

Vestibular and cerebellar contribution to gaze optimality

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Patients with chronic bilateral vestibular loss have large gaze variability and experience disturbing oscillopsia, which impacts physical and social functioning, and quality of life. Gaze variability and oscillopsia in these patients are attributed to a deficient vestibulo-ocular reflex, i.e. impaired online feedback motor control. Here, we assessed whether the lack of vestibular input also affects feed-forward motor learning, i.e. the ability to choose optimal movement parameters that minimize variability during active movements such as combined eye-head gaze shifts. A failure to learn from practice and reshape feed-forward motor commands in response to sensory error signals to achieve appropriate movements has been proposed to explain dysmetric gaze shifts in patients with cerebellar ataxia. We, therefore, assessed the differential roles of both sensory vestibular information and the cerebellum in choosing optimal movement kinematics. We have previously shown that, in the course of several gaze shifts, healthy subjects adjust the motor command to minimize endpoint variability also when movements are experimentally altered by an increase in the head moment of inertia. Here, we increased the head inertia in five patients with chronic complete bilateral vestibular loss (aged 45.4 ± 7.1 years, mean \pm standard deviation), nine patients with cerebellar ataxia (aged 56.7 ± 12.6 years), and 10 healthy control subjects (aged 39.7 ± 6.3 years) while they performed large (75° and 80°) horizontal gaze shifts towards briefly flashed targets in darkness and, using our previous optimal control model, compared their gaze shift parameters to the expected optimal movements with increased head inertia. Patients with chronic bilateral vestibular loss failed to update any of the gaze shift parameters to the new optimum with increased head inertia. Consequently, they displayed highly variable, suboptimal gaze shifts. Patients with cerebellar ataxia updated some movement parameters to serve the minimum variance optimality principle but inaccurately undershot the target leading to an average gaze error of $11.4 \pm 2.0^\circ$. Thus, vestibulopathy leads to gaze variability not only as a result of deficient online gaze control but also a failure in motor learning because of missing error signals. Patients with cerebellar ataxia in our setting can learn from practice—similar to recent findings in reaching movements—and reshape feed-forward motor commands to decrease variability. However, they compromise optimality with inaccurately short movements. The importance of vestibular information for motor learning implies that patients with incomplete bilateral vestibulopathy, and patients with cerebellar ataxia, should be advised to actively move their head whenever appropriate. This way, sensory error signals can be used to shape the motor command and optimize gaze shifts trial-by-trial.

Keywords: cerebellar ataxia; vestibulopathy; motor learning; optimal control; eye-head movements

Introduction

There are many ways of combining eye and head movements to perform large gaze shifts. The unique selection of movements (Guitton and Volle, 1987) suggests an underlying optimization. We have recently shown that movements are optimally selected to minimize gaze variability (Sağlam *et al.*, 2011), as previously proposed for head-fixed saccades (Harris and Wolpert, 1998; van Beers, 2008). This strategy explains the choice of stereotyped kinematics, i.e. eye and head movement durations and velocity profiles, not only in the natural condition but also when the head moment of inertia is experimentally increased in healthy subjects (Fig. 1). Here, we assess the roles of sensory vestibular information and the cerebellum in choosing optimal movement kinematics.

Patients with chronic bilateral loss of vestibular function have large post-movement gaze variability (Maurer *et al.*, 1998) and experience disturbing oscillopsia (Dandy, 1941), which affects

physical and social functioning, and quality of life (Guinand *et al.*, 2012). This has been fully attributed to the fact that online vestibular gaze control, i.e. vestibulo-ocular reflex function, is deficient (for review, see Bronstein, 2004). It is well-known that during active gaze shifts, differential vestibular information signalling the discrepancy between desired and actual head movement is used for online control of eye (Cullen and Roy, 2004) and head (Goldberg and Cullen, 2011). In the light of the findings that movement parameters are chosen to minimize movement variability (saccades: Harris and Wolpert, 1998; van Beers, 2008; gaze shifts: Sağlam *et al.*, 2011), gaze variability in patients with vestibular loss could also reflect an imperfect choice of movement parameters, i.e. a suboptimal feed-forward motor command. A role of vestibular input for motor learning has been suggested in reaching movements (Lackner and DiZio, 2005) and balance control (Day and Cole, 2002; Kuo, 2005; for review, see Fitzpatrick and Day, 2004). However, it is not clear whether

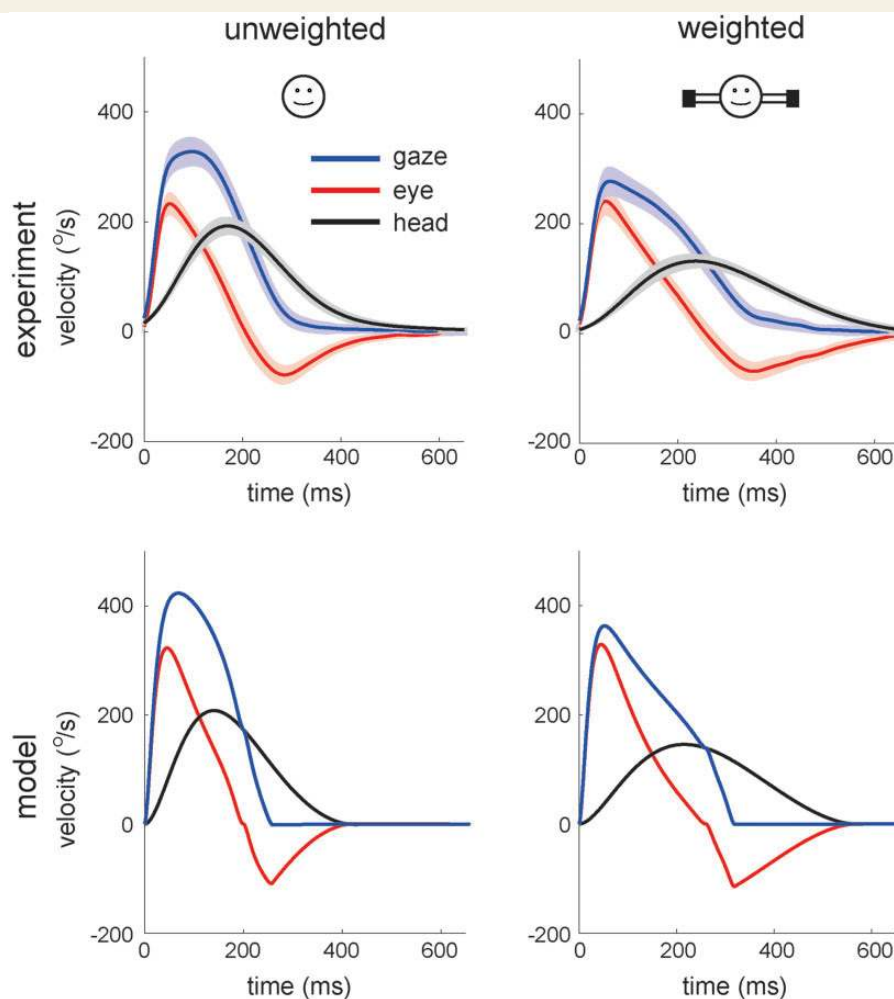


Figure 1 Top: Experimentally observed velocity traces of eye (red), head (black), and gaze (blue) in the unweighted (natural, left) and weighted (increased head moment of inertia, right) conditions. Traces show mean (solid line) and standard error (shaded area) of 10 healthy subjects. Bottom: Simulated eye, head, and gaze velocity traces generated by an optimal control model that minimizes gaze variability (Sağlam *et al.*, 2011). The model accounted not only for the natural velocity profiles but also the changes following an increase in the head moment of inertia, e.g. prolonged eye and head durations, decreased peak head velocity, and increased skewness of the gaze profile.

vestibular signals used for online gaze control are, in addition, necessary to shape the motor command and choose optimal eye-head movement parameters on a trial-by-trial basis.

The cerebellum plays a major role in movement learning (for review, see Bastian, 2006). It is believed to host adaptive internal models (Ito, 1970, 1984; Wolpert *et al.*, 1998; Imamizu *et al.*, 2000) that are necessary to predict the outcome of the motor commands (Wolpert and Miall, 1996; Doya, 1999; Glasauer, 2003; Paulin, 2005; Shadmehr and Krakauer, 2008). Other research suggests that it is also needed to convert desired movements into motor commands (Shidara *et al.*, 1993; Wolpert and Kawato, 1998; Kawato, 1999). Consequently, with cerebellar lesions, movement adaptation to perturbations is impaired (vestibulo-ocular reflex adaptation: Ito, 1998; Kheradmand and Zee, 2011; reaching movements: Smith and Shadmehr, 2005; Rabe *et al.*, 2009). Recently, however, it has been shown that cerebellar patients can adjust their reaching motor behaviour to force fields perturbations (Crisicimagna-Hemminger *et al.*, 2010; Izawa *et al.*, 2012). The question is whether such adjustment applies to other systems, such as gaze control, and whether the behavioural modification reflects the ability to update motor commands and choose new optimal movement parameters.

