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Disruption of Reflexive Attention and Eye Movements in an Individual with a Collicular Lesion

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The superior colliculus (SC) plays a central role in the control of saccadic eye movements and has also been implicated in control of covert spatial attention. While there is a growing body of evidence from studies of awake behaving primates that supports these proposals, direct evidence from humans has been sparse. In the present study we tested a patient with thiamine deficiency and a lesion of the SC, who performed both eye movement tasks (prosaccades and antisaccades, with or without a gap) and a covert spatial attention task assessing inhibition of return (IOR). For eye movements, the gap effect was disrupted, and abnormal saccade metrics occurred, with reflexive eye movements being disrupted moreso than voluntary eye movements. Each of these effects resolved coincident with thiamine treatment. The covert attention task revealed a complete absence of IOR. The unequal disruption of voluntary and reflexive eye movements supports the idea that oculomotor responses can be generated in an independent fashion by frontal cortical and lower level neural systems. The role of the SC and other structures in these orienting processes is discussed.

Introduction

Midbrain structures, including the superior colliculus (SC), play a central role in the control of saccadic eye movements, as demonstrated by data from nonhuman primates (Bell, Fecteau, & Munoz, 2003; Fecteau, Bell & Munoz, 2004; Munoz & Wurtz, 1995a; Munoz & Wurtz, 1995b; Schiller, Sandel & Maunsell, 1987; Wurtz & Goldberg, 1972) as well as humans (Paus, Marrett, Worsley & Evans, 1995). The SC has also been implicated in control of covert spatial attention (Kustov & Robinson, 1996; Posner, Rafal, Choate & Vaughan, 1985). In particular, the SC is thought to play a role in two phenomena that are observed in visual orienting, the gap effect (GE) and inhibition of return (IOR). Behavioral evidence in normal individuals suggests that these two phenomena have interactive effects, suggesting a common underlying mechanism (Abrams & Dobkins, 1994). Here, we present data from a patient with a lesion of the SC tested using these two paradigms.

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Gap Effect

A common way to assess visual orienting in humans is to have an individual fixate a spot on a display screen, and then require the individual to make an eye movement to an eccentric visual target that suddenly appears. The introduction of a temporal gap between the disappearance of the fixation spot and the onset of the visual target reduces the saccadic reaction time (RT) to the target (Fischer & Boch, 1983; Ross & Ross, 1980; Saslow, 1967), a finding known as the gap effect. The gap paradigm also increases the frequency of express saccades (i.e., eye movements having a latency as fast as 100 msec in humans) that may form a separate population independent of the distribution of regular saccadic RTs (Fischer & Ramsperger, 1984). The SC seems critical for generation of these fast saccades, as express saccades are eliminated when the SC is ablated (Schiller et al., 1987).

Further, recent neurophysiological evidence has demonstrated that several classes of neurons in the SC modulate their activity during the gap period and that these modulations correlate with the latency of saccadic reaction time. Superior colliculus "fixation neurons", which are active when the eye is fixated on a certain position and inactive when a saccade is being made, decrease firing during the gap period preceding target onset (Dorris & Munoz, 1995; Dorris & Munoz, 1998; Everling, Dorris, Klein & Munoz, 1999; Everling, Pare, Dorris & Munoz, 1998). Separate populations of saccade related, "movement neurons," in the SC are active preceding or during an eye movement (i.e., buildup and burst neurons). These movement neurons show increasing activity preceding target onset, increase firing during the gap period before a target, and can show an elevated discharge for fast latency express saccades (Dorris, Pare & Munoz, 1997; Dorris & Munoz, 1998; Edelman & Keller, 1996; Everling et al., 1999; Munoz & Wurtz, 1995a; Munoz & Wurtz, 1995b). Thus, neuronal activity in the SC during the gap preceding target appearance is modulated in a manner consistent with changes in saccadic RT and increased occurrence of express saccades. Despite such findings, direct (or even indirect) evidence *in humans* for a collicular role in the gap effect has so far not been available.

Inhibition of Return

Recent neurophysiological evidence has demonstrated that the SC also plays a necessary role in the expression of another attentional phenomenon known as IOR (Bell et al., 2004; Dorris, Klein, Everling & Munoz, 2002; Dorris, Taylor, Klein & Munoz, 1999; see also, Ro, Farnè & Chang, 2003). In a typical IOR paradigm, an individual's attention is reflexively drawn to an eccentric visual location, and if this cue is not predictive of a subsequent target, then their attention is automatically shifted away from this position. Finally, the individual is required to reorient attention to the initially attended eccentric position. IOR, or inhibition of return, refers to the finding that it is more difficult to re-orient to that location after having first attended and then left it, as compared to not having attended or oriented to it beforehand.

In contrast to the gap effect, most of the evidence implicating the SC in IOR comes from behavioral studies of humans and not from neurophysiological studies of primates (but see Bell et al., 2004; Dorris et al., 2002; Fecteau et al., 2004). Evidence for a collicular role in IOR in humans has primarily come from three sources. First, Posner and colleagues studied patients with progressive supranuclear palsy (PSP) in a covert spatial attention task. PSP is a degenerative brain disease that affects neurons in the midbrain,

including the SC, and a common early symptom involves a disruption of eye movements. In the early stages, downward saccades in particular are affected, and then lateral movements as the disease progresses (Richardson, Steel & Olszewski, 1963; Steele, Richardson & Olszewski, 1964). Posner and colleagues found that both initial covert orienting (Posner, Cohen & Rafal, 1982; Rafal, Posner, Friedman, Inhoff & Bernstein, 1988) and later occurring IOR (Posner et al, 1985) were reduced in the vertical direction in PSP patients. This study alone cannot provide definitive evidence for collicular involvement in IOR, since PSP involves widespread degeneration of numerous subcortical areas, and may affect cortical structures as well (Baker & Frank, 1976; Hof, Delacourte & Boras, 1992; Karbe et al., 1992; Vermersche et al., 1994; Verny, Duyckaerts, Agid & Hauw, 1996; Verny, Duyckaerts, Delaere, He & Hauw 1994; Yamauchi et al., 1997; Bergeron et al., 1997).

Converging evidence for collicular involvement in covert orienting in humans was reported by Rafal, Calabresi, Brennan and Sciolto (1989). In this study, Rafal and colleagues demonstrated a visual field asymmetry that they argued was due to the unequal visual field representation that occurs in the innervation of the SC. The visual pathways leading into the SC include both crossed fibers from the nasal hemiretina of the contralateral eye, as well as uncrossed fibers from the temporal hemiretina of the ipsilateral eye. The SC is innervated by more crossed than uncrossed fibers. As a result, visual input from the two nasal hemiretinae (or equivalently, the two temporal visual fields) is more strongly represented in the SC than is information from the two temporal hemiretinae (i.e., nasal visual fields). In their study, Rafal and colleagues (1989) gave subjects a standard covert spatial cueing task where they viewed the display while wearing an eyepatch over one eye. Their subjects showed reduced IOR for stimuli in the nasal visual field compared to the temporal visual field, suggesting that the SC plays a role in generation of IOR. Rafal and associates' study (1989) is consistent with a collicular role in IOR, but the procedures used allow only an indirect test of this hypothesis.

