ENDURING DYSMETRIA AND IMPAIRED GAIN ADAPTIVITY OF SACCADIC EYE MOVEMENTS IN WALLENBERG’S LATERAL MEDULLARY SYNDROME

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SUMMARY

Saccadic eye movements and the adaptive control of their amplitudes were examined in patients with Wallenberg’s lateral medullary syndrome. Half of the patients had permanent saccadic dysmetria. Their primary saccades had asymmetric amplitudes: those made in response to an ipsilateral target step (i.e. to the lesion side) tended to be hypermetric and saccades made in response to a contralateral target step were strongly hypometric. Multiple correction saccades were needed for target fixation.

The adjustment of the amplitude of artificially induced hypermetric saccades, called gain adaptivity, was examined experimentally by using double target steps. The first target step elicited the primary saccade which triggered a further target displacement. This second, intra-saccadic target displacement was opposite to the first target step and caused the primary saccade to overshoot the final target position. In this way a post-saccadic target position error was generated which had to be corrected for foveal fixation. With repetition of this stimulus sequence the saccadic control system of normal subjects made an adjustment in amplitude of the main saccade such that the overshooting gradually diminished. After a few hundred trials primary saccades became orthometric with respect to the final target position; in respect to the first target step they were, however, strongly hypometric. The experimental data show that patients with Wallenberg’s syndrome had a reduced capability to readjust saccadic amplitude. This observation together with the enduring saccadic dysmetria suggest that adaptive gain control of saccades is impaired in patients with lesions restricted to the dorsolateral medulla. It is speculated that these lesions most likely disrupt olivo-cerebellar pathways which are believed to be of paramount importance in visuo-motor adaptation of the cerebellum.

INTRODUCTION

Rapid eye movements used to change the direction of sight are called saccades. A prominent feature of the saccadic system is the velocity and precision of saccades in attaining a target permitting good visual acuity. Saccades are so fast that the nervous system is unable to use visual feed-back to improve their execution. The saccadic system operates in a preprogrammed open-loop fashion and is therefore more sensitive to external and internal disturbances than a system which is controlled by a continuously operating feed-back loop. If errors in acquiring a target occur regularly and consistently, an adaptive mechanism is desirable which detects inappropriate saccadic performance and which recalibrates sensory input-motor output by incorporating error information in the motor program (Miles, 1983). Evidence for rapid and slow adaptive processes by which the
brain maintains optimal oculomotor performance has been accumulating and the most important source of error signal to detect poor performance is visual experience (Henson, 1978; Optican, 1985; Optican and Miles, 1985; Deubel et al., 1986; Optican et al., 1986; Optican et al., 1986; for overview see Berthoz and Melvill Jones, 1985). Where and how the adaptive control or saccadic trajectory occurs is unknown but the cerebellum has been linked to the adaptive control or ‘self-repair’ of eye movement parameters (Ito, 1972; Robinson, 1975; Optican and Robinson, 1980).

In normal subjects, primary or main saccades slightly undershoot a fixation target; overshooting very rarely occurs. A correction saccade in the direction of the main saccade is made with a short latency suggesting preprogramming. It is crucial for the saccadic system to avoid overshooting of the target since the generation of a corrective saccade into the opposite direction is time-consuming due to the necessary inter-hemispheric transfer of the visual information about target position (Henson, 1978; Deubel et al., 1986). With the assumption that visual error signals are essential for the adaptation process, adaptivity of saccadic amplitude was studied by inducing hypermetric saccades artificially (McLaughlin, 1967; Miller et al., 1981; Deubel et al., 1986; Deubel, 1989). Subjects had to track a target which moved in double steps. The first step elicited a primary saccade which triggered a further displacement of the target in the opposite direction of the initial target step. This intra-saccadic target displacement made the primary saccade too large (hypermetric) in respect to the final target position. Thus a consistent post-saccadic position error of the target was elicited which was eliminated by correction saccades. With repetition of the stimulus sequence the amplitude of the primary, hypermetric saccade was progressively reduced in normal subjects within minutes and after only a few hundred trials saccades became orthometric with respect to the final target position (Deubel et al., 1986; Deubel, 1989). These changes in saccadic gain (size of primary saccade divided by the size of the initial target eccentricity) result from the operation of a visually mediated rapid adaptive mechanism that normally functions to minimize post-saccadic position error and to prevent hypermetria of saccades. This experimental paradigm was applied to patients with the lateral medullary, retro-olivary or Wallenberg’s syndrome which are known to have distinct saccadic eye movement disturbances. There have been numerous descriptions of deficits in voluntary and involuntary movements of the limbs and eyes in humans with posterior fossa lesions. In contrast, there has been a paucity of studies concerned with adaptive behaviour in these patients (Gauthier et al., 1979; Weiner et al., 1983; Zee and Optican, 1985; Sanes et al., 1990). The general finding is that patients with cerebellar lesions have reduced visuo-motor adaptation. Examination of adaptivity in patients with Wallenberg’s syndrome in the chronic stage of their disease is of special interest. On the one hand, these patients have a lesion outside the cerebellum in the dorsolateral aspect of the medulla oblongata. These lesions most probably interrupt olivo-cerebellar pathways. Damage to these pathways is assumed to be of major importance for the observed oculomotor disturbances (Hoyt and Frisén, 1975; Waespe and Wichmann, 1990). On the other hand, experimental evidence suggests a crucial role of olivo-cerebellar pathways originating in the inferior olive for the adaptive control of motor performance by the cerebellum (Ito and Miyashita, 1975; Llinás et al., 1975; Ito and Kano, 1982; Ito et al., 1982; McCormick et al., 1985). The idea is that the climbing fibre inputs to the Purkinje cells provide ‘teaching’ signals and the mossy fibre inputs provide important contextual information to establish new
associations or to change the strengths of connections based on the climbing fibre inputs to the Purkinje cells (Marr, 1969). These ideas and assumptions have generated considerable interest in testing visuo-motor adaptivity of saccades in Wallenberg's patients.

