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Saccade sequences as markers for cerebral dysfunction following mild closed head injury

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Abstract: Diffuse axonal injury caused by mild closed head injury (CHI) is likely to affect the neural networks concerned with the planning and execution of sequences of memory-guided saccades. Thirty subjects with mild CHI and thirty controls were tested on 2- and 3-step sequences of memory-guided saccades. CHI subjects showed more directional errors, larger position errors, and hypermetria of primary saccades and final eye position. No deficits were seen in temporal accuracy (timing and rhythm). These results suggest that computerized tests of saccade sequences can provide sensitive markers of cerebral dysfunction after mild CHI.

Keywords: Closed head injury; Diffuse axonal damage; Saccades; Memory-guided sequences

Introduction

Closed head injury

Closed head injuries (CHI) are responsible for a vast number of hospital admissions and days of work lost. The annual incidence of mild traumatic brain injury in the United States has been estimated at around 131 cases per 100,000 persons (Kraus and Nourjah, 1988). In addition, Sosin et al. (1996) estimated the yearly rate of mild to moderate brain injury that does not result in institutionalization at 618 per 100,000 persons (1.5 million cases/year in the USA), with most of these being related to head trauma. They stated that 75% of these cases would seek medical attention but only 25% are admitted to hospital. Jennett (1996) reported the annual admission rates for head trauma in Britain at between 210 and 404 per 100,000 and compares this admission rate to numbers of 93–403 per 100,000 in other countries (Australia, France, South Africa, Spain, Sweden, USA). He indicated that around 80% of these admissions were categorized as mild.

The traditional interpretation of the terms 'mild' and 'moderate' CHI includes a brief loss of consciousness in combination with a post-traumatic amnesia (PTA) duration of less than 24 h followed by disturbances of neurological function (Wrightson and Gronwall, 1998). On the Glasgow coma scale (GCS), the most frequently used clinical tool to grade head injury severity, scores between 13 and the maximum of 15 are classified as mild cases, followed by moderate cases with scores between 9 and 12 and severe cases with scores of 8 or less (Richardson, 2000, p. 10).

Alternatively, Jennett and Teasdale, 1981 (p.90) suggested severity grading based on the duration of

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post-traumatic amnesia (PTA). On their scale, a PTA duration of less than 1 h represents mild head trauma with moderate cases showing PTA durations of up to 24 h. However, PTA can be difficult to assess especially in mild head trauma due to ambiguous information from the patients, who combine own recall and second-hand accounts from witnesses or relatives. In contrast to the GCS, a lack of a standardized procedure in obtaining exact information often makes the PTA scale difficult to use in minor head trauma (Richardson, 2000, pp. 84–86) and there has been debate on where to draw the PTA line for mild cases between 1 h and 24 h post-injury (Alexander, 1995; Wrightson and Gronwall, 1998). Accordingly, Crevits et al. (2000), who studied saccades in mild CHI patients, defined mild CHI as having GCS scores of 13–15 with PTA durations of less than 24 h. We have conformed with this definition in the current study.

Most patients with mild to moderate CHI initially show a disturbance of cognitive functions (slowed information processing, lack of concentration, deficits in attention, learning, short-term memory, etc.) combined with symptoms such as headache, fatigue, dizziness, anxiety, irritability, and increased light or sound sensitivity (Slater, 1989; Wright, 1998). Although these complaints tend to resolve within the first few weeks following CHI, a proportion of CHI patients are at risk of developing post-concussion syndrome (PCS), with persistence of quite disabling symptoms for periods of months or even years beyond the first weeks following the injury (Rutherford et al., 1978; Rimel et al., 1981; Mallinson and Longridge, 1998b).

A combination of psychological and structural factors has been discussed as the underlying cause for PCS (Jane and Rimel, 1982; Jane et al., 1985; Bohnen and Jolles, 1992; Watson et al., 1995) and diffuse axonal damage has been suggested as the cause or at least a contributing factor to PCS (Mittl et al., 1994). Wrightson and Gronwall (1998) suggested that the likelihood of developing persisting problems is unrelated to age, gender or cause of accident.

Neural injury arising from CHI

Even mild CHI can cause extensive neural damage throughout the brain. The contemporary view is that a blow to the head sufficient to cause even brief disturbance of consciousness may produce detectable structural brain damage. Levin et al. (1987) reported on CT and MRI scans undertaken on 20 cases of mild or moderate head injury, 6 of which represented mild cases of head trauma. Lesions were detected in 17 out of 20 patients, with the vast majority of these situated in the frontal and temporal lobes.

Fronto-temporal focal lesions frequently occur in combination with non-focal, 'diffuse brain damage' (Bernad, 1991). The initial forces to the head at the time of the injury produce linear and rotational forces, which cause movement of the brain relative to the skull. This rotation of the brain within the skull does not simply produce contusions at the point of contact between the cerebral hemispheres and the cranium but also produces damaging shearing forces within the brain, which decrease in magnitude from the surface of the brain to its centre (Richardson, 2000, pp. 39–57). Even minor CHIs can induce lesions and diffuse axonal damage or axonal stretching as a result of shearing forces at the time of impact. These diffuse lesions are independent of the original site of impact. Diffuse axonal damage has been well documented in humans (e.g. Blumbergs et al., 1989; Sahuquillo et al., 1989; Crooks et al., 1992; Gieron et al., 1998; Lee et al., 1998; Parizel et al., 1998). CT head scans commonly fail to detect these minute neural lesions but MRI frequently demonstrates diffuse axonal injury following CHI, though predominantly in severely head-injured patients (Levin et al., 1989; Zarkovic et al., 1991; Mendelsohn et al., 1992a,b; Paterakis et al., 2000).