Complementary to this finding is a recent study by Sapir, Soroker, Berger & Henik (1999), who used a covert spatial orienting task in a patient with a unilateral lesion of the right SC. Their patient failed to show IOR in either the temporal visual field of the left eye or the nasal visual field of the right eye. These visual field deficits nicely correlate with the regions of the visual field presumably affected by a lesion of the right SC and provide further evidence for a role of the SC in IOR.[1]

The present study reports data from a patient with a lesion of the SC. This patient was tested in two paradigms commonly used to study eye movements and spatial attention. The first task involved saccadic eye movements either to visual targets (reflexive or visually guided saccades) or in a direction opposite to these targets (voluntary saccades or antisaccades, AS). Both gap and overlap versions of these tasks were included (i.e., the fixation spot was either removed just prior to target onset or it remained in view). Tests on this patient were carried out in two sessions separated by three weeks, the first while he was initially hospitalized and the second after treatment and release. Additionally, he performed two versions of an exogenous spatial cueing task (Posner 1980), one requiring saccades to visual targets and another requiring manual localization responses (this testing occurred during the second testing session). Since previous evidence has suggested that the SC plays a role in the gap and spatial cueing effects, a failure to find disruption of these effects in this patient would

[1]Other evidence for a specifically collicular role in IOR comes from developmental studies (Simion, Valenza, Umilta & Dalla Barba, 1995; Valenza, Simion & Umilta, 1994) and studies of hemianopia patients (Danziger, Fendrich & Rafal, 1997).

necessitate a reconsideration of the presumed role of the SC in modulating spatial orienting in humans. A preliminary report of these findings has appeared previously (Briand, Szapiel & Sereno, 1999).

Methods

Case Description

Patient SR was a 50 year old male with a history of cardiac transplant (secondary to ischemic cardiomyopathy) on chronic immunosuppressive therapy for 11 years; end stage renal disease treated with biweekly hemodialysis; and chronic obstructive pulmonary disease. He was admitted to the hospital with a two week history of fever, mild confusion, diplopia, and several months of poor food intake. Upon initial examination he was found to have continuous adductor spasms of the eyes, decreased ability to look up or abduct either eye, and slight difficulty with downward eye movements. Cognition was described by the admitting neurologist as good.

A magnetic resonance image (MRI) of the brain with gadolinium (degraded by motion artifact) revealed diffuse enhancement of the superior colliculus, pineal regions, and periaqueductal grey matter (see Figures 1a-c). There was also focal enhancement of the mediodorsal thalamus similar to the pathology seen in Wernicke's encephalopathy (Figure 1d), a small round periventricular lesion next to the frontal horn of the right lateral ventricle (Figure 1b, indicated by asterisk), as well as an area near the right superior vermis of the cerebellum (Figure 1a and 1c, indicated by asterisk). A magnetic resonance spectroscopy scan was also performed, although it captured only the upper cortex and not the brainstem or other subcortical structures. The region examined included tissue lateral to the right lateral ventricle and the ventricle itself (i.e., half into tissue, half into the cerebrospinal fluid in the ventricle). This scan showed increased choline and lactic acid, and decreased N-acetyl aspartate (NAA), which could be consistent with either demyelination or malignancy.

A lumbar puncture was performed and the cerebrospinal fluid (CSF) revealed a mild pleocytosis (23 white blood cells, 90% lymphocytes), mildly elevated protein (52.5.mg/dl), and normal glucose. Flow cytometry was performed on the CSF and showed atypical lymphocytes but no clear malignant cells. All cultures and stains were negative for bacteria, fungus, and acid fast bacilli. CSF toxoplasmosis titres were also negative, although serum toxoplasmosis IgG titres were positive (IgM titres were negative). A thiamine level obtained after the first but before the second testing session was mildly below normal (7 nmol/L; normal range is 9-44 nmol/L). Thiamine replacement therapy was initiated 28 days after initial hospitalization (this began 20 days after his first testing session in the reported experiments, and one day before his second testing session).

Both SR's symptoms (particularly the abnormal eye movements) as well as the location of most of his lesions were consistent with Wernicke's encephalopathy (WE). Abnormal eye movements are often observed clinically in patients suffering from WE, with frequently reported symptoms including those of nystagmus, lateral rectus palsy, and problems with conjugate gaze (Victor, Adams & Collins, 1989). Upward eye movements are more commonly affected in WE than are downward movements. Subject SR exhibited all of these signs in one form or another. Brain lesions in WE are usually seen in the periventricular regions of the thalamus, hypothalamus, periaqueductal grey matter, and

