Title

Corrective saccades in acute vestibular neuritis: studying the role of prediction using automated passively-induced head impulses

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ABSTRACT (250 words)

When the demands for visual stabilization during head rotations overwhelm the ability of the vestibulo-ocular reflex (VOR) to produce compensatory eye movements, the brain produces corrective saccades that bring gaze towards the fixation target, even without visual cues (covert saccades). What triggers covert saccades and what might be the role of prediction in their generation are unknown. We studied 14 subjects with acute vestibular neuritis. To minimize variability of the stimulus, head impulses were imposed using a motorized torque generator with the subject on a bite-bar. Predictable and unpredictable (timing, amplitude, direction) stimuli were compared. Distributions of covert corrective saccade latencies were analyzed with a 'LATER' (linear approach to threshold with ergodic rate) approach. On the affected side, VOR gain was higher (0.47±0.28 vs. 0.39±0.22, $p<<0.001$) with predictable than unpredictable head impulses, and gaze error at the end of the head movement was less (5.4±3.3 vs 6.9±3.3 deg $p<<0.001$). Analyzing trials with covert saccades, gaze error at saccade end was significantly less with predictable than unpredictable head impulses (4.2 ±2.8 vs 5.5 ±3.2 deg, $p<<0.001$). Furthermore, covert corrective saccades occurred earlier with predictable than unpredictable head impulses (140±37 vs. 153±37 ms $p<<0.001$). Using a LATER analysis with reciprobit plots, we were able to divide covert corrective saccades into two classes – early and late – with a break point in the range of 88-98ms. We hypothesized two rise-to-threshold decision mechanisms for triggering early and late covert corrective saccades, with the first being most engaged when stimuli are predictable.

Key words: Head impulse, acute vestibular neuritis, saccades, prediction, LATER analysis

New & Noteworthy

We successfully used a LATER (linear approach to threshold with ergodic rate) analysis of the latencies of corrective saccades in patients with acute vestibular neuritis. We found two types of covert saccades: Early (<90ms) and late (>90ms) covert saccades. Predictability lead to an increase in VOR gain and a decrease in saccade latency.

INTRODUCTION

The angular vestibulo-ocular reflex (VOR) is mediated by a three neuron arc that stabilizes gaze on a stationary target during head rotations by generating equal and opposite eye rotations (1-4). If the peripheral vestibular system is impaired, or head acceleration or velocity exceeds the capabilities of the vestibular system (5, 6), the VOR cannot generate the correct response to maintain stable gaze. In this case, other mechanisms compensate for the deficient VOR including corrective saccades that tend to bring the image of the target back to the fovea. These saccades are triggered in the direction of the deficient eye movement both when the head is still moving (covert saccades) and after head has stopped (overt saccades) (7-10). The clinical head impulse test (HIT) assesses vestibular function with brisk, passive rotations of the head in the plane of parallel semicircular canal pairs (11). With the bedside HIT clinicians can usually detect overt corrective saccades after the head movement has stopped but covert saccades, made while the head is rapidly rotating, are much harder to discern at the bedside.

In the last years, the video head impulse test (vHIT) has become an invaluable quantitative diagnostic tool to assess impaired vestibular function, for example, in patients with acute vestibular neuritis, or to screen for vestibular strokes in the emergency department (ED) (12). Using a videooculography (VOG) recording system with a gyroscope, and computer algorithms, the gain (ratio of eye movement to head movement) of the VOR is calculated (13), and both covert and overt catch-up saccades are identified (11, 14-16).

The mechanisms underlying the timing and the amplitude of covert saccades are unclear. Previous studies have proposed triggers for covert saccades including 1) neck proprioceptive signals (17, 18), 2) residual labyrinthine function, and 3) other cues (e.g., pressure from the examiner's hands) that the head is about to or has just begun to rotate (19). Other studies have shown that covert saccades are triggered earlier when head turns are active (20, 21) or, when

passive, if head motion is predictable (15, 22, 23). These findings suggest that corrective saccades are preprogrammed in anticipation of uncompensated head motion.

The problems with most of these studies are that with head impulses imposed by hand the ability to infer mechanisms is hindered because of trial-by-trial variability of the stimulus. In previous attempts to standardize head- and body movements using computer controlled rotational body *en bloc* impulses (crHIT) (18, 24), the stimuli had lower accelerations than conventional head impulses, which did not challenge the capabilities of the VOR to the same degree as higher-acceleration manual head impulses.

