

Neurophysiological Aspects of Eye and Eyelid Movements During Blinking in Humans

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Neurophysiological aspects of eye and eyelid movements during blinking in humans. *J. Neurophysiol.* 83: 166–176, 2000. The neural relationships between eyelid movements and eye movements during spontaneous, voluntary, and reflex blinking in a group of healthy subjects were examined. Electromyographic (EMG) recording of the orbicularis oculi (OO) muscles was performed using surface electrodes. Concurrently, horizontal and vertical eye positions were recorded by means of the double magnetic induction (DMI) ring method. In addition, movement of the upper eyelid was measured by a specially designed search coil, placed on the upper eyelid. The reflex blink was elicited electrically by supraorbital nerve stimulation either on the right or the left side. It is found that disconjugate oblique eye movements accompany spontaneous, voluntary as well as reflex blinking. Depending on the gaze position before blinking, the amplitude of horizontal and vertical components of the eye movement during blinking varies in a systematic way. With adduction and downward gaze the amplitude is minimal. With abduction the horizontal amplitude increases, whereas with upward gaze the vertical amplitude increases. Unilateral electrical supraorbital nerve stimulation at low currents elicits eye movements with a bilateral late component. At stimulus intensities approximately two to three times above the threshold, the early ipsilateral blink reflex response (R_1) in the OO muscle can be observed together with an early ipsilateral eye movement component at a latency of ~ 15 ms. In addition, during the electrical blink reflex, early ipsilateral and late bilateral components can also be identified in the upper eyelid movement. In contrast to the late bilateral component of upper eyelid movement, the early ipsilateral component of upper eyelid movement appears to open the eye to a greater degree. This early ipsilateral component of upper eyelid movement occurs more or less simultaneously with the early eye movement component. It is suggested that both early ipsilateral movements following electrical stimulation do not have a central neural origin. Late components of the eye movements slightly precede the late components of the eyelid movement. Synchrony between late components of eyelid movements and eye movements as well as similarity of oblique eye movement components in different types of blinking suggest the existence of a premotor neural structure acting as a generator that coordinates impulses to different subnuclei of the oculomotor nucleus as well as the facial nerve nucleus during blinking independent from the ocular saccadic and/or vergence system. The profile and direction of the eye movement rotation during blinking gives support to the idea that it may be secondary to eyeball retraction; an extra cocontraction of the inferior and superior rectus muscle would be sufficient to explain both eye retraction and rotation in the horizontal vertical and torsional planes.

INTRODUCTION

Studies of spontaneous and voluntary blinking have revealed the reciprocal innervation between the levator palpebrae superioris (LP) and the orbicularis oculi (OO) muscles (Aramideh et al. 1994b; Björk and Kugelberg 1953; Evinger et al. 1991; Gordon 1951). Immediately before a blink, the activity of the LP muscle ceases, whereas the OO motoneurons produce a short high-frequency burst of activity. At the end of a blink the OO activity turns off and the LP returns to its previous tonic activity (Aramideh et al. 1994b; Becker and Fuchs 1988). Thus the upper eyelid droops due to the inhibition of the tonic activity of the LP followed by the activation of the OO muscle and the release of passive downward forces of the upper eyelids. The upper eyelid opens again when the OO muscle activity has turned off and the LP has returned to its tonic activity. Electrical stimulation of the supraorbital nerve elicits two components in the OO muscle known as blink reflex response: an early oligosynaptic ipsilateral response (R_1) and a late polysynaptic bilateral response (R_2) (Kimura 1970; Ongerboer de Visser and Kuypers 1978; Shahani 1970; Shahani and Young 1972).

Evinger et al. (1984) showed that in guinea pigs, rabbits, and humans, eye movements accompany blinking. In this study it was also demonstrated that eye movements during voluntary and spontaneous blinking have no mechanical origin and in man probably are due to cocontraction of extraocular muscles. In man it has been demonstrated that the eye-globe not only makes a slight displacement of 1–2 mm back into the orbit (Evinger et al. 1984) but also performs a horizontal, vertical (Collewijn et al. 1985; Riggs et al. 1987), and torsional rotation (Straumann et al. 1996). Although it was originally thought that in man the eyes move nasally upward during voluntary and spontaneous blinking (Evinger et al. 1984; Ginsborg and Maurice 1959), the rotation of the eye in straight-ahead position normally is directed nasally downward (Collewijn et al. 1985; Riggs et al. 1987). This rotation also depends on the initial eye position (Riggs et al. 1987). However, to what extent the different extraocular muscles contribute to this combined translational and rotational movement during blinking is not yet known.

Not only blinking is accompanied by eye movements. For example, during prolonged blinking or permanent closure of the eye, lateral and/or vertical conjugate eye movements occur (Collewijn et al. 1985). Resistance against forceful opening of the eye normally induces a conjugate strong upward movement of the eyes (Bell's sign). Furthermore, concurrent with vertical eye movements the upper eyelid moves up and down. Also the

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eye opens a little further on lateral gaze. In addition, under pathological conditions, blinking may facilitate saccadic eye movements (Leigh et al. 1983; Zee et al. 1983). Abnormalities of eyelid movements and eye movements have been reported in disorders of the basal ganglia and/or the midbrain (Berardelli 1985; Jankovic 1988). In essential blepharospasm, eye movement disorders occasionally accompany the spasms of the eyelids (Aramideh et al. 1994a). The interactions between different types of eye and eyelid movements may utilize the same neural circuit (Becker and Fuchs 1988).

So far simultaneous recording of EMG of the OO muscle and eye movements together with monitoring of the eyelid movement during reflex, voluntary, or spontaneous blinking to our knowledge, have never been investigated. In this study the temporal relationship between the different components of eye and eyelid movements during spontaneous, voluntary, and reflex blinking have been established. It is hypothesized that there exists a common premotor structure for all types of blinking that may also operate independently of the saccadic and the vergence systems. Preliminary reports on this study have been published (Bour et al. 1996, 1999; Ongerboer de Visser et al. 1998).

METHODS

Subjects

Seven healthy subjects participated in the present study, including one female subject (*F1*), tested at the age of 22 yr and 6 male subjects (*M1–M6*) with a mean age of 34 yr. Subject participation followed informed consent before inclusion in the study. Test protocols and ethics committee approval was in accordance with the tenets of the Declaration of Helsinki.