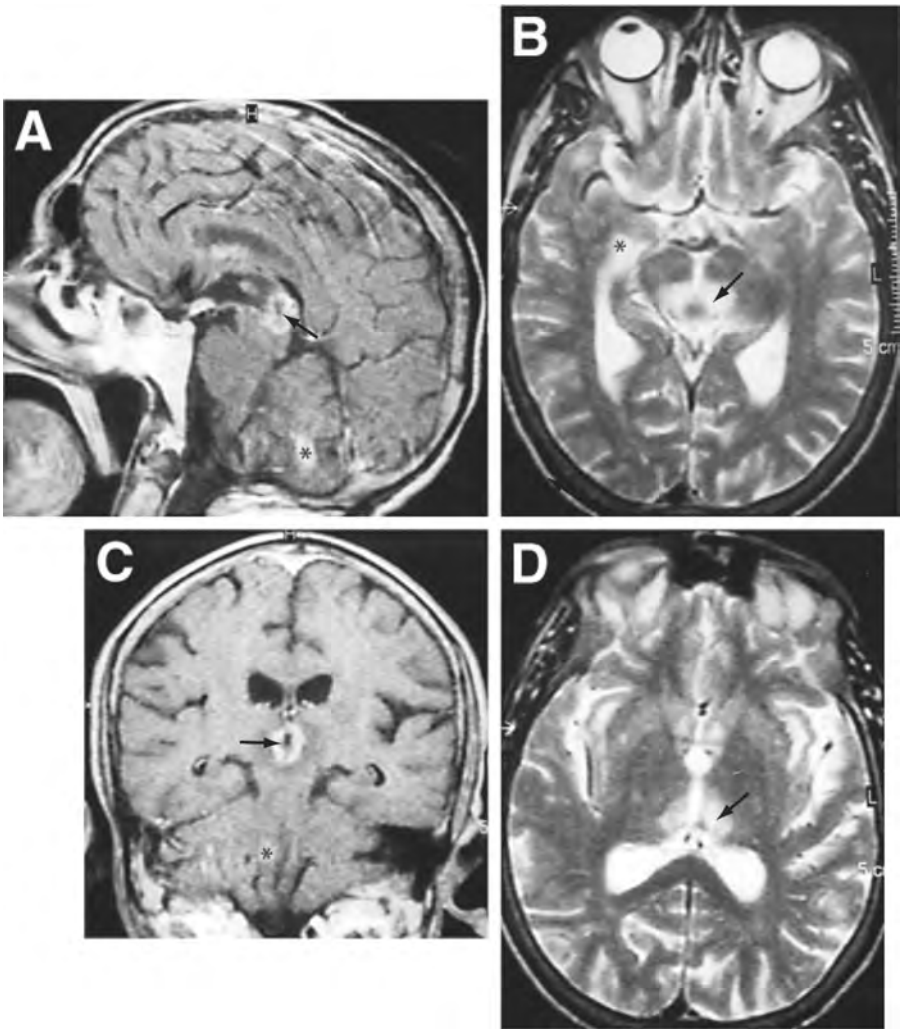

Figure 1. MRI images of brain lesions in patient SR. 1a: Midsagittal T1 weighted image showing hyperdensity in the superior colliculus and adjacent midbrain (indicated by arrow) as well as a rounded hyperdensity in the mid-right cerebellar vermis (indicated by asterisk). 1b: Transverse T2 weighted image showing hyperdensity of the periaqueductal grey region (indicated by arrow) as well as a small round periventricular hyperdensity next to the frontal horn of the right lateral ventricle (indicated by asterisk). 1c: Coronal T1 weighted image showing hyperdensity of the periaqueductal grey region (indicated by arrow) as well as a rounded hyperdensity in the mid-right cerebellar vermis (indicated by asterisk). 1d: Transverse T2 weighted image showing bilateral hyperdensity of the medial dorsal nucleus of the thalamus (left side indicated by arrow).

cerebellar vermis. While less frequent, lesions of the SC also can also occur. SR's profile closely matched this pattern.

Increased CSF protein, as was observed in this patient, may also be elevated in WE up to 50-100 mg/dl (Victor et al., 1989). On the other hand, there is typically no pleocytosis in WE, whereas patient SR did have a mild lymphocytic pleocytosis. The CSF profile

exhibited by SR could also be consistent with an infection (e.g., early fungal, tuberculous, viral, partially treated or resolved bacterial meningitis, or parasitic infection) or active demyelinating disease. The MR spectroscopy scan profile could also support a diagnosis of demyelinating disease which could be consistent with WE (decreased NAA usually reflects neuronal loss). Thus the possibility that SR suffered from demyelinating disease, lymphoma, or infection could not be ruled out.

Interestingly, over a period of 3 weeks, SR's adductor spasms began to wane and eye abduction improved coincident with improved food intake and subsequent thiamine replacement. Eventually he was able to fully abduct his eyes and as the adductor spasm abated, he slowly started to be able to track an upward moving object. However, his smooth pursuit eye movements broke down into saccades, and he had to look up in a gross stepwise fashion.

Wernicke's syndrome is commonly associated with a thiamine deficiency and can occur as a result of chronic alcoholism. Interviews with both the patient and family members indicated that SR had not consumed alcohol in the last several years. However, both poor diet (Devathasan & Koh, 1982; Hinze-Selch, Weber, Zimmermann & Pollmacher, 2000; Waterston & Gilligan 1986; Weder, Ludin & Hoigne, 1982) and hemodialysis (Ihara, Ito, Yanagihara & Nishmura, 1999; Jaghadha, Deck, Halliday & Smyth, 1987; Sandoval, Boria & Gatica, 1997), both of which were part of SR's history, have been previously implicated as factors related to thiamine deficiency and Wernicke's symptoms.[2]

Both the left and right eye were tested in all eye movement tasks on the first testing day. However, technical problems made the right eye data unusable, and all data presented is from SR's left eye.[3]

Chronology of Events for Patient SR

Patient SR first reported diplopia while receiving scheduled hemodialysis on 11/5 (month/day). On 11/7 he was admitted to the hospital and improved diet was initiated. MRI scans were obtained on admission. His first testing session in the reported experiments was on 11/15. The MR spectroscopy was carried out after SR was released from the hospital, on 11/23. A thiamine level was obtained during a follow-up visit to the hospital on 12/5 (thiamine level of 7 nmol/L; normal range is 9-44 nmol/L), and thiamine replacement was initiated the same day. His second testing session was on 12/6. On 12/8 he had another follow-up hospital visit, and his thiamine level had increased dramatically with supplementation (to 1575 nmol/L).

[2]We were unable to definitively conclude that SR's collicular abnormality and accompanying symptoms were specifically due to WE, because he unexpectedly passed away at home before any further diagnostic testing could be carried out and an autopsy was not performed. The pattern of results that follow, wherein performance of some behavioral tasks improved following thiamine treatment, suggests the diagnosis of a possible WE induced collicular lesion that was to some extent reversible. However, as we indicated previously, the presence of other diseases that could have affected the SC could not be ruled out.

[3]The eye tracking system was specifically set up to test the left eye (i.e., illumination levels and position of light source) and was not optimal for testing the right eye. Furthermore, SR's difficulty with vertical eye movements for his right eye made calibration almost impossible (i.e., to calibrate the eye tracker subjects have to gaze at highly eccentric points in horizontal and vertical directions before testing), thus preventing reliable measurement of true eye position.

Cognitive Status

SR was described on 11/7 as being "awake, alert and oriented, with memory and cognition intact". Further neurological assessment showed normal cerebellar function. During the first testing session, we administered the Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975), and his performance was in the normal range. This test is useful in screening for dementia but is not suitable for a full mental status examination. Nevertheless, we administered this test, given the severe time constraints allowed for testing during his initial hospital stay as well as the fact that this test is the most widely used brief screening measure of cognition (Tombaugh and McIntyre, 1992).

Apparatus

Eye movements were recorded using an ISCAN RK-426 eye-tracking system, interfaced with an infrared sensitive camera. Spatial resolution was approximately 0.5 degrees of visual angle, while temporal resolution to detect saccades was set at 6 msec. The subject's head was on a chin rest positioned 72 cm from a computer monitor used to display the stimuli (Sony Trinitron Multiscan sf II). The monitor screen covered a visual area of 25° by 18° from this viewing distance.

Saccade Detection

Saccade latency was calculated using a velocity criterion. The start of a saccade was indicated as soon as the change in eye position went above a velocity of 120°/sec. The end of the saccade was indicated when (a) eye velocity fell below 12°/sec and (b) eye position was within 4.4° of either the left or right target position. When the end of the saccade was determined, the saccade was decided to be "within target" or "in opposite position" and scored as correct or incorrect as appropriate for the task. If a saccade was not successfully completed within 1600 msec of target onset, that trial was replaced in the pool of unfinished trials to be completed later. Feedback following errors consisted of a brief tone.