To determine the contributions of the vestibular system and the cerebellum to learning gaze optimality, we experimentally increased the head moment of inertia in two patient groups, one with complete chronic vestibular loss and one with cerebellar ataxia. After such an increase, movement kinematics must be adjusted to a new optimum (Sağlam *et al.*, 2011). Using our previous optimal control model (Sağlam *et al.*, 2011), we assessed whether the observed changes in movement kinematics are only because of the mechanical effect of increased inertia or whether they imply adaptation of movement parameters. We then determined whether adapted movement parameters reflected an optimization of gaze control in terms of movement variability as predicted by the model, or whether adaptation concerned other aspects of the movement.

Materials and methods

Patients and control subjects

Five patients with neurofibromatosis 2 who had undergone surgery for bilateral vestibular schwannoma several years before the study ['vestibular loss group', aged 45.4 ± 7.1 years, mean \pm standard deviation (SD); three females], nine patients with adult-onset slowly progressive cerebellar ataxia ('cerebellar ataxia group', aged 56.7 ± 12.6 years; six females), and 10 healthy subjects aged 39.7 ± 6.3 years (one female) participated. All groups were age-matched (independent samples median test, $P = 0.083$, see also Supplementary material). All subjects gave their informed consent after explanation of the experimental procedure, which was approved by the ethics committee of the Medical Faculty of Ludwig-Maximilians-University Munich and was in accordance with the Declaration of Helsinki. Healthy subjects did not have any history of balance disorders and a normal neurological, neuro-ophthalmological and -otological exam (including search-coil horizontal head impulses). Patients with vestibular loss had complete bilateral vestibular loss with no response to caloric irrigation,

search-coil head-impulse testing, and galvanic vestibular stimulation. They did not display any cerebellar signs. Table 1 shows scores according to the Scale for the Assessment and Rating of Ataxia (SARA, Schmitz-Hübsch *et al.*, 2006) for the patients with cerebellar ataxia. All patients with cerebellar ataxia also had cerebellar oculo-motor findings (saccadic pursuit, gaze-evoked nystagmus, rebound nystagmus, or downbeat nystagmus). They did not have any signs of peripheral vestibular dysfunction on clinical exam, and on search-coil horizontal head impulse testing. There were no extra-pyramidal signs on clinical examination. Cranial MRI revealed general cerebellar atrophy. After an extensive work-up, patients with cerebellar ataxia were diagnosed with sporadic adult late-onset ataxia of unknown aetiology (seven patients), spinocerebellar ataxia (SCA) type 2 (one patient) and a form of a non-identified genetic ataxia (one patient, both sisters also suffered from cerebellar ataxia).

Experiments

The details of the experimental procedure and data preprocessing are explained elsewhere (Lehnen *et al.*, 2009a). Angular positions of eye and head in space were recorded with the search-coil technique (Robinson, 1963). Coil and target signal data were sampled at a rate of 1 kHz and calibration was performed as described previously (Glasauer *et al.*, 2003). Subjects were instructed to perform gaze shifts naturally in response to flashed targets located horizontally 35° or 40° to the left or to the right of centre. They were asked to maintain gaze position in darkness until a new target appeared. The target was flashed in darkness; it was visible for < 100 ms to prevent visual feedback. The duration for the next target to appear (between 1.6 and 2.4 s) and the target eccentricity (75° or 80°) were randomly assigned to avoid predictive mechanisms. After a control trial ('unweighted condition', 43 target steps), the head moment of inertia was increased by eccentrically placed masses attached to a helmet ('weighted condition', 43 target steps). This gave an additional moment of inertia of 0.0335 kg/m^2 to the normal head moment of inertia, which was assumed to be 0.0148 kg/m^2 , as in Peng *et al.* (1996). This difference corresponds to a 3.3-fold increase. Before the experiments, subjects had no experience with this helmet.

Data analysis

Data analysis was done offline in MATLAB[®] (The Mathworks Inc.). The data were low-pass filtered with a Gaussian filter with a cut-off frequency of 20 Hz. Eye and head movements were detected using a combined velocity-acceleration criterion in interactive software so that detection errors could be corrected manually. Eye-head movements in response to target jumps of 75° and 80° amplitude were analysed. Figure 2 shows typical position and velocity profiles of a representative gaze shift when the head moment of inertia was increased. Eye-in-space, eye-in-head, and head-in-space were labelled as gaze, eye, and head, respectively. Durations, relative contributions of eye and head, oscillation ratio of head movements, peak head velocity, gaze fluctuations, and between-trial variability of gaze shifts were assessed. If any of these parameters fell outside of ± 2 SD from the mean of each subject in each condition, we removed that trial from the analysis, leaving 38.1 ± 2.6 , 34.3 ± 5.6 and 36.1 ± 3.2 (mean \pm SD) of the 43 gaze shifts in the unweighted condition and 36.8 ± 3.0 , 30.5 ± 10.3 and 36.9 ± 2.6 of the 43 gaze shifts for the weighted condition in healthy subjects, patients with vestibular loss, and patients with cerebellar ataxia, respectively. Repeated measures ANOVA (between factor: healthy subject, vestibular loss or cerebellar ataxia

Table 1 Scale for the assessment and rating of ataxia scores of patients with cerebellar ataxia

Subject	Gait	Stance	Sitting	Speech disturbance	Finger chase	Nose–finger test	Fast alternating hand movements	Heel–shin slide	Total points
1	3	2	1	2	2	1	3	2	16
2	1	0	0	0	2	1	2	1	7
3	3	3	2	2	1	1	2	2	16
4	2	2	1	3	2	1	2	2	15
5	4	3	2	3	3	3	3	3	24
6	2	1	1	1	1	1	1	1	9
7	2	1	1	2	2	1	2	3	14
8	2	0	0	1	2	1	2	1	9
9	2	0	0	2	2	1	1	2	10

Schmitz-Hübsch *et al.*, 2006, 0–40 points.