The main goal of our study was to determine how the brain estimates head velocity when labyrinthine function is deficient or absent, and in turn, how that information is used to generate corrective saccades. Here, we used an automated high acceleration HIT device (aHIT) (25) to analyze corrective saccades in response to standardized passive head impulses in patients with acute vestibular neuritis. Comparing responses to predictable versus unpredictable head impulses, we measured the latencies of the first corrective saccades and the gaze error at their beginning and end. To further focus on mechanisms underlying the generation of non-visually guided corrective saccades (covert saccades) we applied the LATER model (linear approach to threshold with ergodic rate, Carpenter and Williams (26)), which has been used to infer mechanisms for triggering saccades to visual targets.

MATERIAL AND METHODS

Patients with acute vestibular neuritis

Patients with acute vestibular neuritis were enrolled as part of a prospective cross-sectional study of patients seen in ED (DETECT—Dizziness Evaluation Tool for Emergent Clinical

Triage). We excluded patients younger than 18 years, if symptoms lasted < 24 h or if the index ED visit was > 72 h after symptom onset. We also excluded patients with other neurological symptoms or signs, new hearing symptoms, or with previous eye movement or vestibular disorders. All patients with acute vestibular neuritis had caloric irrigations, video head impulse tests (vHIT) and a delayed MRI (3-21d after symptom onset), which served as a gold standard for excluding stroke. Patients with a negative MRI and either a pathological HIT or pathological caloric test were diagnosed as acute vestibular neuritis. We also collected information on age and gender.

Experimental Paradigm

Head impulses were performed using an automated device (aHIT™) (25) positioned on a table in front of the seated subject and consisting of a silicone mouthpiece moving on a curved track. Eye and head movements were recorded using an EyeSeeCam^{TM} VOG system with an integrated full inertial measurement unit (IMU) within the VOG infrared camera at a sampling rate of 220Hz.

The patient was seated upright, and the height of the chair was adjusted so that the silicone bite bar was at a comfortable level for the subject. The bite bar was also adjusted with a spirit level to ensure that the axis of rotation was centered about the vertical axis of the subject's head. During head rotations, the patient was asked to bite down on the bite bar firmly to ensure transfer of forces from the motor. All head impulses were delivered in the horizontal plane.

The aHIT™ device was programmed to deliver Gaussian motion profiles with peak angular velocity of either 150°/s or 250°/s, both with peak acceleration 3000°/s^2, i.e., the maximum acceleration deliverable by the device.

In a first step a predictable paradigm was performed with a predictable direction, velocity, amplitude, and timing/cadence between each head impulse. We delivered 10 automated cycles

in the horizontal plane, with each cycle consisting of one impulse to the left and one to the right. The first head impulse always started from the center to lateral position (centrifugal) and the following impulse was from side-to-center (centripetal). Two different types of predictable stimuli were used for each patient: one programmed to reach peak angular velocities of 150°/sec with an amplitude of 10°, and the other peak angular velocities of 250°/sec, with an amplitude of 20°. The timing between the head impulses was constant at 1.2 s.

In a second step, an unpredictable paradigm was used, in which the examiner triggered automated head impulses, always starting from the center position random in direction (right left), timing (range of 2-5 seconds) and with two pairs of fixed speed and amplitude. We used a random sequence generator for test condition and order.

Data Analysis

Data was processed using custom-made Matlab software that identified head and eye movements on individual trials. A first interactive screening of responses selected only those trials in which there were no artifacts on the eye position trace including contaminating eye blinks, noise due to failed pupil detection/segmentation by the recording software, anticipatory eye movements and slippage of the goggles as indicated by the eyes moving before the initiation of the head movement (27, 28). About 20% of trials were discarded at this stage. Corrective saccades were then automatically detected on the high-pass filtered eye velocity trace based on the start (s) and end (e) points when eye velocity rose above or fell below, respectively, 10°/s. Identification of corrective saccades was confirmed by the investigators for each trial. Signal processing was as previously described by Colagiorgio & al (22). The threshold for detecting the onset of head movement was lowered to 5 deg/s given the robotic nature of the stimulator. The gain of the VOR response was calculated as the mean

154 of the ratio between horizontal eye velocity and horizontal head velocity computed over the
155 time interval between the times of peak acceleration and peak velocity of the head.

