Oculomotor Control and Blindsight in Hemidecorticate Patients

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Abstract

The brain's ability to recover from and adopt to a major injury is a fascinating expression of neuroplasticity. *Blindsight* is an intriguing example of these "plastic" properties, revealed by the residual vision that survives ablation of the primary visual cortical area (V1). Although the effects of V1 lesions have been the prime focus of research on blindsight, there also has been considerable interest in the effects of larger lesions, in particular the ablation of one entire hemisphere called hemispherectomy. It is therefore of interest to understand how the brain reorganizes and adapts itself to such a massive injury with regards to blindsight. Given that blindsight is a "visual" phenomenon in the absence of visual cortical circuitry, measuring blindsight using oculomotor responses such as saccadic eye movements, production of which recruits many cortical and subcortical neuronal structures, is an accepted way of demonstrating blindsight and has been used by many groups studying this phenomenon. Research suggests that the superior colliculus (SC) plays a crucial role in blindsight as a relay station transmitting retinal signals to either LGN or pulvinar (Kato, Takaura, Ikeda, Yoshida, & Isa, 2011; Schmid et al., 2010). Thus far, the blindsight phenomenon has been demonstrated in hemispherectomized patients by a forced choice task, fixation shifts, stimulus discrimination, spatial summation effect, and finger pointing.

Despite these studies, no real consensus exists on whether or not hemispherectomized patients can localize targets in their blind hemifield. Here I present a number of new findings that have arisen from my studies of the blindsight phenomenon in three hemispherectomized patients. First, I have found that hemispherectomized patients are able to retain residual vision in their blind hemifield that can affect saccade control. Specifically, we show that in these patients missing an entire hemisphere, an unseen visual stimulus within their blind hemifield can

subliminally influence the timing and accuracy of a saccade directed to that field. Second, I have found that hemispherectomized patients can generate accurate anti-saccades into the blind hemifield despite the absence of the neural circuitry normally required for the vision-to-motor vector inversion process inherent to the generation of these eye movements, and they do so no differently than normal control subjects. Third, I have provided evidence that the superior colliculus may be a main player in blindsight and not merely a relay station, as some previous research suggests. Together, these observations provide new evidence that human brain is capable of major reorganization and plasticity even following such a substantial injury as hemidecortication, as well as highlight the extraordinary ability of the human brain to use compensatory and adaptive strategies to restore normal function.

Keywords: blindsight, hemispherectomy, oculomotor control, superior colliculus

Resumé

La capacité du cerveau à s'adapter suite à un trauma majeur est un phénomène fascinant de la plasticité neuronale. La vision aveugle (« blindsight ») est un exemple intéressant de ces propriétés plastique, qui se manifeste par la vue résiduelle qui survit l'ablation du cortex visuel primaire (V1). De même que le fait que l'effet des lésions V1 est au cœur de la recherche de la vision aveugle, les effets de lésions majeurs font l'objet d'un intérêt marquant, l'ablation d'un hémisphère au complet (hémisphérectomie) étant un spécifiquement. Il est important d'examiner le mécanisme par lequel le cerveau s'adapte et se réorganise après un trauma majeur en relation à la vision aveugle. Étant donné que la vision aveugle est un phénomène « visuel » dans l'absence de circuiterie de la cortex visuel, l'analyse des réactions oculomotrices, comme les saccades oculaires qui impliquent plusieurs structures neurales au niveau cortical et sous-cortical, est une approche bien acceptée pour démontrer la vision aveugle et reconnue parmi les recherchistes. Les résultats des études suggèrent que le colliculus supérieur joue un rôle critique dans la vision aveugle étant un poste de transmission des signaux rétinaux soit au corps géniculé latéral (CGL) ou pulvinar (Kato et autres, 2011; Schmid et autres, 2010). À ce jour, les patients ont démontré le phénomène de la vision aveugle par l'entremise d'une tâche de choix forcé, le changement de fixation visuelle, la différentiation de stimulus, l'effet sommation spatiale et pointer le doigt.

Malgré ces études, il n'existe pas un consensus au sujet des patients qui ont subi des hémisphérectomies et si ces derniers peuvent localiser les cibles dans leur champ de vision aveugle. Dans cette thèse, je présente des résultats ultérieurement inconnus qui ont été observés dans mes recherches au sujet du phénomène de la vision aveugle dans trois patientes hémisphérectomisés. En premier lieu, j'ai constaté que les patients hémisphérectomisés ont retenu de la vision résiduelle dans leur champ de vision aveugle qui peut avoir un effet sur le

contrôle de leurs saccades. En particulier, on a démontré que le timing et précision des saccades au champ de vision aveugle des patients qui manquent un hémisphère au complet, peuvent être influencés au niveau subliminal par un stimulus qui n'est pas visible dans ce champ. En deuxième lieu, j'ai constaté que les patients hémisphérectomisés peuvent faire des antisaccades précises dans leur champ de vision aveugle malgré l'absence de la circuiterie neurale, requise dans le processus d'inversion de vecteur qui est responsable à la génération de ces mouvementes d'œil, et que les patients performent comme les sujets de contrôle. Finalement, je présente de l'évidence que le colliculus supérieur joue un rôle clé dans la vision aveugle et ne sert pas que de poste de transmission comme les recherches précédentes le suggèrent. Vue d'ensemble, ces observations font d'évidence que le cerveau humain possède une plasticité et qu'il est capable d'une réorganisation même suite à un trauma grave comme une hémidécortication, et souligne la capacité extraordinaire du cerveau à employer des stratégies adaptatives afin de remettre ses fonctionnalités à la norme.

*Mon cl*és: vision aveugle, hémisphérectomie, contrôle oculomotrice, colliculus supérieur

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Preface and Contribution of Authors

All research presented in this thesis constitutes an original contribution to the knowledge regarding blindsight and saccade control. Each of chapters 2, 3, and 4 present original results that were either published (chapter 2), are currently submitted for publication or are in the preparation for publication.

Each of the studies presented in Chapters 2, 3 and 4 were designed, performed, analyzed and written by me under the supervision of Dr. Guitton. In case of Chapter 2 and 3, these chapters were co-designed with Dr. Bergeron. The study presented in Chapter 2 entitled "Blindsight after hemidecortication: visual stimuli in blind hemifield influence anti-saccades directed there" was published in the journal Cortex 49:861-76, 2013 (see Appendix B). The study presented in Chapter 3 entitled "Blindsight after hemidecortication: visual distractor in blind hemifield perturbs anti-saccades directed there according to visuo-motor interactions on superior colliculus map" and the study presented in Chapter 4 entitled "Oculomotor control after hemidecortication: One hemisphere encodes normal ipsilateral oblique anti-saccades" are both in preparation for journal submission.

Chapter 1: Oculomotor Control and Blindsight in Hemidecorticate Patients

Neuroplasticity Following a Traumatic Brain Injury

One of the most amazing discoveries in the last century in the field of neuroscience is the fact that the brain is adaptable and capable of adjusting its structural and functional organization in response to experience or injury (Hamaide, Groof, & Van der Linden, 2016). Vision is arguably one of the most used and important senses for a human being; as such the neuronal circuitry for visual processing is extensive and has been shown to be present in frontal, parietal, temporal, and occipital lobes, altogether being comprised of 32 visual areas and 305 connective pathways between them (Felleman & van Essen, 1991). Therefore, whenever there is a brain injury, the likelihood of subsequent visual impairment is very high. Nevertheless, it has been shown that some level of visual restoration is possible via the neuroplastic changes that follow retinal lesions, age related macular degeneration, optic nerve lesions, glaucoma, and various other neurological insults (for review see Sabel, Henrich-Noack, Fedorov, & Gall, 2011). Blindsight, it could be argued, is a result of such neuroplasticity.

Blindsight

A fascinating example of the brain's "plastic" properties is the residual vision that survives ablation of the primary visual cortical area, V1. This phenomenon, called *blindsight*, has been much studied and, in Cowey's (2010) extensive review, defined as "…the ability of patients with clinically blind field defects, caused by damage to the primary visual cortex V1, to detect, localize, and even discriminate visual stimuli that they deny seeing" (p. 3).

Various types of blindsight. Blindsight has been subdivided into types I and II (for review see Danckert & Rossetti, 2005; Huxlin, 2008; Overgaard & Mogensen, 2015; Ptito and

Leh, 2007). Type I blindsight is referred to as a residual visual ability without any awareness of the visual stimulus in the blind hemifield; by comparison, type II blindsight is often described as a "feeling" that something has occurred.

Danckert and Rossetti (2005) proposed an alternative subdivision of the blindsight phenomenon: action-blindsight, attention-blindsight, and agnosopsia. They defined "action-blindsight" as the ability to perform an action, such as pointing or making a saccade, toward an unseen target. This form of blindsight does not require any conscious awareness of the target and it is thought to be mediated by the subcortical retino-tectal pathway. By comparison, "attention-blindsight" involves implicit processing of visual stimuli in the blind hemifield, as demonstrated by using covert spatial orienting, inhibition of return, and motion detection and discrimination. The "attention- and action-blindsight" phenomena are not necessarily mutually exclusive, and in fact attentional processes might be recruited in order to execute "action-blindsight" (Danckert & Rossetti, 2005). Finally, agnosopsia (originally coined by Zeki & Ffytche, 1998) describes the ability of correctly discriminating certain characteristics of the stimuli without any conscious awareness (Danckert & Rossetti, 2005). According to Danckert and Rossetti (2005) Type I blindsight can be equated to agnosopsia, while type II blindsight is comparable to "attention-blindsight".

Blindsight and plasticity. Evidence showing that blindsight is a form of plasticity comes from studies that demonstrated practice effects in detection and localization of targets in the blind hemifield of hemianopic patients. For example, in the early 80s a group of researchers conducted a series of studies measuring practice effects in three patients with unilateral damage to the geniculostriate system using voluntary blink responses for detection and saccadic eye

movements for localization of targets in the blind hemifields of these patients. Their results show a clear improvement in the performance following practice (480-600 trials) (Zihl, 1980; Zihl & Von Cramon, 1980; Zihl & Werth, 1984). More recently, Stoerig (2006) ran a hierarchical regression analyses, to investigate which of the many factors contributes the most to the differences found in blindsight performance. When they compared the patients' age, age at lesion, the size of lesion, the size of the field defect, the age at which they began blindsight testing, and how long they participated in blindsight testing, it was the latter (overall length of blindsight experience) that correlated the highest with performance.

Although the effects of V1 lesions have been the prime focus of research on blindsight, there also has been considerable interest in the effects of larger lesions, in particular and of relevance to the present thesis, the ablation of one entire hemisphere called hemispherectomy. As was noted by Irle (1990) after a quantitative comparison of 283 published studies, the larger the damage to the brain, the more plasticity takes place. It is therefore of interest to understand how the brain reorganizes and adapts itself to such a massive injury with regards to blindsight. Given that blindsight is a "visual" phenomenon in the absence of visual cortical circuitry, measuring blindsight using oculomotor responses such as saccadic eye movements, production of which recruits many cortical and subcortical neuronal structures (as will be discussed in detail below), is an accepted way of demonstrating blindsight and has been used by many groups studying this phenomenon.

I will discuss hemispherectomy, as it pertains to the blindsight phenomenon, later in this thesis, but I will begin by describing the neuroanatomy of the oculomotor system.

Neuronal Circuitry of the Saccadic Oculomotor System

The oculomotor system is involved in the control of four types of eye movements: saccades, smooth pursuit, vergence, and vestibularly driven eye movements. The neural circuitry involved in the production of each of these eye movements is extensive and outside the scope of this thesis. In my research I studied saccade generation in hemidecorticate patients and therefore I will focus here on the neuronal circuitry which controls this oculomotor subsystem.

The neuronal circuitry of the saccadic oculomotor system includes both cortical and subcortical structures. Cortical structures include the frontal eye fields (FEF), lateral intraparietal area (LIP), supplementary eye fields (SEF), and dorsolateral prefrontal cortex (DLPFC). Subcortical structures include the superior colliculus (SC), cerebellum (Cb), substantia nigra pars reticulata (SNr), caudate nucleus (CN), putamen, and thalamus (Th).

The generation of visually-induced saccadic eye movements requires that visual signals be conveyed to the brainstem reticular saccade generator. The SC is considered to be the central relay station (Scudder, Kaneko, & Fuchs, 2002). Visual signals reach the SC via either the direct retinal-collicular pathway projecting to the SC's superficial layers (Munoz, Dorris, Paré, & Everling, 2000), or indirect afferent projection from the frontal cortex (FEF, SEF, DLPFC), parietal cortex (LIP), basal ganglia, and cerebellum (Neggers, Raemaekers, Lampmann, Postma, & Ramsey, 2005; Scudder et al., 2002; Snyder, Batista, and Andersen, 2002) (Fig. 1-1). In addition, FEF and LIP have extensive reciprocal neuronal projections to the SC (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Paré and Wurtz, 2001; Shipp, 2004). Also, SEF and FEF have extensive reciprocal projection to LIP and to each other (Scudder et al., 2002). Notably, while it has been found that the three cortical areas - FEF, SEF, and LIP - have

direct descending projections to the brainstem saccade generator, by-passing the SC (Schiller, True, & Conway, 1980; Scudder et al., 2002), these projections are believed to be functionally insufficient for the production of a correct saccade, which in turn seems to require the relay signal via the SC (Hanes & Wurtz, 2001; Schiller et al., 1980; Scudder et al., 2002). Therefore, it is believed that the majority of cortical saccade-related brain areas influence saccade related activity via projections to the SC (Johnston & Everling, 2008).

Characteristics of Saccades

Various human lesion and neuroimaging studies, as well as primate studies indicate that the extent to which any of the oculomotor areas described above are involved in saccade generation depends on the nature of the saccade, i.e. reflexive, intentional (planned and guided), or predictive (Abel & Douglas, 2007; Broerse, Crawford & den Boer, 2001; Evdokimidis, Mergner, & Lücking, 1992; Gaymard et al., 1998; Spengler et al., 2006).

Reflexive saccades. The sudden appearance of a visual target in the periphery evokes an automatic oculomotor response – a reflexive saccade toward the target (Broerse et al., 2001; Spengler et al., 2006). Reflexive saccades are characterized by fast velocities (Spengler et al., 2006) and are visually guided (Broerse et al., 2001).

In the laboratory setting, it has been shown that visually guided reflexive saccades have an average saccadic reaction time (SRT) of 170-180 ms (Spengler et al., 2006). Additionally, it has been shown that the extinction of the fixation point (FP) prior to target onset and the presentation of a delay period (gap) between the offset of the FP and the target onset lead to bimodal distribution of SRT (Dorris & Munoz, 1995) with the first peak latency of 100 ms or

120 ms (depending on target predictability), termed *express* saccades, and the second peak latency of 140-160 ms, termed regular saccades (Fischer & Boch, 1983).

The superior colliculus is believed to be the main brain structure implicated in the generation of express saccades (Paré & Munoz, 1996). Supporting this conclusion, lesion studies showed that ablation of the SC leads to the loss of the ability to generate express saccades (Schiller, Sandell, & Maunsell, 1987). In addition, studies conducting cell recordings in the SC found distinct neuronal activity associated with express saccade generation (Dorris, Paré, & Munoz, 1997; Edelman & Keller, 1996).

In addition, NHP recordings show that FEF neurons are also very active for express saccades and short-latency visually-guided saccades (Everling and Munoz, 2000).

In contrast, the generation of regular latency saccades involves cortical processing of visual information. Clinical lesion studies, human EEG recordings, and studies examining oculomotor abnormalities linked to psychiatric disorders show that the parietal eye field (PEF)/LIP in the posterior parietal cortex (PPC) is the main cortical structure involved in generation of regular latency reflexive visually driven saccades (Evdokimidis et al., 1992; Gaymard et al., 1998; Spengler et al., 2006).

Intentional saccades. In laboratory settings, the generation of intentional saccades is studied primarily via two experimental paradigms: the anti-saccade task and memory-guided saccade task. In the anti-saccade task, participants are required to suppress a reflexive saccade toward a peripheral target, and instead generate an eye movement toward the mirror location in the opposite visual hemifield. In the memory-guided saccade task, a saccade to a target is made

after a certain time delay (gap) and therefore the visual information about the target's location is absent during the eye movement (Abel & Douglas, 2006; Broerse et al., 2001).

Because intentional saccades are under voluntary control and involve cognitive processing, their latencies are longer than those of reflexive saccades. For example, latencies of memory-guided saccades are greater than 200 ms (Hopp & Fuchs, 2004) and latencies of anti-saccades average at around 350 ms (Mort et al., 2003), compared to 170-180 ms for reflexive saccades (Spengler et al., 2006). Also, when intentional saccades are generated in the absence of existing visual information about target location (e.g. memory-guided saccades), they are less accurate than visually guide saccades because they rely exclusively on an internal representation of the target location (Gnadt, Bracewell, & Andersen, 1991; White, Sparks, & Stanford, 1994). Specifically, memory-guided saccades are characterized by an upward bias (systematic error) and a large scatter of the saccade endpoints (variable error) (White et al., 1994).

Given that the generation of both anti-saccades and memory-guided saccades requires an active suppression of the initial reflexive eye movement towards the target, generation of the intentional saccades involves cortical processing, and includes areas such as DLPFC, FEF, and SEF (Abel & Douglas, 2006; Mort et al., 2003; Broerse et al., 2001; Gaymard et al., 1998; Neggers et al., 2005; Pouget, 2015; Schlag-Rey, Amador, Sanchez, & Schlag, 1997; Spengler et al., 2006). At the same time, although a subcortical structure, basal ganglia is also involved in generation of intentional saccades, as evident by the fact that its neurons show greater firing modulation during anti-saccades compared with pro-saccades (Ford & Everling, 2009; Watanabe & Munoz, 2009; Yoshida & Tanaka, 2009).

Predictive saccades. When the location and timing of the target's appearance are known in advance, the visual system is able to construct an accurate representation of the future position of the target and generate a saccade with an extremely short latency, often less than the 75 ms of express saccades, termed anticipatory saccades (for review see Broerse et al., 2001). In the laboratory setting, generation of predictive saccades is achieved through paradigms that involve learning of simple or complex sequences of target presentations, varying the probability of target appearance at certain locations, presenting the target in the same location over many consecutive trials (training), or indicating the target's exact location with a cue (Cavegn & d'Ydewalle, 1996; Clohessy, Posner, & Rohbart, 2001; Dorris & Munoz, 1998; Evdokimidis et al., 1992; Findlay, 1980; Findlay 1982; Paré & Munoz, 1996).

Various imaging studies (see review e.g., Broerse et al., 2001; Gaymard et al., 1998), electrophysiological recordings (Coe, Tomihara, Matsuzawa, & Hikosaka, 2002), human EEG recordings (Evdokimidis et al, 1992), as well as studies of lesions (Pierrot-Deseilligny et al., 2003) and oculomotor abnormalities associated with obsessive-compulsive disorder (OCD) (Spengler et al., 2006) and Parkinson's disorder (O'Sullivan et al., 1997), demonstrate the involvement of fronto-striatal circuitry in predictive saccade generation, mainly in areas such as DLPFC, FEF, SEF, and the basal ganglia. The FEF and basal ganglia are involved in the generation of predictive saccades primarily by means of its inhibitory projections to SNr, thereby disinhibiting the activity in the SC (for review see Hikosaka, Takikawa, & Kawagoe, 2000). Evidently, an increased saccadic latency in the predictive saccade task has been shown in patients with Parkinson's disease (Broerse et al., 2002; Spenger et al., 2006). Furthermore, there is evidence that an overactive circuitry between the FEF and the basal ganglia results in the

abnormal reduction of saccadic latencies in the predictive saccade task. For example, patients with OCD show a pathophysiological dysfunction of the prefrontal areas (mainly FEF) and the basal ganglia (Busatto et al., 2000). These individuals produce higher frequency of anticipatory saccades with reduced amplitudes (Spenger et al., 2006).

Deficits Associated With Lesions to Oculomotor Areas

The Frontal Eye Field (FEF). In humans the FEF is located in the posterior extremity of the middle frontal gyrus and the precentral sulcus, anterior to the motor cortex (Leigh & Kennard, 2004; Muri, 2006; Pierrot-Deseilligny et al., 2002). Lesion studies have demonstrated that the FEF is involved in the production of volitional saccades, specifically memory-guided and anti-saccades, but not reflexive visually guided saccades (Bender, Tark, Reuter, Kathmann, & Curtis, 2013; Dias & Segraves, 1999; Rivaud, Müri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994). The particular deficits associated with lesions to the FEF region are: an increased percentage of express saccades (Braun, Weber, Mergner, & Schulte-Monting, 1992), exploratory-motor type of visual hemineglect (Heide & Kömpf, 1998), an impairment of saccades to remembered stimuli (Dias & Segraves, 1999; Pierrot-Deseilligny et al., 2003), and an impairment of anti-saccade generation in a task which requires voluntary suppression of a reflexive saccade to a target in favour of an instructed saccade away from the target (Guitton, Buchtel, & Douglas, 1985).

The Lateral Intraparietal Area (LIP). In humans the homologue to the monkey LIP is the Parietal Eye Field (PEF) located in the intraparietal sulcus (Leigh & Kennard, 2004; Pierrot-Deseilligny, Ploner, Muri, Gaymard, & Rivaud-Pechoux, 2002). Two distinct subdivisions, LIPd and LIPv, have been identified in monkey (Blatt, Andersen, & Stoner, 1990); the latter has been

shown to be predominantly involved in oculomotor processing (Chen et al., 2016). Lesions studies involving the parietal cortex reported deficits associated with reflexive saccades, particularly increase in latencies (Heide & Kömpf, 1998; Pierrot-Deseilligny, Rivaud, & Gaymard, 1991a; Terao et al., 2015), hypometric saccades (Heide & Kömpf, 1998; Terao et al., 2015), and poor saccade accuracy when the location of targets is unpredictable (Gaymard et al., 2003). It also appears that it plays a role in the production of express saccades. Specifically, in a very recent study, it has been shown that deactivation (by local injection of muscimol) of LIPv in rhesus monkeys significantly decreases generation of contralateral express saccades (Chen et al., 2016).

The Supplementary Eye Field (SEF). SEF is located in the dorsomedial frontal cortex and anterior to the supplementary motor area (SMA) in the upper part of the paracentral sulcus (Grosbras, Lobel, Van de Moortele, LeBihan, & Berthoz, 1999; Pouget, 2015; Stuphorn & Schall, 2002). Lesion studies suggest that the SEF is involved mainly in the control of saccade sequences. It has been shown that permanent or reversible SEF lesions in both humans and monkeys lead to deficits in SRT and sequence order, but only when sequences of visually- or memory-guided saccades are generated to two or more targets, and not to single targets (Braun et al., 1992; Gaymard, Rivaud, & Pierrot-Deseilligny, 1993; Heide & Kompf, 1998; Müri, Rösler, & Hess, 1994a; Müri, Rivaud, Vermersch, Léger, & Pierrot-Deseilligny, 1995; Pierrot-Deseilligny, Israël, Berthoz, Rivaud, & Gaymard, 1993; Schiller & Chou, 1998, 2000a, 2000b; Sommer & Tehovnik, 1999; Tobler & Müri, 2002), as well as when switching from anti- to pro-saccades is required (Parton et al., 2007). It has also been shown that SEF is involved in the

control of saccades combined with body movements (Chapman, Pace, Cushin, & Corneil, 2012; Israel, Rivaud, Gaymard, Berthos, & Pierrot-Deseilligny, 1995).

The Dorsolateral Prefrontal Cortex (DLPFC). In monkeys DLPFC lies in and dorsal to the principal sulcus; a human homologue location is in area 46 of Brodmann, which lies in the middle frontal gyrus (Pierrot-Deseilligny, Muri, Nyffeler, & Milea, 2005). One of the main and extensively studied oculomotor functions of DLPFC is inhibition of reflexive saccades, as shown by an increase in reflexive erroneous glances toward the target in the anti-saccade paradigm in patients with focal lesions of DPLFC (Ploner, Gaymard, Rivaud-Péchoux, & Pierrot-Deseilligny, 2005). In addition, evidence from lesion studies also shows clear impairments of memory-guided saccades (Brandt, Ploner, Meyer, Leistner, & Villringer, 1998; Braun et al., 1992; Funahashi, Bruce, & Goldman-Rakic, 1993; Heide & Kompf, 1998; Israel et al., 1995; Müri, Vermersch, Rivaud, Gaymard, & Pierrot-Deseilligny, 1996b; Nyffeler et al., 2002; Pierrot-Deseilligny et al., 2005; Pierrot-Deseilligny et al., 2003; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991b; Ploner, Rivaud-PeÂchoux, Gaymard, Agid, & Pierrot-Deseilligny, 1999; Sawaguchi & Iba, 2001); although a more recent study demonstrated that working memory is only affected when the damage extends to more caudally located precentral sulcus (Mackey, Devinsky, Doyle, Meager, & Curtis, 2016). Furthermore, the impairments in the control of timing of predictive saccades have also been shown (Pierrot-Deseilligny et al., 2005; Pierrot-Deseilligny et al., 2003).

Superior Colliculus (SC). SC is a midbrain structure that has been extensively implicated in saccade generation to visual, auditory, and somatosensory targets (Stein, Stanford, & Rowland, 2009; Stein, Wallace, Stanford, & Jiang, 2002). There is one superior colliculus on each side of the brain, and each receives information primarily from the contralateral field (Stein

et al., 2002), specifically from frontal, parietal and visual cortices, as well as from basal ganglia; it then sends command signals to the brainstem saccade generator (Guitton, 1991; Sparks, 1986; Sparks, 2002; Sparks & Hartwich-Young, 1989). Given that the role of the SC in blindsight phenomenon is central to this thesis, I will describe this structure in much detail.

Laminar organization of SC. In mammals the SC is composed of seven cyto-architecturally distinct layers: the stratum zonale (zonal layer), stratum grisium superficiale (superficial grey layer), stratum opticum (optic layer), stratum grisium intermediale (intermediate grey layer), stratum album intermediale (intermediate white layer), the stratum grisium profondum (deep grey layer), stratum album profondum (deep white layer) (for review see May, 2006; Stein et al., 2002). Furthermore, the SC is subdivided into the superficial and deep layers that form two functionally distinct compartments. The *superficial SC (*consisting of the zonal, superficial grey and optical layers) is responsible for mediating visual processing, and the *deep SC* (consisting of the intermediate grey, intermediate white, deep grey and deep white layers) is involved in controling orienting behavior via direct and indirect connections to the brainstem saccade generator.

Sensory neurons in the superficial layers respond exclusively only to visual stimuli (May, 2006); visual responses in the superficial SC may be influenced by direct retinal inputs (of great interest here regarding hemidecorticate patients). Neurons in the deep layers respond to visual, auditory and somatosensory (tactile) stimuli, as well as a combination of multiple modalities (Meredith, Nemitz & Stein, 1987; Meredith & Stein, 1986; Stein et al., 2002; Wallace & Stein, 1996). Many studies show connectivity between the superficial and deep layers (Helms, Ozen &

Hall, 2004; Isa, Endo, & Saito, 1998; Isa & Hall, 2009; Isa & Saito, 2001; Lee, Helms, Augustine, & Hall, 1997).

The neurons in the superficial layers have large well-defined receptive fields that code for the retinal coordinates of visual stimuli presented in the contralateral visual hemifield (Munoz et al., 2000). The topographically-encoded visual map is closely linked to a motor map, whose neurons in the deeper layers code for the gaze shift vector, associated in space with the presentation of specific visual (or other sensory modality) stimuli (for review see King, 2004). Put another way, each point on the motor map codes for a specific vector in retinal coordinates. More specifically, stimuli presented in the foveal locations are coded in the rostral part of the SC, whereas stimuli displayed in the peripheral visual field are coded in the contralateral caudal regions of the SC (for review see King, 2004; Munoz et al., 2000). The metrics of a single saccade are coded by a population of neighbouring cells, rather than a single neuron, due to the overlap in the receptive fields of the SC neurons (Lee, Rohrer, & Sparks, 1988; McIlwain, 1991; Munoz et al., 2000).

The neurons in the superficial layers receive inputs from retinal ganglion cells that are only involved in low acuity vision (Lomber, 2002; Morris, Ohman, & Dolan, 1999; Munoz et al., 2000), as evidenced by the SC processing strictly low spatial frequency information, such as global feature discrimination (Lomber, 2002; Vuilleumier, Armony, Driver, & Dolan, 2003). Finally, until very recently, it was believed that SC was only sensitive to luminance information and lacked completely any sensitivity to short-, medium-, or long-wavelength stimuli that activate S-, M-, and L-cone receptors in the retina, respectively (Basso, 2016). However, Hall and Colby (2016), put this theory to rest by showing in monkeys that SC is sensitive to S-cone

input by demonstrating both neuronal responses and express saccade generation in the SC to S-cone stimuli (Hall & Colby, 2016).

Lesions to the SC. It has been shown that lesionig the neurons in the deep SC with pharmacological agents results in severe deficits in saccade generation; pointing to the SC being a vital component for saccade generation (Hikosaka & Wurtz, 1985a, 1986; Lee et al., 1988; Munoz & Wurtz, 1993b; Hanes & Wurtz, 2001). In fact, a pioneering study conducted by Sprague (1966) attests to how crucial SC's role is in visual and oculomotor control by demonstrating that a complete hemianopia induced by an ablation of the entire occipitotemporal cortex can be reversed by either a) a removal of the contralateral SC, or b) sectioning the collicular commissure – formally known as *Sprague effect.*

Moreover, in addition to its well-established role in controlling orienting movements of eyes and head, some lesion studies demonstrated evidence that SC is also involved in spatial attention (for review see Krauzlis, Lovejoy & Zenon, 2013), such as attention disengagement (de Araujo, Matsumotoa, Ono, & Nishijo, 2015), target selection (McPeek & Keller, 2004), and the covert selection of signals for perceptual judgments (Lovejoy & Krauzlis, 2010).

Basal Ganglia (BG). The Basal Ganglia is a collection of various subcortical nuclei located at the base of the cerebrum (Hikosaka et al., 2000) that include the caudate nucleus (CN), nucleus accumbens, and putamen (PUT) (collectively called striatum), globus pallidus (GP; composed of GPi and GPe, internal and external segment respectively, and ventral pallidum (VP)), substantia nigra (SN; further subdivided as the pars reticulata (SNpr) and pars compacta (SNpc)), and subthalamic nucleus (STN). The striatum and STN comprise the input station and receive projections from the cortex and thalamus; in turn, the output station is comprised mainly

of GPi, and SNpr, sending inhibitory GABAergic projections to the thalamic nuclei and the brainstem, including the superior colliculus and the pedunculopontine nucleus (AuYong, Keener, Bordelon, Portera-Cailliau, & Pouratian, 2016; Hikosaka et al., 2000; Singer, Mink, Gilbert, & Jankovic, 2016).

The basal ganglia are involved in oculomotor as well as skeletal/body movement control. However, for the purpose of this thesis I will only discuss their role in *saccadic* eye movement control; notably in choosing the appropriate signal from the numerous ones originating in the various cortical areas involved in saccade generation. They do so by exerting a removal of a sustained tonic inhibition on the SC (Hikosaka et al., 2000). Specifically, the SNpr sends a sustained tonic inhibition to the intermediate layer of the SC, which is then removed by an inhibition of the SNpr by the CN which itself is activated by a cortical neuronal discharge (Hikosaka et al., 2000; Shires, Joshi, & Basso, 2010). Therefore, as Hikosaka et al. (2000) argue, its key role in the control of the saccadic eye movements is *disinhibition*. Specifically, these authors reason that without the powerful and sustained inhibition of the SC by SNpr, the SC would be overwhelmed by the many convergent excitatory inputs from the various cortical areas. Therefore, such tonic inhibition insures order and a choice of an appropriate input followed by the generation of motor command made possible by the removal of the inhibition via CN's inhibitory input to the SNpr (Hikosaka et al., 2000).

While research on human BG lesion is relatively scarce, a few studies do exist. For example, a study conducted by Vermersch et al. (1996) involves patients with bilateral lesions to the lentiform nucleus which affects the putamen and/or the pallidum. While these patients did not differ significantly from their control counterparts on the performance of either visually

guided - or anti-saccades, they showed an impairment in performance of a saccade sequence task, exhibiting an increase in the percentage of errors. They also showed a significant increase in amplitude of memory guided saccades compared to controls. On the other hand, a recent study conducted by Terao et al. (2016) showed an impairment in the performance of reflexive saccades in patients with a putamen lesion, resulting in the decrease of their amplitude. They also showed that a lesion in the CN resulted in the impairment of the voluntary saccades, causing an increase in latency. Finally, caudate lesions also impaired the ability to inhibit unnecessary reflexive saccades.

Thalamus. The thalamus is situated in the diencephalon (Herrero, Barcio, & Navarro, 2002; Herrero, Insausti, & Estrada, 2015) and is known to be an important sensory and motor relay center. The human thalamus is divided into 50-60 nuclei (Herrero et al., 2002) and is involved in many functions including awareness (Smythies, 1997), attention (Buchel et al, 1998), as well as memory (Engelborghs, Mariën, Martin, & De Deyn, 1998) and language (Johnson & Ojemann, 2000). The two thalamic nuclei implicated in oculomotor control are the ventral thalamus (specifically, the ventroanterior (VA) and the ventrolateral (VL)) and the mediodorsal thalamus (MD) (Mai & Forutan, 2012; Sommer, 2003). The mediodorsal thalamus is associated with "executive" functions by virtue of being interconnected with the prefrontal cortex (Schlag, 2009). In fact, its role in oculomotor control has been argued to be one of internal monitoring of saccades (Schlag, 2009), particularly conveying the corollary discharge information (Sommer & Wurtz, 2002). Indeed, Sommer and Wurtz (2004) tested this hypothesis by inactivating the MD, which resulted in deficits in both the accuracy and the precision of corollary discharge. In contrast, VA and VL are comprised of motor nuclei (Mai & Forutan, 2012; Schlag, 2009;

Sommer, 2003). VL thalamus has been implicated in being involved in the initiation of self-generating saccades and in the accuracy of visually guided saccades (Kronenbuerger et al., 2010). A study conducted by Tanaka (2006) showed that inactivation of the rostral portion of the caudal division of the ventrolateral nucleus and the adjacent area X of the thalamus led to an alteration of the timing of self-initiated saccades. The VA/VL motor thalamus has also been associated with the anti-saccades, particularly being involved in suppression of the unwanted pro-saccades (Kunimatsu & Tanaka, 2010).

Cerebellum. The cerebellum is located posterior to the brainstem and is separated from the cerebrum by an extension of dura matter (Roostaei, Nazeri, Sahraian, & Minagar, 2014). The two areas of the cerebellum implicated in saccade control are the dorsal oculomotor vermis (OMV), specifically lobules V-VII, and the posterior fastigial nucleus (or fastigial oculomotor region (FOR)) (for review see Sun, Barash, & Thier, 2016; Zee & Walker, 2009). The purkinje cells of the OMV inhibit the ipsilateral FOR. Therefore, the effects of lesions in these two regions (OMV and FOR) are opposite in nature (Zee & Walker, 2009). Specifically, while OMV lesions create hypometric ipsiversive and hypermetric contraversive saccades, FOR lesions result in hypermetric ipsiversive saccades and hypometric contraversive saccades. Consequently, bilateral OMV lesion causes bilateral hypometria, and bilateral FOR lesions cause bilateral hypermetria of saccades (Zee & Walker, 2009). It has been suggested that the FOR's function is to overcome the innate hypermetria of the saccadic brain stem burst generator, by terminating the saccade once it reaches its target (Takagi, Zee, & Tamargo, 1998). In addition to dysmetria, it has been shown that lesion of the OMV also leads to an increase in saccade latency and a cessation of anticipatory and express saccade production (Takagi et al., 1998).

Furthermore, the cerebellum has been implicated in sensory-motor adaptation of both reactive (saccades initiated towards the exogenous cues) and voluntary saccades (self-initiated scanning saccades) (for review see Manto et al., 2012). Specifically, it has been demonstrated that patients with the cerebellar damage show impairment in their ability to adjust the amplitude of saccadic eye movements to a systematic change of target position (Alahyane et al., 2008; Golla et al., 2008; Panouilleres et al., 2013; Straube, Deubel, Ditterich, & Eggert, 2001; Xu-Wilson, Chen, Harris, Zee, & Shadmehr, 2009).

Saccade Burst Generator. The saccade burst generator is located in the reticular formation and is composed of various regions (the mesencephalic, pontine, and medullary) with functionally distinct cell types, such as tonic neurons (TN), long-lead burst neurons (LLBNs) and medium-lead burst neurons (MLBNs), which are further subdivided into the excitatory and inhibitory burst neurons (EBN and IBN), and omnipause neurons (OPN) (Gancarz & Grossberg, 1998; Rahafrooz et al., 2008; Scudder et al., 2002). As their names imply, the TNs provide tonic activity and the burst neurons provide a high-frequency burst of action potentials prior to saccades (Scudder et al., 2002). The OPNs discharge during fixation and therefore provide tonic inhibition to the burst neurons. Consequently, for the saccade to take place OPNs must be inhibited (Scudder et al., 2002; Rahafrooz et al., 2008). The local feedback loop composed of these interconnected cells is the final stage of oculomotor processing that provides the signal to the eyes (Gancarz & Grossberg, 1998).

Studies of humans and monkeys with discrete brainstem lesions have indicated that the premotor commands for horizontal saccades are produced within regions of the pons and medulla surrounding the abducens nucleus, while the premotor commands for vertical saccades are

generated within areas of the rostral midbrain surrounding the oculomotor nucleus (Bender, 1980; Büttner-Ennever, Büttner, Cohen, & Baumgartner, 1982; Cohen, Komatsuzaki, & Bender, 1968; Goebel, Komatsuzaki, Bender, & Cohen, 1971; Henn, Lang, Hepp, & Reisine, 1984; Jacobs, Anderson, & Bender, 1973; Kömpf, Pasik, Pasik, & Bender, 1979; Nashold & Gillis, 1967).

As stated earlier in this chapter, LIP, FEF, and SEF project to the SG, but the SC is considered to be the primary source of motor commands to the SG (for review see Scudder et al., 2002).

Hemispherectomy

Here we studied hemispherectomy patients. A hemispherectomy is characterized by a complete cortical removal or a combination of partial removals and anatomical disconnections of the cortex of one hemisphere (for summary see De Almeida, Marino, Aquiar, & Teixeira, 2006). Although human hemispherectomized patients can generate voluntarily both leftward and rightward saccades as shown by our lab (Herter & Guitton, 2004), the precision of saccades to visual targets in the "blind" hemifield is random; indeed, human patients and monkeys hemispherectomized as adults do not recover saccade responses to targets presented in their blind hemifield (Estañol, Romero, Sáenz de Viteri, Mateos, & Corvera, 1980; Herter & Guitton, 2004; Troost, Weber, & Daroff, 1972; Tusa, Zee, & Herdman, 1986).

Thus far, the blindsight phenomenon has been demonstrated in hemispherectomized patients by showing: that they could identify that a target is presented in their blind hemifield in a forced choice task (Perenin & Jeannerod, 1978); fixation shifts to targets in the blind hemifield of young hemipherectomized infants (Braddick et al., 1992); stimulus discrimination in identification tasks (Wessinger, Fendrich, Ptito, Villemure, & Gazzaniga, 1996); finger pointing

to the target (Ptito, Lepore, Ptito, & Lassonde, 1991); the velocity and latency of saccades being affected by a light stimulus in the blind field (Sharpe, Lo, & Rabinovitch, 1979); as well as the "spatial summation effect", whereby an unseen visual stimulus in the blind hemifield affects the manual reaction time indicating, by a button-press, the perceived appearance of a visual target-stimulus in the seeing hemifield (Leh, Mullen, &Ptito, 2006; Tomaiuolo, Ptito, Marzi, Paus, & Ptito, 1997).

Despite these studies, no real consensus exists on whether or not hemispherectomized patients can localize targets in their blind hemifield. While some have shown that they can (studies discussed above), others have failed to demonstrate the blindsight phenomenon in hemispherectomized individuals, attributing any such findings to light scatter (King, Azzopardi, Cowey, Oxbury, & Oxbury, 1996; Stoerig, Faubert, Ptito, Diaconu, & Ptito, 1996).

To add to the mystery, the neural circuitry involved in blindsight still remains to be determined. Currently, two main contenders that are thought to be critical in blindsight are the lateral geniculate nucleus of the thalamus (LGN) and the SC. Specifically, a study conducted by Schmid et al. (2010) using fMRI technique and behavioural methods in V1-lesioned macaque monkeys showed that inactivation of the ipsilesional LGN resulted in the complete abolishment of all extrasriate responses and behavioural detections. These authors point out that neural degeneration following a V1 lesion selectively spares koniocellular-rich layers of LGN that receive input from the SC. At the same time, Kato, Takaura, Ikeda, Yoshida, and Isa (2011), using a visually guided saccade task, demonstrated that inactivation of the ipsilesional SC in V1-lesioned monkeys abolished visually guided saccades to the targets in the affected field. Both groups of researchers proposed that their evidence is suggestive of the crucial contribution the

SC plays as the relay station in blindsight, transmitting the retinal signal to either LGN (Kato et al., 2011; Schmid et al., 2010) or pulvinar (Kato et al., 2011).

It has been shown that hemidecorticate patients generate short-latency contralesional "express saccades" (Reuter-Lorenz, Herter, & Guitton, 2011). This ability normally requires an ipsilateral cortico-SC pathway (Schiller et al., 1987) which is absent on the lesioned side in hemidecorticate patients. So what could be the source of the ipsilesional SC activation? Previous studies have shed some light on the possible neural mechanism contributing to the activation of ipsilesional SC in hemidecorticate patients. Given the considerations in the previous paragraph we must rule out, in these patients, visual signals via LGN to ipsilesional extrastriate cortex. In contrast, it has been shown that there exist innate *bilateral* connections from FEF to the SC, nucleus reticularis tegmenti pontis, and paramedian pontine reticular formation (Crapse & Sommer, 2009; reviewed in Reuter-Lorenz et al., 2011). Also, increased crossed connections from the primary visual cortex to SC occur following experimental hemidecortication in cats (Adelson, Hovda, Villablanca, & Tatsukawa, 1995). Neural machinery in the normal brain subtends bilateral saccade control by a single hemisphere; e.g., FEF and LIP neurons have ipsilateral visual and motor responses (Barash, Bracewell, Fogassi, Gnadt, & Andersen, 1991; Zhang & Barash, 2000, 2004). Such data may explain why the SC remains anatomically intact on the decorticate side following experimental hemidecortication in monkeys (Ptito, Herbin, Boire, & Ptito, 1996; Théoret, Boire, Herbin, & Ptito, 2001) and why normal monkeys hemispherectomized as adults have bilateral saccade control (Tusa et al., 1986).