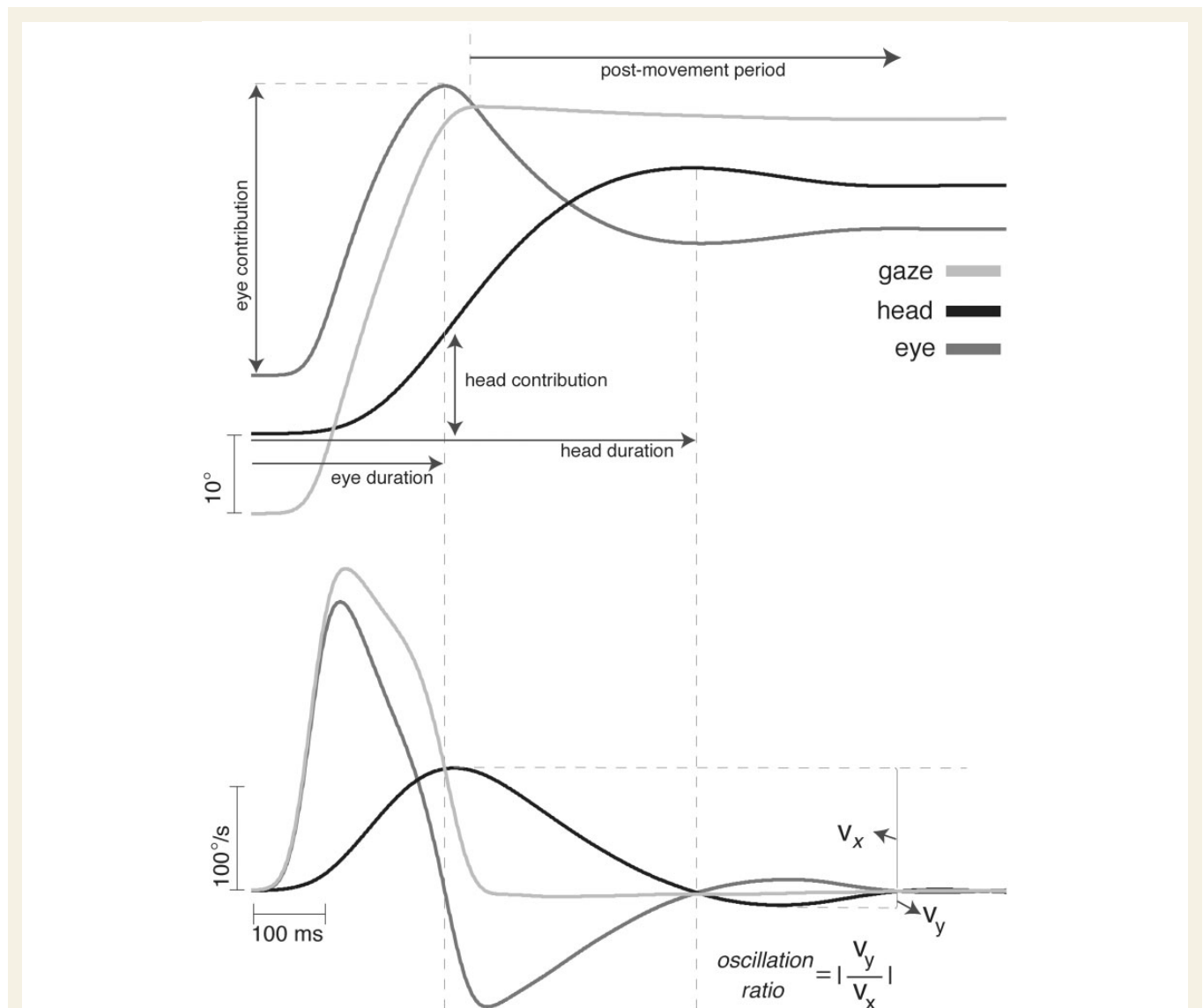


Figure 2 Exemplary gaze shift of a healthy subject with increased head moment of inertia showing eye-in-head (eye), head-in-space (head), and eye-in-space (gaze) position (*top*) and velocity (*bottom*) traces. There were characteristic head oscillations (note how head velocity undershoots the zero line) quantified by the head oscillation ratio, which is the absolute ratio of the first negative peak of head velocity (V_y) to the peak head velocity (V_x). Eye and head movement durations were defined as the time period from gaze shift start until eye and head reach their maximum eccentricities, respectively. The post-movement period was the 600-ms phase after gaze reached maximum eccentricity.

patient; within factor: unweighted or weighted condition) did not reveal any difference in the number of gaze shifts analysed between subjects in any condition [$F(2,21) = 1.81$; $P = 0.188$]. Gaze shift start was when head crossed $6^\circ/s$. In both the unweighted and the weighted conditions the head and eye movements were synchronous, their onsets did not differ for > 15 ms in any of the groups (Two-tailed t -tests, all $P > 0.09$). Eye and head durations were defined as the interval from gaze shift start until the velocity trace crossed zero again. Eye and head contributions were the distances covered by eye and head, respectively, from gaze shift start until the eye reached maximum eccentricity (Fig. 2). The oscillation ratio was calculated as the absolute ratio of the first negative and positive peaks of head velocity (Fig. 2). To investigate whether oscillation ratios changed throughout the 43 trials in the weighted condition, trials were divided into early (first 10) and late (last 33) epochs as the mean oscillation ratio of the healthy subjects dropped to 15% (two time constants) of the initially observed oscillation ratio at about 10 trials [Fig. 4A(1), blue trace]. The 600 ms after gaze reached maximum eccentricity was labelled as 'post-movement period' (Fig. 2). This period was chosen as the natural frequency of the head plant is 1.89 Hz (Peng et al., 1996). Gaze fluctuations were computed for each trial as the variance of gaze position throughout the post-movement period. Gaze error was calculated by subtracting, for each trial, the mean post-movement gaze position from the target position. Before calculating gaze variability between trials, each trial was normalized, i.e. gaze error was subtracted from the position trace. This was done to avoid additional artificial between-trial variability as a result of having 75° and 80° targets steps. Then, the between-trial normal distribution of gaze position was determined for each time point in the post-movement period. These distributions were averaged to represent the between-trial variability of gaze for each subject. The variance of the averaged distribution was taken as between-trial variability of gaze shifts for each subject. Differences in head oscillation ratio, gaze fluctuations, error, variability, eye and head movement durations, relative contributions and peak head velocity between the three groups (healthy, vestibular loss, and cerebellar ataxia), within the two conditions (unweighted and weighted) and in the weighted condition within the early (first 10) and the late (last 33) trials were assessed by repeated measures ANOVA (significance level $P < 0.05$). *Post hoc* Scheffé tests were used for pairwise comparisons. After a group effect, P -values of the *post hoc* Scheffé test were presented in $P(A,B)$ format, where A and B stand for the groups that were compared (H = healthy, BV = bilateral vestibular loss, CA = cerebellar ataxia). After an interaction, each group was omitted from the analysis one by one to detect which group caused the interaction effect. Repeated measures ANOVA was used for normally distributed data, non-parametric alternatives (related-samples Wilcoxon Signed Rank Test or independent-samples Kruskal-Wallis Test) when normality was violated. Normality was assessed with the Kolmogorov-Smirnov test ($P < 0.05$).

Optimal control model

In our previous work (Sağlam et al., 2011), we presented an optimal control model showing that the unique selection of kinematic parameters of eye and head movements serves gaze shift optimality by means of the minimum variance principle (Harris and Wolpert, 1998; van Beers, 2008). The minimum variance model assumes that the post-movement between-trial variability is a consequence of signal dependent and constant noise (van Beers et al., 2004; van Beers, 2007, 2008). The compromise between the consequences of signal dependent and constant noise determines the movement kinematics

(van Beers, 2008). Here, we used the same model to estimate optimality, i.e. cost, of the gaze shifts observed in healthy subjects, patients with vestibular loss, and patients with cerebellar ataxia with and without increased head moment of inertia. The dynamical parameters of eye and head were the same as in the previous model (Sağlam et al., 2011). Further details about the eye and head plant parameters and the optimal control model are available in the Supplementary material. The inputs to the optimal control model were eye and head starting and final gaze positions. They were set according to the experimental data. Kinematic parameters such as eye and head movement durations, and relative eye and head contributions were then determined according to the minimum variance principle. For a given kinematic parameter set (eye and head durations and contributions), we simulated the corresponding gaze shift and computed the cost of that gaze shift. In this way, we could search for the gaze shift with minimum cost in the kinematic parameter space to find the optimal kinematic parameters. With this method, we could assess how close the experimentally observed kinematic parameters were to the optimal ones and see whether subjects updated the parameters in the optimal direction. Simulations were always performed under the assumption that gaze shifts were accurate, i.e. that gaze reached the target at the beginning of the post-movement period. For patients with cerebellar ataxia, where we observed significant gaze undershoot, optimality of shorter gaze shifts was also assessed.

Results

Increasing the head moment of inertia affects head and gaze movements

Figure 3 shows head and gaze velocity profiles for a healthy subject, a patient with vestibular loss, and a patient with cerebellar ataxia. In the natural condition (unweighted, Fig. 3A), head velocity was stable without oscillations. Increasing the head moment of inertia led to characteristic head oscillations (Fig. 3B), more pronounced in patients with vestibular loss and patients with cerebellar ataxia than in healthy subjects. Group analysis revealed that this was true for all groups [Table 2 and Fig. 4A(1 and 2); within-subject factor: unweighted or weighted, $F(1,21) = 101.3$, $P < 0.001$; between-subject factor: group, $F(2,21) = 12.9$, $P < 0.001$; significant interaction, $F(2,21) = 9.8$, $P = 0.001$; *post hoc* Scheffé, $P(H,BV) = 0.001$, $P(H,CA) = 0.036$]. Head oscillations decreased over several gaze shifts in all groups [Fig 4A(1), for representative subjects cf. Fig. 3B and C, repeated measures ANOVA, within factor: early or late trials, $F(1,21) = 10.5$, $P = 0.004$; between factor: group, $F(2,21) = 10.7$, $P = 0.001$; no interaction, $F(2,21) = 0.909$, $P = 0.418$]. In patients with vestibular loss, gaze oscillated together with the head (e.g. Fig. 3B and C). Healthy subjects and patients with cerebellar ataxia compensated for head oscillations by counter-rotation of the eyes. However, this was not perfect (note the difference between gaze velocity and the zero line in the weighted condition, Fig. 3B). Head oscillations caused gaze fluctuations in all groups. To assess gaze fluctuations, we measured the variance of gaze shifts during the post-movement period (Fig. 2). It increased with weight [related samples Wilcoxon Signed Rank Test, $P < 0.001$, Table 2, Fig. 4B(1 and 2)] with the increase being larger in patients with vestibular