156 We calculated the gaze error defined as the difference between head position and eye position
157 at the beginning of the first corrective saccade, and the total error, for which the saccade must
158 compensate, which was defined as the difference between head position at the end of the
159 saccade and eye position at the beginning of the saccade. In addition, we calculated the gaze
160 error at the end (zero-crossing) of each head impulse. We defined 'covert saccades' as those
161 corrective saccades that began before the first zero-crossing of head velocity after the onset of
162 the head impulse. All corrective saccades beginning after the zero-crossing were considered
163 'overt'.

164 The distributions of latencies of covert corrective saccades were interpreted using the LATER
165 model of response time (29), which hypothesizes that the reciprocal of latency in motor
166 responses follows a Gaussian distribution. It considers decision-making processes as a build-
167 up of activity towards a threshold of confidence, triggering a response, e.g., a saccade, when
168 such a level is reached (τ). The model considers the prior probability of a response-evoking
169 stimulus as the starting point S_0 of such build-up of activity, which will occur with a rate r that
170 is drawn from a Gaussian distribution with mean μ and standard deviation σ. We opted for the
171 LATER model because it has been shown to succinctly and quantitatively account for saccade
172 reaction time data in a range of saccade behavioral and decision making tasks (e.g. reading,
173 optokinetic responses, anti saccades, prosaccades, etc). Furthermore it does so with few
174 parameters i.e. , the mean and variance of the rate of rise of the activity leading to a response
175 (30, 31).We hypothesized that the variability in the latency of corrective saccades in response
176 to head impulses could be interpreted using this model considering two competing processes
177 with build-up rates drawn from two different distributions, one responsible for triggering
178 covert saccades and the other triggering overt saccades. The data is presented on a reciprobit

plot in which the cumulative distribution of saccade latencies is drawn on a probit scale (y-axis) as a function of saccade latency represented on a reciprocal time axis. The reciprobit data was then fit with two straight lines, as for visually driven saccades in [26], using a least mean squares algorithm.

Ethics

The institutional review board approved this study (KEK#047/14; approval date 04/24/2014). All patients gave written informed consent.

RESULTS

Stimulus Characteristics

We performed 1067 predictable and 1126 unpredictable head impulses on 15 patients with acute vestibular neuritis using the aHIT device. Due to procedural errors, patient #1 had only unpredictable head impulses, while patient #6 had only predictable ones. Their data was included in all population level analyses. After the first screening of eye and head movements we accepted 477 predictable and 606 unpredictable head impulses. Pooling data from all subjects, fast head impulses, programmed at 250 deg/s peak head velocity, achieved a peak head velocity of 245±34 deg/s and lasted 190±10 ms, while slow head impulses, programmed at 150 deg/s achieved 163±23 deg/s and lasted 130±20 ms.

The durations of fast and slow impulses were not statistically different between predictable and unpredictable trials. Peak head velocities of slow impulses were not statistically different between predictable and unpredictable trials. Peak head velocities of fast impulses were slightly different with predictable trials being 240±20 deg/s and unpredictable trials 249±26 deg/s ($p<0.01$). A more detailed analysis looking at individual subjects highlighted a few patients who had more variability of peak head velocity, possibly due to fluctuating stiffness

of the neck muscles, or some decoupling of the head from the bite bar. The intra-subject variability of peak head velocity, expressed in terms of its standard deviation in the different paradigms, ranged between 2.5 and 19.4 deg/s.

Responses to head impulses

Considering all subjects, the VOR gain in response to head impulses to the pathological side was greater with predictable 0.47±0.28 than unpredictable 0.39±0.22 stimuli ($p<<0.001$). There was no statistical difference in VOR gain toward the healthy side comparing the response to predictable (0.87±0.11) versus unpredictable (0.85±0.12) head impulses. Covert corrective saccades were present in 63.5% of responses to predictable and in 51.5% of responses to unpredictable head impulses. Figure 1 illustrates two examples of head- and eye velocity profiles from the fast predictable and unpredictable head impulse stimuli in two representative subjects. With prediction, covert corrective saccades occurred earlier and their amplitudes were higher (Fig. 1).

Gaze Error

Gaze error at the end of the head movement (head velocity crossing zero) was 5.4±3.3 degrees with predictable and 6.9±3.3 degrees with unpredictable head impulses ($p<<0.001$) (Fig. 2). Including both overt and covert corrective saccades at the end of the first corrective saccade gaze error was 3.6±2.7 degrees in predictable and 4.1±3.2 degrees in unpredictable head impulses ($p=0.066$) (Fig. 3, right hand panel). Considering only covert corrective saccades the gaze error *at the end* of the first saccade was 4.2±2.8 degrees with predictable and 5.5 ±3.2 degrees with unpredictable head impulses ($p<<0.001$) (Fig. 3, left hand panel). The gaze error *at the beginning* of the first corrective saccade was 6.0±4.3 degrees with predictable and 7.4±4.3 with unpredictable head impulses ($p<<0.001$) (Fig. 4, right hand panel). When considering only covert corrective saccades the gaze error at the beginning of the first

corrective saccade was 6.7±4.5 with predictable and 8.7±4.2 with unpredictable head impulses ($p<<0.001$) (Fig. 4, left hand panel).

