipsilesional direction. The difference in percentage of rejected trials, when a trial is limited to 1000ms, may be due to the higher number of corrective saccades generated when the first saccade was in the contralesional direction, as explained above. Unfortunately, the Heide et al (1995) criteria for 'dysmetric second saccades' are not described, so we were unable to analyze our data using the exact methods that they used to obtain Fig. 3 in their paper. These authors argued that their results support the conclusion that parietal patients lack CD for contralesional saccades. However, when our patients were provided more time, we found here that ΣS2 did compensate for variations in ΣS1, although ΣS2 started later on average when the first saccade sequence, ΣS1, was directed contralesionally.

Heide et al. (1995) measured the final eye position (FEP) of ΣS2, at 1000ms after the GO signal and, by comparing this value to the T2 position, they calculated a position error and used it as an indicator of whether a CD had compensated for ΣS1. We also measured the position error at the 1000ms time point on each trial and, as in the Heide et al. (1995) paper, our left patients, indicated by the solid green bars in Fig. 4.5, performed very similarly to the left patients in the Heide study, indicated by the hashed green bars in Fig. 4.5: for left patients, the error was highest in the across hemifield conditions. (In our Fig. 4.5, the Heide et al. (1995) results are adapted from their Fig. 5). For our right patient, PR1, indicated by the solid purple bars in our Fig. 4.5, this error was high in all conditions, and due to her severely hypermetric contralesional saccades. Our results for PR1 are similar to the right patient population tested in the Heide et al. (1995) study (hashed purple bars, from their Fig. 5) in all tasks except the ipsiL-contraL task. Here, our patient's severe

hypermetria resulted in larger errors than those reported by Heide et al. (1995). Note that a by-patient breakdown of the data presented in Fig. 4.5 is available in Suppl. Table 4.7.

Heide et al. (1992) argued that their results, coupled with their measure of the relative percentage of rejected trials (which we could not determine with our data because they did not adequately describe their methods), suggest that patients with parietal lesions lack CD for contralesional saccades, especially in patients with right parietal lesions. We argued above that measuring position error at the end of ΣS2 is not the optimal method for evaluating a CD because large errors in final eye position can occur for these patients (as seen for PR1). Indeed, these large errors can even be seen in the results of the visually-guided task (as seen for PL1). We suggest rather that a better approach is as in our Fig. 4.4: a comparison of ΣS2 versus ΣS1, but only when patients are given sufficient time to complete the task. Indeed, when we performed our ΣS2vsΣS1 regression analysis on the data processed as described above (only considering the first 1000ms of the trial), we found no evidence of CD for any patients in any trial type, whether the first saccade was directed ipsilesionally or contralesionally (Suppl. Table 4.8). Put another way, had we analyzed our data with the Heide et al (1995) approach we would also have concluded, erroneously, that no unilateral parietal patient had a CD in any direction.

4.6 Discussion

Here we tested five patients with parietal lobe lesions on a classic version of the double step task. When our data were analyzed using previously-employed methods, we found results similar to those presented previously in the literature: the contralesional CD appears to be impaired. When our data were analyzed using methods modified to mitigate some of the patients' other oculomotor impairments – e.g., by evaluating corrective saccades and providing sufficient time to complete each trial – there arose evidence that patients with unilateral lesions of the parietal lobe have intact CD for bilateral saccades.

4.6.1 Continued difficulty completing the classic double step task

The first point we must address is why some patients continue to have difficulty completing the classic double step task, despite our evaluation of corrective saccades and the provision of ample time to complete each trial. If the CD system is intact, as we postulate here, why then did PL1 not show evidence of an ipsilesional and contralesional CD and PL4 and PR1 not show evidence of an ipsilesional CD (Table 4.1)?

Psychophysics studies conducted since the Duhamel and Heide studies were published have shed light on specific aspects of attentional and visual processing deficits common to patients with parietal lesions (Baylis et al., 2002). Two results are of particular interest.

First, a 'prior entry effect' was detected in this population (Baylis et al., 2002; Ro et al., 2001; Rorden et al., 1997). This effect manifests as an inability to distinguish the temporal sequence of stimuli presented in different hemifields: an ipsilesional stimulus is always reported to have been seen first unless a contralesional stimulus precedes it by more than 200ms. Recall that targets T1 and T2 were presented briefly and in quick succession in the classic task. This suggests that patients with parietal lesions could have difficulty completing the across-hemifield version of the classic double step task, particularly when T1 is presented in the contralesional hemifield, a result that was reported by Duhamel et al. (1992) and Heide et al. (1995) and is also presented here.

Second, an 'extinction effect' was also detected in patients with parietal lesions, whereby only one of two stimuli is detected when both are presented in the contralesional hemifield (Baylis et al., 2002; Vuilleumier and Rafal, 2000). This could also explain why, in the within-hemifield tasks of previous double step studies and in this study as well, patients often made only a single saccade in the contralesional direction when the targets were presented on this side (Suppl. Table 4.4).

Thus, these new characterizations of attentional and visual processing deficits in patients with parietal lesions question the validity of the classic double step task in

evaluating their CDs for bilateral saccades. The conclusions of Duhamel et al. (1992) and Heide et al. (1995) are thus based on the results of using a task that is susceptible to visual processing errors other than CD and, furthermore, each study rejected many trials which they needn't have, as discussed above.

A particularly interesting finding in the results of our new analysis of Table 4.1, was the most common reason for rejecting a trial in each trial type. When the first saccade was directed ipsilesionally, our most common reasons for rejecting a trial (Suppl. Table 4.3) was either that the patient did not initiate a movement at all (stayed at the location of the extinct FP, which could indicate any number of attentional or visual processing impairments), or executed the saccades in the wrong order (this occurred more often in the ipsiL-contraL-X task, when the targets were presented in opposite hemifields). This latter finding suggests that our patients were indeed displaying the 'prior entry' phenomenon mentioned above, namely when targets are flashed sequentially in opposite hemifields, neglect patients confuse the temporal order of the stimuli. When the first saccade was directed contralesionally, our most common reasons for rejecting a trial (Supp Table 4.4) was either false starts or the patient did not initiate a movement at all (which could, again, indicate any number of attentional and visual processing deficits). For example, in the contraL-ipsiL trial type, patient PL1 frequently only generated a single saccade in the contralesional direction, suggesting that this patient was displaying the 'extinction' phenomenon described above: when two targets are presented in the contralesional hemifield, neglect patients often detect only a single target. In summary, we suggest that the generally accepted impairment of CD for contralesional saccades is based on behaviour that is affected by attentional and visual processing deficits. Interestingly, when we provided enough time and analyzed multiple step saccades, the ability to generate and use a CD for contralesional saccades was observed in four of our five patients.

4.6.2 On the neurophysiology of corollary discharge

A pathway for CD has been proposed by Sommer and Wurtz (2004). They postulate that a CD for contralateral saccades originates in the superior colliculus (SC), a bilateral structure closely linked to brainstem motor circuits for saccades, and ascends unilaterally

from each SC to the frontal eye fields (FEF) via the thalamus (Sommer and Wurtz, 2004a; Sommer and Wurtz, 2004b). In this model, the CD for a contralateral saccade is constrained to each hemisphere. However, this view seems oversimplified. Humans and monkeys with a unilateral thalamic lesion do have an impaired, but not totally absent, CD for contralateral saccades in a double step saccade paradigm (Gaymard et al., 1994; Sommer and Wurtz, 2004b). Moreover, evidence for CDs encoding both ipsilateral and contralateral saccades in a single parietal lobe have been found using neurophysiological recording and focal lesions in monkeys (Colby et al., 2005; Heiser and Colby, 2006). Bilateral CDs in one hemisphere also have been described in humans using imaging studies (Medendorp et al., 2003; Medendorp et al., 2006). Moreover, patients with diverse unilateral cortical lesions conserve a bilateral CD in the double step saccade task: hemispherectomy patients (Rath-Wilson and Guitton, 2015) and patients with frontal lobe lesions (Gaymard et al., 1999; Heide et al., 1995; Rivaud et al., 1994). Finally, we showed here that patients with either left or right parietal lobe lesions have CDs encoding bilateral saccades, supporting the hypothesis that CD about saccades to the left and right is available in each hemisphere.

4.7 Conclusions

The present study suggests that the corollary discharge system is distributed and redundant and thereby resistant to unilateral lesions of the parietal lobe. We also question the validity of the classic double step saccade task as a reliable tool for evaluating CD, specifically in patients with parietal lesions. While overall performance on the task improved when our new data analysis methods were used, only some patients tested here showed evidence of CD for bilateral saccades. The question remains therefore as to how patients with parietal lesions would fare in completing a task better suited to specifically evaluate the use of ipsilesional and contralesional saccade CDs. We used such a task to study hemidecorticate patients and they did well; we predict parietal patients would too.

4.8 Acknowledgements

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5 Refuting the hypothesis that a human parietal lesion impairs saccade corollary discharge

5.1 Preface

The convincing results of Chapter 4 show that some patients with lesions of the parietal lobe (whether of the left or right hemisphere) do indeed have access to corollary discharge (CD) for bilateral saccades, and can integrate this information into the planning and generation of subsequent eye movements. This third study extends our investigation with two modified double step tasks, inspired by those of the hemidecorticate study, designed to mitigate some of the most common attentional impairments attributed to lesions of the parietal lobe. We hypothesize that the continued difficulties of some patients on some of the trial types in the classic double step task may actually be a manifestation of an attentional, memory or visual processing impairment as opposed to being the result of a lack of CD for contralesional saccades.

The modified double step tasks of this study investigate the ability of patients with parietal lesions to monitor bilateral exogenously-driven (first task: 'exogenous task') and endogenously-driven (second task: 'endogenous task') saccades. Every patient tested who completed sufficient trials shows evidence of CD for bilateral saccades in both tasks.

5.2 Abstract

This paper questions the prominent role that the parietal lobe has long been thought to play in the processing of corollary discharges (CD) for saccadic eye movements. A CD copies the motoneurons' signal and sends it to brain areas involved in monitoring eye trajectories when we scan a visual scene. The classic double step saccade task has been used extensively to study CD mechanisms. In this task, two targets (T1 and T2) are quickly (40-150ms) flashed sequentially in the periphery. After the extinction of the fixation point, subjects are requested to make two saccades (S1 and S2), in the dark, to the remembered

locations of the targets in the order they appeared. The success of S2 requires using a CD encoding the vector of S1. Patients with a parietal lobe lesion, particularly on the right, are reported impaired at generating an accurate S2 when S1 is directed contralesionally but not ipsilesionally, thought due to an impaired contralesional CD. In contrast, we hypothesize that the visual processing and attentional deficits that commonly result from lesions of the parietal lobe contribute to failure on the classic double step task. Here, we tested parietal patients that fail in the classic double step task on two modified versions of the double step task, designed to mitigate deficits other than CD that may have confounded previous investigations. In our 'exogenous' task, T2 was presented prior to T1 and for a longer period of time (T2: 800-1200ms, T1: 350ms), than in the classic task. S1 was to T1 and S2 to T2, all in the dark. All parietal patients who completed sufficient trials (5/5) had a CD for contralesional and ipsilesional S1s. In our 'endogenous' task, a single target was presented peripherally for 800-1200ms. Patients were asked, with the extinction of the target and fixation point, to make an endogenous S1 of self-determined amplitude either to left or right, before making S2 to the remembered location of the previously-flashed target. To be successful, a CD of the endogenous S1 – generated in the dark – must be used in the calculation of S2's motor vector. Every parietal patient (6/6) showed evidence of using CDs for endogenous S1s in both the ipsilesional and contralesional directions. Our results support the hypothesis, based on our previous studies of CD mechanisms in hemidecorticate patients, and electrophysiological studies by others in monkey, that CDs for left and right saccades are available to each cortical hemisphere.

5.3 Introduction

We scan our visual surrounds by frequently (~3/s) displacing the high resolution fovea using fast eye movements called saccades. The motor command for a saccade is copied and distributed to many brain areas via a 'corollary discharge' (CD) or 'efference copy' (Sperry, 1950; von Holst and Mittelstaedt, 1950) that enables, for example, the nervous system to: 1) distinguish between self-generated and externally-generated visual events on the retina; 2) maintain an updated internal representation of the position of the eyes in the orbit; and 3) track salient locations in the visual world when the eyes move.

A tool commonly used to study CD mechanisms is the classic double step paradigm (Becker and Jurgens, 1979; Goldberg and Bruce, 1990; Hallett and Lightstone, 1976a; Mays and Sparks, 1980a). In a typical experiment, a subject fixates a central light spot (FP) while two targets (T1 and T2) are rapidly flashed sequentially in the periphery. The subject is required, upon extinction of FP, T1 and T2, to make a sequence of two saccades (S1 and S2) in the dark to the remembered location of each target, in the order they were presented. To perform this task correctly and make an accurate S2, the location of T2 initially defined relative to FP, must be updated after S1. It is thought that the motor command of S1 – i.e., S1's CD – is used together with the retinotopic visual vector of FP to T2, to calculate S2 (Quaia et al., 2010).

Influential studies of patients with a lesioned parietal lobe (Duhamel et al., 1992b; Heide et al., 1995) showed a significant impairment in completing an ipsilesionally-directed second saccade if it followed a contralesionally-directed first saccade. These authors argued that S1's CD, generated by the lesioned hemisphere – particularly a right-side lesion – is not transmitted to the visuo-motor areas of the intact hemisphere that generate S2. Pisella et al. (2011) studied a patient with combined lesions of the right parietal lobe and corpus callosum and argued for right hemisphere dominance for generating CDs for saccades to both left and right (see also Morris et al., 2007).

Evidence suggests that the reported deficits (Duhamel et al., 1992b; Heide et al., 1995) in the double step task are not strictly due to a CD impairment but rather to visual processing deficits, common after lesions of the parietal lobe (Vallar, 1998). In classic double step saccade studies, the targets are flashed very briefly and in quick succession, less than 100ms apart and in close proximity to each other, within or across hemifields. In similar situations, patients with parietal lesions cannot distinguish the temporal sequence of stimuli presented in different hemifields: an ipsilesional stimulus is reported to have been seen first unless a contralesional stimulus precedes it by more than 200ms (Baylis et al., 2002; Ro et al., 2001; Rorden et al., 1997). Furthermore, parietal patients show an 'extinction' phenomenon in which only one of two stimuli is detected when both are presented in the contralesional hemifield (Baylis et al., 2002; Vuilleumier and Rafal, 2000).

Clearly, these impairments render problematic the determination of the cause of failure on the classic double step task.

In monkey, lesions of the lateral intraparietal area lead to 'disrupted metrics' in saccades to memorized targets (Li et al., 1999). Li and Andersen (2001), realizing that this could explain failure in the classic double step task, modified the task. Targets were now presented in the reverse order: T1 flashed after T2 such that only the memory of T2 was required, the first saccade in the dark being directly visually-triggered by T1 (Li and Andersen, 2001). We hypothesized that this variation on the classic task would be more resistant to the negative effects of visual neglect associated with parietal lobe lesions and we applied this new experimental approach to study CD mechanisms in hemidecorticate patients lacking all cortex on one side (Rath-Wilson and Guitton, 2015). We used an additional 'endogenous' task wherein we flashed a single target and asked the patients to make a first saccade, of self-determined amplitude in the dark, before making a second saccade to the previously-seen single target. We found that hemidecorticate patients monitor – via CD – both ipsilesionally- and contralesionally-directed saccades whether driven by external cues or the self. Here we studied parietal patients using the same tasks, and also found preserved CD for both ipsilesional and contralesional saccades.

5.4 Materials and methods

5.4.1 Participants

Six patients with parietal lobe lesions (four left, two right) participated in our study, approved by the Montreal Neurological Institute and Hospital Research Ethics Committee. Participants gave informed and voluntary consent, in accordance with the Declaration of Helsinki. A neurologist experienced in neuroimaging (LK Fellows) and blind to task performance, traced individual lesions from the most recent clinical MRI images directly onto the standard Montreal Neurological Institute (MNI) brain, using MRIcro software (www.mricro.com; Rorden and Brett, 2000). This standard method combines registration and segmentation into a single step, requiring no additional transformations (Kimberg et al., 2007). We used MRIcro software to generate lesion images. Fig. 5.1A-E shows the

reconstructed outline of each lesion in representative axial slices in standard space for each patient tested in this study. In 5/6 cases, the boundaries of the lesions were easily identified. PL1, however, had a chronic ischemic event in the middle cerebral artery territory, the boundaries of which were more difficult to demarcate. The definite areas of injury are shown in Fig. 5.1, mainly affecting white matter underlying the parietal lobe. However, there was evidence of a much more distributed chronic injury in the territory of the posterior branch of the middle cerebral artery as a whole, with parieto-temporal cortical atrophy, atrophy of the posterior insula, widening of the Sylvian fissure, and ex vacuo dilatation of the posterior horn of the left lateral ventricle (raw MRI available in Suppl. Fig. 4.1).

Figure 1F provides further details about each patient. We performed a classic Posner task (Posner, 1980) to evaluate neglect; the mean saccade reaction time for valid trials was subtracted from that in uncued trials separately for ipsilesional (ipsiL) and contralesional (contraL) targets. A Posner effect score was evaluated by subtracting the ipsiL from the contraL values (Posner, 1980). A positive score indicates contralesional neglect (normal score = 0). The Posner effect was highest in PL4 and lowest in PR2.

5.4.2 Stimuli and apparatus

Visual stimuli (MATLAB, Psychophysics Toolbox) were back-projected (Electrohome Marquee 8000 projector, 85Hz, resolution: 1024 x 768 pixels) onto a screen located 57cm from the participant. Monocular eye position (eye opposite targets was patched) was recorded by a video eye-tracker (EyeLink 1000, SR research) with 1000Hz sampling.

Visual stimuli consisted of 0.6° circular light spots. The FP, at screen-centre, and two different colour targets were isoluminant and flashed on a black background. In the control and endogenous tasks, the FP was red and the single target was green. In the exogenous task, the FP was red and, to help subjects distinguish the order in which targets were to be foveated, T1 green and T2 white.

5.4.3 Experimental design

In all experiments, a participant was seated in a dark room with his/her head restrained by a bite bar. Tasks were the same as in Rath-Wilson and Guitton (2015). Targets were in the horizontal plane. Fig. 5.2A-F summarizes, for all tasks, the timing information and expected saccadic eye movement sequences.

Experiments consisted of blocks of 60 trials. Before each block, the camera was calibrated. Between each trial, the screen was briefly illuminated to prevent dark adaptation. Importantly, subjects were given 2500ms to complete each trial. The different values and combinations of target positions are given in Fig. 5.2H. *IpsiL* and *contraL* refer to saccades in the ipsilesional and contralesional directions, respectively.

In the control saccade task (Fig. 5.2A-B), run as individual blocks, the FP and single target (T) were extinguished before the saccade in the dark to T. In the 'exogenous' double step task (Fig. 5.2C-D), T1 and T2 were 'flashed' before the sequential saccades in the dark first to T1, then T2. In this task, T2 was presented first (800-1200ms) and T1 second (350ms). This arrangement provided two advantages: 1) it maximized the accuracy of S1 because it was aimed at T1 that had just been presented; and 2) T2 was presented for a relatively long time, a feature that countered the effects of neglect. We also ran blocks of 'visually-guided' versions of the exogenous task (not illustrated) in which the target(s) remained illuminated throughout a trial. Two exogenous trial types were interleaved within each block: ipsiL blocks consisted of ipsiL-ipsiL and ipsiL-contraL trials; contraL blocks consisted of contraL-contraL and contraL-ipsiL trials.

In the 'endogenous' double step task (Fig. 5.2E-F), after simultaneous extinction of the FP and single target T, participants were required to generate a first saccade (S1) of self-determined amplitude in the direction indicated by the experimenter, followed by a second saccade (S2) to the location of the previously-seen T. Six block types were run, each with one of the tasks of Fig. 5.2F.

Patients were tested in several different sessions lasting a total of about eight hours, with frequent breaks. One right parietal patient (PR2) could not attend all sessions and completed about half the tasks. Two patients (PL1 and PL3) were unable to see the 20° targets because of their blindspots; for these patients, we presented targets at 15° instead of 20°.

5.4.4 Data analysis

For each trial, the target location, target onset, target offset, FP onset, FP offset and the horizontal and vertical eye position signals were stored online for further offline analysis.

5.4.4.1 Accepted trials

Data from all trials were inspected visually by the experimenter. Trials were rejected because: 1) there were significant blink/noise artefacts; 2) initial eye position deviated more than 2° from FP; 3) S1 latencies were less than 100ms or more than 2000ms from the GO signal; 4) the first saccade was in the wrong direction; or 5) there was only a single saccade in a double step task. Suppl. Tables 5.1-5.5 show the breakdown of the number of trials accepted in each trial type.

5.4.4.2 Accepted use of multiple-saccade sequences

Eye velocity was obtained by digitally differentiating the filtered eye position trace. A saccade was accepted if its amplitude exceeded 1° and peak velocity reached 80°/sec. Saccade onset was when eye velocity first exceeded 30°/sec. Saccade reaction time (SRT) was the time between the GO signal (FP-off) and first saccade onset.

In all trial types, parietal patients frequently generated multiple saccades to reach a single goal. Each saccade's onset and offset times and initial and final eye positions were tabulated. We defined ΣS1 and ΣS2 to be the sum, in a single trial, of the amplitudes of all saccades used to reach T1 and T2, respectively. ΣS1 could include up to three saccades

(S1.1, S1.2, S1.3) and ΣS2 up to four saccades (S2.1-S2.4). For every trial, the eye position at the end of the last saccade in each sequence (ΣS1, ΣS2) was dubbed FEP1 and FEP2 respectively, FEP signifying final eye position. Figure 5.2G shows an example eye position trace of right parietal patient, PR1, performing the endogenous double step contraL-ipsiL-X task. Here, PR1 made two endogenous contralesional saccades (ΣS1) and then two saccades (ΣS2) to the remembered location of T, overshot by about 5°.

To ensure consistency in our analyses, it was important to determine reliably the end of ΣS1 and the beginning of ΣS2. To do this, we followed Rath-Wilson and Guitton (2015) and used a combination of direction and intersaccadic time interval to determine which saccades were aimed at which targets. We found consistently across patients and trial types that the time between the end of ΣS1 (FEP1) and the beginning of the first saccade to S2 (S1 Int. 2, Fig. 5.2G) was longer than the time between the two saccades in ΣS1 (S1 Int. 1, Fig. 5.3B). Accounting for multiple saccades improved patients' accuracy (Results). Suppl. Tables 5.6-5.10 give the number of saccades generated by each subject to reach a target location expressed as a percentage of each trial type: most subjects on most tasks performed between one and two saccades in ΣS1 and ΣS2.

5.4.4.3 Corollary discharge

To determine the performance of subjects across trial types, we performed a series of regression analyses that are further explained in the Results section. Note that we only accepted a regression analysis when there were more than six data values available in a given condition.

5.5 Results

We studied the ability of parietal lesion patients to perform two modified versions of the double step task. Each task required the use of corollary discharges (CD) that encoded the first saccade's vector, whether this first saccade was exogenously-driven by a previously-seen visual target or endogenously-driven (self-determined amplitude). Although the literature indicates that parietal patients have a strongly impaired

contralesional CD, we show here that this view is incorrect: in our modified task, parietal patients could generate and use accurate bilateral CDs. Before considering these main results we explain the properties of rejected trials, a critical step in evaluating CD generation.

5.5.1 Exogenous double step flashed task

5.5.1.1 Accepted versus rejected trials

For the control experiment, out of 794 trials in six patients, we accepted 549 (69%). The most common reason for rejecting a trial was false starts (Suppl. Table 5.1). In the exogenous double step task experiment, out of 2809 trials in six patients across all tasks (Suppl. Table 5.2-5.3), we accepted 1554 (55%). We rejected trials principally because subjects generated either only one saccade or made false starts and, in fewer cases, either generated saccades in the wrong order, never initiated the first saccade, or used more than three saccades to reach T1.