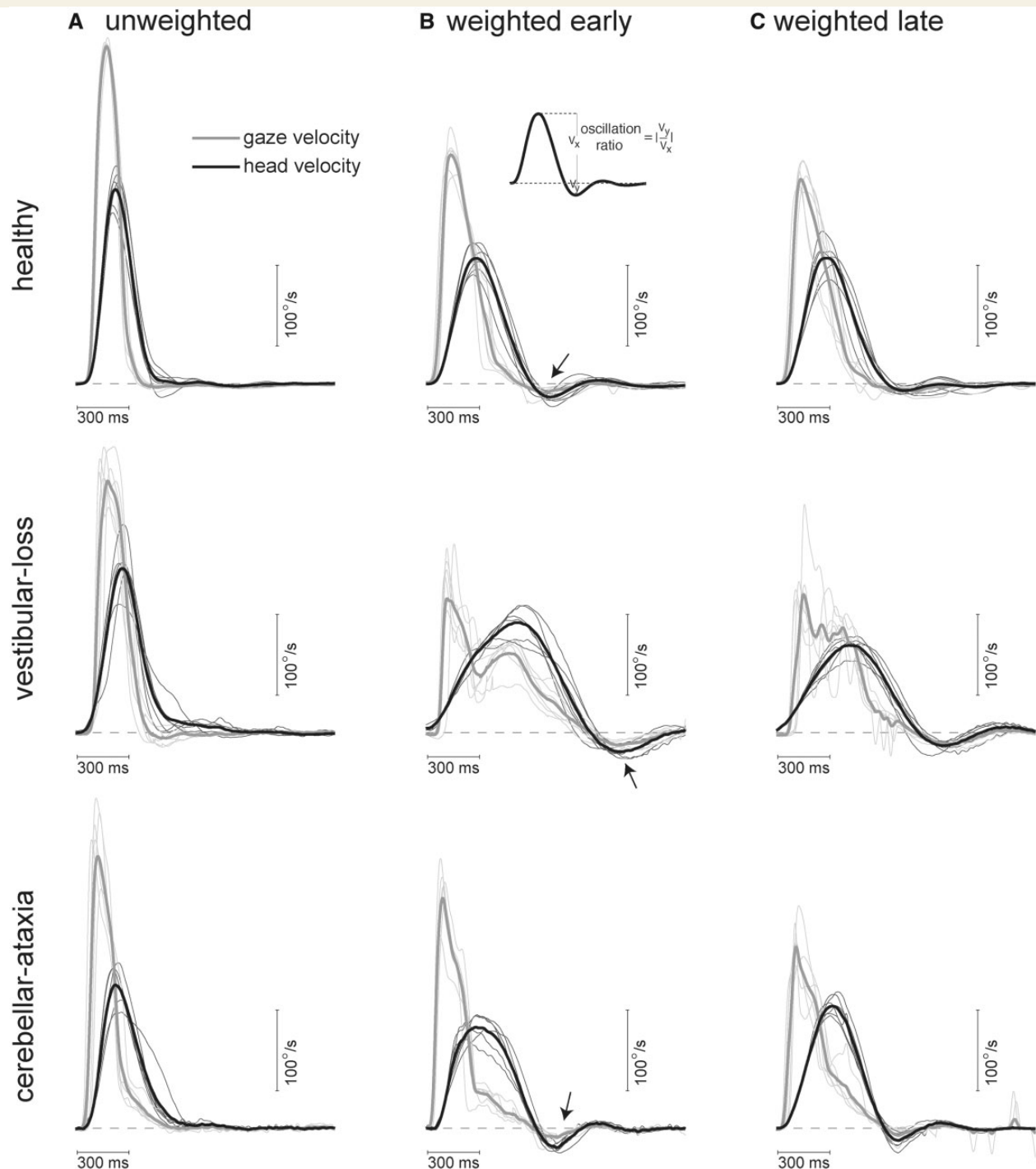


Figure 3 Representative gaze (grey) and head (black) velocity traces of typical subjects (*top*: healthy; *middle*: vestibular-loss patient, *bottom*: patient with cerebellar ataxia, thick lines: mean of the traces) in the unweighted condition (**A**) and with the head moment of inertia increased (weighted, **B** and **C**). In the early (first 10) trials of the weighted condition (**B**), all subjects showed head oscillations (arrows). Head oscillations decreased in the course of the experiment in all subjects [compare early trials (**B**) to late trials (**C**, last 33)]. The healthy subject and the patient with cerebellar ataxia compensated for head oscillations, but still showed some gaze fluctuations (arrows, note how gaze velocity is not zero at the end of the gaze shift). In the patient with vestibular loss, head oscillations reflected as big gaze fluctuations (**B** and **C**, *middle*, note how gaze follows head oscillations).

loss than in healthy subjects and patients with cerebellar ataxia [independent samples Kruskal-Wallis Test, $P < 0.004$, pairwise comparison with independent samples Kruskal-Wallis Test, $P(H,BV) = 0.001$, $P(BV,CA) = 0.012$]. Gaze fluctuations decreased

in the course of the experiment [Fig. 4B(3), related samples Wilcoxon Signed Rank Test, $P = 0.005$]. The decrease was not different among groups (independent samples Kruskal-Wallis Test, $P = 0.219$).

Table 2 Head duration (ms), peak head velocity ($^{\circ}/s$), head contribution ($^{\circ}$), head oscillations, gaze fluctuations (within-trial variance, $^{\circ 2}$) and gaze error ($^{\circ}$) of the three subject groups

	Head duration (ms)			Peak head velocity ($^{\circ}/s$)			Head contribution ($^{\circ}$)		
	Unweighted	Weighted Early	Weighted Late	Unweighted	Weighted Early	Weighted Late	Unweighted	Weighted Early	Weighted Late
Healthy	460.5 \pm 20.1	615.4 \pm 27.7	577.4 \pm 21.1	201.6 \pm 14.0	134.2 \pm 10.6	134.0 \pm 10.4	27.7 \pm 1.5	19.6 \pm 2.6	22.0 \pm 2.2
Vestibular loss	548.4 \pm 106.4	684.4 \pm 96.1	780.8 \pm 119.0	168.9 \pm 31.2	97.6 \pm 15.5	91.6 \pm 8.6	22.2 \pm 4.5	14.1 \pm 4.1	12.3 \pm 3.1
Cerebellar ataxia	516.1 \pm 46.5	561.8 \pm 55.8	640.2 \pm 51.2	166.2 \pm 7.1	102.3 \pm 13.1	117.8 \pm 11.2	21.4 \pm 1.8	11.3 \pm 1.4	14.6 \pm 1.1

	Head oscillations			Gaze fluctuations (degrees ²)			Gaze error ($^{\circ}$)		
	Unweighted	Weighted Early	Weighted Late	Unweighted	Weighted Early	Weighted Late	Unweighted	Weighted Early	Weighted Late
Healthy	2.01 \pm 0.35	8.91 \pm 1.26	5.06 \pm 0.71	0.13 \pm 0.05	0.21 \pm 0.08	0.15 \pm 0.06	6.38 \pm 0.81	7.10 \pm 1.18	6.86 \pm 0.85
Vestibular loss	6.52 \pm 1.31	22.07 \pm 4.73	19.98 \pm 2.80	0.55 \pm 0.20	0.99 \pm 0.12	0.78 \pm 0.18	8.44 \pm 1.18	10.07 \pm 2.32	10.83 \pm 2.06
Cerebellar ataxia	3.92 \pm 0.96	18.14 \pm 2.97	11.81 \pm 2.22	0.10 \pm 0.02	0.27 \pm 0.08	0.19 \pm 0.04	11.94 \pm 1.83	11.53 \pm 1.63	11.45 \pm 2.05

Effects of vestibular and cerebellar dysfunction on gaze accuracy and variability

Gaze fluctuations in the weighted condition reflected as gaze variability between trials (Fig. 5A, $r^2 = 0.85$, $P < 0.001$). A group analysis on post-movement variability revealed that patients with vestibular loss had higher variability compared to the other groups [Fig. 5B, repeated measures ANOVA, $F(2,21) = 15.4$, $P < 0.001$, *post hoc* Scheffé, $P(H,BV) < 0.001$, $P(BV,CA) < 0.001$, for exemplary traces, see Fig. 6B]. Increasing the head moment of inertia increased variability in patients with vestibular loss, but not in patients with cerebellar ataxia and healthy subjects [repeated measures ANOVA, $F(1,21) = 34.6$, $P < 0.001$; interaction, $F(2,21) = 22.7$, $P < 0.001$].