PATIENTS AND METHODS

This report is based on 13 patients with an ischaemia in the lateral medulla and/or the cerebellar territory of the posterior inferior cerebellar artery (PICA), and on two further patients with a sporadic cerebellar cortical atrophy. In most of these patients, eye movement abnormalities in the acute phase of the disease were marked and magnetic resonance imaging (MRI) studies allowed localization of the underlying pathology (Table 1). Patients were examined several months or years after onset of their illness in the chronic stage. Ten patients (patients 1—10) had infarction in the (dorsolateral medulla (i.e. Wallenberg's syndrome) and four of these (patients 1—4) had further infarction in the cerebellar territory of the PICA.

Three further patients (patients 11—13) had infarction in the cerebellar territory of the PICA but none in the lateral medulla (Table 1). Twelve patients had MRIs; patient 6, who had a right-sided medullary lesion had a brain computerized tomography (CT) investigation which disclosed no cerebellar involvement. For patho-anatomical details we refer to our previous study (Waespe and Wichmann, 1990). Table 1 summarizes the diagnosis and the location and extent of the lesions. Mean age of the 13 patients with ischaemic infarction was 52 yrs (range 33—68 yrs; two females, 11 males). Five patients had also participated in our previous study on visual-vestibular interaction (Waespe and Wichmann, 1990). One of the two patients with severe sporadic cerebellar cortical atrophy, aged 29 yrs (patient 14), was still able to walk whereas the second patient (patient 15), aged 49 yrs, was wheelchair-bound.

Seven age-matched normal subjects served as controls. Mean age was 49 yrs (range 34—63 yrs; three females and four males). Informed consent was obtained from all patients and normal subjects.

Experimental design

Saccadic and slow eye movements were first carefully tested using bedside methods. In addition, horizontal and vertical eye movements were recorded (Table 1) with d.c. coupled, bitemporal electro-oculography (EOG) using skin electrodes. Signals were low-pass filtered (30 Hz cut-off frequency) and written out on a rectilinear 6-channel oscillograph for further analysis. Subjects did not wear their corrective glasses or contact lenses during testing. The fixation light was clearly visible to all subjects. Horizontal and vertical saccades were made spontaneously and on command in darkness and in response to step displacement (8—20 deg from the primary position) of a small target light (diameter 2.5 mm) at a distance of 90 cm in the primary position of the eyes.

Experimental protocol

The applied procedure (Fig. 1) was based on the experiments of Deubel et al. (1986) and Deubel (1989). The subject was asked to fixate continuously and to follow a small light spot (laser beam, diameter 2.5 mm) which was rear-projected onto a translucent tangent screen in an otherwise darkened room. There was no background structure. Viewing was binocular and head movements were restricted. The first task consisted of 50—100 trials of single target steps to each side to determine basic parameters of the saccadic reaction. The target light was stepped in rapid succession. The time (between 1 s and 4 s) and location (between 8 deg and 20 deg eccentrically to the primary position) of the target’s steps were selected randomly. The actual experiment consisted of a sequence of 160—200 trials of double steps to each side. In these trials the primary saccade triggered an additional intra-saccadic target displacement which occurred in the direction opposite to the first step. The time interval between the first and second target step was therefore dependent on the latency of the primary saccade which ranged on average between 200 ms and 250 ms. An analogue electronic circuitry detected the primary saccade and triggered the signal to move the target light. The target light jumped to its second, final position well before the primary saccade was completed. The absolute amount of the intra-saccadic displacement (39% and 50% of the initial target step for normal subjects and 39% for patients) was variable and given by the amount of the first target step. The sequence of these double target steps trials formed the adaptation period (adaptation in Fig. 1). The intra-saccadic target
**TABLE 1. SUMMARY OF DIAGNOSIS, LOCATION AND EXTENT OF LESIONS FOR PATIENTS 1–13**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>MRI lesion level of most extensive pathology</th>
<th>Tested after (mths)</th>
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<tr>
<td>1</td>
<td>43</td>
<td>M</td>
<td>W, C</td>
<td><img src="image.png" alt="lesion" /></td>
<td>15</td>
</tr>
<tr>
<td>2</td>
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<td>W, C</td>
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<tr>
<td>3</td>
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<td>W, C</td>
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</tr>
<tr>
<td>4</td>
<td>68</td>
<td>M</td>
<td>W, C</td>
<td><img src="image.png" alt="lesion" /></td>
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</tr>
<tr>
<td>5</td>
<td>64</td>
<td>M</td>
<td>W</td>
<td><img src="image.png" alt="lesion" /></td>
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</tr>
<tr>
<td>6</td>
<td>61</td>
<td>M</td>
<td>W</td>
<td><img src="image.png" alt="lesion" /></td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>M</td>
<td>W</td>
<td><img src="image.png" alt="lesion" /></td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>M</td>
<td>W</td>
<td><img src="image.png" alt="lesion" /></td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>M</td>
<td>W</td>
<td><img src="image.png" alt="lesion" /></td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>F</td>
<td>W</td>
<td><img src="image.png" alt="lesion" /></td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>M</td>
<td>C</td>
<td><img src="image.png" alt="lesion" /></td>
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</tr>
<tr>
<td>12</td>
<td>47</td>
<td>M</td>
<td>C</td>
<td><img src="image.png" alt="lesion" /></td>
<td>8</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>F</td>
<td>C</td>
<td><img src="image.png" alt="lesion" /></td>
<td>4</td>
</tr>
</tbody>
</table>

Magnetic resonance imaging of patients 2, 7, 11 are shown in Fig. 1A—1 in Waespe and Wichmann, 1990. W = Wallenberg; C = cerebellar; r = right; l = left.