In summary, in hemidecorticate patients, apart from a direct pathway from the retina, there are multiple other pathways that can affect SC excitability, e.g.: 1) descending projections

from contralesional cortex (specifically area FEF) to the ipsilesional SC; 2) descending projections from contralesional cortex to the contralesional SC and inhibitory SC commissurals to the ipsilesional SC (Johnston and Everling, 2006**;** Takahashi, Sugiuchi, Izawa, & Shinoda, 2006). Note that in our patients DR and JB there is observed degeneration of the ipsilesional basal ganglia (Tomaiuolo et al., 1997) which otherwise could normally influence the SC (Hikosaka & Wurtz, 1983; reviewed in Hikosaka et al., 2000; Jiang, Stein, & McHaffie, 2003; Munoz & Everling, 2004).

Objectives of the Study

This thesis is concerned broadly with the residual oculomotor and visual functions that result from the complete removal of an entire hemisphere; called a hemispherectomy. Regarding vision, this massive lesion leads to complete blindness in the contralesional visual hemifield. I have focussed on the anti-saccade task which requires the suppression of a reflexive saccade towards a sensory cue in the seeing hemfield, and the generation of a voluntary saccade (an anti-saccade) to the mirror location of that cue in the blind hemfield. A vector inversion has to be performed in order to transform the sensory information in one hemifield into a motor response to the other hemifield. In the normal brain, both hemispheres participate in the vector inversion process inherent to anti-saccade generation (Everling & Munoz, 2000; Munoz & Everling, 2004; Zhang & Barash, 2000, 2004); notably, areas LIP (Zhang & Barash, 2004) and FEF (Moon et al., 2007) bilaterally.

Despite these observations, previous studies in our laboratory have shown that a single hemicortex can perform the direction inversion in the horizontal plane for the *auditory* domain (Reuter-Lorenz et al., 2011). Indeed, all previous studies involving hemispherectomized patients

studied only horizontal anti-saccades. As such, we know nothing of the ability of their single hemisphere to generate ipsilateral oblique anti-saccades. Therefore, one of the objectives of this thesis was to determine whether their remaining hemisphere can perform the vector inversion necessary to convert visual information about the location of a target in the seeing hemifield to a motor command for an oppositely-directed ipsilateral oblique saccade of arbitrary direction; i.e., a contralesional oblique anti-saccade. If so, this would imply that one hemisphere has all the circuitry required to transform a given visual signal into an arbitrary saccade motor program. Indeed, as I will emphasize in the fourth chapter, the generation of oblique anti-saccades present a major challenge to the patient's single hemisphere because one site in visual cortex must communicate with an infinite number of possible sites in oculomotor cortex. Our patients succeeded in this task whereas patients with discrete frontal lobe damage can be strongly impaired in anti-saccades (Guitton et al., 1985).

Another objective of this thesis was to consider blindsight in these patients. Specifically, I set out to determine whether an unseen visual stimulus in the blind hemifield can affect an anti-saccade directed there, a positive observation that would implicate the ipsilesional SC in the blindsight phenomenon. Following a unilateral discrete cortical lesion of V1 that spares the ipsilesional extrastriate visual cortex, it transpires that the ipsilesional SC and LGN are relay stations to surviving extrastriate areas that themselves permit unconscious visual processing. However, following a complete hemispherectomy it is the SC, that remains the only remaining structure to mediate blindsight; in this case "action" blindsight. T*hus, following lesions of all cortical visual structures on one side, as in the hemidecorticate patients studied here, I asked what role the SC plays in generating contralesional saccades to the blind hemifled?* Specifically,

here I investigated whether an unseen visual stimulus (probe) in the blind hemifield can alter the timing and accuracy of a contralesional *anti-saccade* (i.e. ipsilateral to the remaining hemisphere) to the blind hemifield. To the best of my knowledge, there are no studies that have directly measured the effect on saccadic eye movements of a visual stimuli presented in the blind hemifield of hemispherectomized patients. The existence of this effect would be a crucial observation to support the hypothesis that the SC, which has been considered first and foremost as an oculomotor region, is the main structure involved in visual information processing in the blind hemifield of our patients.

To summarize, the overarching hypotheses of this thesis were: 1) we speculated that the retino-tectal pathway to the superior colliculus on the lesioned side preserves its functional relevance and processes visual signals from the blind visual hemifield. Therefore, visual information in the blind hemifield can have an effect on the oculomotor output, although be it subliminally; 2) furthermore, following a substantial injury such as hemispherectomy, the brain is capable of major reorganization, such that a single hemicortex can perform oculomotor tasks, specifically a vector inversion required in oblique anti-saccade generation, a process that normally involves both hemispheres. We tested these hypotheses by performing the following three experiments.

Our first experiement, was designed to investigate whether hemidecorticate patients can subconsciously perceive, via anatomically preserved retino-tectal pathway, visual stimuli in their blind hemifield. We did so by presenting a visual signal (probe) in their blind hemifield in the location towards which the patients were already preparing a saccade (i.e. mirror-location of the target). Because, hemidecorticate patients cannot generate accurate pro-saccades to their blind

hemifield, we used an anti-saccade task, where the target was presented in their seeing hemifield and they were instructed to make an anti-saccade away from the target into their blind hemifield. We sought to determine wether the probe in their blind hemifield would affect the timing and accuracy of the ongoing anti-saccade into that field. A positive finding, would support our hypothesis.

Our second experiment, was devised to examine a hypothesis that the interactions between the probe and preparatory anti-saccade motor activity are occurring in the SC, and therefore descending, retina-to-SC-to-brainstem, signals are involved in the processing of the visual information from the blind hemifield of hemidecorticate patients. To examine this hypothesis, we presented the probe at different positions relative to the anti-saccade goal location, and then looked at whether the probe affects the anti-saccade vector in a manner explained by measured interactions between a saccade's preparatory motor activity and the visual activity evoked by the probe, on the logarithmically encoded motor map of the SC.

In our third and final experiment, we investigate whether one hemisphere can take a visual signal and convert it into a motor command for an ipsilaterally directed anti-saccade of any direction, an action that normally requires both hemispheres. Specifically, we tested whether a single hemisphere is capable of performing complex calculations to generate an oblique anti-saccade, requiring the inversion of both horizontal and vertical components. In addition, we compared the performance of our hemidecorticate patients to normal controls.

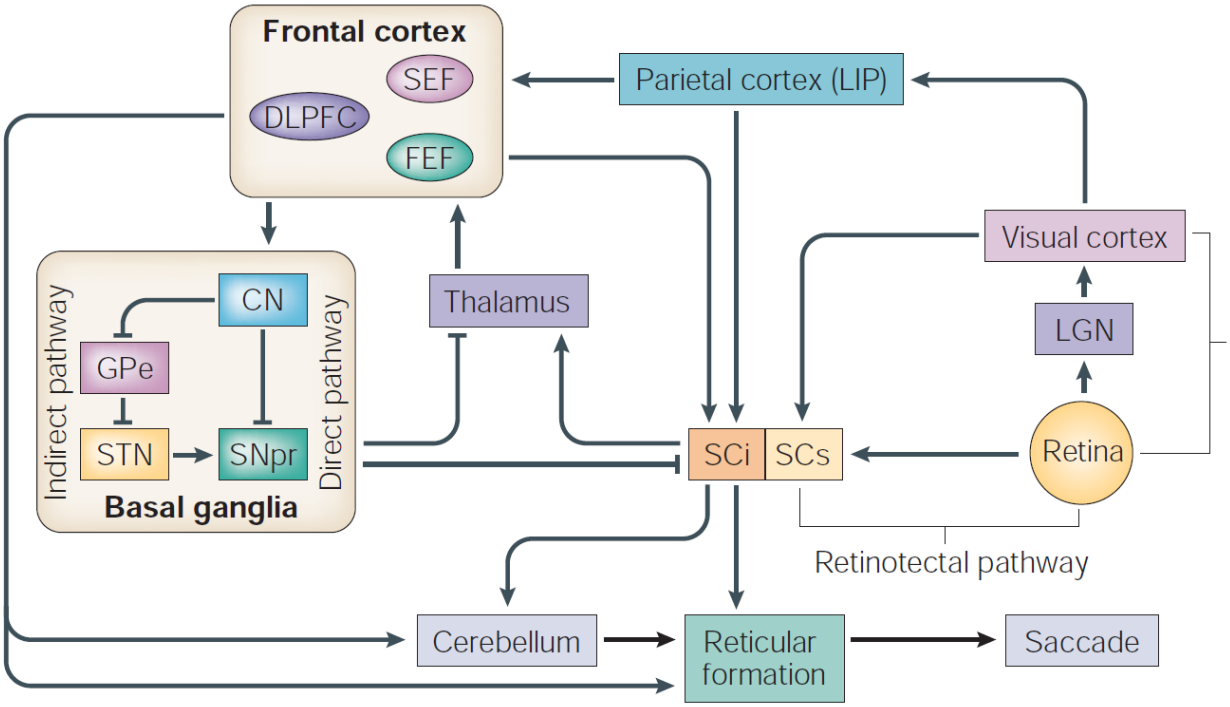


Figure 1-1. Neural circuitry controlling saccadic eye movements. (From Munoz & Everling, 2004; with permission).

Chapter 2: Blindsight after Hemidecortication: Visual Stimuli in Blind Hemifield Influence Anti-Saccades Directed There

Preface

Previous research pertaining to the blindsight phenomenon after hemidecortication has shown that human patients and monkeys hemispherectomized as adults do not recover saccade responses to targets presented in their blind hemifield (Estañol et al., 1980; Troost et al., 1972; Tusa et al., 1986). In this and the following study we ventured out to explore the possibility that although on their own targets presented in the blind hemifield of hemispherectomized individuals do not generate a sufficiently strong enough signal to produce an accurate saccade towards them, they nevertheless get registered by the brain, in particular the midbrain's structure - the superior cilliculus (SC). We therefore designed a set of experiments using an anti-saccade paradigm that allowed to test such hypothesis and demonstrated that targets presented in the blind hemifield do subliminally affect the trajectory and speed of the ipsilesional anti-saccades.

Summary

Patients missing a cortical hemisphere, removed surgically at adulthood, cannot consciously see a visual probe stimulus (P) flashed in their blind contralesional, hemifield. Nevertheless, they have a low-level form of blindsight wherein P can affect the reaction time of a manual response to the appearance of a visual target in their seeing hemifield. This ability is thought to require the pathway from retina to ipsilesional superior colliculus (SC) to cortex of the remaining hemisphere (Leh, Johansen-Berg, & Ptito, 2006). Apart from emitting ascending signals, the SC normally sends saccade commands to the brainstem, a function seemingly conserved after hemidecortication because such patients can generate voluntary and accurate

saccades bilaterally (Herter & Guitton, 2004). However, they cannot generate goal-directed saccades to P in their blind hemifield. We hypothesized that, in hemidecorticate patients, P might influence anti-saccades directed to the blind hemifield, to the mirror location of a visual cue presented in the seeing hemifield. We used anti-saccades because our patients could scale their anti-saccade amplitudes approximately according to different cue locations, thereby permitting us to control the end point of their anti-saccades to the blind hemifield. We identified in these patients a new form of blindsight wherein unseen P, if properly timed at the anti-saccade goal location in the blind hemifield, reduced the reaction time and improved the accuracy of anti-saccades directed to that general location. We hypothesize that P in the blind hemifield produced low-level signals in the ipsilesional SC that, if appropriately located and timed relative to anti-saccade goal and onset, interacted with anti-saccade motor preparatory activity – produced by descending commands to SC from the remaining hemisphere - so as to modify both anti-saccade reaction time and end point. Our results support normally encoded and functionally useful, but subliminal, signals in the retina-to-ipsilesional SC-to-reticular pathway of hemidecorticate patients.

Introduction

A fascinating example of the brain's "plastic" properties is the residual vision that survives ablation of the primary visual cortical area, V1. This phenomenon, called *blindsight*, has been much studied and, in Cowey (2010)'s extensive review, defined as "…the ability of patients with clinically blind field defects, caused by damage to the primary visual cortex V1, to detect, localize, and even discriminate visual stimuli that they deny seeing." (p. 3) Although the effects of V1 lesions have been the prime focus of research on blindsight, there also has been

considerable interest in the effects of larger lesions, in particular and of relevance to the present study, the ablation of one entire hemisphere called a hemispherectomy or hemidecortication. Here we will use the latter term.

The present study focuses on visuo-oculomotor function in hemidecorticate patients, but before delving into our study we return to the effects of V1 lesions for which it is known that, after a recovery period of a few weeks, both monkeys and humans can generate accurate saccades to stimuli in their scotoma (Cowey & Stoerig, 1995; Isa & Yoshida, 2009; Ikeda, Yoshid, & Isa, 2011; Kato et al., 2011; Moore, Rodman, Repp, & Gross, 1995; Pöppel, Held, & Frost, 1973; Sanders, Warrington, Marshall, & Wieskrantz, 1974; Weiskrantz, Warrington, Sanders, & Marshall, 1974; Yoshida, Takaura, Kato, Ikeda, & Isa, 2008). Indeed, it is remarkable that a V1 lesioned monkey can, a few years after surgery, make a saccade in the dark to a previously flashed target (the memory-guided saccade task) in the affected visual field. The midbrain's superior colliculus (SC) is critical to this function. Indeed, on the long-term post-operative after a V1 excision, neurons in the ipsilesional SC show visually triggered bursts, tonic memory activity and presaccadic motor bursts (Takaura, Yoshida, & Isa, 2011). Furthermore, the level of the memory period tonic activity correlates with the accuracy of the monkeys' saccades to targets in the "blind" hemifield. Finally, deactivation of the ipsilesional SC abolishes saccades to stimuli in the "blind" hemifield (Kato et al., 2011). Given the difference between the activity patterns in the ipsilesional and contralesional SCs, Takaura et al. (2011) suggest that these new properties of the ipsilesional SC arise via a reorganization of its reciprocal links with extra-striate areas such as LIP and FEF on the same side.

Here we study the effect of a visual stimulus in the blind hemifield of hemidecorticate patients and consider our observations in the context of the speculated role of the SC as described above. The advantage of studying the patients described herein is that they, when adults, underwent the complete, or near complete, surgical removal of one cortical hemisphere (Methods). By definition, after a complete hemidecortication, all cortical visual and motor areas on one side (in particular, in the context of the preceding paragraph, areas LIP and FEF) are either missing or have been disconnected. The hemidecortication also causes complete retrograde degeneration of the ipsilesional LGN in monkeys (Pasik, Pasik, & Schilder, 1969), but nevertheless, there is anatomical preservation of the ipsilesional SC (Ptito et al., 1996; Théoret et al., 2001; Ueki, 1966). Thus, these patients are unique in that any residual processing of visual information in their blind hemifield excludes all cortical structures on one side and involves visual processing only via the ipsilesional SC (Leh, Ptito, Schönwiesner, Chakravarty, & Mullen, 2010).

Although humans and monkeys hemidecorticated as adults can generate voluntarily both leftward and rightward accurate saccades (Herter & Guitton, 2004), they do not recover saccade responses to targets presented in their blind hemifield (Estañol et al., 1980; Troost et al., 1972; Tusa et al., 1986). This is presumably because, after hemidecortication unlike only V1 ablations, the ipsilesional SC receives no visual signals capable of triggering saccades. However, subthreshold visual signals in the retino-tectal pathway seem to exist because a low level form of blindsight in hemidecorticate patients has been demonstrated whereby an unseen visual stimulus in the blind hemifield affects the manual reaction time, indicated by a button-press, to the appearance of a visual stimulus in the seeing hemifield (“spatial summation effect”) (Leh et al.,

2006; Tomaiuolo et al., 1997). Using the diffusion tensor imaging (DTI) and fMRI techniques in hemidecorticate patients, this effect was suggested to be mediated by ascending crossed signals from the ipsilesional SC to the remaining hemisphere (normal monkey, Crapse & Sommer, 2009; patients, Leh et al., 2006, 2010) and then, to generate the button press, bilateral descending signals from the contralesional cortex to the spinal cord (e.g., Lacroix et al., 2004). Here, we show a blindsight effect on eye movements in these patients which may not require ascending signals from the ipsilesional SC.

In the normal monkey, crossed projections from the frontal eye field on one side to the contralateral SC have been reported (Distel & Fries, 1982; Leichnetz, Spencer, Hardy, & Astruc, 1981; Shook Schlag-Rey, & Schlag, 1990). Thus, in hemidecorticate patients, we would expect the FEF in the remaining hemisphere to project to the ipsilesional SC. Given that the well-established main function of the SC is saccadic eye movement generation, we would expect that saccadic eye movements to the "blind" visual hemifield of hemidecorticate patients, involve the remaining (contralesional) FEF and the ipsilesional SC. As mentioned in the preceding paragraph, signals in the retino-tectal pathway are known to be critical for blindsight in the "spatial-summation-button-press" task. However, such visual signals, by themselves, seem subthreshold for triggering saccades since these patients cannot generate saccades to visual targets in their blind hemifield. Nevertheless, it is possible that retino-tectal visual signals can, subliminally, affect crossed descending motor commands to the ipsilesional SC, thereby affecting the generation of contralesional saccades. This is what we examine here.

We investigated whether an unseen visual probe stimulus in the blind hemifield of hemidecorticate patients can alter the timing and accuracy of an anti-saccade to this hemifield

(see section 2.3, Rationale for tasks) even though the same probe in the blind hemifield fails to elicit an accurate pro-saccade response. We hypothesized that a visual probe in the blind hemifield can, via the retino-tectal tract, generate visually-triggered activity in the ipsilesional SC which, in the pro-saccade task, is insufficiently strong to raise above threshold the activity of collicular saccade-related neurons such that no visually triggered pro-saccade to the blind hemifield can occur. By comparison, in the anti-saccade task, we predicted that the increased visual activity in the ipsilesional SC, due to the presentation of the visual probe stimulus in the blind hemifield at the anti-saccade goal, can interact with and potentiate preparatory SC anti-saccade motor activity, thereby reducing anti-saccade latency and improving accuracy. This prediction was borne out.

Methods

Participants. Three hemidecorticate patients (DR, SE and JB) (Fig. 2-1) participated in this study, which was approved by the Montreal Neurological Institute and Hospital Research Ethics Committee. The participants gave informed and voluntary consent prior to commencement of experimentation.

The case histories of the patients are described elsewhere (Leh et al., 2006; Tomaiuolo et al., 1997) and will be briefly summarized. All three patients underwent a hemidecortication to relieve intractable epilepsy after the age of 17.

DR - 36 at the time of testing - underwent complete *right* hemidecortication including the amygdala and hippocampus at age 17. All remaining cortical tissue on the decorticate side was surgically disconnected from the rest of the brain. SE – 43 at the time of testing - underwent a partial hemidecortication (temporo-parietal-occipital removal) including the amygdala and

hippocampus of the *right* side at age 25. The entire right frontal lobe was spared. JB, who is left-handed, with the language lateralized to the right cortical hemisphere, underwent a two-step complete *left* hemidecortication at about the age of 20. Notably, his left frontal and partially occipital poles were left in place, but surgically disconnected from the rest of the brain. He was 43 at the time of testing.

Importantly, Leh Ptito, Chakravarty, and Strafella (2007) using the diffusion tensor imaging (DTI) technique for identifying axon tracts have reported differences between the subjects, specifically with respect to the involvement in blindsight of a novel ascending tract from the ipsilesional SC to the remaining hemisphere. We will consider, in the Discussion, the link between these findings and our results.

Apparatus. Visual stimuli, generated in MATLAB using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997), 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 57 cm from the participant. We patched one eye of each subject to avoid the possibility that they would converge their eyes in order to reduce the blind region of their visual field. (We did not test for this putative compensatory convergence.) Since all collicular cells within the binocular overlap region of the visual field respond equally well to the two eyes it would not matter what eye is patched. Therefore, we asked each subject which eye they wanted patched. They all preferred the contralesional eye. As we will explain below, subjects SE and DR, with right hemisphere ablations, made leftward anti-saccades into their blind hemifield while JB, who had a left hemisphere ablation, made rightward anti-saccades. Thus, each subject made anti-saccades into their nasal visual hemifield whose implication in blindsight is controversial. Indeed, some studies

in hemianopic patients have suggested a naso-temporal asymmetry in the effect of a distractor in the blind hemifield on the latency of pro-saccades to the seeing hemifield – with a distractor in the nasal hemifield being much less effective (Dodds Machado, Rafal, & Ro, 2002; Rafal, Smith, Cohen, & Brennan, 1990). By comparison, Walker, Mannan, Maurer, Pambakian, and Kennard (2000), also studying hemianopic patients, found no distractor effect in these patients no matter what hemifield was visually stimulated. These reports studied pro-saccades directed away from the blind hemifield. By comparison we show here that an unseen visual stimulus in the blind nasal hemifield does mediate a blindsight effect for anti-saccades directed to the blind hemifield.

Horizontal eye movements were monitored with bi-temporal electro-oculography (EOG). The EOG technique, whose calibration method is simple and calibration time short, was used to facilitate the mobility of the patients who requested frequent breaks. Prior to each recording session, the gain of the EOG signal was calibrated while the subject was fixating at various fixed target locations every 10º within ±30º range. During recording, small drifts were corrected by automatically resetting the EOG output to zero as the participants fixated at the start of each trial. When necessary, experiments were interrupted in order to recalibrate the gain of the EOG signal. The EOG output was exported as a real-time analog signal to an external Analog-to-Digital Converter device (NI6023E, National Instruments), through a simple first order low pass filer with a cut-off frequency of 300 Hz. The eye movement data collection was controlled using REX, a QNX-based real-time data acquisition system (Hayes, Richmond, & Optican, 1982). The eye position signal was sampled by the computer at a rate of 1 kHz. Offline in MatLab, the eye position signal was low pass filtered (zero-phase, cut-off at 30 Hz). Following proper calibration, the filtered EOG signal was linear within 1º over a range of ±30º for all participants.

Rationale for tasks. Our objective was to determine whether a visual probe in a subject's blind hemifield could affect both the timing and accuracy of a saccade directed towards that field. To do this it was important that our subjects could direct saccades to locations in the blind field that we could control experimentally. By controlling the saccade's goal - we could test whether a visual probe at different positions in the blind hemifield relative to that goal could change the saccade endpoint. We could not obtain goal-directed saccades to the blind hemifield, using visual targets, given that the patients could not generate accurate saccades to visual stimuli they could not see (Fig.2-5A). In lieu of visual targets, we considered using auditory targets in the blind hemifield, but hemidecorticate subjects generate very short latency (~100 msec) "express" saccades in this context (Reuter –Lorenz et al., 2011) which offers a very (too) short time window within which to test for a probe-effect. We therefore resorted to using the anti-saccade task because anti-saccade latency is longer than express saccade latency and anti-saccade goal is determined by the position of a visual cue in the seeing hemifield (Guitton et al., 1985). Our patients could generate anti-saccades that went approximately to the mirror location of the cue (Fig.2-5B) and this performance enabled us to study the effect of a probe placed in the blind hemifield exactly at the mirror location of the cue. Because of the natural variability in the amplitude and direction of our patients' anti-saccades, the probe frequently appeared outside the saccade's endpoint. The long anti-saccade latencies gave us a large time window within which to test for a probe-effect on accuracy and latency. We assumed that the putative neural activity, evoked by the probe on the collicular motor map, would interact with the anti-saccade motor preparatory activity and would both improve anti-saccade accuracy and reduce its latency.

Stimuli and procedure. The visual stimulus which could be the target (in the blind hemifield for the pro-saccade task), cue (in the seeing hemifield in the anti-saccade task) or probe (blind hemifield in anti-saccade task), consisted of a circular 0.5º light spot with a luminance level of 0.8 cd/m^2, flashed on a dark background. The spot was presented at fixed locations to the right or left of the fixation point (FP), itself in the middle of the screen and could appear at: ±5º, ±10º, ±20º, ±25º, ±30º. In all tasks, the saccades were made in complete darkness.

To address the issue of whether light scatter was responsible for responses to visual events in the blind hemifield we tested, prior to the main experiments, each participant's response to the 0.5 º light stimulus presented in the natural blind spot of their *intact* visual field. This method has been proposed to be the ideal control for both forms of intraocular scatter (Cowey, 2004). None of the participants could detect this stimulus in their blind spot.

In all experiments, participants were seated in a completely dark room with the head restrained by a bite bar. Each trial began with the presentation of FP alone for a random duration of either 800 ms or 1,200 ms. The experiment consisted of blocks of trials in the following conditions: 1) *pro-saccade to the blind visual hemifield (Fig. 2-2A)*: Immediately following FP's extinction, a target stimulus was presented in the *blind* visual hemifield (left for DR and SE; right for JB) for a brief duration of 86 ms. Since the target was presented in the blind hemifield, and therefore was not consciously detected, the disappearance of FP served as a signal for the initiation of the pro-saccade. The participants were instructed to guess the location of the target and to make a saccade towards the guessed location as quickly as possible. At the end of each trial, the room was illuminated for 1,000 ms before the start of the next trial to prevent dark

adaptation. No patient reported conscious awareness of the target; 2) *"pure" anti-saccade task (Fig. 2-2B)*: Immediately following FP's extinction, a cue was presented in the *seeing* visual hemifield for 86 ms. The appearance of the cue indicated that the subject had to initiate an anti-saccade towards the blind hemifield, to the mirror location of the cue. Participants were instructed to make an anti-saccade as promptly and accurately as possible. At the end of each trial, the room was illuminated for 1,000 ms before the start of the next trial to prevent dark adaptation; 3) *anti-saccade task with the probe presented at the mirror location of the cue after different delays relative to cue onset (Fig. 2-2C)*: this experiment was identical to the "pure" anti-saccade task with the additional presentation of the probe for 86 ms at the cue's mirror location in the blind visual hemifield. For reasons explained in the next paragraph, the probe was presented either simultaneously (to be called mirror-simultaneous) with the cue's presentation or after delays (mirror-delay) of 100 ms, 150 ms, or 200 ms from cue's onset.

Because of the limited number of sessions we had available with each patient, and their own limits on the number of trials/sessions they would accept, we could not perform exhaustive tests in order to test a broad range of delays. To determine a reasonable range of delays we hypothesized that the optimal probe delays should be such that probe-evoked activity should travel down the retino-tectal pathway and reach the ipsilesional SC in time to raise anti-saccade motor preparatory activity to a higher level such that it would reach sooner a threshold for saccade triggering. Thus, the probe should not be presented too close to anti-saccade onset because it would have little effect on SRT. Neither should it be presented so far ahead of an anti-saccade that it would not affect preparatory motor activity in the SC. The mean reaction times for "pure" anti-saccades for DR, SE and JB were 401 ms ± (SD=49), 507 ms ± (SD=101), and 622

ms ± (SD=138), respectively. To guess a range of probe delays we needed to know: 1) the conduction time in the human retinotectal pathway – from retina to superficial layers of the SC - and the time for activity to reach the intermediate layers of the SC; and 2) the duration of anti-saccade motor preparatory activity. We could find no information on the conduction time in humans and so we resorted to using data from monkey. In monkey the latency of visual responses in the superficial layers of the SC (that receive primarily retino-tectal inputs) is in the range 40-50 ms (Wurtz & Mohler, 1976). Given retinal delays, this is in line with the report that the majority of superficial layer SC cells respond to electrical stimulation of the optic chiasm at 6-10 ms (Marrocco & Li, 1977). In humans, saccades are suppressed at a minimum latency of ~60 ms by a visual stimulus flashed in the visual field contralateral to the saccade target (Reingold & Stampe, 2002).

Taken together this information (plus much other) led us to assume for humans a conduction time of ~60 ms in the retino-tectal pathway to the intermediate layers of the SC. We also assumed that the preparatory motor activity in the SC, driving the anti-saccade, precedes this saccade by ~150 ms (Everling, Dorris, Klein, & Munoz, 1999). This suggests that for DR, say, who had an anti-saccade latency of ~400 ms ±50 ms (relative to cue offset), a cue-probe delay of 200 ms should generate probe-induced signals in the SC that appear 140 ms before the mean anti-saccade. By comparison a cue-probe delay of 100 ms should precede by 140 ms anti-saccades that have a latency of 300 ms (i.e., those with 2 SDs shorter than the mean). In theory, this is in time to influence the preparatory activity of many anti-saccades. We therefore began by testing DR with cue probe delays of 100 ms, 150 ms and 200 ms and found the effects described herein. We did not have enough experimental time to examine the effects of longer delays. We

also found that the same delays could be used with SE and JB, with similar effects, thereby suggesting that preparatory activity preceded anti-saccades by much more than 150 ms.

We ran three anti-saccade conditions: 1) "pure" anti-saccade with no probe presentation; 2) “simultaneous”, wherein cue and probe were presented simultaneously but in opposite hemifields; and 3) “delay” wherein probe onset was delayed relative to cue onset by 100, 150 and 200 ms. The pro-saccade condition and 3 anti-saccade conditions were run in 4 different blocks of 56 trials each. Thus, the three different delays were in the same block and were randomly interleaved within each block. Condition presentation was randomly interleaved between participants and within participants between days of testing. No performance feedback was given to the participants at any point during the experiment.

In anti-saccade trials, subjects never knew that a probe was presented in their blind hemifield, but they could have discovered this had they made premature anticipatory saccades towards their blind hemifield, before FP was turned off. We discouraged anticipatory glances by including in each block of anti-saccade trials approximately 12% of catch trials wherein the *cue and probe* were *not* presented and the subject had been instructed to keep fixating FP until the end of the trial. Anti-saccade catch trials were not analyzed because of a lack of saccades. We also included 12% of catch trials in the pro-saccade task wherein the target (cue, Fig. 2-1A) in the blind hemifield was not presented when FP was extinguished. Note that for pro-saccade trials the subjects could not tell the difference between regular and catch trials because they could not see the cue in the blind hemifield. Nevertheless, we included these catch trials to verify whether pro-saccade reaction times and endpoints were affected by the cue. We did analyze the catch trials of pro-saccades and found no effect of the target which we explain in Results, section 3.2.

Data analysis. During each trial, the following experimental quantities were stored online for further offline analysis: target, cue and probe positions, cue-probe delay and EOG eye position signal.

In any one trial, the patients varied in the amount of saccades they produced to the blind hemifield: for both the pro- and anti-saccade trials, JB made mostly single saccades in each condition, SE made mostly 2 saccades, and DR made multiple saccades. Most often, saccades after the first appeared as searching movements because they were not goal directed. The data reported here were based on the patients' initial saccades only, an approach we think is valid given the clear goal-directed nature of the first saccade (to be considered later in relation to Fig. 2-5).

Data were analyzed from all trials except: 1) erroneous pro-saccades in anti-saccade trials (i.e. saccades that were made in the direction toward the cue rather than in the opposite direction); 2) anti-saccades with latencies < 120 ms (since these saccades would most probably be anticipatory in nature); 3) pro- and anti-saccades with latencies > 1,000 ms; 4) EOG signals that contained significant noise and blink artefacts (determined by visual analysis).

Offline we differentiated the eye position trace to give eye velocity. The onset and end of each saccade was identified as the points where velocity increased above and decreased below 40º/s, respectively. Saccadic reaction time (SRT) was calculated as the time difference between the target (or cue) onset and saccade initiation. We considered as outliers the saccades that fell outside ±2SD from the mean anti-saccade *landing* location and these saccades were removed from all further analyses. We used the remaining population of data points to calculate mean

SRT, mean anti-saccade landing location, mean absolute normalized error, and variability of anti-saccade landing location around the mean.

To quantify each participant's lack of ability to make target-related saccades to the blind hemifield, Pearson correlation analyses were performed on pro-saccade-end points compared to the target's locations, as well as on anti-saccade-end points compared to the anti-saccade goal locations.

In the anti-saccade tasks, analyses of mean SRT and mean saccade landing location were performed by using independent design ANOVAs. In addition, we performed the analysis of variability of anti-saccade landing locations around the respective mean landing locations for each cue condition (5°, 10°, 20°, 25°, 30°) in the "pure" and combined mirror-delay (i.e. we combined the trials from all three delays: 100 ms, 150 ms and 200 ms) anti-saccade conditions using two factor independent design ANOVA. This statistical approach was used because of unequal Ns. Because there was a discrepancy in the sample size between various conditions, there was a high probability that homogeneity assumption would be violated. Therefore, in order to control for the risk of type I error experiment-wise post-hoc analyses were performed using the Games-Howell test and the alpha level was set to a stringent level of .01 for all statistical tests (Fidell & Tabachnick, 2003).

To quantify overall performance of each subject in different anti-saccade conditions, we calculated mean absolute normalized error across all saccade goal locations in "pure" anti-saccade and combined mirror-delay conditions. The absolute normalized error was calculated by using the following formula:

$$\left| \frac{\text{saccade goal location} - \text{saccade landing location}}{\text{saccade goal location}} \right|$$

In order to assess the overall effect of probe presentation on the accuracy of saccade landing location, we performed two-tailed unpaired t-test analysis comparing absolute normalized error in the "pure" anti-saccade and combined mirror-delay conditions across all target locations.

We performed a one-way independent design ANOVA in order to compare mean SRT from the pro-saccade to the blind field condition to mean SRT from catch pro-saccade trials. Also, a one-way independent design ANOVA was performed to analyse the difference between SRTs from different target positions in the pro-saccade to the blind field condition.

The data were analyzed using SPSS 15.0 statistical software.

Results

Anti-saccade reaction times. We first determined whether presenting the probe in the blind hemifield affected the anti-saccade reaction time. Visual inspection of the histograms in Fig. 2-3**,** for typical subject SE, shows that there was no difference between the mean anti-saccade reaction times in the “pure” and mirror-simultaneous (zero-delay) anti-saccade conditions (Fig. 2-3A,B) but, compared to these conditions, the probe in the blind hemifield reduced the anti-saccade latency for *all* delays we tested (Fig. 2-3C,E). All patients produced the same result (Fig. 2-4); notably there was a significant and surprisingly equal decrease in latency, relative to the reference conditions, for all three delays in the range 100-200 ms. A one factor (5 experimental conditions: “pure” anti-saccade, mirror-simultaneous, mirror-100 ms delay, mirror-

150 ms delay, mirror-200 ms delay) independent design ANOVA conducted on the saccade reaction time (SRT) data yielded a significant main effect of condition type on SRT, $F(4,1561)=172.316$, $p<.0001$, $F(4, 1188)=95.676$, $p<.0001$ and $F(4, 1080)=61.459$, $p<.0001$ for DR, SE and JB, respectively.

In the case of DR and SE, Levene's tests for homogeneity of variance was reasonably satisfied ($p=.283$ and $p=.934$). Therefore, we performed post-hoc tests using Tukey's honest significance test. The results showed that the mean SRT observed in the "pure" anti-saccade condition was not significantly different from that observed in the mirror-simultaneous condition ($p=.049$ and $p=.959$, for DR and SE respectively). There was no significant difference in the mean SRT between any of the delay conditions (100 ms vs. 150 ms: $p=.468$ and .944, 100 ms vs. 200 ms: $p=.996$ and .963, and 150 ms vs. 200 ms: $p=.242$ and .999, for DR and SE respectively). Moreover, in both patients the mean SRT observed in all three "mirror-delay" conditions were significantly different from both the mean SRT observed in the "pure" anti-saccade and mirror-simultaneous conditions (all $p_s<.001$).

In the case of JB, Levene's tests for homogeneity of variance indicated that the homogeneity assumption has been violated ($p <.01$). Therefore, we performed post-hoc tests using Games-Howell test, which controls the risk of type I error experiment-wise. The results of the multiple comparisons tests computed on the main effect of condition type showed that the mean SRT observed in the "pure" anti-saccade condition was not significantly different from that observed in the mirror-simultaneous condition ($p=.529$). There was no significant difference in the mean SRT between any of the delay conditions (100 ms vs. 150 m: $p=.999$, 100 ms vs. 200 ms: $p=.898$, and 150 ms vs. 200 ms: $p=.732$). Moreover, the mean SRT observed in all three

"mirror-delay" conditions were significantly different from both the mean SRT observed in the "pure" anti-saccade and mirror-simultaneous conditions (all $p_s<.001$).

Pro-saccade reaction times. In pro-saccade trials the subjects knew the target would always be in their blind hemifield and so they used the offset of the fixation point as the cue to make a saccade to the unseen target. Therefore, we should not expect the SRT of their pro-saccades to be comparable to those of visually triggered pro-saccades. Indeed, pro-saccade mean SRTs were above 400 ms in all subjects: DR, 493 ms (SD= ±188); SE, 454 ms (SD= ±178); JB, 412 ms (SD= ±126) (Fig. 4). In normal subjects, pro-saccade SRT is less than the anti-saccade SRT (e.g. Guitton et al., 1985). This was true for our subjects JB and SE. However, in DR, pro-saccade SRT was longer than anti-saccade SRT, which we attribute to DR's perfectionist personality who always tried very hard to see the target in the blind hemifield but, frustratingly, to no avail.

By comparison to the regular trials, the pro-saccade SRTs in *catch trials* for DR, SE and JB were: 510 ms (SD= ±191), 442 ms (SD= ±155) and 423 ms (SD= ±181), respectively. One-way independent design ANOVA showed no significant difference between SRTs of catch trials and real pro-saccade trials to the blind hemifield (p=.527, p=.789 and p=.732, respectively). This observation indicates that the presence of the target in the blind hemifield had no effect on SRT in pro-saccade trials. We speculate that this was because our subjects generated pro-saccades to "default" positions, such that the pro-saccade mean amplitude was about constant and neither related to the target's position, nor indeed to whether or not the target was present, as shown by the catch trials (Fig. 2-5A). This behavior was unlike that in the anti-saccade task (Fig. 2-5B). Therefore, any target related visual activity in the SC (e.g., via the retino-tectal tract) did not

coincide spatially with pro-saccade motor preparatory activity on the SC map. However, in subjects SE and JB there could have been spatial coincidence on the SC map between motor activity and target position for pro-saccades targets at 10°, given that these subjects consistently made about 12° pro-saccades, independent of target position (Fig 2-5A). Thus, for a target at 10° in the pro-saccade task one might expect an interactive effect of the saccade target on SRT, for these subjects. However, in our analysis of JB's and SE's data, we found no statistically significant difference between SRTs for different target positions in the *pro-saccade to the blind field* condition (p=.336 and .222, for SE and JB respectively). Nevertheless, there was a non-significant trend for: JB who had the smallest SRTs for pro-saccade targets at 10°and 20°; and for subject SE who had the largest SRTs when the pro-saccade target was at 25° and 30°. We speculate that the lack of significance in these observations was due to two factors: 1) the large variability in pro-saccade landing locations (Fig. 2-5A), combined with, 2) the relatively small number of trials per pro-saccade target location, on average less than 20.

Comparison of pro-saccade and anti-saccade accuracy in the blind hemifield. Figure 2-5A shows the mean saccade landing location made by patients DR, SE and JB at each probe location in the *pro-saccade* task. It is obvious that pro-saccades to the blind hemifield were not target related. Indeed, the pro-saccades in catch and probe trials had the same landing location. DR made most of her saccades to locations about 5º in the blind hemifield (her 'default' location), which for target offsets >10º resulted in errors that were proportional to the distance between the target's location and the default location. Similarly, SE and JB made saccades mostly to about 12º locations in the blind hemifield. Therefore, for greater target offsets, their errors were also approximately equal to the distance between the probe's location and the

preferred location. This graph indicates that none of the participants could reliably generate an accurate saccade to a target presented in their blind hemifield. This essentially self-evident result based on visual inspection of Fig. 2-5A, was confirmed formally by a Pearson correlation analysis that showed no significant correlation ($r(232)=-.077$, $p=.242$, $r(113)=.056$, $p=.552$ and $r(159)=.045$, $p=.57$, for DR, SE and JB, respectively) between the goal location and the saccade-end location in the pro-saccade task to the blind hemifield.

"Pure" anti-saccades towards the blind hemifield were much more accurate than pro-saccades (Fig. 2-5B). Inspection of Figure 2-5B reveals that subjects DR and SE tended to overshoot the 5º goal location and undershoot 20º, 25º and 30º goal locations. JB, on the other hand, overshot all saccade goal locations. Pearson correlation analysis revealed positive significant correlation between the saccade goal location and the saccade-end location for all three patients ($r(491)=.646$, $p<.0001$, $r(248)=.811$, $p<.0001$ and $r(392)=.705$, $p<.0001$, for DR, SE and JB, respectively).

Accuracy of anti-saccades to the blind hemifield: effect of the probe presented at the mirror location of the cue. The analysis of two factor [delay type (100 ms, 150 ms, 200 ms) and saccade-goal locations (5º, 10º, 20º, 25º, 30º)] independent design ANOVA on mean saccade landing location revealed no significant interaction between the delay type and the saccade-goal locations for any of the three participants, $F(8,409)=.784$, $p=.617$, $F(8, 720)=.317$, $p=.960$ and $F(8, 431)=.678$, $p=.711$ for DR, SE and JB, respectively. Therefore, we combined the data from all three delays and compared the mean anti-saccade landing locations across the different goal locations in the combined mirror-delay conditions versus the "pure" anti-saccade condition.

Figure 2-6 plots mean anti-saccade landing locations in the "pure" anti-saccade and combined mirror-delay conditions. The analysis of two factor independent design ANOVA [condition type (combined mirror-delay vs. "pure" anti-saccade) and saccade-goal locations (5º, 10º, 20º, 25º, 30º)] revealed a significant interaction for patients DR and JB, $F(4,937)=6.348$, $p<.0001$ and $F(4, 853)=7.577$, $p<.0001$, respectively. Subsequent simple main effect analysis of condition type over the five anti-saccade-goal locations revealed, for DR , statistically significant differences between combined mirror-delay and "pure" anti-saccade conditions for 5º ($p=.006$), 25º ($p=.003$), and 30º ($p<.0001$) cue locations, but not for 10º ($p=.09$) and 20º ($p=.164$) cue locations; for JB, simple main effect analysis of condition type over five anti-saccade-goal locations revealed statistically significant differences between combined mirror-delay and "pure" anti-saccade conditions for all saccade-goal locations ($p_s<.0001$). However, as can be seen from Fig. 2-6 (A and C), while for subject DR probe presentation had a tendency to bring the mean saccade-end points closer to anti-saccade goal location (although not statistically significant for goal locations 10º and 20º), for subject JB, the probe had a tendency to reduce the overshoots of saccade goal location produced in his "pure" anti-saccade condition. There nevertheless remained a small overshoot for 5º and 10º goals. However, for anti-saccade-goal locations of 25º and 30º, presentation of the probe resulted in an undershoot of saccade-goal location which was more significant than the original overshoot when no probe was presented (see Fig. 2-6C).

For SE, a two factor [condition type (combined mirror-delay vs. "pure" anti-saccade) and saccade-goal locations (5º, 10º, 20º, 25º, 30º)] independent design ANOVA on the mean anti-saccade landing location revealed no significant interaction ($F(4,978)=.40$, $p=.807$) and no main effect of condition type ($F(1,978)=.795$, $p=.373$). These results indicate that while for subjects

DR (Fig. 2-6A) and JB (Fig. 2-6C) presentation of a probe at the mirror location of the cue had a significant effect on the mean anti-saccade landing location, for subject SE (Fig. 2-6B), it did not.