Optimal gaze shifts not only have low variability, but also accurately reach the target (Harris and Wolpert, 1998; van Beers, 2008). Figure 6 shows gaze positions for a healthy subject, a patient with vestibular loss, and a patient with cerebellar ataxia. Whereas the healthy subject reached the target within the normal range (10% undershoot, Kapoula and Robinson, 1986), the patient with cerebellar ataxia markedly undershot in both conditions (unweighted $19.1 \pm 4.2\%$, Fig. 6C, top; weighted: $21.4 \pm 3.1\%$, Fig. 6C, bottom). This was true for all patients with cerebellar ataxia. Gaze error was larger in patients with cerebellar ataxia compared with healthy subjects [Table 2 and Fig. 6D, repeated measures ANOVA, $F(2,21) = 3.58$, $P = 0.046$, *post hoc* Scheffé's test $P(H,CA) = 0.047$]. In our exemplary figure, the patient with vestibular loss showed similar gaze accuracy to the healthy subject in the unweighted condition (Fig. 6B, top). Increasing the head moment of inertia increased gaze error in the example patient (Fig. 6B, bottom). This was true for all patients with vestibular loss, but not for the other groups, as shown by the significant interaction [Fig. 6D, repeated measures ANOVA, within factor: weight, $F(1,21) = 4.25$, $P = 0.052$ not significant; interaction between weight and group factors, $F(2,21) = 4.00$, $P = 0.034$].

Movement kinematics are optimized in healthy subjects and in cerebellar ataxia but not in patients with vestibular loss

Gaze fluctuations decreased in the course of several gaze shifts with weight [Fig. 4B(3)]. This is in accordance with the minimum-variance principle, which minimizes post-movement variability (Harris and Wolpert, 1998; van Beers, 2008). To serve this principle, the kinematics of head-free gaze shifts, such as movement durations, relative contributions and velocity profiles of eye and head movements must be optimally chosen (Sağlam et al., 2011). We assessed optimality of gaze shift parameters, i.e. movement cost, in healthy subjects, patients with vestibular loss, and patients with cerebellar ataxia and compared them to the simulated parameters predicted by the optimal control model to see whether subjects and patients updated movement kinematics in the optimal direction in the weighted condition. The grey line in Fig. 7A shows simulated movement cost in the weighted condition for different

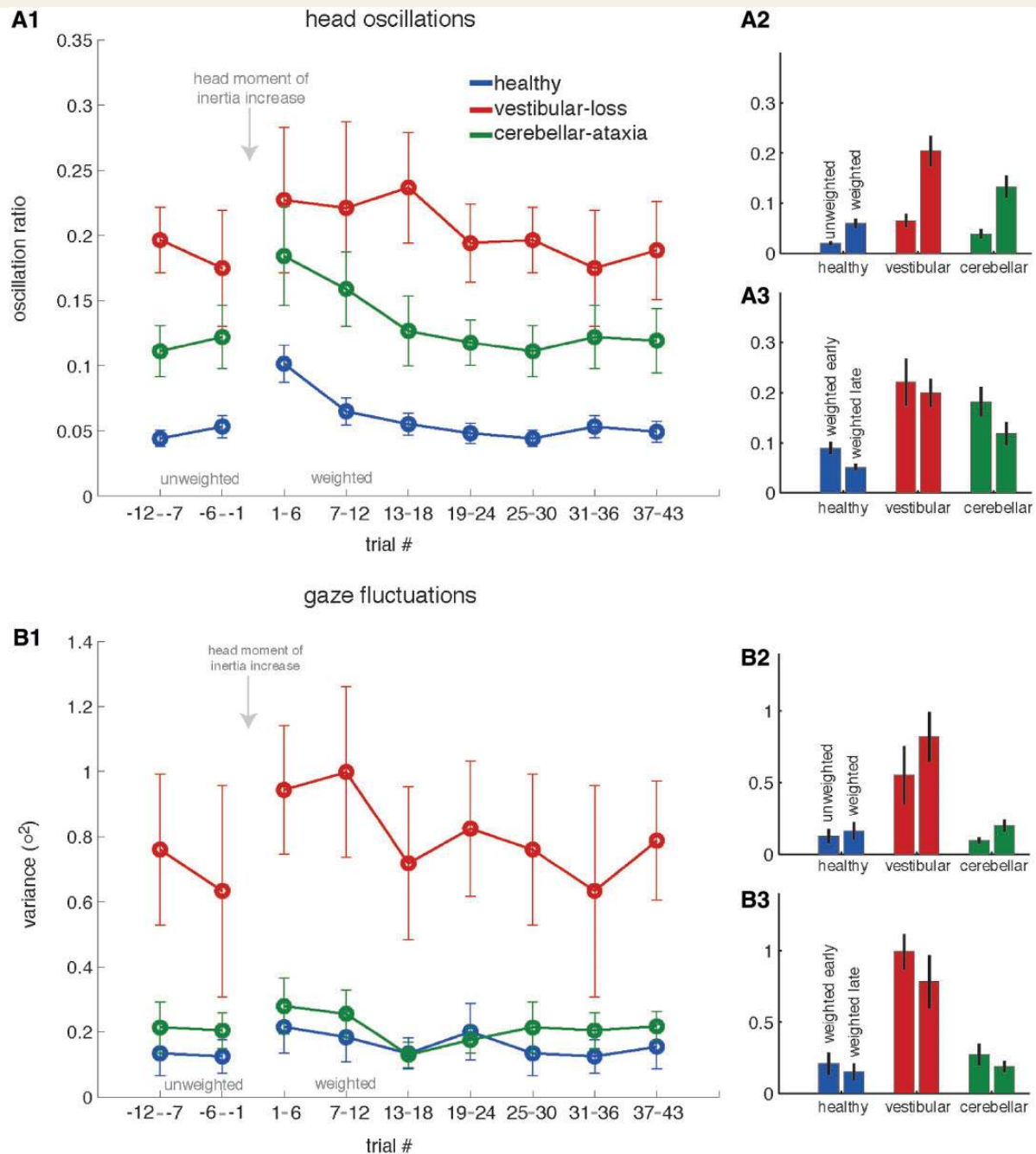


Figure 4 Group results for head oscillations and gaze fluctuations. **(A1)** Head oscillation ratios (mean and SEM) for healthy subjects (blue), vestibular loss (red), and cerebellar ataxia (green) patients. Each circle represents the group mean of the oscillation ratios averaged over the trials indicated by the numbers on the x-axis. Head moment of inertia was increased before the first trial (marked with a grey arrow). Trials in the unweighted condition are labelled with a number smaller than zero. **(A2)** Mean and SEM of head oscillation ratios in the unweighted and weighted conditions. **(A3)** Mean and SEM of head oscillation ratios in the early (first 10) and late (last 33) weighted trials. **(B1–3)** Gaze fluctuations presented as in **(A1–3)**. Head oscillations because of increased head moment of inertia reflected in gaze fluctuations, more in patients with vestibular loss than in healthy subjects or in patients with cerebellar ataxia.

head movement durations. The curve was computed by finding the minimum cost for different hypothetical head movement durations while keeping the other kinematic parameters at their respective optimum. The simulation indicates that retaining the head movement duration optimized for the unweighted condition (grey circle, simulation: 450 ms) would result in a costly gaze shift in the

weighted condition. Therefore, head movement duration has to be updated to the new optimum (grey square, simulation: 570 ms). Increasing the head moment of inertia initially prolonged head movement duration in healthy subjects [from unweighted trials: 460.5 ± 20.1 ms (blue circle) to weighted early trials: 615.4 ± 27.7 ms (blue triangle); $P < 0.001$] exceeding the new