The critical papers of Duhamel et al. (1992) and Heide et al. (1995) established that parietal patients lack a contralesional CD largely on the basis of their failure to generate a second saccade when the first saccade was directed contralesionally. Our data suggest this view is incomplete. Two of our left parietal patients PL2 and PL3, on the contraL-ipsiL trial type, often generated only the first contralesional saccades, ΣS1, with no ΣS2 to T2. Here, we rejected such trials, but both of these patients used a contralesional CD in the remaining accepted trials as shown in a following section.

It is important to note that a lack of ΣS2, after a contralesional ΣS1, does not necessarily prove an impaired CD. We first tested our patients on the same classic double step task used by Duhamel et al. (1992). When analysed using their methods, patients failed at generating S2 more frequently (and, when generated, it was less accurate) after an S1 in the contralesional direction than after an S1 in the ipsilesional direction. When this same data was analyzed using the methods of Heide et al. (1995), we discovered the same

trends. This confirms our population of parietal patients as representative of those used in studies that have proposed the dominant hypothesis that we negate here.

In our exogenous double step task, trials in which the targets were shown on the ipsilesional side were, in all patients, more successful than trials in which the targets were shown on the contralesional side (ipsilesional: 66%, contralesional: 44%). This is likely due to the fact that more contralesional trials were rejected due to false starts, indicating a problem suppressing reflexive saccades in the contralesional direction.

Note that the Posner effect score (Fig. 5.1F) did not correlate with any of the measurable behavioural features of the exogenous double step task: rejected trials; number of saccades used to reach a target; SRT; S1 or S2 accuracy.

One subject (PL3) had consistent difficulty interpreting the colours of the targets. Despite repeated explanations and a seemingly thorough understanding of the task, he would look consistently to the T2 location first and the T1 location second. Thus, when presented with an ipsiL-ipsiL condition (Fig. 5.2D), he made the required movements for an ipsiL-contraL condition and vice versa. He also inverted T1 and T2 for the contraL-contraL and contraL-ipsiL trial types. This behaviour was so consistent that we categorized his trials into the trial types that he was actually performing as opposed to the ones he was asked to perform. Indeed, as these eye movements were performed in the dark, after the targets were extinguished, a CD was still required to be successful in foveating the previously-seen target locations (they were simply executed in the wrong order).

5.5.1.2 Saccade reaction time and intersaccadic time intervals

Recall that multiple saccades were accepted for a given target location on each trial; ΣS1 could include up to three saccades. Fig. 5.3A shows the mean SRT for the *first* saccade (S1.1) in ΣS1 across all trial types for each of the control and exogenous double step experiments. S1.1 SRT had a considerable range, 200-800ms, depending on subject and trial type. Across ipsiL-ipsiL and contraL-contraL trials, the pattern of inter-subject SRT

variability was different, but within a class (e.g., ipsiL-ipsiL, ipsiL-contraL) the pattern was similar.

We used a combination of saccade direction and the time interval between saccades to define the end of ΣS1 and start of ΣS2 (Fig. 5.3B). Figure 5.3B compares, for all trials in which there were two saccades in ΣS1 – there were too few trials with three saccades in ΣS1 – the time intervals between end of S1.1 and start of S1.2 (lightly shaded bars) and the time intervals between the end of S1.2 and start of S2.1 (dark bars). Comparing the height of the dark and shaded bars for each subject showed that the latter interval was consistently significantly longer than the former. This demonstrates that the larger interval, called S1 Int. 2 in Fig. 5.2G, provides a convenient measure of when ΣS1 ends and Σ2 begins. The overall long time between end of ΣS1 and start of ΣS2 emphasizes that it was important to give the patients more than the 1000ms used by Heide et al. (1995) to complete a trial. Our subjects were given 2500ms.

5.5.1.3 Control final eye position accuracy

The insets in Figs. 3C (PL1) and 3D (PR1) show the final eye position (FEP) histograms for *control* trials (Fig. 5.2A) in which each example subject oriented to a 25° target with one, two or three saccades, respectively. The number of saccades that subjects performed in each control trial did not affect their accuracy in orienting to the target location. This is an important validation of our acceptance of multiple saccades to reach a single target location.

The main part of Fig. 5.3C-D shows, for PL1 and PR1, the mean FEP versus T location in the control condition. Error bars are not visible, as standard error of the mean (SEM) was consistently smaller than the marker used to illustrate the mean. Linear regression analysis of the data is given in Suppl. Tables 5.11 and 5.12 (see *Ctl:FEPvsT*) and showed a significant regression coefficient, for all subjects, thereby proving that they could tailor the amplitude of saccades based on remembered target location in both ipsilesional and contralesional directions.

5.5.1.4 Exogenously-driven saccades to T1: FEP1 accuracy

Fig. 5.3E-F shows mean FEP1 (that included up to three saccades) versus T1 location for the exogenous double step task for example subjects PL1 and PR1 in the visually-guided experiments (grey markers) and flashed experiments (coloured markers). SEM bars are too small to be seen. As with the control data, considered in the previous section, the regression equations for each subject were determined for FEP1 in each of the exogenous flashed trial types, ipsiL-ipsiL, contraL-contraL, ipsiL-contraL and contraL-ipsiL (Suppl. Tables 5.11 and 5.12, see *FEP1vsT1,*). For every subject on each task (except PL4 who did not complete enough accepted trials to determine results for the contraL-ipsiL condition) a significant regression coefficient was found, proving that each subject was able to tailor the amplitude of FEP1 based on T1 for both ipsilesional and contralesional direction in the exogenous flashed double step task.

5.5.1.5 Corollary discharge evaluation for exogenously-driven saccades

To analyze the data for accepted trials we plotted, separately for each trial type (Fig. 5.2D), the actual ΣS2 amplitude versus the expected ΣS2 amplitude (=T2–FEP1) that was required to successfully foveate the T2 location for each trial. The data of example patients PL1 and PR1 are presented in Figs. 5.4A and 5.4B respectively. One can appreciate visually that the actual ΣS2 varies convincingly with the expected ΣS2. To confirm this, we performed linear regression analysis on these data (*ΣS2vs(T2-FEP1)* in Suppl. Tables 5.11 and 5.12). A significant slope in the expected direction indicated that the participant was performing ΣS2 in the correct direction and of appropriate amplitude. We found, for each subject and for each trial type – except for PL2 in the contraL-contraL condition – that regression coefficients were significant and in the expected direction. (Note also that PL4 did not complete enough trials in the contraL-ipsiL condition to adequately evaluate performance; see Suppl. Table 5.12). These data show, across all patients and trial types, that in the 20 of 21 cases that we could test, both the left and right parietal patients made ΣS2s of appropriate amplitude and in the correct direction that compensated for variations in ΣS1 across tasks.

Though compelling, the preceding results do not specify unambiguously whether subjects were actually using a motor CD about the vector of ΣS1 or whether they were making visual vector manipulations to calculate ΣS2 using the retinotopic vectors from fovea to T1 and T2 respectively, as in: ΣS2=T2-T1. To resolve this issue, we performed an additional analysis (as in Rath-Wilson and Guitton, 2015): for each subject and for each trial type, we analyzed, independently, saccades to two target combinations (Fig. 5.2H) for which we had the greatest number of accepted trials and inter-target distance greater than 5°. We plotted for each trial the ΣS2 amplitude against its respective ΣS1 amplitude and performed a linear regression analysis to evaluate the relationship between variations in ΣS2 and those in ΣS1 (Fig. 5.5A-D, Table 5.1). A linear relationship between the amplitudes of ΣS2 and ΣS1 for a given target combination can only be explained by a subject using CD information about motor performance in ΣS1 for use in generating ΣS2. (If calculations had been done in visual space there would be no compensation for variations in ΣS1.)

IPSILESIONAL FIRST SACCADES: Fig. 5.5A, third quadrant, shows the results of two ipsiL-ipsiL tasks for PL1 (light and dark blue data points for sets of target positions indicated in the figure's key). For each data set, ΣS2 amplitude varied inversely with ΣS1 amplitude to give the following regression equations: for *ΣS2vsΣS1(ex1)*, y=-0.6x-11.1; and for *ΣS2vsΣS1(ex2)*, y=-0.6x-12.6 (Table 5.1). Thus, despite small variation in the distributions of ΣS1 in the ipsiL-ipsiL conditions (due to the patient's fairly accurate FEP1) and the data points lying well off the single blue dashed line (which indicates perfect performance) PL1's regression coefficients were significant (Table 5.1) indicating compensation for variations in ΣS1. In the two ipsiL-contraL conditions for PL1 (Fig. 5.5C, fourth quadrant) the regression equations were significant: for *ΣS2vsΣS1(ex1),* y=-0.9x-6.5, and for *ΣS2vsΣS1(ex2)*, y=-0.8x-4.2 (Table 5.1). These data indicate that PL1 was using a CD of ipsilesional ΣS1 in generating contralesional ΣS2.

The data for PR1 (Fig. 5.5B and 5.5D) was not as consistent as for PL1. Indeed, in PR1 the regression coefficients were not significant in the ipsiL-ipsiL trial types (Fig. 5.5B, first quadrant): i.e., PR1 did not compensate for the small variations in ΣS1. We cannot know whether these results indicate: 1) a lack of CD; 2) whether the CD signal was not

precise enough to distinguish small variations in FEP1; or 3) whether the 'noise' in the generation of ΣS2 masked the use of CD. Despite the uncertainty about PR1's use of an ipsilesional CD in ipsiL-ipsiL trials, this patient clearly used an ipsilesional CD in both examples of the ipsiL-contraL trial type (Fig. 5.5D, fourth quadrant, blue points), as evidenced by significant regression coefficients (Table 5.1): for *ΣS2vsΣS1(ex1),* y=-0.8x+1.0 (intercept not significant), and for *ΣS2vsΣS1(ex2)*, y=-1.0x+2.8 (intercept not significant).

In summary, every patient who completed the exogenous double step task (PL1, PL2, PL3, PL4 and PR1) showed evidence of a CD for ipsilesional ΣS1 in at least one trial type (Table 5.1).

CONTRALESIONAL FIRST SACCADES: Fig. 5.5A, first quadrant, shows the results of the contraL-contraL tasks for PL1 (light and dark orange data points and single dashed unity line). The regression coefficients (Table 5.1) were significant for each data set: *ΣS2vsΣS1(ex1)*, y=-1.5x+21.0 and for *ΣS2vsΣS1(ex2),* y=-0.9x+18.2. For the two contraL-ipsiL conditions (Fig. 5.5C, fourth quadrant) we also found significant regression coefficients: for *ΣS2vsΣS1(ex1)*, y=-0.8x-4.2 and for *ΣS2vsΣS1(ex2),* y=-1.2x+9.6.

The performance of PR1 was not as consistent as PL1: of the two contraL-contraL example combinations, the regression coefficient for PR1 was significant in only one (Fig. 5.5B, third quadrant, *ΣS2vsΣS1(ex2)*: y=-1.5x-22.9). PR1 did, however, succeed in using a contralesional CD in both examples of the contraL-ipsiL trial type (Fig. 5.5D), second quadrant (*ΣS2vsΣS1(ex1),* y=-1.1x-6.0 and *ΣS2vsΣS1(ex2),* y=-0.8x+2.0; neither intercepts were significant). Indeed, as seen in Table 5.1, each subject, except for PR2, showed evidence of using a contralesional CD in the contraL-contraL trial type, with a significant regression coefficient for at least one example data set. Importantly, every subject showed evidence of contralesional CD in both examples of the contraL-ipsiL trial types (Table 5.1, last column) except PL4, who did not complete enough trials in the contraL task.

In summary, in our exogenous double step task, all subjects who completed sufficient trials showed evidence that CD of the contralesional ΣS1 was used in the generation of ΣS2. Indeed, even PL2 and PL3 – whose pattern of rejected trials could have

been interpreted as due to a lack of CD for contralesional saccades because they frequently did not generate ΣS2 after a contralesional ΣS1 – had significant regression coefficients for all accepted trials of the contraL-ipsiL trial type, and most of the contraL-contraL trial types. Our results differ significantly from those in the literature. Importantly, this was not due to a difference in the size or location of our patients' lesions. Rather, our tests of these patients in the classic double step task, revealed that the above results differed because of: 1) paradigm differences; 2) our acceptance of corrective saccades to reach each target; and 3) the amount of time allowed to complete each trial (see Discussion).

5.5.2 Endogenous double step task

5.5.2.1 Accepted versus rejected trials

Out of a total of 5348 endogenous double step trials in six patients, we accepted 2904 (54%) trials. Most rejected trials had false-starts (Suppl. Tables 5.4 and 5.5) in which the patient, before FP was extinguished, made a saccade to the target location, or initiated an endogenously-driven saccade. We accepted 60% (43%) of trials when the first saccade was to be directed ipsilesionally (contralesionally) (Suppl. Tables 5.4 and 5.5). This difference suggests a deficit in suppressing contralesional saccades.

5.5.2.2 S1 start and intersaccadic time intervals

In the endogenous double step task, patients often made more than one saccade, both for ΣS1 (endogenously-driven) and ΣS2 (towards the previously-seen target). When the first endogenous saccades were directed ipsilesionally, there were fewer multiple-step saccades generated (mean=1.4) than when they were directed contralesionally (mean=1.6, Suppl. Tables 5.9, 5.10). This is important, because in studies in which corrective saccades were not evaluated (Duhamel et al., 1992b), such multiple-step saccades would be falsely categorized as erroneous second saccades; this would happen more often when the first saccade was directed in the contralesional direction, falsely suggesting a lack of CD for contralesional saccades.

Mean S1.1 start time, relative to FP offset, for all endogenous double step trials ranged between 250ms and 450ms depending on subject and trial type. For all trials in which only a single-step endogenous ΣS1 was generated, the mean intersaccadic time interval between the end of ΣS1 and beginning of ΣS2 varied between 200ms and 950ms; subjects were given 2500ms to complete a trial.

5.5.2.3 Endogenously-driven FEP1 range

We did not want subjects to always generate their endogenous saccades to the same spatial location after FP offset because this could create motor memory or practice effects. Therefore, we encouraged our subjects to generate endogenous saccades of various amplitudes. The colour-coded insets in Fig. 5.6A-F, show the FEP1 for each of the accepted trials of each trial type for subjects PL1 (Fig. 5.6A-C) and PR1 (Fig. 5.6D-F). PL1, PR1 and all other subjects varied their FEP1 within each trial type within a range of at least 10°.

5.5.2.4 Corollary discharge evaluation

For the endogenous double step task, we plotted the actual ΣS2 amplitude in each trial against the expected ΣS2 amplitude (=T–FEP1) that was required to successfully foveate T's location. The data of example patients PL1 and PR1 are presented in Figs. 6A-C and 6D-F, respectively. All saccades took place in the dark when all visual stimuli had been eliminated, and the first saccade was self-determined (endogenously-driven), without any external cue as to FEP1 (ΣS1's endpoint). Therefore, any variations in ΣS2 amplitude that correlated with T-FEP1 could only be explained by the subject's ability to monitor ΣS1 amplitude internally via CDs and use this information (along with the visual vector between the original FP and T) to generate ΣS2. A significant slope in the expected direction indicated that the subject was performing ΣS2 in the correct direction and of appropriate amplitude, indicating an effective use of CD. Both example patients did very well at reaching the location of T with ΣS2: their regression equations (Fig. 5.6, Table 5.2) were significant whether ΣS1 was directed ipsilesionally or contralesionally, irrespective of the subsequent direction of ΣS2.

Overall, when the first endogenous saccade, ΣS1, was directed ipsilesionally, every patient showed evidence of compensating for the first saccade, as determined by a significant regression coefficient in at least two of the ipsiL-ipsiL, ipsiL-contraL and ipsiL-contraL–X trial types (Table 5.2). This provides convincing evidence of a CD signal for ipsilesional saccades, because the only information available to the oculomotor system about ΣS1 is the motor command itself. Similarly, and even more surprisingly, for every trial type involving a first contralesional endogenous ΣS1, every parietal patient had a significant regression coefficient, indicating a CD for ΣS1 under all experimental conditions (Fig. 5.6, Table 5.2).

5.6 Discussion

Here we tested six patients with lesions – some extensive – of the parietal lobe (Fig. 5.1) on two versions of the double step task. Our 'exogenous' task involved presenting the targets for a long time (T1: 350ms and T2: 800-1200ms), and presenting T2 prior to T1. In our 'endogenous' task (Rath-Wilson and Guitton, 2015), subjects were shown one target (800-1200ms) and asked to first make a self-generated saccade, in the dark, in a given direction, contralesionally or ipsilesionally depending on the block of trials, before making a second saccade to the remembered location of the previously-seen target. We found, surprisingly, that all patients generated and used corollary discharge (CD) for exogenously- or endogenously-driven saccades directed either contralesionally or ipsilesionally.

5.6.1 Previous double step studies implicating the parietal lobe

The classic double step task has been the primary tool for investigating the CD of saccadic eye movements. In this task, patients with parietal lobe lesions, like those who participated in the present study, have been described as strongly impaired at generating an accurate ipsilesional saccade if it follows a contralesional saccade (Duhamel et al., 1992b; Heide et al., 1995). However, in our study of hemidecorticate patients, we found that the paradigms and analyses used in previous studies are sub-optimal for evaluating patients' performance (Rath-Wilson and Guitton, 2015). In tasks used previously, targets are presented very briefly and in close proximity to each other. Patients with parietal

lesions have trouble distinguishing the temporal presentation of targets in opposite hemifields unless they are separated by more than 200ms (Baylis et al., 2002; Ro et al., 2001; Rorden et al., 1997). In the paradigms of Duhamel et al. (1992) and Heide et al. (1995), T1 and T2 were presented for only 80-140ms and there was no time between the target presentations. Furthermore, when two targets are presented together in the contralesional hemifield, only one may be detected by parietal patients (Baylis et al., 2002; Vuilleumier and Rafal, 2000). This poses a clear problem for interpreting the results of the classic double step tasks. Indeed, failure of the patients to complete the double step task cannot unambiguously be ascribed to a lack of contralesional CD. Additionally, Heide et al. (1995) provided subjects with only 1000ms to complete a trial which, based on our experience, is too brief (Fig. 5.3A-B). Moreover, Duhamel et al. (1992) did not evaluate multiple step saccades, which would lead to a bias in rejecting trials with contralesional first saccades, since these are more likely to involve multiple steps. In a separate study – summarized in Results – we tested our patients on the classic double step task used in the Duhamel and Heide studies and found our patients severely impaired.

Pisella et al. (2011) investigated a patient with both a callosal and a right parietal lesion in the classic double step task and argued for a right-hemisphere dominance for CD generation in humans. Moreover, a lack of CD has been implicated as a possible cause of the common attentional deficit 'hemi-neglect', often suffered by patients with parietal lesions (Pisella and Mattingley, 2004). The present study, together with Rath-Wilson and Guitton (2015), does not support these conclusions: both hemidecorticate and the present parietal patients (five of whom showed evidence of hemi-neglect through their Posner scores (Fig. 5.1F) generated and used a CD for saccades in both directions.

5.6.2 Previous spatiotopic updating studies implicating the parietal lobe

Other studies investigating the right parietal lobe in CD generation, but not with the double step task, do not suggest a specific impairment in monitoring contralesional saccades. One study reported that transcranial magnetic stimulation over the right parietal lobe of normal subjects disrupts trans-saccadic memory for multiple objects for both right and left saccades (Prime et al., 2008). By contrast, another study found that remembering a

target location in space is more impaired in patients with lesions of the right parietal lobe after a saccade directed ipsilesionally, not contralesionally (Russell et al., 2010; Vuilleumier et al., 2007). Studies of inhibition-of-return (IOR), found that patients with long-term lesions of the right parietal lobe (Sapir et al., 2004) and normal control subjects who underwent TMS of the right parietal lobe (van Koningsbruggen et al., 2010) do not remap IOR after a saccade in either direction. These studies indicate that there are perceptual impairments after lesions of the right parietal lobe, but they are unable to specify whether they are due to a lack of CD for contralesional or ipsilesional saccades, or even whether there is any impairment in the CD system at all.

5.6.3 On the neurophysiology of corollary discharge

The present study argues for a preserved CD for bilateral exogenously- and endogenously-driven saccades in patients with a parietal lobe lesion, even knowing they do poorly on the classic double step task. We have previously shown a conserved CD for endogenous saccades in hemidecorticate patients missing an entire cortical hemisphere (Rath-Wilson and Guitton, 2015). Our latter finding argues that mechanisms for endogenously driving bilateral saccades and encoding their CDs are present even in a single hemisphere, thereby rendering the quest to precisely localize the site of CD generation quite daunting since it could be a labile circuit distributed bilaterally according to the available territory and time following a lesion (Heiser and Colby, 2006).

Are CDs for endogenous and exogenous saccades co-localized to a single region and mechanism? Pathways for an ascending CD signal have been proposed to originate in the superior colliculus (SC) (Sommer and Wurtz, 2004a; Sommer and Wurtz, 2004b), a structure closely linked to brainstem motor circuits for saccades and therefore quite agnostic as to the encoding of exogenously- versus endogenously-driven saccades (Kopecz, 1995; Trappenberg et al., 2001). CD information is sent unilaterally from each SC up through the thalamus to the frontal eye fields of the same hemisphere, each side carrying information about contralateral saccades. However, this view of a single ascending CD signal seems oversimplified: monkeys and humans with isolated unilateral lesions in the thalamus have impaired – but not absent – CD for contralateral saccades in a double step

paradigm (Gaymard et al., 1994; Sommer and Wurtz, 2004b). Furthermore, evidence for the wide distribution of CD for bilateral eye movements to each cortical hemisphere is substantial in monkey (Colby et al., 2005; Heiser and Colby, 2006) and human (Medendorp et al., 2003; Medendorp et al., 2006). Importantly, a variety of patients with different unilateral lesion sites, such as hemispherectomy (Rath-Wilson and Guitton, 2015), frontal lobe (Gaymard et al., 1999; Heide et al., 1995; Rivaud et al., 1994), and here parietal lobe, have access to CD for bilateral saccadic eye movements. Our results support the hypothesis that CD for saccades in both directions is available to each hemisphere.

5.7 Acknowledgements

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6 Conclusions

6.1 Summary of findings

This thesis is a compilation of three studies I conducted to investigate the mechanisms of saccade corollary discharge (CD) in neurological patients. As presented in the introduction, previous studies have suggested that lesions of the parietal lobe interrupt CDs for saccades aimed in the contralesional direction; this thesis, as a whole, refutes this hypothesis. I argue here for the existence of a distributed and redundant saccadic eye movement CD system, in which the CD of saccades aimed to the right and to the left are available to each hemisphere of cortex. The results of Chapter 3 show that hemispherectomy patients, who have had an entire hemisphere of cortex removed (including the parietal lobe), use the CD of saccades aimed in either direction to assure the generation of accurate subsequent saccades. Chapter 4 discusses the limitations of the classic double step saccade task for evaluating CD in patients with a parietal lobe lesion, and provides evidence that CDs for contralesional and ipsilesional saccades may be used by this patient population in the generation of subsequent saccades. Chapter 5 shows that patients with a parietal lesion do indeed encode CDs for saccades aimed to the right and left, and use them in the planning and generation of future saccades. This ability is evident when they are tested using an appropriate task. The following is a comprehensive summary of the various findings from the preceding chapters.

6.1.1. Chapter 3

Oculomotor control after hemidecortication: a single hemisphere encodes corollary discharges for bilateral saccades

- In order to investigate CD for ipsilesional and contralesional saccades in hemispherectomy patients, we developed two novel versions of the double step task.
    - The exogenous task was developed to investigate the CD of exogenously-driven saccades in hemispherectomy patients. Unfortunately, since hemispherectomy patients are, by definition, hemianopic, they are unable to see any targets placed

in their contralesional hemifield. Thus, we were only able to test saccades that were exogenously-driven into the ipsilesional hemifield. We developed this exogenous task with the aim of investigating CDs specifically with a modification of several features of the classic double step task: 1) targets were presented at more eccentric locations; 2) 2500ms was provided to complete the task; 3) the targets were on for a longer period of time; 4) the targets were presented in the reverse order (i.e. T2 was presented before T1) and; 5) the targets were different colours.