In order to assess the overall effects of probe presentation across all saccade goal locations, separate two-tailed unpaired *t* tests were conducted for subjects DR, JB, and SE to determine whether there was a difference in the mean absolute normalized error of saccade landing locations between the "pure" anti-saccade and combined mirror-delay conditions (Fig. 2-6D). The data analyses revealed that the mean absolute normalized error ($\bar{E}$) of saccade landing locations in the "pure" anti-saccade condition (DR: $\bar{E}$ =.37, *SD* = .32 and JB: $\bar{E}$ =.59, *SD* = .71) was significantly different from that in the combined mirror-delay condition (DR: $\bar{E}$ =.25, *SD* = .2 and JB: $\bar{E}$ =.37, *SD* = .35), $t(861) = 6.35$, $p < .0001$ and $t(777) = 5.27$, $p < .0001$, for subjects DR and JB, respectively. However, for subject SE, a two-tailed unpaired *t* test revealed that the mean absolute normalized error of saccade landing locations in the "pure" anti-saccade condition ($\bar{E}$ =.29, *SD* = .27) was not significantly different from that in the combined mirror-delay condition ($\bar{E}$ =.29, *SD* = .26), $t(986) = -.13$, $p = .90$.

We also found that presentation of the probe at the mirror location of the cue tended to reduce the variability of individual saccades around the respective mean anti-saccade landing location compared to when no probe was presented in the “pure” anti-saccade condition. We represented this variability by a mean absolute error, calculated by taking an average of absolute distance of each individual anti-saccade from the mean anti-saccade landing location in each saccade-goal location condition (Fig. 2-7). For subjects DR and JB, the analysis of two factor independent design ANOVA [condition type (combined mirror-delay vs. “pure” anti-saccade)

and saccade-goal locations (5º, 10º, 20º, 25º, 30º)] revealed a significant main effect of condition type ($F(1,937)=32.96$, $p<.0001$ and $F(1,853)=67.72$, $p<.0001$, for DR and JB, respectively), indicating that on average the variability of anti-saccade landing locations around the respective mean saccade landing location decreased with probe presentation in the mirror-delay condition compared to "pure" anti-saccade condition (Fig. 2-7A,C). For SE (Fig. 2-7B), the analysis of two factor independent design ANOVA [condition type (combined mirror-delay vs. "pure" anti-saccade) and saccade-goal locations (5º, 10º, 20º, 25º, 30º)] revealed a significant interaction ($F(4,978)=4.43$, $p=.001$). The analysis of simple main effect for condition type over the five saccade-goal locations, revealed no significant difference in variability at 5º ($p=.750$), 20º ($p=.099$) and 30º ($p=.224$) cue conditions, and a significant increase in variability of saccade landing locations around the respective mean saccade landing location at 10º ($p=.003$) and 25º ($p=.022$) cue conditions.

In summary, for subjects DR and JB, presentation of a probe at the anti-saccade goal location (i.e. in the mirror location of a cue) reduced SRT, decreased the variability of anti-saccades, and improved overall accuracy of anti-saccade landing locations. For subject SE, presentation of a probe also reduced SRT, but did not have any effect on mean anti-saccade landing locations, and did not reduce variably of anti-saccade-end points for any of the goal locations.

Discussion

We have revealed two critical and intriguing functions of the single remaining hemisphere of hemidecorticate patients: 1) the ability to generate goal-directed anti-saccades, made in the dark and cued by a briefly presented visual cue in the seeing hemifield; and 2) a

blindsight phenomenon wherein an unseen flashing visual probe in the blind hemifield affected the timing and precision of anti-saccades to that field.

Anti-saccade generation. The anti-saccade task requires the suppression of a reflexive saccade towards a sensory cue, and the generation of a voluntary saccade to the mirror location of that cue, in the absence of any sensory stimulus presented at the anti-saccade goal. Therefore, a vector inversion has to be performed in order to transform the sensory information in one hemifield into a motor response to the other. We showed in Reuter-Lorenz et al. (2011) that our hemidecorticate patients could make anti-saccades away from an *auditory* cue with a latency of about 100 ms less than that shown here in our "pure anti-saccade" condition using a *visual* cue. However, this important difference may not relate wholly to a difference between the processing of auditory versus visual information by the remaining hemisphere. Indeed, in the Reuter-Lorenz study we did *not* require the patients to make anti-saccades that were accurately directed to the mirror location of the auditory cue, whereas in the present study accuracy was a requirement, as shown in Fig. 2-5B.

In the normal brain, both hemispheres participate in the vector inversion process inherent to anti-saccade generation (Everling & Munoz, 2000; Munoz & Everling, 2004; Zhang & Barash, 2000, 2004); notably, areas LIP (Zhang & Barash, 2004) and FEF (Moon et al., 2007) bilaterally. Despite these observations, a single hemicortex is able to perform the direction inversion (auditory domain; Reuter-Lorenz et al., 2011) and vector inversion (visual domain; present results) necessary for generating anti-saccades ipsilateral to itself.

Herter and Guitton (2004) have shown that the single hemicortex in hemidecorticate patients can control, with remarkable accuracy, saccades in both directions, notably ipsiversive

ones. This bilateral accuracy suggests that the patients' intact hemicortex has fully functional bilateral connections with brainstem oculomotor structures, notably the SC. Indeed, innate bilateral connections from frontal oculomotor regions have been observed to the: SC (Distel & Fries, 1982; Leichnetz et al., 1981; Shook et al., 1990), nucleus reticularis tegmenti pontis (Huerta, Krubitzer, & Kaas, 1986; Leichnetz, Smith, & Spencer, 1984; Stanton, Goldberg, & Bruce, 1988) and the paramedian pontine reticular formation (Huerta et al., 1986; Leichnetz et al., 1984; 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). Such connectivity may explain why the SC remains anatomically intact on the decorticate side following experimental hemidecortication in monkeys (Théoret et al., 2001). Involvement of the ipsilesional SC in contralesional saccade generation is supported further by another observation showing that our hemidecorticate patients can generate short-latency “express saccades” to auditory targets ipsilateral to their intact hemicortex (Reuter-Lorenz et al., 2011), a function that normally requires a cortico-SC pathway (Schiller et al., 1987).

The neural machinery that subtends bilateral control by a single hemisphere seems functional in the normal brain because some FEF and LIP neurons have ipsilateral visual and motor responses (Barash et al., 1991; Crapse & Sommer, 2009). FEF neurons with ipsilateral motor responses receive projections from the contralateral SC (Crapse & Sommer, 2009), a projection that in hemidecorticate patients could permit the remaining hemisphere to receive information from the ipsilesional SC. This projection could be the one described by Leh et al. (2006) which becomes more prominent in some hemidecorticate patients. Hence, anti-saccade

generation in our patients would require transferring signals within the FEF and LIP of the one remaining hemisphere, from the majority of contralateral visual neurons to the minority of neurons having ipsilateral motor responses. However, the activity patterns of FEF neurons, anatomically identified as projecting to the contralateral SC, has not been studied.

In summary, anti-saccade production in our patients may have used pre-existing neural circuits which may explain why each subject could perform this task in the first test trials. As we will review below in detail we explain our observed effects of the visual probe on the anti-saccade response as being due to the interaction in the ipsilesional SC of a visual signal and motor preparatory activity. In the normal monkey, the level of motor preparatory activity in some FEF neurons that project ipsilaterally to the SC on the same side begins rising just after cue onset and can occur many hundreds of milliseconds before the onset of contralaterally-directed anti-saccades (Everling & Munoz, 2000). Given the evidence summarized above, similar neurons in the same FEF may exist that project to the contralateral SC and encode preparatory activity for ipsilateral anti-saccades. In our patients, these putative neurons would project from the remaining FEF to the ipsilesional SC and encode contralesional anti-saccades. There is also evidence that the level of excitability of the ipsilesional SC can be modulated directly by the remaining dorsolateral frontal cortex via descending projections to the contralesional SC and then inhibitory SC commissurals to the ipsilesional SC (Johnston & Everling, 2006) and/or indirectly through the ipsilesional or contralesional basal ganglia (reviewed in Hikosaka et al., 2000; Hikosaka & Wurtz, 1983; Jiang et al., 2003; Munoz & Everling, 2004).

Effect of the probe presented in the blind hemifield. Our principal findings were: 1) In all three tested adult-hemidecorticate patients, an unseen small spot of light (the probe) flashed in

their blind hemifield reduced their SRT (Figs. 2-3,4) for cue probe delays of 100 ms, 150 ms, 200 ms, but not 0 ms. 2) The probe improved JB's and DR's performance accuracy by bringing the anti-saccade end-point closer to the cue's mirror location (Fig. 2-6A,C) and reduced the variability of anti-saccade landing locations around their mean (Fig. 2-7A,C). These effects in JB and DR were striking because the same probe stimulus, when presented alone in their blind hemifield, failed to elicit an accurate pro-saccade (Fig. 2-5A), even in blocks of trials where the subject anticipated a presentation of the probe. By comparison to the other subjects, there was no systematic effect of the probe on SE's anti-saccade endpoints (Fig. 2-6B) and variability of SE's anti-saccade landing locations around their mean (Fig. 2-7B).

How can our probe effects be explained physiologically? Our first hypothesis is that the effect of probe-evoked visual signals on the anti-saccade motor command (discussed in the previous section) is mediated by signals in the retino-tectal pathway. The involvement of this pathway from retina to the ipsilesional SC in conveying visual information from the blind hemifield in hemidecorticate patients has been shown by Leh et al. (2010). Our second hypothesis is that the visual signals in the superficial layers of the ipsilesional SC descend to, interact with and modulate preparatory motor activity for anti-saccades in the intermediate visuo-motor layers. Isa (2002) proposed that if the pre-saccadic activity in the intermediate layers of the SC is absent, then the visual signal mediated by superficial layer neurons can reach the intermediate layers but fail to elicit a sufficiently strong burst of activity in the intermediate layers to initiate a motor command for saccade generation. In fact, normally convergent excitatory inputs to the deeper layers from extrastriate cortical structures are necessary for the generation of saccades to visual targets, specifically in the 'regular' latency range (Isa, 2002).

Therefore, to explain the probe effects, we hypothesize that probe-evoked activity in retino-tectal afferents to the ipsilesional SC's superficial layers, descended to the intermediate layers and interacted with and enhanced, anti-saccade motor preparatory activity driven by, say, the FEF of the remaining hemisphere. Put another way, we propose that a preparatory motor signal in the ipsilesional SC, encoding the contralesional anti-saccade, interacted with a probe-induced visual signal, itself too weak to drive a saccade on its own.

In support of the preceding hypothesis, it has been shown by Özen, Augustine, and Hall (2000) that the application of a single brief current pulse to the superficial layer of the rat SC can produce a prolonged burst of excitatory postsynaptic current (as long as 300 ms) in intermediate layer cells. The fact that the effects of the probe on SRT were similar in all subjects, despite the pure anti-saccade SRTs ranging from ~ 400 ms in DR to ~600 ms in JB, suggests that there was long-lasting motor preparatory activity in the ipsilesional SC over which probe-driven neuronal activity could drive an anti-saccade command signals above threshold for saccade initiation, and sooner than in the "pure" anti-saccade case. As reviewed in the preceding section, long lasting preparatory activity for anti-saccades occurs normally.

Our hypothesis also explains why the probe improved anti-saccade *accuracy* in JB and DR: probe-induced activity at the anti-saccade goal location (i.e., the mirror location of the cue) on the SC's motor map interacted with the subject's own erroneously encoded motor activity (Fig. 2-5) so as to move, on the map, the center of gravity of the overall motor activity closer to the goal. Our explanation of why SE's anti-saccade accuracy was not affected by the probe, despite the fact that his SRTs were affected, is because SE has bilaterally intact frontal lobes. We speculate that he "placed" his anti-saccade motor activity near to the correct location on the

ipsilesional SC map such that the only possible effect of the probe was on his SRT, not accuracy. His amplitude-dependent overshoot and undershoots might then have resulted from mechanisms downstream of the SC.

Our postulate that there is interaction in the SC between preparatory motor and retino-tectal visual activity also seems compatible with observations on multisensory interactions in the SC which are strongly enhanced when weakly effective uni-modal stimuli are combined in register (Meredith & Stein, 1996). For example, Leo, Bolognini, Passamonti, Stein, and Làdavas (2008) showed that visual information in the blind hemifield of hemianopic patients can lead to significant improvements in their ability to localize auditory targets, but only when the visual and auditory stimuli are spatially and temporally coincident. However, Wallace and Stein (1994) showed that this cross-modal enhancement in the SC depends on inputs from ipsilateral association cortex, which is clearly lacking in our patients. Thus, the mechanisms underlying the effects of the probe in the present experiments remain enigmatic and may not involve signal enhancement. This is considered further in the next section.

Evidence for an ipsilesional SC, hypoactive to visual stimuli. It is well known that the intermediate layers of the SC are organized to form a motor map that specifies the amplitude and direction of saccades into the contralateral visual field. The rostral portion of the map – encoding the perifoveal representation – has a more complex role being implicated in bilateral microsaccade generation, fixation and smooth pursuit control and is particularly active during attentive fixation of a foveal target (Hafed & Krauzlis, 2009; Hafed & Krauzlis, 2012; Munoz & Guitton, 1989, 1991; Munoz & Wurtz, 1995).

Sprague (1966) made the fascinating observation that a cat, blind due to occipital cortex ablation, recovers the ability to orient to a visual target in the contralesional blind hemifield if the contralesional SC is ablated or the collicular commissure is cut. He argued that the cortical ablation resulted in disequilibrium between the two SCs with the ipsilesional SC depressed due to inhibition by the other SC. Removing the influence of the contralesional SC restores the ipsilesional SC to its normal level of excitability. There is now strong evidence that saccade-related neurons on the motor map can suppress the activity of their contralateral counterparts as well as "fixation" neurons on both sides of the SC (reviewed in Munoz & Fecteau, 2002; Munoz & Istvan, 1998; Takahashi, Sugiuchi, Izawa, & Shinoda, 2005).

In an extension of the Sprague (1966) observations, Hovda and Villablanca (1990) reported that, in adult-hemidecorticate cats, there is a significant depression of oxidative metabolism in the ipsilesional SC compared to the contralesional SC. They speculated that the reduced oxidative metabolism is indicative of the depression of neuronal firing in the ipsilesional SC. Interestingly, after infantile hemidecortication, the metabolic activity and neuronal density in the ipsilesional SC remain normal (Hovda & Villablanca, 1990; Théoret et al., 2001), although this SC has lost 30% of its volume and number of neurons but nevertheless receives retinal inputs and appears to retain some functional properties (Théoret et al., 2001). These differences in the condition of the SC that depend on the time of the hemidecortication, could explain why patients hemidecorticated at a young age can generate saccades to targets in their blind hemifield (Perenin & Jeannerod, 1978), while adult-hemidecorticate animals and humans cannot (Hovda & Villablanca, 1990; Troost et al., 1972; Tusa et al., 1986; and present results).

Evidence for an ipsilesional SC, hyperactive to auditory stimuli; differences between visual and auditory domains. The evidence reviewed just above suggests that following hemidecortication the ipsilesional SC is hypoactive to visual stimuli. By comparison, our study of *auditory* anti-saccades in these patients (Reuter-Lorenz et al., 2011) suggested that the intermediate layers of the ipsilesional SC are hyperactive. Indeed, we found that they generated short latency anti-saccades, and "express" pro-saccades to *auditory* targets in their blind hemifield. The generation of express saccades requires cortico-SC signals because SC ablation eliminates express saccades (Schiller et al., 1987). Therefore, we proposed in Reuter-Lorenz et al. (2011) that short latency auditory saccades to the patients' blind hemifield were facilitated by plastic mechanisms that rendered the ipsilesional SC *hyperactive* in order to facilitate reflexive glances to auditory targets they could hear but, of course, not see.

At first glance, the idea of a hyperactive ipsilesional SC seems compatible with the effects of the visual probe found in the present study, but it appears to contradict the classic observations and interpretations by Sprague (1966), reviewed in the preceding section, on the effects of the removal of descending inputs onto the ipsilesional SC, and the dynamic neural interactions between the two SCs. The seemingly contradictory results of the auditory and visual studies are reconciled by the observation, in visually deprived cats, that there is a significant *decrease* in the quality of visual signal in the affected SC while, at the same time, there is a significant *increase* in the auditory responses compared to normal cats (Rauschecker & Harris, 1983). The latter authors also found auditory responses in the superficial layers of SC following visual deprivation, which are absent in the normal cats. Taken together, these results suggest that in our patients, made hemidecorticate as adults, the ipsilesional SC may be *hyper-responsive to*

auditory stimuli (Reuter-Lorenz et al., 2011) and *hypo-responsive to visual* stimuli (present results). We suggest that this is why we had to use the anti-saccade task in the present experiments to generate preparatory motor activity that itself could be enhanced by visual activity evoked by the probe.

Comparison with other blindsight studies in hemidecorticate patients. Our results are not in full agreement with other tests, in the same patients, of blindsight using the spatial summation effect on a manual button-press reaction time (Leh et al., 2006; Tomaiuolo et al., 1997). In the latter studies, a notable finding was that in patients DR and SE, but *not* JB, the visual probe in the blind hemifield affected the button-press reaction time to the appearance of a light spot in the seeing hemifield (Leh et al., 2006; Tomaiuolo et al., 1997). *By comparison, in the present study we found an effect of the probe on anti-saccades in all three patients*. How can this difference in specifically JB be explained? The manual button-press task requires ascending visual signals to the remaining hemisphere due to the need to activate its motor areas to provide the button-press motor command response. The inter-subject difference in the button-press task was explained in two studies by Leh et al. (2006, 2010) using DTI and fMRI, respectively. In DR and SE, they found evidence for the involvement of the ipsilesional SC and its ascending crossed connection to visually-related cortical areas of the remaining hemisphere, notably FEF. In both patients, these projections are more prominent than in healthy controls. By comparison, they found that patient JB lacked this ascending crossed connection from the ipsilesional SC to the remaining hemisphere. Even his normal ipsilateral ascending projection was reported to be weaker. Accordingly, Leh et al. (2006) suggested that in JB, both SCs had degenerated. However, *the findings of the present study are in contradiction with this conclusion.* Indeed, the

lack of a difference between subjects DR, SE and JB in the present study implies that the effect of the visual probe on anti-saccade interactions in our paradigm was due to signal processing in the descending pathway from retina-to-ipsilesional SC-to-the brainstem saccade burst generator and not in ascending signals from the ipsilesional SC to the remaining hemisphere.

Conclusion

In summary, considerable evidence suggests that following hemidecortication, the absence of ipsilateral cortical inputs to the ipsilesional SC, causes the level of excitation of tecto-reticular neurons (TRNs) in the intermediate layers of the SC to be too low to trigger contralesionally-directed pro-saccades to visual stimuli in the blind hemifield. We propose here that the activity of TRNs in the ipsilesional SC can be raised above the threshold for generating a saccade by superimposing two inputs: 1) a depolarization, via the retino-tectal tract, of a discrete ensemble of TRNs at a particular locus on the motor map; and 2) a low level preparatory motor activity at the same locus. We achieved the latter by using contralesionally-directed anti-saccade and found that they were triggered early and their accuracy was improved by an unseen simple visual probe (light spot) in their blind hemifield. It remains to be proven that the ipsilesional SC truly carries descending probe-evoked visual activity and whether this activity can be modulated by varying the salience of the probe stimulus.

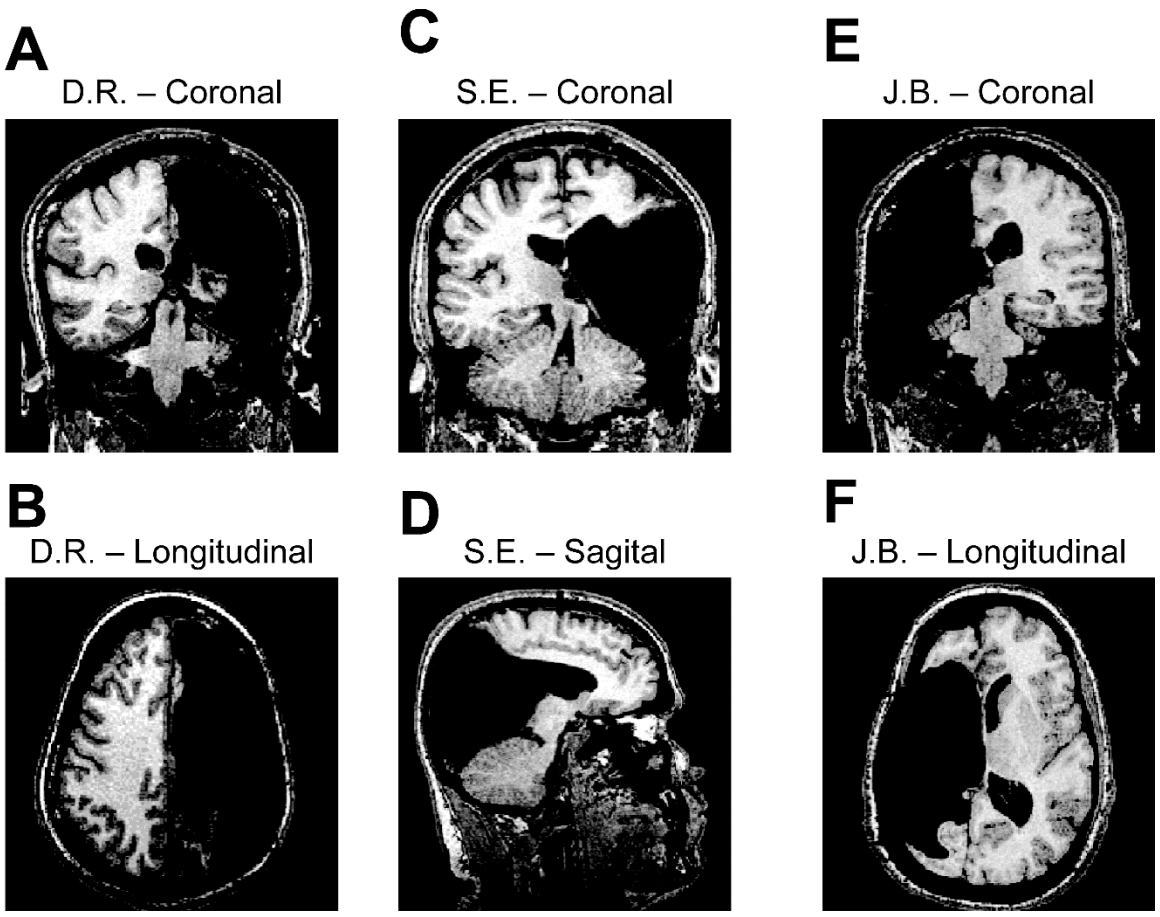


Figure 2-1. MRI scans showing the cortical ablations of the three hemidecorticate patients. **A,B**: Coronal and longitudinal sections, respectively, showing the complete right hemidecortication of patient D.R. **C,D**: Coronal and sagittal sections, respectively, showing the temporal-parietal-occipital lobectomy of patient S.E. **E,F**: Coronal and longitudinal sections, respectively, of the complete functional left hemidecortication of patient J.B. The tissue remaining on the operated left side was disconnected from the rest of the brain. See text for case histories.

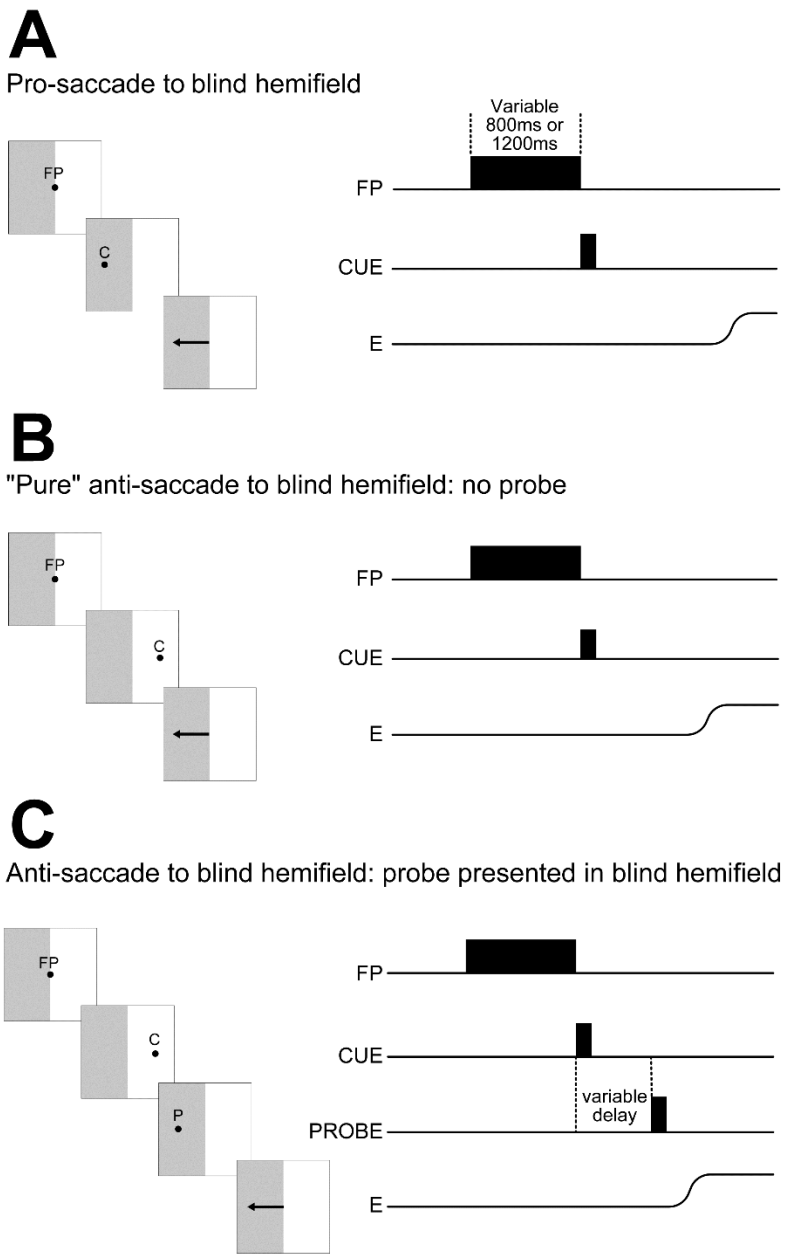


Figure 2-2. Schematic representation of the different experimental tasks. In all tasks the central fixation point (FP) was presented for a random duration of either 800 ms or 1,200 ms. (**A**) *Pro-saccade to the blind hemifield*: Immediately following FP's extinction, a cue

(**C**) was presented in the blind hemifield for 86 msec. Subject was instructed to look to where the cue had appeared. (**B**) *"Pure" anti-saccade task*: Immediately following FP's extinction, a cue was presented in the seeing visual hemifield for 86 ms and the subject was instructed to look to the mirror location. Note, that in this task, no stimulus was presented in the blind hemifield. (**C**) *Anti-saccade task with the probe presented in the blind hemifield*: Immediately following FP's extinction, a cue was presented in the seeing visual hemifield for 86 ms. As in (**B**) above, subject had to look to the mirror location. A probe (P) was presented for 86 ms at the mirror location of the cue in the blind hemifield after variable delays of either 0 ms (i.e. cue and probe presented simultaneously), 100 ms, 150 ms or 200 ms from the onset of the cue. The shaded area represents the blind hemifield.

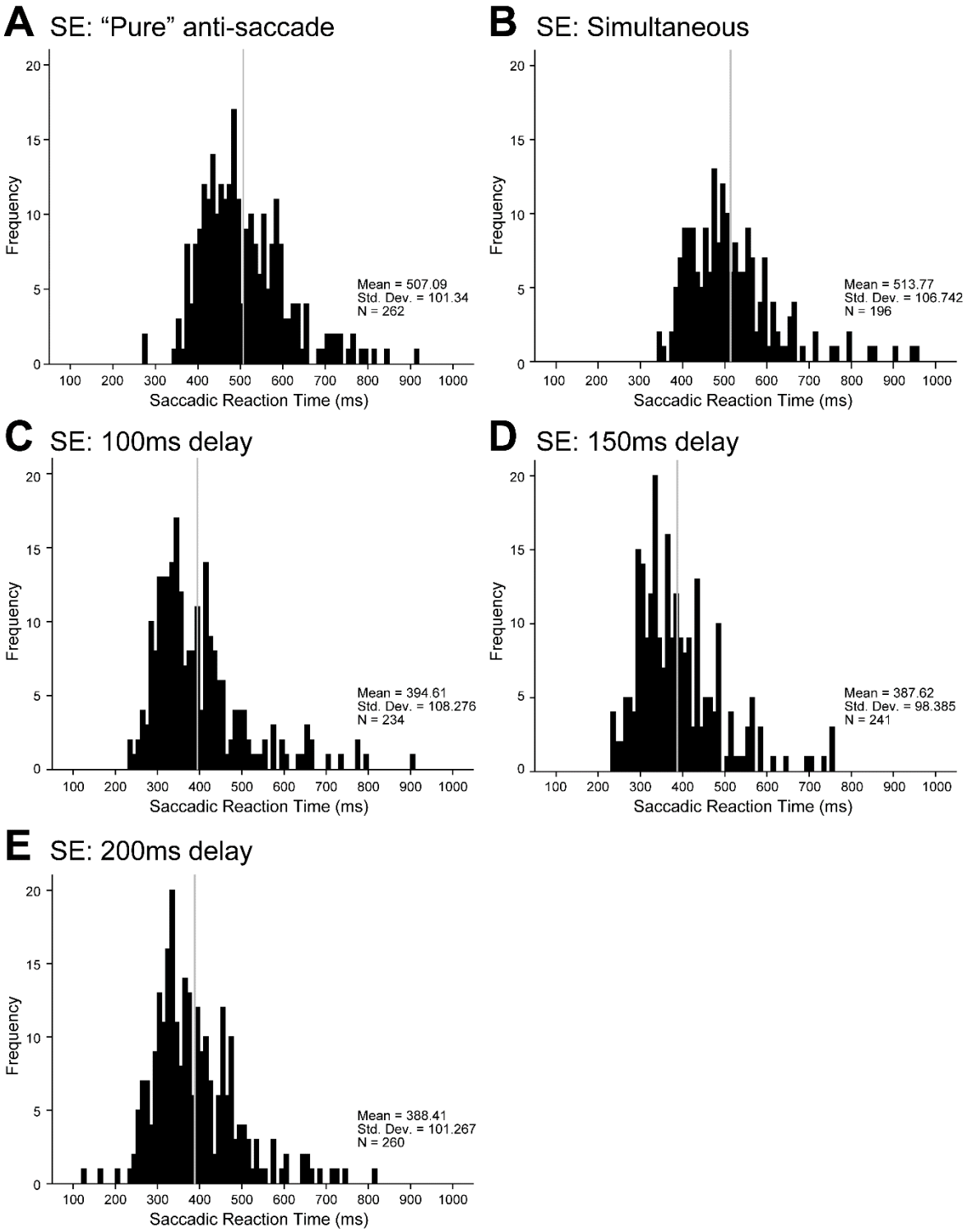

A SE: "Pure" anti-saccade
Mean = 507.09
Std. Dev. = 101.34
N = 262
B SE: Simultaneous
Mean = 513.77
Std. Dev. = 106.742
N = 196
C SE: 100ms delay
Mean = 394.61
Std. Dev. = 108.276
N = 234
D SE: 150ms delay
Mean = 387.62
Std. Dev. = 98.385
N = 241
E SE: 200ms delay
Mean = 388.41
Std. Dev. = 101.267
N = 260
Frequency
Saccadic Reaction Time (ms)

Figure 2-3. Frequency distribution of saccade reaction time in the five different anti-saccade conditions for patient SE. (**A**) "Pure" anti-saccade condition. (**B**) Simultaneous condition in which the delay between the cue and probe was 0 msec. (**C**) condition in which the cue-probe delay was 100 msec. (**D**) 150 ms delay condition. (**E**) 200 ms delay condition. Vertical grey bar through each histogram indicates corresponding mean SRT.

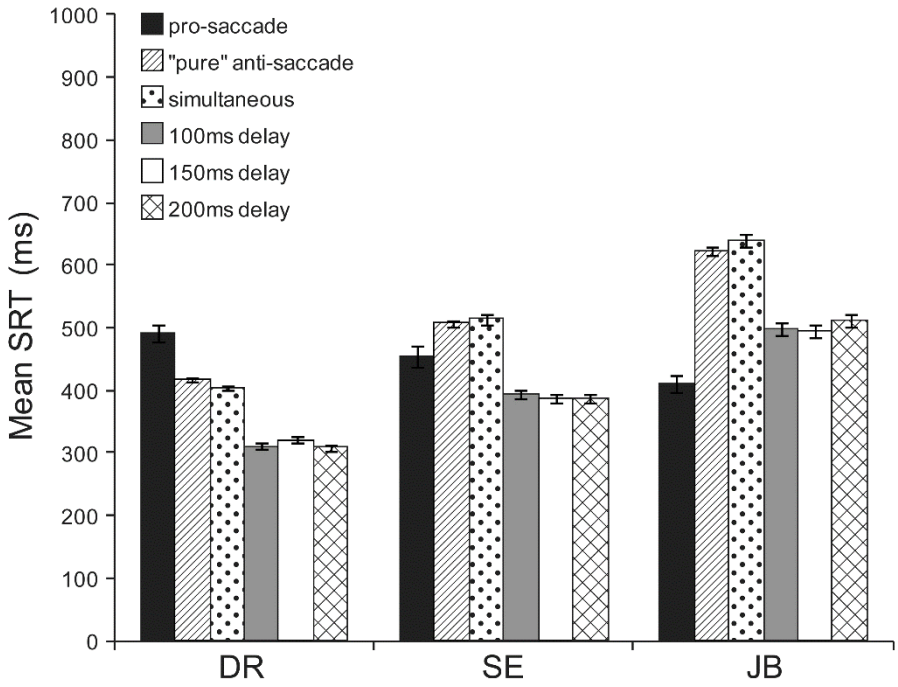


Figure 2-4. Comparison of mean saccade reaction times (SRT) in the five different anti-saccade conditions and the pro-saccade condition for each of subjects DR, SE and JB. For explanation of tasks see Fig. 2 and Methods section. Error bars represent standard error of the mean.

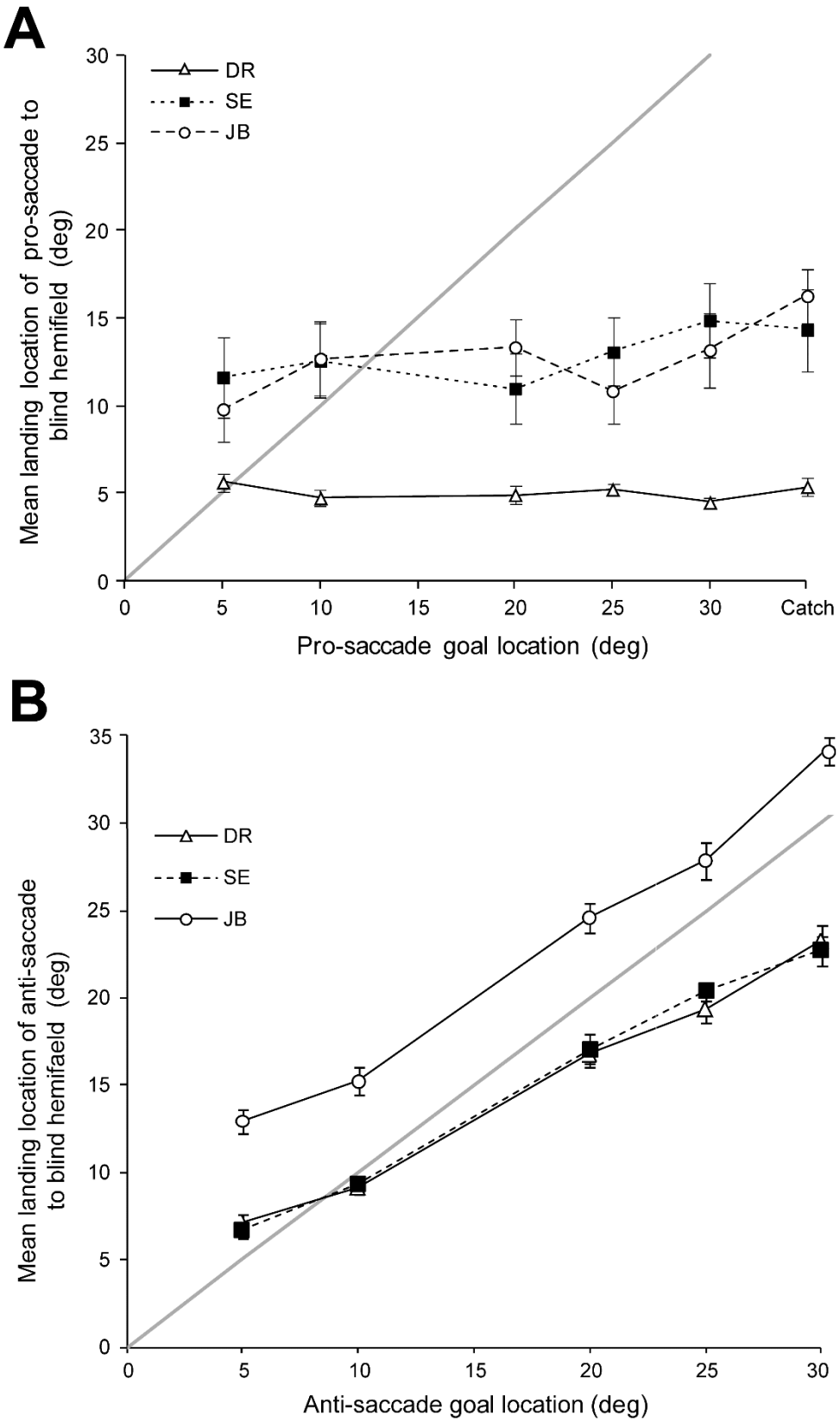

A
DR
SE
JB
Mean landing location of pro-saccade to blind hemifield (deg)
Pro-saccade goal location (deg)
0
5
10
15
20
25
30
Catch
B
DR
SE
JB
Mean landing location of anti-saccade to blind hemifaeld (deg)
Anti-saccade goal location (deg)
0
5
10
15
20
25
30
35

Figure 2-5. Mean saccadic landing locations in the pro-saccade and "pure" anti-saccade to the blind hemifield condition. Mean saccade landing location at each goal location for each of subjects DR, SE and JB in the pro-saccade to the blind hemifield condition (**A**) and "pure" anti-saccade to the blind hemifield condition, in which no probe was presented (**B**). Diagonal line represents unity gain. Error bars represent standard error of the mean.

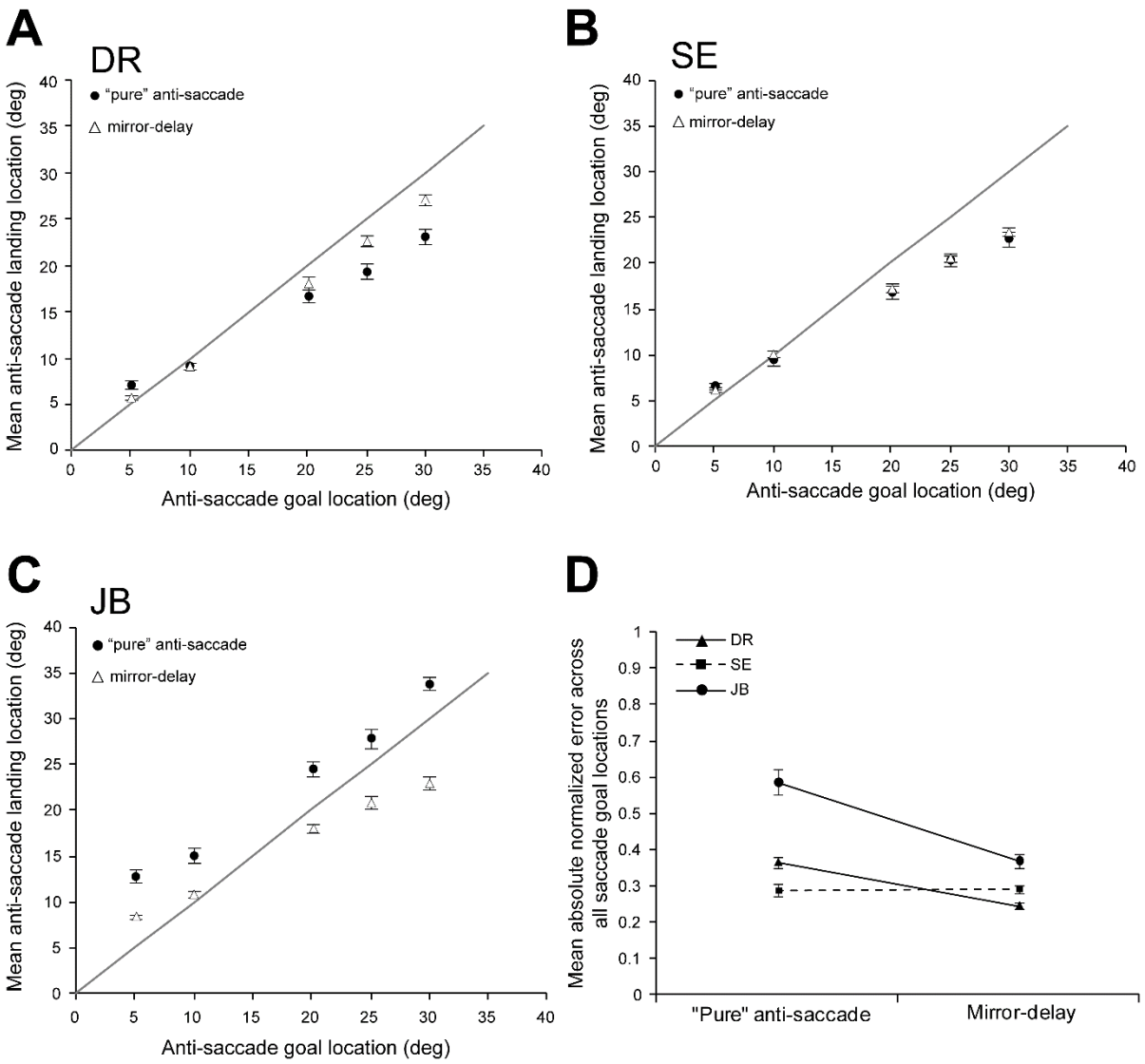


Figure 2-6. Comparison of mean anti-saccade landing location at each goal location in the "pure" anti-saccade and mirror-delay conditions. (**A**) subject DR, (**B**) SE, and (**C**) JB. Diagonal line in each panel represents unity gain. (**D**) Comparison of mean absolute normalized error between anti-saccade end-point and anti-saccade goal location pooled across all goal locations in the "pure" anti-saccade (left column) and mirror-delay (right

column) conditions for subjects DR, SE, and JB. In the mirror-delay conditions, the results for all delays have been pooled. Error bars represent standard error of the mean.