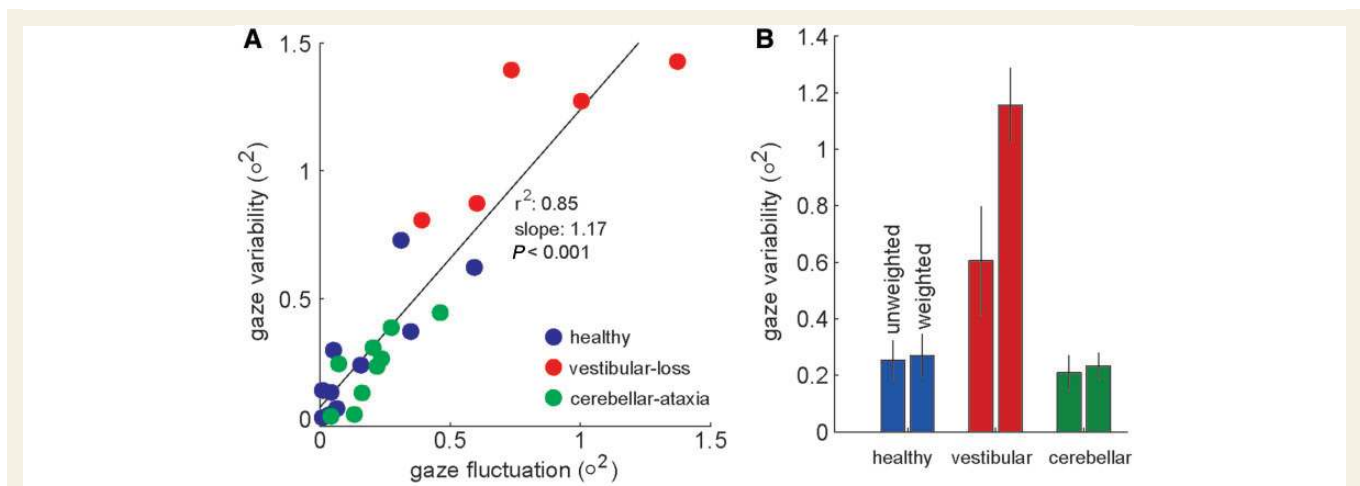


Figure 5 (A) Gaze variability of each subject (blue: healthy subject, red: vestibular-loss patient, green: cerebellar-ataxia patient) plotted against that subject's/patient's gaze fluctuations. Gaze fluctuations were correlated with gaze variability. (B) Group results (mean and SEM) for gaze variability in the unweighted and weighted conditions. Gaze variability increased with weight only in patients with vestibular loss.

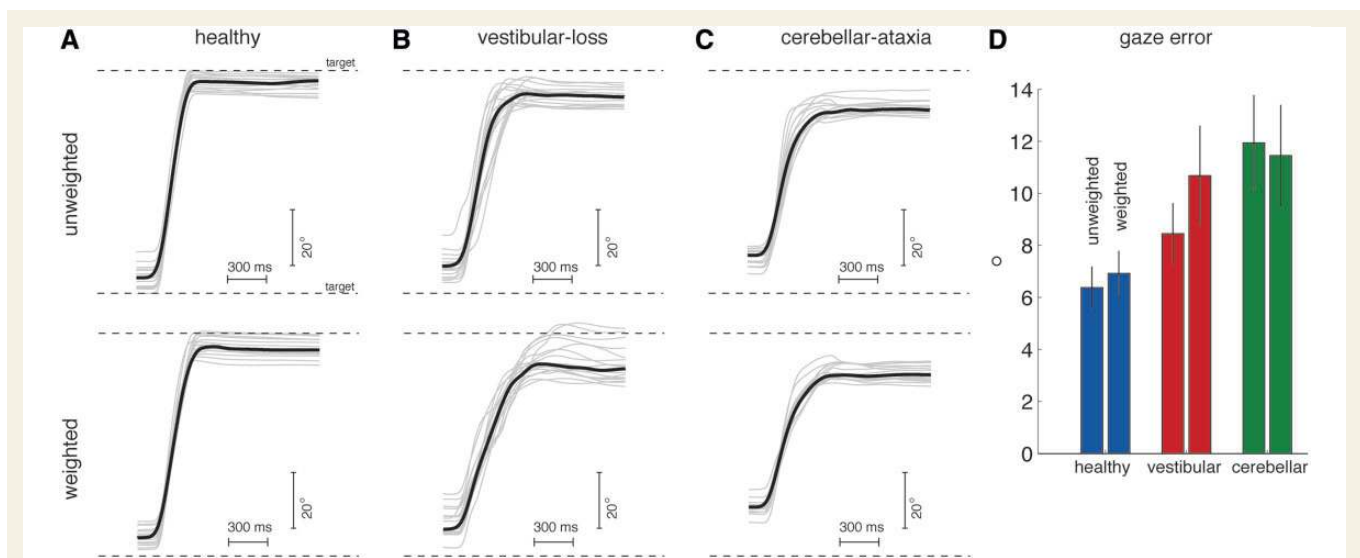


Figure 6 Representative gaze position traces in response to 80° target steps of typical subjects and patients (*top*: unweighted, *bottom*: weighted; **A**: healthy subject, **B**: patient with vestibular loss, **C**: patient with cerebellar ataxia; grey lines are individual traces, black lines show median averages of representative traces; dashed lines display target positions). The healthy subject showed accurate gaze shifts with low variability (**A**, gaze error: unweighted $5 \pm 2^{\circ}$, weighted $5 \pm 2^{\circ}$, mean \pm SD of all trials). The patient with vestibular loss had variable gaze shifts with even more pronounced between-trial variability in the weighted condition (**B**, gaze error: unweighted $8 \pm 3^{\circ}$, weighted $10 \pm 4^{\circ}$). The cerebellar-ataxia patient showed small between trial variability but inaccurately undershot the target in both conditions (**C**, gaze error: unweighted $12 \pm 3^{\circ}$, weighted $13 \pm 2^{\circ}$). (**D**) Group results (mean and SEM) of gaze error for the unweighted and weighted conditions showing that cerebellar subjects markedly undershot the target in both conditions.

optimum (grey square). Over the course of the experiment, head movement duration in healthy subjects decreased (weighted late trials: 577.4 ± 21.1 ms, blue square; $P = 0.011$) towards the new optimum. Only healthy subjects changed head movement duration in the weighted condition [repeated measures ANOVA, within factor: early or late trials, between factor: group, significant interaction $F(2,21) = 3.51$, $P = 0.048$, for values of patients with

vestibular loss and patients with cerebellar ataxia, see Table 2 and Supplementary material].

Figure 7B shows gaze shift cost in the weighted condition as a function of peak head velocity. The simulation results indicate that retaining the peak head velocity optimized for the unweighted condition (grey circle, simulation: $208.0^{\circ}/s$) would result in a costly gaze shift when the head moment of inertia is increased.

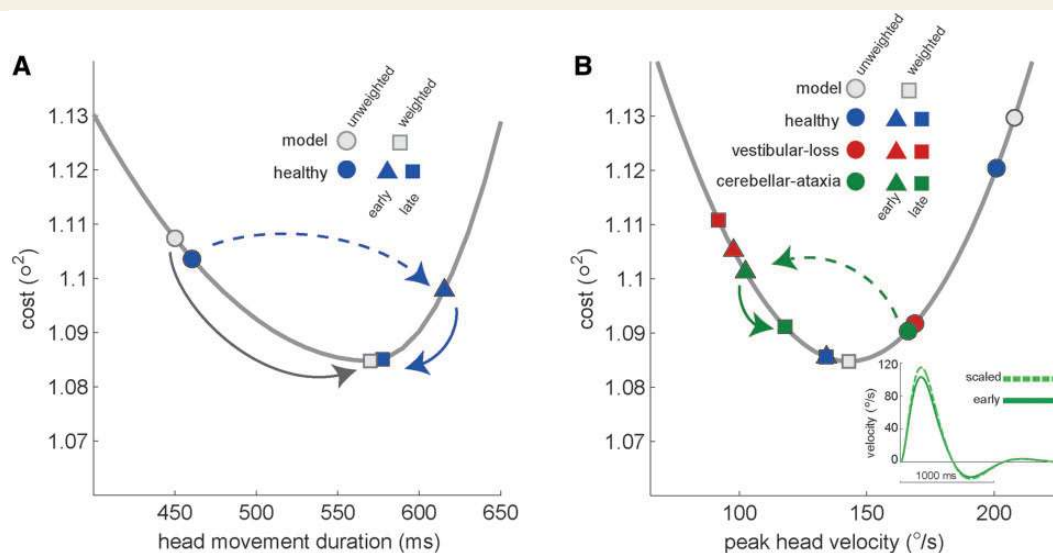


Figure 7 Cost (positional variance) of gaze shifts in the weighted condition computed against different kinematic parameters (for cost calculation, see Supplementary material). **(A)** Cost of gaze shifts for different head movement durations when all other kinematic parameters are optimal. Retaining the head movement duration optimized for the unweighted condition (grey circle) results in higher costs than the new optimum (grey square). Thus, head movement duration should be updated (grey arrow). Healthy subjects had near optimal values for the unweighted condition (blue circle), initially increased the duration in the weighted condition (dashed blue arrow, blue triangle, i.e. mean of early trials with weight), then updated towards the new optimum within several gaze shifts with weight (blue arrow, blue square shows mean of late trials with weight). **(B)** Cost of gaze shifts for different peak head velocities presented as in **A**. Healthy subjects showed near optimal values (blue) whereas patients with vestibular loss had suboptimal velocities (red). Patients with cerebellar ataxia updated peak head velocities towards the optimal value (green arrow). Inset shows that scaling the head command in the early weighted condition (green line, peak velocity: $102.9^\circ/s$, oscillation ratio: 0.18) would increase peak head velocity as observed but would not decrease the head oscillation ratio (green dashed line, peak velocity: $114.7^\circ/s$, oscillation ratio: 0.18). This decrease can be achieved by optimization.