Stimuli

Saccade Tasks. A grey central fixation spot of 0.15° was shown against a black background. Target locations were 7.3° to the left and right of this fixation spot. Target stimuli were 0.2° white squares.

Spatial Cueing. The stimulus display consisted of a grey fixation spot ($0.2 \times 0.2°$) on a black background, flanked by two grey boxes ($1.0 \times 1.0°$) positioned such that their centers were 4.8° to the left and right of fixation. The target stimulus was a green square measuring $0.6 \times 0.6°$ which appeared in the center of one of the two flanking boxes.

Experimental Tasks

SR was tested on two separate days, the first during his initial stay in the hospital. The second testing session was 3 weeks after this, when he was living at home.

Day 1. The right and left eyes were tested separately, while SR wore an eye patch over his nontested eye. SR performed the four tasks described below presented in the order listed for the right eye, and then the same sequence when the left eye was tested. Each of the tasks were run in single blocks of 40 trials.

Saccade—Overlap. The fixation point was turned on to indicate the start of the trial. Eight hundred msec after the subject shifted his gaze to the center, the target stimulus was displayed, with position (left or right) being chosen randomly. This was constrained only by the requirement that there be 40 trials, with equal numbers of targets presented in the left and the right locations. Simultaneous with target onset, a brief 13 msec tone sounded similar to other published studies (Lueck, Tanyeri, Crawford, Henderson & Kennard, 1990, Lueck et al., 1992). The subject responded by making a saccade to the target item following its onset. At the conclusion of the response, the target stimulus was erased and the fixation point replotted to begin the next trial sequence. If a saccade was not initiated within 1000 msec the trial was terminated and rerun later in the block of trials. The target remained in view until the subject responded or until 1000 msec had elapsed.

Saccade—Gap. This task was exactly the same as the saccade—overlap task, with the exception that the fixation point was removed from the screen 187 msec prior to the appearance of the target.[4]

Antisaccade—Overlap. The sequence of events was identical to that for the saccade—overlap task. However, the subject had to make an eye movement in the direction opposite to the target.

Antisaccade—Gap. The sequence of events was identical to that for the saccade—gap task, but the subject had to make an antisaccade.

Day 2. Only the left eye was tested on the second day. The saccade and AS tasks were given, along with a spatial cueing task. All tasks were run in the same order in which they are described. The saccade and antisaccade tasks were run in blocks of 28 trials each, while the spatial cueing tasks had 96 trials each.

Saccade/Antisaccade (S/AS). Horizontal eye movements were measured using saccade-overlap and saccade-gap, as well as AS-overlap and AS-gap

Spatial Cueing. The spatial cueing task used exogenous cues (brightening of a peripheral box, followed by brightening of fixation point to draw attention back to the middle). Cues were not predictive of target location (50% validity). Subsequently, a target (a green square) appeared within either the cued or uncued box at three possible delay periods following the cue: 80, 133 or 1000 msec (this delay period is commonly referred to as SOA, or 'stimulus onset asynchrony'). The task was to indicate the location of the target as quickly as possible. Two versions of the task were given, the first requiring the subject to respond by making a saccade to the target, and the second

[4]For both saccade and AS tasks, we chose to test SR in the gap condition only after he had been first tested in the overlap condition. Our rationale for using this order was that we predicted that SR's collicular damage would disrupt his gap effect. By having the gap condition presented second, we felt that practice effects would actually work against us, as saccadic RTs might improve slightly as SR became more familiar with the testing procedure. Thus, a demonstration of no gap effect even under these biased conditions is all the more impressive. We also did not believe that fatigue is a major issue, given the brief duration of each saccade block (40 or 28 trials) as well as the inclusion of frequent rest periods.

requiring a manual response (keypress). For the latter task SR used the index and middle fingers of his (preferred) right hand. As with the saccade tasks, targets remained in view until either a response occurred or 1000 msec had elapsed. SR was asked to maintain fixation during the manual task (at the fixation point in the center of the screen), and fixation was monitored by the experimenter throughout the experiment. Typically, it has not been common practice to monitor eye movements in studies of manual IOR. However, Khatoon, Briand and Sereno (2002) explicitly examined this issue and report the same cueing effects whether or not subjects made eye movements in conjunction with the manual responses.

Results

Multistep Saccades

Day 1. Examples of SR's typical performance on four trials of the prosaccade task can be seen in Figure 2. Although the majority of his saccades (average 60% across both tasks) appeared relatively normal (Figure 2a), there was a tendency for many to consist of multiple, stepwise shifts from fixation to target (see Figures 2b–d). Table 1 presents the proportion of trials from the various tasks that included multiple steps (i.e., > 1 stop prior to reaching target). The proportion of trials thus affected was 60% for the prosaccade tasks, being somewhat lower (20%) for antisaccades. This difference was significant by Chi-Square ($p < 5 \times 10^{-7}$).

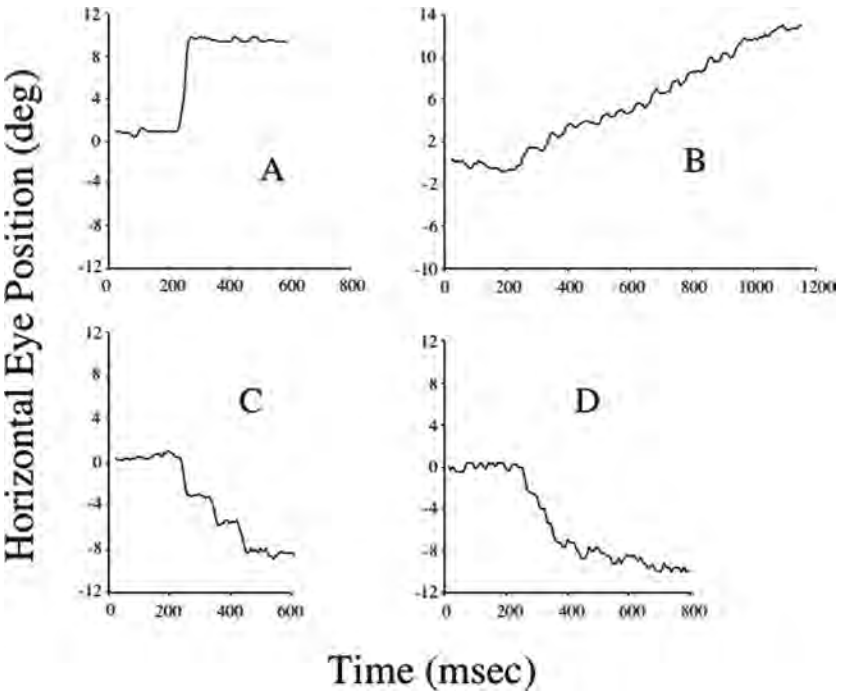

Figure 2. Examples of eye records for the saccade tasks from the first testing session. A normal saccade is indicated in A, while B–D show various degrees of multistepping.