1) Hemispherectomy patients have developed several behavioural adaptations to cope with their hemianopia – notably, they tend to overshoot saccade targets in their blind hemifield and undershoot saccade targets in their seeing hemifield. This ensures that the targets remain in the seeing hemifield of the patient. For this reason, we placed targets at more eccentric locations than are usually used in the classic double step task. This way, we were able to determine more effectively which targets they were aiming for at which times.
2) Hemispherectomy patients also show task-dependent reaction times; we thus provided 2500ms to complete each trial, to ensure that patients would have enough time to attempt the task.
3) We flashed the targets for a longer period of time (T1: 350ms and T2: 1200ms) than what is usually used in the classic task (T1 and T2 between 80-140ms). This was to allow the patients ample time to encode the target locations.
4) We presented the targets in the opposite order than what is usually used: we flashed T2 before T1. Subjects were instructed to look first to the location of T1 (the most recently seen target) before making a saccade to the remembered location of T2. We did this to elicit higher accuracy in the saccades to T1, as has been done in other studies (Li and Andersen, 2001).
5) The targets were isoluminant, but different colours, to help the subject keep track of which target location was to be foveated first.

- The endogenous task was developed for three main purposes: 1) so that we could evaluate CD for ipsiversive saccades in hemispherectomy patients; 2) to determine if the act of retaining two target locations in memory in the exogenous task may be impeding the evaluation of CD and; 3) to determine whether the patients would be able to use the CD for saccades in either direction, in the absence of the possibility of using visual vector manipulations (since there is no T1 in this task).

    1) Since hemispherectomy patients are contralesionally hemianopic, we were unable to elicit target-driven (or exogenous) saccades directed contralesionally. We considered many possibilities for how to investigate saccade-related CD for contralesional saccades; we initially considered using auditory targets to direct the eyes to a specific location in the hemianopic visual field. We decided not to go with this option, however, to avoid complexities that may have arisen from the possible confounding factors of using multisensory stimuli. We decided instead to ask the patients to make a first saccade of self-determined amplitude in a specific direction before making a saccade to the remembered location of the previously seen target.
    2) As described above, other oculomotor deficits may cause artefacts in the investigation of CD, obscuring the absence or presence of CD by affecting behaviour. The endogenous task allowed us to investigate CD when only a single target location was required to be retained in memory, easing the burden on this system.
    3) While the patients' behaviour on the exogenous version of the double step saccade task suggests that they were using CD about the vector of the first saccade in the generation of the second saccade, the endogenous task allowed us to evaluate CD without the possible use of visual vector manipulation. Since there is no visual input about a T1 location, the subjects were required to use CD about the first saccade in order to be successful on the second saccade.

- Together, these two tasks allow a rigorous assessment of CD in hemispherectomy patients; they could also be used in the evaluation of CD for hemianopic patients in general. To our knowledge, this is the first time that a comprehensive test battery has been developed for the evaluation of CD in hemianopic patients.
- The results obtained using our novel tasks show that hemispherectomy patients have CDs for ipsilesional and contralesional saccades, whether endogenously- or exogenously- driven. Furthermore, they are able to use this CD information in the planning and generation of subsequent saccades. To our knowledge, this is the first time that this ability has been demonstrated in hemispherectomy patients.
- This study also evaluated the performance of two control subjects performing the exogenous and endogenous double step saccade tasks. These subjects also demonstrated the use of CD for saccades to the left and right, whether exogenously- or endogenously-driven. To our knowledge, this is the first time control human subjects have been shown to have CD about saccades that were endogenously-driven in the dark, and to use this CD to generate accurate subsequent saccades to previously-flashed target locations.
- Interestingly, we discovered a new behavioural adaptation in hemispherectomy patients: they have trouble generating a saccade that places a relevant target location in their blind field. This was a somewhat incidental finding, as we did not expect to see this behaviour. It was present in both patients (Fig. 3.6B and 3.8B), however, and is likely explained by their general reluctance to place relevant regions of the visual scene into their blind field. This behaviour was notably more obvious in the endogenous ipsiL-contraL task (Fig. 3.8B) than in the exogenous ipsiL-contraL task (Fig. 3.6B).

6.1.2 Chapter 4

The classic double step saccade task is an imperfect tool for evaluating corollary discharge in parietal lesion patients

- In this study, we show that some patients with a lesion of either the left or the right parietal lobe use CD about ipsilesional and contralesional saccades when performing a classic double step task. To our knowledge, we are the first to claim that patients with such lesions use CD when completing this task.

- We then show why individual previous studies developed the differing conclusion that a parietal lesion abolishes CD for contralesional saccades. Specific analysis methods used in each study were inappropriate for the investigation of saccade CD and led to results that falsely suggested a lack of contralesional CD.
- We also suggest that the classic double step task is an imperfect tool for evaluating CD. Lesions of the parietal lobe commonly result in a host of visual processing and attentional deficits that confound performance on the classic double step task, leading to difficulties distinguishing the cause of failure on the task.

6.1.3 Chapter 5

Refuting the hypothesis that human parietal lesion impairs saccade corollary discharge

- In order to better investigate CD for bilateral saccades in parietal lesion patients, we tested the same cohort of parietal patients used in Chapter 4 on an adapted version of the endogenous and exogenous double step tasks used in Chapter 3. We show that patients with a parietal lesion (some of the left hemisphere and some of the right) use CD about bilateral saccades to complete our modified versions of the double step task. To our knowledge, this is the first time that patients with a parietal lesion have been shown, unambiguously, to have CD about ipsilesional and contralesional saccades, whether endogenously- or exogenously-driven. Furthermore, they are shown to use this CD information in the planning and generation of subsequent saccades.
- The results of this study thus also serve to confirm the findings of Chapter 4. The same patients with parietal lesions who were originally shown to fail at the classic double step task are shown to use CD to complete the modified double step tasks successfully. This confirms our hypothesis that the classic double step task used previously is an imperfect tool to investigate saccade CD in patients with parietal lesions. It also confirms our hypothesis that patients with a lesion of the parietal lobe generate CD for saccades aimed to the right and left, contrary to the dominant hypothesis postulated by previous studies.

6.2 General discussion

Here I would like to put the above findings into greater context, and explain the research course that we took throughout the three studies.

The study of hemispherectomy patients allows unique insight into the inherent capacity of a single hemisphere of cortex for reorganization and plasticity. They are remarkably competent across many domains considering the volume of cortex removed; researchers within my lab and others have extensively studied their abilities in the field of oculomotor control. They can generate accurate, bilateral saccadic eye movements. They generate express saccades in both directions. They have developed behavioural adaptations similar to those of other hemianopic patients. In fact, no oculomotor deficit has been characterized in hemispherectomy patients that cannot be attributed to a behavioural adaptation developed to mitigate the effects of hemianopia. Despite their large cortical loss, their lack of impairments in oculomotor saccade control leads to intriguing questions concerning the inherent abilities of a single hemisphere of cortex, as well as its capacity for plasticity and reorganization.

In our initial discussions concerning the topics I would study during my stay in the lab, we came up with many possible experiments we could run with the hemispherectomy patients. We decided that I would assess their CD for bilateral saccades. The reason this particular question intrigued us so, and the reason why we chose this topic over others, were many-fold. Hemispherectomy patients anecdotally perceive a stable visual world, and have done so since their surgeries. Previous studies have already shown that they retain other normal oculomotor functions. We surmised – correctly – that CD for bilateral saccades would also be in place.

Upon reaching the conclusions of our first study, many questions presented themselves about the mysterious pathways and mechanisms of saccade CD. The parietal lobe has been heavily implicated in the processing of CD, through monkey recording and stimulation studies, as well as through human lesion and imaging studies. Research investigating the exact role of this area in the processing of CD presented diverse findings.

Results of monkey studies performed by Colby and others suggest that CD about saccades aimed to the right and left are encoded in both parietal lobes. These studies do not align with parietal lesion studies in human which suggest the interruption of normal CD processing for saccades following a lesion of this area. Those studies investigating CD through various psychophysics studies using perceptual remapping measures do not form a consensus about the deficits that result from parietal lesions. Indeed, conflicting findings within this field make it nearly impossible to form a picture of what this brain region might be contributing to the CD system, although deficits in many forms abound. Studies investigating CD through the use of the classic double step task, however, present a more cohesive story. As explained extensively above, two primary papers investigated the role of the parietal lobe in the processing of CD for use in the double step saccade task (Duhamel et al., 1992b; Heide et al., 1995). Both studies suggest that a lesion of the parietal lobe (particularly when it is on the right side) abolishes CD for contralesionally-directed saccades. Our findings in the hemispherectomy study are not fully compatible with this hypothesis. If the loss of an entire hemisphere of cortex does not lead to the abolition of CD for contralesional saccades, how can a discrete lesion have such a specific and devastating effect?

This discontinuity led us to consult a field of study entitled positive neurology, reinvigorated by the recent publication of a book by N. Kapur (Kapur, 2011). The general field concerns itself with approaching the field of neurology from a non-traditional perspective; its objective is to give new insight into cortical reorganization and plasticity by quantifying and assessing the positive outcomes of brain lesions. There exist several examples in the literature of what has been dubbed a 'lesion-load-paradox', in which larger lesions result in less impairment than smaller more isolated lesions. This questions some of the oldest postulates in the field of neurology; these findings are incompatible with the law of mass action, for example. We considered that we may have stumbled upon another example of this 'lesion-load-paradox'. Could it be that a massive brain lesion, such as a hemispherectomy, could lead to a more efficient recruitment of plastic mechanisms, and thus result in fewer deficits than a smaller, more isolated lesion? The logical conclusion drawn from the comparison of our findings in hemispherectomy patients with the previous

findings concerning saccade CD in parietal lesion patients certainly suggested that this might be the case.

Since the double step saccade tasks used in our study of hemidecorticate patients differed significantly from those used in the previous parietal studies, we decided that it would be worthwhile to test a cohort of patients with parietal lesions on our new double step saccade tasks. If the patients with parietal lesions were still impaired on these modified versions of the task, and demonstrated a lack of CD for contralesional saccades, we could state with certainty that we were indeed observing an example of the 'lesion-load-paradox'. Since no two lesions are ever the same – and, indeed, no two cohorts of lesion patients – we also opted to test our patients on a reproduction of the classic double step task used in the Duhamel et al. (1992) study. We hypothesized that a possible criticism of simply testing a new group of parietal patients on our modified tasks may arise suggesting that our group of parietal patients simply didn't have the same lesions as those studied in the past. How could we tell if our patients had lesions resembling those of the patients of previous studies? We thus determined that an important control would be to investigate whether our cohort of patients performed similarly to those of previous studies when tested using the same task used in these studies. If they behaved similarly, we could then ask how they perform on our novel double step tasks. If they did not, we would be open to the possibility that our group of patients may not be representative of the groups studied in the past.

As Chapter 4 illustrates, our patients performed very similarly to those of earlier studies when tested on a similar version of the classic double step task using the methods described by these studies. In our thorough investigation of these previous studies (which we conducted with the main purpose of being able to replicate their methods as completely as possible) we came across some details which we considered might be problematic. As described thoroughly above, Duhamel et al. (1992) did not evaluate corrective saccades to each target. Our experience testing hemispherectomy patients (and even control subjects), suggested to us that this might be an oversight; we thought it likely that patients with parietal lesions may make multiple saccades to reach a target location. Heide et al. (1995)

only provided the patients 1000ms to complete the task. The results of our hemispherectomy study suggested that this may not be enough time to allow parietal patients the chance to complete the task. Finally, each study employed, in our opinion, an imperfect method of evaluating CD. The whole point of using the double step saccade task is to evaluate whether variations in S1 amplitude are taken into account in the planning and generation of S2. The absolute accuracy of either saccade is really beside the point; if, on a trial by trial basis, small variations in S1 correlate with small variations in S2, then a CD about S1 must be available to the planning areas of S2. Each of the previous studies found the mean amplitudes of S1 and S2, which, in our opinion, completely destroys the power of the double step saccade task to evaluate CD.

We thus re-analyzed the data we collected using the classic double step task, and this time we included corrective saccades and evaluated the eye trace for up to 2500ms after the GO signal. We then employed what we believe is a better method of evaluating CD: applying regression analysis to our population of S1 and S2 amplitudes. When we did this, we found that some patients had CD for ipsilesional saccades (two of the five patients) and most had CD for contralesional saccades (four of five patients). This was a surprising result; some patients with discrete parietal lesions have CD for bilateral saccades! The logical next question was why some patients showed evidence of using CD for saccades in either direction while others did not. Since this ability did not seem to correlate to any discernable lesion characteristic (lesion size, location or age), we wondered what else could be causing these differing behaviours. Also, even the patients who showed evidence of CD for bilateral saccades still failed to complete the majority of trials in the classic double step task. Since lesions of the parietal lobe are often associated with a myriad of attentional deficits, we hypothesized that these might contribute to their difficulties with this task, which involves very quickly flashing targets very close together. Further research revealed several candidate attentional deficits that could explain the behaviours we observed in the results of the classic double step task. The next challenge was to design a task that would mitigate some of these attentional deficits, and allow us to evaluate CD without the confounding effects of these deficits. Of course, this task already existed – we had developed it for our hemispherectomy study.

We tested the same cohort of patients on our endogenous and exogenous double step saccade tasks. We found, unambiguously, that each patient was able to track saccades directed to both the right and left, as seen in Chapter 5, refuting the hypothesis that patients with lesions of the parietal lobe do not have CD about saccades directed contralesionally.

Thus, we must conclude that our observations are not supportive of a 'lesion-load-paradox' at least within the CD context. Patients with a lesion of the parietal lobe and hemispherectomy patients have CDs for bilateral saccades. The sum of our observations seems to suggest, instead, that the CD for bilateral saccades is available to each cortical hemisphere for processing. Whether these findings are evidence of an inherent bilateral pathway or of extensive plasticity following traumatic brain lesions remains a mystery. This finding, however, aligns quite cohesively with the results of the monkey studies mentioned above, that found that each parietal area encodes information about saccades aimed to the left and right. Thus our findings present a missing link between non-human primate studies and human studies that have been independently seeking to understand the saccade CD system. We propose that with each saccade, CD is distributed extensively throughout the brain to sensorimotor systems that update in real time, allowing the perception of a stable visual world and an accurate internal representation of the position of the fovea with respect to objects in the visual scene.

6.3 Limitations

There exist limitations in each study of this thesis. The first and most obvious is inevitably present in all lesions studies. Patients across the board behave differently from one another. There is a large variability in ability and deficit in human lesion patients; distilling the common attributes that result from the lesions is a primary challenge. Furthermore, each patient presents with a slightly different lesion. As can be seen in the lesion trace figures (especially Fig. 4.1 and 5.1), large variability in lesion size and location are inevitable consequences of studies of this type. Furthermore, lesion studies provide an avenue for exploring correlative associations between lesions and deficit; there is no

guarantee of causation. Nonetheless, studying lesion patients provides considerable insight into crude anatomical and physiological organization, paving the way for future more precise studies, perhaps involving non-human primates.

Another point of difficulty in conducting these studies was how best to categorize saccades in the double step saccade tasks. Direction of the saccade alone was often not a sufficient indicator of which target the patient was aiming for; corrective saccades aimed to both the right and left for both T1 and T2 rendered the categorization of saccades difficult. As described in the studies above, we used a combination of saccade directionality and intersaccadic time interval to bin saccades as being directed to either T1 or T2. This was the best strategy we could devise, and we applied it consistently throughout all the studies. It was, however, sometimes difficult to categorize saccades. We were unable to come up with a better system, however, and we think the one we used was the best possible option.

6.4 Suggestions for future study

This thesis shows that patients with lesions of the parietal lobe, and hemispherectomy patients, have intact CD about saccades directed ipsilesionally and contralesionally. An interesting avenue for future studies would be to further characterize this CD system in these patients.

- Is the CD system for smooth pursuit movements in parietal patients fully intact as well?
- Can each group of patients track gaze movements to the right and left? In other words, how would they perform on a head-free version of the double step saccade task?

Another important question concerns the physiology and anatomy within the parietal lobe itself. This is a large area of cortex, that has many diverse functions and damage to which causes a vast array of deficits, including problems with speech, attention, reading, writing and visuospatial stability. It would be interesting to investigate specific functions of different areas of the parietal lobe itself. This is starting to be carried out as technology advances, allowing the introduction of precise, reversible lesions into healthy subjects.

Imaging studies allowing more specific investigation into structure and function of the parietal lobe in eye movement studies would also prove useful. MEG provides a high temporal resolution option for investigating the contribution of various brain areas at different times to specific tasks. The possibilities for investigation are truly limitless in this capacity.

Another interesting question relates to the differences in the CD system between the exogenous saccade generating machinery and the endogenous saccade generating machinery in healthy control subjects. We only tested a few control subjects on our modified tasks, although I think it would be a valuable addition to the literature to perform a comprehensive study of these systems in control subjects. Is the CD system equally precise for exogenous and endogenous saccades? I would hypothesize that they are quite similar; if CD originates within the SC, then it should essentially carry the same information for saccades of equal vectors, whether they are exogenously or endogenously driven. A study of this nature would give insight into the pathways and mechanisms of saccade CD.

The finding of our hemispherectomy study is what led us to question the dominant hypothesis concerning CD in patients with parietal lesions. We encourage studies in these patients, as they allow investigation into the abilities of a single hemisphere of cortex. These patients are evidence of the truly remarkable capacity of the human cortex for reorganization and plasticity; studying their abilities is one of the best ways to gain insight into this most mysterious of phenomena.

6.5 Concluding remarks

Keeping track of one's own movements is a vital process that enables the interpretation of the external environment; redundancy within this system is a way of ensuring its integrity, despite insults to the brain. I argued here for the existence of a distributed and redundant saccadic eye movement CD system, in which the CD of saccades aimed to the right and to the left are available to each hemisphere of cortex.

The saccade CD system presents a simple model of a complex motor-oversight mechanism that the brain employs throughout all motor systems. Gaining insight into the physiology of this system provides clues to some of the deepest mysteries underlying brain function, including the signal processing language of the brain, the mechanisms underlying the speed and precision of our constant sensorimotor transformations, and cortical organization and redundancy. Revealing these mysteries gives clues about our evolutionary past, and provides keys to medical and technological advances for the future.

Figures

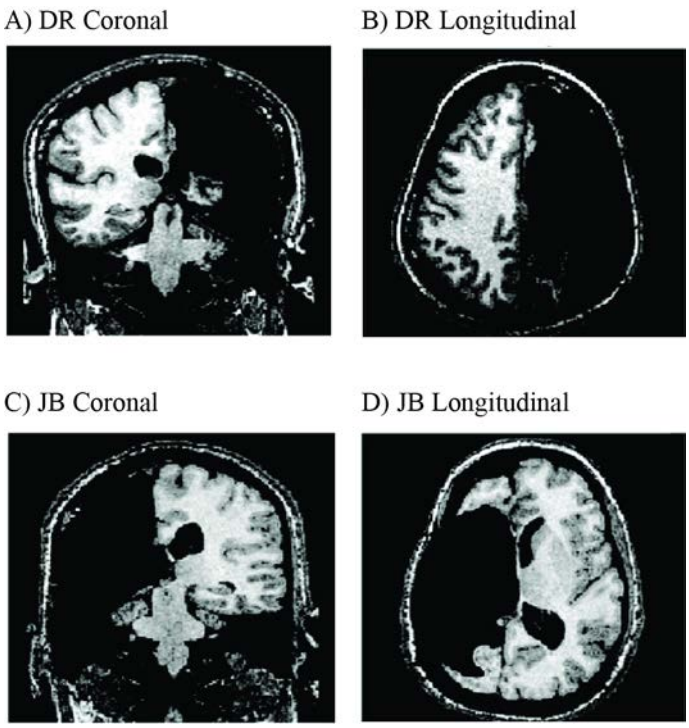


Fig. 3.1: Patient lesions – Magnetic Resonance Imaging (MRI) scans showing the cortical ablations of the tested hemidecorticate subjects. Coronal (A) and longitudinal (B) sections showing the complete right hemidecortication of DR. Coronal (C) and longitudinal (D) sections showing the complete functional left hemidecortication of JB. The occipital and frontal poles were left in place in JB to prevent hemosiderosis but were surgically disconnected from the rest of the brain. See text for case histories.

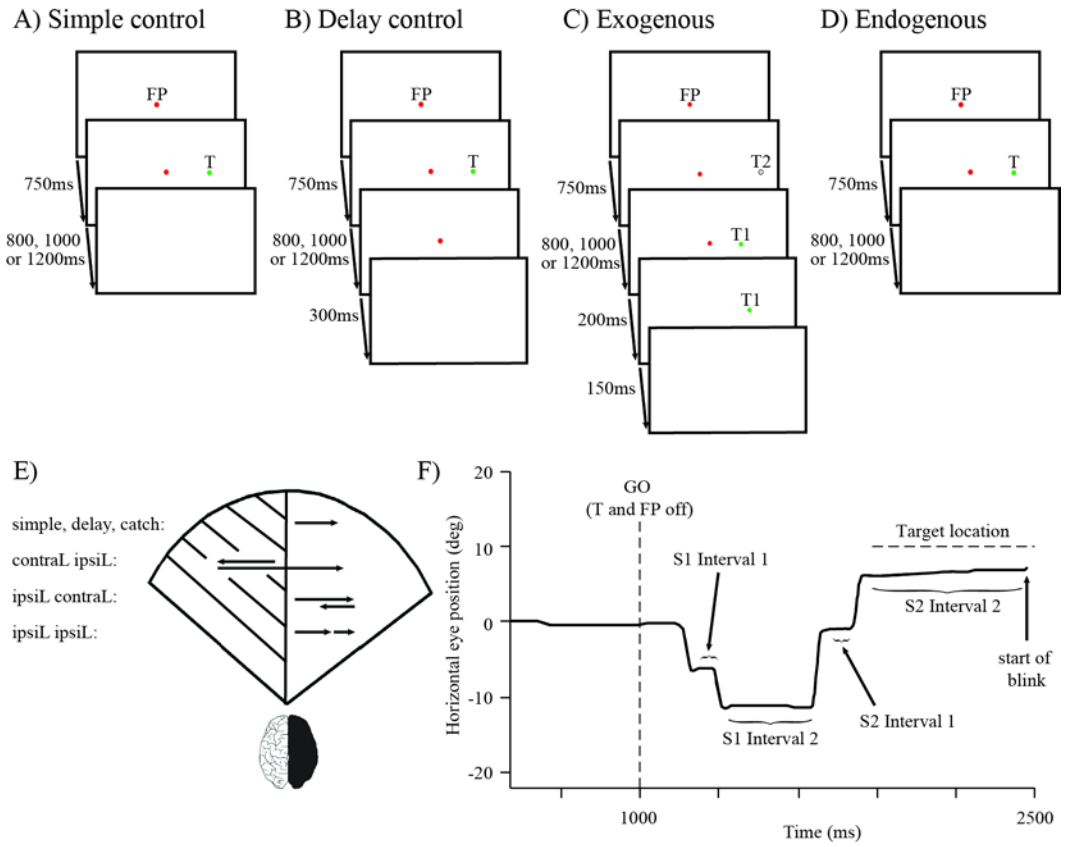


Fig. 3.2: Experimental paradigm and analysis – Paradigms for the different experimental tasks including control experiments (A, B), exogenous experiments (C) and endogenous experiments (D). In all tasks, the central FP was presented for 750ms before the targets were presented; in all tasks the extinguishing of the FP indicated the Go signal for the subject. (A) Simple control experiment: a single target was presented for 800, 1000 or 1200ms and extinguished simultaneously with the FP. (B) Delay control experiment: a single target was presented for 800, 1000 or 1200ms and extinguished 300ms before the FP. (C) Exogenous experiments: two targets were presented in the seeing field of the subject. T2 was presented first for 800, 1000 or 1200ms followed by T1 for 200ms with the FP illuminated and 150ms after the FP was extinguished. (D) Endogenous experiments: one target was presented in the seeing field of the subject for 800, 1000 or 1200ms and extinguished with the FP; subjects were instructed to make an eye movement of self-determined amplitude in the direction indicated, before making a second eye movement to the remembered location of the previously seen target. (E) Schema of the expected eye movement for each experiment (A-D). (F) Sample horizontal eye movement trace (filtered with a 20Hz low pass band filter) for subject DR performing the endogenous contraL-ipsiL task.