Corrective saccades: Latencies and distribution

Considering all first corrective saccades, for head impulses toward the affected side the latency was 159±48 ms with predictable and 180±52 ms with unpredictable head impulses ($p<<0.001$) (Fig. 5, right hand panel). Considering only covert corrective saccades, for head impulses toward the affected side the latency was 140±37 ms in predictable head impulses and 153±37 ms in unpredictable ones ($p<<0.001$) (Fig. 5, left hand panel). For head impulses toward the healthy side, considering all first corrective saccades, latencies were 262±95 ms and 250±89 ms, for predictable and unpredictable head impulses, respectively, which were not significantly different ($p=0.52$).

LATER analysis and model simulation

The reciprobit plot presenting the LATER analysis of latencies of covert corrective saccades toward the pathological side shows two distributions for responses to both predictable and unpredictable head impulses (Fig. 6), with earlier covert saccades represented by the shallower line and later covert saccades by the steeper line. The break point in the fit of latencies was at 86 ms for unpredictable impulses and at 97 ms for predictable head impulses. Based on the data shown in Fig. 5, for predictable stimuli the mean saccade latency of early covert saccades was 64±13ms (range 36 and 81 ms) and for late covert saccades 115±18 ms (range 86 and 159ms,). For unpredictable stimuli, the mean saccade latency of early covert saccades was 80±19ms (range 36 and 95 ms) and for late covert saccades 124±17ms (range 100 and 195 ms).

Based on a model from Noorani and Carpenter (30), which posits two competing saccade triggering circuits , Figure 7), we simulated the overall distribution of covert saccade latencies

during both predictable and unpredictable head impulses. The model has a "MAIN unit" and an "EARLY unit" (See Figure 7). To simulate the response to unpredictable impulses model parameters for the MAIN unit were threshold τ=1, a mean rate μ=9 and standard deviation σ=1.1, which made decisions in an average of τ/μ=0.11 seconds. The EARLY unit of the model had a threshold τ_E=1.2, a mean rate μ_E=0 and standard deviation σ_E=9.2. To simulate the responses to predictable head impulses, only one change was necessary; the threshold of the EARLY unit was decreased to τ'_E=0.9 (Fig. 7). The shifting point between the two distributions of early and late covert saccades latencies was fit at 85 ms for unpredictable head impulses and at 96 ms for the predictable ones.

DISCUSSION

In this study we investigated the VOR in patients with an acute vestibular neuritis emphasizing the mechanisms affecting the triggering of corrective saccades and reducing how far the eye is off target (gaze error) during the movement of the head and when the head stops moving (here defined when head velocity crosses zero). Our results support a central role of prediction in the trigger mechanism and reducing gaze error. As previous studies have shown, when head impulses are predictable, a higher proportion of corrective saccades are covert (15). Moreover, both the gaze error at the end of the first corrective saccade and the gaze error at the end of the head movement were less when head impulses were predictable. This finding suggests that knowing the direction of head motion is advantageous for the VOR in patients with unilateral loss of function.

The influence of prediction on the gain of the VOR

On the affected side with *predictable* head impulses, the VOR gain was significantly higher than with predictable head impulses. On the other hand, there were no significant differences in corrective saccade metrics or VOR gain for head impulses to the healthy side. In previous

studies that showed a difference in VOR gain with prediction, the patients either had chronic vestibular hypofunction (32) or made active head impulses (20, 33). Previous studies on the interaural translational VOR (tVOR) also showed that expectation had a strong effect on both the gain of the VOR response and on the latency of the first corrective saccade, which were respectively higher and lower, respectively, in predictable vs unpredictable trials (34). On the other hand, in a study using passive head impulses in patients after removal of their vestibular schwannomas, the VOR gains were not larger with predictable than with unpredictable impulses (23). Note that in this study, which used manual head impulses and therefore with more stimulus variation compared with motorized head impulses, a different testing paradigm had been used (inward versus outward head impulses). A recent study used the SHIMP (suppression head impulse paradigm) paradigm on healthy subjects, in which the subject fixates upon a target that is rotating with the head, and must make corrective saccades to bring the eyes back to the target after being taken away by the intact VOR (35). Using the SHIMP paradigm with predictable and unpredictable cues, there were higher VOR gains for inward, toward the center, head impulses (35). For the predictable testing paradigm, however, we did not distinguish inward from outward head impulses since the head was moving from center to lateral and vice versa.