Animal studies have confirmed that even minor blows to the head can result in diffuse axonal damage (Povlishock et al., 1983; Jane et al., 1985). Levin et al. (1992) reported intracranial lesions in patients with mild to moderate CHI. Mittl et al. (1994) showed MRI-based evidence of diffuse axonal injury in patients with mild head injury and normal CT head scans. Most of these lesions were located at the grey–white matter junction with some located in deep white matter. The authors considered that these lesions may represent the pathological substrate underlying the post-concussion syndrome associated with deficits in cognitive functioning. Servadei et al. (1994) described a case of a mild head-injured patient with diffuse axonal injury extending into the brainstem.

At a cellular level, most of the neural damage following CHI is triggered by uncoordinated harming responses resulting from the compromised functional integrity of the CNS as well as the disruption of the intra-cellular balances (Armstead, 1999; Knoblach et al., 1999; Trembovler et al., 1999; Vagnozzi et al., 1999; Morrison et al., 2000). The death of damaged neurons also adversely affects undamaged neurons that have synaptic connections with injured nerve cells. The retraction of synaptic terminals causes anterograde and retrograde transneural degeneration of otherwise undamaged neurons (Kandel et al., 1991, pp. 258–263).

Neural damage and eye movements

Anatomical substrates for the planning and execution of saccades include a vast number of cortical and subcortical areas and pathways such as the frontal eye field (FEF), the dorsolateral prefrontal cortex (DLPFC), the supplementary motor area (SMA), the posterior parietal cortex (PPC), the middle temporal area (MT), and the occipital lobe with the striate cortex. Subcortical structures include the thalamus, superior colliculus (SC) and structures in the brainstem. The complexity and the distribution of this network make it vulnerable to functional deficits caused by neural damage resulting from CHI. Frontal areas, such as the FEF play a crucial role in voluntary eye movements, including memory-guided saccades (e.g. Pierrot-Deseilligny et al., 1991b, 1995; Rivaud et al., 1994; Gaymard et al., 1999). The DLPFC contributes to spatial short-term memory (Gaymard et al., 1998a; Ploner et al., 1999) and suppression of saccades (Pierrot-Deseilligny et al., 1991b). The PPC provides an interface between sensory and motor structures (Andersen, 1995; Connolly et al., 2000; DeSouza et al., 2000) and plays an important role in visuospatial orientation (Heide et al., 1995), important for oculomotor and also limb movement coordination. The interdependency of neural activity in the DLPFC and the PPC shown by Chafee and Goldman-Rakic (2000) in memory-guided saccades illustrates the importance of the functional integrity of the entire neural network necessary for proper eye movement function. The SMA is directly involved in planning and execution of intentional eye movements, including the task of memory-guided sequences of saccades (Gaymard et al., 1990, 1993). Sites involved in oculomotor and limb sensory–motor processing are often co-located within these areas, such as SMA or PPC (Picard and Strick, 1996, 1997; Andersen et al., 1998) and can also show functional involvement in higher cognitive processes such as direction of attention, short-term memory, response inhibition and higher information processing, (Roberts et al., 1994; Corbetta et al., 1998; McPeek et al., 1999; Klein et al., 2000; Nieman et al., 2000; Snyder et al., 2000).

It would be reasonable to expect that the neural damage caused by CHI is likely to disrupt the complex neural networks concerned with the planning and execution of eye movements. In particular, the task of memory-guided sequences, which involves most of the anatomical substrates involved in oculomotor control, is well suited to demonstrate the adverse effects of neural injury. Studies on neurodegenerative disorders such as Parkinson's disease (Crawford et al., 1989; Lueck et al., 1992; Vermersch et al., 1994; Hodgson et al., 1999; Blekher et al., 2000; Rivaud-Pechoux et al., 2000) or neurological disorders such as Tourette's Syndrome (Straube et al., 1997; LeVasseur et al., 2001) have demonstrated the adverse effects of neural dysfunction on oculomotor processing using single memory-guided saccades and memory-guided sequences. Brain lesions caused by infarction have also been shown to affect the planning and execution of memory-guided saccades, including memory-guided sequences (Gaymard et al., 1990, 1993, 1998b, 1999; Pierrot-Deseilligny et al., 1991b; Vermersch et al., 1999).

Closed head injury and eye movements

Only limited attention has been paid to eye movements following CHI. Williams et al. (1997) found saccade deficits in 16 patients with severe traumatic head injury (mean PTA of 43.7 days). Their findings included prolonged latencies of reflexive saccades, antisaccades and simple memory-guided saccades, smaller numbers of self-paced saccades, hypometria of reflexive saccades and increased response errors on antisaccades and simple memory-guided saccades. Glass et al. (1995) reported 'impersistent' execution of saccades in nine moderate–severely head-injured patients (coma duration 1 to 20 days) in

terms of number of saccades initiated within 500 ms of stimulus presentation and falling within 50% of the expected target amplitude. Mulhall et al. (1999) studied bedside examinations of antisaccades, single memory-guided saccades and self-paced saccades in a group of 19 cases of head trauma and detected a significant difference only in a lower number of self-paced saccades in the head-injured group. They compared their findings to results from infrared oculographic tests of saccades and concluded that bedside tests of saccades have only limited value in patients with head trauma. Crevits et al. (2000) found no abnormalities of single remembered saccades and antisaccades in 32 patients with mild CHI. Conversely, Mosimann et al. (2000) reported increased latencies and larger position errors in addition to increased response errors on single memory-guided saccades and antisaccades in whiplash patients with persisting symptoms.