...step induced a consistent post-saccadic position error which had to be corrected. Initially, errors were large and corrected by correction saccades. However, as shown by Deubel et al. (1986) in normal subjects, only 150–200 trials are needed to adaptively change the gain of the primary saccade. This adjustment of saccadic amplitude is direction-specific (Miller et al., 1981; Deubel et al., 1986). After this sequence of double target steps, 30–50 control trials with single target steps were given again without intra-saccadic displacement of the target. Subjects were not able to recognize the experimental procedure (McLaughlin et al., 1968; Miller et al., 1981). Thus, it is very unlikely that the effects described below were obtained by volitional control (Hallett, 1978).
WALLENBERG'S SYNDROME

control adaptation

over-/undershoot (%) = 100 x \( \frac{a}{b} - 1 \)

Fig. 1. Sketch of the experimental sequence, before and after the adaptation paradigm single target steps (control) were given. The adaptation paradigm consists of alternating double target steps. The target was set back after the first step and this second step was triggered by the primary or main saccade made in response to the first target step. One or several correction saccades were made for final fixation of the target (see Fig. 9). The final target position served as the starting position for the next trial into the opposite direction. Double target steps were delivered in the same session to both directions.

Pursuit eye movements during visual-vestibular interaction were also tested with sinusoidal stimulation (period 4 s, peak velocity 55 deg/s for smooth pursuit eye movements, and 63 deg/s for vestibular stimulation). We refer for details of these latter testings to our previous paper (Waespe and Wichmann, 1990).

Normal values

Normative values for the ability to change adaptively the amplitude of saccades as a function of trials using the 39% and 50% paradigm is shown in Fig. 7A for seven normal subjects and for five of these seven normal subjects, respectively. Values were averaged for blocks of 10 successive trials (Figs 7, 8, 10).

Data analysis

Saccade data such as velocity, amplitude, duration, latency and accuracy were extracted from the chart records by hand. Velocity was measured by evaluating the hand-drawn slopes of the eye position trace and saccadic amplitude was measured as peak-to-peak change of eye position (Fig. 1). The inter-saccadic interval is defined as the time between the end of a saccade and the beginning of the following (corrective) saccade. To express the amplitude of saccades relative to the size of the target steps the equation in Fig. 1 was used. Overshooting of saccades is indicated by a positive sign; undershooting by a negative sign.

Magnetic resonance imaging studies

For details we refer to our previous report (Waespe and Wichmann, 1990). The location and extent of the ischaemic lesions in the patients are summarized in Table 1.

RESULTS

Single target step experiments

Normal subjects

Normal subjects regularly undershoot the target. Undershooting of primary saccades relative to the size of the target step is between -5% and -10% (Becker and Fuchs, 1969; Deubel et al., 1986). In our seven control subjects undershooting was on average -6.7% (SD = 2.5%). Latency of the primary saccade to the step change
of the target light was between 200 ms and 250 ms. In one representative subject this latency was on average 212.5 ms (SD = 22.5 ms). The duration of the interval between the end of the primary and the beginning of the secondary (first corrective) saccade was shorter. It was on average 162 ms (SD = 20 ms) when the primary saccades overshot the target (mean overshoot +17.5%) and 147 ms (SD = 22 ms) when the primary saccades undershot the target (mean undershoot −23%). As normal subjects very rarely have hypermetric or strongly hypometric saccades, measurements were taken from the initial trials during and after the adaptation paradigm when saccades were highly dysmetric. These values of the latency of correction saccades in or opposite the direction of the primary saccades correspond to those reported in the literature (Becker and Fuchs, 1969; Henson, 1978).

**Patients**

Figure 2 gives a typical example of the saccadic abnormalities found in five of our patients, all with Wallenberg’s syndrome. Primary saccades made in response to an ipsilateral (lesion side) target step were often hypermetric whereas those made in response to a contralateral (normal side) target step were consistently hypometric (except in patient 10), forcing the patient to make multiple saccades for foveal fixation of the target.

![Figure 2](image_url)

**FIG. 2.** A, traced records of horizontal eye movements in patient 8 in response to ipsi- (right side, r) and contralateral (left side, l) single target steps. The position of the target is indicated by the broken line. The target steps to the lesion side or normal side are marked by an upward or downward arrow, respectively. Ipsilateral primary saccades are slightly hypo- or hypermetric, contralateral primary saccades are hypometric, multiple corrective saccades in the direction of the primary saccade were made to refixate the target. These corrective saccades could bring the eyes even into a position eccentric to the target, so that oppositely directed corrective saccades are made for refixation (second trace in A). B, in darkness, in response to remembered target steps of the same magnitude of 16 deg, a saccadic asymmetry was observed similar to that when the target was visible.
During the inter-saccadic intervals the eyes remained motionless or drifted slowly in the direction of the correction saccades (Fig. 2A). Corrective saccades could bring the eyes even to a position beyond the target. Thus, gaze could overshoot the target either with the primary saccade or with a cascade of correction saccades. If gaze overshot the target, backward directed corrective saccades were necessary for refixation. When patients were placed in total darkness and instructed to continue to refixate between the imagined locations of the previously visible target the asymmetry of saccades persisted (Fig. 2B).

**Velocity and latency of primary saccades.** In all patients the latency of primary saccades as well as mean peak velocities of saccades were within normal ranges (Becker and Fuchs, 1969; Baloh et al., 1975). Figure 3 shows the velocity of primary and correction saccades as a function of amplitude in patient 8, this relationship being representative for all other patients. Average velocity of saccades of 30 deg amplitude was between 400 deg/s and 473 deg/s (average 435 deg/s, patients 6, 8–10, 12), and latency of the primary saccades ranged between 214 ms and 247 ms (average 225 ms, same patients).