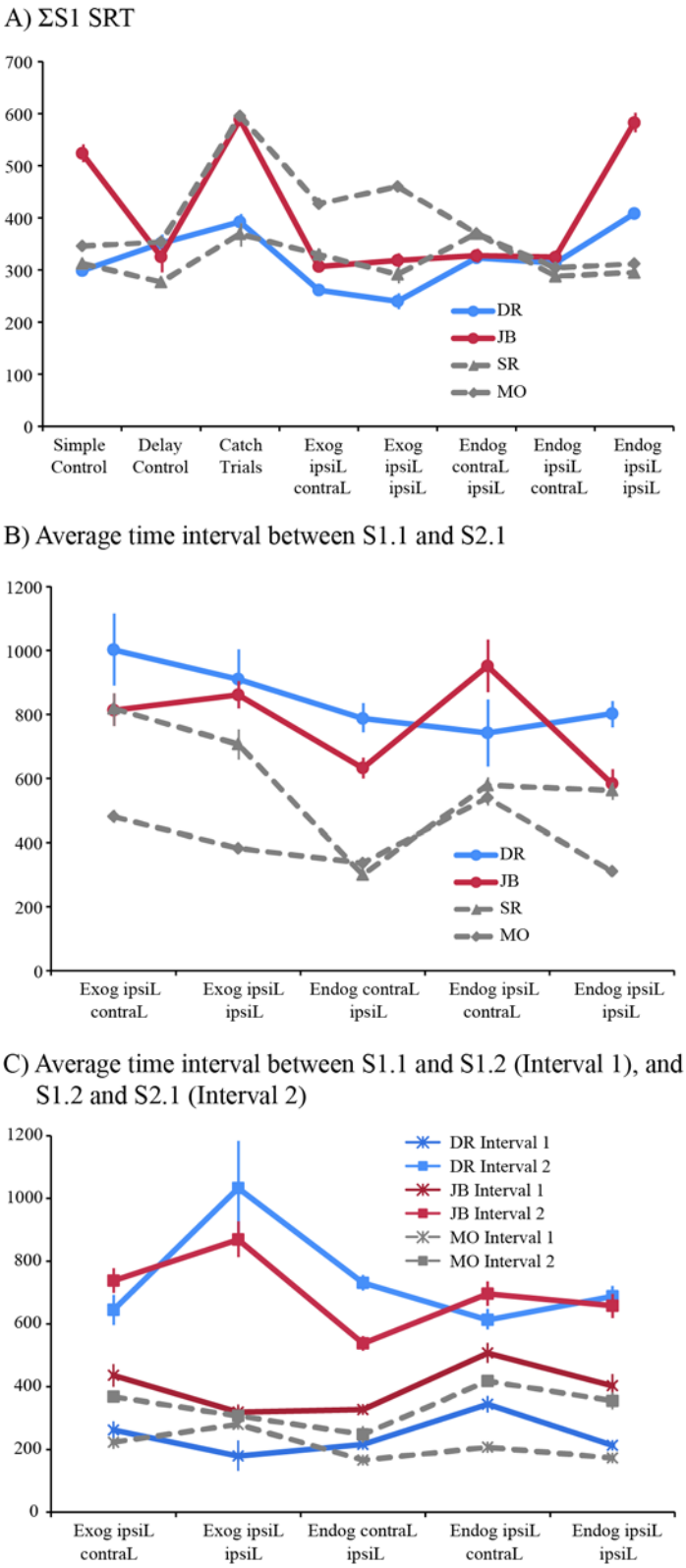


Fig. 3.3: SRT – Analysis of saccade reaction time for DR (blue), JB (red) and controls (grey). (A) Average ΣS1 SRT across trial types. (B) Average time interval between the end of ΣS1 and the beginning of ΣS2 for all trials in which a single saccade was generated to reach the first target location. (C) Average time intervals between S1.1 and S1.2 (Interval 1, indicated by stars (*)) as well as S1.2 and S2.1 (Interval 2, indicated by squares (■)) for all those trials in which two saccades were generated to reach the first target. In all plots, error bars represent the standard error of the mean.

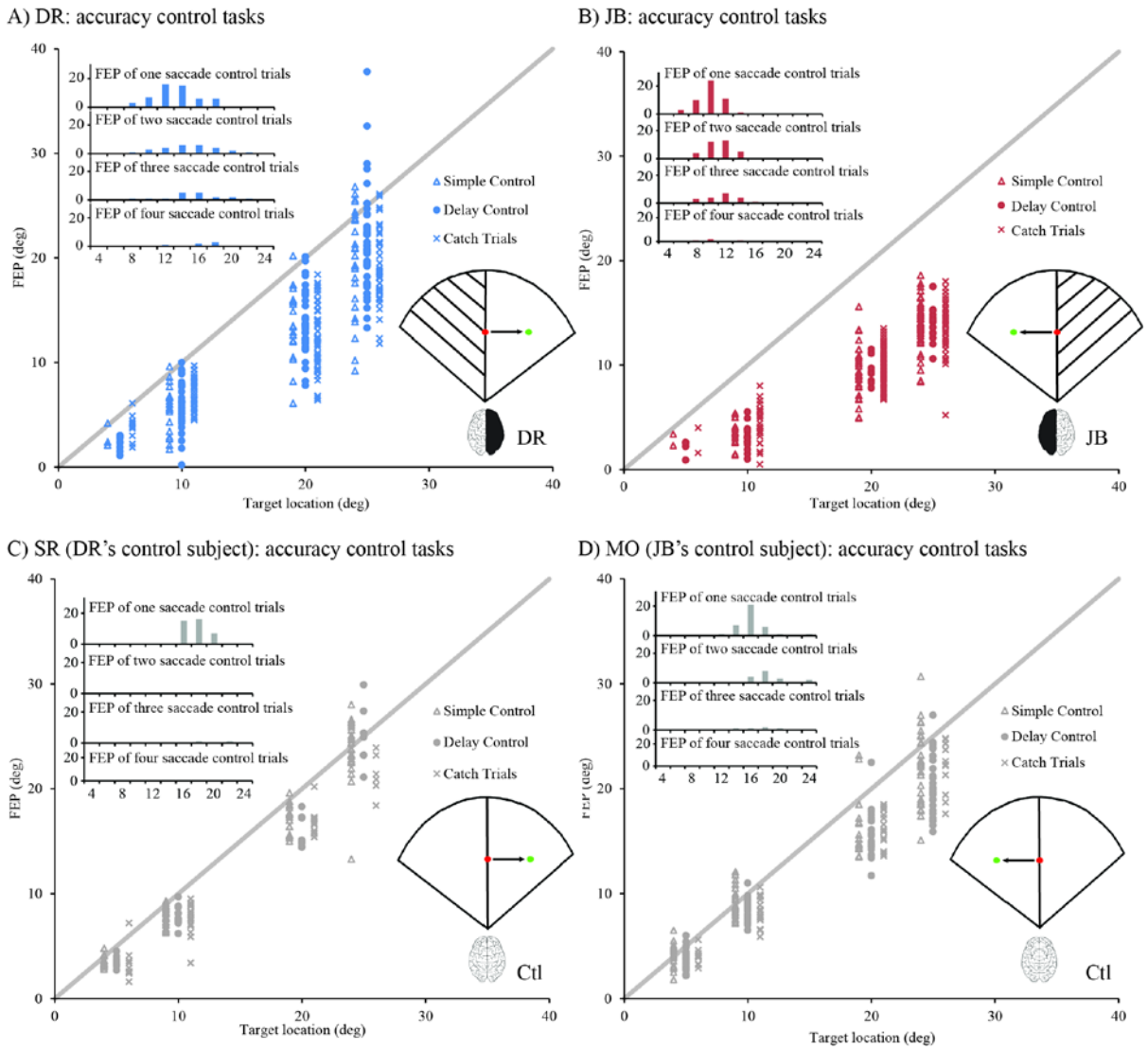


Fig. 3.4: Control experiment accuracy – Results of control experiments for targets in the seeing hemifield and catch trials of the exogenous series for DR (A), JB (B), SR (C) and MO (D). Triangles (▲): simple control trials; circles (●): delay control trials; crosses (X): catch trials. FEP on the y axis refers to the FEP at the end of the last saccade in the trial (up to four saccades were accepted on a given trial as described in the Methods section). Diagonal line represents unity gain. Inset graphs show histograms for simple and delay control trials to the 20° target location for each subject (A, B, C, D); the first line of the inset graph shows the FEP after trials in which only a single saccade was performed and the subsequent lines show the FEP after multiple saccades were performed within a single trial.

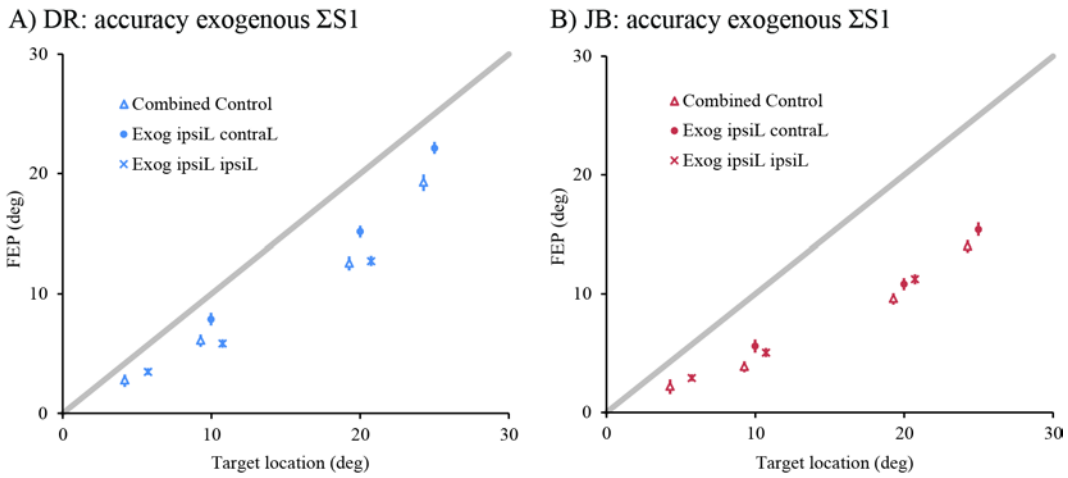


Fig. 3.5: Exogenous S1 accuracy – Results of S1 for the exogenous series of experiments for DR (A) and JB (B). Triangles (▲): combined control trials; circles (●): exogenous ipsiL-contraL; crosses (X): exogenous ipsiL-ipsiL. Note that in this figure, only controls trials in which the subject performed one or two saccades to reach the target location were included; any trials that involved three or four saccades to reach the target location were not included. FEP on the y axis refers to the FEP at the end of the last saccade in S1. Diagonal line represents unity gain. Error bars represent standard error of the mean.

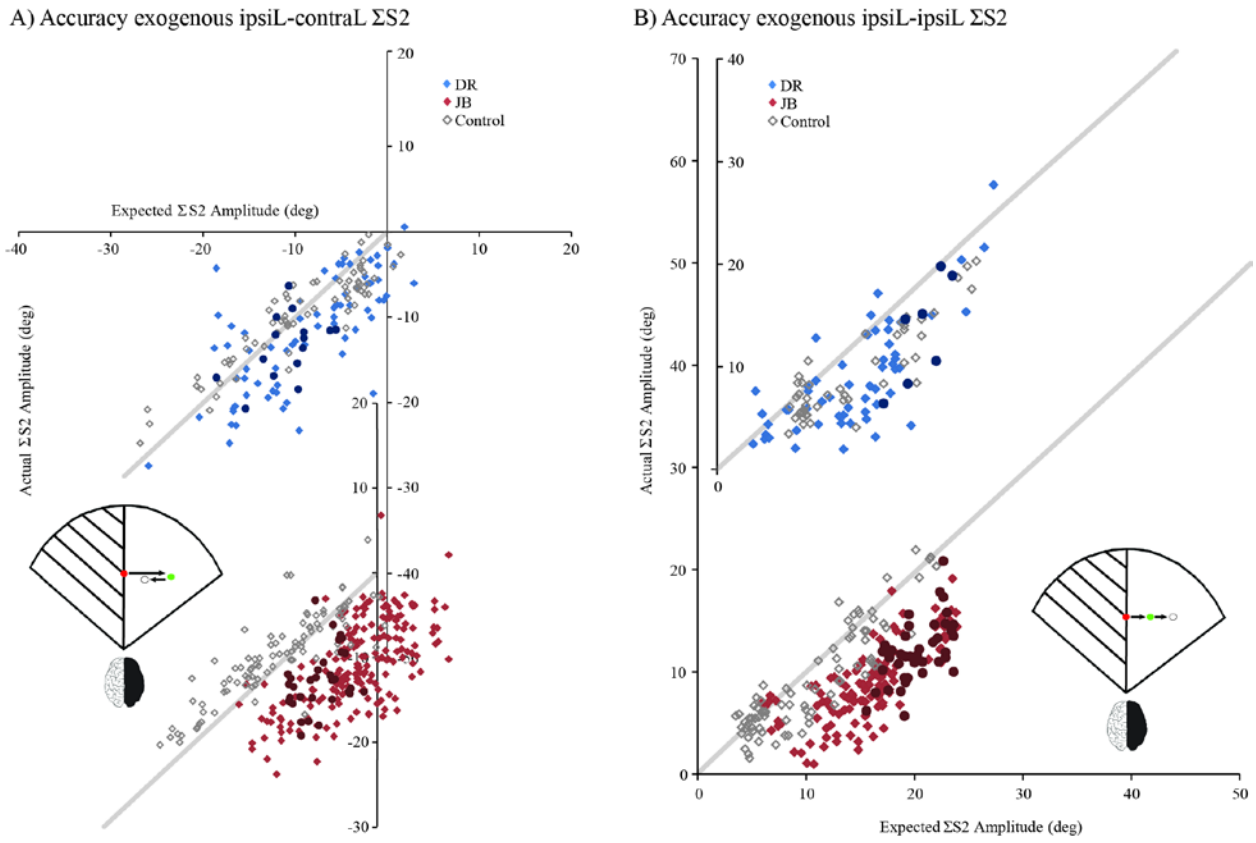


Fig. 3.6: Exogenous S2 accuracy – Results of the exogenous series of experiments. (A, B) Blue diamonds represent the results of DR for the ipsiL-contraL (A) and ipsiL-ipsiL (B) trial types respectively. Red diamonds represent the results of JB for the ipsiL-contraL (A) and ipsiL-ipsiL (B) trial types respectively. The grey outline diamonds represent the results of each subject's respective control subject for each trial type. Darker circles represent some of the trials in which the distance between targets was equal to 15°; they are further represented in Fig. 7.

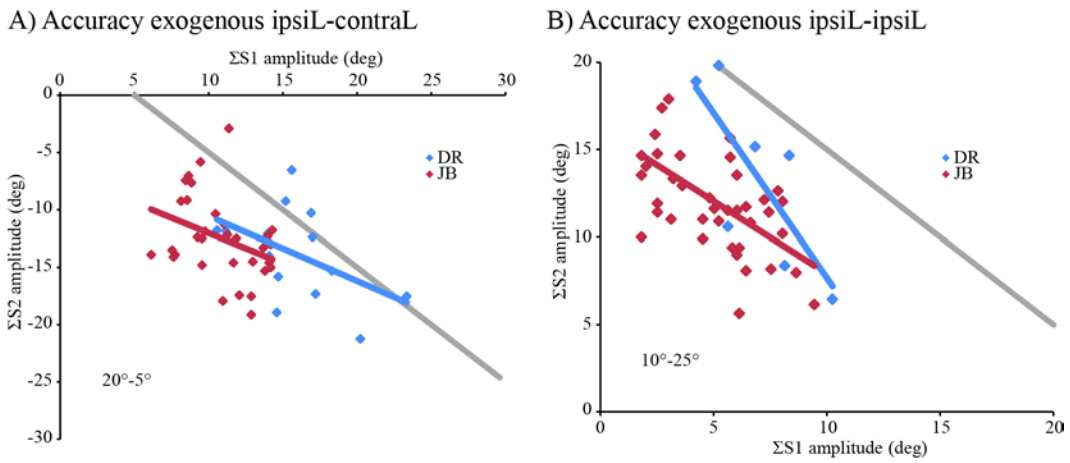


Fig. 3.7: Within trial-type accuracy – Results of some of the exogenous trials with a 15° distance between T1 and T2; blue diamonds represent DR data and red diamonds represent JB data. (A) Exogenous ipsiL-contraL trials in which T1 = 20° and T2 = 5°and (B) exogenous ipsiL-ipsiL trials in which T1 = 10° and T2 = 25°. Regression lines are indicated for each subject ($P<0.05$).

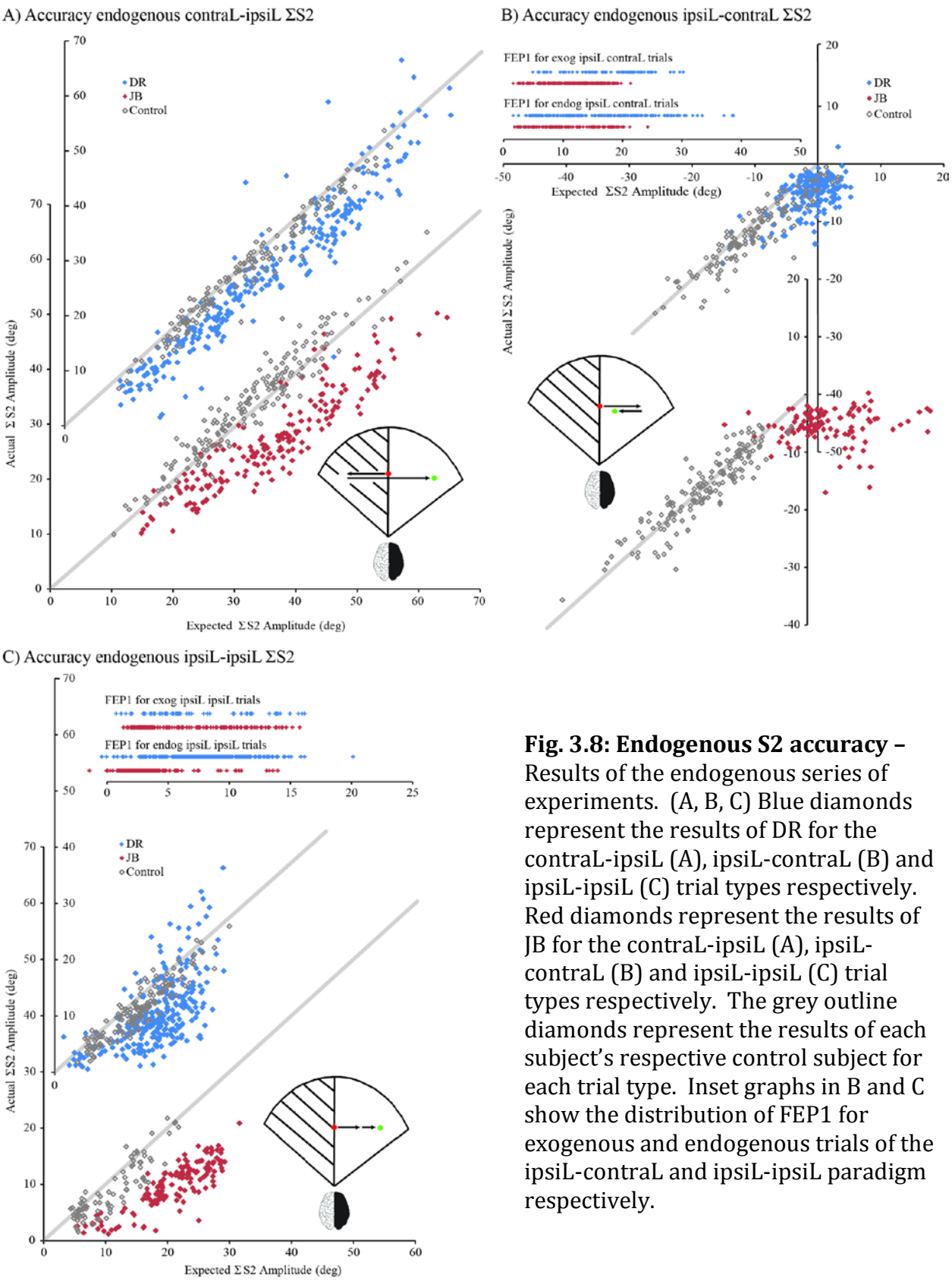
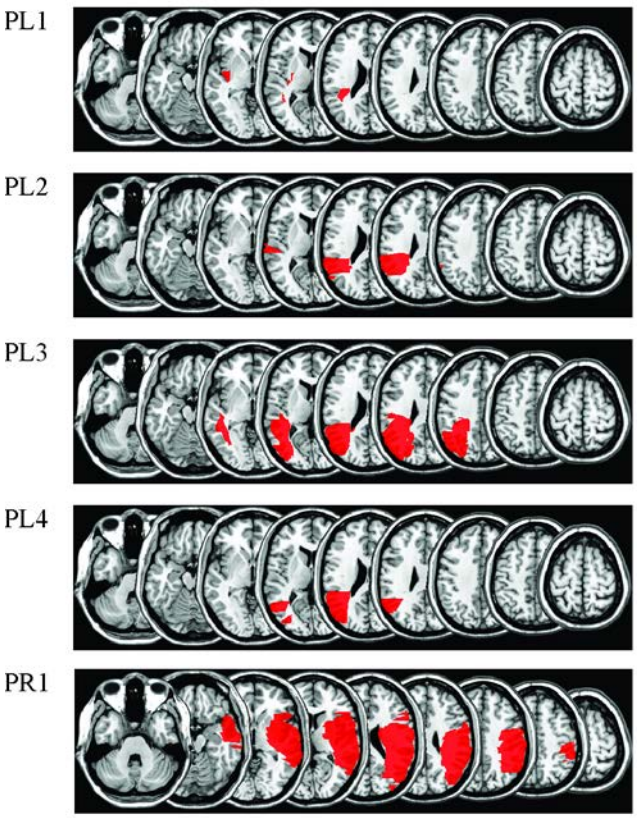


Fig. 3.8: Endogenous S2 accuracy – Results of the endogenous series of experiments. (A, B, C) Blue diamonds represent the results of DR for the contraL-ipsiL (A), ipsiL-contraL (B) and ipsiL-ipsiL (C) trial types respectively. Red diamonds represent the results of JB for the contraL-ipsiL (A), ipsiL-contraL (B) and ipsiL-ipsiL (C) trial types respectively. The grey outline diamonds represent the results of each subject's respective control subject for each trial type. Inset graphs in B and C show the distribution of FEP1 for exogenous and endogenous trials of the ipsiL-contraL and ipsiL-ipsiL paradigm respectively.

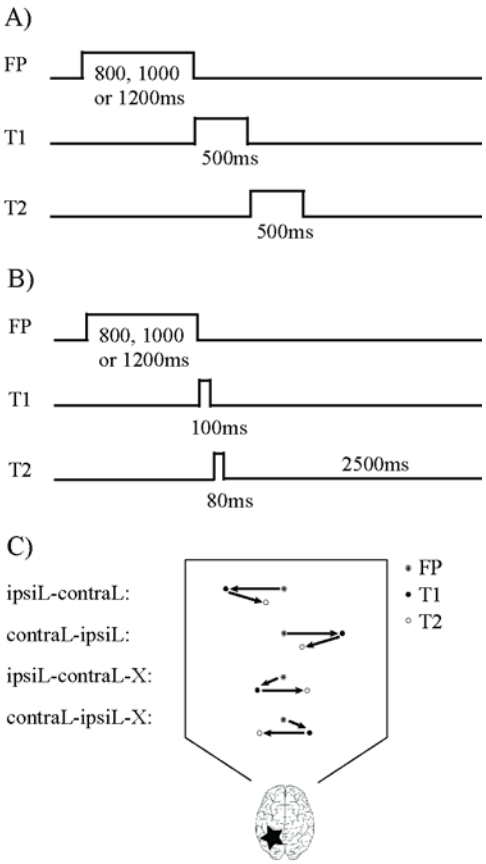
A)



B)

Subject	*Side of lesion*	*Handedness*	*Years since injury*	*Posner score (ms): contraL$_{(v-u)}$-ipsiL$_{(v-u)}$*
PL1	Left	Right	18	28.2
PL2	Left	Right	9	41.8
PL3	Left	Right	9	63.5
PL4	Left	Left	6	68.9
PR1	Right	Right	8	63.3

Fig. 4.1: Patient lesion traces and details – (A) Representative axial slices of the 'MNI brain' depicting lesion traces for left and right patients. (B) Details about the patients and their lesions, and the results of our Posner cueing task (see Methods).