Based on evidence of widespread axonal damage in mild CHI (see above) we considered that oculomotor function should be impaired in many cases of mild CHI, despite such deficits not being evident on clinical examination. Although studies on eye movement deficits in neuro-degenerative diseases have shown the utility of sequences of memory-guided saccades to detect adverse effects of neural damage (see above), this study is the first to use this paradigm in the context of head trauma. This study was part of a larger project incorporating tests for eye and upper-limb movements in combination with neuropsychological testing following mild head trauma. We wished to establish whether the expected deficits in oculomotor function would be sufficiently substantial to warrant a prospective study relating motor deficits with the recovery following mild CHI.

Methods

Participants

The study aimed at including mild and moderate cases of CHI, although the final CHI group comprised only mild cases of CHI. Inclusion criteria were: aged 15 to 40 years, documented CHI within the previous 2 days, Glasgow coma scale (GCS) score between 9 and 15, disturbance of consciousness (e.g., stunned or loss of consciousness) of less than 20 min, post-traumatic amnesia (PTA) of less than 24 h, and adequate command of the English language.

Exclusion criteria were: influence of alcohol or psychoactive drugs at time of injury, regular intake of psychoactive drugs or medication, history of current central neurological disorders or presence of a psychiatric condition, evidence of structural brain damage or hematoma on CT head scan (if available as part of the clinical assessment, seven participants had received a CT head scan), oculomotor deficits upon clinical examination, presence of strabismus, skull fractures (including jaw and facial fractures), or past history of severe head injury.

The final CHI group comprised 30 subjects. Causes: rugby (13), motor vehicle accidents (7), horse riding (2), bicycle accidents (2), hit by cricket ball (1), hit by soccer ball (1), assault (1), work accidents (1) and other causes (2). The mean age for the patient group ($N = 30$) was 22.2 years (SD 7.1, range 15–37). The patient mean for years of education was 12.8 (SD 1.86). All patients had a GCS score between 13 and 15 (13: 2 cases; 14: 5 cases; 15: 23 cases). Twenty-five patients had a confirmed loss of consciousness (mean = 2.56 min, SD = 3.27). The duration of the post-traumatic amnesia ranged from 3 min to 4 h (mean = 34.4 min, SD = 60.6). All patients completed the tests within 9 days of their injury (mean 4.2, SD 1.8, range 2–9 days).

The control group consisted of subjects with no prior history of moderate or severe CHI, no current central neurological disorder or psychiatric condition, and no regular intake of psychoactive drugs or medication. The controls were matched to the CHI group with respect to age ($\leq \pm 3$ years for subjects >18 years, $\leq \pm 1$ year for participants <18 years), gender and educational background (years of education, ± 2 years for participants >18, $\leq \pm 1$ year for subjects <18). Over 50% of the control group was recruited from friends or siblings of CHI patients. The mean age for the control group was 22.4 years (SD 7.0, range 15–37). The control mean for years of education was 13.2 (SD 2.1).

Apparatus

Eye movements were recorded using the infra-red scleral reflection oculography technique (Reulen et

al., 1988, IROG, Skalar Medical, The Netherlands). Eye position signals were low-pass filtered at 100 Hz, sampled and digitized at 200 Hz, displayed on the operator's computer screen, and recorded on disk for off-line analysis.

Subjects were seated in a darkened room with head movements restrained by a bite bar. Eye movements were generated using a horizontal LED bar 1.5 m in front of the subject. Calibration for each eye was obtained before each test. The tests were generated and recorded by a PC running the *EMMA* (eye movement measurement and analysis) program (Muir et al., 2001).

Saccadic sequences paradigm

A central fixation LED appeared for 2000 ms and then jumped to a pre-defined number of successive horizontal eccentric positions 5° or 15° on either side of the central fixation point, 1000 ms for each position and with the final sequence position always being the centre fixation LED. Subtest A comprised six different sequences with two eccentric target positions (i.e., 2-step sequences) and three practice repetitions per sequence. Subtest B comprised six different sequences with three eccentric target positions (i.e., 3-step sequences) and five practice repetitions per sequence (Fig. 1). During practice, a buzzer sounded coincident with each target relocation. After the last target was extinguished, the subject had to repeat the sequence in darkness and without the buzzer, as accurately as possible in terms of the position and timing of the sequence. Before the start of subtest A, subjects were exposed to a rehearsal sequence to familiarize themselves with the test.

Key measures were the number of directional errors, the number of saccades per step, gain of the primary saccade (G_p), gain of the final eye position (G_f) and the mean position error (PE) for all steps throughout each sequence. Gains and position error for each step were calculated as

$$G_p = EP_p/SP$$
$$G_f = EP_f/SP$$
$$PE = |(EP_f - SP)/SP| \times 100$$

where EP_p is the eye position after the primary saccade, EP_f is the final eye position and SP is the