Table 1
Percentage of Trials in Saccade and Antisaccade Tasks with Stepwise Eye Movements (> 1 Stop Prior to Arrival at Target)

	Day 1	Day 2
Saccades	60.0	9.1
Antisaccades	20.0	3.5

Day 2. The rate of multistep eye movements remained higher for saccades than for antisaccades, but was not statistically significant ($p > .22$, see Table 1).

Day 1 versus 2. As can be seen in Table 1, the proportion of trials including multistep saccades was much lower on the second day than on the first. This decrease was highly significant by Chi-Square for saccades ($p < 3 \times 10^{-9}$) as well as antisaccades ($p < .006$).

Response Latency

To provide some context to the data from patient SR, we include in Table 2 data from 10 control subjects from another study of eye movements in elderly subjects (Amador, Cain, Briand, Schiess & Sereno, 2003) whose ages ranged from 44 to 62 with a mean of 54.1 years old. These subjects only participated in a single testing session (Day 1). Even though these eye movement effects are fairly well established in the literature (Klein, Rischer,

Table 2
Average Response Latency in Milliseconds and Percent Errors in Parentheses on Both Days of Testing as a Function of Task and Gap Condition

	Patient SR		
	Overlap	Gap	Gap Effect
Saccade			
Day 1	308 ± 11.33 (0)	312 ± 15.83 (2.5)	−4 (–2.5)
Day 2	292 ± 10.9 (3.6)	244 ± 10.8 (3.7)	48[a] (−0.1)
Antisaccade			
Day 1	376 ± 28.1 (35.3)	357 ± 39.8 (55.9)	19 (–20.6[c])
Day 2	415 ± 30.1 (33.3)	397 ± 22.3 (25.9)	18 (7.4)
	Control Subjects (n = 10)		
	Overlap	Gap	Gap Effect
Saccade			
Day 1	296 ± 13.93 (1.6)	237 ± 9.25 (1.6)	59[b] ± (0)
Antisaccade			
Day 1	448 ± 34.83 (24.9)	380 ± 18.56 (37.5)	68[b] ± (–12.6[a])

[a] $p < .005$.
[b] $p < .03$.
[c] $p < .06$.

Hartnegg, Heiss & Roth, 2000), we thought it useful to provide a sample to illustrate the kind of performance that would be expected for people in this age range. There were some differences in methodology between these control subjects and patient SR that would tend to increase saccade latencies for the control subjects: namely, (1) there was a variable fixation interval (either 400 or 800 ms) required before the target instead of a single fixed 800 ms interval; (2) gap and overlap trials for a given saccade task were intermixed and randomly presented instead of being blocked; and (3) there was no tone presented at target onset (see Larrison, Briand & Sereno, 2004, Figure 2 for the effects of such task differences in these eye movement tasks in normal subjects). There were also a few minor differences: (1) there was a total of 48 trials per task condition (e.g., saccade gap) instead of 40 trials; (2) the fixation spot was 0.2° instead of 0.15°; and (2) the targets were presented with an eccentricity of 7.0° instead of 7.3°. In all other aspects, the stimuli and procedures were identical.

Day 1. Saccades with latencies greater than 700 msec and faster than 100 msec were excluded from analysis (4.8% of all trials). The average latencies from the remaining trials of the four saccade tasks are shown in Table 2. The gap effects for the saccade and AS conditions ($RT_{overlap}$ - RT_{gap}) were assessed using Mann-Whitney tests. There was no significant difference between the gap and overlap conditions for either the saccade tasks (-4 msec, $z = 0.29$, $p > .38$) or the antisaccade tasks (19 msec, $z = 0.51$, $p > .30$).

Day 2. Table 2 also shows the RTs for the saccade and AS tasks in both overlap and gap conditions for the second day of testing. As can be seen, SR showed a robust gap effect on the second day for saccades (48 msec, $z = 2.98$, $p < .002$) but there was no gap effect for antisaccades (18 msec, $z = 0.46$, $p > .32$).

Day 1 versus 2. Comparison of RTs on Day 1 versus 2 revealed that whereas the saccade overlap task showed no change in RT on Day 2 (16 msec, $z = 0.71$, $p > .24$), the saccade-gap condition was significantly faster on Day 2 (68 msec, $z = 2.88$, $p < .01$). Response latencies in the AS tasks showed no effect of Day (-39 msec, $z = 0.64$, $p > .26$, and -40 msec, $z = 0.88$, $p > .28$ for AS overlap and gap conditions respectively).

Errors

Day 1. Error data are also presented in Table 2. The significance of gap effects in errors was determined by using Chi-Squared to compare the number of errors in different testing conditions. Overall data showed no difference in error rate for overlap and gap conditions for saccades (-2.5%, $p > .17$). For antisaccades, there was a marginally significant 20.6% increase in errors in the gap condition ($p < .06$).

Day 2. There was no evidence for a gap effect in errors for either saccades (<1%, $p > .97$) or antisaccades (7.4%, $p > .56$).

Day 1 versus 2. There was no difference in error rate for the two saccades tasks ($p > .22$ for both saccade and saccade-gap). The AS overlap condition showed no difference in error rates between Days 1 and 2 (-2.0%, $p > .87$). However, error rates were significantly lower on Day 2 for the AS gap condition (-30%, $p < .01$).

Summary—Eye Movement Tasks

Subject SR performed these eye movement tasks during his initial hospitalization, and approximately three weeks later following thiamine replacement. The two main findings in the first day of testing were that SR did not show a gap effect for the saccade task, and his saccades appeared abnormal and showed considerable multistepping. On the second day, not only was there a significant gap effect for saccades, but the number of multistep eye movements was greatly reduced. Furthermore the number of AS errors was reduced on the second day.

Spatial Cueing Tasks

Again, to provide some context to the spatial cueing data from patient SR, we include in Figure 3 data from 8 control subjects from another published study of spatial cueing in elderly control subjects (Briand, Hening, Poizner & Sereno, 2001) whose ages ranged from 66 to 82 with a mean of 72.6 years old. Even though these cueing effects are fairly well established in the literature for younger subjects, we thought it useful to provide a sample to illustrate the kind of performance that would be expected for elderly people. There were some minor differences in methodology for these elderly control subjects: (1) the subjects were tested on only one version of the task (96 trials), requiring a saccade to the target (and not tested on the manual version); and (2) the positions of the two grey boxes were 5.8° to the left and right of fixation (instead of 4.8°). In all other aspects, the stimuli and procedures were identical.