D)

Trial type	*Possible target combinations*
• *ipsiL-contraL &* *contraL-ipsiL*	[T1(6,0) → T2(2,-1.5)] [T1(-6,0) → T2(-2,-1.5)]
• *ipsiL-contraL-X &* *contraL-ipsiL-X*	[T1(3,-1.5) → T2(-3,-1.5)] [T1(-3,-1.5) → T2(3,-1.5)]

Fig. 4.2: Experimental paradigm – Timing information and expected eye movement sequences for our different experimental tasks including the visually-guided double step task (A) and the flashed double step task (B). (C) Schematic movement sequences for each trial type depicted by arrows for an example left parietal patient. (D) Possible target combinations for each trial type.

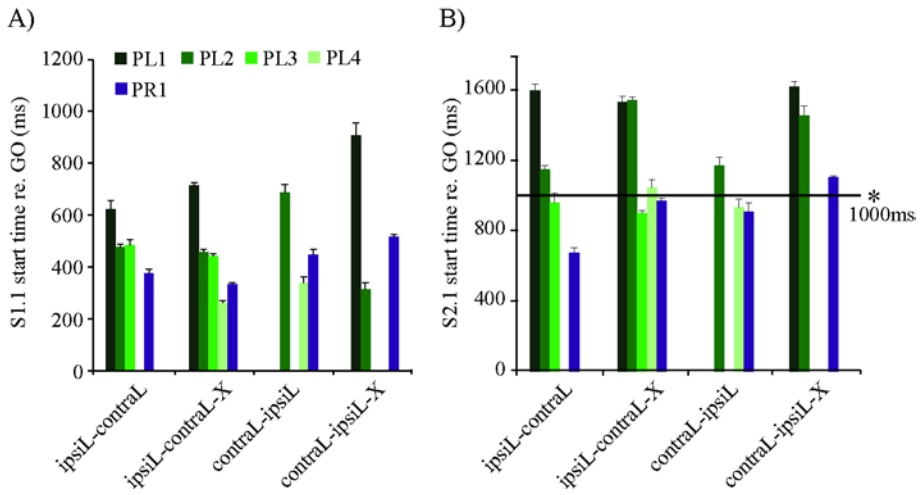


Fig. 4.3: Saccade timing – (A) Mean saccade start time re. GO (FP-off) of the first saccade in ΣS1 (S1.1) for all accepted flashed double step trials for each trial type in all subjects. Error bars represent SEM. Note that some bars are missing because we only performed this analysis when more than six trials were accepted within a certain trial type by a patient. (B) Mean saccade start time of the first saccade in ΣS2 (S2.1) for all accepted flashed double step trials for each trial type in all subjects. Line drawn at 1000ms indicates the end of the trial in our Heide et al. (1995) analysis methods.

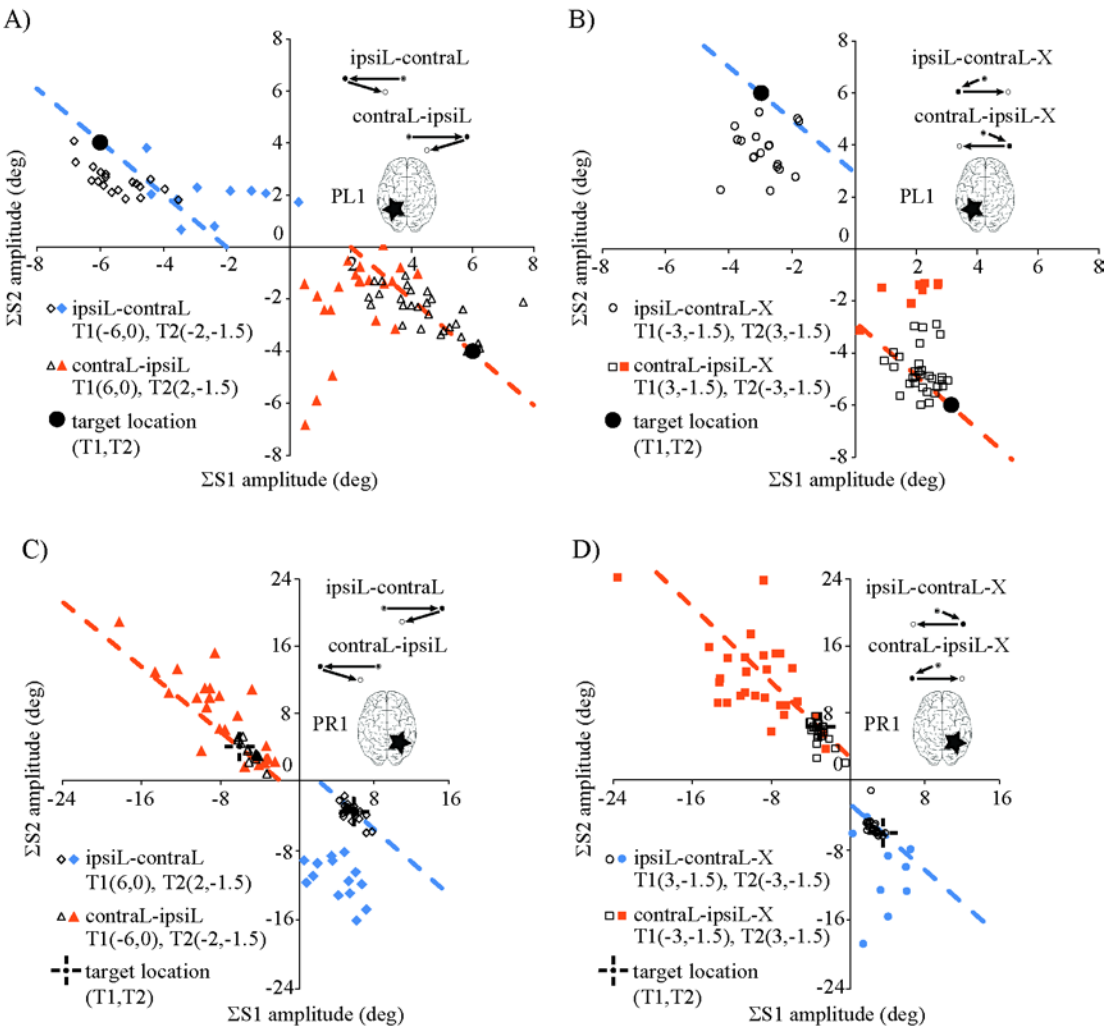


Fig. 4.4: S2 accuracy – Accuracy of ΣS2 for the classic double step flashed experiment using our analysis by determining whether variations in the overall amplitude of ΣS1 are compensated by ΣS2. ΣS2 versus ΣS1 is shown for each trial type in two example target combinations and for each subject: PL1 (A, B) and PR1 (C, D). Blue diamonds: ipsiL-contraL trials; orange triangles: contraL-ipsiL; blue circles: ipsiL-contraL-X; orange squares: contraL-ipsiL-X. The black outlined markers indicate the results of the respective trial types in the visually-guided task. The black circle indicates the goal location for each trial type, scaled to the size of the targets relative to each axes' coordinate system. The star around the dot in C and D is meant as a visual aid since the black circle is small, and hidden behind the data points. Diagonal dashed lines represent perfect performance in each of the respective target combinations.

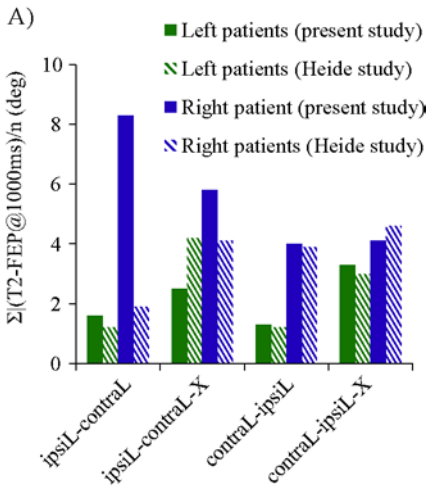
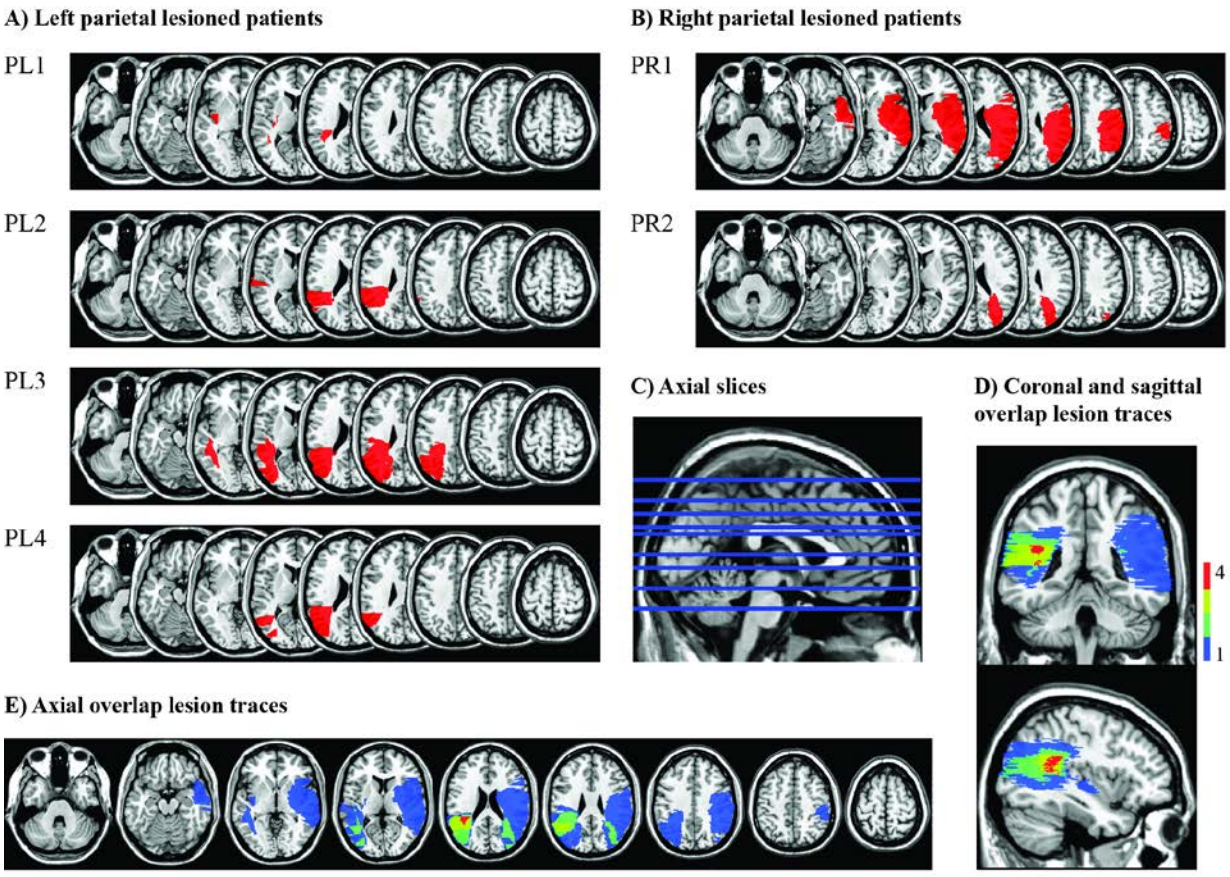


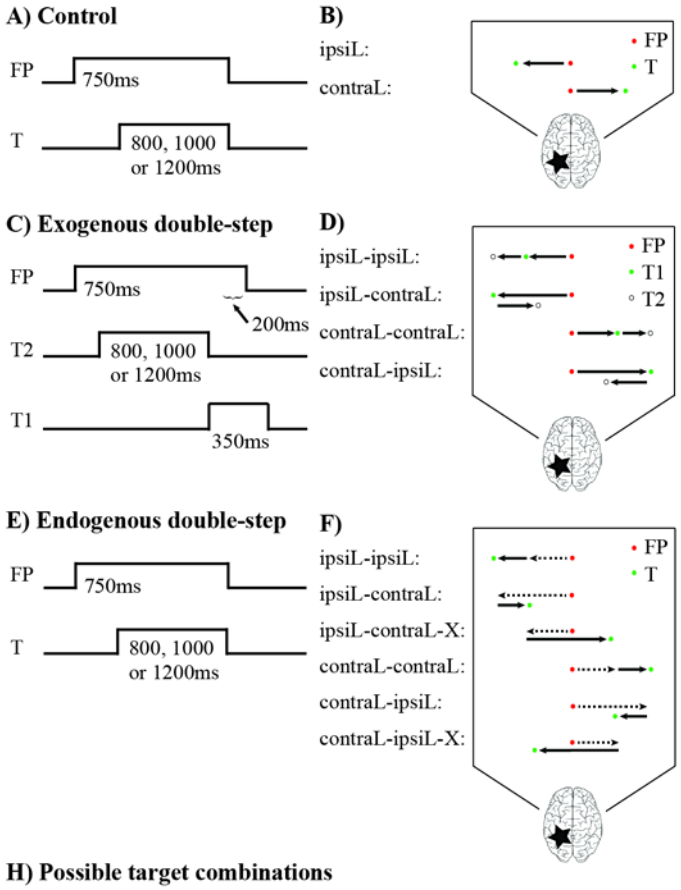
Fig. 4.5: Heide analysis of S2 accuracy – Mean absolute eye position error relative to T2 at 1000ms from GO (FP-off) for all left patients (weighted average; shown in green) and our single right patient (shown in purple). Hashed bars depict data from Heide et al. (1995), adapted from their Fig.5.



F) Patient and lesion characteristics

Subject	*Side of lesion*	*Handedness*	*Etiology*	*Years since injury*	*Psychoactive medications*	*Posner score (ms): contraL$_{(v-u)}$-ipsiL$_{(v-u)}$*
PL1	Left	Right	Stroke	18	N/A	28.2
PL2	Left	Right	Stroke	9	anticonvulsant	41.8
PL3	Left	Right	Stroke	9	N/A	63.5
PL4	Left	Left	Stroke	6	N/A	68.9
PR1	Right	Right	Stroke	8	anticonvulsant, antidepressant	63.3
PR2	Right	Right	Benign meningioma	10	anticonvulsant	-41.2

Fig. 5.1: Patient lesion traces and details - Representative axial slices of the 'MNI brain' depicting lesion traces for (A) left and (B) right patients. (C) Mid-sagittal view indicating slice locations, and (D) overlapped slices in coronal, sagittal and (E) axial coordinates. (F) Details about the patients and their lesions.



H) Possible target combinations

Trial type	*Possible target combinations*
Controls	
• *ipsiL / contraL*	T = ±5, ±10, ±20, ±25
Exogenous double-step	
• *ipsiL-ipsiL / contraL-contraL*	[T1,T2] = ±[5,10], ±[5,20], ±[5,25], ±[10,20], ±[10,25], ±[20,25]
• *ipsiL-contraL / contraL-ipsiL*	[T1,T2] = ±[25,20], ±[25,10], ±[25,5], ±[20,10], ±[20,5], ±[10,5]
Endogenous double-step	
• *ipsiL-ipsiL & contraL-contraL*	T = ±10, ±20, ±25, ±30
• *ipsiL-contraL & contraL-ipsiL & ipsiL-contraL-X & contraL-ipsiL-X*	T = ±5, ±10, ±20, ±25

G) PR1: ex. trace of endogenous contraL-ipsiL-X

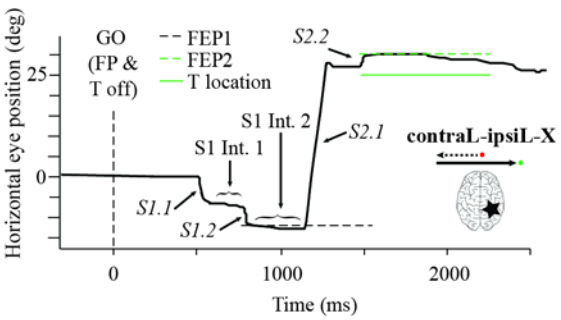


Fig. 5.2: Experimental paradigm and analysis – Timing information and expected eye movement sequences for our different experimental tasks including the control task (A, B), the exogenous double step task (C, D) and the endogenous double step task (E, F). Note that a visually-guided version of the exogenous double-step task was also conducted (not shown), in which the targets remained on for the duration of the trial. (B, D, F) Schematic movement sequences depicted by arrows for an example left parietal patient. Dashed lines indicate a saccade that is endogenously-driven, i.e. of self-determined amplitude. (H) All possible target combinations for each task. In the control and endogenous tasks only one target was shown per trial. (G) Sample horizontal eye position trace (filtered with a 20Hz low-pass band filter) for subject PR1 performing the endogenous contraL-ipsiL-X task with target at 25°. The initial endogenous displacement (ΣS1) contained two saccades: S1.1 and S1.2. There were also two saccades in ΣS2 to the target: S2.1 and S2.2.

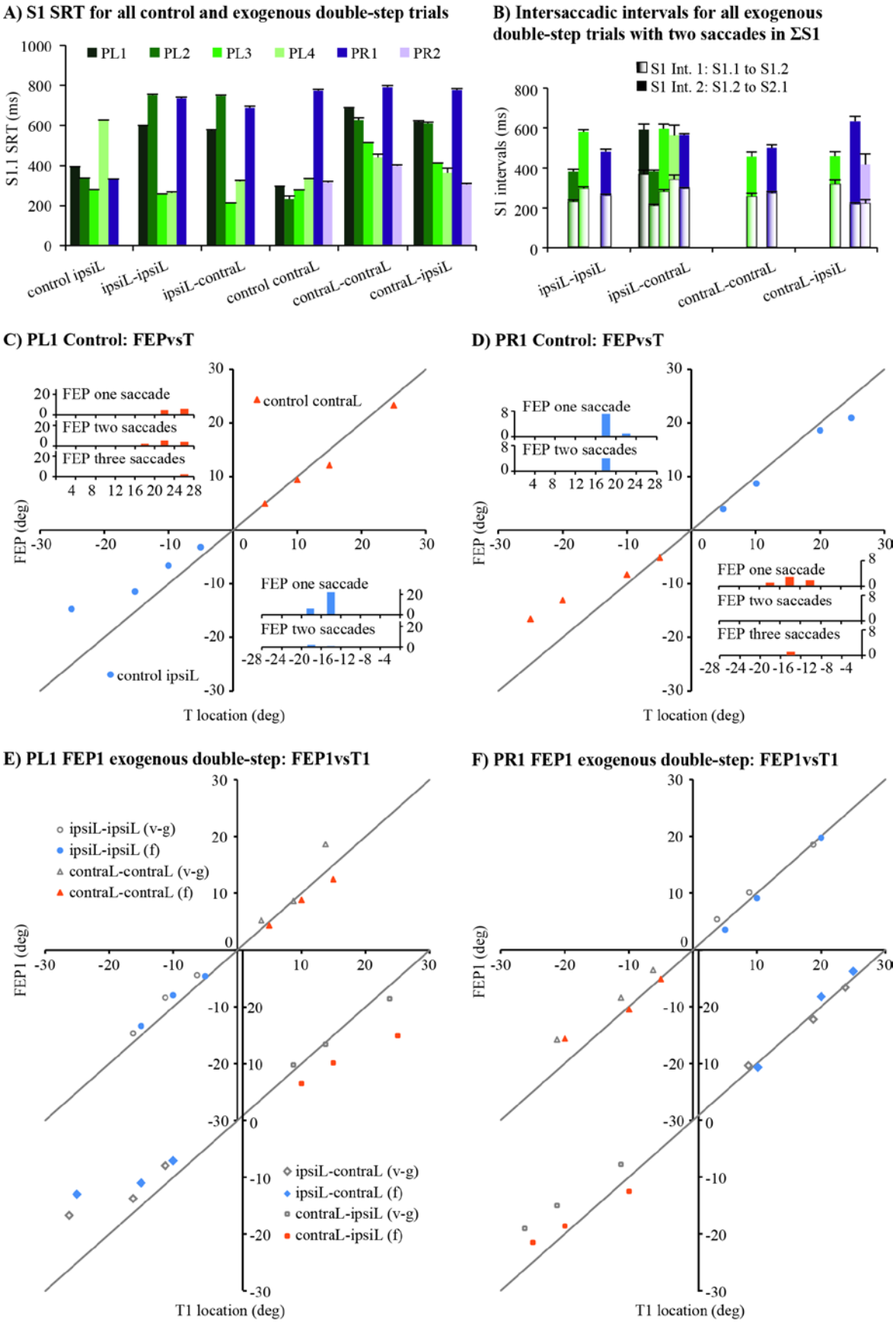

A) S1 SRT for all control and exogenous double-step trials
PL1
PL2
PL3
PL4
PR1
PR2
S1.1 SRT (ms)
control ipsiL
ipsiL-ipsiL
ipsiL-contraL
control contraL
contraL-contraL
contraL-ipsiL
B) Intersaccadic intervals for all exogenous double-step trials with two saccades in ΣS1
S1 Int. 1: S1.1 to S1.2
S1 Int. 2: S1.2 to S2.1
S1 intervals (ms)
ipsiL-ipsiL
ipsiL-contraL
contraL-contraL
contraL-ipsiL
C) PL1 Control: FEPvsT
FEP one saccade
FEP two saccades
FEP three saccades
control contraL
control ipsiL
FEP (deg)
T location (deg)
D) PR1 Control: FEPvsT
FEP one saccade
FEP two saccades
FEP three saccades
FEP (deg)
T location (deg)
E) PL1 FEP1 exogenous double-step: FEP1vsT1
ipsiL-ipsiL (v-g)
ipsiL-ipsiL (f)
contraL-contraL (v-g)
contraL-contraL (f)
ipsiL-contraL (v-g)
ipsiL-contraL (f)
contraL-ipsiL (v-g)
contraL-ipsiL (f)
FEP1 (deg)
T1 location (deg)
F) PR1 FEP1 exogenous double-step: FEP1vsT1
FEP1 (deg)
T1 location (deg)

Fig. 5.3: SRT, control accuracy and exogenous S1 accuracy – (A) Saccade reaction times of first saccade in ΣS1 for all accepted control and exogenous double-step (flashed) trials for all subjects. Note that PR2 only participated in half of the experiments. Error bars represent SEM. (B) Average intersaccadic time intervals for all exogenous double-step trials with two saccades in ΣS1 (referring to Fig 2G, shaded bars represent S1 Int. 1 [i.e., S1.1 to S1.2] and solid bar represents S1 Int. 2 [S1.2 to S2.1]). Error bars represent SEM. (C, D) Results of control experiments for PL1 (C) and PR1 (D) indicated by average FEP for all trials with the same T location; error bars, representing SEM are too small to be seen. Blue circles: ipsiL trials; orange triangles: contraL trials. Note the FEP here refers to the FEP at the end of the last saccade in the trial (up to four saccades were accepted on a given trial as described in the Methods section). Diagonal line represents unity gain. Inset graphs in C and D show histograms for all control trials to the 25° target location for each subject; the first line of the inset graph shows the FEP after trials in which a single saccade was performed within a trial and the subsequent lines show the FEP after two and three saccades were performed within a single trial, respectively. (E, F) Accuracy of FEP1 for each trial type of the exogenous double-step task for PL1 (E) and PR1 (F). Blue circles: ipsiL-ipsiL trials; orange triangles: contraL-contraL; blue diamonds: ipsiL-contraL; orange squares: contraL-ipsiL. The grey outlined markers indicate the results of each subject's respective visually-guided control experiment in each trial type. Again, error bars are too small to be seen as SEM was consistently smaller than the marker used to illustrate the mean. Diagonal lines represent unity gain.