**Accuracy of target-directed primary saccades.** Five patients (patients 2, 4, 6, 8, 10; Table 2) had asymmetric amplitudes of saccades: primary saccades in response to an ipsilateral target step were often hypermetric and larger than saccades made in response to a contralateral target step which regularly undershot the target. Mean over- and undershoot was +3.3% and -21.4%, respectively, for all five patients. Fifty-one percent of all primary saccades made by these five patients to the ipsilateral side, overshot the target by more than +2.5%. Patients 2, 4, 6, 8 made multiple corrective saccades in

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**Fig. 3.** Mean peak velocities (ordinate) of primary and corrective saccades as a function of amplitude (abscissa) in patient 8.
TABLE 2. ACCURACY OF PRIMARY SACCADES IN RELATION TO TARGET POSITION

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Ipsilateral</th>
<th>Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overshoot &gt;2.5%</td>
<td>Primary saccade (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary saccade (%)</td>
</tr>
<tr>
<td>1</td>
<td>-16.5 (7.3)</td>
<td>19.0</td>
</tr>
<tr>
<td>2</td>
<td>+2.0 (8.8)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-16.0 (16.0)</td>
<td>8.5</td>
</tr>
<tr>
<td>4</td>
<td>+5.0 (12.5)</td>
<td>57.0</td>
</tr>
<tr>
<td>5</td>
<td>-6.0 (3.5)</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>6</td>
<td>+3.5 (11.0)</td>
<td>48.0</td>
</tr>
<tr>
<td>7</td>
<td>-2.8 (5.8)</td>
<td>18.0</td>
</tr>
<tr>
<td>8</td>
<td>+0.1 (12.0)</td>
<td>37.0</td>
</tr>
<tr>
<td>9</td>
<td>-4.0 (5.8)</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>10</td>
<td>+6.0 (6.2)</td>
<td>61.5</td>
</tr>
<tr>
<td>11</td>
<td>-7.5 (5.0)</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>12</td>
<td>-7.5 (3.0)</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>-11.5 (7.8)</td>
<td>-</td>
</tr>
<tr>
<td>Normal</td>
<td>-6.7 (2.5)</td>
<td>&lt;2.0</td>
</tr>
</tbody>
</table>

Mean of overshooting (+) or undershooting (−) with (1 SD). Percentage of target overshoot by more than +2.5% by the primary saccade or by multiple saccades.

Response to contralateral target steps (Figs 2A, 5). In 15.2% of all trials with target steps to the contralateral side, either (seldom) the primary saccade or (most often) a cascade of corrective saccades brought the eyes lateral to the target, overshooting the target by more than +2.5%. In patients 1, 3, 7, although the target was undershot on average by the main saccades in both directions, in a considerable percentage of trials the target was overshot by the primary saccade or by a cascade of corrective saccades (Table 2). The distribution of the amplitudes of primary saccades relative to ipsilateral and contralateral target steps is shown for patients 8, 10 in Fig. 4. The relative accuracy of primary saccades and the percentage of target overshoot by more than 2.5% by single or multiple saccades is summarized for each patient in Table 2.

Duration of inter-saccadic intervals. Figure 5 shows the latency of correction saccades as a function of hypometria in patient 8. The latencies were increasingly larger when correction saccades brought the eyes near the target; the latency reached its largest value when the target position was overshot by the cascade of correction saccades and the following correction saccade was oppositely directed. Figure 6 summarizes for patients 8, 10 the latencies of the secondary (first corrective) saccade as a function of under- and overshooting of the primary saccade. As the primary saccades to the contralateral side rarely overshot the target for trials with single target steps, additional data for overshooting primary saccades were taken from the adaptation trials, i.e. from trials with double target steps. The latencies of the first corrective saccade were shorter for single target steps to which the patient habitually under- or overshot the target, than the corresponding latencies of corrective saccades which rarely occurred under normal conditions or which were induced during the adaptation trials. Note that latencies of correction saccades before (closed circles) and after (open squares) adaptation are comparable. Table 3 summarizes this finding for four patients. The average duration of the intervals between primary and secondary (first corrective) saccades was 214 ms.
WALLENBERG'S SYNDROME

Fig. 4. Distribution of the accuracy of primary saccades relative to the target step (abscissa) in patients 10 (A, B) and 8 (C, D). Bin width on the abscissa is ±5%. A, B mean overshoot for 126 ipsilateral primary saccades in A is +6% (SD = 6.2%). 61.5% of all primary saccades overshot the target by more than +2.5% and only 8% undershot the target by more than −2.5% (absolute value >2.5). Mean undershoot for 119 contralateral primary saccades in B is −7% (SD = 5.3%). Less than 1.5% of all saccades overshot the target by more than +2.5%, but 73.5% undershot the target by more than −2.5%. In C, D, on average the 110 ipsilateral primary saccades in C were normometric (average 100.1%, SD = 12%), nevertheless 37% of all saccades overshot the target by more than +2.5% and 29.5% of all primary saccades undershot the target by more than −2.5%. In D the 101 contralateral saccades undershot the target on average by −23% (SD = 16.5%); 7.5% of all primary saccades overshot the target by more than +2.5%, and 90% undershot the target by more than −2.5%.

and 99.8 ms, respectively, when the primary saccades to the ipsi- or contralateral side were too short (undershooting between −2.5% and −30%). The difference of 114 ms in latencies may be explained by the fact that primary saccades regularly undershot the target for steps to the contralateral but not to the ipsilateral side. For target steps to the ipsilateral side undershooting rarely occurred under normal conditions. The intersaccadic interval was 135 ms and 228.5 ms, respectively, when the primary saccades to the ipsi- or contralateral side were too large (overshooting between +2.5% and +30%). Again, the difference of 93 ms in latencies is probably due to the fact that under normal conditions the primary saccades habitually overshot the target for steps to the ipsilateral but not to the contralateral side.
FIG. 5. Duration of inter-saccadic intervals (ordinate in milliseconds) between primary and first corrective saccades and between subsequent correction saccades in patient 8 as a function of under- and overshooting of saccades relative to the size of contralateral target steps. When the primary saccades undershot the target by $-46\%$ (SD = 11.5\%) the mean duration between the primary and secondary saccade was 44 ms (SD = 18 ms) (marked by a single arrow). When the secondary (first corrective) saccade undershot the target by $-24.9\%$ (SD = 8.4\%) the inter-saccadic interval between the primary and secondary corrective saccade was 50.5 ms (SD = 21 ms) (double arrow). The secondary corrective saccade still undershot the target by $-9.8\%$ (SD = 5.6\%), the latency between the secondary and tertiary corrective saccade was 84.5 ms (SD = 43 ms) (triple arrow). The tertiary corrective saccade overshot the target by $+7\%$ (SD = 4.3\%), the average interval between the tertiary and quaternary corrective saccade, the latter directed opposite to the former, was 290 ms (SD = 82.5 ms). The latency of the primary saccades is 230 ms (SD = 46 ms) (marked with an asterisk).

