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Do Predictive Mechanisms Improve the Angular Vestibulo-Ocular Reflex in Vestibular Neuritis?

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Key Words
Vestibular neuritis · Vestibulo-ocular reflex · Head impulses

Abstract
Recovery from vestibular neuritis (VN) is often incomplete which leads to persistent vestibular imbalance during rapid head movements. Patients with unilateral vestibular lesions have a larger gain of the horizontal vestibulo-ocular reflex during active compared to passive head movements. To test whether this gain increase is related to predictive mechanisms we studied 15 patients with VN and 14 control subjects during predictable and unpredictable passive horizontal head impulses in the light and darkness. The vestibulo-ocular reflex showed a significantly shorter latency and higher gain in the light for predictable head impulses towards the ipsilesional side. However, this effect is small and might contribute but cannot exclusively account for the gain increase during active head movements.

Introduction

Vestibular neuritis (VN) is defined as a sudden spontaneous unilateral deficit of the peripheral vestibular organ without hearing impairment and no signs of brain stem dysfunction. Patients complain of rotatory vertigo and postural imbalance and have a horizontal spontaneous nystagmus with a torsional component and ipsilesional lateropulsion. These signs and symptoms of acute vestibular imbalance disappear within a few weeks. In contrast, dynamic vestibular imbalance often persists over months to years and results in persisting dizziness and oscillopsia during rapid head or body movements. Accordingly, the horizontal vestibulo-ocular reflex (VOR) often remains asymmetrical [Aw et al., 2001], particulary in the high frequency range as assessed by rapid head impulses [Schmid-Priscoveanu et al., 2001]. The head impulse test [Halmagyi and Curthoys, 1988] examines the relation between head and eye velocity during rapid head movements. It is an excellent tool to study the VOR and to identify a horizontal semicircular canal paresis. When eye movements are recorded with the scleral search coil technique, dynamic VOR deficits of single semicircular canals can be detected by head impulses in the appropriate canal planes [Aw et al., 2001; Cremer et al., 1998]. Thus, this technique also provides ideally suited condi-

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tions to investigate context-dependent differences in VOR performance.

It is unknown why some VN patients show effective functional recovery and others do not. It has been suggested that well-compensated patients learn to use other behavioural strategies [Curthoys and Halmagyi, 1999]. VOR gain in patients with unilateral vestibular lesions is larger during active (self-generated) than passive (manually generated) head movements [Black et al., 2005; Della Santina et al., 2002; Halmagyi et al., 2003]. Therefore we asked whether this difference is at least in part related to the better predictability of active head movements. To eliminate confounds resulting from self-generated movement we compared VOR responses to predictable versus unpredictable, passive head impulses.

Subjects and Methods

Control Subjects

Fourteen healthy subjects (9 males, 5 females; mean age 40 ± 17 years, range 23–63 years) without any history or clinical signs of vestibular or neurological disease participated in the study.

Patients with Idiopathic Sudden Unilateral Vestibular Hypofunction

Fifteen patients (10 males, 5 females; mean age 53 ± 10 years, range 35–71 years) with the first unilateral vestibular deficit were included in the study after written and informed consent had been obtained. The study was in accordance with the ethical principles of the Declaration of Helsinki 1964 for research involving human subjects, and it was approved by the local ethics committee of the University of Lübeck. Patients were diagnosed to have unilateral vestibular neuritis by clinical criteria (subacute onset of rotatory vertigo with postural imbalance, horizontal nystagmus with rotatory component to the contralesional side, clinical evidence for canal paresis by the Halmagyi-Curthoys head impulse test, no evidence of central vestibular or oculomotor signs) and bilateral caloric irrigation with at least 25% canal paresis of the affected side. None of the patients reported auditory symptoms. Search coil recordings were obtained on average 5.5 days after the onset of vestibular symptoms when spontaneous nystagmus was absent on fixation. Neurological history and neurological examination were otherwise unremarkable in all patients.