Eye movement recording

The eye movements of both eyes were measured with the double magnetic induction method (DMI) described by Bour et al. (1984). The subject's head was positioned in a homogeneous alternating primary magnetic field with constant amplitude. Horizontal as well as vertical eye positions were derived from a secondary magnetic field picked up by a detection coil placed in front of the eye. Gold-plated metallic rings attached to the subject's eye (anesthetized with one droplet of 0.4% solution of Oxybuprocainehydro-chloride) generate this secondary field, and its strength is related to the rotation of the rings. Magnetic field strength is measured with a phase-locked amplitude technique (Robinson 1963), and within the range of -15 to 15° , raw eye signals do not deviate $>5\%$ from linearity. Beyond this range, signals become nonlinear and saturate at $\sim 25^\circ$. The cross talk between left and right eye position is $<5\%$. In horizontal direction this cross talk is negative, and in vertical direction it is positive. This means that the difference between left and right eye in horizontal direction (vergence) increases maximally up to 5% . Possible differences between left and right eye in vertical direction (hyperdeviation) decreases maximally up to 5% . For this under- and overestimation of left and right eye differences due to cross talk is accounted for, whenever it is necessary. Within the linear range, the average resolution is 5 minarcs. The subject's head was stabilized by a chin rest and a head tie to reduce drift and head movements. With this head stabilization, the baseline drift did not exceed 20 minarcs over a 20-min period. Despite these previously mentioned inaccuracies, that can be neglected for the purpose of this study, in comparison to the search coil method (Collewijn 1975; Robinson 1963), the use of magnetic fields and the absence of wires makes this electromagnetic

eye movement recording method with a ring particularly appropriate for recordings with the eyelids closed.

Eyelid movement recording

Upper eyelid movement was monitored using a modified magnetic search coil technique, as was described by Evinger et al. (1991). The electromagnetic field employed for the eye movement recording was also used to record the eyelid movements. A very fine wire coil consisting of 10 turns of a Teflon-coated copper wire, 0.05 mm OD, was attached to the upper eyelid. The weight of the coil was negligible, and it did not appear to hinder eyelid movements. Calibration before the experiment mapped the output voltage of the eyelid coil to the $+90$ and -90° position. Between these two extremes the relation between voltage and angle of rotation was supposed to change in a sinusoidal fashion, and measured coil voltages were converted accordingly to upper eyelid angles.

EMG recording

EMG recordings were performed from OO muscles, using Ag/AgCl surface electrodes placed over the lower eyelids (Ongerboer de Visser and Goor 1974), simultaneously with recording of eye and eyelid movements. The supraorbital nerve was stimulated with the cathode placed over the supraorbital foramen and the anode 2 cm higher and lateral on the forehead. Impedance of the electrodes was always <5 k Ω . The EMG apparatus (Medelec Sapphire) used for amplification of the EMG signals simultaneously was used to apply constant current pulses with a duration of 0.2 ms. To avoid that the alternating primary electromagnetic fields with a frequency of 30 and 40 kHz were picked up by the EMG electrode leads, and the EMG amplifiers extra shielding and filtering was applied.

Data acquisition

Raw signals of horizontal, vertical positions of the eyes and vertical position of the upper eyelid were low-pass filtered (-3 dB at 150 Hz, 2nd-order Bessel filter). The low-pass filter of the EMG amplifiers was set to 500 Hz and the high-pass filter at 1 Hz (12 dB/oct). All signals were digitized with a sample frequency of 1,000 Hz and stored in the computer. The sweep time was 500 ms with a 25-ms prestimulus interval. Data analysis was performed off-line.

Calibration and paradigms

To calibrate the positions of both eyes, at the beginning of each experimental session, the subjects were asked to track, as accurately as possible, a single red circular laser spot of light that was back-projected on a white translucent screen by means of a scanning mirror device. The spot diameter was 0.4° , and its luminance was 20 cd/m 2 . A dimly illuminated background was used. Laser spots jumped either in horizontal or vertical direction -10 to $+10^\circ$ away from straight-ahead position. The subject was asked to fixate these different target positions successively, and the obtained raw eye position signals were used to calibrate the data.

Target positions were arranged in a regular 5 by 5 array, and the horizontal and vertical distance between the targets was 5° . One of the 25 different targets (laser spot) was shown, and the subject was asked to fixate the target. Eye and eyelid movements were recorded during voluntary and reflex blinks while the subject was successively fixating the different target positions.

RESULTS

Eye movement components and EMG responses during blink reflex

In all subjects measured, disconjugate oblique eye movements accompanied spontaneous, voluntary, and reflex blink-

ing. Trajectory profiles in Fig. 1A at straight-ahead position demonstrated that the oblique movements of both eyes during voluntary blinking were directed nasally and downward. Depending on the gaze position before blinking, the amplitude and direction of the eye movements during blinking varied in a systematic fashion. Concurrent with the increase of upward gaze, the downward directed vertical component increased. With abduction the nasally directed horizontal component of eye movement increased during blinking. At $\sim 10\text{--}20^\circ$ downward gaze and $10\text{--}20^\circ$ in adduction, the eye movements during blinking were at minimum. Electrical stimulation of the supraorbital nerve elicited eye movements as well as blinks (Fig. 1, B and C). Under all conditions (Fig. 1, A–C) the beginning of the trajectory is quite straight compared with the end. After the turning point (reverse of direction and velocity) trajectories become curved, and at the end of the blink the eye slowly drifts back to the initial position. Comparison of Fig. 1B with Fig. 1C shows especially ipsilateral to the side of stimulation, that with high stimulus intensity return trajectories become more curved, indicating larger differences between profiles and phases of horizontal and vertical components.

In Fig. 2 components of horizontal and vertical eye movement during electrical stimulation are shown together with simultaneously recorded EMG activity of the orbicularis oculi muscle in the same subject as Fig. 1. The examples shown here illustrate for right as well as left side stimulation the difference in response profiles between high and low current. During all conditions eyes were in straight-ahead position before blinking. Only with stimuli of near supramaximal intensity or higher an R_1 blink reflex response occurred in the OO muscle ipsilateral to the side of stimulation with a latency of $\sim 10\text{--}12$ ms (see *top left panel* of Fig. 2A and *top right panel* of Fig. 2B). Concurrent with this R_1 blink reflex response, a small early component in the eye movement was observed with a latency between 15 and 20 ms. This early eye movement component can also be observed in the trajectories of Fig. 1C. Both in Fig. 1B as well as in Fig. 1C, the data samples of the first 30 ms after electrical stimulation are plotted with bold symbols. If there is no movement during this first 30-ms period, the samples plotted with bold symbols coincide to one symbol (as shown in Fig. 1B) both for the right and the left eye. However, when ipsilateral to the side of stimulation there was a small movement during the first 30 ms a trajectory of bold samples is observed (Fig. 1C, *right panel*). Comparison of the bold samples during the first 30-ms period between the left eye and the right eye shows that ipsilateral to the side of stimulation the eye already has moved. Furthermore, the R_2 blink reflex response started 10–20 ms earlier than the late component of the eye movement. This can be observed in Fig. 2, A and B, by comparison of E_h and E_v with OO_{EMG} contralateral to the side of stimulation.