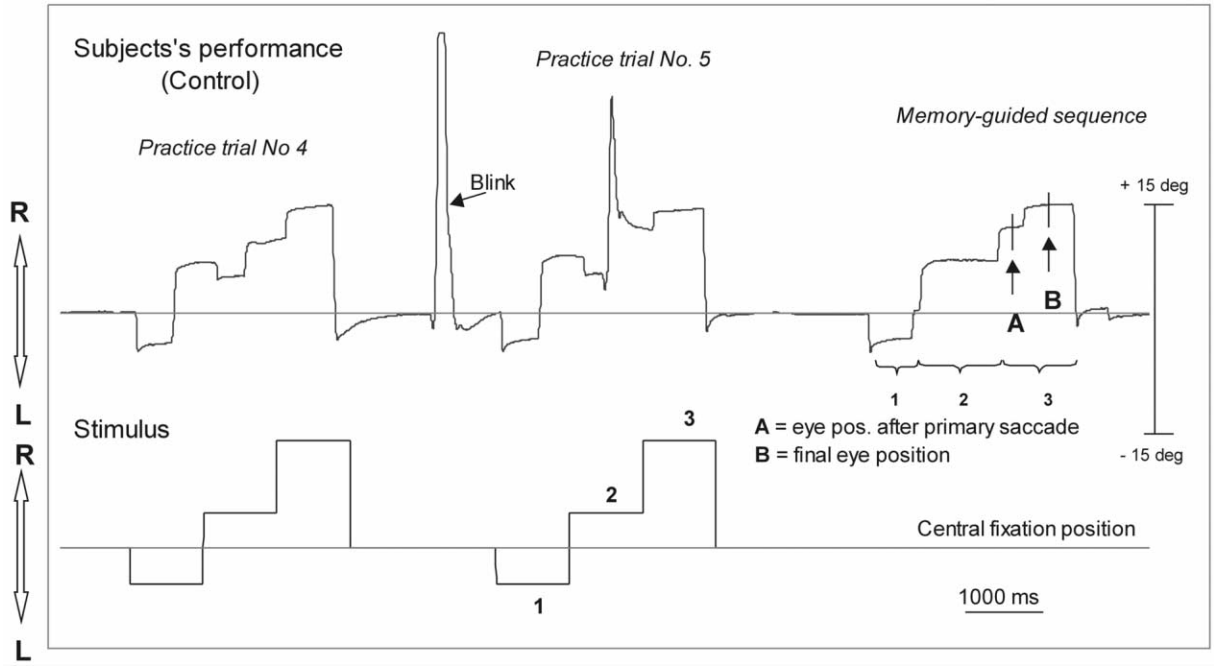

Fig. 1. Paradigm for memory-guided sequences of saccades (subtest B, 3-step sequence)

stimulus position. The mean position error for a sequence j was calculated as

$$\text{Mean PE}_{\text{sequence}\,j} = (\text{PE}_{\text{step1}\,j} + \text{PE}_{\text{step2}\,j} + \ldots + \text{PE}_{\text{step}nj})/n$$

An amplitude error was also derived. This approach was based on the view that a sequence of saccades could be perceived as a motor pattern rather than a sequence of locations in 3-dimensional space (Ditterich et al., 1998). That is, the subject is considered to store a sequence of motor commands rather than the independent target positions themselves. This motor pattern of amplitudes and rhythm would then be performed as a series of motor commands independent from spatial validation. The amplitude error represents the deviation (%) from the expected amplitude per step, based on the final amplitudes. The amplitude error (AE) for a step k was calculated as

$$\text{AE step}_k = \frac{|(\text{EPf step}_k - \text{EPf step}_{k-1})| - |(\text{SP step}_k - \text{SP step}_{k-1})|}{|(\text{SP step}_k - \text{SP step}_{k-1})|} \times 100$$

The mean amplitude error for a sequence j was calculated as

$$\text{Mean AE}_{\text{sequence}\ j} = (\text{AE}_{\text{step1}\,j} + \text{AE}_{\text{step2}\,j} + \ldots + \text{AE}_{\text{step}nj})/n$$

The absolute time index (ATI) served as a measure of the subject's overall timing.

$$\text{ATI} = T_\text{r}/T_\text{s}$$

where T_r is the subject's total response time, T_s is the duration of the sequence.

The inter-response interval (IRI) served as a measure for the subject's ability to maintain a constant rhythm during a sequence. The IRI for a particular step k was calculated as

$$\text{IRI}_k = T_{rk}/T_\text{r} - T_{sk}/T_\text{s}$$

where T_{rk} is the subject's response time for step k and T_{sk} is the stimulus presentation time for step k. The proportion of one particular step within the whole performance is compared its expected proportion (subtest A: $T_{sk}/T_\text{s} = 0.5$; subtest B: $T_{sk}/T_\text{s} = 0.333$), as all stimulus steps are exactly 1.0 s long. Therefore, subjects with a total performance time of, for example, 1.8 s and individual steps of 0.6 s duration would still have a perfect rhythm within their performance. The mean IRI for a sequence j was calculated as

$$\text{Mean IRI}_{\text{sequence}\ j} = (\text{IRI}_{\text{step1}\,j} + \text{IRI}_{\text{step2}\,j} + \ldots + \text{IRI}_{\text{step}nj})/n$$

Data analysis

Analysis of the eye movement data used analysis options provided in the *EMMA* program (Muir et al., 2001). Results were then analyzed statistically using *Statistica* (© Statsoft). The data were shown to have differences in variances between the groups, and skewed distributions on most measures. Hence, a non-parametric Wilcoxon Matched-Pairs statistic was used for between-group comparisons. Differences between groups were considered significant for p-values of ≤ 0.05. The analysis comprised 30 matched pairs. ANOVA was used to compare saccade subsets of different amplitudes (5, 10, 15, 20 and 30°), based on the pooled saccades per group for each amplitude tier, independent of the place of particular amplitude steps within sequences.

In the following results, the values presented of PE, AE, G_p, G_f, ATI, IRI, response errors and numbers of saccades are the means of the above values over all sequences in the particular subtest.

Results

Response errors (directional errors)

The CHI group showed a significantly higher number of response errors (directional errors) in the longer sequences of memory-guided saccades (subtest B, three steps, 10.4% vs 2.6%, $p = 0.003$, Table 1), but no difference for short sequences (subtest A, two steps, 4.2% vs 1.7%, $p = 0.183$, Table 1). This likely reflects a relationship between cognitive load and tendency for error.

Number of saccades per sequence

Both groups took, on average, the same number of saccades to reach the final performance (Table 1).