Experimental Protocol

After pitching the head 30° downward in the starting position, passive head impulses in the horizontal canal plane were applied manually in two different conditions: (1) unpredictable for direction and onset of head impulse (unpredictable condition) and (2) predictable for direction and onset (predictable condition). In the unpredictable condition, 20 head impulses to the right and 20 to the left were delivered in a pseudorandom order at different intervals (range: 4–6 s). In the predictable condition, 20 head impulses were delivered first in one direction and then 20 in the other direction at regular time intervals (5 s). The time intervals and directions were given to the investigator by short beep sounds by headphones (audible for the investigator only). Half of the subjects started with the unpredictable condition, the others with the predictable condition. The direction of the initial 20 head impulses in the predictable condition was varied so that half of the patients started to their paretic side. Subjects were demonstrated the head impulses prior to the recordings. They were instructed that one condition will contain always the same (predictable) direction of head impulses whereas the other condition will vary in direction and onset. Prior to each condition, they were informed about the type of the following condition.

All subjects were instructed to fixate a central target (at a distance of 1.4 m) during the head impulse test. One group of subjects performed the head impulse test in the light with a black-white grid for stronger retinal stimulation (8 patients, 5 control subjects), a second group in darkness with a central red laser fixation point (7 patients, 9 controls).

Eye and Head Movement Recording

Eye and head movements were recorded with the scleral search coil system (Remmel Laboratories, Ashland, Mass., USA) with 3D coils (Skalar, Delft, the Netherlands) [Rambold et al., 1998]. Semicircular canal function was analysed by high-acceleration, small-amplitude head impulses [Rambold et al., 2005].

Data Analysis

Eye and head position calibration was performed using a combined offline in vitro and in vivo technique [Rambold et al., 1998, 2002]. Eye movements were filtered with a Gaussian low-pass filter (cut-off frequency 100 Hz), and eye-in-head and head-in-space position were calculated in a right-handed coordinate system [Rambold et al., 1998]. Head movement onset was determined by an initial head velocity exceeding 3°/s. Only head impulses of low amplitude (20–30°), high velocity (150–500°/s) and high acceleration (4,000–12,000°/s^2) were analysed. Head velocity trials which deviated more than 2 standard deviations from the mean head peak velocity were excluded from further analysis. Active head movements were largely excluded (1) by exercise of passive head impulses prior to search coil recordings, (2) when the investigator noticed neck muscle tension or active head movements and (3) if head velocity exceeded 3°/s prior to the acoustic signal. Head movements were analysed by an interactive program (using Matlab 6.5; The Mathworks, Natick, Mass., USA). The onset of each head movement was inspected trial by trial and corrected if necessary. Head impulses with dispersed velocity profiles (e.g. multiple velocity peaks) were dismissed from further analysis to exclude potential active head movements. Eye movement onset was defined when eye velocity was faster than head velocity at its determined onset within an interval of 20 ms before and 80 ms after head movement onset [Aw et al., 1996], i.e. anticipatory saccades were largely excluded. Latency was defined as the time from the onset of head movement to eye movement onset (fig. 1a). VOR velocity gain was calculated within the first 30–75 ms of the head impulse [Halmagyi et al., 2003]. Statistically significant differences were assessed by the Wilcoxon test ($p < 0.05$), reported data are depicted as the mean ± standard error of mean.

Results

Head impulses reached up to 250–400°/s and analysis reliably detected semicircular canal paresis (fig. 1b, c).

Eye latency in the light was on average 5.8 ms significantly longer in VN patients (mean: 10.2 ± 0.8 ms) than in control subjects (4.4 ± 0.7 ms). Increase in latency was found during head impulses not only to the ipsilesional (mean: 12.6 ± 1.38 ms), but also to the contralesional side (mean: 8.0 ± 0.6 ms; fig. 2a). However, latency was significantly shorter during ipsilesional head impulses in the predictable condition in the light when intra-individual differences (fig. 2b; 5.3 ± 2.2 ms; $p < 0.05$) between the predictable and unpredictable conditions were calculated. In contrast, there were no significant differences in the darkness condition and when head impulses were performed to the contralesional side (fig. 2b).

VN patients had on average a horizontal VOR gain of 0.48 ± 0.04 on the ipsilesional side and 0.73 ± 0.02 on the contralesional side (fig. 1c, 2c, d) which was significantly lower when compared with healthy control subjects (0.93 ± 0.02). Control subjects did not show any side-specific differences.