Figure 3 represents for another subject peak to peak amplitudes (A) and latencies (B) of left and right eye movement responses with varying stimulus intensity during left side stimulation. Initial eye position for all responses was straight ahead. When the stimulus intensity increased from 5 to 20 mA, the peak-to-peak amplitude of the horizontal movement of the left eye [$E_h(OS)$] increased from 1° to $\sim 6^\circ$, and the peak-to-peak amplitude of the horizontal component of the right eye [$E_h(OD)$] and of the vertical components of left [$E_v(OS)$] and right eye [$E_v(OD)$] increased from 1° to $\sim 3^\circ$. In Fig. 3B

latencies are plotted of the first eye position deflection ($>0.1^\circ$). With increasing stimulus intensity, latencies of the late eye movement component all decreased from $\sim 80\text{--}90$ ms to $\sim 30\text{--}40$ ms. When the stimulus intensity was approximately two to three times above the threshold value of ~ 4 mA, concurrent with the ipsilateral early R_1 blink reflex response in the OO muscle, the ipsilateral early eye movement component could be observed; the response showed either a late component or both an early and late component. Because of the presence of either one or two components at 10 and 15 mA in the *top left panel* of Fig. 3B [$E_h(OS)$], this results in 2 distinct latency values. At 20 mA there are always two components resulting in an early latency value only. The latencies of this early component decreased from ~ 25 to 15 ms, when the stimulus increased from 10 to 20 mA.

Latencies of eye movements, eyelid movements, and EMG responses

To determine more definitively the time relationship between eye movement and eyelid closure during blinking, simultaneously movement of the upper eyelid was recorded in four healthy subjects by placing a specially designed search coil on the outer surface of the upper eyelid. Figure 4, A and B, shows the right eye movement, the right eyelid movement, and the EMG activity of the left and right OO muscles in response to a stimulus current intensity of 8 mA in *subject F1*. Figure 4, A and B, represents the data for left and right side stimulation, respectively. The R_2 blink reflex response in the OO muscle always preceded eye and eyelid movements. Eye movements slightly preceded eyelid movement. A small early component of right eye movement could be seen with right supraorbital nerve stimulation.

Figure 5, A and B, shows the eye and eyelid movement and the EMG responses at a stimulus current intensity of 20 mA in the same subject as in Fig. 4. In comparison with the responses shown in Fig. 4, A and B, all responses had larger amplitudes and shorter latencies. The R_1 blink reflex response and the early component of the eye movement ipsilateral to the side of stimulation are clearly present now, although the early component is still rather small in comparison to the late component of the eye movement. Remarkably, Fig. 5B shows an early component also in the eyelid movement, which before eyelid closure shortly appeared to open the eye to a slightly greater degree. This latter component coincided with the start of the R_1 blink reflex response. The calculated eyelid velocity, also shown in Fig. 5B, demonstrates this more clearly. The latency of the late component of the eyelid movement in this subject was found to be significantly larger than the latency of the late component of the eye movement, irrespective of the stimulus current (see Figs. 4, A and B, and 5, A and B). The latency of the early component of the eyelid movement appeared to be slightly shorter than the early component of the eye movement (see Fig. 5B).

Relationships between the stimulus intensity and latencies of the eye movement and the latencies of the eyelid movement are plotted in Fig. 6A for the same subject as in Fig. 5 and for another subject in Fig. 6B. Both the early and the late components are depicted. With increasing stimulus intensity the latency of eyelid movement tended to decrease with a similar course as the latency of eye movement. At a stimulus intensity

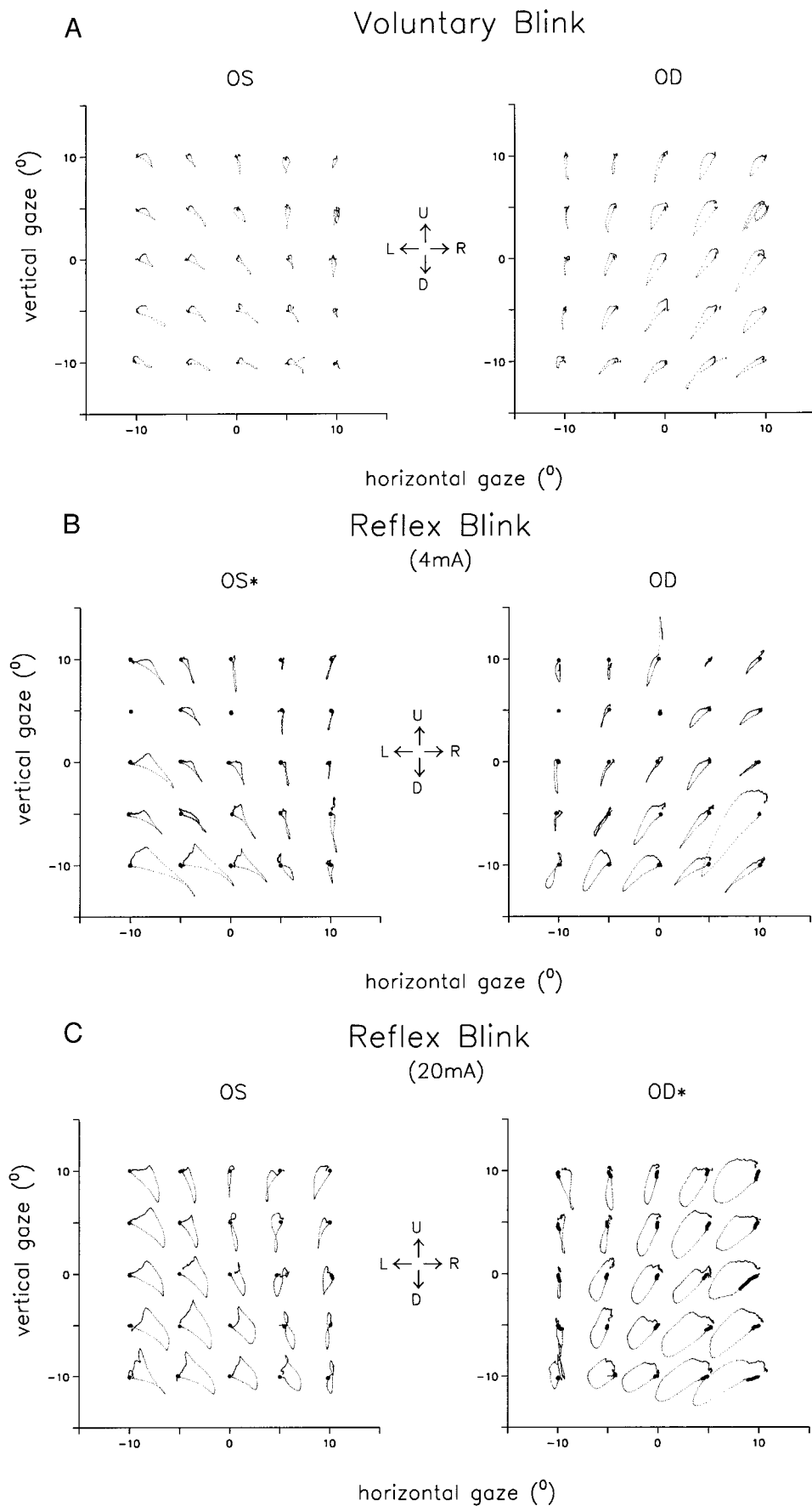


FIG. 1. A: voluntary blinking trajectories for both eyes are shown in *subject M3*. The initial eye position was varied across 25 gaze positions. Trajectories of the left and the right eye during the same blinks are shown at corresponding gaze angle in *left panel* (OS) and *right panel* (OD), respectively. The letters U, D, L, and R placed at the arrows in the middle indicate up, down, left, and right, respectively. Trajectories of both eyes during electrical stimulation of the supraorbital nerve are also depicted. B and C: eye movements in *subject M3* during reflex blinking at a left side (OS*), low current 4-mA stimulation, and at 20-mA high current stimulation of the right side (OD*), respectively.