TABLE 1

Saccadic performance — errors, accuracy, timing, number of saccades

Measure		CHI ($n = 30$)		Controls ($n = 30$)		Difference		p-level
		Mean	SD	Mean	SD	Absolute	(%)	
Directional errors (%)								
Subtest A (2 steps)		**4.2**	9.0	**1.7**	5.5	2.5	151	0.183
Subtest B (3 steps)		**10.4**	11.5	**2.6**	5.2	7.8	300	0.003
Accuracy								
Primary saccade gain (G_p):								
Subtest A (2 steps)		**1.06**	0.24	**0.97**	0.14	0.09	9	0.115
Subtest B (3 steps)		**1.11**	0.30	**0.96**	0.18	0.15	16	0.019
Gain final eye position (G_f):								
Subtest A (2 steps)		**1.25**	0.24	**1.12**	0.14	0.13	12	0.020
Subtest B (3 steps)		**1.35**	0.42	**1.13**	0.20	0.22	19	0.016
Position error (PE, %):								
Subtest A (2 steps)		**40**	21	**26**	17	14	53	0.001
Subtest B (3 steps)		**57**	45	**33**	17	24	73	0.006
Amplitude error (AE, %):								
Subtest A (2 steps)		**30**	18	**19**	10	11	59	0.016
Subtest B (3 steps)		**43**	27	**26**	16	17	65	0.005
Absolute time index (ATI)								
Subtest A (2 steps)		**1.11**	0.21	**1.13**	0.15	−0.02	2.1	0.585
Subtest B (3 steps)		**1.01**	0.13	**1.02**	0.12	0.01	0.6	0.765
Inter-response interval (IRI)								
Subtest A (2 steps)		**0.1**	0.05	**0.09**	0.04	0.011	12.5	0.130
Subtest B (3 steps)		**0.09**	0.04	**0.08**	0.03	0.011	14.6	0.158
Number of saccades								
Subtest A	step 1	**1.61**	0.53	**1.63**	0.49	0.02	1.2	0.674
	step 2	**2.93**	0.55	**2.8**	0.54	0.13	4.6	0.344
Subtest B	step 1	**1.56**	0.45	**1.43**	0.38	0.13	9.1	0.200
	step 2	**1.58**	0.39	**1.61**	0.38	0.03	2.1	0.981
	step 3	**3.03**	0.65	**2.91**	0.53	0.11	3.8	0.537

Spatial accuracy

The CHI group showed significantly poorer spatial accuracy on final eye position as measured by the position error (subtest A, two steps, 40% vs 26%, $p = 0.001$, Table 1; subtest B, three steps, 57% vs 33%, $p = 0.006$, Table 1). The comparison of individual steps of subtest A and B showed larger position and amplitude errors of the CHI group on all steps (Table 2). Following the split into different saccade amplitudes (5, 10, 15, 20 and 30°) these differences in position error were significant for 10, 15 and 20° amplitudes (Table 3). Increased position errors were mostly matched by abnormally large saccadic gains. The CHI group had hypermetric responses in both subtest A (final gain 1.25 vs 1.12, $p = 0.02$) and subtest B (final gain 1.35 vs 1.13, $p = 0.016$; primary saccade gain 1.11 vs 0.96, $p = 0.019$). These results remained in most cases following the split into either individual sequence steps as well as separate amplitude tiers (Tables 2 and 3). The hypermetria was more pronounced for smaller target amplitudes with group differences in primary saccade gain of 27% (5° amplitudes) and 20% (10° amplitudes), whereas for 30° amplitudes this difference had narrowed to about 3.4% (Table 3), indicating an inverse relationship between amplitude size and magnitude of position errors. A similar trend existed for the gain of the final eye position, with differences of around 27% for 5 and 10° amplitudes and of about 3.9% for 30° steps.

TABLE 2
Saccadic performance — position error and mean gains per individual steps

Measure	CHI ($n = 30$)		Controls ($n = 30$)		Difference		p-level
	Mean	SD	Mean	SD	Absolute	(%)	
Remembered sequences (subtest A)							
Position error (PE, %):							
Step 1	**31.96**	21.49	**19.98**	10.78	11.98	59.96	0.020
Step 2	**46.47**	23.55	**30.83**	17.53	15.64	50.73	0.003
Amplitude error (AE, %):							
Step 1	**31.96**	21.49	**19.98**	10.78	11.98	59.96	0.020
Step 2	**28.76**	15.77	**18.33**	11.05	10.43	56.90	0.013
Primary saccade gain (G_p):							
Step 1	**1.01**	0.29	**0.92**	0.17	0.09	9.78	0.089
Step 2	**1.10**	0.27	**1.01**	0.22	0.09	8.91	0.184
Gain final eye position (G_f):							
Step 1	**1.21**	0.26	**1.08**	0.15	0.13	12.04	0.030
Step 2	**1.29**	0.3	**1.16**	0.21	0.13	11.21	0.028
Remembered sequences (subtest B)							
Position error (PE, %):							
Step 1	**38.33**	22.3	**26.61**	17.1	11.72	44.04	0.011
Step 2	**67.27**	48.3	**42.61**	20	24.66	57.87	0.000
Step 3	**48.98**	38.5	**28.18**	21	20.80	73.81	0.010
Amplitude error (AE, %):							
Step 1	**38.33**	22.3	**26.61**	17.1	11.72	44.04	0.011
Step 2	**39.36**	24.9	**24.45**	13.6	14.91	60.98	0.014
Step 3	**48.73**	34.5	**26.13**	16.3	22.60	86.49	0.003
Primary saccade gain (G_p):							
Step 1	**1.06**	0.23	**0.92**	0.23	0.14	14.85	0.009
Step 2	**1.24**	0.48	**1.06**	0.30	0.18	16.71	0.125
Step 3	**1.07**	0.33	**0.91**	0.24	0.16	17.16	0.044
Gain final eye position (G_f):							
Step 1	**1.25**	0.26	**1.04**	0.24	0.21	19.74	0.002
Step 2	**1.44**	0.60	**1.23**	0.30	0.22	17.51	0.171
Step 3	**1.33**	0.41	**1.12**	0.24	0.21	18.41	0.020