The horizontal VOR gain differed between the predictable and unpredictable conditions when head impulses were performed to the ipsilesional side. There was a small but significant intra-individual gain increase of 2.8 ± 0.8% during head impulses to the ipsilesional side in the predictable condition in the light (black-white grid, $p < 0.02$; fig. 2d). In contrast, this effect was not seen in darkness (LED fixation) and with contralesional head impulses. There were no significant differences in head ve-

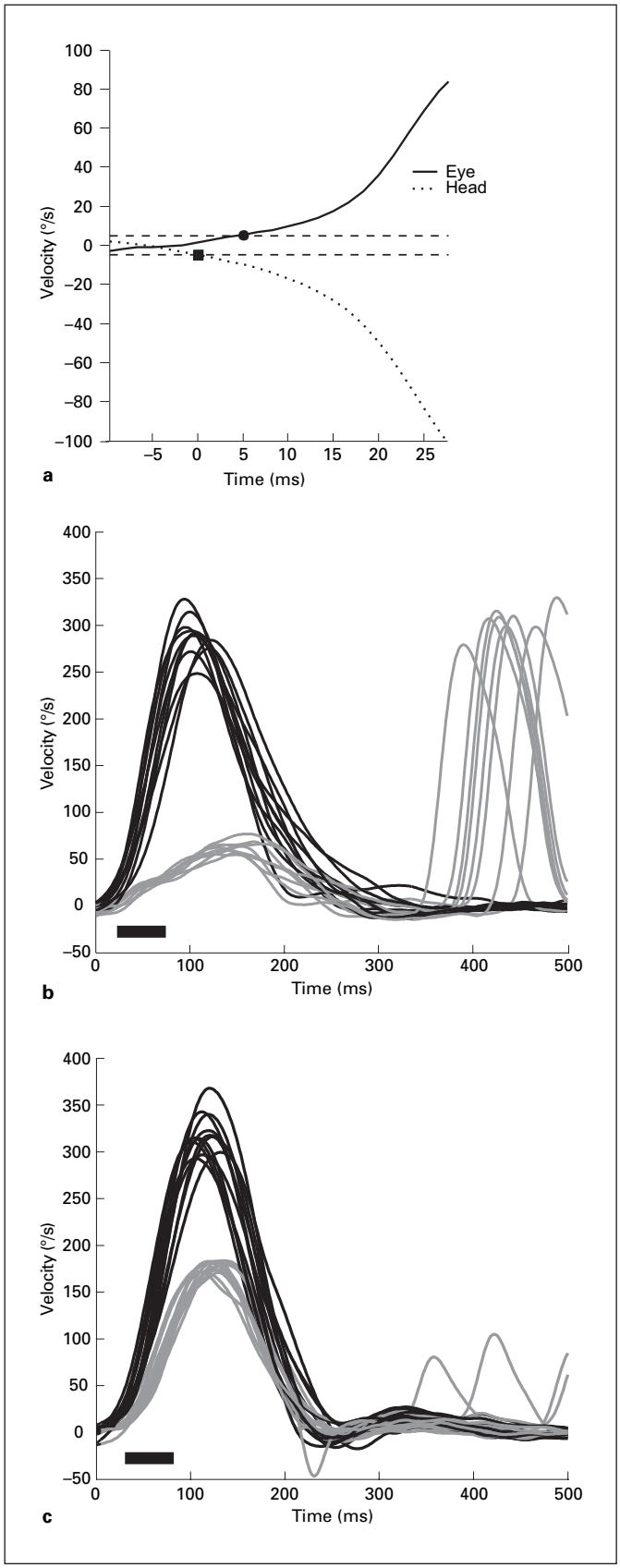

Fig. 1. a Head (dotted line) and eye (solid line) velocity traces are shown to illustrate how latency of eye movement onset was determined. The lower dashed parallel horizontal line indicates when the initial head velocity exceeds 3°/s, the upper dashed line reflects the threshold for eye movement onset (eye faster than head velocity) derived from head velocity at its determined onset in this trial (see Methods). Latency was defined as the time from the onset of head movement to eye movement onset, e.g. 6 ms in this single trial example of a control subject. **b**, **c** Velocity traces of head-in-space (black lines) and eye-in-head (grey lines) of 1 patient with a left VN are shown in the light during horizontal head impulses to the left (ipsilesional, **b**) and right (contralesional, **c**) sides. Velocity data have been inverted for better comparison. Corrective saccadic eye movements occur after the end of the head impulse. The black bar indicates the interval (first 30–75 ms of the head impulse) in which VOR velocity gain was calculated (**b** gain of 0.2; **c** gain of 0.58).