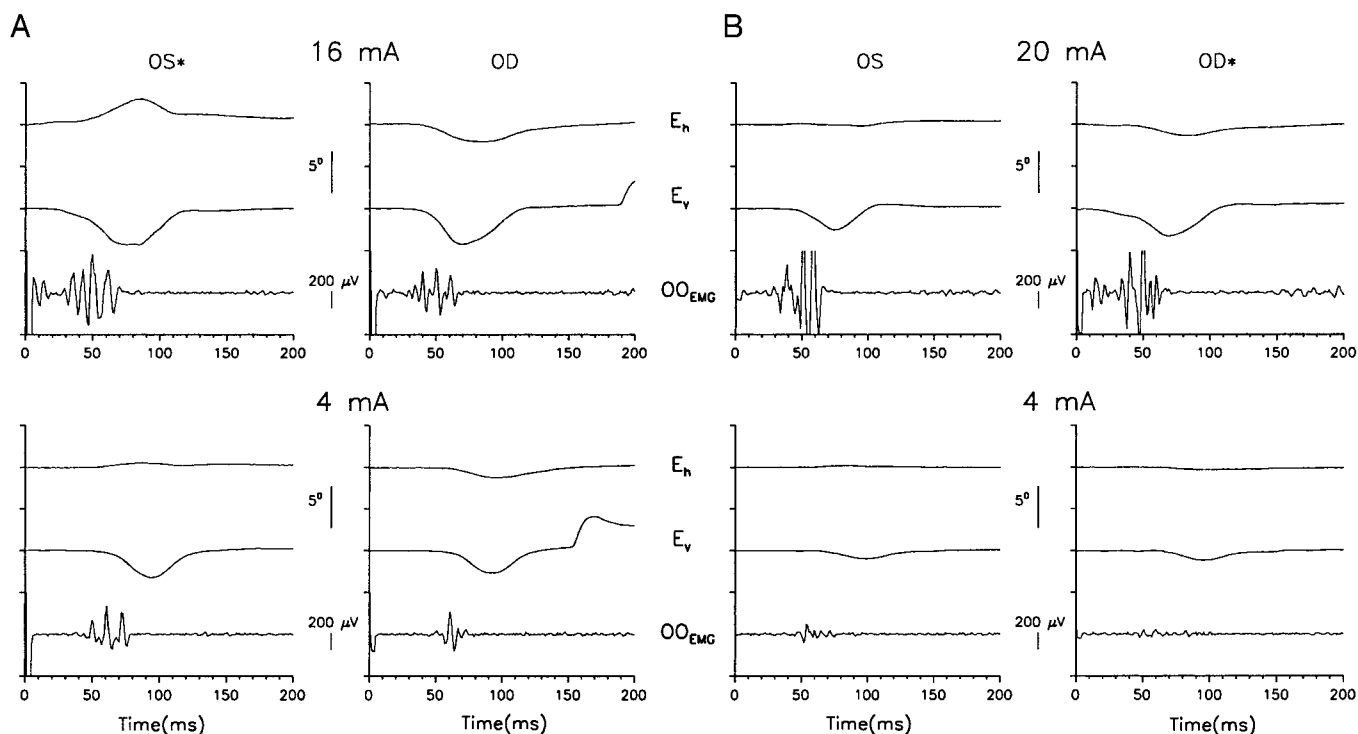


FIG. 2. Horizontal (E_h) and vertical (E_v) eye movement components and electromyogram (EMG) of the orbicularis oculi (OO_{EMG}) of left eye (1st and 3rd panel) and right eye (2nd and 4th panel) for subject M3 are shown. Upward deflections relate to rightward eye movement for the horizontal component or upward eye movement for the vertical component. A: the supraorbital nerve of the left eye (OS*) was stimulated with a current of 16 mA (top 2 panels) and 4 mA (bottom 2 panels), respectively. B: the supraorbital nerve of the right eye (OD*) was stimulated with a current of 20 mA (top 2 panels) and 4 mA (bottom 2 panels), respectively.

of 10–15 mA ipsilateral to the side of stimulation, the latency decreased discontinuously due to the switch from late to early component. Therefore the mean latencies of the contralateral late component, connected by the dashed line, is also depicted.

The similar eyelid/eye movement latency relationship is clearly demonstrated by the difference latency between upper eyelid movement and the concomitant horizontal and vertical eye movement component as depicted in Fig. 7, A–C, for three

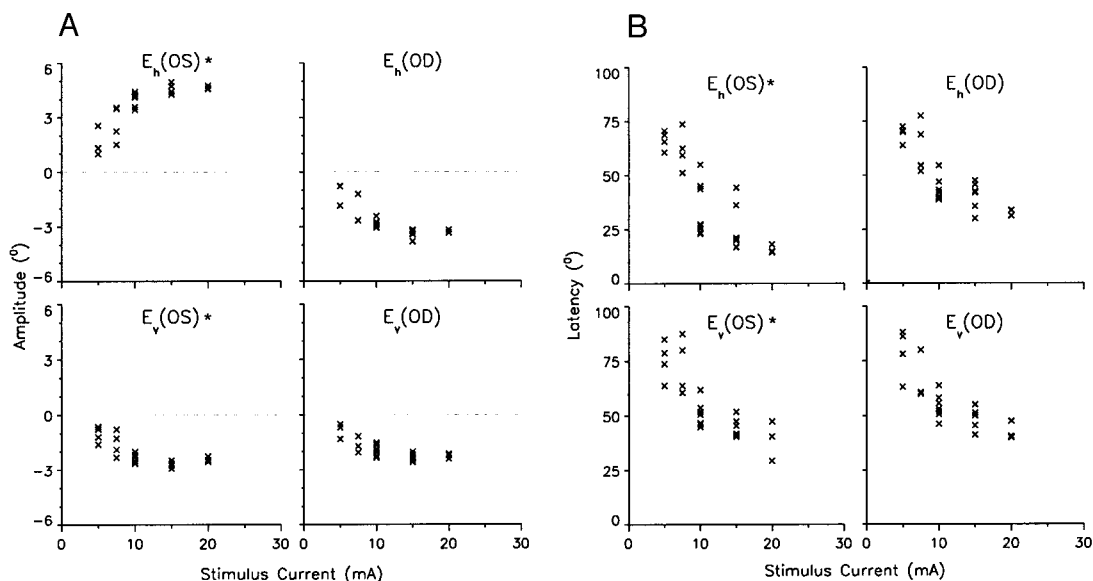


FIG. 3. Relationship between stimulus intensity and amplitude (A) of eye movement responses of horizontal [$E_h(OD)$ and $E_h(OS)$] and vertical components [$E_v(OD)$ and $E_v(OS)$] for subject M5 are shown. Upward deflections relate to rightward eye movement for the horizontal component or upward eye movement for the vertical component. The relationship between stimulus intensity and latency (B) of eye movement responses of horizontal [$E_h(OD)$ and $E_h(OS)$] and vertical components [$E_v(OD)$ and $E_v(OS)$] for this subject are shown in Fig. 3B. Data are obtained following stimulation of the left supraorbital nerve indicated by the asterisk. Note the occurrence of an early component in the top left panel of Fig. 3B.