Adjustment experiments

In these experiments the target was shifted intra-saccadically opposite to the initial first target step, resulting in a large overshoot of the primary saccade and thus in a target position error (see Patients and methods for details). This overshoot was corrected by one or several saccades in the opposite direction of the primary saccade.

Normal subjects

After 150–200 trials the amplitude of the primary saccades was adjusted relative to the final target position. This is shown in Fig. 7A (b, adaptation) as a decrease of the percentage overshoot relative to the final target position. Adjustment is complete for the paradigm with 39\% target overshoot (filled circles in Fig. 7A). After the adaptation period control saccades made to single target steps undershot the target by $-15\%$ to $-17\%$ (c) as compared with control values of $-6\%$ to $-7\%$ before adaptation (a). The amount of adaptation in our normal subjects is quite similar to that found by Deubel et al. (1986). With 50\% target overshoot (open circles) adaptation was not yet complete after 200 trials. Undershoot of control saccades after adaptation was between $-20\%$
A ipsilateral  

B contralateral  

C ipsilateral  

D contralateral  

Fig. 6. Inter-saccadic interval (ordinate) between primary and secondary (primary correction) saccades as a function of over- and undershooting of the primary saccade (abscissa) in patients 10 (A, B) and 8 (C, D). Measurements were taken in trials before, during and after adaptation experiments. Note that when the primary saccades had the tendency to overshoot (A, C, for ipsilateral steps) or undershoot (B, D, for contralateral steps) the target under normal conditions (filled circles), the latency is shorter than in trials in which the primary saccades rarely or never over- or undershot the target (see also Table 3). Latency measurements in these instances were possible only in trials during (filled squares) and after (open squares) the adaptation paradigm.

and -22%. Adaptation also occurs during the control period in (c) with repetition of trials the amount of hypometria progressively decreases.

Patients

The adaptation paradigm of Deubel et al. had been applied so far to normal subjects only. To test for its sensitivity we applied it to two patients who suffered from sporadic cortical cerebellar atrophy. On the basis of experimental work cited in the Introduction no adjustment of saccadic eye movements was expected to occur.

Patients 14 and 15 with severe cerebellar cortical atrophy. Both patients had hypermetric saccades, a feature well known to occur in degenerative cerebellar disease. Post-saccadic drift was either not present or minimal. Mean saccadic overshoot was +5%
TABLE 3. DURATION OF INTERSACCADIC INTERVALS

<table>
<thead>
<tr>
<th>Patient no.</th>
<th></th>
<th>Undershooting</th>
<th></th>
<th>Overshooting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-2.5% to -30%</td>
<td></td>
<td>+2.5% to +30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral</td>
<td></td>
<td>Ipsilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contralateral</td>
<td></td>
<td>Contralateral</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>241.0 (36.5)</td>
<td>93.5 (61.5)</td>
<td>179.0 (71.5)</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>-11.0 (5.0)</td>
<td>-17.0 (7.0)</td>
<td>+14.0 (8.0)</td>
</tr>
<tr>
<td>6</td>
<td>D</td>
<td>217.0 (37.0)</td>
<td>97.0 (30.0)</td>
<td>130.5 (20.0)</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>-7.8 (3.6)</td>
<td>-20.0 (6.2)</td>
<td>+8.8 (5.0)</td>
</tr>
<tr>
<td>8</td>
<td>D</td>
<td>190.0 (50.0)</td>
<td>88.5 (46.5)</td>
<td>106.5 (27.0)</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>-12.5 (6.5)</td>
<td>-19.5 (7.7)</td>
<td>+13.0 (6.5)</td>
</tr>
<tr>
<td>10</td>
<td>D</td>
<td>208.5 (30.2)</td>
<td>120.0 (35.0)</td>
<td>124.0 (36.5)</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>-8.0 (3.2)</td>
<td>-15.0 (6.1)</td>
<td>+14.7 (7.9)</td>
</tr>
<tr>
<td>Mean</td>
<td>D</td>
<td>214.0 (21.0)</td>
<td>99.8 (13.9)</td>
<td>135.0 (31.0)</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>-9.8 (2.3)</td>
<td>-17.9 (2.3)</td>
<td>+10.1 (4.3)</td>
</tr>
</tbody>
</table>

Mean duration of intervals between primary saccade and secondary (first correction) saccade, when the primary saccade is undershooting (between -2.5% and -30%) or overshooting (between +2.5% and +30%) the target for ipsi- and contralateral target steps. Duration (D) in milliseconds (1 SD) and amount of under or overshooting in percentages (1 SD).

FIG. 7. A, relative over- and undershoot of primary saccades of normal subjects for the 39% target overshoot paradigm (filled circles; n = 7) and the 50% target overshoot paradigm (open circles; n = 5). Each data point represents the average (vertical bar is 1 SD) of 10 successive trials. In control trials before adaptation (a) the averaged undershoot is between -5% and -8%, after adaptation in (c) between -14% and -23%. B, saccadic adaptation in patient 14 with a sporadic cerebellar cortical atrophy. Average values with 1 SD are for trials into both directions. Gain adaptivity of saccades is lost: there is no decrease in the amount of hypermetria during adaptation (b), and control values before (a) and after (c) the adaptation trials are similar.
(SD = 12%) in patient 14, and +16% (SD = 5.5%) in patient 15 in control trials. Both patients were unable to change the gain of their primary saccades during the adaptation paradigm. They made correction saccades in the direction of the second target step for refixation of the target during the whole period of adaptation. The latency between the primary, hypermetric saccade and the following correction saccade was 170 ms (SD = 20.5 ms, patient 14) and 165 ms (SD = 22.5 ms, patient 15). These values are in the range of those of normal subjects (162 ms, see section on normal subjects). As shown in Fig. 7B for patient 14, no decrease in the amount of hypermetria of primary saccades occurred during the adaptation trials (b). Loss of gain adaptivity was also demonstrated by unchanged amplitudes of saccades in control trials after the adaptation period. In patients 14, 15 the amount of overshoot after the adaptation trials (c) was +5.5% (SD = 13.5%) and +14% (SD = 5%), respectively, and thus identical to the overshoot in control trials before adaptation (a).