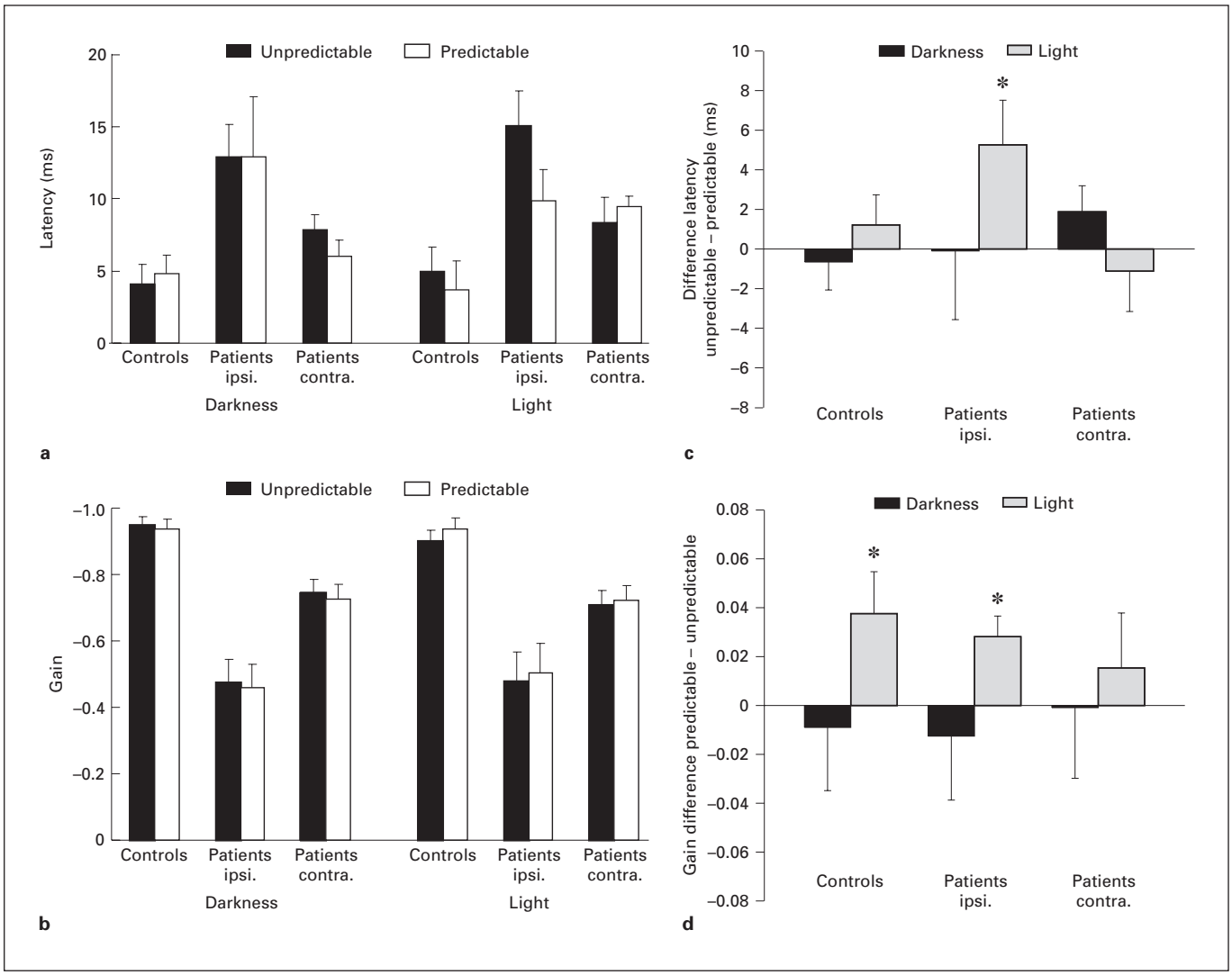

Fig. 2. Latency (**a**) and velocity gain (**b**) of angular VOR in the light and darkness are shown, separated for the ipsi- and contralesional sides in the predictable (open bars) versus unpredictable condition (hatched bars) in the light (right) and darkness (left). Mean intra-individual differences between predictable and unpredictable impulses are shown for latency (**c**) and gain (**d**) in the light (grey) and darkness (black) conditions (unpredictable minus predictable value). Bars represent means and standard errors. * $p < 0.05$: significant intra-individual differences. contra. = Contralesional; ipsi. = ipsilesional.