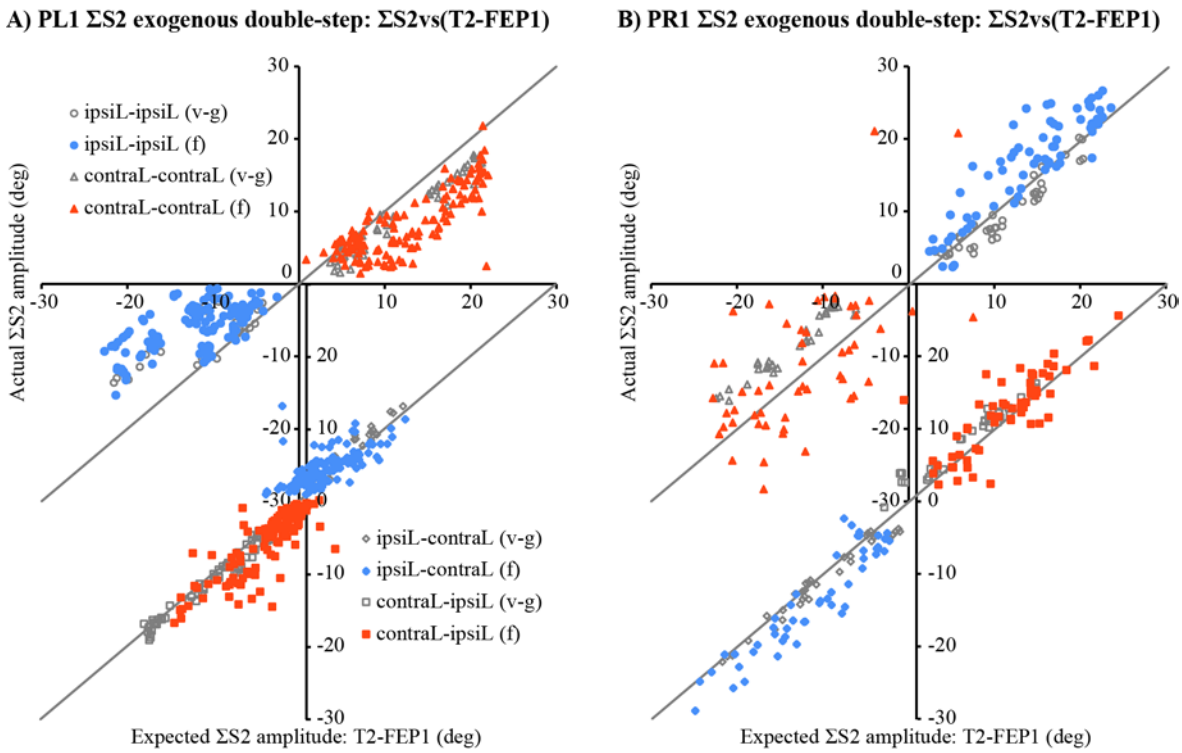


Fig. 5.4: Exogenous S2 accuracy – Accuracy of ΣS2 for all accepted trials in the exogenous double-step tasks, displayed as actual ΣS2 amplitude (including multistep saccades to T2), as a function of the expected ΣS2 amplitude (=T2-FEP1) for perfect performance for PL1 (A) and PR1 (B). Blue circles: ipsiL-ipsiL trials; orange triangles: contraL-contraL; blue diamonds: ipsiL-contraL; orange squares: contraL-ipsiL. The grey outlined markers indicate the results of each subject's respective visually-guided experiment in each trial type. Diagonal line represents unity gain.

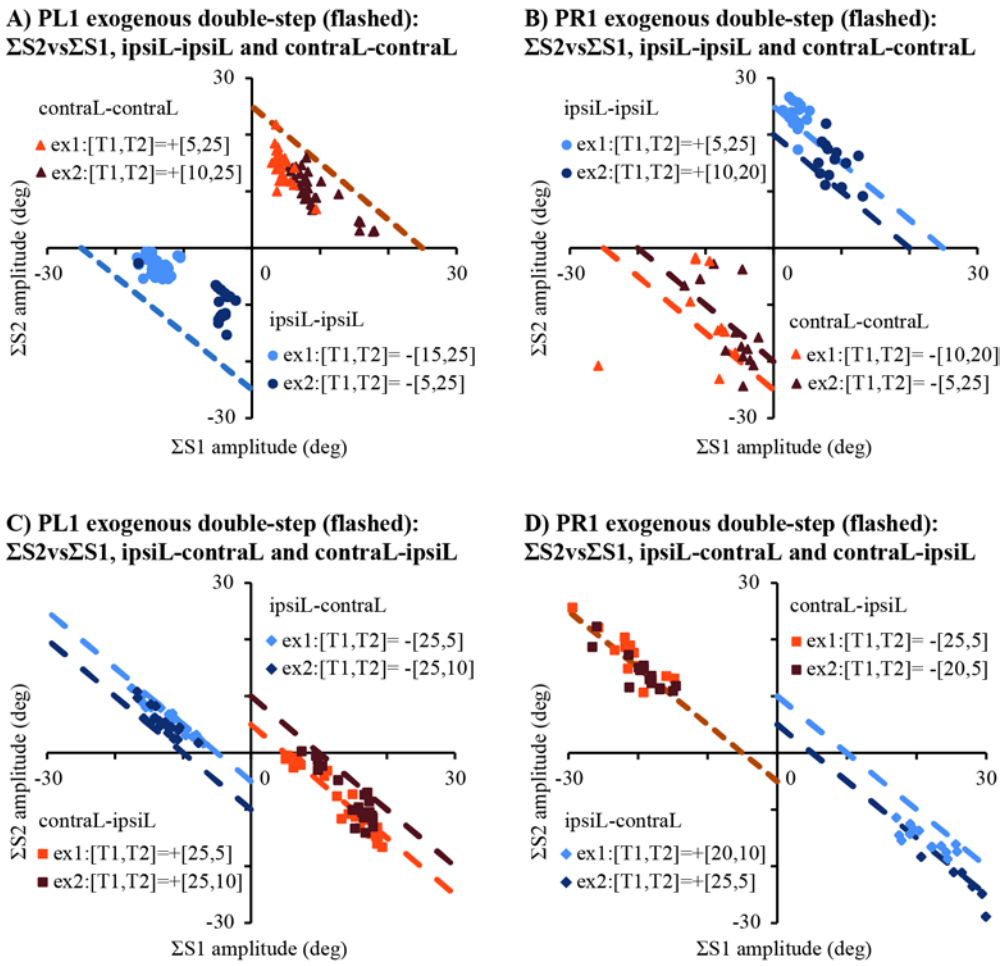


Fig. 5.5: Within trial-type accuracy – Accuracy of ΣS2 for the exogenous double step flashed experiment evaluated by determining whether variations in the overall amplitude of ΣS1 are compensated by ΣS2. ΣS2 versus ΣS1 is shown for each trial type in two example target combinations and for each subject: PL1 (A, C) and PR1 (B, D). Blue circles: ipsiL-ipsiL trials; orange triangles: contraL-contraL; blue diamonds: ipsiL-contraL; orange squares: contraL-ipsiL. Diagonal dashed lines represent perfect performance in each of the respective target combinations.

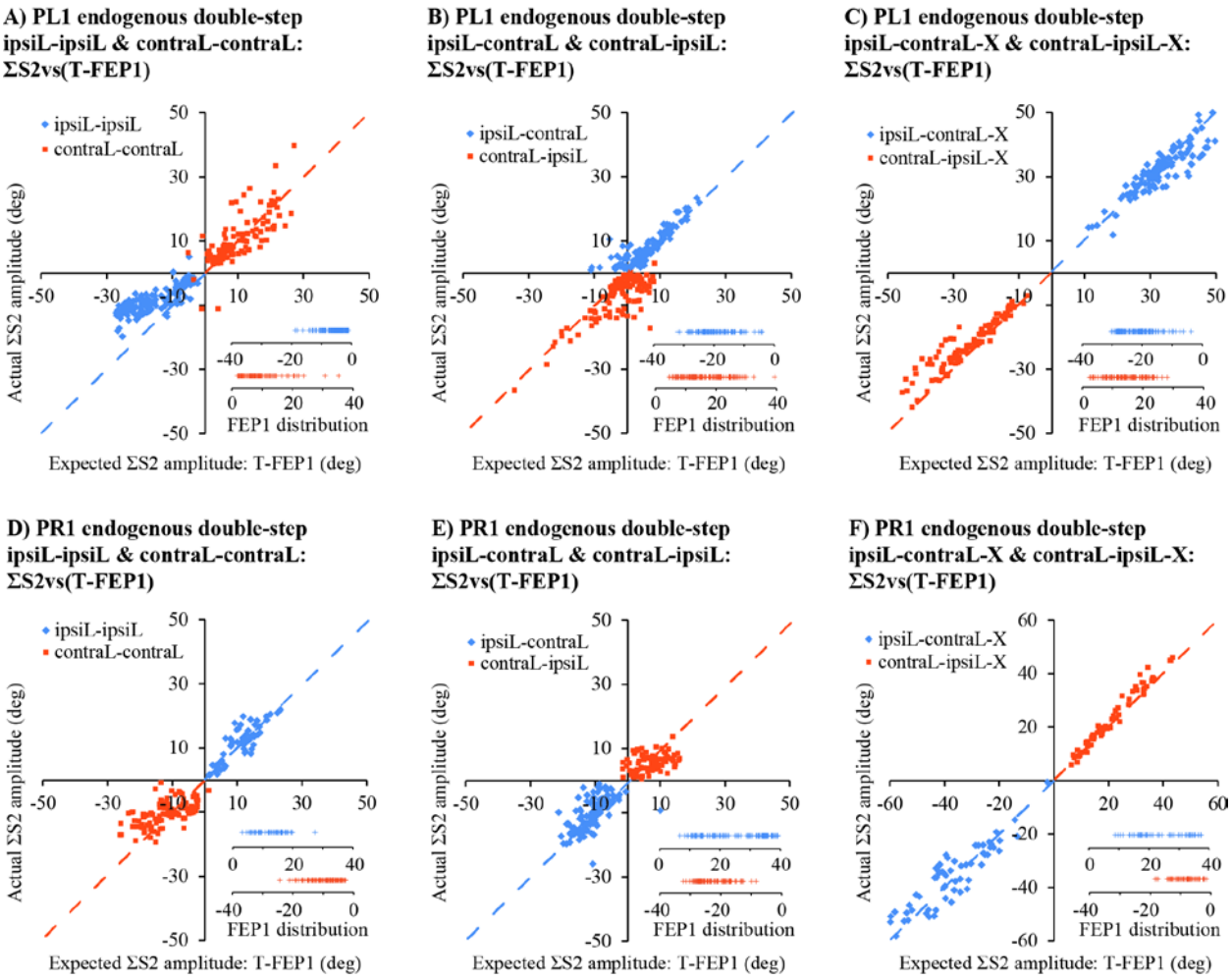


Fig.5.6: Endogenous S2 accuracy – Accuracy of ΣS2 for all accepted trials in the endogenous double step tasks, displayed as actual ΣS2 amplitude (including multistep saccades to T) as a function of the expected ΣS2 amplitude (=T-FEP1) for perfect performance for PL1 (A, B, C) and PR1 (D, E, F). Blue diamonds: results for all trials with ipsilesional first saccade; orange squares: trials with contralesional first saccade. Diagonal dashed lines represent unity gain. Inset graphs show the distribution of final eye positions (FEP1) after end of multiple-step saccades in endogenous ΣS1 including trials with one, two and three saccades; blue crosses: FEP1 for ipsilesional first saccade; orange crosses: FEP1 for contralesional first saccade.

Tables

Table 4.1: Our analysis (ΣS2vsΣS1) of classic double step flashed data for each of our patients

	ipsiL-contraL		**ipsiL-contraL-X**		**contraL-ipsiL**		**contraL-ipsiL-X**	
Patient	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*
PL1[+]	0.05 (10)	-0.1x**+1.6**	(1)[a]	[a]	0.27 (21)	[++]**0.9x-4.0**[++]	0.63 (8)	[++]**0.6x-2.5**[++]
PL2	0.41 (21)	**-0.7x+0.7**	0.79 (15)	**-1.5x**+0.6	0.59 (16)	**-0.7x**-0.5	0.29 (11)	-0.7x-0.6
PL3	0.51 (8)	**-0.8x**+0.2	(2)[a]	[a]	0.63 (19)	**-0.8x**-0.5	(5)[a]	[a]
PL4	(5)[a]	[a]	0.11 (7)	-0.3x+2.4	0.93 (7)	**-0.9x+1.5**	(6)[a]	[a]
PR1[+]	0.26 (14)	-0.5x**-9.1**	0.01 (9)	-0.2x-**10.2**	0.69 (24)	**-1.0x**-0.2	0.36 (28)	**-0.6x**+5.7

For each patient and for each trial type, the r^2 value, the number of accepted trials evaluated in each condition (*n*), and the regression equation (*Reg. eq.*) are given above.
Reg. eq. and r^2 values indicate relationship between:

ΣS2vsΣS1: ΣS2 amplitude (y=) and ΣS1 amplitude (x).

Bold type indicates significance within regression equation ($p<0.05$)

a: subject did not complete enough trials to determine reliable value ($n<7$)

[+]: indicates patient whose data is depicted in figures

[++]: coefficient significant, but in unexpected direction; no evidence of CD

Table 4.2: Saccade amplitude of second saccade of trial (S2amp): Analysis of our double step flashed data in our patients using the same approach as Duhamel et al. (1992), Tables 2 and 3

	ipsiL-contraL		**ipsiL-contraL-X**		**contraL-ipsiL**		**contraL-ipsiL-X**	
Expected S2amp (T2-T1)		**4°**		**6°**		**-4°**		**-6°**
Patient	*(n)*	*Stand.⁺ S2amp in deg (std)*	*(n)*	*Stand.⁺ S2amp in deg (std)*	*(n)*	*Stand.⁺ S2amp in deg (std)*	*(n)*	*Stand.⁺ S2amp in deg (std)*
PL1	(10)	1.8 (0.9)	(1)	1.0 (0)	(21)	-1.1 (1.8)	(8)	-1.0 (2.0)
PL2	(21)	2.6 (1.4)	(15)	1.1 (3.7)	(16)	-2.5 (1.7)	(11)	-2.5 (0.9)
PL3	(8)	4.5 (3.2)	(2)	3.3 (1.6)	(19)	-3.5 (2.2)	(5)	-0.3 (1.4)
PL4	(5)	3 (1.4)	(7)	1.5 (2.1)	(7)	-0.6 (2.2)	(6)	-3.4 (4.1)
Total	**44**		**25**		**63**		**30**	
Weighted average		**2.8**		**1.4**		**-2.1**		**-1.9**
PR1	(14)	**5.2** (5.1)	(9)	**5.1** (5.4)	(24)	**0.3** (7.1)	(28)	**-0.4** (6.4)
		3.5		**4.8**		**-0.9**		**-2.2**

For each patient and for each trial type, the number of trials evaluated (*n*) and the mean S2 amplitude on each trial type are given above (standard deviation in brackets: std).
⁺: S2 amplitude is standardized so that a positive value indicates the contralesional direction and a negative value indicates the ipsilesional direction.
◯ : circled values are the results published in Duhamel et al. (1992)

Table 5.1: Exogenous double step results summary for all accepted trials for each patient

Patient	**ipsiL-ipsiL**		**ipsiL-contraL**		**contraL-contraL**		**contraL-ipsiL**	
analysis	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*
PL1⁺								
ΣS2vsΣS1(ex1)	0.34(36)	**-0.6x-11.1**	0.74(20)	**-0.9x-6.5**	0.42(30)	**-1.5x+21.0**	0.86(23)	**-0.8x-4.2**
ΣS2vsΣS1(ex2)	0.31(20)	**-0.6x-12.6**	0.86(23)	**-0.8x-4.2**	0.72(26)	**-0.9x+18.2**	0.80(20)	**-1.2x+9.6**
PL2								
ΣS2vsΣS1(ex1)	0.88(21)	**-2.3x-28.2**	0.58(23)	**-1.3x**-9.8	0.64(11)	**-1.5x+35.2**	0.53(15)	**-1.4x**+10.9
ΣS2vsΣS1(ex2)	0.68(13)	**-0.9x-22.0**	0.26(21)	**-0.8x**-2.7	0.74(7)	**-1.8x+25.5**	0.50(13)	**-1.3x**+10.2
PL3								
ΣS2vsΣS1(ex1)	0.17(19)	-0.4x**-11.7**	0.56(14)	**-0.8x**-8.1	0.12(25)	-0.6x+**16.6**	0.76(23)	**-1.1x+7.0**
ΣS2vsΣS1(ex2)	0.52(12)	**-1.2x-24.7**	0.60(10)	**-1.6x-20.9**	0.33(19)	**-1.5x+22.8**	0.66(9)	**-0.7x**+1.1
PL4								
ΣS2vsΣS1(ex1)	0.88(7)	**-1.5x-19.7**	0(13)	0.0x+11.6	(4)[a]	[a]	(2)[a]	[a]
ΣS2vsΣS1(ex2)	(5)[a]	[a]	0.36(10)	-0.9x-6.5	(3)[a]	[a]	(1)[a]	[a]
PR1⁺								
ΣS2vsΣS1(ex1)	0.01(21)	-0.3x**+24.0**	0.77(15)	**-0.8x**+1.0	0.01(13)	0.1x-10.7	0.77(15)	**-1.0x**-2.9
ΣS2vsΣS1(ex2)	0.14(14)	-0.7x**+20.9**	0.80(7)	**-1.0x**+2.8	0.43(10)	**-1.5x-22.9**	0.74(13)	**-0.8x**-1.4
PR2								
ΣS2vsΣS1(ex1)	[b]	[b]	[b]	[b]	0.03(10)	-0.3x**-21.3**	0.81(9)	**-1.1x**-6.0
ΣS2vsΣS1(ex2)					0.16(8)	-0.5x**-23.5**	0.85(7)	**-0.8x**+2.0

For each patient and for each trial type, the r^2 value, the number of accepted values in each condition (*n*), and the regression equation (*Reg. eq.*) are given above. *Reg. eq.* and r^2 values indicate relationship between:

ΣS2vsΣS1: ΣS2 amplitude (y=) and ΣS1 amplitude (x).

Bold type indicates significance (<0.05) within regression equation

a: patient did not complete enough trials to determine reliable value (*n*<7)

b: patient was not available to participate in the task

⁺: indicates patient whose data is depicted in figures

Table 5.2: Endogenous double step results summary for all accepted trials for each patient

	Ipsilesional endogenous first saccade					
Patient	**ipsiL-ipsiL**		**ipsiL-contraL**		**ipsiL-contraL-X**	
analysis	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*
PL1[+]						
ΣS2vs(T-FEP1)	0.65(145)	**0.5x-1.3**	0.76(100)	**0.7x+3.9**	0.83(119)	**0.8x+5.1**
PL2						
ΣS2vs(T-FEP1)	0.71(139)	**0.7x-2.8**	0.23(79)	**0.4x+5.8**	0.04(84)	0.3x**+26.1**
PL3						
ΣS2vs(T-FEP1)	0.40(155)	**0.4x-2.3**	0.38(143)	**0.8x+1.7**	0.83(154)	**0.8x+2.9**
PL4						
ΣS2vs(T-FEP1)	0.24(71)	**0.2x-3.4**	0.01(22)	-0.1x**+3.4**	0.48(44)	**0.5x+8.0**
PR1[+]						
ΣS2vs(T-FEP1)	0.73(59)	**0.9x**+1.5	0.38(121)	**0.6x-3.4**	0.80(63)	**0.8x-6.0**
PR2						
ΣS2vs(T-FEP1)	b	b	b	b	0.42(51)	**0.6x**-2.3
	Contralesional endogenous first saccade					
Patient	**contraL-contraL**		**contraL-ipsiL**		**contraL-ipsiL-X**	
analysis	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*analysis*	$r^2(n)$	*Reg. eq.*
PL1[+]						
ΣS2vs(T-FEP1)	0.56(108)	**0.8x+2.6**	0.65(138)	**0.7x-5.2**	0.88(106)	**0.8x-2.2**
PL2						
ΣS2vs(T-FEP1)	0.17(70)	**0.3x+12.3**	0.46(33)	**0.8x-6.6**	0.66(101)	**0.7x-14.3**
PL3						
ΣS2vs(T-FEP1)	0.55(100)	**0.7x+5.1**	0.58(174)	**0.7x-3.7**	0.95(99)	**0.9x**-1.3
PL4						
ΣS2vs(T-FEP1)	0.32(35)	**0.4x+3.2**	0.27(32)	**0.3x-2.9**	0.63(22)	**0.7x**-5.4
PR1[+]						
ΣS2vs(T-FEP1)	0.35(102)	**0.3x-6.1**	0.12(87)	**0.2x+4.4**	0.97(65)	**1.1x**+0.1
PR2						
ΣS2vs(T-FEP1)	0.29(43)	**0.5x-5.3**	0.67(32)	**0.8x+8.7**	b	b

For each patient and for each trial type, the r^2 value, the number of accepted values in each condition (*n*), and the regression equation (*Reg. eq.*) are given above. *Reg. eq.* and r^2 values indicate relationship between:

ΣS2vs(T-FEP1): actual ΣS2 amplitude (y=) and expected ΣS2 amplitude defined as T-FEP1 (x).