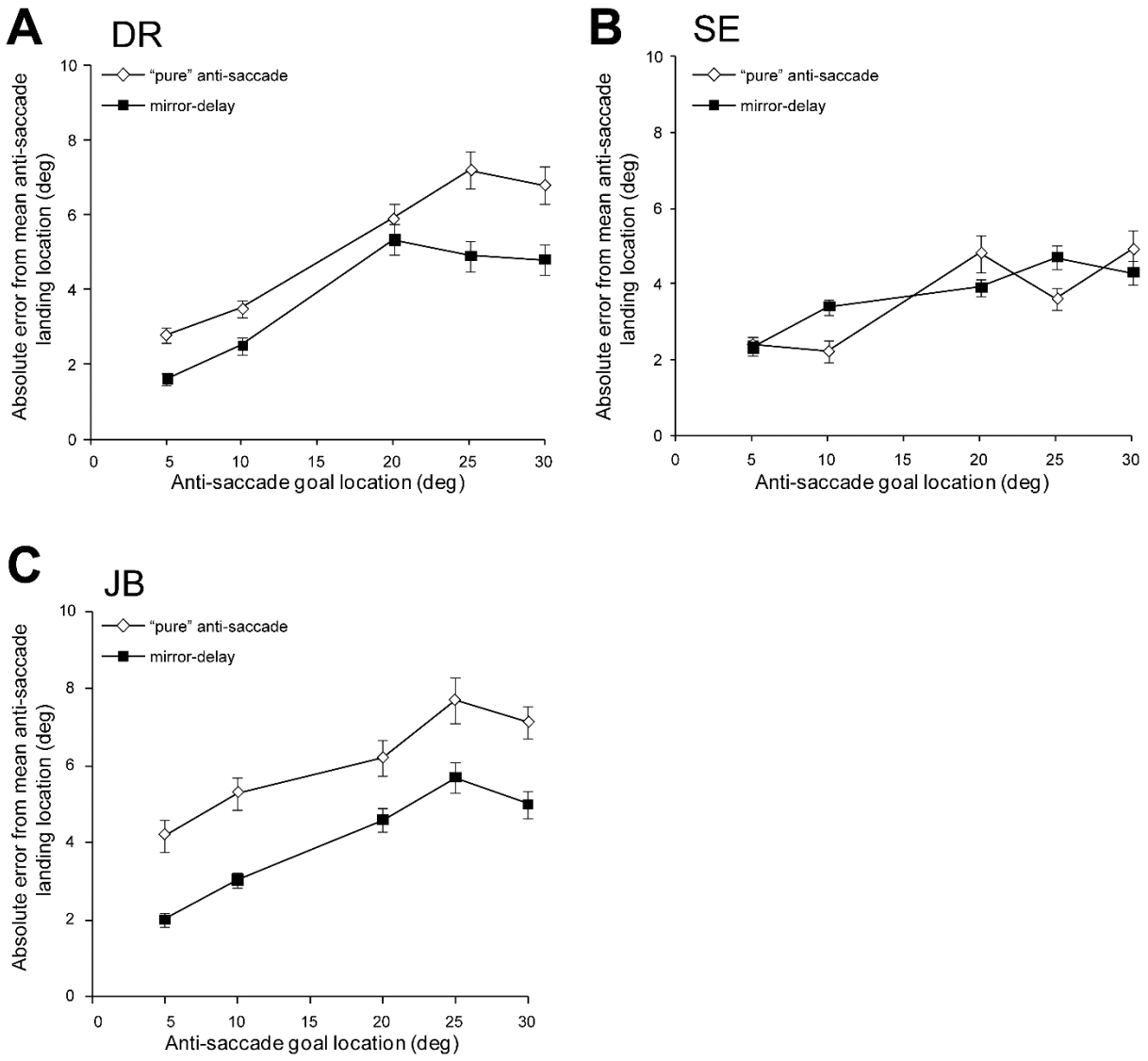


Figure 2-7. Absolute error from the mean anti-saccade landing location in the "pure" anti-saccade and mirror-delay conditions. Results for subjects DR (**A**), SE (**B**) and JB (**C**). In the mirror-delay conditions, the results for all delays have been pooled. Error bars represent standard error of the mean.

Chapter 3: Blindsight after Hemidecortication: Visual Distractor in Blind Hemifield Perturbs Anti-Saccades Directed There According To Visuo-Motor Interactions on Superior Colliculus Map

Preface

In the previous chapter, we showed that a spot of light presented in the blind hemifield of a hemidecorticate patient, at the exact goal of an intended anti-saccade, improved the accuracy of this saccade. Although that study demonstrated a role of the retino-tectal pathway in blindsight, it did not provide direct evidence that interactions between the probe and anti-saccade motor activity were indeed occurring in the SC. The reason for it is twofold: first, in these patients there exist an ascending pathway from the ipsilesional SC to the intact hemisphere (Crapse & Sommer, 2009; Leh et al., 2006); second, it has been shown that the FEF of the remaining hemisphere in normal monkeys (Crapse & Sommer, 2009), as well as our hemidecorticate patients (Leh et al., 2010) can control both ipsilesional and contralesional saccades via bilateral projections to the SC. The results discussed in the previous chapter revealing blindsight in hemidecorticate patients, suggest a possible role of the retino-tectal pathway but leave open the question of whether ascending or descending signal from SC are involved. This question is examined in the ensuing sections.

Summary

In the previous chapter, we provided new evidence that a visual target (probe) presented in the blind hemifield can alter the timing and accuracy of anti-saccade going to that location. We hypothesized that the visual activity generated by the probe in the ipsilesional SC is insufficient to generate the motor command, but it can interact with and potentiate preparatory

SC anti-saccade motor activity, thereby reducing anti-saccade latency and improving accuracy. The purpose of this study was to investigate whether probes presented in different locations from the anti-saccade goal would affect the timing and accuracy of the ongoing anti-saccades to the blind hemifield and skew their trajectories according to visual-motor signal interactions on SC logarithmically encoded retinotopic map (Dorris, Olivier, & Munoz, 2007). Specifically, each patient was asked to generate a horizontal anti-saccade towards the blind hemifield, to the mirror location of a visual cue presented at various randomly chosen locations on the horizontal meridian of the seeing hemifield. After a slight delay, a probe was presented at the non-mirror location. We found that for probes presented rostral to the anti-saccade goal, there was a strong *interactive* effect for probes near and an *inhibitory* effect for probes far from saccade motor activity. By comparison, we found no effect on the anti-saccade if the probe was presented caudal to its goal. These observations suggest that the ipsilesional SC in hemidecorticate patients receives visual information from the blind hemifield via the retino-tectal tract, which interacts with a descending motor signal driven by a crossed contralesional frontal-to-ipsilesional colliculus pathway (Crapse & Sommer, 2009).

Introduction

Visual information from the retina can reach visual cortex via two main ascending subcortical routes: through the lateral geniculate nucleus (LGN) and superior colliculus (SC). The former carries the signals related to conscious visual processing, while the latter is the more primitive retino-tectal pathway thought to contribute to unconscious visual abilities called "blindsight" (reviewed in Cowey, 2010; Stoerig & Cowey, 2007; Weiskranz et al., 1974). Blindsight refers to the ability of subjects, with lesions of cortical visual areas, to respond to

visual stimuli presented in blind regions of their visual field, even though they are unaware consciously of the presence or nature of the visual input.

Hemidecorticate patients present a unique opportunity to study blindsight mediated by the retino-tectal pathway. In these patients, one cortical hemisphere has been completely removed surgically; a lesion that prevents cortical visual processing of contralesional stimuli. The lack of visual cortical structures on the decorticate side leads to complete retrograde degeneration of LGN (Pasik et al., 1969), but there is anatomical preservation of the ipsilesional SC (Ptito et al., 1996; Théoret et al., 2001; Ueki, 1966).

In hemidecorticate patients that exhibit blindsight, the transformation of visual information in their blind hemifield, to the cortical signals that mediate a button-press response, is thought to be mediated via the pathway from retina-to-ipsilesional-SC-to-cortex of the remaining hemisphere (Leh et al., 2006; Leh et al., 2010; Tomaiuolo et al., 1997). In Savina, Bergeron, and Guitton (2013) we speculated that their pathway from retina-to-ipsilesional-SC-to brainstem can contribute subliminal signals that influence an ongoing saccade motor program so as to improve the precision of an anti-saccade (Savina et al., 2013). However, this pathway is incapable itself of directly generating saccades. Further evidence for the role of the retino-tectal pathway in generating saccades is provided by Kato et al. (2011) who showed that following a lesion of V1 in monkey, visually-guided saccades are still possible but abolished by inactivating the ipsilesional SC.

In Savina et al. (2013) we tested one hemidecorticate patient described as having blindsight when tested in a button press task (Leh et al., 2006). We tested another that lacked the button-press blindsight. We found that a visual probe presented, at an anti-saccade goal location,

in the blind hemifield of both patients affected the anti-saccade motor response. We speculated that this was due to interactions, in the ipsilesional SC, between a probe-evoked visual response and anti-saccade motor preparatory activity. Here we present strong evidence for involvement of the ipsilesional SC in human blindsight, based on the experimental approach of Dorris et al. (2007) who found in monkey SC that motor preparatory and visual signals converge in the intermediate and deep layers of the SC and interact on a logarithmically encoded retinotopic map. Specifically, Dorris et al. (2007) found that: 1) visual distracters generating SC activity rostral to the saccade target affected the saccade end-point much more than when distracter activity was caudal to the saccade goal; and 2) distractors close to the saccade target enhanced the saccade motor discharge and deviated the saccade trajectory while distractors further away suppressed the motor activity. Here we found a very similar effect on anti-saccades to the blind hemifield. Essentially, an unseen visual probe presented briefly in the blind hemifield, just before and in different positions relative to an anti-saccade goal, influenced the trajectory of the resulting anti-saccade according to interactions on a logarithmic motor map. The distractor-evoked visual activity in SC appeared to combine with the anti-saccade motor preparatory activity to change the locus of the resulting anti-saccade motor command on the ipsilesional SC motor map in line with the results of Dorris et al. (2007). Thus, for probes rostral to the anti-saccade goal, there was a strong interactive effect for probes near and an inhibitory effect for probes far from saccade motor activity. By comparison, we found no effect on the anti-saccade if the distractor was presented caudally (as in Dorris et al., 2007) from its goal. Our data provide unique evidence for a functional role of visual signals carried by the retino-tecto-reticular pathway in humans.

Methods

Participants. Two hemidecorticate patients (DR and SE) (Fig. 2-1) participated in this study, which was approved by the Montreal Neurological Institute and Hospital Research Ethics Committee. The participants gave informed and voluntary consent prior to commencement of experimentation.

The case histories of the patients are described elsewhere (Leh et al., 2006; Tomaiuolo et al., 1997) and will be briefly summarized. Both patients underwent a hemidecortication to relieve intractable epilepsy after the age of 17.

At age 17, as a young adult, DR underwent complete right hemidecortication including the amygdala and hippocampus. All remaining cortical tissue on the decorticate side was surgically disconnected from the rest of the brain. She was 36 at the time of testing. SE – 43 at the time of testing - underwent a partial hemidecortication (temporo-parietal-occipital removal) including the amygdala and hippocampus of the right side at age 25. The entire right frontal lobe was spared.

Apparatus. Visual stimuli, generated in MATLAB using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997), 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 57 cm from the participant. We patched a contralesional eye of each subject to avoid the possibility that they would converge their eyes in order to reduce the blind region of their visual field. (We did not test for this putative compensatory convergence.) As such, the subjects, both with right hemisphere ablations, made leftward anti-saccades into their blind hemifield.

Horizontal eye movements were monitored with bi-temporal electro-oculography (EOG). The EOG technique, whose calibration method is simple and calibration time short, was used to facilitate the mobility of the patients who requested frequent breaks. Prior to each recording session, the gain of the EOG signal was calibrated while the subject was fixating at various fixed target locations every 10º within ±30º range. During recording, small drifts were corrected by automatically resetting the EOG output to zero as the participants fixated at the start of each trial. When necessary, experiments were interrupted in order to recalibrate the gain of the EOG signal. The EOG output was exported as a real-time analog signal to an external Analog-to-Digital Converter device (NI6023E, National Instruments), through a simple first order low pass filer with a cut-off frequency of 300 Hz. The eye movement data collection was controlled using REX, a QNX-based real-time data acquisition system (Hayes et al., 1982). The eye position signal was sampled by the computer at a rate of 1 kHz. Offline in MatLab, the eye position signal was low pass filtered (zero-phase, cut-off at 30 Hz). Following proper calibration, the filtered EOG signal was linear within 1º over a range of ±30º for all participants.

Stimuli and procedure. The visual stimulus which could be a cue (in the seeing hemifield) or a probe (in the blind hemifield), consisted of a circular 0.5º light spot with a luminance level of 0.8 cd/m2, flashed on a dark background. Participants were seated in a completely dark room with the head restrained by a bite bar. Each trial began with the presentation of the FP alone for a random duration of either 800 ms or 1,200 ms. Immediately following FP's extinction, a cue was presented in the seeing visual hemifield for 86 ms. It was presented randomly at: 5º, 10º, 20º, 25º, or 30º. The appearance of the cue indicated that the subject had to initiate an anti-saccade towards the blind hemifield to the mirror location of the

cue. Unbeknownst to the participants, after delays of 100 ms, 150 ms, or 200 ms relative to cue's onset, we presented a probe for 86 ms at 15º and 20º locations (which were always at the non-mirror location of the cue) in the blind hemifield (Fig. 3-1). The delays were determined for the same reasons as in our previous experiment because the data for the two studies were collected concomitantly. The three different delays were in the same block and were randomly interleaved within each block. In total, we run 4 blocks of 56 trials each.

Participants were instructed to make anti-saccades as promptly and accurately as possible. The saccades were made in complete darkness. At the end of each trial, the room was illuminated for 1,000 ms before the start of the next trial to prevent dark adaptation. No performance feedback was given to the participants at any point during the experiment.

To address the issue of whether light scatter was responsible for responses to visual events in the blind hemifield we tested, prior to the main experiments, each participant's response to the 0.5º light stimulus presented in the natural blind spot of their intact visual field. This method has been proposed to be the ideal control for both forms of intraocular scatter (Cowey, 2004). None of the participants could detect this stimulus in their blind spot.

We discouraged anticipatory glances by including in each block approximately 12% of catch trials wherein the cue and probe were not presented and the subject had been instructed to keep fixating FP until the end of the trial.

Data analysis. During each trial, the following experimental quantities were stored online for further offline analysis: target, cue and probe positions, cue-probe delay and EOG eye position signal.

Data were analyzed from all trials except: (1) erroneous pro-saccades in anti-saccade trials (i.e., saccades that were made towards the cue rather than in the opposite direction); (2) anti-saccades with latencies <120 ms (since these saccades would most probably be anticipatory in nature); (3) anti-saccades with latencies >1000 ms; (4) EOG signals that contained significant noise and blink artefacts (determined by visual analysis); (5) catch trials.

Offline we differentiated the eye position trace to give eye velocity. The onset and end of each saccade was identified as the points where velocity increased above and decreased below 40^{o}/sec, respectively. Saccade reaction time (SRT) was calculated as the time difference between the target (or cue) onset and saccade initiation. We considered as outliers the saccades that fell outside ±2SD from the mean anti-saccade landing location and these saccades were removed from all further analyses. We used the remaining population of data points to calculate mean SRT and mean anti-saccade landing location.

Analyses of mean SRT and mean anti-saccade landing location were performed by using one-way independent design ANOVAs. We compared mean SRT and mean anti-saccade landing location in the non-mirror condition to those of "mirror" and "pure" anti-saccade conditions reported previously in Savina et al. (2013). Because of the discrepancy in sample size between various conditions, there was a high probability that homogeneity assumption would be violated. Therefore, in order to control for the risk of type I error experiment-wise post-hoc analyses were performed using the Gamese Howell test and the alpha level was set to a stringent level of 0.01 for all statistical tests (Fidell & Tabachnick, 2003).

The data were analyzed using the SPSS 18.0 statistical software.

Interpretation of data in terms of interactions on SC motor map. Dorris et al. (2007) presented a visual distractor just prior to a saccadic eye movement and studied the resulting patterns of interaction in the SC between the visual and motor discharges. They determined the spatio-temporal conditions under which the distractor-induced visual discharge and motor preparatory discharge summated so as to perturb the saccade trajectory. Their observations are summarized in their Fig. 3B, shown here (with permission) in part in the inset to our Fig. 3-3A. This plot shows that distractors presented just before a saccade and spatially between the saccade target and the initial fixation point are the most likely to perturb a saccade's trajectory. They also found that SC microstimulation, at thresholds below that for evoking saccades, also perturbed the saccade trajectory.

Here, we reasoned that the same phenomenon should be present in the SC of our hemidecorticate patients, if subtended by collicular mechanisms. We therefore assumed that the probe-induced visual discharge interacted with the preparatory motor activity for the anti-saccade to the blind hemifield. We assume that the strength and location of the interaction between the hills determines the amplitude of the resulting anti-saccade and is determined by the center of gravity between the visual and motor hills; itself related to the distance between the two hills.

On the SC map, the probe-induced visual discharge can be represented by a bell-shaped Gaussian "hill" of about 2mm diameter, independent of its location on SC map (Dorris et al., 2007). There are two types of motor-related neurons: burst neurons also have a Gaussian hill discharge profile with a width of ~2mm; buildup neurons have an asymmetric discharge profile with the rostral portion (pointing to the map's "zero" location) and caudal portions, about 2 mm

and 1mm respectively. The former is thought responsible for the observation by Dorris et al. (2007), and here, that interactions between rostral distractors (here called probes) and motor discharges are strongest for probes flashed rostral to the motor discharge.

For the sake of simplicity in our model we assume two Gaussian hills whose relative heights will be evaluated by a model fit as follows:

MODEL: As in Dorris et al. (2007) we assume a motor map of the SC represented by the equation (from Ottes, Van Gisbergen, & Eggermont, 1986):

$$u = 1.4\{\ln(1 + R/3)\} \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where R in degrees, is the retinal eccentricity of the peak of the gaussian discharge distribution due to the probe, and u is the corresponding rostro-caudal distance in millimeters measured tangential to the map.

The distance, Δx, between the peaks of two Gaussian hill on the map – one representing the horizonatal anti-saccade motor discharge (Rasm), the other the probe-induced visual discharge (Rpr) on the horizontal meridian, is given by:

$$\Delta x = 1.4\{\ln(1 + R_{as}/3) - \ln(1 + R_{pr}/3)\}$$

$$= 1.4\{\ln[(3 + R_{as})/(3 + R_{pr})\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

The next step is to calculate the "centre of gravity" (CofG) between the 2 "hills" – visual and motor - of neural activity. A simple assumption is that the hills are Gaussian shaped wherein their height (h) is proportional to their area. Therefore, the distance (d_{pb}) between the CofG and the peak of the probe-induced hill (h_{pb}) is:

$$d_{pb} = [h_{as}/(h_{pr} + h_{as})]\,\Delta x \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where h_{as} and h_{pr} are the heights of the anti-saccade motor hill and probe-induced visual hill, respectively.

Combining equations 2 and 3 yields:

$$d_{pb} = 1.4\ [h_{as}/(h_{pr} + h_{as})]\ \ln[(3 + R_{as})/\ (3 + R_{pr})]\ \text{.....}(4)$$

In the Results section (Fig. 3-3) we will show that the theoretical framework expressed by Equation 4 explains well our experimental results, thereby supporting the role of the retino-tectal pathway in the blindsight phenomenon studied here: notably mediating visuo-motor interactions on SC map.

Results

Mean anti-saccade landing location; interactions between a visual probe and anti-saccade motor program. We call "inboard-probe" the condition wherein the probe was presented between the fixation point and the anti-saccade's goal in the blind hemifield which was at the mirror location of the anti-saccade's cue in the seeing hemifield. By definition, an "outboard- probe" was presented beyond the anti-saccade's goal. We performed a one factor (4 levels: mirror condition, "pure" anti-saccade condition, "inboard" non-mirror condition, "outboard" non-mirror) independent design ANOVA for each cue location.

Probe presented at 15º "outboard" of anti-saccade goal. PATIENT DR (Fig. 3-2A): In the case of DR and a 5º anti-saccade goal, the analysis of mean anti-saccade landing location when the probe was presented at 15º (P15), "outboard" of the anti-saccade goal, revealed a significant main effect ($F(2,146) = 7.32$, $p = 0.001$). The results of the multiple comparisons tests computed on the main effect of condition type showed that the mean anti-saccade landing location in the "pure" anti-saccade condition was significantly different from both the mean anti-

saccade landing locations in the mirror and non-mirror conditions (p =0.005 and 0.002, respectively). A visual inspection of Fig. 3-2A indicates that a probe presented at 15º did not deviate mean anti-saccade landing location towards itself. Indeed, there was no significant difference between anti-saccade landing locations in the mirror and non-mirror (probe at 15º) conditions (p =0.306).

At the 10º anti-saccade goal, the analysis of mean landing locations when the probe was presented at 15º revealed no significant main effect ($F(2,182) = 1.904$, $p = .152$).

PATIENT SE (Fig. 3-2B): In the case of SE, the analysis of mean landing locations when the probe was presented at 15º (P15) did not reveal a significant main effect at either the 5º cue location ($F(2,198) = .864$, $p = .423$) or the 10º cue location ($F(2,242) = 1.338$, $p = .264$).

Probe presented at 15º "inboard" of anti-saccade goal. PATIENT DR (Fig. 3-2A): Visual inspection of Fig.3-2A, suggests that the probe at 15º (P15), inboard of an anti-saccade goal, significantly deviated the mean anti-saccade landing location towards itself at all anti-saccade goals. However, the analysis of mean anti-saccade landing locations when the probe was presented at 15º revealed no significant main effect at 20º anti-saccade goals ($F(2,206) = 2.437$, $p = .09$); specifically there was no significant difference between the non-mirror (P15) and mirror conditions. However, looking at Fig. 3-2A, we can clearly see that the probe presented at the 20º mirror location clearly brought the eye closer to 20º, whereas the non-mirror probe at 15º (P15) brought the eye closer to itself. One could argue that the reason we failed to find a significant difference between the mirror and non-mirror conditions is that the distance between the probe's location (15º) and the intended anti-saccade location (20º) is very small. We therefore ran a separate one way independent ANOVA with just two factors (mirror vs. non-mirror conditions).

The results of this analysis revealed a significant main effect ($F(1,112) = 4.89$, $p = .029$), indicating that when the probe is presented at the non-mirror location from the anti-saccade goal, it significantly deviates the eye to itself.

Conversely, at the 25º and 30º anti-saccade goal locations, statistical analyses revealed a significant main effect of condition type ($F(2,215) = 9.237$, $p = 0.001$ and $F(2,212) = 13.781$, $p = 0.001$, respectively). We performed post-hoc analyses on the data which showed that when the anti-saccade goals were at either 25º or 30º, the anti-saccade landing locations significantly differed from each other in all three conditions ($p<0.05$).

PATIENT SE (Fig. 3-2B): In the case of SE, the analysis of mean anti-saccade landing locations when the probe was presented at 15º (P15), inboard of the anti-saccade goals at 20º and 25º, revealed no significant main effect of condition type ($F(2,247) = 0.891$, $p = 0.412$ and $F(2,288) = 0.711$, $p = 0.492$, respectively). However, as in the case of DR, a visual inspection of Fig.3-2B suggests for SE that when the anti-saccade goal was at 30º and the probe was presented at 15°, the anti-saccades' mean landing location was deviated towards the probe's location. Indeed, at the 30º anti-saccade goal location, the analysis showed a significant main effect ($F(2,262) = 7.143$, $p = 0.001$). The results of the multiple comparisons tests revealed for the 30º anti-saccade goal, a significant difference between the mirror and the non-mirror, P15, conditions ($p=0.001$), and a significant difference between the "pure" anti-saccade condition and the P15 condition ($p=0.045$). There was no significant difference between the "pure" anti-saccade and mirror conditions ($p=0.927$).

Probe presented at 20º "outboard" of anti-saccade goal. PATIENT DR (Fig. 3-2C). Visual inspection of Fig. 3-2C, data for 5º anti-saccade goal locations, suggests that a probe

presented at 20º (P20) does not deviate anti-saccade landing locations towards itself. The analysis of mean landing locations when the probe was presented at 20º revealed a significant main effect at 5º anti-saccade goal locations ($F(2,152) = 7.67$, $p = 0.001$). The results of the post-hoc analyses showed that the mean anti-saccade landing location in the "pure" anti-saccade condition was significantly different from both the mean anti-saccade landing locations in the mirror and non-mirror conditions ($p = 0.005$ and 0.001, respectively). There was no significant difference between anti-saccade landing locations in the mirror and non-mirror, P20, conditions ($p = 0.392$).

As visual inspection suggests, at 10º anti-saccade goal locations, the analysis of mean landing locations revealed no significant main effect ($F(2,179) = 2.947$, $p = 0.055$).

PATIENT SE (Fig. 3-2D): In the case of SE, the analysis of mean landing locations when the probe was presented at 20º did not reveal a significant main effect at either 5º or 10º cue locations ($F(2,211) = 0.992$, $p = 0.373$ and $F(2,247) = 0.718$, $p = 0.489$, respectively).

Probe presented at 20º "inboard" of anti-saccade goal. PATIENT DR (Fig. 3-2C): In the case of DR, the analyses of mean landing locations, when the probe was presented at 20º (P20), revealed a significant main effect at both the 25º and 30º anti-saccade goal locations ($F(2,210) = 4.401$, $p = 0.013$ and $F(2,194) = 8.858$, $p = 0.001$, respectively). Further post-hoc analyses of the data showed that at both the 25º and 30º anti-saccade goal locations there was a significant difference between the amplitudes of "pure" anti-saccade and the amplitudes of anti-saccades in the mirror conditions ($p = .014$ and $p = 0.007$, for anti-saccade goals of 25º and 30º, respectively). There was also a significant difference between the mirror and non-mirror (P20º) conditions ($p = 0.018$ and $p = 0.001$, respectively), as well as a significant difference between the

"pure" anti-saccades to the 30º anti-saccade goal location and the respective anti-saccade with the probe at 20º in the non-mirror condition (p=0.031). However, there was no significant difference between the "pure" anti-saccades to 25º anti-saccade goal location and the respective anti-saccade with the probe at 20º in the non-mirror condition (p=0.786).

In summary for DR in the trials with the probe at 20º and anti-saccade goals at 25º there was a significant difference between anti-saccade endpoint in: mirror versus non- mirror probes, and "pure" anti-saccades versus mirror; but not "pure" anti-saccades versus non-mirror probes. For anti-saccade goals at 30º, there was a significant difference between anti-saccade endpoint in: mirror versus non- mirror probes; "pure" anti-saccades versus non-mirror probes; and "pure" anti-saccades versus mirror.

PATIENT SE (Fig.3-2D). For SE when the probe was presented at 20º, the analyses of mean landing locations did not reveal a significant main effect at either 25º or 30º anti-saccade goals locations ($F(2,271) = .462$, $p = 0.631$ and $F(2,246) = 1.134$, $p = 0.323$, respectively).

Data suggests interactions on the motor map of the superior colliculus. Dorris et al. (2007) showed in monkey that a distractor flashed at different positions relative to a saccade target can affect the saccade vector in a manner explained by measured interactions, on the logarithmically encoded motor map of the SC, between a saccade's preparatory motor activity and the visual activity evoked by the distractor. Their result is reproduced and summarized in our schematic in the inset to Fig. 3-3.

In the previous section, our analysis of the data in Fig. 3-2 suggested a mechanism in the SC of our hemidecorticate patient DR, compatible with the Dorris et al. (2007) result in monkey. Indeed, we found important and significant differences in the anti-saccade endpoint depending

on whether the probe was either at the anti-saccade goal, mirror location, or at an off-goal, non-mirror location (Fig. 3-2). To show and quantify this effect as it relates to activity on the SC map, we plotted (Fig. 3-3 and Methods) the postulated location, in millimeters on the SC map, of the peak in the activity profile encoding the actual anti-saccade amplitude (vertical axis) when the probe was presented at the non-mirror location at either 15º (P15, Fig. 3-3A) or 20º (P20, Fig. 3-3B). This quantity was plotted versus the location of the peak of motor activity when the probe was presented at the anti-saccade goal location (mirror location, horizontal axis). We used the same mapping function as in Dorris et al. (2007) and first defined by Ottes et al. (1986), notably: $u = 1.4*\ln(1 + R/3)$ where *u* is the distance from the SC's foveal representation measured in millimetres along the SC map's horizontal meridian, and *R* is the retinal eccentricity (degrees) encoding the saccade amplitude (Methods).

For DR, we see in Fig. 3-3 that the effect of the probe was particularly strong and significant when it was presented "inboard", as in Dorris et al. (2007), between the SC map's "zero" and the anti-saccade's goal location. Thus, when the probe was presented at 15º inboard of the anti-saccade goal (P15), relative to when it was at the location of the anti-saccade goal itself, (mirror position, Fig. 3-3, abscissa) there were strong effects such that for P15 the actual anti-saccade amplitude was heavily drawn towards the probe, as if the anti-saccade's motor activity was drawn towards the distracter (probe) at 15º. By comparisons, the effects of the probe at 15º were minimal when it was outboard of the anti-saccade goal. There was a hint that when the anti-saccade motor goals were far from outboard probes, the probe actually suppressed anti-saccade motor activity such that its position was shifted on the SC map more rostral to locations encoding smaller saccades. As a result the resulting anti-saccade amplitude was less than it

should be, a result similar to the observations of Dorris et al. (2007) for large distractor-saccade goal distances. In DR the effects of the probe at 20º were similar to those for 15 º probes.

For SE, the effects of the probe at 15º or 20º were small but qualitatively similar: the probe when presented inboard tended to draw an anti-saccade towards itself. We explain the weak effects in SE as being due to this patient having a frontal lobe, perhaps leading to a stronger and narrower anti-saccade motor command.

Anti-saccade reaction time. For the analysis of SRT, we pooled the data from the three delays because we found (see Savina et al., 2013) that there were no significantly different effects in anti-saccade SRT and end-point error between the three delays. We also pooled, for each subject, all the data from the 15º and 20º non-mirror probe conditions and subsequently divided these data into two distinct groups: probes "inboard" and probes "outboard". To analyse the data, we conducted a one factor (4 experimental conditions: "pure" anti-saccade, mirror-delay, non-mirror "inboard", and non-mirror "outboard") independent design ANOVA.

With respect to DR, the results showed a significant main effect of condition type ($F(3,1050) = 208.961$, $p = 0.001$). Post-hoc analysis of the main effect showed a significant difference between the non-mirror "inboard" condition and all the other conditions ($p<.05$). Similarly, the "pure" anti-saccade condition significantly differed from all the other conditions ($p<.05$). There was no difference between the non-mirror "outboard" and the mirror conditions ($p=.945$). The visual inspection of the graph representing these results shows that SRT in the "pure" anti-saccade condition (no probe) was the longest, while that of the non-mirror "inboard" condition was the shortest (Fig.3-4)

In the case SE, the results showed a significant main effect of condition type ($F(3,1561) = 105.035$, $p = 0.001$). We performed multiple comparisons tests and found a significant difference between the "pure" anti-saccade condition and all the other conditions ($p_s = 0.001$), where SRT in the "pure" anti-saccade condition is significantly longer than those of mirror, "outboard", and "inboard" conditions (Fig. 3-4). There was no significant difference between the remaining conditions ($p > 0.05$).

Discussion

The results of the present study provide unique evidence for a visuo-motor role involving the retino-tecto-reticular pathway in blindsight; notably how an unseen visual stimulus, in the blind hemifield of a hemidecorticate patient, can influence the trajectory and timing of a saccade directed to that field. Indeed, although a visual stimulus in the blind hemifield cannot on its own trigger a goal-directed saccade (Savina et al., 2013), we provide evidence here that the SC in hemidecorticate patients receives visual information from the blind hemifield via the retino-tectal tract, which in turn influences a saccade motor command via the tecto-reticular pathway. However, before asserting the involvement of this retino-tecto-reticular pathway we need here to consider two issues: 1) evidence that blindsight-related visual signals in these patients are carried by the retino-tectal pathway; and 2) that they are then conveyed to brainstem saccade control areas via visuo-motor interactions occurring in the SC.

Prior studies of blindsight requiring a button press response do not distinguish between the retino-tecto-intact hemisphere and retino-tecto-reticular pathways. In Savina et al. (2013) we showed that a spot of light presented in the blind hemifield of a hemidecorticate patient, at the goal of an anti-saccade, improved the accuracy of this saccade. Although that

study demonstrated a role of the retino-tectal pathway in blindsight, it did not provide strong evidence that interactions between the probe and anti-saccade motor activity were indeed occurring in the SC. This is because, first there is an ascending pathway from the ipsilesional SC to the intact hemisphere (Crapse & Sommer, 2009), specifically in the patients studied here (Leh et al., 2007). This is compatible with imaging studies that have revealed activation of extrastriate visual areas in the remaining hemisphere of hemidecorticate patients, following the presentation of a visual stimulus in their blind hemifield (Bittar, Ptito, Faubert, Dumoulin, & Ptito 1999). Second, the frontal eye field of the remaining hemisphere in normal monkeys can control both ipsilesional and contralesional saccades (Crapse & Sommer, 2009; discussed in Savina et al., 2013) via bilateral projections to the SC. Such a pathway has been reported for hemidecorticate subjects (Leh et al., 2006). For example, in DR a right-lesioned hemidecorticate patient, a retino-tectal signal can reach the left FEF and then a motor signal sent downward again to the saccade control areas in the ipsilesional reticular formation.

In Savina et al. (2013), we showed that a visual probe, flashed at an anti-saccade goal in the blind hemifield of hemidecorticate patients, improves the accuracy of their anti-saccades. Whether or not this effect was carried by the retino-tecto pathway was unclear because of mixed evidence. Indeed, Leh et al. (2010) argued for the retino-tectal pathway by showing that blindsight in these patients was abolished when visual stimuli were selected to be carried by retinal S-cones, thought not to contribute to the retino-tectal pathway. By comparison Bompas and Sumner (2008) presented a contradictory view arguing that the retino-tectal pathway does carry S-cone signals. Much evidence now shows that SC cells do respond to S-cone inputs and that debates regarding S-cone contributions to blindsight relate to issues regarding the control of

neural response latency and stimulus contrast and not that of the SC in mediating blindsight (Basso, 2016; Hall & Colby, 2014, 2016). Put another way, the extensive discussion in Hall and Colby (2014) supports the retino-tectal pathway for carrying blindsight signals given that the interpretation of experiments based on the responses of the S-cone pathway did not account for slow S-cone responses. The evidence for the retino-tectal pathway being involved in mediating blindsight is even stronger in hemidecorticate patients that lack all visual areas on one side, and have their SC (Ptito et al., 1996), but not their LGN (Pasik et al., 1969) preserved.

The responses in our anti-saccade task (Savina et al., 2013) revealing blindsight in hemidecorticate patients, suggest a possible role of the retino-tectal pathway but leave open the question of whether ascending or descending signal from SC are involved. This question is examined in the ensuing sections.

On whether the visuo-motor interactions described here involve ascending or descending collicular pathways. We begin by considering the possibility that the contra-lesionally directed anti-saccades that we have described here are controlled by a sub-population of neurons in the FEF of the intact hemisphere, that control saccades directed ipsilateral to itself (Crapse & Sommer, 2009; Peel, Johnston, Lomber, & Corneil, 2014). If the log-map nature of the interactions we have described here are occurring in the FEF, then our data (Fig. 3-3) require that these ipsi-FEF cells project to the ipsilesional SC and are arranged in a topographic map similar to that in the SC.

Older mapping studies suggested that the topographic organisation of contraversive saccades in the FEF is different from that in the SC (Bruce & Goldberg, 1985; Robinson & Fuchs, 1969). To complicate matters, recent studies show that the FEF contains two topographic

maps of contraversive saccades (Savaki, Gregoriou, Bakola, & Moschovakis, 2015) each also with a topography different from the SC. To complicate matters even more, here we are considering saccades directed ipsiversive to the remaining hemisphere and the topographical organization of these ipsi-FEF cells is unknown. Indeed, the topographical organization of FEF neurons controlling controversive saccades is still being debated and we know nothing about that of those cells controlling ipsiversive saccades. It would be surprising if the ipsi-FEF cells were topographically encoded as in SC, but not the contraversive FEF cells. These considerations support our hypothesis that the interactions we are considering here occur in the involvement, not of a loop involving the remaining hemisphere, but of the ipsilesional retino-tecto-reticular pathway.

Involvement of the tecto-reticular pathway. The retino-tectal pathway projects to the superficial layers of the SC (reviewed in May, 2006) and there is evidence for communication between superficial and intermediate layers as reviewed next. Isa (2002) argued that if pre-saccadic activity in the intermediate layers of the SC is absent, then the visual signal mediated by superficial layer neurons can reach the intermediate layers but fail to elicit a sufficiently strong burst of activity in the intermediate layers to initiate a motor command for saccade generation. He postulated that convergent excitatory inputs to the deeper layers are necessary for the generation of saccades to visual targets. Therefore, to explain the probe effects we saw here, we hypothesize that probe-evoked activity in retino-tectal afferents to the ipsilesional SC's superficial layers, descended to the intermediate layers and interacted with and enhanced anti-saccade motor preparatory activity driven by, say, the FEF of the remaining hemisphere via a crossed contralesional frontal-to-ipsilesional collicular pathway (Crapse & Sommer, 2009). Put

another way, we propose that a preparatory motor signal in the ipsilesional SC, encoding the contralesional anti-saccade, interacted with a probe-induced visual signal, itself too weak to drive a saccade on its own. Further, electrophysiological evidence in support of the preceding arguments has shown that the application of a single brief current pulse to the superficial layer of the rat SC can produce a prolonged burst of excitatory postsynaptic current (as long as 300 ms) in intermediate layer cells (Özen et al., 2000).

Our observation that the probe decreased the anti-saccade reaction time in both patients, despite the "pure" anti-saccade SRTs ranging from ~ 400 ms in DR to ~550 ms in SE, suggests that there was long-lasting motor preparatory activity in the ipsilesional SC over which probe-driven neuronal activity could drive an anti-saccade command signals above threshold for saccade initiation, and sooner than in the "pure" anti-saccade case. The effect of the probe on SE's anti-saccade precision was much less than for DR, which is in line with SE having a much longer saccade reaction time and the assumed consequent lower level of preparatory activity at the time of probe presentation, soon after cue offset.

Our results explained by interactions on the SC log map. Here we provide strong evidence for involvement of the ipsilesional SC because the effect of the probe on the anti-saccade amplitude can be predicted by assuming interactions between visual and motor neural discharges on the SC's logarithmically encoded visuo-motor map (Dorris et al., 2007; Ottes et al., 1986). By comparison, as we have discussed above, the critical cortical motor area, the frontal eye field, is not structured according to such a non-linear map.

Each point on the motor map, in intermediate layers of the SC, codes for a specific vector in retinal coordinates. Stimuli presented in peri-foveal locations are coded in the rostral part of

the SC, whereas stimuli displayed in the peripheral visual field are encoded in the contralateral caudal regions of the SC (King, 2004; Munoz et al., 2000; reviewed in the book edited by Hall and Moschovakis, 2004). The metrics of a saccade are coded by the discharge of a population of neighbouring SC neurons which have overlapping receptive fields (Lee et al., 1988; McIlwain, 1991; Munoz et al., 2000). Importantly, the retinotopic representations of the visual map in the SC's superficial layers and the motor map just below, are coextensive and, as stated in the Methods, organized according to a logarithmic function (Ottes et al., 1986; see equation in Methods and Fig. 3-3). Small to large amplitude saccades are encoded rostro-caudally on the map, by a continuous nonlinear function. This organization implies that the distance in millimetres between two rostral SC sites that encode respectively, say 5º and 10º horizontal saccades is much larger than the distance between the two caudal sites that encode, say, 25º and 30º horizontal saccades.

Munoz and Wurtz (1995a) found two categories of saccade related cells in the intermediate and deep layers of monkey SC that they named buildup and burst neurons. In the former a saccade-related motor discharge (burst) is preceded by a period of lower activity. This preamble, or buildup, activity starts soon after the presentation of the visual signal and lasts until a burst linked to saccade initiation. It is thought that these cells are involved in target selection and saccade preparation. Munoz and Wurtz (1995b) also found that the rostro-caudal firing frequency profile of motor activity in buildup neurons, encoding a horizontal saccade vector on the SC's motor map resembles an asymmetric Gaussian, with the zone of activity rostral to the peak extending further rostrally than the activity caudal to the peak, which falls off more steeply.

Put another way, relative to the location of the peak discharge, the level of firing on the map fall off more gently rostrally than caudally.

Of relevance to the present findings, Munoz and Wurtz (1995b) proposed that modifying the motor-related activity of buildup cells, at points lying rostral to their site of peak activity, should be most effective in perturbing a saccade. Dorris et al. (2007) followed up this prediction and determined how neural activity, visually-evoked by a flashed "distractor", modified the vector of an impending saccade. They found that an interaction on the SC's motor map between saccade motor-preparatory activity and distractor-evoked activity was strongest for probes presented rostral to the site encoding the vector of a horizontal saccade (see inset to Fig. 3-3A). Our results are in remarkable agreement with these observations (Figs. 3-2, 3). Indeed, when we plotted the effect of the probe when it was flashed off the anti-saccade's goal location ("non-mirror", ordinate of Fig. 3-3), versus when the probe was flashed at the anti-saccades goal ("mirror", abscissa of Fig. 3-3), the effect was clearly strongest when probes were presented "inboard". For example, in DR for the "inboard" condition, a probe at the 15º map location drew the anti-saccades, with goals of 20º, 25º and 30º towards itself, as shown in Figs. 3-2A, 3. By comparison there was little effect of "outboard" probes. These results are qualitatively remarkably similar to the observations of Dorris et al. (2007) in the monkey SC (colored inset to Fig. 3-3). For 20º "inboard" probes in DR the effect was similar for anti-saccade goals of 25º and 30º.

Equation 4 in Methods provides a theoretical framework explaining these results. In Fig. 3-3A, B we plot for DR two predictions of equation 4 assuming, respectively, that the height of the probe-induced "hill" of visual activity is equal to 0.5 or 1.0 times the height of the hill

representing the anti-saccade's preparatory motor activity. One can see that the simple mechanisms embodied in equation 4 explain remarkably well the effect of an "inboard" probe at 15º on anti-saccades directed to goals in the blind hemifield at 20º, 25º and 30º; and for an "inboard" probe at 20º on anti-saccades with goals at 25º and 30º. The theoretical level of interaction, as shown by the dotted and full lines, predicts that for DR the level of probe-evoked activity was between 0.5-1.0 times the motor activity, numbers which are close to the results of Dorris et al. (2007) (e.g. their Fig. 2) showing strong effects of inboard distractor on saccade trajectories. The present results are the first quantitative evidence for *functional* visuo-motor interactions on the SC map in blindsight, provided by a signal in the retino-tectal pathway not too different from normal. For DR when the 15º and 20º probes lie "outboard" of the anti-saccade goals, the points lie closer to the diagonal unity line showing less effect of the probe, compared to what the theory predicts. This again is in line with Dorris et al. (2007) and could be caused by the asymmetric motor preparatory discharge discussed above (see inset of Fig. 3-3A).