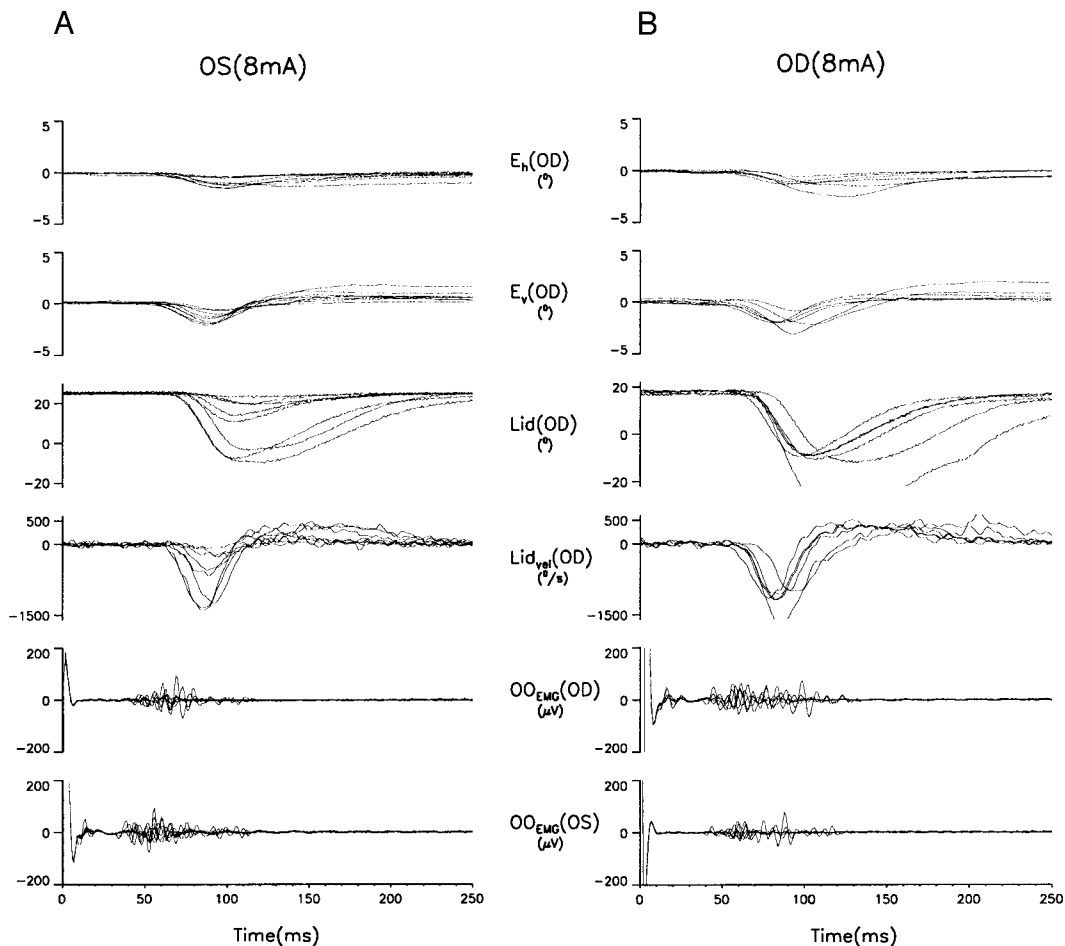


FIG. 4. For subject F1, depicted from top to bottom: horizontal [$E_h(OD)$], vertical [$E_v(OD)$] eye movement of the right eye, upper eyelid movement [$Lid(OD)$] and upper eyelid velocity [$Lid_{vel}(OD)$] for the right eye and EMG of the right orbicularis oculi [$OO_{EMG}(OD)$] and the left orbicularis oculi [$OO_{EMG}(OS)$]. Several responses after electrical stimulation of left (A) and right (B) supraorbital nerve with an 8-mA current are superimposed. Upward deflections relate to rightward eye movement for the horizontal component, upward eye movement for the vertical component and upward movement or upward velocity of the upper eyelid.

different subjects. The horizontal dashed lines in Fig. 7 represent the mean of all data points, and they demonstrate that, with respect to the early component, the eyelid movement slightly seems to precede the corresponding horizontal and vertical eye movement for two out of three subjects. With respect to the late component, eyelid movement for all three subjects does initiate on average 5–10 ms later than the corresponding eye movements. There are minor latency differences between the means of horizontal and vertical components.

Statistical analysis

A statistical analysis was performed on the various latencies for all seven subjects. The latency of horizontal and vertical eye movement as well as the latency of the eyelid movement and latencies of the R_1 and R_2 responses were determined interactively by computer with a marker. No statistically significant difference was found between the mean latency of the horizontal and the mean latency of the vertical eye movement responses, and therefore the latencies of horizontal and vertical eye movement responses were pooled. At supramaximal stimulation, mean latency of the ipsilateral early eye movement component was 14.6 ± 3.4 (SE) ms, and mean latency of the

bilateral late eye movement component was 42.9 ± 3.4 ms. Also at supramaximal stimulation, mean latency of the late component of eyelid movement for four subjects was 49.4 ± 5.8 ms. The dependency on stimulus intensity of the late component of eyelid movement as well as the late component of eye movement were compared for four subjects. Eyelid movement latency and eye movement latency appeared to be highly correlated ($r > 0.9$; $P < 0.001$), and the mean difference in latency between eyelid and eye movement was approximately constant and independent of stimulus intensity. Regardless of stimulus intensity, the late component of eye movement occurred an average of 8.3 ± 2.0 ms earlier than the late component of eyelid movement. This latency delay between eye movement and eyelid movement was much smaller than the total range (~ 40 ms) across which the individual latencies varied as a function of stimulus intensity (see also Fig. 6, A and B).