Bold type indicates significance (<0.05) within regression equation

b: patient was not available to participate in the task

[+]: indicates patient whose data is depicted in figures

Supplementary materials

Suppl. Table 3.1: Breakdown of accepted trials for analysis

Subject	Task	Total trials	Total correct	Main reason for error
DR	Simple	157	73 (46%)	Falsestarts
	Delay	180	122 (68%)	Blinks
	Catch trials	207	138 (67%)	No movements
	Exog ipsiL-contraL	317	87 (27%)	Too many steps in S1
	Exog ipsiL-ipsiL	265	64 (24%)	Falsestarts
	Endog contraL-ipsiL	417	284 (68%)	Falsestarts
	Endog ipsiL-contraL	470	207 (43%)	Only one movement
	Endog ipsiL-ipsiL	480	287 (60%)	Only one movement
	Total	**2493**	**1262 (51%)**	
JB	Simple	180	102 (57%)	Falsestarts
	Delay	180	48 (27%)	Falsestarts
	Catch trials	230	141 (61%)	Falsestarts
	Exog ipsiL-contraL	320	218 (68%)	Falsestarts
	Exog ipsiL-ipsiL	289	162 (56%)	Only one movement
	Endog contraL-ipsiL	359	190 (53%)	Falsestarts
	Endog ipsiL-contraL	533	120 (42%)	Falsestarts
	Endog ipsiL-ipsiL	358	147 (41%)	Only one movement
	Total	**2449**	**1128 (46%)**	
SR	Simple	117	107 (91%)	Falsestarts
	Delay	43	39 (91%)	No movements
	Catch trials	47	46 (98%)	Falsestarts
	Exog ipsiL-contraL	73	69 (95%)	Falsestarts
	Exog ipsiL-ipsiL	50	47 (94%)	Falsestarts
	Endog contraL-ipsiL	154	145 (94%)	Only one movement
	Endog ipsiL-contraL	150	127 (85%)	Only one movement
	Endog ipsiL-ipsiL	154	142 (92%)	Falsestarts
	Total	**788**	**722 (92%)**	
MO	Simple	117	105 (90%)	Falsestarts
	Delay	120	114 (95%)	Falsestarts
	Catch trials	56	56 (100%)	NA
	Exog ipsiL-contraL	94	92 (98%)	Only one movement
	Exog ipsiL-ipsiL	84	81 (96%)	Only one movement
	Endog contraL-ipsiL	177	166 (94%)	Only one movement
	Endog ipsiL-contraL	171	161 (94%)	Only one movement
	Endog ipsiL-ipsiL	178	165 (93%)	Only one movement
	Total	**997**	**940 (94%)**	

Suppl. Table 3.2: Breakdown of number of saccades per trial

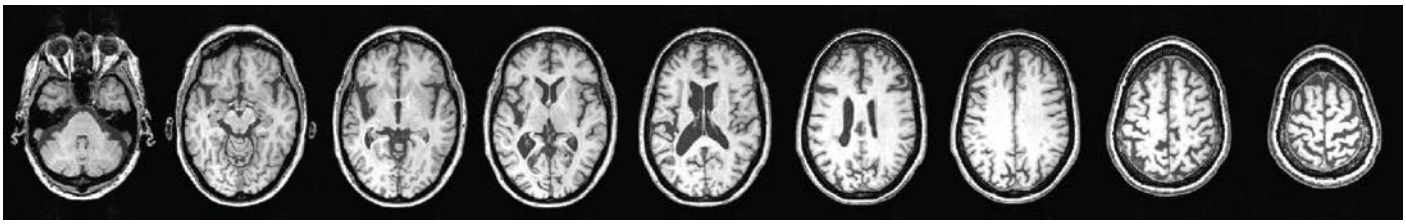
Subject	Task	Percentage of trials with the indicated number of saccades									
		S1					S2				
		1	2	3	4	Mean*	1	2	3	4	Mean*
DR	Simple	63	25	10	1	1.47					
	Delay	50	25	16	9	1.84					
	Catch	61	22	14	2	1.55					
	Exog IC	38	62			1.62	62	28	9	1	1.49
	Exog II	91	9			1.09	53	44	3	0	1.50
	Endog CI	50	50			1.50	49	35	10	6	1.73
	Endog IC	30	70			1.70	87	11	1	1	1.16
	Endog II	69	31			1.31	54	34	10	2	1.60
JB	Simple	66	24	10	0	1.44					
	Delay	63	29	8	0	1.45					
	Catch	41	36	18	4	1.84					
	Exog IC	82	18			1.18	46	38	15	1	1.71
	Exog II	84	16			1.16	43	41	15	1	1.74
	Endog CI	61	39			1.39	40	45	13	2	1.57
	Endog IC	53	47			1.47	78	21	1	0	1.23
	Endog II	83	17			1.17	39	46	14	1	1.81
SR	Simple	99	1	0	0	1.01					
	Delay	97	0	3	0	1.06					
	Catch	96	2	2	0	1.06					
	Exog IC	99	1			1.01	91	9	0	0	1.09
	Exog II	98	2			1.02	96	4	0	0	1.04
	Endog CI	90	10			1.10	81	18	1	0	1.20
	Endog IC	70	30			1.30	88	12	0	0	1.12
	Endog II	98	2			1.02	82	17	1	0	1.19
MO	Simple	86	10	4	0	1.18					
	Delay	92	7	1	0	1.09					
	Catch	48	45	7	0	1.59					
	Exog IC	73	27			1.27	88	12	0	0	1.12
	Exog II	84	16			1.16	69	30	1	0	1.32
	Endog CI	92	8			1.08	84	16	0	0	1.16
	Endog IC	78	22			1.22	80	14	5	1	1.26
	Endog II	75	25			1.25	64	31	5	0	1.41

*Here, mean refers to the mean number of saccades generated by each subject, in each trial type to attain each target location.

Suppl. Table 3.3: Compensation for ΣS1

Subject	Task	Coordinate	Correlation	Regression
DR	Exog ipsiL-contraL	Spatiotopic	0.53	0.8x-5.6
		Retinotopic	0.05	0.2x-14.7
	Exog ipsiL-ipsiL	Spatiotopic	0.58	0.8x-0.7
		Retinotopic	0.18	0.4x+1.7
	Endog contraL-ipsiL	Spatiotopic	0.90	x-4.3
		Retinotopic	0.70	1.5x+5.5
	Endog ipsiL-contraL	Spatiotopic	0.30	0.5x-4.9
		Retinotopic	0.08	-0.1x-3.7
	Endog ipsiL-ipsiL	Spatiotopic	0.39	0.8x-1.7
		Retinotopic	0.35	0.7x-5.7
JB	Exog ipsiL-contraL	Spatiotopic	0.69	0.7x+9.2
		Retinotopic	0.08	0.3x+13.4
	Exog ipsiL-ipsiL	Spatiotopic	0.71	0.7x+2.2
		Retinotopic	0.04	0.2x-4.9
	Endog contraL-ipsiL	Spatiotopic	0.74	0.7x+0.2
		Retinotopic	0.22	-0.5x+19.1
	Endog ipsiL-contraL	Spatiotopic	0.04	5.7
		Retinotopic	0.03	-0.1x+4.8
	Endog ipsiL-ipsiL	Spatiotopic	0.61	0.6x+2.7
		Retinotopic	0.44	0.5x+2.0
SR	Exog ipsiL-contraL	Spatiotopic	0.85	0.8x-3.3
		Retinotopic	0.08	0.3x-13.1
	Exog ipsiL-ipsiL	Spatiotopic	0.78	0.8x+0.8
		Retinotopic	0.24	0.3x+3.0
	Endog contraL-ipsiL	Spatiotopic	0.97	x-0.1
		Retinotopic	0.65	1.1x+13.3
	Endog ipsiL-contraL	Spatiotopic	0.84	0.8x-3.9
		Retinotopic	0.12	0.3x-16.4
	Endog ipsiL-ipsiL	Spatiotopic	0.87	0.9x-0.7
		Retinotopic	0.53	0.5x-1.1
MO	Exog ipsiL-contraL	Spatiotopic	0.72	0.7x+2.1
		Retinotopic	0.15	0.4x+13.0
	Exog ipsiL-ipsiL	Spatiotopic	0.79	0.9x+0.9
		Retinotopic	0.18	0.4x-2.2
	Endog contraL-ipsiL	Spatiotopic	0.91	x+1.6
		Retinotopic	0.29	-0.7x-23.0
	Endog ipsiL-contraL	Spatiotopic	0.83	0.9x+2.1
		Retinotopic	0.01	0.1x+17.8
	Endog ipsiL-ipsiL	Spatiotopic	0.83	x
		Retinotopic	0.53	0.7x+2.1

Suppl. Fig. 4.1: MRI image slices of PL1



Suppl. Table 4.1: Breakdown of number of trials with indicated number of saccades in our analysis of the classic double step task data for each patient (ipsilesional first saccade)

Patient	**Number of trials with the indicated number of saccades**								
Task	**S1**				**S2**				
	1	**2**	**3**	**Mean***	**1**	**2**	**3**	**4**	**Mean***
PL1									
ipsiL-contraL	9 (90%)	1 (10%)	0	1.1	7 (70%)	2 (20%)	1 (10%)	0	1.4
ipsiL-contraL-X	1 (100%)	0	0	1.0	1 (100%)	0	0	0	1.0
PL2									
ipsiL-contraL	19 (90%)	1 (5%)	1 (5%)	1.1	18 (86%)	3 (14%)	0	0	1.1
ipsiL-contraL-X	15 (100%)	0	0	1.0	13 (87%)	2 (13%)	0	0	1.1
PL3									
ipsiL-contraL	7 (88%)	1 (12%)	0	1.1	7 (88%)	1 (12%)	0	0	1.1
ipsiL-contraL-X	2 (100%)	0	0	1.0	2 (100%)	0	0	0	1.0
PL4									
ipsiL-contraL	5 (100%)	0	0	1.0	4 (80%)	1 (20%)	0	0	1.2
ipsiL-contraL-X	6 (86%)	1 (14%)	0	1.1	5 (72%)	2 (28%)	0	0	1.3
PR1									
ipsiL-contraL	11 (79%)	2 (14%)	1 (7%)	1.3	5 (36%)	5 (36%)	4 (29%)	0	2.0
ipsiL-contraL-X	6 (67%)	3 (33%)	0	1.3	5 (56%)	2 (22%)	2 (22%)	0	1.7
Total	**81/92 (88%)**	**9/92 (10%)**	**2/92 (2%)**	**1.1**	**67/92 (72%)**	**18/92 (20%)**	**7/92 (8%)**	**0/92 (0%)**	**1.3**

*Here, mean refers to the mean number of saccades generated by each patient, in each trial type to attain each target location.

Suppl. Table 4.2: Breakdown of number of trials with indicated number of saccades in our analysis of the classic double step task data for each patient (contralesional first saccade)

Patient	**Number of trials with the indicated number of saccades**								
Task	**S1**				**S2**				
	1	**2**	**3**	**Mean***	**1**	**2**	**3**	**4**	**Mean***
PL1									
contraL-ipsiL	16 (76%)	5 (24%)	0	1.2	17 (81%)	2 (10%)	1 (5%)	1 (5%)	1.4
contraL-ipsiL-X	5 (63%)	3 (38%)	0	1.4	7 (88%)	1 (13%)	0	0	1.1
PL2									
contraL-ipsiL	12 (75%)	4 (25%)	0	1.3	11 (69%)	4 (25%)	1 (6%)	0	1.4
contraL-ipsiL-X	11 (100%)	0	0	1.0	8 (73%)	1 (9%)	2 (18%)	0	1.4
PL3									
contraL-ipsiL	17 (89%)	2 (11%)	0	1.1	16 (84%)	1 (5%)	0	2 (10%)	1.4
contraL-ipsiL-X	3 (60%)	2 (40%)	0	1.4	4 (80%)	1 (20%)	0	0	1.2
PL4									
contraL-ipsiL	4 (57%)	3 (43%)	0	1.4	4 (57%)	2 (29%)	1 (14%)	0	1.6
contraL-ipsiL-X	4 (67%)	1 (17%)	1 (17%)	1.5	4 (66%)	2 (33%)	0	0	1.3
PR1									
contraL-ipsiL	10 (42%)	11 (46%)	3 (13%)	1.7	7 (29%)	7 (29%)	5 (21%)	5 (21%)	2.3
contraL-ipsiL-X	14 (50%)	6 (21%)	8 (29%)	1.8	6 (21%)	8 (29%)	9 (32%)	5 (18%)	2.5
Mean	**96/145 (66%)**	**37/145 (26%)**	**12/145 (8%)**	**1.4**	**84/145 (58%)**	**29/145 (20%)**	**19/145 (13%)**	**13/145 (9%)**	**1.7**

*Here, mean refers to the mean number of saccades generated by each patient, in each trial type to attain each target location.

Suppl. Table 4.3: Breakdown of number of accepted classic double step task trials for each trial type for each patient in our analysis (ipsilesional first saccade)

Patient	Task	Total trials	Total accepted	Total rejected	Main reason for error
PL1					
	ipsiL-contraL	37	10 (27%)	27 (73%)	Only one ipsiL movement
	ipsiL-contraL-X	32	1 (3%)	31 (97%)	No movement
	Total	**69**	**11 (16%)**	**58 (84%)**	
PL2					
	ipsiL-contraL	64	21 (33%)	43 (67%)	Falsestarts
	ipsiL-contraL-X	55	15 (27%)	40 (73%)	Wrong order
	Total	**119**	**36 (30%)**	**83 (70%)**	
PL3					
	ipsiL-contraL	25	8 (32%)	17 (68%)	No movement
	ipsiL-contraL-X	28	2 (7%)	26 (93%)	No movement
	Total	**53**	**10 (19%)**	**43 (81%)**	
PL4					
	ipsiL-contraL	26	5 (19%)	21 (81%)	No movement
	ipsiL-contraL-X	25	7 (28%)	18 (72%)	No movement
	Total	**51**	**12 (24%)**	**39 (76%)**	
PR1					
	ipsiL-contraL	43	14 (33%)	29 (67%)	Wrong order
	ipsiL-contraL-X	41	9 (22%)	32 (78%)	Wrong order
	Total	**84**	**23 (27%)**	**61 (73%)**	

Suppl. Table 4.4: Breakdown of number of accepted classic double step task trials for each trial type for each patient in our analysis (contralesional first saccade)

Patient	Task	Total trials	Total accepted	Total rejected	Main reason for error
PL1					
	contraL-ipsiL	47	21 (45%)	26 (55%)	Only one contraL movement
	contraL-ipsiL-X	41	8 (20%)	33 (80%)	No movement
	Total	**88**	**29 (33%)**	**59 (67%)**	
PL2					
	contraL-ipsiL	59	16 (27%)	43 (73%)	Falsestarts
	contraL-ipsiL-X	48	11 (23%)	37 (77%)	Falsestarts
	Total	**107**	**27 (25%)**	**80 (75%)**	
PL3					
	contraL-ipsiL	33	19 (58%)	14 (42%)	No movement
	contraL-ipsiL-X	34	5 (15%)	29 (85%)	No movement
	Total	**67**	**24 (36%)**	**43 (64%)**	
PL4					
	contraL-ipsiL	30	7 (23%)	23 (77%)	Wrong order
	contraL-ipsiL-X	35	6 (17%)	29 (83%)	Only one contraL movement
	Total	**65**	**13 (20%)**	**52 (80%)**	
PR1					
	contraL-ipsiL	38	24 (36%)	14 (64%)	Blinks
	contraL-ipsiL-X	53	28 (53%)	25 (47%)	Falsestarts
	Total	**91**	**52 (57%)**	**39 (43%)**	

Suppl. Table 4.5: Breakdown of number of trials which were accepted using our analysis methods and were subsequently rejected when processed using Heide et al. (1995) methods because ΣS2 began after 1000ms after the start of the trial

Patient	**ipsiL-contraL**	**ipsiL-contraL-X**	**contraL-ipsiL**	**contraL-ipsiL-X**
PL1	9/10 (90%)	1/1 (100%)	21/21 (100%)	8/8 (100%)
PL2	9/21 (43%)	8/15 (76%)	13/16 (81%)	8/11 (73%)
PL3	1/8 (12%)	1/2 (50%)	7/19 (37%)	4/5 (80%)
PL4	0/5 (0%)	5/7 (71%)	5/7 (71%)	4/6 (66%)
Total (left patients)	**19/44 (43%)**	**15/25 (60%)**	**46/63 (73%)**	**25/30 (83%)**
PR1	**4/14 (29%)**	**4/9 (44%)**	**11/24 (46%)**	**15/28 (54%)**
	All ipsiL first saccades (right and left patients):	**42/92 (46%)**	**All contraL first saccades (right and left patients):**	**96/145 (66%)**

Suppl. Table 4.6: Our analysis (ΣS2vsΣS1) of the classic double step data processed as in Duhamel et al. (1992) for each patient (i.e.: only the first two saccades in each trial were evaluated)

	ipsiL-contraL		**ipsiL-contraL-X**		**contraL-ipsiL**		**contraL-ipsiL-X**	
Patient	*r^2(n)*	*Reg. eq.*	*r^2(n)*	*Reg. eq.*	*r^2(n)*	*Reg. eq.*	*r^2(n)*	*Reg. eq.*
PL1	0.02(10)	-0.1x**+1.5**	(1)[a]	[a]	0.00(21)	0.1x-1.2	0.03(8)	0.4x-1.5
PL2	0.25(21)	**-0.5x**+1.1	0.81(15)	**-1.5x**+0.4	0.00(16)	-0.1x-2.1	0.07(11)	-0.4x-1.4
PL3	0.71(8)	**-1.3x**-2.7	(2)[a]	[a]	0.70(19)	**-0.9x**+0.5	(5)[a]	[a]
PL4	(5)[a]	[a]	0.01(7)	-0.3x+0.8	0.59(7)	**-1.3x**+5.0	(6)[a]	[a]
PR1	0.00(14)	-0.1x-4.8	0.00(9)	-0.7x-3.4	0.19(24)	**-1.1x**-5.4	0.4(28)	**-1.0-6.0**

For each patient and for each trial type, the r^2 value, the number of accepted trials evaluated in each condition (*n*), and the regression equation (*Reg. eq.*) are given above.
Reg. eq. and r^2 values indicate relationship between:

ΣS2vsΣS1: ΣS2 amplitude (y=) and ΣS1 amplitude (x).

Bold type indicates significance within regression equation ($p<0.05$)

a: subject did not complete enough trials to determine reliable value ($n<7$)

Suppl. Table 4.7: Analysis of our double step flashed data using the same approach as Heide et al. (1995), Fig. 5: absolute saccade end-position error measured 1000ms after trial start, (Σ|(T2-EP@1000ms)|/n)***

	ipsiL-contraL		**ipsiL-contraL-X**		**contraL-ipsiL**		**contraL-ipsiL-X**	
T2 location		**-2°**		**3°**		**2°**		**-3°**
Patient	*(n)*	*T2-EP@1000ms in deg (std)*	*(n)*	*T2-EP@1000ms in deg (std)*	*(n)*	*T2-EP@1000ms in deg (std)*	*(n)*	*T2-EP@1000ms in deg (std)*
PL1	(1)	0.4 (0)	(0)		(0)		(0)	
PL2	(12)	1.6 (1.4)	(7)	2.4 (1.1)	(3)	1.5 (1.3)	(3)	4.0 (0.3)
PL3	(7)	1.4 (1.1)	(1)	2.6 (0)	(12)	1.4 (1.2)	(1)	3.6 (0)
PL4	(5)	1.3 (1.2)	(2)	2.9 (0.8)	(2)	0.2 (0.1)	(2)	2.2 (1.5)
Total	**23**		**10**		**17**		**6**	
Weighted average		**1.6**		**2.5**		**1.3**		**3.3**
		~1.1		**~3.0**		**~1.1**		**~4.1**
PR1	(10)	**8.3** (3.6)	(5)	**5.8** (3.8)	(13)	**4.0** (3.2)	(13)	**4.1** (2.0)
		~2.0		**~4.5**		**~4.0**		**~5.0**

For each patient and for each trial type, the number of trials evaluated (*n*) and the absolute mean T2 minus eye position (EP) at 1000ms after the GO signal (i.e.: absolute eye position error from T2 at 1000ms after trial start) are given above (standard deviation in brackets: std).

◯ : circled values are the results published in Heide et al. (1995)

***: the main values presented in this table are represented graphically in Fig. 5

Suppl. Table 4.8: Our analysis (ΣS2vsΣS1) of the classic double step data processed as in Heide et al. (1995) for each patient (i.e.: only trials in which ΣS2 began before 1000ms after the start of the trial were evaluated and ΣS2 amplitude was determined using the eye position at 1000ms)

	ipsiL-contraL		**ipsiL-contraL-X**		**contraL-ipsiL**		**contraL-ipsiL-X**	
Patient	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*	$r^2(n)$	*Reg. eq.*
PL1	(1)[a]	[a]	(0)[a]	[a]	(0)[a]	[a]	(0)[a]	[a]
PL2	0.21(12)	-0.7x+0.6	0.44(7)	**-**0.6x+1.0	(3)[a]	[a]	(3)[a]	[a]
PL3	0.5(7)	-0.7x+0.9	(1)[a]	[a]	0.09(12)	-0.7x+1.1	(1)[a]	[a]
PL4	(5)[a]	[a]	(2)[a]	[a]	(2)[a]	[a]	(2)[a]	[a]
PR1	0.04(10)	0.3x**-10.4**	(5)[a]		0.05(13)	-0.2x+1.5	0.06(13)	-0.3x+2.3

For each patient and for each trial type, the r^2 value, the number of accepted trials evaluated in each condition (*n*), and the regression equation (*Reg. eq.*) are given above.
Reg. eq. and r^2 values indicate relationship between:

ΣS2vsΣS1: ΣS2 amplitude (y=) and ΣS1 amplitude (x).

Bold type indicates significance within regression equation ($p<0.05$)

a: subject did not complete enough trials to determine reliable value ($n<7$)

Suppl. Table 5.1: Breakdown of control trials accepted for analysis

Patient	Task	Total trials	Total accepted	Total rejected	Main reason for error
PL1	Control				
	ipsiL	118	101 (86%)	16 (14%)	False starts
	contraL	115	81 (70%)	34 (30%)	False starts
PL2	Control				
	ipsiL	112	43 (38%)	69 (62%)	False starts
	contraL	53	8 (15%)	45 (85%)	False starts
PL3	Control				
	ipsiL	60	54 (90%)	6 (10%)	False starts
	contraL	60	56 (93%)	4 (7%)	No movement
PL4	Control				
	ipsiL	59	53 (90%)	6 (10%)	False starts
	contraL	60	48 (80%)	12 (20%)	False starts
PR1	Control				
	ipsiL	53	41 (77%)	12 (23%)	False starts
	contraL	50	33 (66%)	17 (34%)	False starts
PR2	Control				
	ipsiL	[a]	[a]	[a]	[a]
	contraL	54	31 (57%)	23 (43%)	False starts

a: patient not available to participate in this task

Suppl. Table 5.2: Breakdown of exogenous double step task trials with ipsilesional first saccade accepted for analysis

Patient	Task	Total trials	Total accepted	Total rejected	Main reason for error
PL1	Exogenous double step flashed				
	ipsiL-ipsiL	193	135 (70%)	58 (30%)	Only one ipsiL sac
	ipsiL-contraL	180	138 (77%)	42 (23%)	Only one ipsiL sac
	Total	**373**	**273 (73%)**	**100 (27%)**	
PL2	Exogenous double step flashed				
	ipsiL-ipsiL	139	89 (64%)	50 (36%)	Wrong order
	ipsiL-contraL	144	104 (72%)	40 (28%)	Wrong order
	Total	**283**	**193 (68%)**	**90 (32%)**	
PL3	Exogenous double step flashed				
	ipsiL-ipsiL	92	90 (98%)	2 (2%)	Too many S1s
	ipsiL-contraL	83	61 (73%)	22 (27%)	Too many S1s
	Total	**175**	**151 (86%)**	**24 (14%)**	
PL4	Exogenous double step flashed				
	ipsiL-ipsiL	106	44 (42%)	62 (58%)	False starts to T2
	ipsiL-contraL	111	49 (44%)	62 (66%)	False starts to T2
	Total	**217**	**93 (43%)**	**124 (57%)**	
Total (all left patients)		**1048**	**710 (68%)**	**338 (32%)**	
PR1	Exogenous double step flashed				
	ipsiL-ipsiL	104	72 (69%)	32 (31%)	False starts to T2
	ipsiL-contraL	103	49 (48%)	54 (52%)	Wrong order
	Total	**207**	**121 (58%)**	**86 (42%)**	
Total (all right patients)		**207**	**121 (58%)**	**86 (42%)**	

Suppl. Table 5.3: Breakdown of exogenous double step task trials with contralesional first saccade accepted for analysis

Patient	Task	Total trials	Total accepted	Total rejected	Main reason for error
PL1	Exogenous double step flashed				
	contraL-contraL	181	136 (75%)	45 (25%)	Only one contraL sac
	contraL-ipsiL	156	107 (69%)	49 (31%)	Only one contraL sac
	Total	**337**	**243 (72%)**	**91 (27%)**	
PL2	Exogenous double step flashed				
	contraL-contraL	102	41 (40%)	61 (60%)	Only one contraL sac
	contraL-ipsiL	116	57 (49%)	59 (51%)	Only one contraL sac
	Total	**218**	**98 (45%)**	**120 (55%)**	
PL3	Exogenous double step flashed				
	contraL-contraL	201	129 (64%)	72 (36%)	Only one contraL sac
	contraL-ipsiL	113	51 (45%)	62 (55%)	False starts to T2
	Total	**314**	**180 (57%)**	**134 (43%)**	
PL4	Exogenous double step flashed				
	contraL-contraL	91	14 (15%)	77 (85%)	False starts to T2
	contraL-ipsiL	117	6 (5%)	111 (95%)	False starts to T2
	Total	**208**	**20 (10%)**	**188 (90%)**	
	Total (all left patients)	**1077**	**541 (51%)**	**533 (49%)**	
PR1	Exogenous double step flashed				
	contraL-contraL	151	53 (35%)	98 (65%)	False starts to T2
	contraL-ipsiL	152	60 (39%)	92 (61%)	False starts to T2
	Total	**303**	**113 (37%)**	**190 (63%)**	
PR2	Exogenous double step flashed				
	contraL-contraL	86	32 (37%)	54 (63%)	Doesn't start at 0
	contraL-ipsiL	88	37 (42%)	51 (58%)	Doesn't start at 0
	Total	**174**	**69 (40%)**	**105 (60%)**	
	Total (all right patients)	**477**	**182 (48%)**	**295 (62%)**	