locity (predictable: 255 ± 9.8°/s, unpredictable impulses: 260 ± 10.2°/s) or head acceleration (predictable: 6264 ± 339.3°/s², unpredictable impulses: 5841 ± 149.6°/s², $p > 0.05$) during head impulses towards the ipsilesional side in the light. Likewise, latency to peak head velocity did not differ between both conditions (unpredictable head impulses: 100.4 ± 4.7 ms, predictable impulses: 103.2 ± 4.6 ms). The level of vestibular paresis did not differ between head impulses performed in the light and darkness. There was no correlation between VOR gain deficit and the intra-individual gain difference between the predictable and unpredictable conditions. Results were independent of the sequence of head impulses, i.e. either first in the predictable and then in the unpredictable condition or vice versa.

Control subjects showed an intra-individual gain increase of 3.6 ± 2.3% in the predictable as compared with the unpredictable condition.

Discussion

The study was designed to investigate the role of prediction in the VOR gain increase during active as compared with passive head impulses [Della Santina et al., 2002; Halmagyi et al., 2003]. Active and passive head impulses constitute several differences [Black et al., 2005]. Responses to active head movements may include preprogrammed responses and a prediction of the sensory consequences of the head movement, e.g. subjects may learn to predict their own gaze errors [Black et al., 2005]. Since there are no active head movements without these predictive components, one cannot control this confounding factor in this active condition. However, passive head impulses allow to control some aspects of prediction, e.g. onset and direction certainty. Therefore, we compared passive head impulses under two conditions: a predictable and an unpredictable condition with respect to onset and direction certainty.

In accordance with previous studies of patients with peripheral de-afferentation [Halmagyi et al., 2003] and VN [Aw et al., 2001], our patients had not only a reduced horizontal VOR gain during passive head impulses towards the lesioned side, but also a moderately reduced gain for impulses to the contralesional side [Aw et al., 2001]. Probably, this contralesional gain decrease does not reflect recovery of the peripheral vestibular nerve but rather ineffective central compensation [Palla and Straumann, 2004]. According to our data predictive mechanisms do not contribute to central up-regulation of the contralesional VOR gain [Palla and Straumann, 2004].

Comparing the predictable and unpredictable conditions intra-individually our study reveals a decreased VOR latency and increased gain for predictable as compared to unpredictable head impulses which indicate small angular VOR improvement probably by predictive mechanisms. These predictive mechanisms are visually dependent since the effects were only found in the light but not in the darkness condition. Conversely, the VOR improvement cannot be explained by visual mechanisms alone since it was not obtained in the light condition when head impulses were unpredictable. This indicates that only the combination of predictable head impulses and a visually enhanced VOR facilitates the VOR improvement. This appears to be a specific effect since it was only found for head impulses to the ipsilesional side. This gain improvement is probably not caused by different head velocities or different levels of the canal paresis in both conditions during predictable versus unpredictable head impulses.

However, the VOR improvement in the predictable condition was small and can probably not account for the considerable gain improvement for active as compared to passive head impulses [Black et al., 2005; Della Santina et al., 2002; Halmagyi et al., 2003]. This difference has been related to enhanced sensitivity of second-order vestibular neurons to active head movements [Halmagyi et al., 2003] which is different for self-generated and passive head movements [McCrea et al., 1999]. In contrast to vestibular afferents [Cullen and Minor, 2002], there are some experimental data suggesting that the vestibular system is able to dissociate active from passive head movements at the level of the vestibular nuclei [Cullen and Roy, 2004]. The latter receive converging input from cerebellar and numerous cortical areas involved in cognitive aspects of vestibular function, e.g. the parieto-insular vestibular cortex [Akbarian et al., 1994] and extravestibular cues presumably supplying motor efference copy signals (review in Fukushima [1997]). Thus, with these properties the vestibular nucleus neurons are likely to be influenced by predictive mechanisms. Future studies should try to investigate whether this small predictive effect can (1) be enhanced by vestibular training and (2) explain why some VN patients show good and others poor recovery. According to our data it is likely that additional factors contribute to the VOR gain increase during active head movements: first, predictable preprogrammed responses inherently associated with active head impulses [Della Santina et al., 2002; Halmagyi et al., 2003] and, second, neck proprioceptive afferents which are predicted and possibly cancelled in the active condition.

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