Patients with Wallenberg's syndrome. Patients 1 and 3 will not be discussed further. Their primary saccades to the ipsilateral side showed a large undershoot of more than −12%. The other eight patients were separated into two groups on criteria discussed below. Patients 5, 7, 9 constituted the first group and patients 2, 4, 6, 8, 10 the second group.

In Group 1 (patients 5, 7, 9), the patients had fairly symmetrical target-directed saccades (Table 2). In patient 7, 18% and 6.5% of all primary saccades overshot the target for ipsi- and contralateral steps, respectively. The curve in Fig. 8A suggests that these three patients had on average a decreased gain adaptivity for ipsilateral saccades. After 150–200 trials primary saccades still overshot the target by about +8% to +11%. Adaptivity for contralateral saccades was similar to that of normal subjects: after 150–200 trials of double target steps saccadic overshoot was minimal.

In Group 2 (patients 2, 4, 6, 8, 10) the saccades to the ipsilateral side overshot the target and saccades to the opposite side undershot the target in single target step trials (Table 2). The relative overshoot of ipsi- or contralateral saccades for the initial trials of the adaptation paradigm was greater or smaller than in control subjects (Fig. 8B). There was a tendency of the overshoot of ipsilateral primary saccades to decrease with increasing numbers of trials during the adaptation paradigm, but after 200 trials primary saccades still overshot the final target position on average by +20% to +25%. Control saccades to the ipsilateral side after the adaptation period slightly undershot the target, on average by −1% to −5%. Control saccades before the adaptation period overshot the target, on average by +1% to +2.5%.

In control trials the primary saccades undershot the target on average by about −16% to −20% (Fig. 8B) in the contralateral direction. The amplitude of primary saccades was further decreased by the application of double target steps: in control trials after the adaptation period the target was undershot on average by −26% to −29%. The gain of primary saccades to the contralateral side further decreased during the period of adaptation (b) despite the fact that primary saccades were on average hypometric in respect to the final target position (except for the initial 10 trials in Fig. 8B). However, during the whole period of adaptation the final target position was occasionally overshot by primary saccades and more often by cascades of correction saccades, similar to trials with single target steps. It is noteworthy that a further corrective saccade could occur in the direction of the first target step (and thus in the wrong direction) despite the fact
Fig. 8. Gain adaptivity of ipsilateral and contralateral saccades in patients 5, 7, 9 (A; heavy line), and in patients 2, 4, 6, 8, 10 (B; heavy line) for the 39% adaptation paradigm, compared with gain adaptivity of seven normal subjects (closed circles). Same display as in Fig. 7. Mean values with the 67% confidence level (dashed areas) are separated for ipsi- (first trace in A, B) and contralateral (second trace) saccades. For details see text.
that the target was overshot by the previous correction saccade (arrow in Fig. 9B, C). This overshoot transferred the target to the opposite side of the fovea. This kind of wrongly directed corrective saccades was, however, observed only during the initial trials of the adaptation paradigm.

Figure 10 shows gain adaptivity for patient 10. Between the first and second run of the adaptation paradigm there was a rest period of 5 min. A slight gain reduction for
ipsilateral saccades occurred during the first run (filled circles) as can be seen from the control values after the adaptation period. The initial overshoot in control trials after a rest of 5 min during the second run (open circles) was similar to that of the first run (filled circles). During the second run of the adaptation paradigm, overshoot after 200 trials was still +25%. For contralateral directed saccades, gain adaptation was present and it was retained after a 5 min rest period. Control trials (open circles in a) before the second run of the adaptation paradigm were consistently less than the corresponding values before the first run (filled circles). Control values for single target steps in (c) after the first and second run of the paradigm were similar. Although a slight overshoot occurred during the second run of the adaptation paradigm, this overshoot was not sufficient to further decrease the amplitude of the first saccade. Similar results were obtained in patients 2, 7, 8.

Patients 11–13 with cerebellar ischaemia alone. Their capability for saccadic readjustment was normal. Adaptation occurred slightly faster than in control subjects: after 100 to 130 trials adaptation was already complete (not shown).

Additional observations

Saccadic lateropulsion. Gaze shifts in the vertical plane had a horizontal component of the trajectory in five patients (patients 2, 4, 6, 8, 10). With upwards directed saccades the trajectory deviated to the lesion side, and with downward directed saccades the trajectory deviated to the normal side. This kind of deviation was found in patients 2, 4, 6, 10. In patient 8 the trajectory of upwards saccades was deviated to the normal side and that of downward saccades to the lesion side. Deviation was dependent on the size of the vertical saccade, it ranged between 1 deg and 10 deg.

Amplitude of fast phases of vestibulo-ocular reflex (VOR). If goal-directed saccades to the ipsi- and contralateral direction were asymmetric, this asymmetry was also observed for fast phases during the VOR: fast phases directed to the ipsilateral side were larger than those to the contralateral side. As an example, in patients 2, 8, ipsilateral directed fast phases had an average amplitude of 16.6 deg (SD = 8.4 deg) and 7 deg (SD = 5.5 deg), respectively, contralateral directed fast phases had an amplitude of 5.2 deg (SD = 3 deg) and 1.6 (SD = 1.3 deg), respectively.

Gain of VOR, smooth pursuit (SP) and VOR suppression. Values were mostly abnormal in patients 2, 4, 6, 8, 10. Vestibulo-ocular reflex gain was between 1 and 1.43 (normal range 0.71–0.97); SP gain varied between 0.19 and 0.82 (normal range 0.84–0.97). Vestibular-ocular reflex suppression was abnormal in all patients with a low SP gain to stimulation into the same direction.