Finally, the R_2 blink reflex response of the OO muscle always preceded both the late component of the eye movement and the downward eyelid movement. The delay between the R_2 blink reflex response and the downward movement of the eyelid depended on the stimulus intensity and varied among subjects. At low current (slightly above threshold) this delay

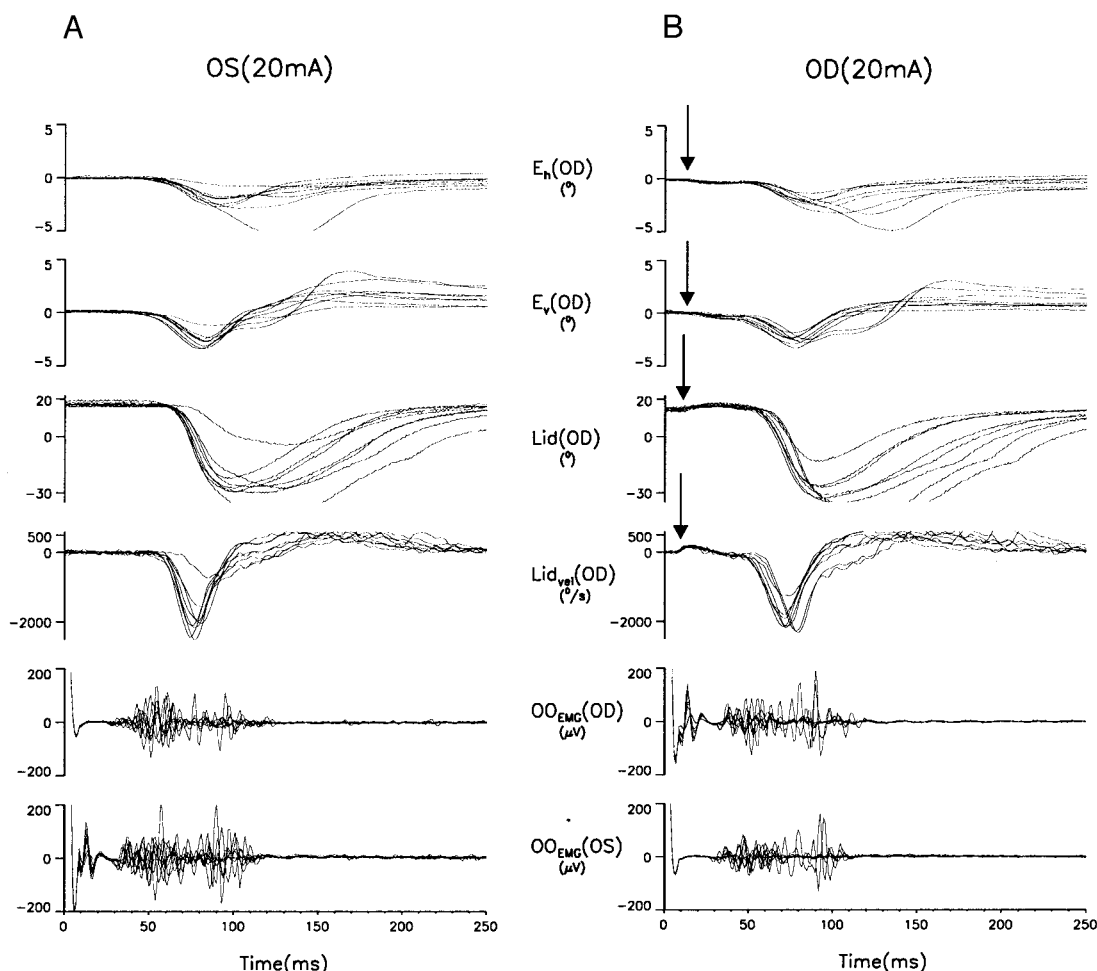


FIG. 5. Similar responses of the same subject as in Fig. 4, however, now the current intensity for both left (A) and right (B) supraorbital nerve stimulation is 20 mA. Arrows in the right column indicate the start of the early component.

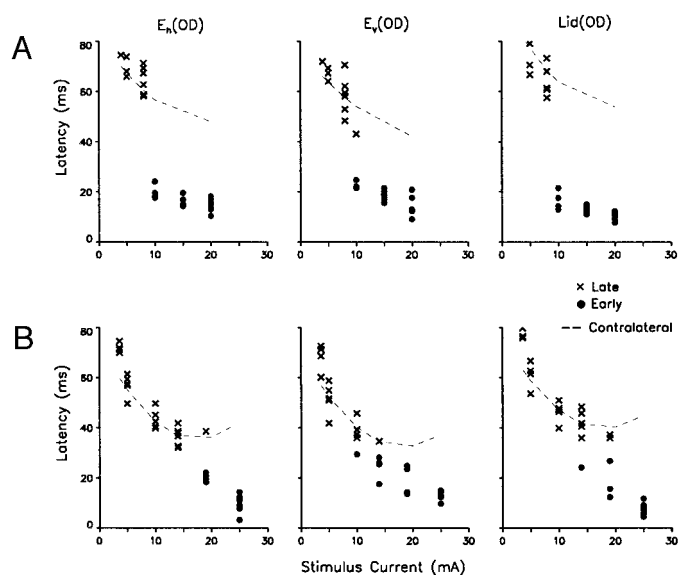


FIG. 6. For subject F1 (A) and subject M3 (B), the latency of the early (\times) and late (\bullet) responses of the horizontal component [$E_h(OD)$] and vertical component [$E_v(OD)$] of the eye movement and the movement of the upper eyelid [$Lid(OD)$] are shown. Dashed line depicts the average of the response latencies of the contralateral side.

ranged from 20 to 35 ms. At high current (about supramaximal) the mean latency for four subjects of the R_2 blink reflex response was 30.4 ± 2.3 ms. So the delay between R_2 blink reflex response and late component of eyelid movement (49.4 ± 5.8 ms) on average for four subjects is 19 ± 8.1 ms.

DISCUSSION

General findings and comparison with earlier studies

Eye movements accompany eyelid movements during spontaneous, voluntary, and reflex blinking. In all healthy subjects, trajectories of these eye movements across various gaze directions demonstrate similar patterns of downward and nasalward eye movements regardless of type of blinking. An increase of upgaze before blinking increases the downward directed vertical component, whereas an increase of abduction before blinking increases the nasally directed horizontal component of eye movement during blinking. These results are for straight-ahead eye position in accordance with findings of Collewyn et al. (1985) and for various gaze directions in agreement with the results of Riggs et al. (1987) during voluntary and spontaneous blinking. At ~ 10 – 20° downward gaze and 10 – 20° in adduction, eye movements during blinking were at minimum. The latter finding is in accordance with psychophysical results of