Temporal accuracy (timing and rhythm)

No difference was found on the absolute time index (subtest A: 1.11 vs 1.13, $p = 0.585$, Table 1; subtest B: 1.01 vs 1.02, $p = 0.77$, Table 1). In addition, the ability to keep a steady rhythm within the sequence was not impaired in the CHI group, as evidenced by similar mean inter-response intervals (subtest A: 0.1 vs 0.09, $p = 0.13$, Table 1; subtest B: 0.09 vs 0.08, $p = 0.16$, Table 1).

Discussion

The results indicate that mild CHI can adversely affect the performance of memory-guided sequences of saccades, despite there being no oculomotor deficits on clinical examination. The CHI group showed increased directional errors and impaired spatial accuracy with abnormal hypermetria but no impairments on timing, rhythm or number of saccades per sequence.

Our study is the first to examine memory-guided sequences following head trauma, in contrast to earlier studies which included only tests of single memory-guided saccades (Williams et al., 1997; Crevits et al., 2000; Mosimann et al., 2000). The study of Crevits et al. (2000) is of particular interest, as they incorporated patients with mild CHI only and found no deficits in latencies or response errors in single memory-guided saccades. Their selection cri-

TABLE 3
Accuracy of memory-guided sequences (subtest B) keyed by amplitude (pooled saccade populations)

Amplitude	CHI ($n = 30$)		Controls ($n = 30$)		Difference		p-level
	Mean	SD	Mean	SD	Absolute	(%)	
Position error (PE, %):							
5°	**52.20**	51.08	**37.03**	52.42	15.16	40.95	0.062
10°	**70.84**	85.17	**39.82**	43.95	31.02	77.90	0.000
15°	**25.59**	28.22	**17.13**	14.70	8.46	49.39	0.013
20°	**51.17**	75.57	**34.48**	38.48	16.69	48.40	0.019
30°	**35.18**	32.09	**25.90**	28.37	9.28	35.84	0.103
Primary saccade gain (G_p):							
5°	**1.26**	0.57	**0.99**	0.64	0.27	27.12	0.005
10°	**1.19**	0.79	**0.99**	0.55	0.20	20.14	0.015
15°	**0.87**	0.35	**0.85**	0.26	0.02	2.73	0.618
20°	**1.17**	0.82	**1.00**	0.49	0.17	16.75	0.037
30°	**0.99**	0.46	**0.96**	0.35	0.03	3.35	0.672
Gain final eye position (G_f):							
5°	**1.42**	0.60	**1.12**	0.63	0.30	26.89	0.002
10°	**1.50**	0.99	**1.19**	0.56	0.32	26.65	0.001
15°	**1.09**	0.37	**0.97**	0.22	0.12	12.35	0.010
20°	**1.34**	0.85	**1.20**	0.48	0.13	10.89	0.108
30°	**1.13**	0.46	**1.09**	0.37	0.04	3.86	0.591

teria were similar to our own (GCS 13–15, PTA < 24 h, impaired consciousness) and eventually comprised 25 non-intoxicated mild CHI patients. However, all cases had the maximal GCS score of 15, only 15 had lost consciousness, none exceeded a PTA of 1 h (the mean PTA was not indicated), and 7 patients had no PTA at all. Consequently, it is unclear whether their finding of no oculomotor deficits was due to their having a substantially milder group than our own or was because single memory-guided saccades are less susceptible to the effects of mild CHI than memory-guided sequences. Similar to our findings, Mosimann et al. (2000) found an increased number of unwanted reflexive saccades (response errors) as well as increased position errors on single memory-guided saccades in whiplash patients with persisting symptoms. Whiplash injuries frequently have similar causes to CHI and can occur concomitantly in some cases, especially after motor vehicle accidents. Although the locations of damage can differ from CHI, symptoms are similar to those occurring after mild CHI and can persist for up to several years (Mallinson and Longridge, 1998a,b).

In our study, increased position errors occurred mainly in the form of a pronounced hypermetria (see Tables 1 and 2). Higher position errors on the CHI side were matched by increased amplitude errors on all steps in subtest A and subtest B (Table 2), indicating that deficits in accuracy were not only based on independent errors in spatial accuracy but on the decreased ability of the CHI patients to accurately program and execute a learned motor sequence or motor program. This also implies that the CHI group was less able to benefit from corrective movements to subjectively perceived errors in amplitude.

Ohtsuka et al. (1989) stated that position errors of more than 5° in single memory-guided saccades tend to be followed by a corrective saccade. Ditterich et al. (1998) also discussed the subject's tendency to correct perceived errors with corrective saccades in sequences of memory-guided saccades. We compared the degree to which our groups made a corrective saccade towards the expected target position during the sequences (i.e., the tendency to go further if they had undershot the expected amplitude or to go back if their primary saccade had gone too far). We found that both groups made secondary corrective saccades in the 'correct' direction in about 64% of all saccades (CHI 63.3% vs controls 65.8%), indicating that both groups tended to perceive errors

equally well but with the controls being far more able to maintain an accurate performance throughout the sequence. We did not, however, assess the mean magnitude of these corrective movements. Bock et al. (1995) calculated that about 60% of a position error would be corrected and considered this correction mechanism as evidence for the existence of extraretinal inputs to the saccadic generator, which are used to maintain an accurate motor performance. Thus, the deficits found in our CHI group in the memory-guided sequences could be due to difficulty in accurately storing a sequence of saccades, memorizing a faulty motor program, or erroneous input of extraretinal information leading to ineffective correction of perceived errors. Interestingly, there was no difference in the number of saccades in any of the steps of the memory-guided sequences. Similarly, Williams et al. (1997) found no difference in the average number of saccades in single memory-guided saccades in severely head-injured patients.