Time constant of eye position integrator. Patients 2, 4, 6, 8, 10 with overt saccadic dysmetria had the shortest time constant of the integrator in darkness, ranging between 2.3 s and 9.2 s (normal >15s).

Other oculomotor disturbances. Two patients (1, 6) had monocular torsional nystagmus of the ipsilateral eye in primary position or when looking to the lesion side. All other patients had no spontaneous nystagmus in the primary position. Three patients (4, 6, 8) had square wave jerks and three patients (2, 4, 6) had skew deviation with, in one patient (2), vertical double vision when looking towards the lesion side. In none of the patients did the eyes deviate tonically to one side in darkness.
**WALLENBERG’S SYNDROME**

**DISCUSSION**

**Persistent saccadic dysmetria in Wallenberg’s patients**

Half of the patients with an ischaemic lesion in the lateral medulla oblongata, either with (patients 2, 4) or without (patients 6, 8, 10) involvement of the cerebellum, had overt saccadic dysmetria months or years after onset of their illness. All these patients also had horizontal deviation of the trajectory of vertical saccades, called saccadic lateropulsion (Kommerell and Hoyt, 1973). About 50% of the target-directed primary saccades to the lesion side were hypermetric; those to the normal side were, except in patient 10, mostly hypometric. The remaining patients also had signs of saccadic dysmetria. Although the gain of their primary saccades was on average within or below normal limits, in a considerable percentage of trials the target was overshot by a single (the primary) saccade or by multiple correction saccades. In normal subjects saccadic overshoot of a target is exceptional, at least for the range of target steps used in this study. In a cascade of correction saccades the inter-saccadic interval was dependent on the amount of undershooting of the initial saccade. Latencies could be as short as 50 ms, a value only rarely found in normal subjects under special conditions (Bahill et al., 1975; Becker and Jürgens, 1979). Visually induced correction saccades in normal subjects have a latency above 110 ms (Becker, 1976; Henson, 1978; Becker and Jürgens, 1979). Thus, if the error of the primary, hypometric saccade is large, one or several corrective saccades occur with very short latency, too short to be induced by retinal error signals (Becker, 1976). Corrections of large position errors are therefore executed in the ‘extraretinal mode’ (Becker and Jürgens, 1979). By falling habitually much too short of the target with the main saccade, the direction and amplitude of the correction saccade would be known prior to onset. However, in our patients there seems to be uncertainty about the amplitude of the correction to be made because in many instances the cascade of correction saccades resulted in a target overshoot. An ‘extraretinal’ mode of programming short-latency correction saccades is also suggested by the observation that during the first trials of the adaptation paradigm a corrective saccade was often made in the wrong direction. This correction saccade carried the target even further away from the fovea to the other side of the retinal hemifield (Fig. 9). This retinal position error signal did not prevent the occurrence of a further corrective saccade in the wrong direction, probably because the visual error signal was first transmitted to the hemisphere contralateral to that which received the initial error signal elicited by the first target step. The necessary interhemispheric transfer probably prolonged the time of processing of the visual information by the saccadic system.

**Cerebellar lesions and saccadic dysmetria**

Saccadic dysmetria is a well-known feature in primates with cerebellar cortical or medial nuclei lesions (Ritchie, 1976; Selhorst et al., 1976; Zee et al., 1976; Optican and Robinson, 1980; Vilis and Hore, 1981). Saccadic reaction times and velocities are within normal limits as in patients with Wallenberg’s syndrome. Most often, overshoot dysmetria occurs, but also a variety of patterns of dysmetria has been observed. In monkeys with bilateral vermal and paravermal lesions the pattern of dysmetria was eye position dependent. Saccades from an eccentric position towards the primary position were larger than those from the primary position towards eccentric positions (Ritchie,
We did not test our patients for this kind of eye position-dependent dysmetria, saccades had to be made from the ipsi- into the contralateral hemifield and vice versa. Reversible unilateral lesions of medial cerebellar nuclei (nucleus fastigius and interpositus) induced horizontal deviation of vertical saccades to the lesion side (Vilis and Hore, 1981). Similar deviations of the trajectory of vertical saccades were observed in those patients with the lateral medullary syndrome who showed dysmetria of horizontal saccades. In the study of Vilis and Hore (1981), 75% of all ipsilateral goal-directed saccades were hypermetric whereas 40% of the contralateral saccades were equally hypo- or hypermetric. The suggestion was made that the cerebellum is involved in tuning some internal estimate of extracocular muscle strength (Vilis and Hore, 1981). Overestimation of muscle strength would result in hypometric saccades. Efference copy signals of saccadic performance would wrongly signal that the target is reached before the eyes actually get there (depending upon muscle strength). As a consequence the saccadic eye movements would be terminated too early. Hypermetric saccades occur with underestimation of muscle strength and saccades are terminated too late. It is premature to speculate on the mechanisms which underly enduring saccadic dysmetria in patients with Wallenberg's syndrome. The simplest model of the saccadic system assumes that the magnitude of a saccade is determined by a comparison between desired eye or target position and a predicted actual eye position based on efference copy (Robinson, 1981). This comparison results in an eye position error signal. If the eyes are driven by this signal until the error signal becomes zero the eyes would at this point stop moving.

If the saccadic system computed the location of the target in relation to space, the initial eye position before a saccade would also be information essential to the functioning of the saccadic system. Dysmetria may result from misrepresentation of the error signal or of eye or target position. When saccadic dysmetria is permanently manifest, it could also mean that adaptive mechanisms can no longer compensate for it as dysmetria has become too large, or that the mechanisms themselves are disturbed. The adaptive process may be disrupted in any of its component parts, i.e. the ‘error’ inputs that signal the need for adaptation, the central networks that calculate the necessary readjustments or the outputs that mediate corrective command signals to the premotor structures. Cerebellar lesions, more specifically of the posterior vermis, could cause inappropriate gain adjustments of saccadic amplitudes resulting in dysmetria (Robinson, 1975; Zee et al., 1976; Optican and Robinson, 1980). Even with practice, cerebellar patients never learned to correct their dysmetria (Zee et al., 1976).