For SE the effects of probes at 15º and 20º on anti-saccade amplitude were less than for DR, but certainly present, especially near probes at 20º, suggesting a sharper drop-off in his ratio hpr/has (Methods, equation 4) with distance from probe. We can speculate that SE, whose frontal lobe on the lesioned side had not been excised, could generate a stronger and narrower anti-saccade motor command. However, probes did affect his anti-saccade reaction times across all amplitudes, suggesting more complex spatio-temporal interactions than our simple model embodies.

On the effect of probes on anti-saccade reaction time. Interestingly, we also found that presentation of a probe at any non-mirror location –"inboard" and "outboard"- shortened the

anti-saccade reaction times. However, as considered above there was a different inboard-outboard spatial effect on saccade endpoint. How can we explain this? According to Munoz and Wurtz's (1995b), the size of the active zone of buildup neurons depends on the saccade amplitude; they estimated the active zone to be ≈ 2 mm in collicular coordinates for 5º saccades and ≥ 3mm for saccades of ≥ 20º. Furthermore, while only 40% of the buildup cells are active for the 5º horizontal saccades, > 60% of the buildup cells are active for saccades ≥ 20º. Therefore, we can speculate for the *spatial domain* that a probe at 15º can affect the spatial location of an anti-saccade with motor activity at 25º ("inboard" probe) while not affecting an anti-saccade with motor activity at 5º ("outboard" probe). This is because for the same distance separation in degrees the distance in mm is much larger from 15º to 5º than from 15º to 25º. Is there an equivalent temporal asymmetry? For DR there was: "inboard" probes affected SRT more than outboard probes (Fig. 3-4). However, there was no inboard-outboard asymmetry in SE. We conclude from Fig. 3-3 that in SE this was due to the small probe-induced visual signal compared to the motor signal, which was arguably augmented by his intact frontal lobe on the leasioned side.

Conclusion

Because the retinal projection to the SC carries more than 10%, or about 150,000, of the fibers in the optic nerve (Perry & Cowey, 1984), the SC is an excellent candidate to mediate "blindsight". The question arises as to whether the SC is merely a relay station to extrastriate areas - and it is those areas that permit unconscious visual processing – or whether the colliculus per se subsumes some of the functions revealed in studies of blindsight. The present study sheds light on the role the SC plays in "blindsight". We designed our study of hemidecorticate patients

to examine whether the pathway from retina to the ipsilesional SC to pons carries visual signals which, subliminally, can affect saccades directed contralesionally. We demonstrated that hemidecorticate patients can generate anti-saccades with trajectories affected by the position and timing of an unseen visual probe in their blind hemifield. Importantly, the nature of the probe's influence can be predicted by interactions on a logarithmically-encoded map, characteristic of the SC. This is the first demonstration of a role of the ipsilesional SC in the *functional* processing of visual information in the blind hemifield via inputs from the retina to the superficial layers of SC to its motor layers themselves activated by anti-saccade motor signals from a reorganized contralesional intact hemisphere.

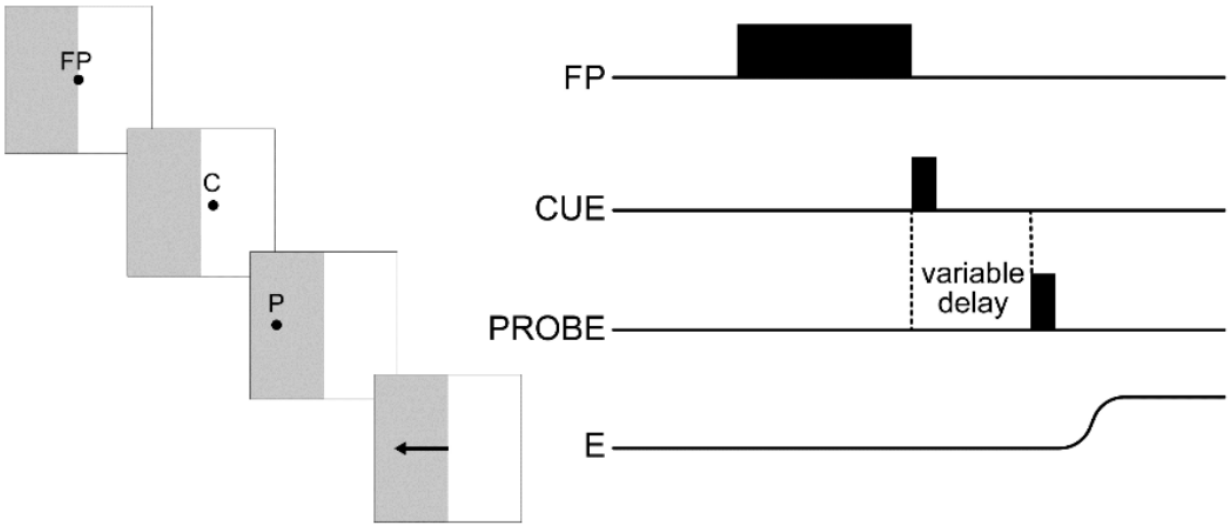
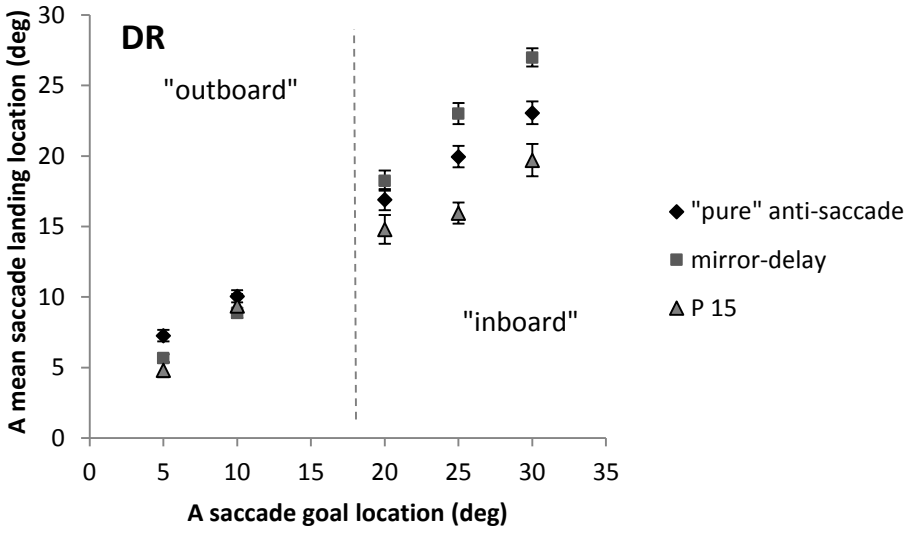
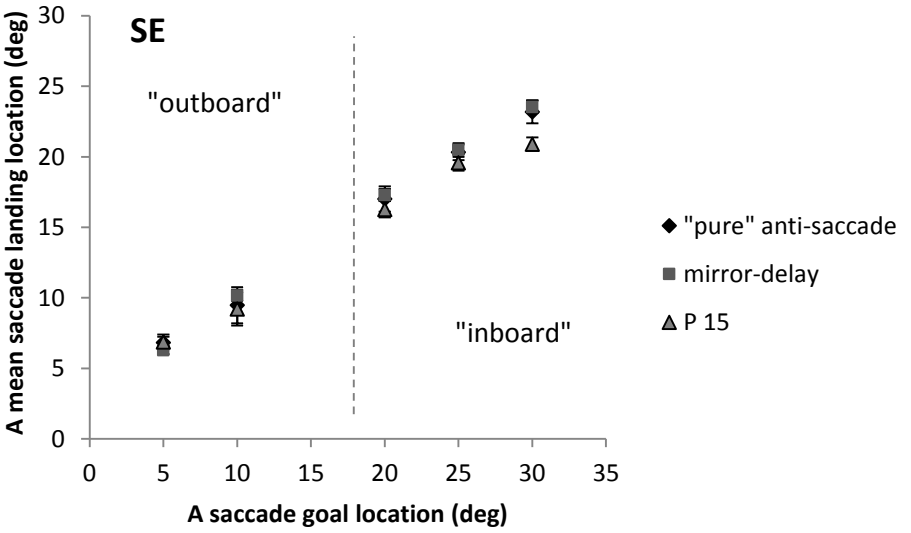


Figure 3-1. Schematic representation of the experimental tasks. The central fixation point (FP) was presented for a random duration of either 800 ms or 1,200 ms. Immediately following FP's extinction, a cue was presented in the seeing visual hemifield for 86 ms and the subject was instructed to look to the mirror location. A probe (P) was presented for 86 ms at either 15^{o} or 20^{o} in the blind hemifield after variable delays of either 100 ms, 150 ms or 200 ms from the onset of the cue. The shaded area represents the blind hemifield.

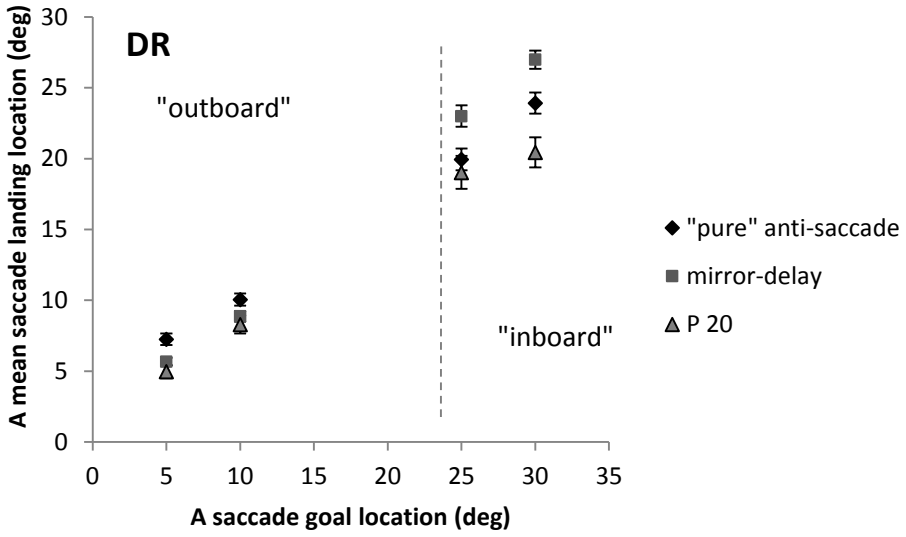
A)


DR
"outboard"
"inboard"
A mean saccade landing location (deg)
A saccade goal location (deg)
0
5
10
15
20
25
30
35
"pure" anti-saccade
mirror-delay
P 15

B)


SE
"outboard"
"inboard"
A mean saccade landing location (deg)
A saccade goal location (deg)
0
5
10
15
20
25
30
35
"pure" anti-saccade
mirror-delay
P 15

C)



D)

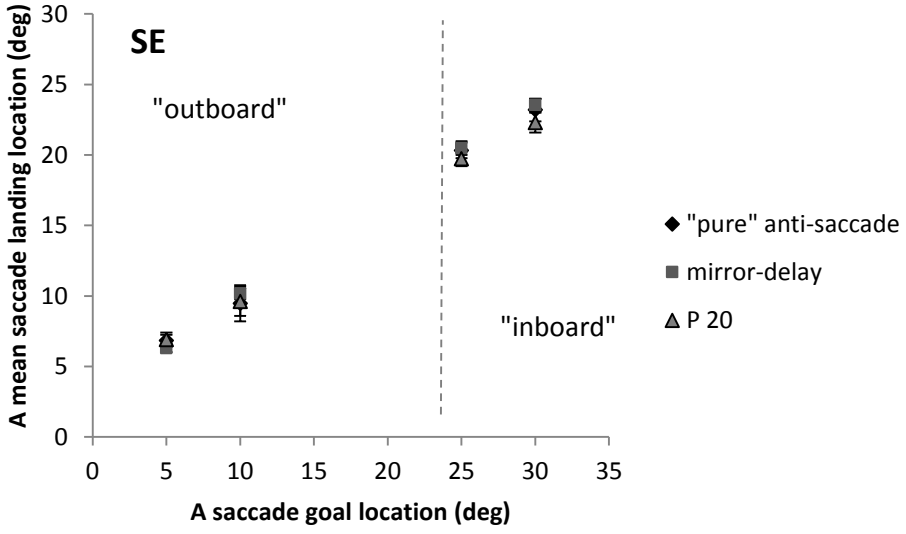


Figure 3-2. Comparison of mean anti-saccade landing location at each goal location in the "pure" anti-saccade, mirror-delay and non-mirror conditions. **A,B**: at 15^{o} subjects DR

and SE, respectively; **C,D**: at 20^{o} subjects DR and SE, respectively. Error bars represent standard error of the mean.

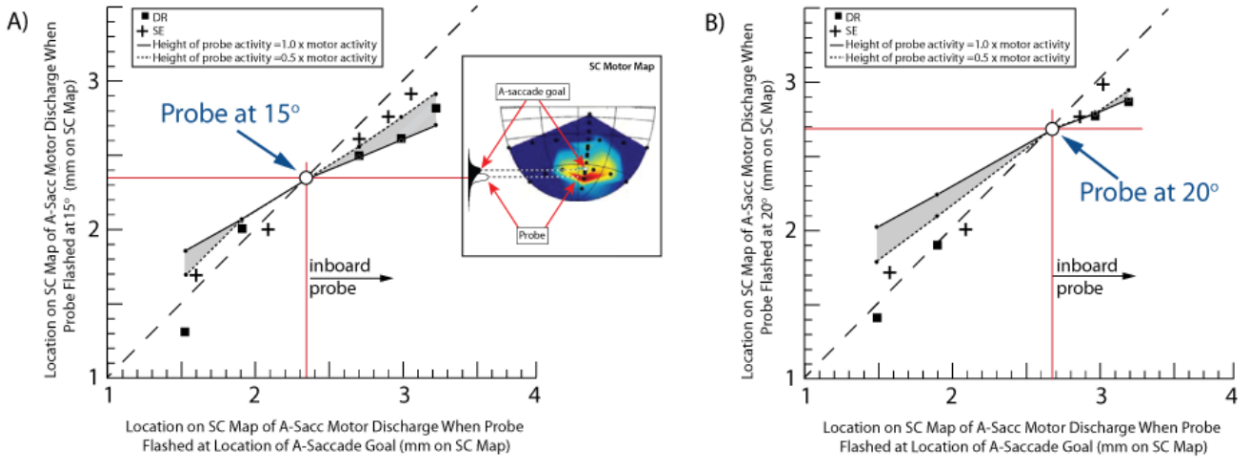


Figure 3-3. Effect of flashed visual probe on anti-saccade endpoint. Comparison of the anti-saccade amplitude when a visual probe was flashed at the anti-saccade goal (abscissa) to when the probe was flashed at either 15º (**A**) or 20º (**B**) in the blind hemifield (ordinate). The dotted and solid lines show that the theoretical framework expressed by a simple model of interactions between Gaussian hills on the SC map (Equation 4, see Methods) explains well our experimental results as explained in text. The inset in (**A**) summarizes the observations reported by Dorris et al. (2007) (see main text for further explanation).

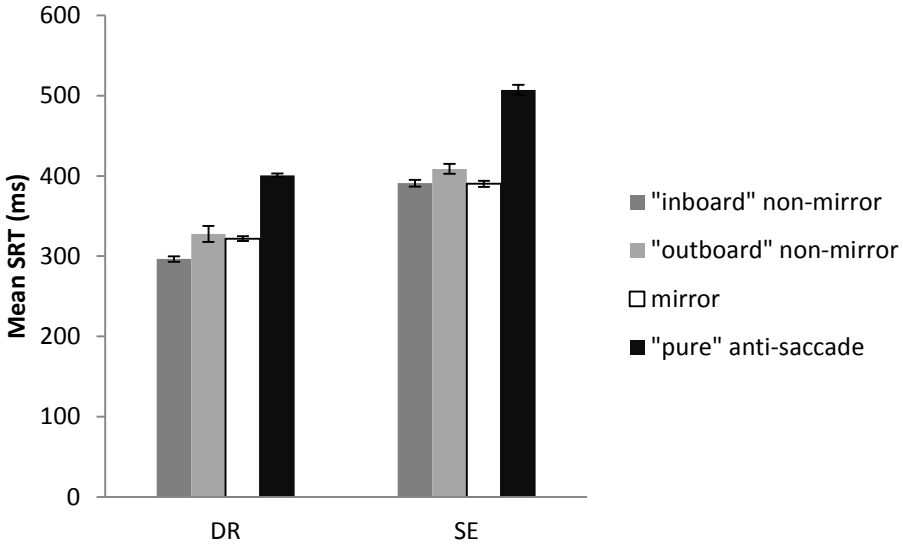


Figure 3-4. Mean saccadic reaction time. Comparison of mean saccade reaction times (SRT) in the four different anti-saccade conditions of subjects DR and SE. For explanation of tasks see Methods section. Error bars represent standard error of the mean.

Chapter 4: Oculomotor Control after Hemidecortication: One Hemisphere Encodes Normal Ipsilateral Oblique Anti-Saccades

Preface

Previous studies have observed that both hemispherectomized patients (Estañol et al., 1980; Troost et al., 1972) and monkeys (Tusa et al., 1986) generate grossly inaccurate pro-saccades to their blind hemifield ipsilateral to the intact hemicortex. In Chapters 2 and 3 we showed that our hemispherectomized patients were able to generate accurate *horizontal* anti-saccades to the blind hemifield. We therefore demonstrated that a full hemidecortication does not abolish anti-saccade control, in striking contrast with the well-known important impairments due to discrete lesions of say the frontal lobes (e.g., Guitton et al., 1985; Ploner et al., 2005). In this chapter we investigate our patients' ability to generate *oblique* anti-saccades. Anti-saccades, particularly oblique ones having both horizontal and vertical components, are generated via very complicated bilateral and interacting brain circuits involving cortical and subcortical structures. Here we not only examine hemispherectomized patients' ability to generate both horizontal and oblique anti-saccades, but also compare it to the performance of the individuals with a completely intact brain.

Summary

A critical question in neurology is how the brain reorganizes its structure and function following injury. Here, we consider oculomotor control following a massive brain lesion, a hemispherectomy. We used the *oblique* anti-saccade task which requires the suppression of a saccade towards a visual cue, flashed anywhere in a patient's seeing hemifield, and the generation, in the dark, of an anti-saccade to the opposite blind hemifield at the mirror location

of the cue. Anti-saccades require a visuo-motor vector inversion that normally involves bilateral interactions between frontal, parietal and subcortical structures across both hemispheres. Oblique anti-saccades present a major challenge to the patient's single hemisphere because one site in visual cortex must communicate with an infinite number of possible sites in oculomotor cortex. Patients with discrete frontal lobe damage can be strongly impaired in anti-saccades. By contrast, hemispherectomy patients performed oblique anti-saccades normally, contrasting with their permanent contralesional hemianopia and severe hemiparesis.

Introduction

It is well known that the brain reorganizes its structure and function to compensate for injury. Hemidecorticate patients, who have had an entire cerebral hemisphere removed to relieve intractable epilepsy, are particular interesting in this regard. When the hemispherectomy is performed in infancy, patients recover bilateral vision but, if operated later, become hemianopic, in the contralesional hemifield (Werth, 2006). Similarly, patients impaired preoperatively in contralesional limb motor control, particularly of the hand, retain this impairment following hemispherectomy post-infancy (e.g., Devlin et al., 2003; Pulsifer et al., 2004; van Empelen Jennekens-Schinkel, Buskens, Helders, & van Nieuwenhuizen, 2004). In contrast to these lasting deficits, the ability to generate bilateral horizontal saccadic eye movements survives adult hemispherectomy across many tasks in humans (Herter & Guitton, 2004; Rath-Wilson & Guitton, 2015, 2015; Reuter-Lorenz et al. 2011; Savina et al., 2013) and monkeys (Tusa et al., 1986), suggesting that neural circuits for generating rightward and leftward saccades are present innately in each hemisphere.

The anti-saccade task (Hallett, 1978) is particularly relevant to the study of bilateral saccade control and its limits. In this task a cue, say visual, is presented in one hemifield and the observer is required to suppress a reflexive glance to this stimulus, and generate a voluntary anti-saccade in the opposite direction - to the mirror location of the cue - in the absence of any visual target being presented there (Guitton et al., 1985; Munoz & Everling, 2004). For a hemispherectomy patient to generate an anti-saccade, the single hemisphere itself must: 1) inhibit the contralateral "pro-saccade" towards the cue in its seeing hemifield; 2) invert the fixation-point-to-cue vector; and 3) generate the ipsilateral (i.e., contralesional) anti-saccade.

These oculomotor abilities stand in contrast to the extensive experimental data showing that each hemisphere controls saccades contralateral to itself. In the normal brain, anti-saccade generation involves, bilaterally, areas such as the dorso-lateral prefrontal cortex (DLPFC), frontal eye field (FEF), supplementary eye field (SEF), lateral intraparietal cortex (LIP) and basal ganglia (Everling et al., 1999; Moon et al., 2007; Munoz & Everling, 2004; Watanabe & Munoz, 2011; Yoshida & Tanaka, 2016; Zhang & Barash, 2000; Zhang & Barash, 2004). By definition, a complete hemidecortication eliminates all cortical areas on one side, specifically those listed above that are critical to anti-saccade generation. A hemispherectomy also causes complete retrograde degeneration of the ipsilesional lateral geniculate nucleus (LGN) (Pasik et al., 1969) eliminating the possibility that retinal information from the blind hemifield crosses to the intact hemisphere. However, there is anatomical preservation of the contralesional and ipsilesional superior colliculi (SC) (Ptito et al., 1996; Theoret et al., 2001; Ueke, 1966) thereby providing a subcortical substrate for bilateral saccade control via, say, the FEF in the intact

hemisphere known to contain descending neurons that control ipsilateral and contralateral saccades (Crapse & Sommer, 2009).

In the *horizontal* anti-saccade task, a strong bilateral impairment in the ability to suppress disallowed reflexive saccades to the cue results from discrete lesions restricted to the DLPFC on one side (Guitton et al., 1985; Ploner et al., 2005). Lesions to either the FEF or parietal lobe also result in anti-saccade deficits (Machado & Rafal, 2004; reviewed in Rafal, 2006). In striking contrast, a complete hemispherectomy impairs horizontal anti-saccade control less than that following discrete unilateral cortical lesion: hemidecorticate patients can generate accurate horizontal anti-saccades (Reuter-Lorenz et al., 2011; Savina et al., 2013). Thus, their single hemisphere can process the location of a multisensory cue on the horizontal meridian of their seeing hemifield; calculate the vector inversion, and generate a horizontal ipsilateral anti-saccade.

While it is remarkable that hemispherectomy patients can generate accurate contralesional horizontal anti-saccades, it is of interest to determine whether their single hemisphere can perform a more challenging task, notably that of implementing the vector inversions and motor signals for contralesional *oblique* anti-saccades. Indeed, oblique anti-saccades present a critical challenge for the single remaining hemisphere because the cue activates a unique locus in the brain's retinotopically encoded visual areas which ultimately must be "translated" to connect functionally to motor areas controlling an infinite number of possible ipsilateral saccade vectors. Furthermore, because the SC on one side of the mid-brain represents the contralateral half of the visual retinal space, horizontal saccades depend upon representation within only one colliculus. However, saccades made to targets on the vertical meridian, require

motor signals within both the left and right SCs. This could present a challenge for the hemidecorticate brain since there is a disequilibrium between the two colliculi, with the ipsilesional SC being inhibited by the contralesional one (Hovda and Villablanca, 1990; Savina et al., 2013; Sprague, 1966).

Why is the SC so critical? The immediate premotor commands for horizontal saccades are produced within regions of the pons and medulla surrounding the abducens nucleus, while the premotor commands for vertical saccades are generated within areas of the rostral midbrain surrounding the oculomotor nucleus (Bender, 1980; Büttner-Ennever, Büttner, Cohen, & Baumgartner, 1982; Cohen, Komatsuzaki, & Bender, 1968; Goebel, Komatsuzaki, Bender, & Cohen, 1971; Henn, Lang, Hepp, & Reisine, 1984; Jacobs, Anderson, & Bender, 1973; Kömpf, Pasik, Pasik, & Bender, 1979; Nashold & Gillis, 1967.) The SC is considered to be the critical source of motor commands to the brainstem circuitry (Hanes & Wurtz, 2001; Johnston & Everling, 2008; Schiller et al., 1980; Scudder et al., 2002). Therefore, the fact that hemispherectomized patients have a hypoactive ipsilesional SC, and given its critical role in controlling contralesional saccades, it is of interest to investigate whether a hemispherectomy detrimentally affect saccades that involve both colliculi, such as *oblique* anti-saccades.

Thus, the goal of the present study was to determine whether *oblique* anti-saccade generation also survives hemidecortication. Research on oblique anti-saccade generation in a normal population is scarce (Koehn, Roy, & Barton, 2008) and does not exist for human patients with brain lesions. Here, a visual cue located in the seeing hemifield, off the horizontal meridian, requires inverting one or both of the horizontal and vertical vectors within the same hemisphere.

We found that hemidecorticate patients generated comparatively normal *oblique* anti-saccades, in striking contrast to their important and enduring limb motor impairments.

Materials and methods

Subjects. Three controls and three hemidecorticate patients (DR, SE and JB, Fig. 2-1) participated in this study, which was approved by the Montreal Neurological Institute and Hospital Research Ethics Committee. The participants gave informed and voluntary written consent prior to commencement of experimentation.

All three patients underwent a hemidecortication to relieve intractable epilepsy. Their case histories are described elsewhere (Leh et al., 2006; Tomaiuolo et al., 1997) and only summarized here.

DR - 37 at the time of testing - suffered from Rasmussen's chronic encephalitis with seizure onset at age 5. At age 17 she underwent complete right hemidecortication including the amygdala and hippocampus. All remaining cortical tissue on the decorticate side was surgically disconnected from the rest of the brain.

SE had a left hemiparesis at birth and had seizure onset at age 7. He was diagnosed with a porencephalic cyst and underwent a partial hemidecortication (temporo-parietal-occipital removal) including the amygdala and hippocampus on the right side at age 25, but sparing the entire right frontal lobe. He was 44 at the time of testing.

JB, who is left-handed, with the language lateralized to the right cortical hemisphere, underwent a two-step complete left hemidecortication at the age of 20 to relieve intractable epilepsy due to a porencephalic cyst with seizure onset at age five. Notably, his left frontal and

partial occipital poles were left in place, but surgically disconnected from the rest of the brain. JB was 44 at the time of testing.

All three patients had a dense contralesional hemianopia at the time of testing. The contralesional fingers and arm of DR and JB were paralyzed and motor control of the contralesional leg was impaired.

Apparatus. Visual stimuli, generated in MATLAB using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997), were back-projected at 85 Hz with an Electrohome Marquee 8000 projector (projection resolution, 1024 x 768 pixels) onto a screen located at a distance of 57 cm from the participant. Horizontal and vertical monocular eye movements (the eye contralateral to the lesioned side was patched) were monitored with a high speed (250Hz) eye tracking system (ASL).

We patched one eye of each subject. This was done in order to avoid the possibility that our patients would converge their eyes in order to reduce the blind region of their visual field. (We did not test for this putative compensatory convergence.) Each subject chose which eye they wanted patched and for all it was their contralesional eye. All our controls preferred to patch their left eye. Since all collicular cells within the binocular overlap region of the visual field respond equally well to the two eyes it would not matter what eye is patched. The visual cue informing partially (see next section) the vector of the anti-saccade was presented in a patient's seeing hemifield. Subjects SE and DR, with right hemisphere ablations, made leftward anti-saccades into their blind hemifield while JB, who had a left hemispherectomy, made rightward anti-saccades.

Stimuli and procedure. The visual cue consisted of a dimly lit 0.5^{o} grey dot with a luminance level of 0.8 cd/m^2, presented randomly at one of 12 fixed locations across the upper or lower visual hemifield, and, depending on the patient, in their seeing ipsilesional hemifield either to the right or left of the fixation point (FP), itself in the middle of the screen. For the control subjects, all visual cues were presented in their right visual hemifield. A cue could appear at one of the following coordinates:(H5°,V20°),(10°, 10°), (10°,20°), (20°, 10°), (20°,20°), (30°, 10°), (5°,-20°), (10°, -10°), (10°,-20°), (20°, -10°), (20°,-20°), (30°, -10°). In all tasks, the anti-saccades were made in complete darkness.

The experiment consisted of blocks of trials in the following conditions.1) O*blique anti-saccade to the blind hemifield inverting only the horizontal vector coordinates (H-inversion)*. Each trial began with the presentation of FP alone for a random duration of either 800 ms or 1,200 ms. Immediately following FP's extinction, a visual cue was presented in the seeing visual hemifield for a brief duration of 86 ms. The appearance of the cue indicated that the subject had to initiate an anti-saccade towards the opposite hemifield (which was always the blind hemifield for our patients), to the mirror horizontal location of the cue but remaining in the same upper or lower visual field. Participants were instructed to make an anti-saccade as promptly and accurately as possible. At the end of each trial, the room was illuminated for 1,000 ms before the start of the next trial to prevent dark adaptation. 2) *Oblique anti-saccade to the blind hemifield inverting both horizontal and vertical vectors (H-V inversion)*. Here the participants were instructed to make an anti-saccade to the mirror location of the cue to both the opposite horizontal (left or right) and vertical (upper or lower) hemifields.

The H-inversion and H-V-inversion blocks were randomly interleaved between participants and within participants between days of testing. No performance feedback was given to the participants at any point during the experiment.

Data analysis. During each trial, the following experimental quantities were stored: cue position and duration; anti-saccade reaction time (= time difference between the cue onset and anti-saccade initiation); anti-saccade duration, and landing position. The onset and end of each anti-saccade were identified as points where velocity increased above and decreased below 40º/s, respectively. The error of eye position at anti-saccade end with respect to the mirror location of the cue was calculated offline (i.e. manually) for each trial according to the criteria described below.

The exclusion criteria in our analysis procedure were:(1) erroneous pro-saccades in anti-saccade trials (i.e., saccades made towards the cue rather than to the opposite hemifield); (2) anti-saccade with latencies < 120 ms (such saccades would most probably be anticipatory in nature); (3) anti-saccade with latencies > 1,000 ms; (4) signals that contained significant noise and blink artefacts (determined by visual inspection); (5) anti-saccades that fell outside ±2SD from the mean anti-saccade landing location, considered as outliers. We used the remaining population of data points to calculate mean anti-saccade reaction time (SRT) and mean anti-saccade landing location. We calculated Delta Theta ($\Delta\Theta$) and Delta R (ΔR) in polar coordinates and used them as measures of accuracy, as considered below.

Angular error, Delta Theta ($\Delta\Theta$), was calculated in each trial by taking the difference between the required anti-saccade goal angle and the actual anti-saccade angle. We calculated:

Mean absolute $\Delta\Theta = (\Sigma \mid \Delta\Theta \mid)/n$ and Mean signed $\Delta\Theta = (\Sigma\Delta\Theta)/n$, where n = number of observations.

Error in anti-saccade amplitude, Delta R (ΔR) was calculated by taking the difference between the actual anti-saccade amplitude and the "ideal" amplitude between the initial fixation point and the goal. We calculated: Mean absolute $\Delta R = (\Sigma \mid \Delta R \mid)/n$, and Mean signed $\Delta R = (\Sigma\Delta R)/n$, where n = number of observations.

ANOVA: We analyzed our patients' performance by using 5 separate two factor mixed design ANOVAs comparing patients and controls on the measurements of mean SRT, mean signed ΔΘ, mean ABS ΔΘ, mean signed ΔR, and mean ABS ΔR; where the between-subjects variable was participant type (2 levels: controls and patients) and the within-subjects variable was hemifield type (2 levels: upper and lower hemifields). The data were analyzed using SPSS 18.0 statistical software.

BAYES FACTOR ANALYSIS: In addition to the classical statistical analysis (i.e. ANOVA), we also performed a Bayes Factor analysis, to determine the validity of the significance or none significance of the results (Dienes, 2014). The Bayesian approach evaluated the strength of evidence for the null (H_0) or alternative (H_1) hypothesis, by providing the probability of which hypothesis was more likely to be correct, and therefore should be favored on the basis of the available data (Masson, 2011). More specifically, we computed a Bayes factor (BF), which was converted into the estimated posterior probabilities (p_{BIC}) in order to determine whether the data favored the null or alternative hypothesis. The BF was calculated using the following formula (Masson, 2011):

$$BF = e^{(\Delta BIC)/2},$$

where BIC is the Bayesian Information Criteria, estimating the maximum likelihood of an event occurring; in other words, BF quantifies the hypothesis's "goodness of fit to data" (Masson, 2011). ΔBIC represents the difference in BIC values for the competing null and alternative hypotheses, according to the following formula:

$$\Delta BIC = n \times \ln(1-\eta^2_p)+(k_{H1}-k_{H0})\times \ln(n),$$

where ln is the natural logarithm function, n is either the number of subjects in the independent sample design, or the number of independent observations in the repeated measures design. In the latter case we used the following formula to calculate n,

$$n = s(c-1),$$

where s is the number of subjects and c is the number of conditions each subject was tested on. Finally, $k_{H1}-k_{H0}$ represents the difference in the number of free parameters between the two models, and it equals the degrees of freedom associated with an effect when H_0 and H_1 are contrasted.

The BF was then converted to the posterior probability (p_{BIC}) that the data favors the null hypothesis using the following formula,

$$p_{BIC}(H_0/D) = BF/BF+1$$

The posterior probability that the data favors the alternative hypothesis was calculated as follows:

$$p_{BIC}(H_1/D) = 1- p_{BIC}(H_0/D)$$

The strength of the evidence identified by the posterior probability values was defined as follows: weak (.50-.75), positive (.75-.95), strong (.95-.99) or very strong (>.99) (as suggested by Raftery, 1995; reviewed in Masson, 2011).

In the Results section we present our analyses by first stating the result of the ANOVA, followed by an evaluation of its conclusion using Bayesian analysis. For example in our analysis of *absolute delta R (ΔR) in the H-inversion condition* we found a significant main effect of hemifield type, i.e., an upper vs. lower hemifield difference ($F(1,4) = 10.42$, $p = .03$) and the Bayes factor analysis gave:

$$\eta_p^2 = .723,\ BF = .05,\ p_{BIC}(H_0/D) = 0.05,\ p_{BIC}(H_1/D) = 0.95$$

which indicates positive to strong evidence for the effect of hemifield.

Finally, because hemidecorticate patients are rare, the number (3) of patients we could test was small. We chose to study 3 control subjects to match the patient group and to avoid skewing the results in favor of control subjects. Consequently, the data we collected had the potential of being noisy. Therefore, in addition to the standard ANOVA, we performed an additional analysis using a *single-case* methodology developed by J.R. Crawford (Crawford & Howell, 1998; Crawford & Garthwaite, 2002). In this method an individual patient's score is compared to the control sample; and it is specifically designed to be used with very small sample sizes of even < 5 (Crawford & Garthwaite, 2002). It is essentially "a modified independent sample t-test in which the individual is treated as a sample of M = 1, and therefore does not contribute to the estimate of the within group variance" (Crawford & Garthwaite, 2002, p. 1197). To perform this modified t-test, we used a program downloaded from the first author's website at the following address:

http://homepages.abdn.ac.uk/j.crawford/pages/dept/Single_Case_Effect_Sizes.htm.

Using this method we compared individual patient's scores of mean signed ΔΘ, mean ABS ΔΘ, mean signed ΔR, mean ABS ΔR, and mean SRT to the respective scores of our control sample.

Results

Overview of the observations. To familiarize the reader with our observations, we begin by showing, for the H and H-V inversion conditions, respectively, the mean anti-saccade landing locations for each goal position and each participant in the hemidecorticate and control groups, respectively.

Recall that in DR and SE, the hemispherectomy was on the right side, and for JB on the left. To facilitate comparing the behaviors across subjects, the data in Fig. 4-1 were "normalized" as if all patients had a left-sided hemispherectomy. (This conveniently places goals in the right visual hemifield.) The insets in Fig. 4-1A and 4-1C show, respectively, a schematic coronal section of a brain, defining the removed left side, and the distinction between seeing and blind hemifields. A cue was shown in the intact *seeing* hemifield (filled diamond in inset) and the anti-saccade goal in the blind hemifield is defined by an open square. Note that for a given cue position, the goal location, in the H-inversion and H-V-inversion conditions were very different. No stimulus was ever presented at the goal location. The inset to Fig. 4-1A shows an actual anti-saccade landing location (black circle) and defines the measures $\Delta\Theta$ and ΔR (Methods). The former is the angular error between the vectors to the goal and landing locations, respectively. The latter is the error in R.

Each subject's performance is illustrated in Fig. 4-1 by a color-coded circle indicating the mean anti-saccade endpoint, linked to its respective goal location by a straight line coded according to goal location.

Visual inspection of each panel in Fig. 4-1 reveals the "noisy" behavior of all subjects, and suggests no clear difference in anti-saccade control between patients and controls. This

conclusion will be largely confirmed by our statistical analyses, but before we present these formal comparisons we briefly introduce the reader to the data in Fig. 4-1 in search of specific behavioral patterns.

H-INVERSION, PATIENTS (Fig. 4-1A): In this paradigm, a patient had to invert only the horizontal component of the anti-saccade cue location.

C*ues in the upper visual hemifield*: DR systematically overshot the horizontal and undershot the vertical components, respectively. JB was accurate for 1/3 of goals (at vertical 20º). For the remaining goals he was accurate in either the horizontal or vertical component, but not both. There was a tendency to aim for a common region around V20º. SE maintained accuracy in the vertical component but in the horizontal component tended to a default position at H15º.

Cues in the lower visual hemifield: DR was quite accurate in the H-component, but in the V-component tended to land at -10º for all vertical goal offsets. JB tended to saccade to a common vertical position at ~15º and frequently undershot the horizontal component. SE tended to aim his V component towards a common location at V10º -15º and to undershoot the H component at the larger H values.

H-V INVERSION, PATIENTS (Fig. 4-1C): In this paradigm, a patient had to invert both the horizontal and vertical components of the anti-saccade cue location.

Cues in the upper visual hemifield: DR tended to overshoot the vertical component, the opposite to her behavior in the H-inversion condition, and aimed for a common vertical region V20º -25º. JB tended to aim for a region lying between H10º -20º and V10º -20º, a behavior similar to that in H-inversion. SE also tended to aim for a common region between V5º -15º and H10º -20º.

Cues in the lower visual hemifield: DR tended to aim all her anti-saccades to a common end-point in the vicinity of about H10º and V15º; a behavior quite different than in the H-inversion condition. By comparison, JB behaved as in H-inversion and undershot H while tending to a common region for the V component.

H and H-V INVERSION in CONTROL SUBJECTS: We have seen in the above overview of patients (Fig. 4-1A, C) that the orientation and length of the line that links the anti-saccade goal to the respective anti-saccade end-point (representing anti-saccade error), seems specific to each participant, is quite variable and renders it difficult to identify a trend in the difference between each subject group, or between conditions. Thus, rather than attempt to "dissect" each control subject's specific behavior we asked whether a control subject resembled a patient.

In H-inversion: control S1 resembled SE for both the upper and lower visual hemifields; S2 resembled DR for the upper hemifield and resembled no patient for the lower hemifield; and S3 resembled DR for the upper hemifield and JP for the lower hemifield.

In H-V Inversion: control S1 resembled DR in upper hemifield and no patient in the lower hemifield; S2 and S3 resembled SE in both upper and lower hemifields.

The above impressions provided by visual inspection suggests that our patients and control subjects behaved roughly the same. Indeed, our statistical analyses below confirm this conclusion.

Statistical analyses: ANOVA. H-INVERSION: *Absolute delta Theta* $\Delta\Theta$ (Fig.4-2A): Analyses of the *mean absolute value of* $\Delta\Theta = (\Sigma \mid \Delta\Theta \mid)/n$, revealed: **1**) no significant main effect of hemifield ($F(1,4) = 5.71$, $p = .08$) with *positive* evidence for an alternative to the null hypothesis ($\eta_p^2 = .588$, BF=.17, $p_{BIC}(H_0/D) = 0.15$, $p_{BIC}(H_1/D) = 0.85$); **2**) no significant main

effect of participant type (F(1,4) = .22, p = .67) with *weak* evidence for the null hypothesis (η_p^2=.051, BF=2.09, $p_{BIC}(H_0/D) = 0.68$, $p_{BIC}(H_1/D) = 0.32$); and **3**) no interaction [F(1,4) = .0001, p = .99] with *weak* evidence for the null hypothesis (η_p^2=.001, BF=2.44, $p_{BIC}(H_0/D) = 0.71$, $p_{BIC}(H_1/D) = 0.29$).

Signed delta Theta (ΔΘ) (Fig.4-3A): Statistical analysis of the *mean signed value of* ΔΘ= (ΣΔΘ)/n revealed: **1**) no significant main effect of hemifield (F(1,4) = 1.32, p = .31), with *weak* evidence for the null hypothesis (η_p^2=0.248, BF=1.04, $p_{BIC}(H_0/D) = 0.51$, $p_{BIC}(H_1/D) = 0.49$); **2**) no significant main effect of participant type (F(1,4) = 3.59, p = .13) with *weak* evidence for the effect of participant type (η_p^2=0.474, BF=0.356, $p_{BIC}(H_0/D) = 0.26$, $p_{BIC}(H_1/D) = 0.74$); and **3**) no significant interaction (F(1,4) = .055, p = .83), with *weak* evidence for the null hypothesis (η_p^2=0.013, BF=2.355, $p_{BIC}(H_0/D) = 0.70$, $p_{BIC}(H_1/D) = 0.30$).

Absolute Delta R (ΔR) (Fig.4-4A): These analyses revealed: **1**) a significant main effect of hemifield type (F(1,4) = 10.42, p = .03), with *strong* evidence for the effect of hemifield; i.e. against the null hypothesis (η_p^2=.723, BF=.05, $p_{BIC}(H_0/D) = 0.05$, $p_{BIC}(H_1/D) = 0.95$). Notably, both groups of participants performed better in the upper hemifield; **2**) no significant main effect of participant type (F(1,4) = 1.69, p = .26), with *weak* evidence for the effect of participant type (η_p^2=.29, BF=.85, $p_{BIC}(H_0/D) = 0.46$, $p_{BIC}(H_1/D) = 0.54$); and **3**) no interaction (F(1,4) = 6.67, p = .06), with *positive* evidence for interaction; i.e., against the null hypothesis (η_p^2=.63, BF=.12, $p_{BIC}(H_0/D) = 0.11$, $p_{BIC}(H_1/D) = 0.89$).