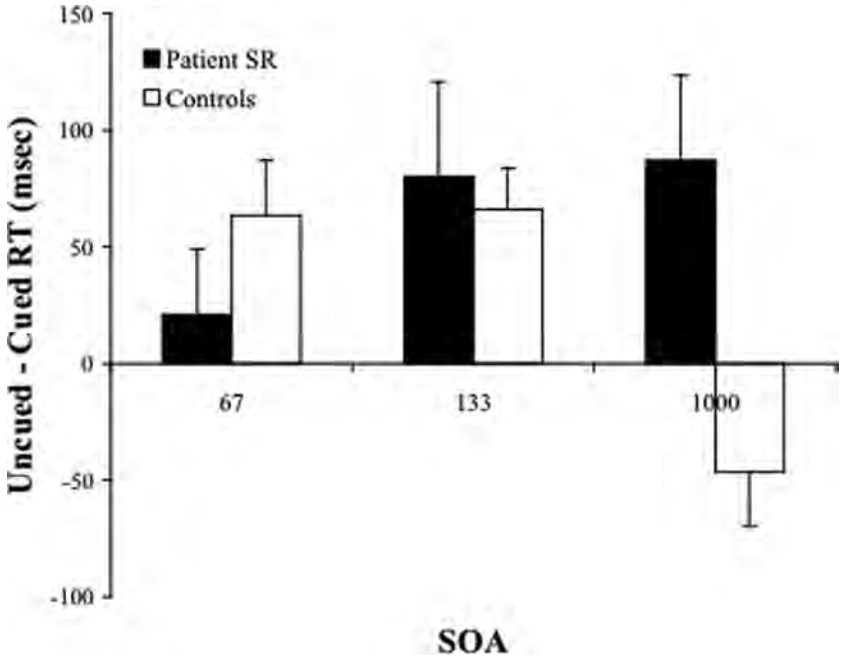

Figure 3. Mean RTs (and % errors) for saccadic and manual responses in the spatial cueing task, as a function of cue type and SOA.

Response Latency

Mean RTs from the spatial attention tasks were subjected to an ANOVA with Response (saccadic or manual), Cue (valid or invalid) and Stimulus Onset Asynchrony (SOA) as factors[5]. Cue was significant ($F_{1,15} = 10.06$, $p < .007$), with valid cues leading to faster RT. Figure 3 shows this cue effect (difference in RT for valid and invalid trials) across the different SOAs. Response was also significant, with saccades being faster than manual responses (378 vs. 553 msec respectively, $F_{1,15} = 75.76$, $p < .0001$). The SOA × Cue interaction was not significant ($F_{2,30} = 1.32$, $p > .28$), with net facilitation being observed at all SOAs, most importantly at the 1000 msec SOA.

The second-order interaction between Response, Cue and SOA was significant ($F_{2,30} = 4.96$, $p < .02$; see Table 3), since the pattern of facilitation varied between Responses at the shortest SOAs. However, neither manual nor saccadic responses showed IOR at the longest cue-target SOA. Furthermore, the facilitation at the 1000 msec SOA is not caused by the presence of a small number of deviant responses that bias the overall average. This can be seen in Figure 4, which shows the cumulative distribution of RT (CD_{RT}) for cued and uncued trials for each SOA and response combination. Facilitation is indicated when the CD_{RT} for the cued condition is to the left of that for the uncued condition, whereas inhibition (i.e., IOR) is indicated when the CD_{RT} for the cued condition is shifted to the right of the uncued condition. In particular, note that at the 1000 msec SOA, where IOR should be occurring, the RT distribution for cued trials is still shifted to the left for both saccadic and manual responses, indicating faster responses relative to that for uncued trials.

Errors. Analysis of errors on the spatial cueing task revealed only a significant main effect of Response ($F_{1,15} = 6.82$, $p < .02$), with more errors on the manual task than the saccadic task (5.2% vs 0.0%).

Table 3
Mean RT and Error Rate in the Spatial Cueing Task as a Function of Response Mode (Saccadic or Manual), SOA and Cue

	Cued	Uncued	Uncued - Cued
Saccade - 80	356 (0.0%)	427 (0.0)	71 (0.0)
Saccade - 133	336 (0.0)	340 (0.0)	4 (0.0)
Saccade - 1000	392 (0.0)	414 (0.0)	22 (0.0)
Manual - 80	534 (0.0)	494 (6.3)	-40 (6.3)
Manual - 133	468 (6.3)	637 (20.0)	169 (13.7)
Manual - 1000	531 (0.0)	653 (0.0)	122 (0.0)

[5]We analyzed the IOR data by performing a three factor repeated measures ANOVA (Response × Cue Type × SOA). This was conducted as follows: (1) for each condition, missing trials (e.g., due to errors or anticipations) were replaced with that cell's mean RT. (2) Each row in the repeated measures ANOVA consisted of the n^{th} trial in each cell/condition, for example the first row (the first "subject") consisted of the RTs from the first trial presented in each of the testing conditions, the second row consisted of the RTs from the second trial presented in each testing condition, down through to the last (16^{th}) row (the last RT from each testing condition). In effect, each successive trial within a testing condition was treated as coming from a different subject, but sets of trials corresponding to the n^{th} instance of each type were treated as coming from the same subject.

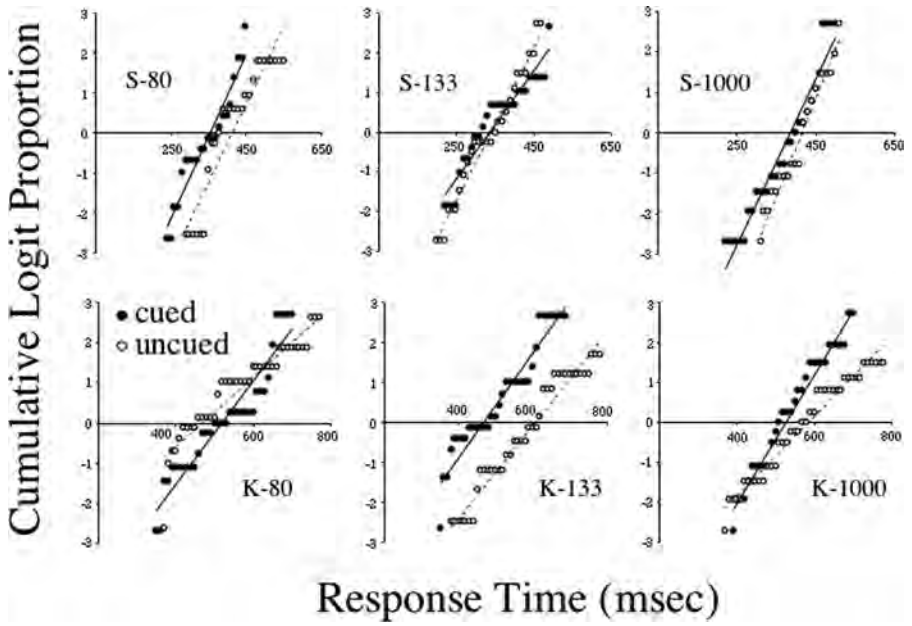

Figure 4. Cumulative distribution of RT (CD_{RT}) for cued and uncued trials for each SOA and response combination. The RT distributions are plotted as linear probit functions. Also included are the best fitting functions from the regression analyses for the cued and uncued conditions (solid lines for cued and dashed for uncued). Note that at the 1000 msec SOA, the distribution of cued trials is shifted to the left of that for uncued trials for both saccadic and manual responses, indicating facilitation rather than IOR.