Hypermetria of memory-guided saccades executed in darkness has been reported (Zingale and Kowler, 1987; Israel, 1992; in Petit et al., 1996). Ohtsuka et al. (1989) also noted that initial memory-guided saccades tend to overshoot the expected amplitude and are frequently followed by a corrective saccade, especially when the position errors exceed 5°. They further suggested a negative correlation between target amplitude and size of position error (amplitude of 20°: position error $= 7.7 \pm 5.4°$; 40°: $5.8 \pm 4.5°$; 60°: $6.7 \pm 4.3°$; 80°: $3.2 \pm 3.3°$) which is consistent with the results from our control group showing similar position errors, as well as the CHI group, although with increased position errors. In contrast to the reports of hypermetria in memory-guided saccades in normal subjects, Ploner et al. (1999) observed hypometria in memory-guided saccades in patients with unilateral ischaemic lesions to the frontal eye field (FEF) and the dorsolateral prefrontal cortex (DLPFC). Crawford et al. (1989) reported hypometria in single memory-guided saccades in patients with idiopathic Parkinson's Disease. Similarly, Vermersch et al. (1994, 1999) reported hypometria in single memory-guided saccades in Parkinsonian patients and a patient with a caudate nucleus lesion. Hodgson et al. (1999) found hypometria in sequences of memory-guided saccades in patients with mild to moderate Parkinson's Disease and suggested the disruption of short-term spatial memory representations as underlying cause for the observed saccade deficits.

Cerebral lesions as cause for impaired saccade sequences after mild CHI

It is likely that the deficits in performance of memory-guided sequences are the result of neural damage, which can follow even mild cases of head trauma (e.g. Mittl et al., 1994). The deficits on memory-guided sequences indicate that the proper functioning of the corresponding networks of cortical and subcortical structures was disrupted by mild CHI. The consequent functional impairments likely affected the ability to accurately store or retrieve spatial information as well as the capacity to efficiently program a motor sequence and to relay the motor commands to the eyes.

However, as MRI scanning was not available for this study, we are unable to quantify or localize the extent of neural damage in the patients. Consequently, there is uncertainty about the factor composition triggering the impaired motor output, that is, the question of whether cortical dysfunction or damage to subcortical pathways was primarily responsible for the observed deficits.

The non-focal character of diffuse axonal injury (DAI), in combination with the heterogeneous functional structure of the oculomotor system, makes it difficult to assign eye movement deficits in response accuracy or spatial accuracy in our CHI group to distinct or specific cerebral regions. However, the impaired CHI performance on sequences of memory-guided saccades suggests impaired function of the SEF/SMA in combination with deficits originating in the PEF/PPC, FEF and DLPFC (Pierrot-Deseilligny et al., 1991b; Anderson et al., 1994; Gaymard et al., 1999), as demonstrated by decreased spatial accuracy and increased response errors.

Considerable evidence is available to demonstrate that lesions affecting the proper function of certain cortical areas impair eye movements (e.g. Guitton et al., 1985; Gaymard et al., 1990, 1993; Pierrot-Deseilligny et al., 1991a,b, 1991c; Thier et al., 1991; Keating, 1993). Lesions of PPC, FEF and DLPFC impair single remembered saccades (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991b), whereas se-

quences of remembered saccades are impaired following lesions of the SMA (Gaymard et al., 1990, 1993), and also the hippocampal formation (Muri et al., 1994a). Muri et al. showed that transcranial magnetic stimulation over the SMA (Muri et al., 1994b, 1995) and the PPC (Muri et al., 1996) adversely affected sequences of memory-guided saccades and single memory-guided saccades with increased errors in amplitude and prolonged latencies. PET studies (Anderson et al., 1994; O'Sullivan et al., 1995; Sweeney et al., 1996) confirm the contribution of the SMA to memory-guided saccades but also support the participation of other areas such as FEF, DLPFC, thalamus or PPC. Research in monkeys confirms the importance of the PPC, in particular the left lateral bank of the intraparietal sulcus for saccade-related sensory–motor transformation in memory-guided saccades (Gnadt and Andersen, 1988; Gnadt et al., 1991). Neural damage to the PPC or its connections with the SC might have contributed to inaccurate memory-guided saccades in the CHI group, although there are indications that inaccuracies of memory-guided saccades can have their origin downstream from the SC (Stanford and Sparks, 1994). The DLPFC contributes to spatial short-term memory (O'Sullivan et al., 1995; Gaymard et al., 1998a) and accuracy of memory-guided saccades is impaired by transcranial magnetic stimulation over the DLPFC (Brandt et al., 1998). Walker et al. (1998) reported impairments of spatial working memory and executive functioning in a patient with lesions to the prefrontal cortex. In general, the FEF and the DLPFC play an important role in the generation and suppression of voluntary saccades (Guitton et al., 1985; Pierrot-Deseilligny et al., 1995; Ploner et al., 1999), including memory-guided saccades. Sakai et al. (1998) pointed out the importance of frontal areas such as the DLPFC and the pre-SMA for visuomotor sequence learning, which also involves a shift from activation of frontal areas in early learning stages to mainly parietal areas in later stages. These findings support the argument that neural dysfunction originating in frontal and pre-frontal cortical areas may have contributed to the saccade deficits of the CHI group.