Therefore, peak head velocity should be updated to the new optimum (grey square, simulation: $144.0^\circ/s$). Increasing the head moment of inertia decreased peak head velocity in healthy subjects [from unweighted trials: $201.6 \pm 14.0^\circ/s$ (blue circle) to weighted early trials: $134.2 \pm 10.6^\circ/s$ (blue triangle); $P < 0.001$]. The resulting value did not change over the course of the weighted trials ($P = 0.962$) as it was already close to the new optimum (blue square, weighted late trials: $134.0 \pm 10.4^\circ/s$, $P = 0.378$). Increasing the head moment of inertia also decreased peak head velocity in patients with cerebellar ataxia [from unweighted trials: $166.2 \pm 7.1^\circ/s$ (green circle) to weighted early trials: $102.3 \pm 13.1^\circ/s$ (green triangle); $P < 0.001$]. Over several gaze shifts with weight, peak head velocity increased ($P = 0.015$) in patients with cerebellar ataxia (green square, weighted late trials: $117.8 \pm 11.2^\circ/s$) so that towards the end of the experiment (late trials), peak head velocity was closer to the optimal point. Only patients with cerebellar ataxia, but not patients with vestibular loss updated peak head velocity towards the optimal point [repeated measures ANOVA, significant interaction between early–late and group factors, $F(2,21) = 3.57$, $P = 0.046$, for values of patients with vestibular loss, see Table 2 and Supplementary material]. Such an increase in peak head velocity without optimization, e.g. by simply scaling the head motor command, would not suffice to decrease the head oscillation ratio (inset in Fig. 7B).

Figure 8A shows gaze shift costs. This reflects how well the selected movement kinematics serve gaze optimality. Patients with vestibular loss were the least successful (highest cost). They had high cost in both the unweighted and the weighted condition and failed to optimize any of the kinematic parameters (see Supplementary material for an analysis of all parameters). Under the condition of reaching the target accurately, patients with cerebellar ataxia' gaze shifts were closer to optimality than those of patients with vestibular loss but less than healthy subjects. When the experimentally observed undershoot of patients with cerebellar ataxia (Fig. 6C) was taken into account, i.e. when smaller gaze shifts were simulated, the cost of patients with cerebellar ataxia was the same as that of healthy subjects' (Fig. 8A). The simulations predicted that the undershoot strategy should be realized by decreasing head contribution (Fig. 8B, compare light and dark grey squares). Healthy subjects' head contributions were 27.7 ± 1.5 , 19.6 ± 2.6 , and $22.0 \pm 2.2^\circ$ in the unweighted, weighted early and late conditions, respectively (Fig. 8B, blue marks). In contrast, patients with cerebellar ataxia had $21.4 \pm 1.8^\circ$, $11.3 \pm 1.4^\circ$ and $14.6 \pm 1.1^\circ$ of head contributions in those conditions (Fig. 8B, green marks). In accordance with the predictions, measured head contributions in patients with cerebellar ataxia were lower than those of healthy subjects [repeated measures ANOVA, group factor $F(2,21) = 4.50$, $P = 0.024$; weight factor $F(1,21) = 48.4$, $P < 0.001$; no interaction $F(2,21) = 0.605$, $P = 0.555$, see also Table 2 and Supplementary material].

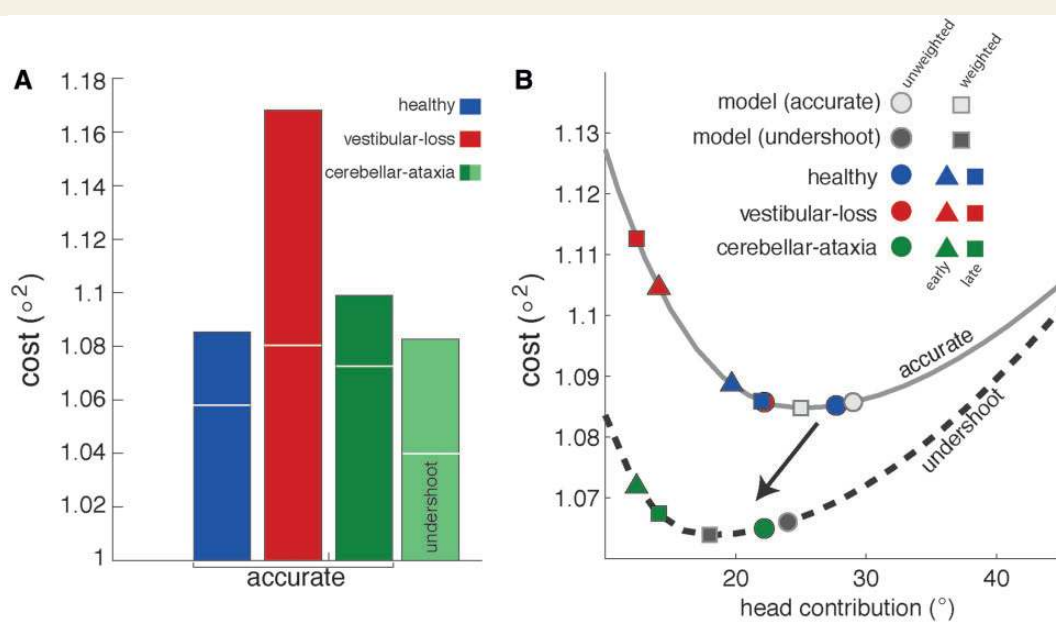


Figure 8 (A) Cost of gaze shifts in the weighted condition computed by all kinematic parameters. For an accurate gaze shift, costs calculated by the observed kinematic parameters are highest in patients with vestibular loss (red) and lowest in healthy subjects (blue). Patients with cerebellar ataxia (dark green) would be in between. White lines indicate the cost levels in the unweighted condition. If the experimentally observed additional (to healthy) 5° undershoot is considered, kinematic parameters of patients with cerebellar ataxia also achieve low costs (light green). (B) Cost of gaze shifts for different head contributions presented as in Fig. 7. Dashed grey line shows the cost curve for an additional 5° -undershoot. Simulation results indicate that for an optimal undershoot strategy, only head contribution should be decreased (arrow), i.e. the undershoot should be realized by the head, not the eye.

Discussion

In healthy subjects, gaze shifts are chosen to minimize variability of final gaze position (Harris and Wolpert, 1998; van Beers, 2008; Sağlam *et al.*, 2011). In the present study, when the head inertia was increased, healthy subjects and patients with cerebellar ataxia updated movement parameters to serve this principle. However, gaze shifts of patients with cerebellar ataxia consistently undershot the target. Kinematic parameters of gaze shifts, both with normal head inertia and after adaptation, were appropriate for the smaller amplitudes. Thus, patients with cerebellar ataxia performed less variable, but inaccurate movements. In contrast, patients with vestibular loss failed to optimize kinematic parameters and displayed highly variable gaze shifts.

Vestibular signals contribute to motor learning and not only online control

Our study both confirms the importance of vestibular online feedback mechanisms for gaze stabilization and shows that vestibular input is relevant for feed-forward motor learning.

Our optimal control model served as a normative model describing the optimal way to perform a gaze shift rather than a mechanistic model making claims about actual implementations of mechanisms leading to optimal behaviour. Thus, we used the model as a tool to assess optimality of observed gaze shifts. We attributed the trial-by-trial improvements in optimality to

feed-forward motor learning. In contrast, we assessed the efficiency of vestibular online feedback control in gaze optimization by comparing healthy and vestibular subjects during the first trials with weight, when online control becomes most obvious.

Vestibular online feedback control

Vestibular signals are well known to be used during the movement (online) to compare the actual movement to the expected outcome (Roy and Cullen, 2001; Cullen, 2004; Cullen and Roy, 2004) and to compensate for perturbations (Shupert and Horak, 1996; Lehnen *et al.*, 2009a, b; Boulanger *et al.*, 2012). The differential vestibular signalling is encoded by the vestibular-only neurons in the vestibular nuclei (Roy and Cullen, 2001). Extra-vestibular feedback, such as proprioception and vision, assist online control (Bronstein *et al.*, 1995; Maurer *et al.*, 1998), but are insufficient to fully compensate for perturbations (Leopold *et al.*, 1983; Bronstein and Hood, 1986; Huygen *et al.*, 1991). Similarly, proprioceptive feedback did not suffice for online control in our experiment with increased head moment of inertia: depending solely on proprioceptive input, patients with vestibular loss displayed higher head oscillations and gaze fluctuations in the early trials, i.e. when online control is most relevant, than healthy subjects. This is in line with recent findings that healthy subjects can preserve gaze accuracy despite head perturbations (Boulanger *et al.*, 2012). They use differential vestibular signals, possibly encoded by vestibular-only neurons, to single out head deviations from the expected movement and correct the eye movement online accordingly.