Signed Delta R (ΔR) (Fig.4-5A): Statistical analysis of *signed* ΔR revealed: **1**) a borderline significant main effect of hemifield (F(1,4) = 7.83, p = .05), with *positive* evidence for the effect of hemifield (η_p^2=.662, BF=.09, $p_{BIC}(H_0/D) = 0.08$, $p_{BIC}(H_1/D) = 0.92$). Once again,

both groups of participants did better in the upper hemifield; **2**) there was a significant main effect of participant type ($F(1,4) = 79.16$, $p = .001$), where controls performed better than patients, with *very strong* evidence supporting the effect of participant type; i.e., against the null hypothesis (η_p^2=.95, BF=.0003, $p_{BIC}(H_0/D) = 0.01$, $p_{BIC}(H_1/D) = 0.99$); and **3**) no significant interaction ($F(1,4) = 3.55$, $p = .13$), with *weak* evidence for the interaction effect (η_p^2=.47, BF=.36, $p_{BIC}(H_0/D) = 0.27$, $p_{BIC}(H_1/D) = 0.73$);

Saccadic Reaction Time (SRT) (Fig.4-6A): Analyses of SRT revealed: **1**) no significant effect of participant type ($F(1,1) = 0.5$, $p = .52$), with *weak* evidence for the null hypothesis (η_p^2=0.111, BF=1.7, $p_{BIC}(H_0/D) = 0.63$, $p_{BIC}(H_1/D) = 0.37$); **2**) no significant effect of hemifield type ($F(1,4) = 1.25$, $p = .33$), with *weak* evidence for the null hypothesis (η_p^2=0.237, BF=1.09, $p_{BIC}(H_0/D) = 0.52$, $p_{BIC}(H_1/D) = 0.48$); and **3**) no interaction ($F(1,4) = 3.42$, $p = .14$), with *weak* evidence for an interaction effect (η_p^2=0.461, BF=0.38, $p_{BIC}(H_0/D) = 0.28$, $p_{BIC}(H_1/D) = 0.72$). Thus, controls and patients had similar reaction times in both experiment conditions. (As an aside and by comparison, note that discrete lesions of the parietal lobe substantially increase contralesional horizontal anti-saccade latency; as reviewed in Rafal, 2006).

H-V INVERSION: *Absolute delta Theta* $\Delta\Theta$ (Fig.4-2B): We found: **1**) a significant main effect of hemifield ($F(1,4) = 10.18$, $p = .033$), with *strong* evidence for the effect of hemifield; i.e., against the null hypothesis (η_p^2=0.718, BF=0.055, $p_{BIC}(H_0/D) = 0.05$, $p_{BIC}(H_1/D) = 0.95$). In this case however, overall anti-saccades toward the upper hemifield had larger mean absolute $\Delta\Theta$ than anti-saccades toward the lower hemifield in both groups of participants. We also found: **2**) a significant main effect of participant type ($F(1,4) = 8.38$, $p = .044$), with *positive* evidence for the effect of participant type (η_p^2=0.677, BF=0.08, $p_{BIC}(H_0/D) = 0.07$, $p_{BIC}(H_1/D) = 0.93$),

wherein controls had an overall larger mean absolute ΔΘ than did patients; and **3**) no significant interaction ($F(1,4) = 4.67$, $p = .097$), with *positive* evidence for an interaction effect (η_p^2=0.539, BF=.24, $p_{BIC}(H_0/D) = 0.19$, $p_{BIC}(H_1/D) = 0.81$).

Signed delta Theta (ΔΘ) (Fig.4-3B): Statistical analysis revealed: **1**) no significant main effect of hemifield ($F(1,4) = 2.72$, $p = .174$), with *weak* evidence for the main effect of hemifield (η_p^2=0.405, BF=0.516, $p_{BIC}(H_0/D) = 0.34$, $p_{BIC}(H_1/D) = 0.66$), **2**) no significant interaction ($F(1,4) = 5.99$, $p = .071$), with *positive* evidence for an interaction effect (η_p^2=.599, BF=.158, $p_{BIC}(H_0/D) = 0.14$, $p_{BIC}(H_1/D) = 0.86$); and **3**) a significant main effect of participant type ($F(1,4) = 8.95$, $p = .04$), wherein patients performed better than controls, with *positive* evidence for the effect of participant type (η_p^2=0.691, BF=.0699, $p_{BIC}(H_0/D) = 0.07$, $p_{BIC}(H_1/D) = 0.93$).

Absolute Delta R (ΔR (Fig. 4-4B): Statistical analysis revealed: **1**) borderline significant main effect of hemifield ($F(1,4) = .54$, $p = .05$) demonstrating a better performance in the upper hemifield, with *weak* evidence for the null hypothesis (η_p^2=0.119, BF=1.67, $p_{BIC}(H_0/D) = 0.63$, $p_{BIC}(H_1/D) = 0.37$); **2**) no significant effect of participant type ($F(1,4) = 4.95$, $p = .09$), with *positive* evidence for the effect of participant type (η_p^2=0.553, BF=0.22, $p_{BIC}(H_0/D) = 0.18$, $p_{BIC}(H_1/D) = 0.82$); and **3**) no significant interaction ($F(1,4) = .07$, $p = .81$), with *weak* evidence for the null hypothesis (η_p^2=0.017, BF=2.34, $p_{BIC}(H_0/D) = 0.70$, $p_{BIC}(H_1/D) = 0.30$).

Signed Delta R (ΔR) (Fig.4-5B): Statistical analysis revealed: **1**) no significant main effect of hemifield ($F(1,4) = 4.61$, $p = .09$), with *positive* evidence for the effect of hemifield (η_p^2=0.535, BF=0.25, $p_{BIC}(H_0/D) = 0.20$, $p_{BIC}(H_1/D) = 0.80$); **2**) no significant effect of participant type ($F(1,4) = .5$, $p = .52$), with *weak* evidence for the null hypothesis (η_p^2=0.111, BF=1.73, $p_{BIC}(H_0/D) = 0.63$, $p_{BIC}(H_1/D) = 0.37$); and **3**) no significant interaction ($F(1,4) = .26$, p

= .64), with *weak* evidence for the null hypothesis (η_p^2=0.061, BF=2.034, $p_{BIC}(H_0/D) = 0.67$, $p_{BIC}(H_1/D) = 0.33$).

Saccadic Reaction Time (SRT) (Fig.4-6B): Analyses of SRT revealed: **1**) no significant effect of participant type (F(1,4) =0.7, p =.45), with *weak* evidence for the null hypothesis (η_p^2=0.149, BF=1.5, $p_{BIC}(H_0/D) = 0.60$, $p_{BIC}(H_1/D) = 0.40$); **2**) no significant effect of hemifield type (F(1,4) =3.59, p =.13), with *weak* evidence for the effect of hemifield type (η_p^2=0.473, BF=.36, $p_{BIC}(H_0/D) = 0.26$, $p_{BIC}(H_1/D) = 0.74$); and **3**) no interaction (F(1,4) =.18, p =.69) with *weak* evidence for the null hypothesis (η_p^2=0.042, BF=2.15, $p_{BIC}(H_0/D) = 0.68$, $p_{BIC}(H_1/D) = 0.32$).

ANOVA results summary.

Controls vs. patients. H-INVERSION: In this task subjects had to invert only the horizontal component of the vector from central fixation to the visual cue. Control subjects performed significantly better (p = 0.01) than patients in the measure of mean signed ΔR with the Bayesian Factor analysis demonstrating a 99% decisive likelihood of this result occurring again.

By comparison there was no difference in performance between patients and controls in the measures of mean absolute ΔR, mean absolute ΔΘ, and mean signed ΔΘ. This result indicates that hemidecorticate patients were as successful as control subjects at rotating the angle of their vector inversion motor response to the goal but were less successful in controlling the precise mean amplitude of their anti-saccade response. Additionally, the two groups did not differ in SRT measure.

H-V INVERSION: In this task subjects had to invert both the horizontal and vertical components of the vector from central fixation to the visual cue. Here controls and patients

performed equally well in controlling R, as given by the measures of signed ΔR and ABS ΔR. By comparison, analyses of ABS ΔΘ and signed ΔΘ showed that patients performed better than controls with, respectively, the 93% and 93.5% decisive likelihoods of these results occurring again. These results indicate that patients do better than controls at controlling the direction of their anti-saccades when both horizontal and vertical vectors must be inverted. This surprising result could be due to a practice effect obtained by the patients in our prior studies (Reuter-Lorenz et al., 2011; Savina et al., 2013).

Upper vs. lower hemifield. H-INVERSION: The ANOVA analysis of absolute and signed ΔR in the H inversion condition demonstrated a significantly better performance of both groups of participants in the upper hemifield, which was supported by the Bayesian Factor analysis. By comparison, there were no hemifield effects for all measures of ΔΘ.

H-V INVERSION: The ANOVA analysis of ABS ΔR (but not signed ΔR) revealed better performance in the upper hemifield by both groups of participants. By comparison, the ANOVA analysis of ABS ΔΘ (but not signed ΔΘ) revealed that both groups of participants performed significantly better for anti-saccades directed to the lower hemifield, with the 95% decisive likelihood of this result occurring again. To summarize this section: both groups of participants had a more accurate R to upper hemifield and more accurate Θ to lower hemifield.

Single-case analyses. *Signed Delta Theta (ΔΘ)*: In H-inversion condition, a modified independent sample two-tailed t-test analysis of the difference between DR score and the control group revealed no significant difference ($p = .95$). Similarly there was no significant difference between individual scores of patients SE and JB and those of control group ($p = .59$ and $p = .36$,

respectively). Likewise, in H-V inversion none of the patients significantly differed from the control group (DR: p = .52, SE: p = .69, JB: p = .52).

Absolute Delta Theta (ΔΘ): In H-inversion condition, a modified independent sample two-tailed t-test analysis of the difference between DR, SE, and JB individual scores and the control group revealed no significant difference (DR: p = .42, SE: p = .72, JB: p = .99). Likewise, in H-V inversion none of the patients significantly differed from the control group (DR: p = .9, SE: p = .62, JB: p = .69).

Signed Delta R (ΔR): A modified independent sample two-tailed t-test analysis of *signed* Δ*R* revealed that once again none of the patients significantly differed from control group (DR: p = .2 and p = .69, SE: p = .18 and p = .26, JB: p = .17 and p = .69, in H- and H-V conditions respectively).

Absolute Delta R (ΔR): A modified independent sample two-tailed t-test did not reveal any significant differences between the individual patients' scores and that of the control group (DR: p = .99 and p = .72, SE: p = .79 and p = .27, JB: p = .45 and p = .65, in H- and H-V conditions respectively).

SRT: Similarly to the results described above, a modified independent sample two-tailed t-test analysis of *SRT* revealed that none of the patients significantly differed from control group in either H or H-V conditions (DR: p = .68 and p = .63, respectively; SE: p = .6and p = .57, respectively; JB: p = . 24 and p = .13, respectively).

In summary, all of the aforementioned single-case analyses showed that individual patients did not significantly differ from the control group on any of the measurements in any of the conditions.

Erroneous reflexive glances. For the control subjects the average percent of reflexive saccades in H and H-V inversion conditions were 4.6% (C1: 5.2%, C2: 3.4% and C3: 5.2%) and 5.3% (C1: 7.4%, C2: 5.9% and C3: 2.5%), respectively. For the patients the average percent of reflexive saccades in the H and H-V inversions were 3.3% (DR: 3.6%, SE: 2.8% and JB: 3.4%) and 14.4% (DR: 8.6%, SE: 7.2% and JB: 27.4%), respectively. Therefore, there is almost a threefold increase in erroneous saccades in patient group from control group in H-V inversion.

Discussion

Comparison of patients and controls. An anti-saccade towards the blind hemifield of a hemidecorticate patient requires the remaining hemisphere to: 1) suppress a contralateral pro-saccade toward a visual cue flashed in the seeing hemifield; and 2) generate an ipsilateral anti-saccade based on a vector inversion of the non-executed pro-saccade to the cue. This visuo-motor processing is normally attributed to coordinated neural activity in and between two hemispheres (Munoz & Everling, 2004), but in our patients this neural processing was regrouped into one.

Here we studied two types of inversion of the fixation-to-cue vector: in different blocks of trials we asked our patients to invert only the horizontal vector (H-inversion); or both the horizontal and vertical vectors (H-V inversion). We will first discuss the results pertaining to the differences in performance between the control and patient groups, and then we will describe the upper vs. lower hemifield asymmetry in performance.

The ANOVA concluded that the patients were normal in most measures, specifically in their reaction times in both H- and-H-V inversion, in *ABS* $\Delta\Theta$, *signed* $\Delta\Theta$ and *ABS* ΔR in H-inversion and in *ABS* ΔR and *signed* ΔR in H-V inversion condition. In some measures however,

results of ANOVA suggested that patients performed better than controls, such as in *signed* $\Delta\Theta$ and *ABS* $\Delta\Theta$ in H-V inversion. By comparison, controls were superior to patients in only one case: *signed* ΔR in H-inversion condition. Overall, the ANOVA indicated that patients behaved normally or better in 9/10 measures. Furthermore, the "single-case" analysis approach concluded that each patient's performance was similar to that of the control group. Taken together, both analyses strongly suggest that patients behaved normally.

Patients were also normal in the frequency of erroneous reflexive glances that they generated in the H-inversion condition. However, in H-V inversion, they generated more erroneous reflexive saccades than controls arguably because this task requires inversion of both the horizontal and vertical components of the cue vector thereby posing a greater challenge to the neural circuits of the remaining hemisphere. Actually, if the preparation of the anti-saccade motor signal is slow, this could allow the motor activity for a reflexive glance to reach threshold first (Guitton et al., 1985). Indeed, this is supported by the finding that our patient JB generated significantly larger percentage of reflexive saccades compared to other patients and controls in H-V inversion condition, and his SRT in H-V inversion condition was also significantly longer than SRTs of other patients and controls in both H - and - H-V inversion conditions. JB's results suggest that his preparation of the anti-saccade motor signal was slow, which could explain why he produced such a large amount of reflexive erroneous pro-saccades.

With respect to upper vs. lower hemifield asymmetries in accuracy, we found in the H-inversion condition that both normal control subjects and patients performed significantly better in the upper hemifield - i.e. cue presented in the upper hemifield - regarding the control of R, be it *ABS* ΔR or *signed* ΔR. In H-V inversion condition both groups controlled better R, as

measured by *ABS* ΔR, but not *signed* ΔR, to the upper hemifield (cue in lower hemifield) and Θ as measured by *ABS* $\Delta\Theta$, but not *signed* $\Delta\Theta$, to the lower hemifield (cue in upper hemifield). Overall, across all conditions there is perhaps a small upper hemifield advantage for the precise encoding of cue location.

Comparison to previous studies. In normal subjects, oblique anti-saccade endpoints, in H-V inversion, have been reported to cluster about the 45º diagonals (Koehn et al., 2008). Neither our control subjects nor our patients showed this "diagonal effect"; arguably due to differences in the respective paradigms. Koehn et al. (2008) presented anti-saccade cues around a semicircle of constant radius (~ 10º) and at four positions along the circle in the upper and four in the lower hemifield respectively. By comparison, our cues were not on a semicircle, were more scattered and, in all trials, had at least one component at a larger amplitude than 10º. Thus, it is possible that the "diagonal effect" only holds for an ensemble of cue locations that have some predictability about future cue location as in Abegg, Rodriguez, Lee, & Barton (2010). Note also that Koehn et al. (2008) combined data from upper and lower visual fields in their analysis, whereas we did not, because of clear hemifield asymmetries with a somewhat more precise control of anti-saccade amplitude (R) to the upper field across both of our conditions.

In human studies, a directional asymmetry exists with a *lower field* advantage in tasks that test: detection using manual reaction-times (Tartaglione, Favale, & Benton, 1979), contrast sensitivity (Carrasco, Talgar, & Cameron, 2001; Skrandies, 1985a; Skrandies, 1985b), spatial resolution (Talgar & Carrasco, 2002), perception of illusory contours (Rubin, Nakayama, & Shapley, 1996), and discrimination of differences in motion, contrast and hue (Levine & McAnany, 2005). Neurophysiological studies of *sensory* processing mechanisms also support a

lower rather than an upper visual field advantage: 1) higher density of ganglion cells in the superior retina (Curcio & Allen, 1990); 2) superior representation of the lower visual field in striate and extrastriate areas (Galletti, Fattori, Gamberini, & Kutz, 1999; Liu, Heeger, & Carrasco, 2006); 3) stronger visual activity in the occipital area for stimuli in the lower visual field (Kuba, Peregrin, Vit, & Hanusova, 1982; Portin, Vanni, Virsu, & Hari, 1999; Tzelepi, Ioannides, & Poghosyan, 2001).

By comparison, with respect to *attentional* processing, the evidence points towards an upper visual field advantage, such as higher attentional sensitivity and faster attentional shift to objects in the upper visual field (Zhou & King, 2002), and upper visual field preference during visual search task (Kraft, Sommer, Schmidt, & Brandt, 2011). Attentional processing, involving both top-down control, to prevent attention capture by the cue, and an attentional shift from the cue to the opposite location, is a fundamental part of the *anti*-saccade paradigm. If our results were explainable by pure sensory encoding, then the above observations would suggest better encoding of R and Θ in the lower hemifield for H-inversion and in the upper hemifield for H-V inversion. Of course, this is not what we found. In fact, our finding of a more precise control of anti-saccades in the *upper* visual field suggests that attentional processing mechanisms are responsible for the hemifield asymmetry exhibited by our participants.

Finally, Hafed and Chen (2016) reported upper visual field (UVF) vs. lower visual field (LVF) asymmetry in the primate superior colliculus. Specifically, they found that neurons representing the UVF have smaller receptive fields, as well as that they have a more finely tuned spatial frequency. Interestingly, they found that for memory-guided saccades there was no difference in reaction times between UVF and LVF, but the accuracy (landing error) was better

in the UVF. Evidently, these results are congruent with our findings. Specifically, while the SRT of anti-saccades in our experiment did not significantly differ in the upper and lower visual hemifields, the error of the amplitude (ΔR) of the anti-saccades in both groups of participants was much smaller in the upper hemifield than lower hemifield for H-inversion. This is compatible with both the Hafed and Chen (2016) results and the attention literature.

As for H-V inversion the situation is more complex given that the cue is in one visual hemifield while the motor command is to the opposite hemifled field. We found in H-V inversion an upper visual hemifield advantage for ΔR (cue in lower field), but lower hemifeld advantage for ΔΘ (cue in upper field). We could speculate here on attentional versus sensory effects in the precision of encoding, but we cannot offer a convincing explanation for the discrepancy in our finding between ΔR and ΔΘ with respect to hemifield asymmetry. There is clearly a multifaceted influence on the behavioral output.

In summary, previous research and our findings indicate that while there is certainly an upper vs. lower visual filed asymmetry, the neural mechanism behind it is complex and task dependent. It encompasses various sensory and attentional processing, as well as different brain structures.

Anatomical and functional correlates of normal anti-saccade generation. Early imaging studies identified a bilateral fronto-parietal circuit involved in the cue-to-goal vector inversion process and subsequent anti-saccade generation (Doricchi et al., 1997; reviewed in Hutton & Ettinger, 2006), but the slow dynamics of the PET and fMRI techniques precluded insight into the temporal and interhemispheric neural mechanisms involved in cancelling a reflexive glance to the cue and in generating the voluntary anti-saccade motor command. More

recently, the use of magneto-encephalography has suggested that the vector inversion process takes place simultaneously in both the intraparietal area and frontal eye fields (McDowell et al., 2005; Moon et al., 2007). However, the most refined understanding of the neural processes involved in anti-saccade generation has been provided by neural recordings in the frontal lobe (FEF, SEF, DLPFC), LIP and, subcortically, the caudate nucleus (CN) of the basal ganglia and the SC (reviewed in: Munoz & Everling, 2004; Watanabe & Munoz, 2011).

In the *normal* brain, two types of neurons in each of the left and right SCs and FEFs play a critical role in the bilateral mechanisms of anti-saccade generation and have similar discharge characteristics: 1) fixation neurons (FNs) discharge tonically during fixation and pause during saccades; while 2) saccade neurons (SNs) do the opposite; they are silent during fixation and burst just before and during the saccade. (FNs are also involved in micro-saccade generation (Hafed, Chen, & Tian, 2015)). Normally, before say a rightward anti-saccade, the tonic activity, in both the left and right hemispheres, of FNs in the SC and FEF is enhanced after cue-presentation to the left of fixation. FN discharge acts in part to prevent a forbidden leftward reflexive glance to the cue which could be generated by the cue-evoked visual burst in the right SC and FEF. The cue–evoked activity in the right SC is also prevented from reaching threshold by unknown inputs. At the same time the activity in the left FEF and left SC builds up to a burst that eventually surpasses a threshold and encodes the correct rightward anti-saccade.

To create the burst on left-side SNs, encoding the rightward anti-saccade, requires normally a vector inversion which is thought to be made in visual, not motor, coordinates (Collins et al., 2008). Visual neurons in LIP may play a role in this process (Zhang & Barash, 2000, 2004). For, say, a rightward anti-saccade these neurons in the left LIP show a delayed

visual burst relative to the burst in the right LIP, itself triggered in response to the visual cue on the left side. Damage to this parietal region in humans disrupts vector inversion and ipsilesional anti-saccades are impaired (Nyffeler, Rivaud-Pechoux, Pierrot-Deseilligny, Diallo, & Gaymard, 2007). (Here we could not study visually-cued ipsilesional anti-saccades.) The FEF may also be implicated in this vector inversion process (discussed in Munoz & Everling, 2004). The basal ganglia (CN and substantia nigra (Watanabe & Munoz, 2011)) on each side are also involved in suppressing reflexive saccades and in generating rightward volitional anti-saccades. Remarkably, here, all these vector inversion processes could be done by a single hemisphere.

Involvement of the superior colliculus. The SC's proximity to the brainstem saccade generator has led to interpretations of anti-saccade reflexive errors in terms of the excitability state of its motor map. In cats, hemispherectomized as adults, the ipsilesional SC becomes hypoactive as compared to the contralesional SC, in line with interrupted excitatory descending ipsilateral cortical projections to SC (Hovda & Villablanca, 1990). Parietal lesions are compatible with this effect: they lead to fewer reflexive saccades towards contralesional versus ipsilesional cues (Rafal, 2006). In contrast, increased reflexive glances to contralesional cues occur after frontal lobe lesions in a visual anti-saccade task and in hemispheretomy patients (including DR, tested here) in an auditory anti-saccade task; both groups linked to a hyperexcitable ipsilesional SC (Guitton et al., 1985; Machado & Rafal, 2004; Reuter-Lorenz et al., 2011).

Here, our observations support a normal bilateral state of the SC in our visual anti-saccade task: our hemispherectomy patients had a normal percentage of reflexive saccades to the ipsilesional cue in their seeing hemifield in H-inversion condition and normal latencies of

contralesional anti-saccades into their blind hemifield in both H- and - H-V inversion conditions. However, in H-V inversion condition the patients exhibited an almost a threefold increase in the erroneous pro-saccades towards the cue. Notably, as was stated earlier, our patients had an extensive practice of performing horizontal anti-saccade (i.e. H-inversion) for our previous study (Savina et al., 2013), which could explain their normal performance in H-inversion condition. However, in an arguably more complex task of both horizontal and vertical vector inversion, the patients made many more reflexive saccades to the cue than controls. Such observations suggest both task and lesion-dependent effects on SC excitability. The SC threshold hypothesis must be refined to account for the complex network involving different bilateral cortical areas, task complexity, and the different demands of visual versus auditory tasks.

Hemispherectomy versus smaller lesions. A discrete unilateral lesion of a subregion of the DLPFC, corresponding to Brodmann's area 46, leads to a high rate of *bilateral* reflexive errors (Guitton et al., 1985; Ploner et al., 2005). By comparison, unilateral frontal lobe lesions involving the FEF lead to increases in only contralesional reflexive glances and in contralesional anti-saccade latency (Machado & Rafal, 2004; reviewed in Rafal, 2006). In contrast, our patients with massive lesions had normal anti-saccade latencies in both conditions and only an increase in contralesional reflexive glances in the H-V condition.

Regarding the parietal lobe, its role in anti-saccade generation may lie in the vector inversion process inherent to converting a cue signal into an oppositely directed anti-saccade command (Nyffeler et al., 2007; Zhang & Barash, 2000, 2004). Following the arguments of Nyffeler et al. (2007), for a discrete unilateral lesion of say the left parietal lobe, the visual vector from the fixation point to the ipsilesional cue on the left is inverted successfully in the right

intact hemisphere but cannot be transferred to the lesioned left hemisphere, such that contralesionally-directed rightward anti-saccades should be impaired. Our observation that anti-saccades directed away from the missing hemisphere - i.e., contralesionally – were normal, indicates that all the visuo-motor transformations can occur in the single intact hemisphere.

In summary, lesions of discrete cortical regions can lead to deficits that are not present following a hemispherectomy, perhaps because our patients had specific practice; but their practice was in horizontal, not oblique, anti-saccades. This opens an interesting window into the mechanisms of brain plasticity, considered briefly below.

Innate bidirectional saccade control by a single hemisphere. The remarkably normal oculomotor abilities of our hemispherectomy patients, here and in other studies (Herter & Guitton, 2004), are possible only after the brain's plasticity mechanisms have been exploited to permit one hemisphere to take over all bilateral visuo-saccade command functions. One suggested mechanism for recovery of function following brain injury has been the redundancy of brain circuits with alternative, but previously inactive pathways, becoming functionally relevant (reviewed in Chen, Cohen, & Hallett, 2002). For example, motor improvements have been linked to the reinforcement of an innate ipsilateral corticospinal tract (Benecke, Meyer, & Freund, 1991; Chen et al., 2002).

In the saccade system, the prime connections from cortex to SC are ipsilateral, but hemidecorticate patients generate short-latency contralesional "express saccades" (Reuter-Lorenz et al., 2011); an ability that normally requires a now absent ipsilesional cortico-SC pathway (Schiller et al., 1987). However, there exists innate bilateral connections from FEF to the SC, nucleus reticularis tegmenti pontis, and paramedian pontine reticular formation (Crapse

& Sommer, 2009; reviewed in Reuter-Lorenz et al., 2011). Also, increased crossed connections from cortex to SC occur following experimental hemidecortication in cats (Adelson et al., 1995). Neural machinery in the normal brain subtends bilateral saccade control by a single hemisphere; e.g., FEF and LIP neurons have ipsilateral visual and motor responses (Barash et al., 1991; Zhang & Barash, 2000, 2004). Such data may explain why the SC remains anatomically intact on the decorticate side following experimental hemidecortication in monkeys (Ptito et al., 1996; Théoret et al., 2001) and why normal monkeys hemispherectomized as adults have bilateral saccade control (Tusa et al., 1986).

Apart from direct cortico-SC projections, multiple other pathways can affect SC excitability, e.g.: 1) descending projections from contralesional frontal cortex to the contralesional SC and inhibitory SC commissurals to the ipsilesional SC (Johnston & Everling, 2006; Takahashi et al., 2006); and 2) the ipsilesional or contralesional basal ganglia (reviewed in Hikosaka et al., 2000; Hikosaka & Wurtz, 1983; Jiang et al., 2003; Munoz & Everling, 2004).

Conclusion

The "rules" that govern recovery of oculomotor function following lesions are extremely complex and depend on: the extent and location of a lesion; the relative amount and location of remaining tissue and its relationship to subcortical structures like the SC; and the existence of innate bilateral saccade control circuitry. Thus, our observations in hemidecorticate patients require careful consideration of: 1) anti-saccades as a biomarker; and 2) the "one-site, one-function, one-deficit" approach to understand cortical function.

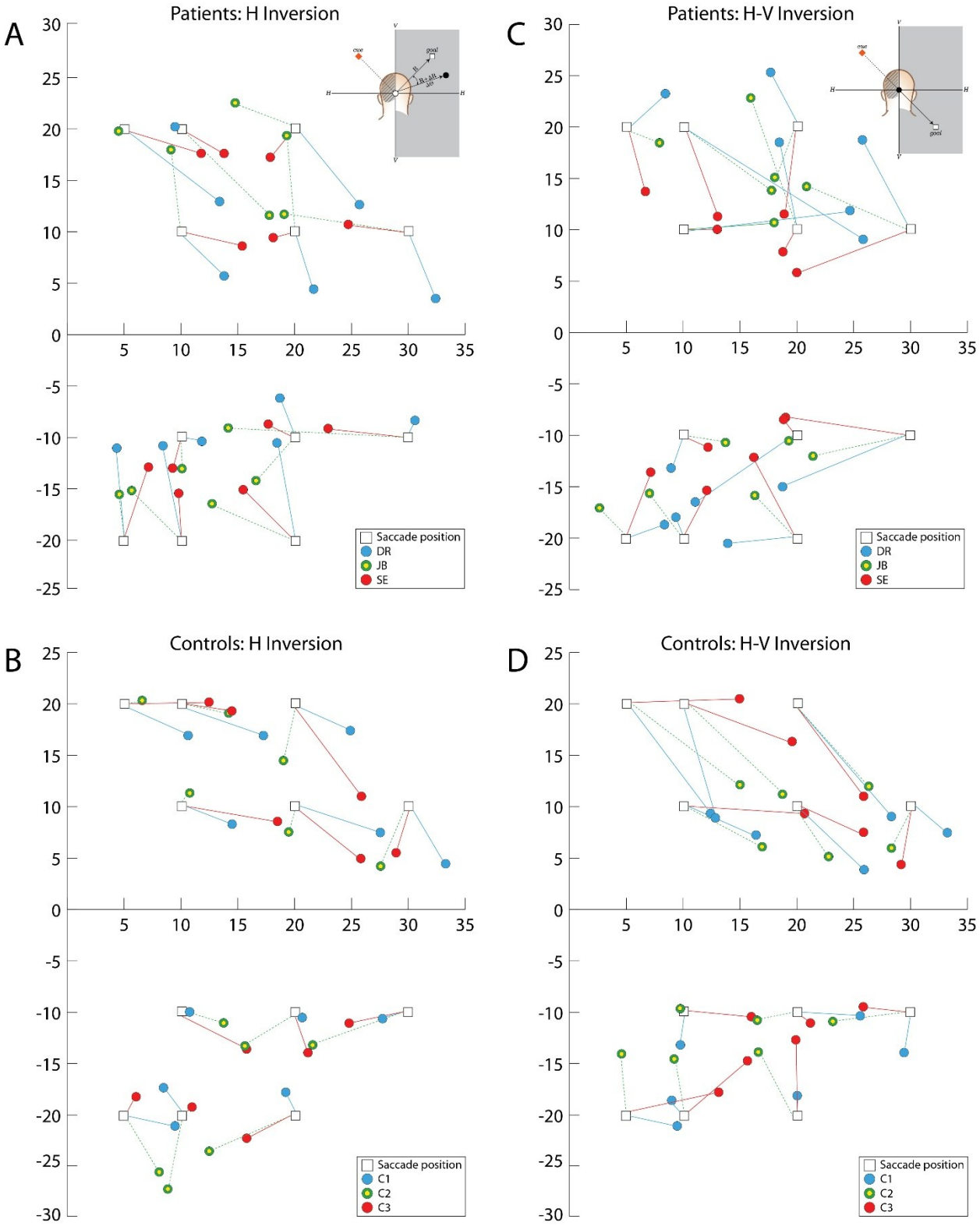
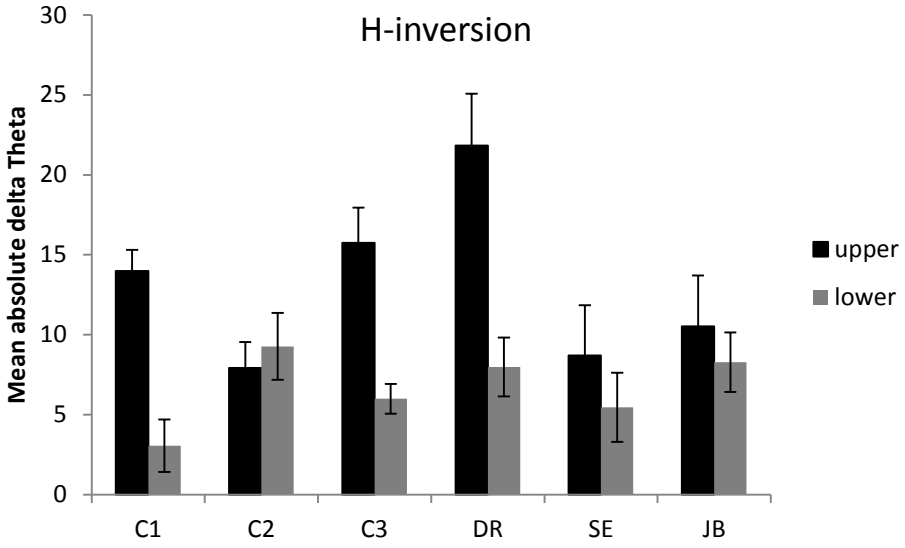

A
Patients: H Inversion
Saccade position
DR
JB
SE
C
Patients: H-V Inversion
Saccade position
DR
JB
SE
B
Controls: H Inversion
Saccade position
C1
C2
C3
D
Controls: H-V Inversion
Saccade position
C1
C2
C3

Figure 4-1. Performance of patients and controls in the two types of oblique anti-saccade trials. **A,B**: H-inversion in which only an inversion of the horizontal component of the vector from fixation point to Cue was requested; and **C,D**: H-V inversion in which both the H and V components were inverted. Insets in **A** and **C** show a schematic coronal section of a brain, defining the removed left side, and the distinction between seeing and blind hemifields. In the insets (**A** and **C**), the cue is indicated by the filled diamond and the anti-saccade goal by an open square. The inset in (**A**) shows an actual anti-saccade landing location (black circle) and defines the measures $\Delta\Theta$ and ΔR (Methods). Each subject's performance is illustrated by a color-coded circle indicating the mean anti-saccade endpoint, linked to its respective goal location by a straight line coded according to goal location.

A



B

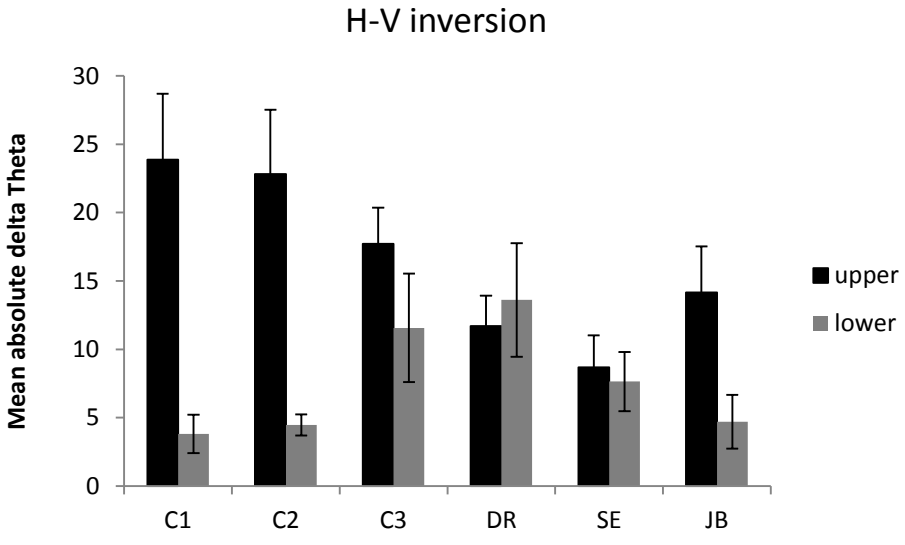
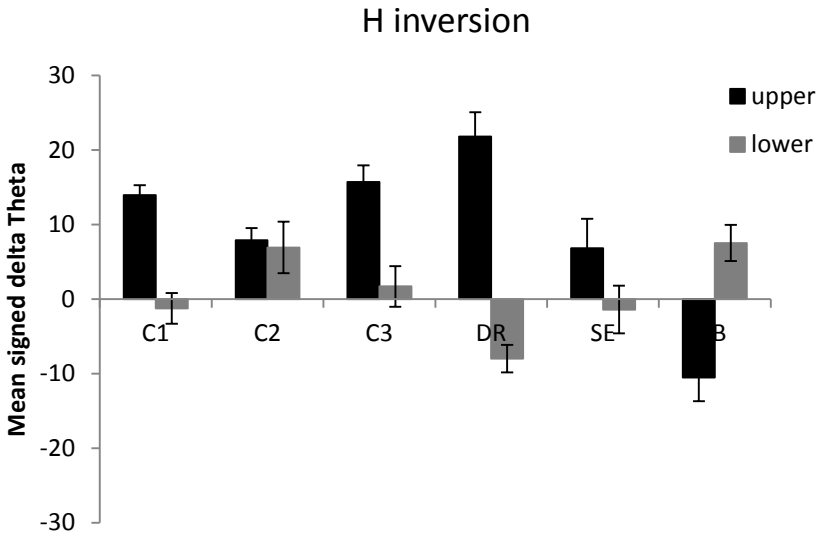


Figure 4-2. Mean absolute delta theta (Δθ). **A,B**: Mean absolute value of delta theta (Δθ) in the H and H-V inversion conditions, respectively. Error bars represent standard error of the mean.

A



B

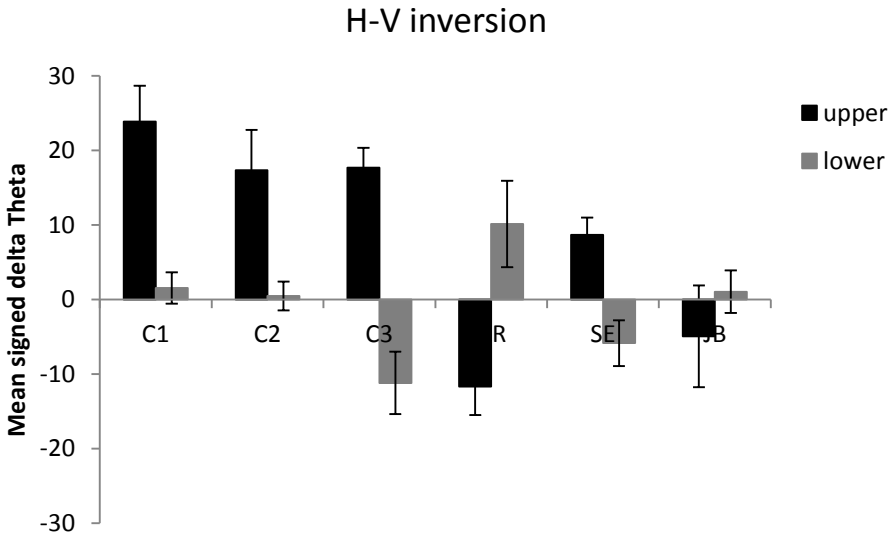
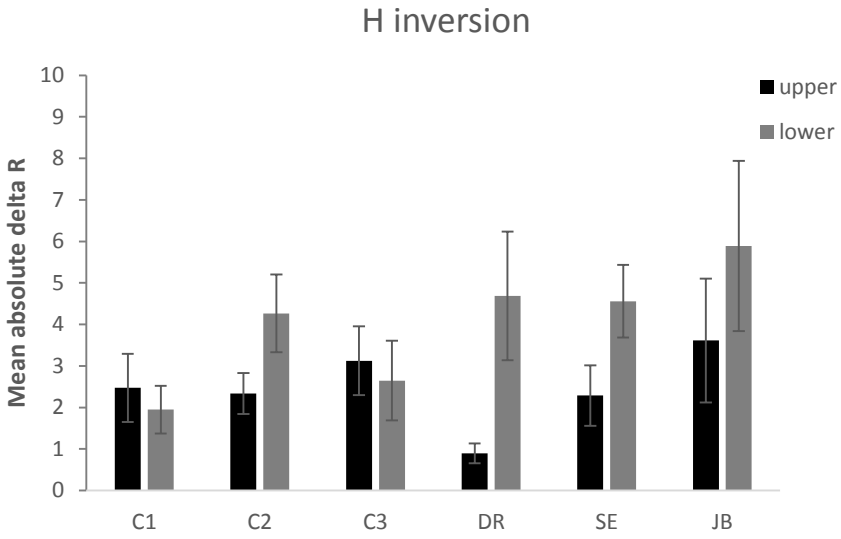


Figure 4-3. Mean signed delta theta (Δθ). **A,B**: Mean signed value of delta theta (Δθ) in the H and H-V inversion conditions, respectively. Error bars represent standard error of the mean.

A



B

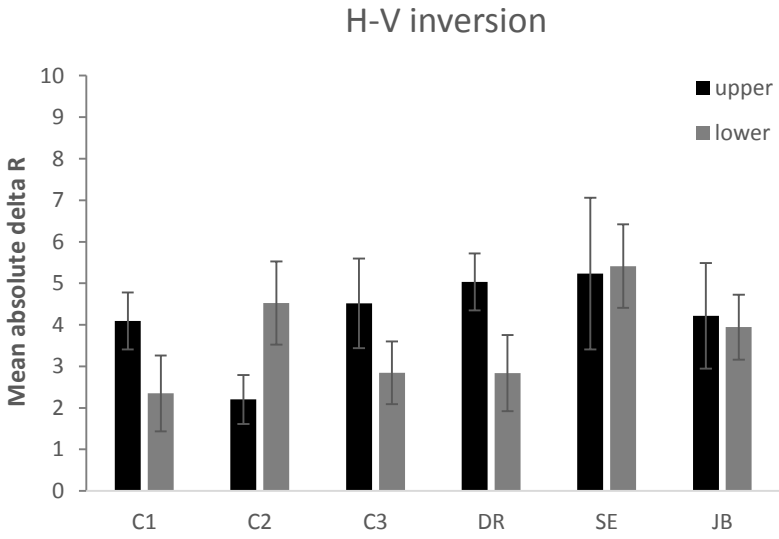
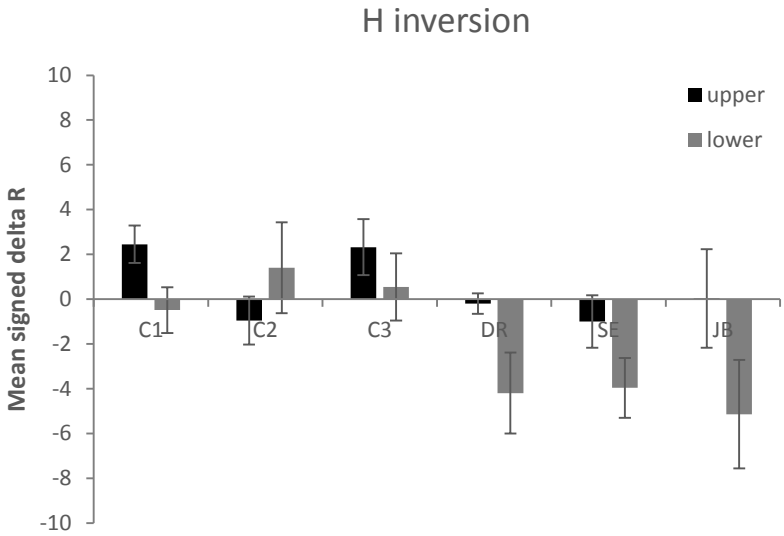


Figure 4-4. Mean absolute ΔR. **A,B**: Mean absolute ΔR in the H-inversion and H-V inversion conditions, respectively. Error bars represent standard error of the mean.