It has been shown that most of the diffuse neural damage is located at the grey and white matter junction (Mittl et al., 1994), in some cases extending into the deeper white matter and the brainstem. Important relay pathways within the oculomotor and sensory–motor networks pass through these areas. Diffuse axonal injury (DAI) may cause the disruption of motor network pathways important for intra-cerebral communication and information relay to motor neurons. Several studies on primates and other animals have demonstrated such connections (Tusa and Ungerleider, 1988; Leichnetz, 1989; Andersen et al., 1990; Tian and Lynch, 1996). PET and MRI studies have also helped illuminate the functional anatomy of motor processing in humans, showing that their motor networks involved in oculomotor coordination are in general comparable to the findings from non-human primates (Anderson et al., 1994; Kawashima et al., 1995, 1998). The oculomotor network involves, amongst others, projections from the PPC to the frontal cortex (PEF to FEF/SEF), connections between FEF/SEF and the intramedullary lamina of the thalamus, the SC and the cerebellar vermis in addition to separate projections form the PPC (PEF) to the SC, and direct pathways from the frontal cortex to the saccade generators in the brainstem. Chafee and Goldman-Rakic (2000) found an interdependency of neural activity in the DLPFC and the PPC in memory-guided saccades which underlines the suggestion of considerable intra-cerebral communication and the importance of the corresponding neural pathways for the relay of information and motor commands. Electrophysiologal studies in monkeys (Everling et al., 1999; Everling and Munoz, 2000) have shown that neural activity in cortical areas such as the FEF is closely correlated to neural activity in the SC and the saccadic burst neurons in the brainstem, showing that cortical areas directly regulate neural activation patterns in lower regions (Dorris et al., 1997; Dorris and Munoz, 1998; Everling et al., 1999). Eye movement deficits are to be expected should the functional integrity of the corresponding neural pathways be compromised, as is often the case in CHI.

The subjects were also assessed on several neuropsychological tests with high cognitive loads. The complete neuropsychological data are the subject of a separate publication (in preparation). In essence, the CHI group showed deficits on several of these tests including the Paced Auditory Serial Addition Task, Trail Making Test B, Single Digit Modali-

ties Test, the California Verbal Learning Test, and two subtests of the Wechsler Abbreviated Scale of Intelligence, the Vocabulary Test and Matrix Reasoning. However, we found very few correlations between neuropsychological test results and measures of memory-guided sequences of saccades. This lack of association suggests that the deficits on memory-guided sequences of saccades may incorporate additional aspects of cerebral dysfunction following mild CHI, which appear to be independent from cognitive functions assessed by neuropsychological testing.

The present observation of abnormalities of sequences of memory-guided saccades in combination with reports of deficits on antisaccades and self-paced saccades (Heitger et al., 2001a) as well as impairment of upper-limb sensory–motor function following mild CHI (Heitger et al., 2001b) presents a picture of widespread impairment of motor functions originating in the frontal and the parietal cortex. This picture is consistent with the results of research on the biomechanics of CHI (Wilson, 1990; Ommaya, 1995) and previous studies incorporating neuropsychological testing (Levin et al., 1987, 1992; Mattson and Levin, 1990; Duncan et al., 1997), showing that damage seems to occur mostly in frontal and fronto-temporal parts of the brain, leaving occipital areas and the cerebellum largely unharmed. Further support for this view is the finding that oculomotor smooth pursuit is largely preserved following mild CHI (Heitger et al., 2001a), suggesting that occipital areas and the cerebellum seem to be less affected in mild CHI. Further, the cerebellar vermis mediates the subconscious saccadic adaptation of reflexive saccades (Desmurget et al., 2000), which is unaffected by mild CHI (Heitger et al., 2001c). The absence of deficits on timing and rhythm (i.e., temporal accuracy) on memory-guided sequence performance in our experiment would also appear consistent with this suggestion, as these functions are at least in part mediated by the cerebellum (Ivry et al., 1988).

Concluding remarks

Results from our study indicate that, although oculomotor function may appear normal on clinical examination, mild CHI can cause deficits in the performance of memory-guided sequences of saccades. It is likely that these deficits are caused by neural damage resulting from diffuse cerebral lesions. The observed abnormalities indicate dysfunction originating in frontal and dorso-parietal cortical areas either through direct cortical lesions or through damage to neural pathways originating in or connecting these areas.

Our results suggest that abnormalities of memory-guided saccades may provide sensitive markers of impaired neurophysiological functioning after mild CHI. The deficits on memory-guided sequences add to other evidence of altered motor function following mild CHI, such as impairments of antisaccades, self-paced saccades, and aspects of upper-limb sensory–motor performance. The findings indicate a potential use for computerized eye movement tests to supplement clinical and neuropsychological patient assessment following mild head trauma.

It will be important to determine how soon the deficits in saccades resolve following injury, and whether there is a correlation with the persistence of symptoms and the development of post-concussion syndrome (PCS), as there is currently no accurate mean to determine the likelihood of developing PCS in a patient with mild or moderate CHI.

Abbreviations

ATI	absolute time index
CHI	closed head injury
CT	computer tomography
DAI	diffuse axonal injury
DLPFC	dorsolateral prefrontal cortex
EMMA	eye movement measurement and analysis
FEF	frontal eye field
GCS	Glasgow coma scale
IRI	inter-response interval
LED	light emitting diode
MRI	magnetic resonance imaging
MT	middle temporal area
PCS	post-concussion syndrome
PEF	parietal eye field
PET	positron emission tomography
PPC	posterior parietal cortex
PTA	post-traumatic amnesia
SC	superior colliculus
SD	standard deviation
SEF	supplementary eye field
SMA	supplementary motor area

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QUERIES:

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