**Rapid saccadic gain adaptivity**

The two patients with cerebellar cortical atrophy not only had overshooting dysmetria, but their capability of gain adjustment of the hypermetria, if it was further increased artificially by using double target steps, was lost. This supports the idea that cerebellar cortical structures in humans are involved in gain adjustment of saccadic eye movements.

Although a direct comparison of the capability for saccadic gain adaptation in patients with Wallenberg's syndrome with that in normal subjects is difficult because the amplitudes of the control saccades are different in both groups, the results suggest impaired saccadic gain adaptivity in the patient group. The amplitude of ipsilaterally directed hypermetric saccades did decrease adaptively to some degree, but after delivery of 200 double target steps to each side, primary saccades were still hypermetric. Figure 7A
suggests that the drive for saccadic readjustment is stronger with larger target position errors. Due to the already hypermetric saccades in single target step experiments, the target position error was initially larger in patients 2, 4, 6, 8, 10 than in normal subjects in the 39% double target paradigm (Fig. 8B) but comparable to the error in the 50% paradigm in normal subjects (about 30% overshoot for the initial 10 trials, Figs 7A, 8A). Yet, after 200 trials saccadic overshoot was still between 20% and 25% in patients as compared with 5% in normal subjects. The amplitude of contralaterally directed hypometric saccades is not increased adaptively as it would be expected from the experiments of Deubel et al. (1986) in normal subjects. These authors showed that the amplitude of undershooting primary saccades slowly increased adaptively if the second target step was in the direction of the first target step. The further decrease in amplitude of already hypometric primary saccades observed in our patients may be due to the occasional target overshoot either by the main saccade or by a cascade of correction saccades. Deubel et al. (1986) showed that the amplitude adaptively decreased even though only one-third of all primary saccades overshot the target in the double target-step paradigm. The occurrence of only a certain percentage of hypermetric saccades is sufficient to prevent hypermetria. As mentioned above, the persistent saccadic dysmetria in patients with Wallenberg’s syndrome already suggested that gain adaptivity of saccadic eye movements may be impaired; the results of the examination of saccadic gain adaptivity itself are in agreement with that idea. This kind of adaptive control which is accomplished within minutes has been called rapid saccadic adaptation as opposed to gradual saccadic adaptation which takes hours or days to develop (Optican, 1985). By the former mechanism the saccadic system tries to maintain hypometria, and by the latter it compensates for post-saccadic ocular drift. A note of caution should be made. We recorded the movements of the two eyes as a single movement. Vilis et al. (1983) demonstrated that the degree of saccadic dysmetria induced by medial cerebellar nuclei lesions is different in the two eyes. Thus it is possible that the degree of saccadic dysmetria and of impaired gain adaptivity is different in the two eyes of our patients.

Suggested functional-anatomical correlations

Functional-structural correlations in the lateral medullary syndrome are hypothetical. In a previous paper we suggested that olivo-cerebellar pathways are likely to be interrupted (Hoyt and Frisén, 1975; Waespe and Wichmann, 1990). After having crossed in the brainstem, these fibres run in the inferior peduncle to the cerebellum and are most probably damaged in the lateral aspect of the medulla. It is important to note that the lesion in Wallenberg’s syndrome is unilateral, interrupting olivo-cerebellar fibres to the ipsilateral cerebellum only. Saccadic dysmetria has not yet been observed in animals after destruction of the inferior olivary nucleus or inactivation of its fibres. Animals, however, were not trained to fixate between different targets. Patients with inferior olivary nucleus degeneration were not reported to have saccadic dysmetria (Ridley et al., 1987). None of our patients had opsoclonus or palatal myoclonus which may be observed with inferior olivary nucleus degeneration. How disruption of olivo-cerebellar fibres interferes with the mechanism of saccadic gain adaptivity may only be speculated upon. Disrupted olivo-cerebellar fibres may transmit retinal error signals and/or signals representing eye position or muscle strength to cerebellar Purkinje cells. These signals which provide information about the actual or predicted performance of the saccadic system would
then no longer reach cerebellar cortical circuits. Alternatively, chronic inferior olivary nucleus deafferentation results in a reduced efficacy of the inhibitory action of Purkinje cells, decoupling them functionally from their target cells in the cerebellar nuclei (Karachot et al., 1987). Thus, even if cerebellar cortical circuits received normal mossy fibre input signals, inhibitory Purkinje cell action on their target cells which are involved in the mediation of amplitude command signals of saccades would be less effective due to the mere disruption of climbing fibre input activity, irrespective of the specific information carried by the damaged climbing fibres. Animal experiments are generally in support of a crucial role for the inferior olivary nucleus and its fibres in the acquisition and retention of adaptive effects on motor responses such as the vestibulo-ocular reflex (Ito and Miyashita, 1975; Robinson, 1976; Haddad et al., 1980; Demer and Robinson, 1982; Ito, 1982) or the conditioned eyelid response (McCormick et al., 1985; Mauk et al., 1986).

Conclusion
Clinical and experimental evidence support the notion that cerebellar processes, either intrinsic to the cerebellar cortex or involving its input and output pathways, are involved in adaptive control of motor responses. The results of the present study suggest that in Wallenberg’s syndrome, structures or pathways in the lateral medulla which are necessary to continuously modulate saccadic gain, whether by processing or transferring visual or eye position signals or efference copy signals, are lesioned. The observation that saccadic gain adaptivity induced by retinal position error signals is impaired, suggests that the disrupted structures or pathways process or transmit visual error signals which are necessary for adaptive gain control of saccades by the cerebellum. Although precise structural-functional correlations are not possible in Wallenberg’s syndrome, we suggest that the persistent saccadic eye-movement abnormalities are most likely the effect of disrupted olivo-cerebellar fibres which run in the posterior peduncle to the cerebellum.

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