Discussion

Both saccadic eye movements and covert spatial attention were disrupted in this patient with bilateral damage to the superior colliculus.

Eye Movements

Two aspects of patient SR's eye movements were disrupted on his first day of testing. First, SR failed to show a gap effect. Second, his saccades showed a high degree of multistepping. An important aspect of SR's performance on the eye movement tasks was that he showed remarkable improvement on the second day of testing three weeks later, coincident with thiamine replacement. In this second session, SR showed a gap effect for saccades, and the multistepping so prevalent in his eye movements in the earlier session was largely eliminated. In addition, SR showed a significant improvement in error rates in the AS gap condition on the second day of testing compared to the first, whereas errors in the AS overlap condition remained virtually unchanged.

Voluntary versus Reflexive Eye Movements

One important aspect of our data is that the incidence of multistep eye movements was significantly lower for antisaccades (AS) than for saccades. This suggests that whatever was causing the steplike eye movements affected voluntary and reflexive eye movements

differently. Given this possibility, we compared the rate of stoppages on AS trials where SR made a correct response (voluntary saccade away from the target) to those trials where he made an error (saccade to the stimulus). We found a nonsignificant trend suggesting that AS trials with errors had a higher rate of multistepping than did correctly executed antisaccades ($p < .09$). This trend is consistent with the observation that SR showed significantly more steplike eye movements for reflexive than for voluntary saccades overall.

To our knowledge, this is the first study in humans to demonstrate a dissociation in the metrics of voluntary and reflexive saccades with better performance occurring in the more difficult eye movement task. Such evidence supports the idea that oculomotor responses that are modulated via frontal or prefrontal systems can be elicited in an independent fashion from eye movements controlled largely or exclusively by lower level systems.

Role of Practice

Very few studies have been conducted on collicular patients. We did not anticipate that SR would have a thiamine deficiency, nor that he would improve in the second testing. However, with respect to the saccade and antisaccade tasks with gap and overlap, we have previously shown (Larrison-Faucher, Matorin & Sereno, 2004) that normal subjects as well as schizophrenic patients do not show a significant change in performance in these tasks across sessions (12) or days (3). In addition, some of the improvements in SR's performance were mainly occurring in certain conditions where practice per se was unlikely to be a factor (e.g., see discussion above concerning more multistepping in the reflexive saccade task). Finally, the gap effect is the difference in performance in two identical saccade tasks with the only change being the removal of the fixation point immediately preceding the target onset. Hence, the emergence of the gap effect in the saccade task is not easily attributed to a practice effect without proposing ad hoc differential effects of practice (e.g., improvement in the gap paradigm but not the overlap paradigm). Thus, although we cannot rule out possible practice effects in this particular patient, we feel it is unlikely that his improvements were due to practice effects.

Role of Thiamine Deficiency

We think it is possible that SR's improved saccadic performance was related to treatment he was given during and after his initial hospitalization and diagnosis (i.e., improved food intake and thiamine replacement). As mentioned in the Case Description, SR's behavioral symptoms and pattern of brain lesions were consistent with Wernicke's Encephalopathy (WE). Both eye movement abnormalities and other symptoms in WE have previously been shown to improve following treatment with thiamine (Baker & Frank, 1976; Cole, Turner, Frank, Baker & Leevy, 1969; Hahn, Berguist, Alcorn, Chamberlain & Bass, 1998; Victor et al., 1989; Yamamoto et al., 1981). SR's prior history of poor diet and hemodialysis would place him at risk for thiamine deficiency, and thus the treatment he received between his initial and later testing session (consisting of improved diet and thiamine supplementation) could account for his improved performance on the saccadic tasks. The fact that explicit thiamine replacement began just one day before SR's second testing session is not problematic since it has been shown that dramatic improvement of Wernicke symptoms can occur within hours of thiamine treatment. Furthermore, while his thiamine level was just slightly below the low end of the normal range when it was assessed, SR had been on an improved diet for the four previous weeks (i.e., since his initial hospitalization).

Thus, SR's thiamine level when originally hospitalized, as well as when he was first tested by us, was very likely well below normal.

Inhibition of Return

Despite the improved saccadic performance in the second session, evidence for a continued abnormality of eye movements and attention is shown by SR's performance in the spatial cueing task on Day 2. While SR showed facilitation in responses to stimuli appearing at cued locations for short SOAs, he did not show any inhibition of return. This was true for both saccadic and manual versions of the spatial cueing procedure. We have previously used this exact paradigm with hundreds of subjects (Briand, Larrison & Sereno, 2000; Larrison, Ferrante, Briand & Sereno, 2000), including normal controls as old as 80 years (Briand et al., 2001). We consistently observe robust IOR effects at long SOAs in these subject populations, so SR's performance is highly atypical.[6]

Influence of Specific Lesions

SR's case was not simple, as his lesions were not restricted to the SC. Besides the collicular lesion, SR had lesions of adjacent midbrain areas (periaqueductal gray matter) and of the mediodorsal thalamus (see Figure 1), as well as a small right frontal subcortical lesion and an area of the right cerebellar vermis. We believe, however, that both the lack of IOR and the disrupted performance of reflexive saccades are related to the SC lesion, as we discuss below.

1. Superior Colliculus. Our present findings of deficits in IOR, saccade metrics, and gap effects is consistent with a collicular role in reflexive eye movements. Sapir and colleagues (1999) reported that a unilateral SC lesion eliminated IOR in one hemifield but not the other. Furthermore, Dorris, Klein, Everling, and Munoz (2002) found a reduced sensory response to targets from recordings in the SC of monkeys performing in an IOR task. In the present case a bilateral lesion affected the SC, and IOR was totally eliminated. When considered together with these other results, the present finding that patient SR exhibited no IOR is strong evidence implicating the SC as a necessary component for IOR, and implicates the SC in covert spatial attention in humans. We should also point out that the cueing procedure we used (involving a dual-exogenous cue) may be more sensitive to detection of IOR effects than is the single-cue procedure employed by Sapir et al. in their study (Briand et al., 2000; Sapir, Henik, Dobrusin & Hochman, 2001). That is, in a single cue design, there are several factors that can influence the development of IOR, including voluntary and reflexive processes, making it difficult to be able to identify the defective process when there are differences. For example, Sapir and associates (2001) found an apparent IOR deficit in schizophrenics using a single-cue IOR paradigm. However, when a dual-cue was used (i.e., cue peripheral location and then the fixation point), this deficit was greatly reduced if not eliminated (see also, Larrison-Faucher, Briand &

[6]While IOR is robust with this paradigm, not every subject in a given study will show it. For the study in which we originally reported the control data used here (Briand et al., 2001), 6 of 8 controls showed IOR, and 6 of 7 PD patients showed the effect. While it could be argued that SR's data is merely due to his being one of that minority of individuals who fail to show IOR, we feel this would be an unjustified assumption. The converging evidence in the literature of a SC/IOR connection suggests a more parsimonious explanation, that is, that the collicular damage observed in SR is somehow the cause.