Vestibular contribution to feed-forward motor control

Recently, van Beers *et al.* (2013) showed that variability of head movements reflect on final gaze variability even in the presence of a functional online vestibular feedback. Together with our results, this suggests that online vestibular feedback does not suffice to reach optimal movement kinematics. If it did, healthy subjects in our study would already have optimal movements in the early trials with the head moment of inertia increased. However, they achieved optimal kinematic parameters only in the course of several gaze shifts with weight. In contrast with healthy subjects, patients with vestibular loss failed to update feed-forward motor commands in the course of the experiment with weight. They showed persistently suboptimal kinematic parameters leading to high variance and movement cost. This indicates that vestibular signals are relevant also for trial-by-trial motor optimization. We suggest that, similar to online vestibular control, vestibular information signalling the discrepancy between desired and actual movements (Roy and Cullen, 2001, 2004; Cullen, 2004; Brooks and Cullen, 2013) is used for preprogrammed optimization. Boulanger *et al.* (2012) discuss that vestibular-only neurons (Roy and Cullen, 2001) might project to the circuits for online gaze correction. In our setting, optimization was observed when there was a discrepancy between desired and actual head movements, i.e. during head oscillations at early trials with weight. Therefore, we suggest that vestibular-only neurons might also provide input to mechanisms that optimize gaze movements. Lack of such optimization because of the missing vestibular error signal contributes to the high between-trial gaze variability in patients with vestibular deficiency in the natural condition (Maurer *et al.*, 1998). Importantly, movements in patients with vestibular loss were already suboptimal in the unweighted condition. This means that even the visual information available during gaze shifts before the experiment in these chronic patients (vestibular loss for many years) was not sufficient to select optimal movement parameters on a trial-by-trial basis and that optimization depends on vestibular signalling not only in the absence of visual information (flashed target in our experiment). The role of the vestibular system in feed-forward optimal motor control is in line with suggestions for a similar use of vestibular information in goal-directed reaching movements (Lackner and DiZio, 2005) and balance control (Fitzpatrick and Day, 2004).

Other mechanisms

Short of sufficient online and optimal preprogrammed control, patients with vestibular loss are left with alternative strategies such as dampening the head plant by co-contraction (Shupert and Horak, 1996; Keshner, 2000) or restricting the head movements (Maurer *et al.*, 1998; Goebel *et al.*, 2007) to improve gaze performance in the weighted condition. Such mechanism could explain the small but insufficient decrease in gaze fluctuations in patients with vestibular loss in our experiment from early to late trials.

Optimization for the wrong target in patients with cerebellar ataxia

Our study suggests that patients with cerebellar ataxia optimize motor commands to decrease variability, but are inaccurate.

Optimization in patients with cerebellar ataxia

The cerebellum is well known to be important for motor learning (Ito, 2002; Bastian, 2006) and cerebellar disease is associated with a deficit to adapt to movement perturbations (arm movements: Martin *et al.*, 1996; Maschke *et al.*, 2004; Smith and Shadmehr, 2005; Rabe *et al.*, 2009; saccades: Optican *et al.*, 1985; Straube *et al.*, 2001; Golla *et al.*, 2008). Only recently has it been suggested that patients with cerebellar ataxia can adapt to perturbations that are presented gradually in small rather than large steps (Criscimagna-Hemminger *et al.*, 2010). In our experiment, patients with cerebellar ataxia updated kinematic parameters (head velocity), and decreased oscillations, gaze fluctuations, and thus variability, over the course of several trials with weight. Updating head velocity would not decrease oscillations if it were simply achieved by upscaling the motor command (Fig. 7B, inset). Therefore, the decrease in oscillations together with the increase in head velocity indicates that the preprogrammed motor control was re-optimized. Conventionally, optimal control of movements relies on accurate internal models that provide motor commands leading to desired movements and predict consequences of applied motor commands (Wolpert and Kawato, 1998; Todorov, 2004). Recently, it has been shown that adaptable internal models of eye and head dynamics are essential to learn optimal eye and head movement parameters (Saeb *et al.*, 2011). Izawa *et al.* (2012) demonstrated that patients with cerebellar ataxia adapted motor commands possibly by updating inverse model dynamics, i.e. the internal model needed to convert desired movements into proper commands. However, cerebellar patients failed to update forward model dynamics and to predict sensory consequences of motor commands. Together with our results, this could mean that the mechanisms that optimize gaze kinematics involve inverse model dynamics outside the cerebellum rather than cerebellar forward model dynamics.

Inaccuracy in patients with cerebellar ataxia

Although our patients with cerebellar ataxia could optimize gaze, they did this for the wrong target. They markedly undershot the target in both the natural and the weighted conditions. Similarly to our results, Federighi *et al.* (2011) reported that head-fixed saccades in patients with late-onset cerebellar ataxia followed the optimal main sequence, but were inaccurate. In addition to movement kinematics, accuracy also plays a role in optimality (Todorov, 2004). Hypometria leads to suboptimal gaze shifts because of the lack in accuracy and, in addition, because a second, corrective movement with additional costs becomes necessary to reach the target. Hypometria has been associated with oculomotor vermal lesions (saccades: Büttner and Fuhry, 1995; Takagi *et al.*, 1998; Kheradmand and Zee, 2011) and observed in patients with cerebellar ataxia (saccades: Vahedi *et al.*, 1995; Federighi *et al.*, 2011; head-free gaze shifts: Shimizu *et al.*, 1981). Smaller gaze shifts could be a result of reduced eye or head contributions. Our model suggested that, to serve optimality, the head movement should be reduced. Indeed, patients with cerebellar ataxia reduced head contribution in the weighted condition. This, again, indicates that patients with cerebellar ataxia can make use of an optimal strategy.

Why patients with cerebellar ataxia are inaccurate, but optimize motor commands

It is astonishing that cerebellar subjects were able to optimize kinematics but at the same time failed to improve accuracy. A possible explanation might be that cerebellar subjects could learn from small errors, in our case oscillations, and not from large gaze errors. Several studies have documented the difference in how humans learn from small, or gradually presented, versus large, abrupt errors (prism adaptation: Hatada *et al.*, 2006; reach adaptation: Kagerer *et al.*, 1997; Klassen *et al.*, 2005; Huang and Shadmehr, 2009). Cerebellar lesions seem to affect these learning mechanisms separately. Cerebellar dentate nucleus inactivation in monkeys disrupts adaptation to small, but not large errors (Robertson and Miall, 1999). Conversely, cerebellar cortex impairments in mice affect motor skill learning from large, but not small errors (Boyden *et al.*, 2006). Only recently has it been suggested that also in human cerebellar ataxia, which impairs cerebellar cortical function, patients can adapt to perturbations that are presented gradually in small rather than large steps (Criscimagna-Hemminger *et al.*, 2010). In our setting, this could be translated to patients' ability to optimize the motor commands to decrease (small error) oscillations. Failure of patients with cerebellar ataxia to accurately reach the target could be attributed to their inability to interpret large errors, i.e. target displacements.

Conclusion

In summary, we used optimal control theory to explain movement kinematics in patients with vestibular loss and with cerebellar ataxia. We showed that vestibular signals contributed to motor optimization. Consequently, patients with bilateral vestibular failure did not achieve optimal movements, which lead to extremely variable gaze shifts. Our patients with cerebellar ataxia could optimize movement parameters to compensate for small errors caused by the unwanted head oscillations, but did so for the wrong target.

Knowledge about the motor learning abilities in these patients will be relevant to develop tailored neuro-rehabilitation programs predicated on motor learning. In particular, the importance of vestibular input for motor learning suggests that patients with partial vestibular insufficiency should be advised to actively move their heads and refrain from strategies to avoid head movements. In this way the residual vestibular input during active head turns could be used to shape the motor command, optimize gaze shifts, and calibrate the head-movement efference copy to stabilize gaze. Physiological and clinical evidence as a basis for rehabilitation in patients with bilateral vestibulopathy is scarce (Herdman, 2013) but—in line with our results—recent findings in unilateral vestibular hypofunction suggest that head movements might be the critical component for a successful outcome (Strupp *et al.*, 1998; Clendaniel, 2010; Hillier and McDonnell, 2011; Herdman, 2013). The fact that patients with cerebellar ataxia in our experiment could make use of this sensory error signal suggests that they, too, should profit from frequent head movements.

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Supplementary material

Supplementary material is available at *Brain* online.

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