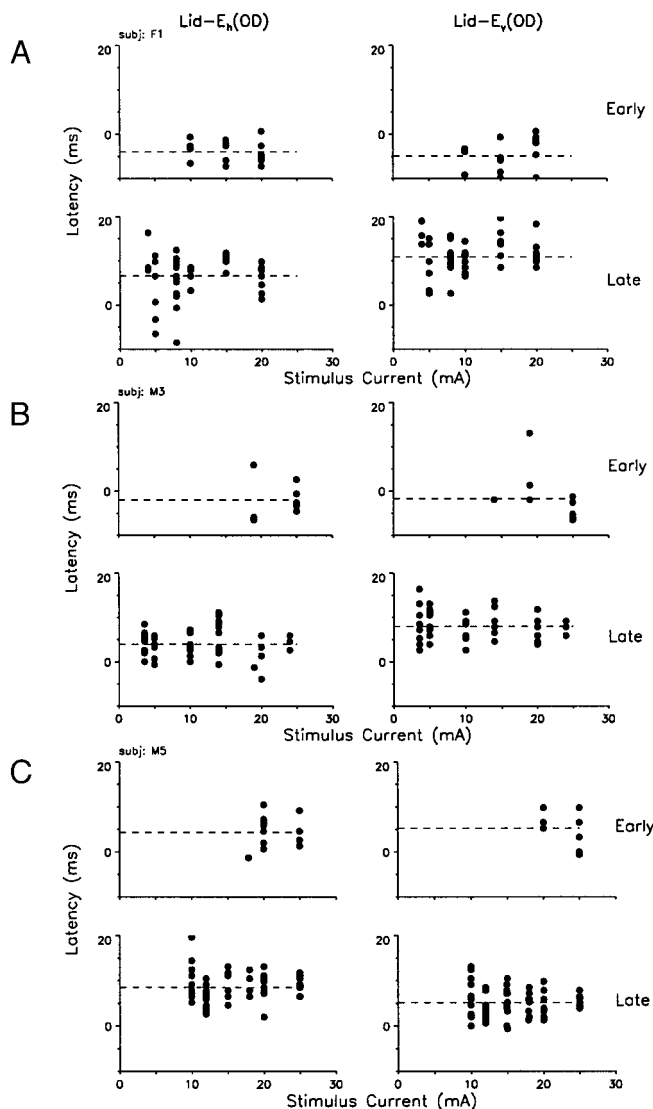


FIG. 7. For the early and late responses, measured in *subject F1* (A), *subject M3* (B), and *subject M5* (C), the difference between the upper eyelid movement and the horizontal eye movement $Lid(OD) - E_h(OD)$ in the left panels and the difference between the upper eyelid movement and the vertical eye movement $Lid(OD) - E_v(OD)$ in the right panels are shown. Differences are calculated from the same data as shown in Fig. 6. Horizontal dashed lines indicate the average of all data points of each figure.

Ginsborg and Maurice (1959) reporting minimum eye rotation during blinking by looking slightly downward and $\sim 10^\circ$ inward. This study now demonstrates that similar patterns of eye movements also exist during reflex blinking particularly at low current stimulation.

Neural activation of extraocular muscles versus passive movement of the eyeball

How is the neural activation of the auxiliary extraocular muscles that leads to this characteristic eye movement pattern during different types of blinking? Figures 4 and 5 demonstrate that the eyeball deflects from its gaze position before blinking almost with the same velocity as it returns back to the initial gaze position. Furthermore, irrespective of stimulus current amplitude, within ~ 150 – 200 ms after electrical stimulation the

eye globe returns to the initial position with an accuracy of ~ 1 – 2° . Thus the total period that the eye moves during blinking subtends ~ 100 – 200 ms. Consequently, this should imply that at the end of the blink, during opening of the eyelid, the eye returns to the initial eye position by active contraction of the extraocular muscles rather than by a passive movement. The latter should rotate the eyes more slowly to the position before blinking with a time constant of ~ 200 ms (Robinson 1981).

Which extraocular muscles are inhibited or (over)activated and to what degree during blinking cannot uniquely derived from the eye movements. In alert rabbit, Evinger and Manning (1993) measured EMG activity of extraocular muscles during reflex blinks and found that all extraocular muscles with the exception of the superior oblique were activated. In alert cat, it was reported (Delgado-Garcia et al. 1990) that 10% of the antidromically identified abducens motoneurons ipsilateral to the side of air-puff stimulation were active. Simultaneous recordings of motoneurons located in other oculomotor nuclei were not performed. In human, concurrent with the nasalward and downward movement at straight-ahead position during blinking, there is also a retraction of the eyes (Evinger et al. 1984) together with an extorsion (Straumann et al. 1996). In the study of Evinger et al. (1984), it is suggested that cocontraction of several or all of the extraocular muscles retracts the eyeball into the orbit, secondarily rotating the eye toward some primary rest position. The latter study also demonstrated vigorous burst of activity during blinking both in rabbit superior rectus and inferior rectus. An EMG study by Esteban and Salinero (1979) demonstrated in man during spontaneous and reflex blinking a reciprocal activity in the levator palpebrae muscle and the superior rectus muscle. Whereas in the levator palpebrae a brief inhibition was observed that abruptly ended, in the rectus superior a brief phasic overactivation was seen. Furthermore, Bratzlavsky and Van der Eecken (1975) found evidence for the presence of a 10- to 20-ms duration reflex response in lateral rectus muscle, 24–30 ms after electrical supraorbital skin stimulation. This reflex was not observed in the medial rectus. To obtain a more definite picture of the cocontraction of extraocular muscles during blinking in man, simultaneous motoneuronal recordings in different oculomotor nuclei particularly in monkey would be required. However, following the previous findings and the present results, we suggest that during spontaneous, voluntary, and reflex blinking a brief concurrent overactivation of both the superior and inferior rectus muscles occurs. This cocontraction of the vertical recti explains the retraction of the eyeball into the orbit. A possibly stronger phasic contraction of the inferior rectus than the superior rectus in straight-ahead position may account for the depression of the eyes. As a tertiary action both the overactivation of the superior rectus and inferior rectus may explain at least partly the adduction of the eye in straight-ahead position. It is not clear how much the lateral rectus muscle activity, as observed by Bratzlavsky and Van der Eecken (1975), reduces the nasalward directed component introduced by the tertiary action of the vertical recti. Because it is assumed that during blinking in straight-ahead position the phasic contractile force of the inferior rectus is somewhat stronger than that of the superior rectus, the secondary action of these vertical recti overall may lead to extorsion. In summary, an extra cocontraction of the inferior and superior rectus muscle during blinking

would be sufficient to give a simple explanation for both eye retraction and eye rotation in the horizontal, vertical, and torsional plane. As a consequence, the fast return to the eye position before blinking might not be explained by active contraction of the extraocular muscles. On the contrary, the passive elastic force of the eyeball and surrounding tissue that is provoked by an extra cocontraction of vertical recti and the concurrent translation of the eyeball back into the orbit might account for this fast return to the initial eye position. During an almost pure rotation, which occurs for instance during saccades, this translational force is absent. Our results and the hypothesis about the exerted forces of the different extraocular muscles in fact gives support to the idea of Evinger et al. (1984) that eye rotation, as observed during blinking, might be secondary to eyeball retraction.

Gaze dependency of eye movements during blinking

To what degree the extraocular muscles are activated and whether this activation pattern depends on the position of the eyeball in the orbit also remains ambiguous. A first possible explanation may be that activation and/or inhibition of the different extraocular muscles during blinking always occurs with the same degree independent of gaze position before blinking. The change of the eye movement trajectory depending on gaze position during blinking then may be simply explained by the plant characteristics. This means that the systematic change of amplitude and direction of the eye movement as a function of gaze position is caused by the fact that the degree of passive elastic forces of the extraocular muscles and the ocular tissue depends on muscle-length and gaze position. In combination with a constant neural activation of the muscles independent of gaze position, this may explain the characteristic eye movement pattern as shown in Fig. 1, A–C. An alternative but more improbable explanation may be that the neural activation of the extraocular muscles varies with gaze position before blinking. This could imply that before blinking the gaze position has to be stored (neural integrator) and fed back to the neural motor command to explain how after blinking the eyes come back to their initial position within a quite high accuracy. An interaction between the blink generating neural structures and the saccadic system, which has an accurate position control mechanism via an internal feedback loop (Robinson 1981), could account for this kind of neural integrator. However, this last hypothesis requires in fact a quite complicated neural control for an eyelid movement.