A



B

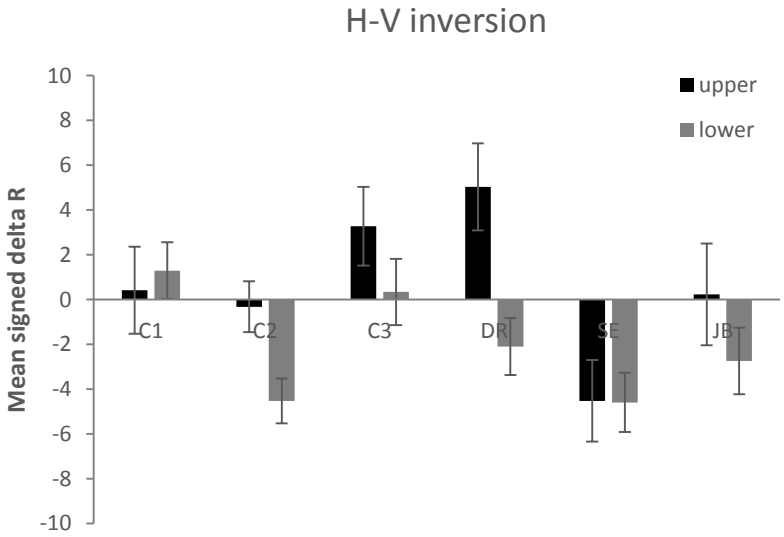
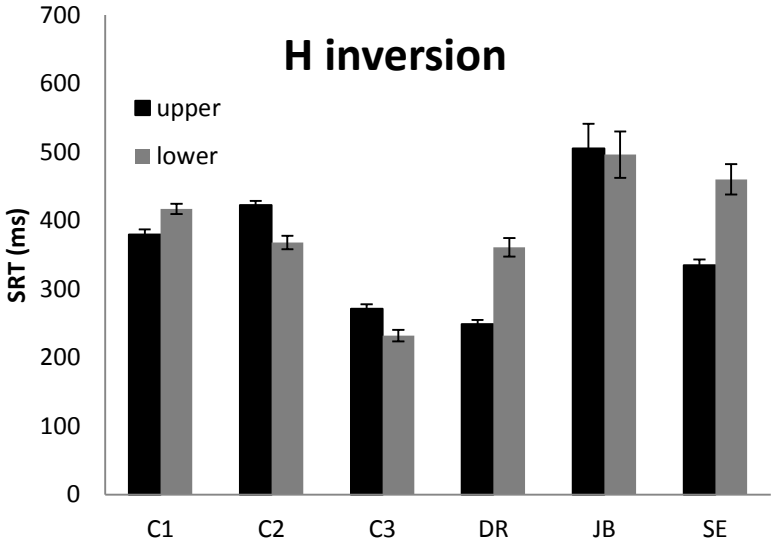


Figure 4-5. Mean signed ΔR. **A,B**: Mean signed ΔR in the H-inversion and H-V inversion conditions, respectively. Error bars represent standard error of the mean.

A


H inversion
upper
lower
SRT (ms)
700
600
500
400
300
200
100
0
C1
C2
C3
DR
JB
SE

B

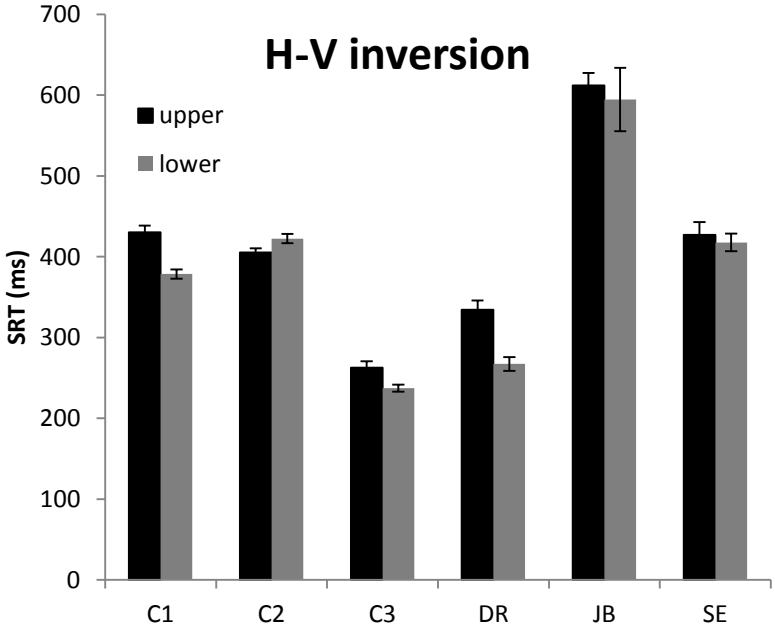

H-V inversion
upper
lower
SRT (ms)
700
600
500
400
300
200
100
0
C1
C2
C3
DR
JB
SE

Figure 4-6. Anti-saccade reaction time. Mean anti-saccade reaction time (SRT) in the (**A**) H- inversion, and (**B**) H-V inversion conditions, for each participant. Error bars represent standard error of the mean.

Chapter 5: General Conclusions and Summary

In this thesis I have presented the results of three experiments that, together, contribute to our understanding of the blindsight phenomenon (Chapter 2 and 3), as well as provide a comprehensive study of oculomotor control in hemispherectomized patients (Chapter 4). Remarkably, despite having such an extensive brain injury, these patients not only recovered residual visual abilities in the form of blindsight, but also showed no deficits in oblique anti-saccade generation, a complex oculomotor function that requires both hemispheres in neurologically intact individuals. By using different tasks, I made novel observations regarding the patients' capabilities in saccade control. These findings are applicable to our understanding of hemispherectomized patients, as well as to our understanding of basic neurophysiological mechanisms and capacity for neural repair. Therefore, the research presented here contributes knowledge on the extraordinary plasticity of the human brain. At the same time, these findings question the often accepted "linear" relationship between the area of damage in the brain and the associated functional deficits. The work presented here confirms what others (Kapur et al., 2013; Sabel et al., 2011) have argued as well, that deducing the function of a lesioned brain region on the basis of the related behavioral impairment, can be misleading.

Unconscious Visual Processing Within the Blind Hemifield

The first and a key finding of this study is that hemispherectomized patients retain residual vision in their blindfield that can affect saccade control. Specifically, we show that in patients missing an entire hemisphere, an unseen visual stimulus within their blind hemifield can subliminally influence the timing and accuracy of a saccade directed to that field. This blindsight phenomenon is surprising given that these patients cannot generate saccades to the same stimulus

presented alone in their blind hemifield. These findings suggest the existence of functionally relevant oculomotor signals on the lesioned side in the retino-tectal pathway in adult-hemispherectomized patients. We also show that these patients can generate accurate anti-saccades into their blind hemifield despite the absence of the neural circuitry normally required for the vector inversion process inherent to the generation of these eye movements. We believe that our findings have considerable implications on current and future research in this domain.

SC – Not Merely a Relay Station!

By using a task that maximally solicits a retino-tectal pathway, we provide evidence that superior colliculus is an important structure in blindsight and not merely a relay station, as some previous research suggests. Specifically, we show that an unseen visual probe presented briefly in the blind hemifield, just before and in different positions relative to an anti-saccade goal, influences the trajectory of the resulting anti-saccade. Critically, the probe effect on the amplitude of the resulting anti-saccade followed the pattern of interactions between visual and motor neural discharges on the SC's logarithmically encoded visuo-motor map; thus, indicating that "action" blindsight could involve an unexplored, purely subcortical, route from retina to superficial SCi to deep SCi to pontine circuits commanding saccades.

A Single Hemicortex Performs Visuomotor Functions On Par With a Full Brain

The final key finding of this study is the fascinating capability of a single hemicortex to do functions, such as anti-saccade generation no differently than a normal brain. Here, we have shown that there is no difference between the hemispherectomized patients and normal controls in their performance of the oblique anti-saccade task. This is both significant and surprising for two reasons: 1) the normal contralesional anti-saccade behavior that we describe in our patients,

contrasts with the effects of a discrete unilateral frontal cortical lesion (described by others and in Guitton et al. 1985; Machado & Rafal, 2004; reviewed in Rafal, 2006) which can produce severe anti-saccade impairments even long-term post-operatively; 2) production of even horizontal anti-saccades normally requires interactions between frontal, parietal and subcortical structures across both hemispheres. Hence, one can argue that oblique anti-saccades, having both horizontal and vertical components, should present even more of a challenge to a single hemicortex than horizontal anti-saccades, as it involves very complicated bilateral and interacting brain circuits involving cortical and subcortical structures.

Summary

In summary, these findings indicate that human brain is capable of major reorganization and plasticity even following such a substantial injury as hemidecortication. Here, we not only demonstrate a restoration post-hemispherectomy of some visual abilities in the form of blindsight, but also a normal performance on the oculomotor task that typically requires interactions of multiple structures of both hemispheres. The present work, complemented by our day to day interactions with hemidecorticate patients has vividly emphasized deficiencies in the traditional lesion-deficit model of neurology (Kapur et al., 2013), and instead highlights the extraordinary ability of the human brain to use compensatory and adaptive strategies to restore normal function.

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Appendix A: Study Approval Certificate

MONTREAL NEUROLOGICAL INSTITUTE AND HOSPITAL
McGill University

INSTITUT ET HÔPITAL NEUROLOGIQUES DE MONTRÉAL
Université McGill

May 14, 2009

Dr. Daniel Guitton
Complex Neural Systems
Montreal Neurological Institute & Hospital
Room 776

Re: **5.i.** **GUID 2001/1**
Oculomotor Control in Hemidecorticate Patients (CIHR #202670)
PI: Dr. Daniel Guitton
- Application for Continuing Review signed April 30, 2009
- Consent Form, English version June 6, 2007

Dear Dr. Guitton,

Thank you for submitting your **Application for Continuing Review** for the above-cited research protocol.

The above submission, reviewed by the full REB at the February 19, 2009 meeting, was found to be acceptable for continuation at the McGill University Health Centre (MUHC). This was entered accordingly into the minutes of the REB meeting.

The re-approval of the study is valid until September 13, 2009

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of Aat least once per year,@ it is the responsibility of the investigator to submit an Application for Continuing Review to the REB prior to expiry. However, should the research conclude for any reason prior to approval expiry, you are required to submit a Termination Report to the board once the data analysis is complete to give an account of the study findings and publication status.

The Research Ethics Boards (REBs) of the McGill University Health Centre are registered REBs working under the published guidelines of the Tri-Council Policy Statement, in compliance with the APlan d=action ministériel en éthique de la recherche et en intégrité scientifique@ (MSSS, 1998) and the Food and Drugs Act (2001.06.07), acting in conformity with standards set forth in the (US) Code of Federal Regulations governing human subjects research and functioning in a manner consistent with internationally accepted principles of good clinical practice.

Should any revision to the study or other development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval of the amendment.

We trust this will prove satisfactory to you. Thank you for your consideration in this matter.

Yours very truly,

Eugene Bereza, MD CM, CCFP
Chair, MNH/I Research Ethics Board
EB/ah

Meeting of February 19, 2009

3801 rue University
Montréal, Québec
Canada H3A 2B4

Téléphone : (514) 398-6644
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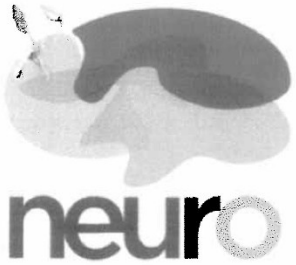

Research Ethics Board
Comité d'éthique de la recherche

June 28, 2012

Dr. Daniel Guitton
MNI/H, Room 786

RE: **Application for Continuing Review**
Oculomotor Control in Hemidecorticate Patients (CIHR #202670). (GUID 2001/1)
- E-mail dated June 14, 2012;
- Application for Continuing Review signed June 14, 2012;
- Consent Form, English and French (version June 14, 2012).

Dear Dr. Guitton,

At its full board meeting of June 26, 2012 held in room 636 of the Montreal Neurological Institute and Hospital ("MNI/H"), the Research Ethics Board of the MNI/H ("MNI/H REB") has endorsed the expedited review of the above-mentioned application.

We are pleased to inform you that as an exceptional measure and considering the justification submitted by the PI, this research was found to be acceptable for continuation at the McGill University Healthcare Centres ("MUHC").

The study is reapproved until Sepember 13, 2012.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the investigator to submit an Application for Continuing Review to the REB prior to expiry. Please be advised that should the protocol reach its expiry before a Continuing Review has been submitted, the data collected after the expiry date may not be considered valid. However, should the research conclude for any reason prior to approval expiry, you are required to submit a Termination Report to the board once the data analysis is complete to give an account of the study findings and publication status.

The Research Ethics Boards (REBs) of the McGill University Health Centre are registered REBs working under the published guidelines of the *Tri-Council Policy Statement*, in compliance with

the *Plan d'action ministériel en éthique de la recherche et en intégrité scientifique* (MSSS, 1998) and the *Food and Drugs Act* (2001.06.07), acting in conformity with standards set forth in the (US) *Code of Federal Regulations* governing human subjects research and functioning in a manner consistent with internationally accepted principles of good clinical practice.

Should any revision to the study or other development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval of the amendment.

We trust this will prove satisfactory to you. Thank you for your consideration in this matter.

Yours very truly,

Eugene Bereza, MD CM, CCFP
Chair, MNH/I Research Ethics Board
EB/bp

Site d'étude: Institut Neurologiques de Montréal
Titre de projet : Études des mécanismes visuo-oculomoteurs chez le patient hemispherectomisé

Juin 2012

INSTITUT & HÔPITAL NEUROLOGIQUE DE MONTRÉAL FORMULAIRE DE CONSENTEMENT D'ÊTRE SUJET DANS DES ÉTUDES SUR LES MOUVEMENTS DES YEUX ET DE LA TÊTE

1) **Titre du projet :**

Études des mécanismes visuo-oculomoteurs chez le patient hemispherectomisé.

2) **Raison de l'étude :**

Nous désirons comprendre comment l'hémisphère résiduel contrôle les mouvements oculaires dirigés vers des cibles visuelles présentées dans les hémi-champs aveugle et voyant respectivement.

3) **Méthodes** :

Dans le laboratoire, vous serez assis(e) sur une chaise et on vous couvrira un oeil. Une fois bien installé(e) dans la chaise, on vous demandera de serrer légèrement entre vos dent une tige en bois - elle-même fixe par rapport au labo - qui assure que votre tête sera immobile pendant le protocol expérimental. Pour débuter un essai expérimental dans la série « Anti-saccade » vous devrez fixer, avec l'œil voyant, un point lumineux (point de fixation) qui apparaîtra sur un écran placé devant vous. Ce point s'éteindra et un autre point lumineux apparaîtra en vision périphérique. Vous devrez, suivant l'instruction qu'on vous donnera, soit regarder le nouveau point soit regarder de l'autre côté du point de fixation. Dans une autre série d'essaies expérimentaux appelée « double-saccades » deux points lumineux apparaitrons successivement en vision périphérique et vous devrez les regardez successivement dans l'ordre de leurs apparition.

Les mouvements de vos yeux seront mesurés à l'aide d'électrodes apposées de chaque côté de votre tête, telle une mesure de l'EEG que vous avez subie auparavant dans vos visites cliniques. Il se peut aussi que nous mesurions vos mouvements oculaires avec une caméra vidéo spécialisée.

Une séance expérimentale durera approximativement une heure et nous en organiserons deux le matin et deux l'après-midi. Chaque expérience sera composée de plusieurs blocs d'essais. Entre chaque essai, vous pourrez détendre les muscles de votre bouche en cessant de mordre la tige de

bois. Entre chaque séance, vous pourrez prendre une pause de 15 minutes. Vous pourrez arrêter les tests expérimentaux à n'importe quel moment.

4) **Avantages de l'étude** :

Nous espérons que l'information obtenue au cours de la présente étude nous permettra de mieux comprendre le cerveau humain, tout particulièrement les systèmes oculo-moteur et visuel. Ceci pourra, on l'espère, à long terme, améliorer le diagnostic et le traitement de certains désordres neurologiques, spécialement ceux qui affectent la vision et le mouvement. Par contre, vous ne tirerez de cette étude aucun bénéfice ; elle n'aura non plus aucun impact négatif sur vous.

5) **Désavantages** :

Vous pourrez ressentir un certain degré d'inconfort et de fatigue causé par votre concentration sur la tâche ou votre position dans la chaise. Aussi léger que soit cet inconfort, rappelez-vous que vous pourrez, en tout temps, arrêter l'expérience.

6) **Effets sur vos traitements médicaux (si vous en recevez) de participer a cette étude :**

Les études comportementales auxquelles vous allez participer n'auront aucune répercussion sur les traitements ou tests diagnostiques que vous pourriez subir.

7) **Confidentialité de cette étude :**

Les résultats de notre étude demeureront confidentiels. Aucune information personnelle ne sera transmise à une tierce partie sans votre accord écrit. Votre nom ne sera pas dévoilé dans les publications des résultats de la présente étude. Nous allons cependant conserver votre nom dans nos dossiers, au cas où, à une date ultérieure, nous décidions de poursuivre notre étude. Les mesures de vos mouvements de la tête et des yeux seront gardes dans des fichiers dans les mémoires de nos ordinateurs. Ces fichiers ne porteront pas votre nom mais un code. Le lien entre ce code et votre nom sera sauf gardé dans un livre de bord dans le bureau du Dr Guitton et seulement lui et les étudiants en charge de cette étude y aurons accès.

Pour permettre une vérification de nos dossiers, le Conseil d'éthique de l'Institut neurologique de Montréal, ou le personnel mandaté par lui pour assurer la qualité de l'archivage, pourra avoir accès aux résultats de l'étude. Ces derniers seront conservés pendant 5-10 ans dans nos ordinateurs, sous forme digitale et sous un code que nous seuls connaissons.

Site d'étude: Institut Neurologiques de Montréal
Titre de projet : Études des mécanismes visuo-oculomoteurs chez le patient hemispherectomisé

DÉCLARATION DE CONSENTEMENT :

Je ..... ai lu le texte ci-dessus, en présence du ou des expérimentateur(s) suivant(s).....

.....

Je comprends les procédures, les avantages et les désavantages de l'étude. Ils m'ont été clairement expliqués et je choisis librement de participer à cette étude.

De plus, je comprends que je peux exiger plus de renseignements et d'explications sur les tests, avant ou après les avoir passés, que je peux me retirer de l'étude si j'en éprouve le besoin et que l'information sur ma personne sera gardée confidentielle.

SIGNATURE, SUJET.....DATE.....

SIGNATURE, CHERCHEUR .....DATE.....

Date de version: 14 juin 2012

Site d'étude: Institut Neurologiques de Montréal
Titre de projet : Études des mécanismes visuo-oculomoteurs chez le patient hemispherectomisé

DÉCLARATION DE CONSENTEMENT :

Je ..... ai lu le texte ci-dessus, en présence du ou des expérimentateur(s) suivant(s).....

.....

Je comprends les procédures, les avantages et les désavantages de l'étude. Ils m'ont été clairement expliqués et je choisis librement de participer à cette étude.

De plus, je comprends que je peux exiger plus de renseignements et d'explications sur les tests, avant ou après les avoir passés, que je peux me retirer de l'étude si j'en éprouve le besoin et que l'information sur ma personne sera gardée confidentielle.

SIGNATURE, SUJET.....DATE.....

SIGNATURE, CHERCHEUR .....DATE.....

Date de version: 14 juin 2012

Appendix B: Reprint of Previously Published Manuscript Presented in Chapter 2

CORTEX 49 (2013) 861–876

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Journal homepage: www.elsevier.com/locate/cortex

Research report

Blindsight after hemidecortication: Visual stimuli in blind hemifield influence anti-saccades directed there

*Olga Savina, Andre Bergeron and Daniel Guitton**

Montreal Neurological Institute, McGill University, Canada

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ABSTRACT

Patients missing a cortical hemisphere, removed surgically at adulthood, cannot consciously see a visual probe stimulus (P) flashed in their blind contralesional, hemifield. Nevertheless, they have a low-level form of blindsight wherein P can affect the reaction time of a manual response to the appearance of a visual target in their seeing hemifield. This ability is thought to require the pathway from retina-to-ipsilesional superior colliculus (SC) to cortex of the remaining hemisphere (Leh et al., 2006a, 2006b, 2009). Apart from emitting ascending signals, the SC normally sends saccade commands to the brainstem, a function seemingly conserved after hemidecortication because such patients can generate voluntary and accurate saccades bilaterally (Herter and Guitton, 2004). However, they cannot generate goal-directed saccades to P in their blind hemifield. We hypothesized that, in hemidecorticate patients, P might influence anti-saccades directed to the blind hemifield, to the mirror location of a visual cue presented in the seeing hemifield. We used anti-saccades because our patients could scale their anti-saccade amplitudes approximately according to different cue locations, thereby permitting us to control the end point of their anti-saccades to the blind hemifield. We identified in these patients a new form of blindsight wherein unseen P, if properly timed at the anti-saccade goal location in the blind hemifield, reduced the reaction time and improved the accuracy of anti-saccades directed to that general location. We hypothesize that P in the blind hemifield produced low-level signals in the ipsilesional SC that, if appropriately located and timed relative to anti-saccade goal and onset, interacted with anti-saccade motor preparatory activity – produced by descending commands to SC from the remaining hemisphere – so as to modify both anti-saccade reaction time and end point. Our results support normally encoded and functionally useful, but subliminal, signals in the retina-to-ipsilesional SC-to-reticular pathway of hemidecorticate patients.

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0010-9452/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
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1. Introduction

A fascinating example of the brain's "plastic" properties is the residual vision that survives ablation of the primary visual cortical area, V1. This phenomenon, called *blindsight*, has been much studied and, in Cowey (2010)'s extensive review, defined as "…the ability of patients with clinically blind field defects, caused by damage to the primary visual cortex V1, to detect, localize, and even discriminate visual stimuli that they deny seeing" (p. 3). Although the effects of V1 lesions have been the prime focus of research on blindsight, there also has been considerable interest in the effects of larger lesions, in particular and of relevance to the present study, the ablation of one entire hemisphere called a hemispherectomy or hemidecortication. Here we will use the latter term.

The present study focuses on visuo-oculomotor function in hemidecorticate patients, but before delving into our study we return to the effects of V1 lesions for which it is known that, after a recovery period of a few weeks, both monkeys and humans can generate accurate saccades to stimuli in their scotoma (Cowey and Stoerig, 1995; Isa and Yoshida, 2009; Ikeda et al., 2011; Kato et al., 2011; Moore et al., 1995; Pöppel et al., 1973; Sanders et al., 1974; Weiskrantz et al., 1974; Yoshida et al., 2008). Indeed, it is remarkable that a V1 lesioned monkey can, a few years after surgery, make a saccade in the dark to a previously flashed target (the memory-guided saccade task) in the affected visual field. The midbrain's superior colliculus (SC) is critical to this function. Indeed, on the long-term post-operative after a V1 excision, neurons in the ipsilesional SC show visually-triggered bursts, tonic memory activity and pre-saccadic motor bursts (Takaura et al., 2011). Furthermore, the level of the memory period tonic activity correlates with the accuracy of the monkeys' saccades to targets in the "blind" hemifield. Finally, deactivation of the ipsilesional SC abolishes saccades to stimuli in the "blind" hemifield (Kato et al., 2011). Given the difference between the activity patterns in the ipsilesional and contralesional SCs, Takaura et al. (2011) suggest that these new properties of the ipsilesional SC arise via a reorganization of its reciprocal links with extrastriate areas such as Lateral Intraparietal (LIP) and Frontal Eye Field (FEF) on the same side.

Here we study the effect of a visual stimulus in the blind hemifield of hemidecorticate patients and consider our observations in the context of the speculated role of the SC as described above. The advantage of studying the patients described herein is that they, when adults, underwent the complete, or near complete, surgical removal of one cortical hemisphere (Methods). By definition, after a complete hemidecortication, all cortical visual and motor areas on one side (in particular, in the context of the preceding paragraph, areas LIP and FEF) are either missing or have been disconnected. The hemidecortication also causes complete retrograde degeneration of the ipsilesional Lateral Geniculate Nucleus (LGN) in monkeys (Pasik et al., 1969), but nevertheless, there is anatomical preservation of the ipsilesional SC (Ptito et al., 1996; Théoret et al., 2001; Ueki, 1966). Thus, these patients are unique in that any residual processing of visual information in their blind hemifield excludes all cortical structures on one side and involves visual processing only via the ipsilesional SC (Leh et al., 2010).

Although humans and monkeys hemidecorticated as adults can generate voluntarily both leftward and rightward accurate saccades (Herter and Guitton, 2004), they do not recover saccade responses to targets presented in their blind hemifield (Estañol et al., 1980; Troost et al., 1972; Tusa et al., 1986). This is presumably because, after hemidecortication unlike only V1 ablations, the ipsilesional SC receives no visual signals capable of triggering saccades. However, subthreshold visual signals in the retino-tectal pathway seem to exist because a low-level form of blindsight in hemidecorticate patients has been demonstrated whereby an unseen visual stimulus in the blind hemifield affects the manual reaction time, indicated by a button-press, to the appearance of a visual stimulus in the seeing hemifield ("spatial summation effect") (Leh et al., 2006a, 2006b; Tomaiuolo et al., 1997). Using the diffusion tensor imaging (DTI) and Functional Magnetic Resonance Imaging (fMRI) techniques in hemidecorticate patients, this effect was suggested to be mediated by ascending crossed signals from the ipsilesional SC to the remaining hemisphere (normal monkey, Crapse and Sommer, 2009; patients, Leh et al., 2006a, 2006b, 2010) and then, to generate the button press, bilateral descending signals from the contralesional cortex to the spinal cord (e.g., Lacroix et al., 2004). Here, we show a blindsight effect on eye movements in these patients which may not require ascending signals from the ipsilesional SC.

In the normal monkey, crossed projections from the frontal eye field on one side to the contralateral SC have been reported (Distel and Fries, 1982; Leichnetz et al., 1981; Shook et al., 1990). Thus, in hemidecorticate patients, we would expect the FEF in the remaining hemisphere to project to the ipsilesional SC. Given that the well established main function of the SC is saccadic eye movement generation, we would expect that saccadic eye movements to the "blind" visual hemifield of hemidecorticate patients, involve the remaining (contralesional) FEF and the ipsilesional SC. As mentioned in the preceding paragraph, signals in the retino-tectal pathway are known to be critical for blindsight in the "spatial-summation-button-press" task. However, such visual signals, by themselves, seem subthreshold for triggering saccades since these patients cannot generate saccades to visual targets in their blind hemifield. Nevertheless, it is possible that retino-tectal visual signals can, subliminally, affect crossed descending motor commands to the ipsilesional SC, thereby affecting the generation of contralesional saccades. This is what we examine here.

We investigated whether an unseen visual probe stimulus in the blind hemifield of hemidecorticate patients can alter the timing and accuracy of an anti-saccade to this hemifield (see section 2.3, Rationale for tasks) even though the same probe in the blind hemifield fails to elicit an accurate pro-saccade response. We hypothesized that a visual probe in the blind hemifield can, via the retino-tectal tract, generate visually-triggered activity in the ipsilesional SC which, in the pro-saccade task, is insufficiently strong to raise above threshold the activity of collicular saccade-related neurons such that no visually-triggered pro-saccade to the blind hemifield can occur. By comparison, in the anti-saccade task, we predicted that the increased visual activity in the

ipsilesional SC, due to the presentation of the visual probe stimulus in the blind hemifield at the anti-saccade goal, can interact with and potentiate preparatory SC anti-saccade motor activity, thereby reducing anti-saccade latency and improving accuracy. This prediction was borne out.

2. Methods

2.1. Participants

Three hemidecorticate patients (DR, SE and JB) (Fig. 1) participated in this study, which was approved by the Montreal Neurological Institute and Hospital Research Ethics Committee. The participants gave informed and voluntary consent prior to commencement of experimentation.

The case histories of the patients are described elsewhere (Leh et al., 2006a, 2006b; Tomaiuolo et al., 1997) and will be briefly summarized. All three patients underwent a hemidecortication to relieve intractable epilepsy after the age of 17.

At age 17, as a young adult, DR underwent complete *right* hemidecortication including the amygdala and hippocampus. All remaining cortical tissue on the decorticate side was surgically disconnected from the rest of the brain. SE underwent a partial hemidecortication (temporo-parietal-occipital removal) including the amygdala and hippocampus of the *right* side at age 25. The entire right frontal lobe was spared. JB, who is left-handed, with the language lateralized to the right cortical hemisphere, underwent a two-step complete *left* hemidecortication at about the age of 20. Notably, his left frontal and partially occipital poles were left in place, but surgically disconnected from the rest of the brain.

Importantly, Leh et al. (2006a, 2006b) using the DTI technique for identifying axon tracts have reported differences between the subjects, specifically with respect to the involvement in blindsight of a novel ascending tract from the ipsilesional SC to the remaining hemisphere. We will consider, in the Discussion, the link between these findings and our results.

2.2. Apparatus

Visual stimuli, generated in MATLAB using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997), were back-projected at 85 Hz with an Electrohome Marquee 8000 projector (projection resolution, 1024 × 768 pixels) onto a screen located at a distance of 57 cm from the participant. We patched one eye of each subject to avoid the possibility that they would converge their eyes in order to reduce the blind region of their visual field. (We did not test for this putative compensatory convergence.) Since all collicular cells within the binocular overlap region of the visual field respond equally well to the two eyes it would not matter what eye is patched. Therefore, we asked each subject which eye they wanted patched. They all preferred the contralesional eye. As we will explain below, subjects SE and DR, with right hemisphere ablations, made leftward anti-saccades into their blind hemifield while JB, who had a left hemisphere ablation, made rightward anti-saccades. Thus, each subject made anti-saccades into their nasal visual hemifield whose implication in blindsight is controversial. Indeed, some studies in hemianopic patients

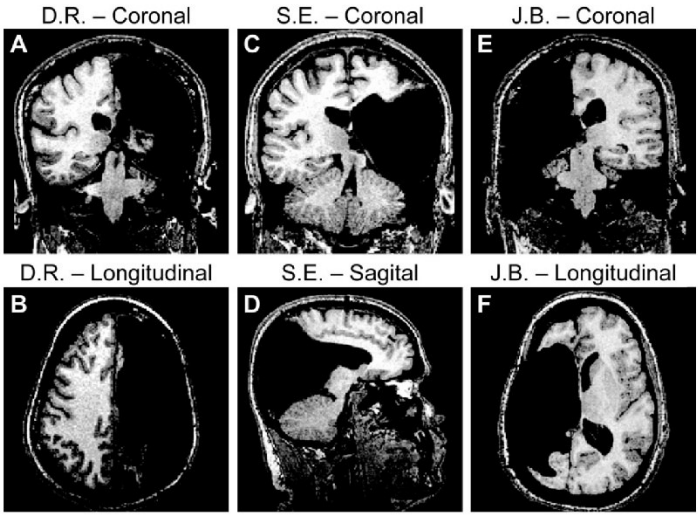

Fig. 1 – Magnetic Resonance Imaging (MRI) scans showing the cortical ablations of the three hemidecorticate patients we studied. (A, B) Coronal and longitudinal sections, respectively, showing the complete right hemidecortication of patient D.R. (C, D) Coronal and sagittal sections, respectively, showing the temporal-parietal-occipital lobectomy of patient S.E. (E, F) Coronal and longitudinal sections, respectively, of the complete functional left hemidecortication of patient J.B. The tissue remaining on the operated left side was disconnected from the rest of the brain. See text for case histories.

have suggested a naso-temporal asymmetry in the effect of a distractor in the blind hemifield on the latency of pro-saccades to the seeing hemifield – with a distractor in the nasal hemifield being much less effective (Dodds et al., 2002; Rafal et al., 1990). By comparison, Walker et al. (2000), also studying hemianopic patients, found no distractor effect in these patients no matter what hemifield was visually stimulated. These reports studied pro-saccades directed away from the blind hemifield. By comparison we show here that an unseen visual stimulus in the blind nasal hemifield does mediate a blindsight effect for anti-saccades directed to the blind hemifield.

Horizontal eye movements were monitored with bi-temporal electro-oculography (EOG). The EOG technique, whose calibration method is simple and calibration time short, was used to facilitate the mobility of the patients who requested frequent breaks. Prior to each recording session, the gain of the EOG signal was calibrated while the subject was fixating at various fixed target locations every 10° within ±30° range. During recording, small drifts were corrected by automatically resetting the EOG output to zero as the participants fixated at the start of each trial. When necessary, experiments were interrupted in order to recalibrate the gain of the EOG signal. The EOG output was exported as a real-time analog signal to an external Analog-to-Digital Converter device (NI6023E, National Instruments), through a simple first order low pass filer with a cut-off frequency of 300 Hz. The eye movement data collection was controlled using REX, a QNX-based real-time data acquisition system (Hayes et al., 1982). The eye position signal was sampled by the computer at a rate of 1 kHz. Offline in MatLab, the eye position signal was low pass filtered (zero-phase, cut-off at 30 Hz). Following proper calibration, the filtered EOG signal was linear within 1° over a range of ±30° for all participants.

2.3. *Rationale for tasks*

Our objective was to determine whether a visual probe in a subject's blind hemifield could affect both the timing and accuracy of a saccade directed towards that field. To do this it was important that our subjects could direct saccades to locations in the blind field that we could control experimentally. By controlling the saccade's goal – we could test whether a visual probe at different positions in the blind hemifield relative to that goal could change the saccade-end point. We could not obtain goal-directed saccades to the blind hemifield, using visual targets, given that the patients could not generate accurate saccades to visual stimuli they could not see (Fig. 5A). In lieu of visual targets, we considered using auditory targets in the blind hemifield, but hemidecorticate subjects generate very short latency (~100 msec) "express" saccades in this context (Reuter-Lorenz et al., 2011) which offers a very (too) short time window within which to test for a probe-effect. We therefore resorted to using the anti-saccade task because anti-saccade latency is longer than express saccade latency and anti-saccade goal is determined by the position of a visual cue in the seeing hemifield (Guitton et al., 1985). Our patients could generate anti-saccades that went approximately to the mirror location of the cue (Fig. 5B) and this performance enabled us to study the effect of a probe placed in the blind hemifield exactly at the mirror location of the cue. Because of the natural variability in the amplitude and direction of our patients' anti-saccades, the probe frequently appeared outside the saccade's end point. The long

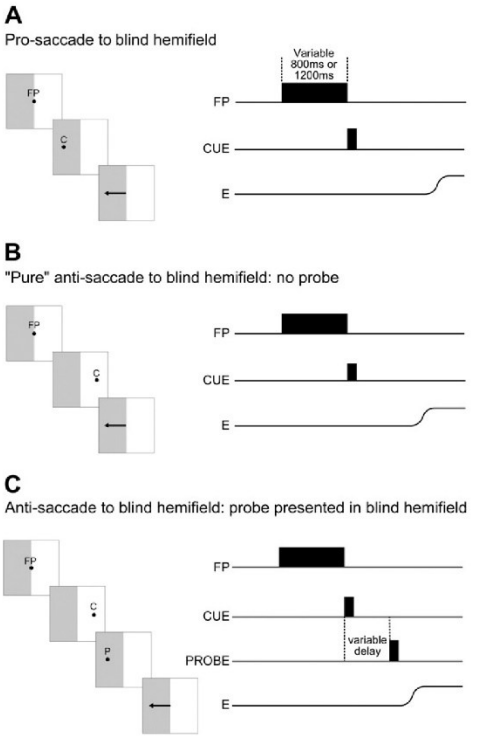

Fig. 2 – Schematic representation of the different experimental tasks. In all tasks the central FP was presented for a random duration of either 800 msec or 1200 msec. (A) *Pro-saccade to the blind hemifield*: immediately following FP's extinction, a cue (C) was presented in the blind hemifield for 86 msec. Subject was instructed to look to where the cue had appeared. (B) *"Pure" anti-saccade task*: immediately following FP's extinction, a cue was presented in the seeing visual hemifield for 86 msec and the subject was instructed to look to the mirror location. Note, that in this task, no stimulus was presented in the blind hemifield. (C) *Anti-saccade task with the probe presented in the blind hemifield*: immediately following FP's extinction, a cue was presented in the seeing visual hemifield for 86 msec. As in (B) above, subject had to look to the mirror location. A probe (P) was presented for 86 msec at the mirror location of the cue in the blind hemifield after variable delays of either 0 msec (i.e., cue and probe presented simultaneously), 100 msec, 150 msec or 200 msec from the onset of the cue. The shaded area represents the blind hemifield.

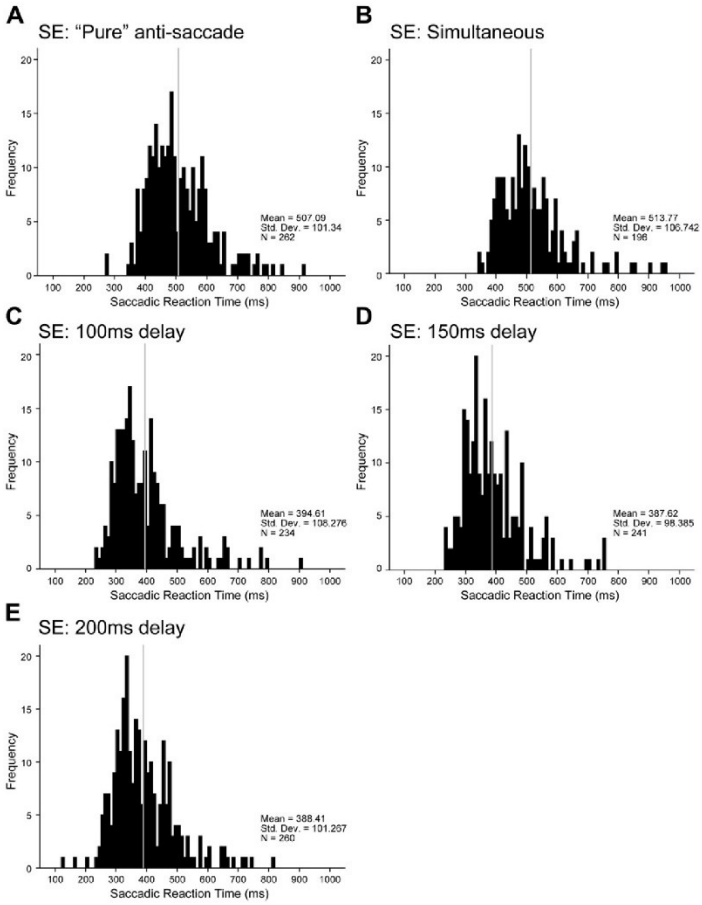

Fig. 3 – Frequency distribution of saccade reaction time in the five different anti-saccade conditions for patient SE. (A) "Pure" anti-saccade condition. (B) Simultaneous condition in which the delay between the cue and probe was 0 msec. (C) Condition in which the cue-probe delay was 100 msec. (D) 150 msec delay condition. (E) 200 msec delay condition. Vertical gray bar through each histogram indicates corresponding mean SRT.

anti-saccade latencies gave us a large time window within which to test for a probe-effect on accuracy and latency. We assumed that the putative neural activity, evoked by the probe on the collicular motor map, would interact with the anti-saccade motor preparatory activity and would both improve anti-saccade accuracy and reduce its latency.

2.4. *Stimuli and procedure*

The visual stimulus which could be the target (in the blind hemifield for the pro-saccade task), cue (in the seeing hemifield in the anti-saccade task) or probe (blind hemifield in anti-saccade task), consisted of a circular .5° light spot with a luminance level of .8 cd/m^2,flashed on a dark background. The spot was presented at fixed locations to the right or left of the fixation point (FP), itself in the middle of the screen and could appear at: ±5°, ±10°, ±20°, ±25°, ±30°. In all tasks, the saccades were made in complete darkness.

To address the issue of whether light scatter was responsible for responses to visual events in the blind hemifield we tested, prior to the main experiments, each participant's response to the .5° light stimulus presented in the natural blind spot of their *intact* visual field. This method has been proposed to be the ideal control for both forms of intraocular scatter (Cowey, 2004). None of the participants could detect this stimulus in their blind spot.

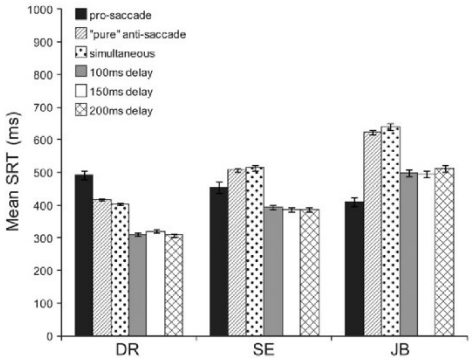

Fig. 4 – Comparison of mean saccade reaction times (SRT) in the five different anti-saccade conditions and the pro-saccade condition for each of subjects DR, SE and JB. For explanation of tasks see Fig. 2 and Methods section. Error bars represent standard error of the mean.

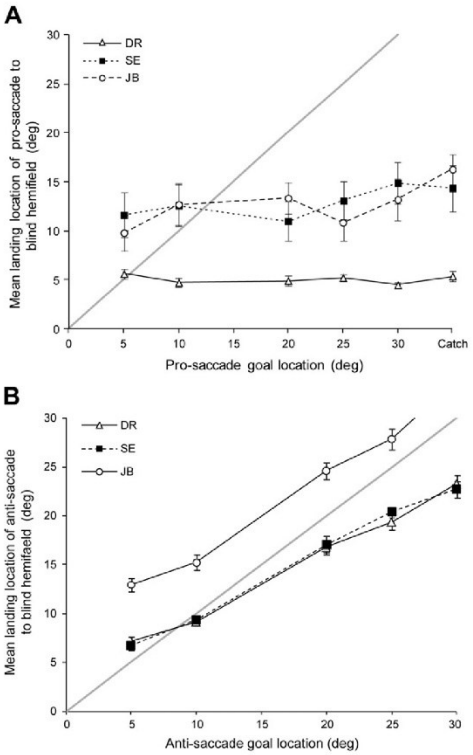

Fig. 5 – Mean saccade landing location at each goal location for each of subjects DR, SE and JB in the pro-saccade to the blind hemifield condition (A) and "pure" anti-saccade to the blind hemifield condition, in which no probe was presented (B). Diagonal line represents unity gain. Error bars represent standard error of the mean.