Suppl. Table 5.4: Breakdown of endogenous double step task trials with ipsilesional first saccade accepted for analysis

Patient	Task	Total trials	Total accepted	Total rejected	Main reason for error
PL1	Endogenous double step				
	ipsiL-ipsiL	239	145 (61%)	94 (39%)	Blinks
	ipsiL-contraL	178	100 (56%)	78 (44%)	False starts
	ipsiL-contraL-X	123	119 (97%)	4 (3%)	False starts
	Total	**540**	**364 (67%)**	**176 (33%)**	
PL2	Endogenous double step				
	ipsiL-ipsiL	179	139 (78%)	40 (22%)	False starts
	ipsiL-contraL	178	79 (44%)	99 (56%)	False starts
	ipsiL-contraL-X	85	84 (99%)	1 (1%)	False starts
	Total	**442**	**302 (68%)**	**140 (32%)**	
PL3	Endogenous double step				
	ipsiL-ipsiL	175	155 (89%)	20 (11%)	False starts
	ipsiL-contraL	175	143 (82%)	32 (18%)	Only one ipsiL sac
	ipsiL-contraL-X	178	154 (87%)	24 (13%)	No real movement
	Total	**528**	**452 (86%)**	**76 (14%)**	
PL4	Endogenous double step				
	ipsiL-ipsiL	120	71 (59%)	49 (41%)	False starts
	ipsiL-contraL	180	22 (12%)	158 (88%)	False starts
	ipsiL-contraL-X	169	44 (26%)	125 (74%)	False starts
	Total	**469**	**137 (29%)**	**332 (71%)**	
Total (all left patients)		**1979**	**1255 (63%)**	**724 (37%)**	
PR1	Endogenous double step				
	ipsiL-ipsiL	155	59 (38%)	96 (62%)	False starts
	ipsiL-contraL	237	121 (51%)	116 (49%)	False starts
	ipsiL-contraL-X	70	63 (90%)	7 (10%)	False starts
	Total	**462**	**243 (53%)**	**219 (47%)**	
PR2	Endogenous double step				
	ipsiL-ipsiL	a	a	a	a
	ipsiL-contraL	a	a	a	a
	ipsiL-contraL-X	153	51 (33%)	102 (67%)	False starts
	Total	**153**	**51 (33%)**	**102 (67%)**	
Total (all right patients)		**615**	**294 (48%)**	**321 (52%)**	

a: patient not available to participate in this task

Suppl. Table 5.5: Breakdown of endogenous double step task trials with contralesional first saccade accepted for analysis

Patient	Task	Total trials	Total accepted	Total rejected	Main reason for error
PL1	Endogenous double step				
	contraL-contraL	180	108 (60%)	72 (40%)	False starts
	contraL-ipsiL	180	138 (77%)	42 (23%)	False starts
	contraL-ipsiL-X	180	106 (59%)	74 (41%)	False starts
	Total	**540**	**352 (65%)**	**188 (35%)**	
PL2	Endogenous double step				
	contraL-contraL	175	70 (40%)	105 (60%)	False starts
	contraL-ipsiL	167	33 (20%)	134 (80%)	False starts
	contraL-ipsiL-X	167	101 (60%)	66 (40%)	False starts
	Total	**509**	**204 (40%)**	**305 (60%)**	
PL3	Endogenous double step				
	contraL-contraL	171	109 (64%)	62 (36%)	No movement
	contraL-ipsiL	232	174 (75%)	58 (25%)	No movement
	contraL-ipsiL-X	120	99 (83%)	21 (17%)	False starts
	Total	**523**	**382 (73%)**	**141 (27%)**	
PL4	Endogenous double step				
	contraL-contraL	120	35 (29%)	85 (71%)	False starts
	contraL-ipsiL	180	32 (18%)	148 (82%)	False starts
	contraL-ipsiL-X	120	22 (18%)	98 (82%)	False starts
	Total	**420**	**89 (21%)**	**331 (79%)**	
	Total (all left patients)	**1992**	**1027 (52%)**	**965 (48%)**	
PR1	Endogenous double step				
	contraL-contraL	195	101 (52%)	94 (48%)	False starts
	contraL-ipsiL	167	87 (52%)	80 (48%)	False starts
	contraL-ipsiL-X	167	65 (39%)	102 (61%)	False starts
	Total	**529**	**253 (48%)**	**276 (52%)**	
PR2	Endogenous double step				
	contraL-contraL	117	43 (37%)	74 (63%)	False starts
	contraL-ipsiL	116	32 (28%)	84 (72%)	False starts
	contraL-ipsiL-X	[a]	[a]	[a]	[a]
	Total	**233**	**75 (32%)**	**158 (68%)**	
	Total (all right patients)	**762**	**328 (43%)**	**434 (57%)**	

a: patient not available to participate in this task

Suppl. Table 5.6: Breakdown of number of saccades per trial in control tasks accepted for analysis

Patient	Task	Percentage of trials with the indicated number of saccades				
		1	**2**	**3**	**4**	**Mean***
PL1	Control					
	ipsiL	92	8	0	0	1.1
	contraL	57	38	5	0	1.5
PL2	Control					
	ipsiL	24	56	15	0	1.9
	contraL	53	42	0	5	1.6
PL3	Control					
	ipsiL	69	20	11	0	1.4
	contraL	57	41	2	0	1.5
PL4	Control					
	ipsiL	51	42	8	0	1.6
	contraL	52	40	6	2	1.6
PR1	Control					
	ipsiL	80	18	2	0	1.2
	contraL	90	8	2	0	1.1
PR2	Control					
	ipsiL	a	a	a	a	a
	contraL	6	61	13	19	2.4

a: patient not available to participate in this task
*Here, mean refers to the mean number of saccades generated by each patient, in each trial type to attain each target location.

Suppl. Table 5.7: Breakdown of number of saccades per trial in exogenous double step tasks with ipsilesional first saccade accepted for analysis

Patient	Task	Percentage of trials with the indicated number of saccades								
		S1				S2				
		1	2	3	Mean*	1	2	3	4	Mean*
PL1	Exogenous double step flashed									
	ipsiL-ipsiL	99	1	0	1.0	93	7	0	0	1.1
	ipsiL-contraL	96	4	0	1.0	90	9	0	1	1.1
PL2	Exogenous double step flashed									
	ipsiL-ipsiL	84	15	1	1.2	78	18	3	1	1.3
	ipsiL-contraL	73	25	2	1.3	60	38	3	0	1.5
PL3	Exogenous double step flashed									
	ipsiL-ipsiL	70	28	2	1.3	49	41	9	1	1.6
	ipsiL-contraL	52	23	26	1.8	67	31	0	2	1.4
PL4	Exogenous double step flashed									
	ipsiL-ipsiL	91	9	0	1.1	80	18	2	0	1.2
	ipsiL-contraL	86	14	0	1.1	61	33	6	0	1.5
PR1	Exogenous double step flashed									
	ipsiL-ipsiL	79	21	0	1.2	53	36	7	4	1.6
	ipsiL-contraL	31	57	12	1.8	73	20	6	0	1.3

*Here, mean refers to the mean number of saccades generated by each patient, in each trial type to attain each target location.

Suppl. Table 5.8: Breakdown of number of saccades per trial in exogenous double step tasks with contralesional first saccade accepted for analysis

Patient	Task	Percentage of trials with the indicated number of saccades							
		S1				S2			
		1	2	3	Mean*	1	2	3	4	Mean*
PL1	Exogenous double step flashed									
	contraL-contraL	99	1	0	1.0	91	7	1	0	1.1
	contraL-ipsiL	95	5	0	1.1	84	15	1	0	1.2
PL2	Exogenous double step flashed									
	contraL-contraL	88	12	0	1.1	78	22	0	0	1.2
	contraL-ipsiL	95	5	0	1.1	84	12	4	0	1.2
PL3	Exogenous double step flashed									
	contraL-contraL	91	7	1	1.1	62	35	3	0	1.4
	contraL-ipsiL	40	40	20	1.8	73	26	0	0	1.3
PL4	Exogenous double step flashed									
	contraL-contraL	79	14	7	1.3	57	14	21	7	1.8
	contraL-ipsiL	67	33	0	1.3	83	17	0	0	1.2
PR1	Exogenous double step flashed									
	contraL-contraL	66	25	9	1.4	64	26	8	2	1.5
	contraL-ipsiL	70	23	7	1.4	70	27	3	0	1.3
PR2	Exogenous double step flashed									
	contraL-contraL	91	9	0	1.1	41	38	16	6	1.9
	contraL-ipsiL	84	16	0	1.2	57	27	16	0	1.6

*Here, mean refers to the mean number of saccades generated by each patient, in each trial type to attain each target location.

Suppl. Table 5.9: Breakdown of number of saccades per trial in endogenous double step tasks with ipsilesional first saccade accepted for analysis

Patient	Task	Percentage of trials with the indicated number of saccades								
		S1				S2				
		1	2	3	Mean*	1	2	3	4	Mean*
PL1	Endogenous double step									
	ipsiL-ipsiL	86	14	0	1.2	72	24	3	0	1.3
	ipsiL-contraL	77	22	1	1.2	54	41	5	0	1.5
	ipsiL-contraL-X	73	24	3	1.3	31	40	18	8	2.0
PL2	Endogenous double step									
	ipsiL-ipsiL	67	29	5	1.4	65	31	36	0	2.4
	ipsiL-contraL	38	51	11	1.7	71	23	8	0	1.4
	ipsiL-contraL-X	61	37	2	1.4	27	32	29	11	2.2
PL3	Endogenous double step									
	ipsiL-ipsiL	70	27	3	1.3	45	41	14	1	1.7
	ipsiL-contraL	44	38	17	1.7	79	19	2	0	1.2
	ipsiL-contraL-X	82	18	0	1.2	55	43	2	0	1.5
PL4	Endogenous double step									
	ipsiL-ipsiL	84	13	3	1.2	80	17	3	0	1.2
	ipsiL-contraL	81	5	14	1.3	45	50	5	0	1.6
	ipsiL-contraL-X	59	23	18	1.6	2	41	32	25	2.8
PR1	Endogenous double step									
	ipsiL-ipsiL	63	27	10	1.5	53	41	7	0	1.6
	ipsiL-contraL	27	41	31	2.0	50	33	15	1	1.7
	ipsiL-contraL-X	54	38	8	1.5	73	24	2	0	1.3
PR2	Endogenous double step									
	ipsiL-ipsiL	a	a	a	a	a	a	a	a	a
	ipsiL-contraL	a	a	a	a	a	a	a	a	a
	ipsiL-contraL-X	61	29	10	1.5	37	31	20	12	2.1

a: patient not available to participate in this task

*Here, mean refers to the mean number of saccades generated by each patient, in each trial type to attain each target location.

Suppl. Table 5.10: Breakdown of number of saccades per trial in endogenous double step tasks with contralesional first saccade accepted for analysis

Patient	Task	Percentage of trials with the indicated number of saccades								
		S1				S2				
		1	2	3	Mean*	1	2	3	4	Mean*
PL1	Endogenous double step									
	contraL-contraL	30	50	20	1.9	42	42	15	1	1.7
	contraL-ipsiL	51	42	7	1.6	43	36	19	2	1.8
	contraL-ipsiL-X	67	29	4	1.4	39	56	6	0	1.7
PL2	Endogenous double step									
	contraL-contraL	76	23	1	1.3	60	33	7	0	1.5
	contraL-ipsiL	28	59	13	1.9	50	38	13	3	1.8
	contraL-ipsiL-X	33	60	7	1.7	34	46	18	2	1.9
PL3	Endogenous double step									
	contraL-contraL	57	39	4	1.5	55	38	7	0	1.5
	contraL-ipsiL	75	23	2	1.3	88	11	1	0	1.1
	contraL-ipsiL-X	43	47	11	1.7	69	29	2	0	1.3
PL4	Endogenous double step									
	contraL-contraL	60	40	0	1.4	46	26	20	9	1.9
	contraL-ipsiL	22	34	44	2.2	91	6	3	0	1.1
	contraL-ipsiL-X	41	59	0	1.6	41	36	18	5	1.9
PR1	Endogenous double step									
	contraL-contraL	72	25	4	1.3	50	39	10	1	1.6
	contraL-ipsiL	63	32	5	1.4	49	40	7	3	1.6
	contraL-ipsiL-X	26	64	11	1.9	50	39	8	2	1.6
PR2	Endogenous double step									
	contraL-contraL	67	19	14	1.5	42	37	12	9	1.9
	contraL-ipsiL	13	41	47	2.4	44	44	13	0	1.7
	contraL-ipsiL-X	a	a	a	a	a	a	a	a	a

a: patient not available to participate in this task
*Here, mean refers to the mean number of saccades generated by each patient, in each trial type to attain each target location.

Suppl. Table 5.11: Control and exogenous double step results for all accepted trials with ipsilesional first saccade

Patient	**ipsiL-ipsiL**			**ipsiL-contraL**		
analysis	$r^2(n)$	*Reg. eq.*	*P*	$r^2(n)$	*Reg. eq.*	*P*
PL1[+]						
Ctl:FEPvsT	0.89(101)	**0.6x-1.1**	<0.001[a]/<0.01[a]			
FEP1vsT1	0.78(135)	**0.9x**-0.1	<0.001[a]/0.77	0.43(138)	**0.3x-4.8**	<0.001[a]/<0.001[a]
ΣS2vs(T2-FEP1)	0.42(135)	**0.4x-1.2**	<0.001[a]/0.03[a]	0.45(138)	**0.5x+2.9**	<0.001[a]/<0.001[a]
ΣS2vsΣS1(ex1)	0.34(36)	**-0.6x-11.1**	<0.001[a]/<0.001[a]	0.74(23)	**-0.9x-6.5**	<0.001[a]/<0.01[a]
ΣS2vsΣS1(ex2)	0.31(20)	**-0.6x-12.6**	<0.01[a]/<0.001[a]	0.86(20)	**-0.8x-4.2**	<0.001[a]/<0.001[a]
PL2						
Ctl:FEPvsT	0.89(43)	**0.8x**-1.2	<0.001[a]/0.15			
FEP1vsT1	0.54(89)	**0.8x-2.0**	<0.001[a]/<0.01[a]	0.38(104)	**0.5x-8.0**	<0.001[a]/<0.001[a]
ΣS2vs(T2-FEP1)	0.32(89)	**0.6x-6.3**	<0.001[a]/<0.001[a]	0.54(104)	**0.8x+5.7**	<0.001[a]/<0.001[a]
ΣS2vsΣS1(ex1)	0.88(21)	**-2.3x-28.2**	<0.001[a]/<0.001[a]	0.58(23)	**-1.3x**-9.8	<0.001[a]/0.08
ΣS2vsΣS1(ex2)	0.68(13)	**-0.9x-22.0**	<0.001[a]/<0.001[a]	0.26(21)	**-0.8x**-2.7	0.02[a]/0.61
PL3						
Ctl:FEPvsT	0.84(54)	**0.7x**-0.4	<0.001[a]/0.56			
FEP1vsT1	0.52(90)	**0.6x-5.2**	<0.001[a]/<0.001[a]	0.77(61)	**0.8x**-1.5	<0.001[a]/0.20
ΣS2vs(T2-FEP1)	0.59(90)	**0.8x**-1.0	<0.001[a]/0.18	0.52(61)	**0.5x+1.9**	<0.001[a]/<0.01[a]
ΣS2vsΣS1(ex1)	0.17(19)	-0.4x**-11.7**	0.08/<0.01[a]	0.56(14)	**-0.8x**-8.1	<0.01[a]/0.11
ΣS2vsΣS1(ex2)	0.52(12)	**-1.2x-24.7**	<0.01[a]/<0.001[a]	0.60(10)	**-1.6x-20.9**	<0.01[a]/0.03[a]
PL4						
Ctl:FEPvsT	0.86(53)	**0.8x-3.5**	<0.001[a]/<0.001[a]			
FEP1vsT1	0.82(44)	**0.8x-1.8**	<0.001[a]/0.04[a]	0.64(49)	**0.7x-4.5**	<0.001[a]/<0.01[a]
ΣS2vs(T2-FEP1)	0.69(44)	**0.9x**+2.5	<0.001[a]/0.17	0.65(49)	**0.8x+4.0**	<0.001[a]/<0.001[a]
ΣS2vsΣS1(ex1)	0.88(7)	**-1.5x-19.7**	<0.01[a]/<0.001[a]	0(13)	0.0x+11.6	0.95/0.20
ΣS2vsΣS1(ex2)	(5)[b]	[b]	[b]	0.36(10)	-0.9x-6.5	0.07/0.52
PR1[+]						
Ctl:FEPvsT	0.96(41)	**0.9x**-0.3	<0.001[a]/0.53			
FEP1vsT1	0.90(72)	**1.1x-1.9**	<0.001[a]/<0.001[a]	0.84(49)	**1.1x**-1. 9	<0.001[a]/0.19
ΣS2vs(T2-FEP1)	0.81(72)	**1.0x+2.7**	<0.001[a]/<0.01[a]	0.87(49)	**1.0x-2.2**	<0.001[a]/<0.01[a]
ΣS2vsΣS1(ex1)	0.01(21)	-0.3x**+24.0**	0.62/<0.001[a]	0.77(15)	**-0.8x**+1.0	<0.001[a]/0.70
ΣS2vsΣS1(ex2)	0.14(14)	-0.7x**+20.9**	0.18/<0.001[a]	0.80(7)	**-1.0x**+2.8	0.02[a]/0.68

For each patient and for each trial type, the r^2 value, the number of accepted values in each condition (*n*), the regression equation (*Reg. eq.*), and the *P* value for the regression coefficient and intercept are given above. *Reg. eq.* and r^2 values indicate relationship between:

Ctl:FEPvsT: FEP (y=) and target location (x), as in Fig. 3B and 3C;

FEP1vsT1: FEP1 (y=) and target location (x), as in Fig. 3D and 3E;

ΣS2vs(T2-FEP1): actual ΣS2 amplitude (y=) and expected ΣS2 amplitude defined as T2-FEP1 (x), as in Fig. 4B and 4C;

ΣS2vsΣS1: ΣS2 amplitude (y=) and ΣS1 amplitude (x), as in Fig. 5.

a: indicates a significant P value, **bold** type indicates significance within regression equation

b: patient did not complete enough trials to determine reliable value (*n*<7)

[+]: indicates patient whose data is depicted in figures

Suppl. Table 5.12: Control and exogenous double step results for all accepted trials with contralesional first saccade

Patient	**contraL-contraL**			**contraL-ipsiL**		
analysis	*r^2(n)*	*Reg. eq.*	*P*	*r^2(n)*	*Reg. eq.*	*P*
PL1[+]						
Ctl:FEPvsT	0.93(81)	**0.9x**+0.1	<0.001[a]/0.91			
FEP1vsT1	0.63(136)	**0.8x**+0.3	<0.001[a]/0.62	0.46(107)	**0.5x**+1.7	<0.001[a]/0.15
ΣS2vs(T2-FEP1)	0.64(136)	**0.6x**+0.6	<0.001[a]/0.26	0.67(107)	**0.9x-2.4**	<0.001[a]/<0.001[a]
ΣS2vsΣS1(ex1)	0.42(30)	**-1.5x+21.0**	<0.001[a]/<0.001[a]	0.86(24)	**-0.8x-4.2**	<0.001[a]/<0.001[a]
ΣS2vsΣS1(ex2)	0.72(26)	**-0.9x+18.2**	<0.001[a]/<0.001[a]	0.80(20)	**-1.2x+9.6**	<0.001[a]/<0.001[a]
PL2						
Ctl:FEPvsT	0.97(8)	**0.7x**+1.8	<0.001[a]/0.13			
FEP1vsT1	0.21(41)	**0.5x+7.2**	<0.01[a]/<0.001[a]	0.47(57)	**0.7x+4.0**	<0.001[a]/<0.05[a]
ΣS2vs(T2-FEP1)	0.06(41)	-0.4x+**16.4**	0.11/<0.001[a]	0.67(57)	**1.2x**-1.2	<0.001[a]/0.37
ΣS2vsΣS1(ex1)	0.64(11)	**-1.5x+35.2**	<0.01[a]/<0.001[a]	0.53(15)	**-1.4x**+10.9	<0.01[a]/0.19
ΣS2vsΣS1(ex2)	0.74(7)	**-1.8x+25.5**	<0.01[a]/<0.01[a]	0.50(13)	**-1.3x**+10.2	<0.01[a]/0.25
PL3						
Ctl:FEPvsT	0.83(56)	**0.7x+2.8**	<0.001[a]/<0.001[a]			
FEP1vsT1	0.38(129)	**0.4x+5.2**	<0.001[a]/<0.001[a]	0.22(51)	**0.5x**+5.2	<0.001[a]/0.11
ΣS2vs(T2-FEP1)	0.06(129)	**0.2x+6.3**	<0.01[a]/<0.001[a]	0.68(51)	**0.7x-3.7**	<0.001[a]/<0.001[a]
ΣS2vsΣS1(ex1)	0.12(25)	-0.6x+**16.6**	0.09/<0.001[a]	0.76(23)	**-1.1x+7.0**	<0.001[a]/0.02[a]
ΣS2vsΣS1(ex2)	0.33(19)	**-1.5x+22.8**	<0.01[a]/<0.001[a]	0.66(9)	**-0.7x**+1.1	<0.01[a]/0.69
PL4						
Ctl:FEPvsT	0.89(48)	**0.6x+5.8**	<0.001[a]/<0.001[a]			
FEP1vsT1	0.48(14)	**0.6x**+4.0	<0.01[a]/0.09	(6)[b]	[b]	[b]
ΣS2vs(T2-FEP1)	0.46(14)	**0.6x**+0.7	<0.01[a]/0.75	(6)[b]	[b]	[b]
ΣS2vsΣS1(ex1)	(4)[b]	[b]	[b]	(2)[b]	[b]	[b]
ΣS2vsΣS1(ex2)	(3)[b]	[b]	[b]	(1)[b]	[b]	[b]
PR1[+]						
Ctl:FEPvsT	0.86(33)	**0.6x-2.5**	<0.001[a]/<0.001[a]			
FEP1vsT1	0.43(53)	**0.7x**-2.1	<0.001[a]/<0.10	0.51(60)	**0.6x-6.6**	<0.001[a]/<0.001[a]
ΣS2vs(T2-FEP1)	0.39(53)	**0.8x**-0.8	<0.001[a]/0.71	0.67(60)	**0.9x+2.5**	<0.001[a]/0.02[a]
ΣS2vsΣS1(ex1)	0.01(13)	0.1x-10.7	0.79/0.11	0.77(15)	**-1.0x**-2.9	<0.001[a]/0.41
ΣS2vsΣS1(ex2)	0.43(10)	**-1.5x-22.9**	<0.01[a]/<0.001[a]	0.74(13)	**-0.8x**-1.4	<0.001[a]/0.59
PR2						
Ctl:FEPvsT	0.81(31)	**0.8x**-0.7	<0.001[a]/0.61			
FEP1vsT1	0.62(32)	**0.9x**+0.2	<0.001[a]/0.87	0.39(37)	**1.2x**+5.3	<0.001[a]/0.31
ΣS2vs(T2-FEP1)	0.54(32)	**1.0x**-3.5	<0.001[a]/0.15	0.84(37)	**1.0x+4.8**	<0.001[a]/<0.001[a]
ΣS2vsΣS1(ex1)	0.03(10)	-0.3x-**21.3**	0.61/<0.001[a]	0.81(9)	**-1.1x**-6.0	<0.001[a]/0.14
ΣS2vsΣS1(ex2)	0.16(8)	-0.5x-**23.5**	0.33/<0.01[a]	0.85(7)	**-0.8x**+2.0	<0.01[a]/0.57

Legend identical to that of Suppl. Table 11.

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What's the best way to court a saccade?

Smooth pursuit.