Origin of early component of eyelid and eye movement

During the electrically elicited blink reflex previous to the bilateral late eye movement component, a new, unilateral early eye movement component can be identified with higher currents. Another new finding is that during reflex blinking the upper eyelid shows an early component before eyelid closure that appears to open the upper eyelid to a greater degree concurrent with the presence of the early eye movement component, ipsilateral to the stimulation side. Latencies of the early component of eye movement are found to be 14.6 ± 3.4 ms, and the early component of eyelid movement are not significantly different from these values. Amplitudes of the early components are always significantly smaller than the late com-

ponents of eye movement and eyelid movement, although both increase with stimulus strength. The origin of these small early ipsilateral components is unclear. Based on their latencies, it is likely that the early components of eye and eyelid movement are not generated in the brain stem. The reason for that is as follows. In our control group the R_2 blink reflex response in the OO muscle on average precedes the beginning of the eyelid closure by 19 ± 8.1 ms (Evinger 1995). Consequently, the delay between the start of the inhibition of the tonic activity of the motoneurons of the levator palpebrae muscle and the resulting downward movement of the upper eyelid should also approximate 19 ± 8.1 ms. Levator palpebrae muscle and extraocular muscle activities that are responsible for the early components of eye and eyelid movement therefore have to precede these movements by a period ranging from 10.9 to 27.1 ms. However, the latency of the early components of eye and eyelid movement on average is found to be ~ 15 ms. This implies that with respect to these early components at maximum there is 4 ms left for neural conduction and/or delays. In fact, the early components probably could be a result of direct activation by the electrical stimulus of the extraocular muscles. Another argument against neural generation within the brain stem of these early components is that they are not bilateral. As has been shown by Stava et al. (1994) bilateral gating mechanisms regulate blink duration. Motoneurons also project bilaterally (Schmidtke and Büttner-Ennever 1992) to the levator palpebrae muscles of the left and the right eye. Thus the ipsilateral early components of eye movement and eyelid movement, occurring at higher stimulus intensities, are probably caused by a direct electrical stimulation of the motor nerves of the extraocular muscles or of the extraocular muscles itself, ipsilateral to the side of stimulation. The observed early transient opening of the eyelid before a blink could result from activation of Müller's muscle (Small et al. 1995). However, Müller activation gives rise to bilateral eyelid raising, whereas our results demonstrate unilateral eyelid opening before eyelid closure.

Common origin and neural substrate for eyelid and eye movements

Because the mean latency difference (8.3 ± 2.0 ms) between the late eye movement components and upper eyelid closure do not change significantly across the range of various stimulus current intensities, this probably reflects a conduction and/or synaptic delay. Moreover, the late component of eye movement always precedes the upper eyelid closure, which may imply that ascending projections from the trigeminal complex first reach some of the motoneurons of the extraocular muscles of the eye and subsequently the motoneurons of the levator palpebrae muscle. Nevertheless, it is possible that viscoelastic properties of the upper eyelid make it react more slowly to muscle activation than eye movements. The fact that eye movements are initiated first again emphasizes that during blinking these movements cannot be due to mechanical forces of the upper eyelid movement but rather are of neural origin. Similar latency decrease for both eye movement and eyelid movement with increasing stimulus intensity indicates that they probably have the same origin, i.e., the sensory threshold mechanism of the trigeminal neurons.

Of further interest now is the anatomic framework in the

brain stem that may explain the combined rotational and translational movement of the eyeball and the eyelid closure during blinking. Previous studies (Aramideh et al. 1997; Cruccu et al. 1987; Evinger et al. 1991; Kugelberg 1952; Ongerboer de Visser and Kuypers 1978; Pellegrini et al. 1995; Shahani 1970) have shown that in humans the central pathway, for the R1 and R2 response are different. However, the pathways that are responsible for the inhibition of the levator palpebrae muscle and the cocontraction of the extraocular muscles during blinking are not known. Furthermore, recent studies of Basso and Evinger (1996) and Basso et al. (1996) in rat provide evidence for a basal ganglia modulation of reflex blinking via the colliculus superior, the nucleus raphe magnus, and the spinal trigeminal complex. The influence of the superior colliculus in the neuronal circuits of the blink reflex also have been demonstrated by a study of Gnadt et al. (1997) in monkey. Microstimulation of the caudal part of intermediate and deep layers of the superior colliculus appeared to be most effective in suppression of the blink reflex. A possible substrate for mediating this collicular suppression is a class of tonic, inhibitory cells in the pons: the omnipause neurons (OPNs). Most OPNs are contained within the nucleus raphe interpositus (Büttner-Ennever et al. 1988; Strassman et al. 1987), and they are also part of the saccadic pulse generator. Microstimulation of OPNs will stop saccades in midflight (Keller 1977). In addition, microstimulation of the region where OPNs are located, which are specifically quiet during blinking, suppresses reflex blinking in monkeys (Mays and Morrisse 1995). The superior colliculus also plays an important role in the generation of saccadic eye movements (Ottes et al. 1986; Scudder 1988; Waitzman et al. 1991; Wurtz and Goldberg 1972). Munoz and Wurtz (1993) have found cells (fixation cells) in the intermediate layer of the rostral colliculus in primates that exhibit tonic activity during fixation and pause during most saccadic movements. Conversely, in the intermediate layers of the caudal superior colliculus, cells have been demonstrated that are silent during fixation and burst for saccadic eye movements. This finding is somewhat in contrast with the result of Gnadt et al. (1997), who found that the most effective collicular stimulation site for inhibiting the blink reflex is at the caudal part. However, this lowest threshold site is slightly deeper located than the region of the saccade-related cells in the superior colliculus.

No coherent neuronal framework can be derived from these studies that explains the eye movements occurring with blinking or interactions between oculomotor and blink motor systems. However, we propose that the concurrent activation of extraocular muscles and inhibition of levator palpebrae muscle during blinking have a common origin. Similar to the saccadic pulse generator, this eye-blink generator may be composed of different premotor structures located in the brain stem including separate OPNs for blinking. This eye-blink generator is supposed to function independent of the basic types of eye movement such as the ocular saccadic and/or vergence systems and could operate in parallel with the main basic ocular motor systems. The similarity of disconjugate eye movement patterns independent of the type of blinking as found in this study argues in favor of a parallel input to the eye-blink neural generator. Future anatomic and/or histological studies have to be carried out in primates to provide further evidence for the existence of an eye-blink generator and its structure.

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