In all experiments, participants were seated in a completely dark room with the head restrained by a bite bar. Each trial began with the presentation of FP alone for a random duration of either 800 msec or 1200 msec. The experiment consisted of blocks of trials in the following conditions: (1) *pro-saccade to the blind visual hemifield* (Fig. 2A): immediately following FP's extinction, a target stimulus was presented in the *blind* visual hemifield (left for DR and SE; right for JB) for a brief duration of 86 msec. Since the target was presented in the blind hemifield, and therefore was not consciously detected, the disappearance of FP served as a signal for the initiation of the pro-saccade. The participants were instructed to guess the location of the target and to make a saccade towards the guessed location as quickly as possible. At the end of each trial, the room was illuminated for 1000 msec before the start of the next trial to prevent dark adaptation. No patient reported conscious awareness of the target; (2) *"pure" anti-saccade task* (Fig. 2B): immediately following FP's extinction, a cue was presented in the *seeing* visual hemifield for 86 msec. The appearance of the cue indicated that the subject had to initiate an anti-saccade towards the blind hemifield, to the mirror location of the cue. Participants were instructed to make an anti-saccade as promptly and accurately as possible. At the end of each trial, the room was illuminated for 1000 msec before the start of the next trial to prevent dark adaptation; (3) *anti-saccade task with the probe presented at the mirror location of the cue after different delays relative to cue onset* (Fig. 2C): this experiment was identical to the "pure" anti-saccade task with the additional presentation of the probe for 86 msec at the cue's mirror location in the blind visual hemifield. For reasons explained in the next paragraph, the probe was presented either simultaneously (to be called mirror-simultaneous) with the cue's presentation or after delays (mirror-delay) of 100 msec, 150 msec, or 200 msec from cue's onset.

Because of the limited number of sessions we had available with each patient, and their own limits on the number of trials/sessions they would accept, we could not perform exhaustive tests in order to test a broad range of delays. To determine a reasonable range of delays we hypothesized that the optimal probe delays should be such that probe-evoked activity should travel down the retino-tectal pathway and reach the ipsilesional SC in time to raise anti-saccade motor preparatory activity to a higher level such that it would reach sooner a threshold for saccade triggering. Thus, the probe should not be presented too close to anti-saccade onset because it would have little effect on SRT. Neither should it be presented so far ahead of an anti-saccade that it would not affect preparatory motor activity in the SC. The mean reaction times for "pure" anti-saccades for DR, SE and JB were 401 msec ± [Standard Deviation (SD) = 49], 507 msec ± (SD = 101), and 622 msec ± (SD = 138), respectively. To guess a range of probe

delays we needed to know: (1) the conduction time in the human retino-tectal pathway – from retina to superficial layers of the SC – and the time for activity to reach the intermediate layers of the SC; and (2) the duration of anti-saccade motor preparatory activity. We could find no information on the conduction time in humans and so we resorted to using data from monkey. In monkey the latency of visual responses in the superficial layers of the SC (that receive primarily retino-tectal inputs) is in the range 40–50 msec (Wurtz and Mohler, 1976). Given retinal delays, this is in line with the report that the majority of superficial layer SC cells respond to electrical stimulation of the optic chiasm at 6–10 msec (Marrocco and Li, 1977). In humans, saccades are suppressed at a minimum latency of ~60 msec by a visual stimulus flashed in the visual field contralateral to the saccade target (Reingold and Stampe, 2002).

Taken together this information (plus much other) led us to assume for humans a conduction time of ~60 msec in the retino-tectal pathway to the intermediate layers of the SC. We also assumed that the preparatory motor activity in the SC, driving the anti-saccade, precedes this saccade by ~150 msec (Everling et al., 1999). This suggests that for DR, say, who had an anti-saccade latency of ~400 msec ± 50 msec (relative to cue offset), a cue-probe delay of 200 msec should generate probe-induced signals in the SC that appear 140 msec before the mean anti-saccade. By comparison a cue-probe delay of 100 msec should precede by 140 msec anti-saccades that have a latency of 300 msec (i.e., those with 2 SDs shorter than the mean). In theory, this is in time to influence the preparatory activity of many anti-saccades. We therefore began by testing DR with cue-probe delays of 100 msec, 150 msec and 200 msec and found the effects described herein. We did not have enough experimental time to examine the effects of longer delays. We also found that the same delays could be used with SE and JB, with similar effects, thereby suggesting that preparatory activity preceded anti-saccades by much more than 150 msec.

We ran three anti-saccade conditions: (1) "pure" anti-saccade with no probe presentation; (2) "simultaneous", wherein cue and probe were presented simultaneously but in opposite hemifields; and (3) "delay" wherein probe onset was delayed relative to cue onset by 100, 150 and 200 msec. The pro-saccade condition and 3 anti-saccade conditions were run in 4 different blocks of 56 trials each. Thus, the three different delays were in the same block and were randomly interleaved within each block. Condition presentation was randomly interleaved between participants and within participants between days of testing. No performance feedback was given to the participants at any point during the experiment.

In anti-saccade trials, subjects never knew that a probe was presented in their blind hemifield, but they could have discovered this had they made premature anticipatory saccades towards their blind hemifield, before FP was turned off. We discouraged anticipatory glances by including in each block of anti-saccade trials approximately 12% of catch trials wherein the *cue and probe* were *not* presented and the subject had been instructed to keep fixating FP until the end of the trial. Anti-saccade catch trials were not analyzed because of a lack of saccades. We also included 12% of catch trials in the pro-saccade task wherein the target (cue, Fig. 1A) in the blind hemifield was not presented when FP was extinguished. Note that for pro-saccade trials the subjects could not tell the difference between regular and catch trials because they could not see the cue in the blind hemifield. Nevertheless, we included these catch trials to verify whether pro-saccade reaction times and endpoints were affected by the cue. We did analyze the catch trials of pro-saccades and found no effect of the target which we explain in Results, section 3.2.

2.5. *Data analysis*

During each trial, the following experimental quantities were stored online for further offline analysis: target, cue and probe positions, cue-probe delay and EOG eye position signal.

In any one trial, the patients varied in the amount of saccades they produced to the blind hemifield: for both the pro- and anti-saccade trials, JB made mostly single saccades in each condition, SE made mostly 2 saccades, and DR made multiple saccades. Most often, saccades after the first appeared as searching movements because they were not goal directed. The data reported here were based on the patients' initial saccades only, an approach we think is valid given the clear goal-directed nature of the first saccade (to be considered later in relation to Fig. 5).

Data were analyzed from all trials except: (1) erroneous pro-saccades in anti-saccade trials (i.e., saccades that were made in the direction towards the cue rather than in the opposite direction); (2) anti-saccades with latencies <120 msec (since these saccades would most probably be anticipatory in nature); (3) pro- and anti-saccades with latencies >1000 msec; (4) EOG signals that contained significant noise and blink artefacts (determined by visual analysis).

Offline we differentiated the eye position trace to give eye velocity. The onset and end of each saccade was identified as the points where velocity increased above and decreased below 40°/sec, respectively. Saccade reaction time (SRT) was calculated as the time difference between the target (or cue) onset and saccade initiation. We considered as outliers the saccades that fell outside ±2SD from the mean anti-saccade *landing* location and these saccades were removed from all further analyses. We used the remaining population of data points to calculate mean SRT, mean anti-saccade landing location, mean absolute normalized error, and variability of anti-saccade landing location around the mean.

To quantify each participant's lack of ability to make target-related saccades to the blind hemifield, Pearson correlation analyses were performed on pro-saccade-end points compared to the target's locations, as well as on anti-saccade-end points compared to the anti-saccade goal locations.

In the anti-saccade tasks, analyses of mean SRT and mean saccade landing location were performed by using independent design Analysis of Variances (ANOVAs). In addition, we performed the analysis of variability of anti-saccade landing locations around the respective mean landing locations for each cue condition (5°, 10°, 20°, 25°, 30°) in the "pure" and combined mirror-delay (i.e., we combined the trials from all three delays: 100 msec, 150 msec and 200 msec) anti-saccade conditions using two factor independent design ANOVA. This statistical approach was used because of unequal Ns. Because there was a discrepancy in the sample size between

various conditions, there was a high probability that homogeneity assumption would be violated. Therefore, in order to control for the risk of type I error experiment-wise post-hoc analyses were performed using the Games–Howell test and the alpha level was set to a stringent level of .01 for all statistical tests (Fidell and Tabachnick, 2003).

To quantify overall performance of each subject in different anti-saccade conditions, we calculated mean absolute normalized error across all saccade-goal locations in "pure" anti-saccade and combined mirror-delay conditions. The absolute normalized error was calculated by using the following formula:

$$\left|\frac{\text{saccade goal location} - \text{saccade landing location}}{\text{saccade goal location}}\right|$$

In order to assess the overall effect of probe presentation on the accuracy of saccade landing location, we performed two-tailed unpaired *t* test analysis comparing absolute normalized error in the "pure" anti-saccade and combined mirror-delay conditions across all target locations.

We performed a one-way independent design ANOVA in order to compare mean SRT from the pro-saccade to the blind field condition to mean SRT from catch pro-saccade trials. Also, a one-way independent design ANOVA was performed to analyze the difference between SRTs from different target positions in the pro-saccade to the blind field condition.

The data were analyzed using SPSS 15.0 statistical software.

3. Results

3.1. *Anti-saccade reaction times*

We first determined whether presenting the probe in the blind hemifield affected the anti-saccade reaction time. Visual inspection of the histograms in Fig. 3, for typical subject SE, shows that there was no difference between the mean anti-saccade reaction times in the "pure" and mirror-simultaneous (zero-delay) anti-saccade conditions (Fig. 3A and B) but, compared to these conditions, the probe in the blind hemifield reduced the anti-saccade latency for *all* delays we tested (Fig. 3C–E). All patients produced the same result (Fig. 4); notably there was a significant and surprisingly equal decrease in latency, relative to the reference conditions, for all three delays in the range 100–200 msec. A one factor (5 experimental conditions: "pure" anti-saccade, mirror-simultaneous, mirror-100 msec delay, mirror-150 msec delay, mirror-200 msec delay) independent design ANOVA conducted on the saccade reaction time (SRT) data yielded a significant main effect of condition type on SRT, $F(4,1561) = 172.316$, $p < .0001$; $F(4, 1188) = 95.676$, $p < .0001$ and $F(4, 1080) = 61.459$, $p < .0001$ for DR, SE and JB, respectively.

In the case of DR and SE, Levene's tests for homogeneity of variance was reasonably satisfied ($p = .283$ and $p = .934$). Therefore, we performed post-hoc tests using Tukey's honest significance test. The results showed that the mean SRT observed in the "pure" anti-saccade condition was not significantly different from that observed in the mirror-simultaneous condition ($p = .049$ and $p = .959$, for DR and SE respectively). There was no significant difference in the mean SRT between any of the delay conditions (100 msec *vs* 150 msec: $p = .468$ and .944, 100 msec *vs* 200 msec: $p = .996$ and .963, and 150 msec *vs* 200 msec: $p = .242$ and .999, for DR and SE respectively). Moreover, in both patients the mean SRT observed in all three "mirror-delay" conditions were significantly different from both the mean SRT observed in the "pure" anti-saccade and mirror-simultaneous conditions (all $p_s < .001$).

In the case of JB, Levene's tests for homogeneity of variance indicated that the homogeneity assumption has been violated ($p < .01$). Therefore, we performed post-hoc tests using Games–Howell test, which controls the risk of type I error experiment-wise. The results of the multiple comparisons tests computed on the main effect of condition type showed that the mean SRT observed in the "pure" anti-saccade condition was not significantly different from that observed in the mirror-simultaneous condition ($p = .529$). There was no significant difference in the mean SRT between any of the delay conditions (100 msec *vs* 150 msec: $p = .999$, 100 msec *vs* 200 msec: $p = .898$, and 150 msec *vs* 200 msec: $p = .732$). Moreover, the mean SRT observed in all three "mirror-delay" conditions were significantly different from both the mean SRT observed in the "pure" anti-saccade and mirror-simultaneous conditions (all $p_s < .001$).

3.2. *Pro-saccade reaction times*

In pro-saccade trials the subjects knew the target would always be in their blind hemifield and so they used the offset of the FP as the cue to make a saccade to the unseen target. Therefore, we should not expect the SRT of their pro-saccades to be comparable to those of visually-triggered pro-saccades. Indeed, pro-saccade mean SRTs were above 400 msec in all subjects: DR, 493 msec (SD = ±188); SE, 454 msec (SD = ±178); JB, 412 msec (SD = ±126) (Fig. 4). In normal subjects, pro-saccade SRT < anti-saccade SRT (e.g., Guitton et al., 1985). This was true for our subjects JB and SE. However, in DR, pro-saccade SRT > anti-saccade SRT which we attribute to DR's perfectionist personality who always tried very hard to see the target in the blind hemifield but, frustratingly, to no avail.

By comparison to the regular trials, the pro-saccade SRTs in *catch trials* for DR, SE and JB were: 510 msec (SD = ±191), 442 msec (SD = ±155) and 423 msec (SD = ±181), respectively. One-way independent design ANOVA showed no significant difference between SRTs of catch trials and real pro-saccade trials to the blind hemifield ($p = .527$, $p = .789$ and $p = .732$, respectively). This observation indicates that the presence of the target in the blind hemifield had no effect on SRT in pro-saccade trials. We speculate that this was because our subjects generated pro-saccades to "default" positions, such that the pro-saccade mean amplitude was about constant and neither related to the target's position, nor indeed to whether or not the target was present, as shown by the catch trials (Fig. 5A). This behavior was unlike that in the anti-saccade task (Fig. 5B). Therefore, any target-related visual activity in the SC (e.g., via the retino-tectal tract) did not coincide spatially with pro-saccade motor preparatory activity on the SC map. However, in subjects SE and JB there could have been

spatial coincidence on the SC map between motor activity and target position for pro-saccades targets at 10°, given that these subjects consistently made about 12° pro-saccades, independent of target position (Fig. 5A). Thus, for a target at 10° in the pro-saccade task one might expect an interactive effect of the saccade target on SRT, for these subjects. However, in our analysis of JB's and SE's data, we found no statistically significant difference between SRTs for different target positions in the *pro-saccade to the blind field* condition ($p = .336$ and .222, for SE and JB respectively). Nevertheless, there was a non-significant trend for: JB who had the smallest SRTs for pro-saccade targets at 10° and 20°; and for subject SE who had the largest SRTs when the pro-saccade target was at 25° and 30°. We speculate that the lack of significance in these observations was due to three factors: (1) the large variability in pro-saccade landing locations (Fig. 5A), combined with, (2) the relatively small number of trials per pro-saccade target location, on average less than 20.

3.3. *Comparison of pro-saccade and anti-saccade accuracy in the blind hemifield*

Fig. 5A shows the mean saccade landing location made by patients DR, SE and JB at each probe location in the *pro-saccade* task. It is obvious that pro-saccades to the blind hemifield were not target related. Indeed, the pro-saccades in catch and probe trials had the same landing location. DR made most of her saccades to locations about 5° in the blind hemifield (her 'default' location), which for target offsets >10° resulted in errors that were proportional to the distance between the target's location and the default location. Similarly, SE and JB made saccades mostly to about 12° locations in the blind hemifield. Therefore, for greater target offsets, their errors were also approximately equal to the distance between the probe's location and the preferred location. This graph indicates that none of the participants could reliably generate an accurate saccade to a target presented in their blind hemifield. This essentially self-evident result based on visual inspection of Fig. 5A, was confirmed formally by a Pearson correlation analysis that showed no significant correlation [$r(232) = -.077$, $p = .242$, $r(113) = .056$, $p = .552$ and $r(159) = .045$, $p = .57$, for DR, SE and JB, respectively] between the goal location and the saccade-end location in the pro-saccade task to the blind hemifield.

"Pure" anti-saccades towards the blind hemifield were much more accurate than pro-saccades (Fig. 5B). Inspection of Fig. 5B reveals that subjects DR and SE tended to overshoot the 5° goal location and undershoot 20°, 25° and 30° goal locations. JB, on the other hand, overshot all saccade-goal locations. Pearson correlation analysis revealed positive significant correlation between the saccade-goal location and the saccade-end location for all three patients [$r(491) = .646$, $p < .0001$, $r(248) = .811$, $p < .0001$ and $r(392) = .705$, $p < .0001$, for DR, SE and JB, respectively].

3.4. *Accuracy of anti-saccades to the blind hemifield: effect of the probe presented at the mirror location of the cue*

The analysis of two factor [delay type (100 msec, 150 msec, 200 msec) and saccade-goal locations (5°, 10°, 20°, 25°, 30°)] independent design ANOVA on mean saccade landing location revealed no significant interaction between the delay type and the saccade-goal locations for any of the three participants, $F(8,409) = .784$, $p = .617$, $F(8,720) = .317$, $p = .960$ and $F(8,431) = .678$, $p = .711$ for DR, SE and JB, respectively. Therefore, we combined the data from all three delays and compared the mean anti-saccade landing locations across the different goal locations in the combined mirror-delay conditions versus the "pure" anti-saccade condition.

Fig. 6 plots mean anti-saccade landing locations in the "pure" anti-saccade and combined mirror-delay conditions. The analysis of two factor independent design ANOVA [condition type (combined mirror-delay *vs* "pure" anti-saccade) and saccade-goal locations (5°, 10°, 20°, 25°, 30°)] revealed a significant interaction for patients DR and JB, $F(4,937) = 6.348$, $p < .0001$ and $F(4,853) = 7.577$, $p < .0001$, respectively. Subsequent simple main effect analysis of condition type over the five anti-saccade-goal locations revealed, for DR, statistically significant differences between combined mirror-delay and "pure" anti-saccade conditions for 5° ($p = .006$), 25° ($p = .003$), and 30° ($p < .0001$) cue locations, but not for 10° ($p = .09$) and 20° ($p = .164$) cue locations; for JB, simple main effect analysis of condition type over five anti-saccade-goal locations revealed statistically significant differences between combined mirror-delay and "pure" anti-saccade conditions for all saccade-goal locations ($p_s < .0001$). However, as can be seen from Fig. 6(A and C), while for subject DR probe presentation had a tendency to bring the mean saccade-end points closer to anti-saccade goal location (although not statistically significant for goal locations 10° and 20°), for subject JB, the probe had a tendency to reduce the overshoots of saccade-goal location produced in his "pure" anti-saccade condition. There nevertheless remained a small overshoot for 5° and 10° goals. However, for anti-saccade-goal locations of 25° and 30°, presentation of the probe resulted in an undershoot of saccade-goal location which was more significant than the original overshoot when no probe was presented (see Fig. 6C).

For SE, a two factor [condition type (combined mirror-delay *vs* "pure" anti-saccade) and saccade-goal locations (5°, 10°, 20°, 25°, 30°)] independent design ANOVA on the mean anti-saccade landing location revealed no significant interaction [$F(4,978) = .40$, $p = .807$] and no main effect of condition type [$F(1,978) = .795$, $p = .373$]. These results indicate that while for subjects DR (Fig. 6A) and JB (Fig. 6C) presentation of a probe at the mirror location of the cue had a significant effect on the mean anti-saccade landing location, for subject SE (Fig. 6B), it did not.

In order to assess the overall effects of probe presentation across all saccade-goal locations, separate two-tailed unpaired *t* tests were conducted for subjects DR, JB, and SE to determine whether there was a difference in the mean absolute normalized error of saccade landing locations between the "pure" anti-saccade and combined mirror-delay conditions (Fig. 6D). The data analyses revealed that the mean absolute normalized error ($\bar{E}$) of saccade landing locations in the "pure" anti-saccade condition (DR: $\bar{E} = .37$, SD = .32 and JB: $\bar{E} = .59$, SD = .71) was significantly different from that in the combined mirror-delay condition (DR: $\bar{E} = .25$, SD = .2 and JB: $\bar{E} = .37$, SD = .35), $t(861) = 6.35$, $p < .0001$ and

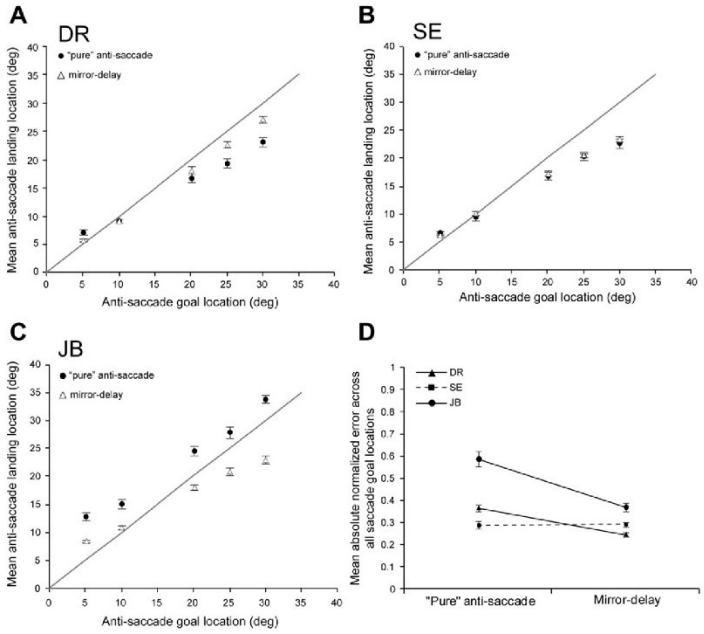

Fig. 6 – Comparison of mean anti-saccade landing location at each goal location in the "pure" anti-saccade and mirror-delay conditions. In the latter, the results for all delays have been pooled. (A) Subject DR, (B) SE, and (C) JB. Diagonal line in each panel represents unity gain. (D) Comparison of mean absolute normalized error between anti-saccade-endpoint and anti-saccade goal location pooled across all goal locations in the "pure" anti-saccade (left column) and mirror-delay (right column) conditions for subjects DR, SE, and JB. Error bars represent standard error of the mean.

$t(777) = 5.27$, $p < .0001$, for subjects DR and JB, respectively. However, for subject SE, a two-tailed unpaired t-test revealed that the mean absolute normalized error of saccade landing locations in the "pure" anti-saccade condition ($\bar{E} = .29$, SD = .27) was not significantly different from that in the combined mirror-delay condition ($\bar{E} = .29$, SD = .26), $t(986) = -.13$, $p = .90$.

We also found that presentation of the probe at the mirror location of the cue tended to reduce the variability of individual saccades around the respective mean anti-saccade landing location compared to when no probe was presented in the "pure" anti-saccade condition. We represented this variability by a mean absolute error, calculated by taking an average of absolute distance of each individual anti-saccade from the mean anti-saccade landing location in each saccade-goal location condition (Fig. 7). For subjects DR and JB, the analysis of two factor independent design ANOVA [condition type (combined mirror-delay *vs* "pure" anti-saccade) and saccade-goal locations (5°, 10°, 20°, 25°, 30°)] revealed a significant main effect of condition type [$F(1,937) = 32.96$, $p < .0001$ and $F(1,853) = 67.72$, $p < .0001$, for DR and JB, respectively], indicating that on average the variability of anti-saccade landing locations around the respective mean saccade landing location decreased with probe presentation in the mirror-delay condition compared to "pure" anti-saccade condition (Fig. 7A and C). For SE (Fig. 7B), the analysis of two factor independent design ANOVA [condition type (combined mirror-delay *vs* "pure" anti-saccade) and saccade-goal locations (5°, 10°, 20°, 25°, 30°)] revealed a significant interaction [$F(4,978) = 4.43$, $p = .001$]. The analysis of simple main effect for condition type over the five saccade-goal locations, revealed no significant difference in variability at 5° ($p = .750$), 20° ($p = .099$) and 30° ($p = .224$) cue conditions, and a significant increase in variability of saccade landing locations around the respective mean saccade landing location at 10° ($p = .003$) and 25° ($p = .022$) cue conditions.

In summary, for subjects DR and JB, presentation of a probe at the anti-saccade goal location (i.e., in the mirror location of a cue) reduced SRT, decreased the variability of anti-saccades, and improved overall accuracy of anti-saccade landing locations. For subject SE, presentation of a probe also reduced SRT, but did not have any effect on mean anti-saccade landing locations, and did not reduce variably of anti-saccade-end points for any of the goal locations.

4. Discussion

We have revealed two critical and intriguing functions of the single remaining hemisphere of hemidecorticate patients: (1)

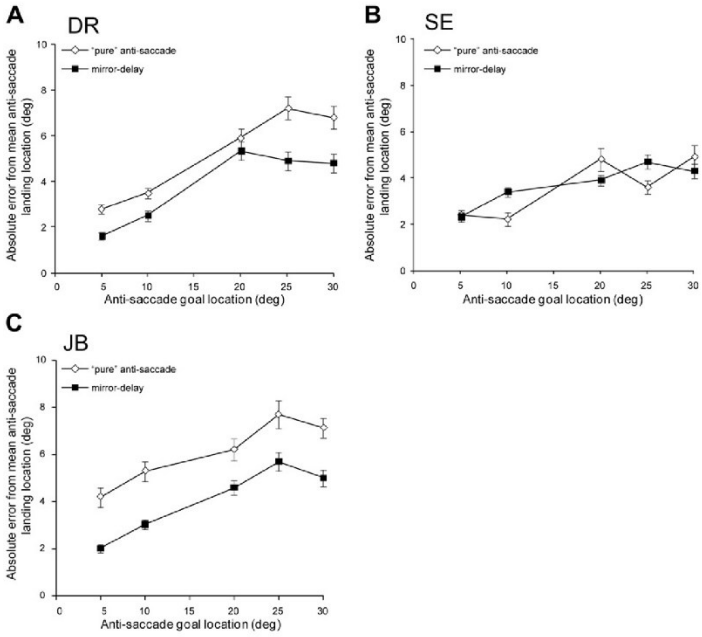

Fig. 7 – Absolute error from the mean anti-saccade landing location in the "pure" anti-saccade and mirror-delay conditions. In the latter, the results for all delays have been pooled. Results for subjects DR (A), SE (B) and JB (C). Error bars represent standard error of the mean.

the ability to generate goal-directed anti-saccades, made in the dark and cued by a briefly presented visual cue in the seeing hemifield; and (2) a blindsight phenomenon wherein an unseen flashing visual probe in the blind hemifield affected the timing and precision of anti-saccades to that field.

4.1. *Anti-saccade generation*

The anti-saccade task requires the suppression of a reflexive saccade towards a sensory cue, and the generation of a voluntary saccade to the mirror location of that cue, in the absence of any sensory stimulus presented at the anti-saccade goal. Therefore, a vector inversion has to be performed in order to transform the sensory information in one hemifield into a motor response to the other. We showed in Reuter-Lorenz et al. (2011) that our hemidecorticate patients could make anti-saccades away from an *auditory* cue with a latency of about 100 msec less than that shown here in our "pure anti-saccade" condition using a *visual* cue. However, this important difference may not relate wholly to a difference between the processing of auditory versus visual information by the remaining hemisphere. Indeed, in the Reuter-Lorenz study we did *not* require the patients to make anti-saccades that were accurately directed to the mirror location of the auditory cue, whereas in the present study accuracy was a requirement, as shown in Fig. 5B.

In the normal brain, both hemispheres participate in the vector inversion process inherent to anti-saccade generation (Everling and Munoz, 2000; Munoz and Everling, 2004; Zhang and Barash, 2000, 2004); notably, areas LIP (Zhang and Barash, 2004) and FEF (Moon et al., 2007) bilaterally. Despite these observations, a single hemicortex is able to perform the direction inversion (auditory domain; Reuter-Lorenz et al., 2011) and vector inversion (visual domain; present results) necessary for generating anti-saccades ipsilateral to itself.

Herter and Guitton (2004) have shown that the single hemicortex in hemidecorticate patients can control, with remarkable accuracy, saccades in both directions, notably ipsiversive ones. This bilateral accuracy suggests that the patients' intact hemicortex has fully functional bilateral connections with brainstem oculomotor structures, notably the SC. Indeed, innate bilateral connections from frontal oculomotor regions have been observed to the: SC (Distel and Fries, 1982; Leichnetz et al., 1981; Shook et al., 1990), nucleus reticularis tegmenti pontis (Huerta et al., 1986; Leichnetz et al., 1984; Stanton et al., 1988) and the paramedian pontine reticular formation (Huerta et al., 1986; Leichnetz et al., 1984; Shook et al., 1990; Stanton et al., 1988). Furthermore, an increased number of crossed connections from cortex to the SC have been observed following experimental hemidecortication in cats (Adelson et al., 1995). Such connectivity may explain why the SC remains anatomically intact on the

decorticate side following experimental hemidecortication in monkeys (Théoret et al., 2001). Involvement of the ipsilesional SC in contralesional saccade generation is supported further by another observation showing that our hemidecorticate patients can generate short latency "express saccades" to auditory targets ipsilateral to their intact hemicortex (Reuter-Lorenz et al., 2011), a function that normally requires a cortico-SC pathway (Schiller et al., 1987).

The neural machinery that subtends bilateral control by a single hemisphere seems functional in the normal brain because some FEF and LIP neurons have ipsilateral visual and motor responses (Barash et al., 1991; Crapse and Sommer, 2009). FEF neurons with ipsilateral motor responses receive projections from the contralateral SC (Crapse and Sommer, 2009), a projection that in hemidecorticate patients could permit the remaining hemisphere to receive information from the ipsilesional SC. This projection could be the one described by Leh et al. (2006a, 2006b) which becomes more prominent in some hemidecorticate patients. Hence, anti-saccade generation in our patients would require transferring signals within the FEF and LIP of the one remaining hemisphere, from the majority of contralateral visual neurons to the minority of neurons having ipsilateral motor responses. However, the activity patterns of FEF neurons, anatomically identified as projecting to the contralateral SC, has not been studied.

In summary, anti-saccade production in our patients may have used pre-existing neural circuits which may explain why each subject could perform this task in the first test trials. As we will review below in detail we explain our observed effects of the visual probe on the anti-saccade response as being due to the interaction in the ipsilesional SC of a visual signal and motor preparatory activity. In the normal monkey, the level of motor preparatory activity in some FEF neurons that project ipsilaterally to the SC on the same side begins rising just after cue onset and can occur many hundreds of milliseconds before the onset of contralaterally-directed anti-saccades (Everling and Munoz, 2000). Given the evidence summarized above, similar neurons in the same FEF may exist that project to the contralateral SC and encode preparatory activity for ipsilateral anti-saccades. In our patients, these putative neurons would project from the remaining FEF to the ipsilesional SC and encode contralesional anti-saccades. There is also evidence that the level of excitability of the ipsilesional SC can be modulated directly by the remaining dorsolateral frontal cortex via descending projections to the contralesional SC and then inhibitory SC commissurals to the ipsilesional SC (Johnston and Everling, 2006) and/or indirectly through the ipsilesional or contralesional basal ganglia (Hikosaka and Wurtz, 1983; reviewed in Hikosaka et al., 2000; Jiang et al., 2003; Munoz and Everling, 2004).

4.2. *Effect of the probe presented in the blind hemifield*

Our principal findings were: (1) In all three tested adult-hemidecorticate patients, an unseen small spot of light (the probe) flashed in their blind hemifield reduced their SRT (Figs. 3 and 4) for cue-probe delays of 100 msec, 150 msec, 200 msec, but not 0 msec. (2) The probe improved JB's and DR's performance accuracy by bringing the anti-saccade-end point closer to the cue's mirror location (Fig. 6A and C) and reduced the variability of anti-saccade landing locations around their mean (Fig. 7A and C). These effects in JB and DR were striking because the same probe stimulus, when presented alone in their blind hemifield, failed to elicit an accurate pro-saccade (Fig. 5A), even in blocks of trials where the subject anticipated a presentation of the probe. By comparison to the other subjects, there was no systematic effect of the probe on SE's anti-saccade-endpoints (Fig. 6B) and variability of SE's anti-saccade landing locations around their mean (Fig. 7B).

How can our probe effects be explained physiologically? Our first hypothesis is that the effect of probe-evoked visual signals on the anti-saccade motor command (discussed in the previous section) is mediated by signals in the retino-tectal pathway. The involvement of this pathway from retina to the ipsilesional SC in conveying visual information from the blind hemifield in hemidecorticate patients has been shown by Leh et al. (2010). Our second hypothesis is that the visual signals in the superficial layers of the ipsilesional SC descend to, interact with and modulate preparatory motor activity for anti-saccades in the intermediate visuo-motor layers. Isa (2002) proposed that if the pre-saccadic activity in the intermediate layers of the SC is absent, then the visual signal mediated by superficial layer neurons can reach the intermediate layers but fail to elicit a sufficiently strong burst of activity in the intermediate layers to initiate a motor command for saccade generation. In fact, normally convergent excitatory inputs to the deeper layers from extrastriate cortical structures are necessary for the generation of saccades to visual targets, specifically in the 'regular' latency range (Isa, 2002). Therefore, to explain the probe effects, we hypothesize that probe-evoked activity in retino-tectal afferents to the ipsilesional SC's superficial layers, descended to the intermediate layers and interacted with and enhanced, anti-saccade motor preparatory activity driven by, say, the FEF of the remaining hemisphere. Put another way, we propose that a preparatory motor signal in the ipsilesional SC, encoding the contralesional anti-saccade, interacted with a probe-induced visual signal, itself too weak to drive a saccade on its own.

In support of the preceding hypothesis, it has been shown by Özen et al. (2000) that the application of a single brief current pulse to the superficial layer of the rat SC can produce a prolonged burst of excitatory postsynaptic current (as long as 300 msec) in intermediate layer cells. The fact that the effects of the probe on SRT were similar in all subjects, despite the pure anti-saccade SRTs ranging from ~400 msec in DR to ~600 msec in JB, suggests that there was long-lasting motor preparatory activity in the ipsilesional SC over which probe-driven neuronal activity could drive an anti-saccade command signals above threshold for saccade initiation, and sooner than in the "pure" anti-saccade case. As reviewed in the preceding section, long-lasting preparatory activity for anti-saccades occurs normally.

Our hypothesis also explains why the probe improved anti-saccade *accuracy* in JB and DR: probe-induced activity at the anti-saccade goal location (i.e., the mirror location of the cue) on the SC's motor map interacted with the subject's own erroneously encoded motor activity (Fig. 5) so as to move, on the map, the center of gravity of the overall motor activity closer to the goal. Our explanation of why SE's anti-saccade

accuracy was not affected by the probe, despite the fact that his SRTs were affected, is because SE has bilaterally intact frontal lobes. We speculate that he "placed" his anti-saccade motor activity near to the correct location on the ipsilesional SC map such that the only possible effect of the probe was on his SRT, not accuracy. His amplitude-dependent overshoot and undershoots might then have resulted from mechanisms downstream of the SC.

Our postulate that there is interaction in the SC between preparatory motor and retino-tectal visual activity also seems compatible with observations on multisensory interactions in the SC which are strongly enhanced when weakly effective uni-modal stimuli are combined in register (Meredith and Stein, 1996). For example, Leo et al. (2008) showed that visual information in the blind hemifield of hemianopic patients can lead to significant improvements in their ability to localize auditory targets, but only when the visual and auditory stimuli are spatially and temporally coincident. However, Wallace and Stein (1994) showed that this cross-modal enhancement in the SC depends on inputs from ipsilateral association cortex, which is clearly lacking in our patients. Thus, the mechanisms underlying the effects of the probe in the present experiments remain enigmatic and may not involve signal enhancement. This is considered further in the next section.

4.3. *Evidence for an ipsilesional SC, hypoactive to visual stimuli*

It is well known that the intermediate layers of the SC are organized to form a motor map that specifies the amplitude and direction of saccades into the contralateral visual field. The rostral portion of the map – encoding the perifoveal representation – has a more complex role being implicated in bilateral microsaccade generation, fixation and smooth pursuit control and is particularly active during attentive fixation of a foveal target (Hafed et al., 2009; Hafed and Krauzlis, 2012; Munoz and Guitton, 1989, 1991a, 1991b; Munoz and Wurtz, 1995a, 1995b).

Sprague (1966) made the fascinating observation that a cat, blind due to occipital cortex ablation, recovers the ability to orient to a visual target in the contralesional blind hemifield if the contralesional SC is ablated or the collicular commissure is cut. He argued that the cortical ablation resulted in disequilibrium between the two SCs with the ipsilesional SC depressed due to inhibition by the other SC. Removing the influence of the contralesional SC restores the ipsilesional SC to its normal level of excitability. There is now strong evidence that saccade-related neurons on the motor map can suppress the activity of their contralateral counterparts as well as "fixation" neurons on both sides of the SC (reviewed in Munoz and Fecteau, 2002; Munoz and Istvan, 1998; Takahashi et al., 2005).

In an extension of the Sprague (1966) observations, Hovda and Villablanca (1990) reported that, in adult-hemidecorticate cats, there is a significant depression of oxidative metabolism in the ipsilesional SC compared to the contralesional SC. They speculated that the reduced oxidative metabolism is indicative of the depression of neuronal firing in the ipsilesional SC. Interestingly, after infantile hemidecortication, the metabolic activity and neuronal density in the ipsilesional SC remain normal (Hovda and Villablanca, 1990; Théoret et al., 2001), although this SC has lost 30% of its volume and number of neurons but nevertheless receives retinal inputs and appears to retain some functional properties (Théoret et al., 2001). These differences in the condition of the SC that depend on the time of the hemidecortication, could explain why patients hemidecorticated at a young age can generate saccades to targets in their blind hemifield (Perenin and Jeannerod, 1978), while adult-hemidecorticate animals and humans cannot (Troost et al., 1972; Tusa et al., 1986; Hovda and Villablanca, 1990; and present results).

4.4. *Evidence for an ipsilesional SC hyperactive to auditory stimuli; differences between visual and auditory domains*

The evidence reviewed just above suggests that following hemidecortication the ipsilesional SC is hypoactive to visual stimuli. By comparison, our study of *auditory* anti-saccades in these patients (Reuter-Lorenz et al., 2011) suggested that the intermediate layers of the ipsilesional SC are hyperactive. Indeed, we found that they generated short latency anti-saccades, and "express" pro-saccades to *auditory* targets in their blind hemifield. The generation of express saccades requires cortico-SC signals because SC ablation eliminates express saccades (Schiller et al., 1987). Therefore, we proposed in Reuter-Lorenz et al. (2011) that short latency auditory saccades to the patients' blind hemifield were facilitated by plastic mechanisms that rendered the ipsilesional SC *hyperactive* in order to facilitate reflexive glances to auditory targets they could hear but, of course, not see.

At first glance, the idea of a hyperactive ipsilesional SC seems compatible with the effects of the visual probe found in the present study, but it appears to contradict the classic observations and interpretations by Sprague (1966), reviewed in the preceding section, on the effects of the removal of descending inputs onto the ipsilesional SC, and the dynamic neural interactions between the two SCs. The seemingly contradictory results of the auditory and visual studies are reconciled by the observation, in visually deprived cats, that there is a significant *decrease* in the quality of visual signal in the affected SC while, at the same time, there is a significant *increase* in the auditory responses compared to normal cats (Rauschecker and Harris, 1983). The latter authors also found auditory responses in the superficial layers of SC following visual deprivation, which are absent in the normal cats. Taken together, these results suggest that in our patients, made hemidecorticate as adults, the ipsilesional SC may be *hyper-responsive to auditory* stimuli (Reuter-Lorenz et al., 2011) and *hypo-responsive to visual* stimuli (present results). We suggest that this is why we had to use the anti-saccade task in the present experiments to generate preparatory motor activity that itself could be enhanced by visual activity evoked by the probe.

4.5. *Comparison with other blindsight studies in hemidecorticate patients*

Our results are not in full agreement with other tests, in the same patients, of blindsight using the spatial summation

effect on a manual button-press reaction time (Leh et al., 2006a, 2006b; Tomaiuolo et al., 1997). In the latter studies, a notable finding was that in patients DR and SE, but *not* JB, the visual probe in the blind hemifield affected the button-press reaction time to the appearance of a light spot in the seeing hemifield (Leh et al., 2006a, 2006b; Tomaiuolo et al., 1997). *By comparison, in the present study we found an effect of the probe on anti-saccades in all three patients.* How can this difference in specifically JB be explained? The manual button-press task requires ascending visual signals to the remaining hemisphere due to the need to activate its motor areas to provide the button-press motor command response. The inter-subject difference in the button-press task was explained in two studies by Leh et al. (2006a, 2006b, 2009) using DTI and fMRI, respectively. In DR and SE, they found evidence for the involvement of the ipsilesional SC and its ascending crossed connection to visually-related cortical areas of the remaining hemisphere, notably FEF. In both patients, these projections are more prominent than in healthy controls. By comparison, they found that patient JB lacked this ascending crossed connection from the ipsilesional SC to the remaining hemisphere. Even his normal ipsilateral ascending projection was reported to be weaker. Accordingly, Leh et al. (2006a, 2006b) suggested that in JB, both SCs had degenerated. However, *the findings of the present study are in contradiction with this conclusion.* Indeed, the lack of a difference between subjects DR, SE and JB in the present study implies that the effect of the visual probe on anti-saccade interactions in our paradigm was due to signal processing in the descending pathway from retina-to-ipsilesional SC-to-the brainstem saccade burst generator and not in ascending signals from the ipsilesional SC to the remaining hemisphere.

5. Conclusion

In summary, considerable evidence suggests that following hemidecortication, the absence of ipsilateral cortical inputs to the ipsilesional SC, causes the level of excitation of tecto-reticular neurons (TRNs) in the intermediate layers of the SC to be too low to trigger contralesionally-directed pro-saccades to visual stimuli in the blind hemifield. We propose here that the activity of TRNs in the ipsilesional SC can be raised above the threshold for generating a saccade by superimposing two inputs: (1) a depolarization, via the retino-tectal tract, of a discrete ensemble of TRNs at a particular locus on the motor map; and (2) a low-level preparatory motor activity at the same locus. We achieved the latter by using contralesionally-directed anti-saccade and found that they were triggered early and their accuracy was improved by an unseen simple visual probe (light spot) in their blind hemifield. It remains to be proven that the ipsilesional SC truly carries descending probe-evoked visual activity and whether this activity can be modulated by varying the salience of the probe stimulus. The measurement of neck-muscle activity may reveal this. Indeed, in previous work, Rezvani and Corneil (2008) showed that pre-saccadic low-level activity in the intermediate layer of the SC – called here motor preparatory activity – correlates with neck-muscle Electromyography (EMG) activity compatible with a contralateral head turning strategy. With Dr. B. Corneil, we now have preliminary evidence showing probe-evoked EMG activity in the neck muscles of DR performing an anti-saccade task similar to the one in this paper (Rath-Wilson et al., Society for Neuroscience, Abstract number 914.16, 2011).

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Douglas Munoz <doug.munoz@queensu.ca>

Wed 2017-10-04 5:31 AM

To:Olga Savina <olga_savina@hotmail.com>;

Hi,

Yes you have my permission.

Doug Munoz

From: Olga Savina [mailto:olga_savina@hotmail.com]
Sent: Tuesday, October 03, 2017 1:40 PM
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Dear Dr. Munoz,
My name is Olga Savina. I am a PhD student in Dan Guitton's lab. I am writing to you to ask for a permission to use one of the figures (fig. (a) in Box 1) from the article: "Look away: The anti-saccade task and the voluntary control of eye movements" (2004) in my PhD thesis.

Thank you.

Sincerely,
Olga Savina