Sereno, 2002). Thus, particularly in clinical populations, a cue-back procedure appears better suited to detecting differences in purely reflexive IOR effects. Our study thus demonstrates a collicular role in IOR and rules out other factors (i.e., a failure to reorient attention away from the cued location) as being the cause of the IOR deficit shown by SR.

SR's saccadic performance is also consistent with collicular involvement. A lesion study in primates carried out by Keating, Kenney, Gooley, Pratt and McGillis (1986) compared the effects of lesions of SC to lesions of the pretectum and mediodorsal thalamus on saccadic performance. Keating et al. found that following each type of lesion the range of saccadic eye movements was severely restricted (10–12 deg at its worst), and more importantly, saccades to targets within the restricted range were hypometric, showing multiple corrective eye movements of the type initially displayed by SR. However, they also reported that disruption of horizontal eye movements *required* damage to the SC, as damage to thalamic areas alone did not affect horizontal saccades. Thus, damage to the SC generated the same type of steplike horizontal saccades that SR showed in the first testing session. Further support for a link between the SC lesion and patient SR's saccadic performance is a case study reported by Heywood and Ratcliff (1975). Heywood et al. tested a patient whose right SC was surgically removed. Their patient showed a significant degree of multistepping during saccades contralateral to the lesion. Thus we feel that the pattern of disrupted, steplike saccades shown by patient SR in the present study strongly implicates the SC.

In another case study of a SC lesion, Pierrot-Deseilligny, Rosa, Masmoudi, Rivaud, and Gaymard (1991) found that a unilateral lesion of the right SC resulted in slowed saccadic RTs to targets contralateral to the lesion as well as reduced gain (they reported no data on corrective saccades). Furthermore, their subject also showed evidence for a reduced ability to inhibit reflexive saccades in both an AS task and a fixation task. This latter result suggests that SC lesions can lead to poor AS performance (i.e., more AS errors), which could have contributed to the intrusion of target-directed saccades when SR was performing the AS tasks in the present study.

Unlike our results with SR, the subject in Pierrot-Deseilligny et al.'s study (1991) showed a gap effect for the saccade task, even for saccades contralateral to the SC lesion. One critical difference between that study and the present one is that our patient's collicular lesion was bilateral. The discrepancy between their result and ours could possibly be accounted for if their subject's performance was mediated by the unaffected left SC, for example if there was a sparing of some fixation neurons which could mediate the gap effect. Finally, Pierrot-Deseilligny, Rivaud, Pillon, Fournier and Agid (1989) also report data from patients with progressive supranuclear palsy (PSP) tested in both gap and overlap paradigms that did show a gap effect.

2. Mediodorsal Thalamus. In the study by Keating and colleagues (1986), they also reported that vertical eye movements could be disrupted by thalamic lesions alone and did not require SC damage. This latter finding is in agreement with human work that suggests that lesions of the mediodorsal thalamus interfere with vertical eye movements but not horizontal eye movements (Deleu, 1997). Thus, patient SR's difficulty with upward and downward gaze, initially noted when he was hospitalized, may be related to his mediodorsal thalamic lesions (thalamic lesions are typically present in WE).

These thalamic lesions may also have affected SR's voluntary AS performance. The mediodorsal thalamic nucleus projects most heavily to the prefrontal regions (Goldman-Rakic & Porrini, 1985; Kievit & Kuypers, 1977; Pandya & Barnes, 1987; Tobias, 1975) that have been shown to be important for antisaccade performance (Doricci et al., 1997;

Goldman-Rakic & Porrini, 1985; Sweeney, Mintun & Kwee, 1996). Hence it is possible that this lesion affected performance on the antisaccade task, in particular contributing to an inability to inhibit erroneous eye movements to the target.

3. Cortical Lesion. SR's cortical lesion was of uncertain origin or age, and even its location provides few clues as to its potential influence on behavior. Thus, its impact on our data cannot be determined.

4. Cerebellar Lesion. We noted a slight hyperdense lesion of the right cerebellar vermis. Unilateral ablations of the vermis in primates have been found to lead to decreased gain for saccades ipsilateral to the lesion (Takagi, Zee & Tamargo, 1998). While this could imply that the multistepping saccades we observed in SR were related to the cerebellar lesion, it is important to point out that we found no evidence of any asymmetry in the distribution of these. In the condition displaying the most disruption (i.e., saccades on Day 1), the frequency of multistepping was equal for saccades to the left and the right (60% in each direction). Based on the data of Takagi et al. (1998), this would not be expected in SR's case if the difficulties with gain were caused by a unilateral lesion of the cerebellar vermis.

Dissociation Between Gap Effect and IOR

A final point raised by our data concerns what could be construed as a dissociation between the gap effect and IOR. On the second day of testing, SR showed a gap effect in the saccade task while he failed to show any IOR. If each of these effects is mediated by the SC, why were they not both absent (or both present)? The gap effect presumably reflects the operation of processes related to *initial orienting* to stimuli (either by covert spatial attention or overtly via saccades), whereas IOR reflects a bias against *re-orienting* to previously attended stimuli or locations. Thus, the data from SR suggests that initial orienting to stimuli may recover more quickly, or be more resilient to damage to the SC, than does the inhibition of re-orienting. One possible explanation could be that the latter inhibitory process is more physiologically or computationally complex, and hence more prone to failure following neural damage. Alternatively, the neural circuitry underlying the gap and IOR effects may be sufficiently distinct that the two do not map entirely onto one another. In summary, the present study showed that both eye movements and covert spatial attention were affected in a person with lesions of the midbrain, including large portions of the SC in particular. This is supportive of the suspected role of the SC in both overt and covert spatial orienting, although the possible influences of other lesions cannot be ruled out entirely. In addition, each of the deficits we reported in this case, with the notable exception of IOR, appeared to be alleviated when patient SR was tested in a follow-up session, which we attribute to treatment of thiamine deficiency. Finally, our data indicate that reflexive eye movements were more disrupted than were voluntary eye movements. This in turn supports the idea that internally and externally guided eye movements can be generated via separable neural systems.

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