Corrective saccade latency and prediction

Corrective saccade latency was significantly greater with unpredictable head impulses, which accords with previous studies in which latencies of corrective saccades following inward (presumed predictable) head impulses were lower than those generated during outward (more unpredictable) head impulses after acute unilateral vestibular nerve deafferentation (15). A decreased latency of corrective saccades was also reported with active (self-generated) head impulses (36). Iwasaki et al. studied whole body impulses (rotation *en bloc*) in patients with unilateral or bilateral vestibular dysfunction and patients showed more overt saccades than

patients tested with conventional head-on body head impulses, however, the proportion of covert saccades remained unchanged (18). A tighter clustering of corrective saccades in response to head impulses, which was also present in some of our patients (Fig. 1) has also been reported with predictive stimuli (35), active head movements or in the presence of light (37). We also cannot exclude any quick phase suppression effects during the early phase of a head impulse (0-60ms), which can be seen, for example, with quick phases of post-rotatory induced nystagmus (38).

Saccade accuracy and prediction

We observed a significantly smaller gaze error with predictable than with unpredictable head impulses for both gaze errors at the end of the head impulse (Fig. 2) and gaze errors at the end of the first covert corrective saccade (Fig 3) . These findings suggest that the knowledge of the expected direction and/or speed of head movement during head impulse tests gives the ocular motor system an advantage when using saccades to overcome deficiencies in the VOR.

Vestibular (covert) saccades versus visually induced saccades

Relatively little is known about covert corrective saccades, triggered by nonvisual stimuli, compared to saccades induced to visual stimuli. Our study shows that with both predictable and unpredictable head impulses there may be a proportion of covert saccades having latencies below 90ms, i.e., corrective saccades may be triggered earlier with vestibular than with visual stimuli (26). Using the LATER analysis model (26), we analyzed the distributions of the reaction times of covert saccades in analogy to the short-latency visually-induced saccades with the head still. Saccades in response to visual targets include express saccades (short latencies ~90ms) elicited with a visual gap stimulus, (fixation target is extinguished before the new visual target appears) (39), longer-latency visually induced saccades with the head still, for example to an overlap stimulus (fixation target remains on after the new visual

target appears) and predictive, anticipatory saccades which are generated by expectation of the appearance of a target (40). Carpenter et al (31) distinguished three types of visually induced saccades with the head still within the short latency region: express saccades, early saccades and late saccades. While express saccades show a bimodal reaction time distribution with a LATER analysis (two slopes separated by one flat, horizontal slope (31)), in our study, early, non-visually induced covert saccades form a subpopulation of saccades lying on a shallow slope in a reciprobit plot (figure 6A, right panel) that is distinct from the steeper slope characterizing later covert saccades.

Similarly, our LATER analysis showed two separate distributions of the latencies of covert saccades in both conditions (predictable and unpredictable head impulses), which are not immediately evident in a cursory view of saccade latency histograms. There was a main distribution for saccades occurring later than about 90ms (late covert saccades) and an early one for those occurring earlier (<90ms) (early covert saccades, Fig.6). To account for these distinct distributions we propose two rise-to-threshold decision mechanisms for triggering saccades in this time frame. One mechanism triggers most corrective saccades, which occurred toward the end of the time window. The other mechanism triggers the earliest saccades (< 90ms after the head movement begins). Terms such as 'covert' or 'overt' saccades are derived from clinically performed HITs and describe the ability of the physician to discern saccades. This qualitative terminology, however, might be better supplanted when quantitative eye movement recordings are available. They allow for a quantitative classification of corrective saccades based on timing relative to the parameters of the head movement. Saccades occurring <90ms after the head impulse onset might be called "early covert" saccades.

Initiation and triggers of early corrective saccades

We found a significantly smaller gaze error with predictable head impulses at the onset of the first corrective saccades (Fig. 4). We did not find a constant threshold or cluster of gaze errors as a triggering cue for initiation of corrective saccades. Naturally, the lower saccade latencies with predictable head impulses led to smaller gaze errors at saccade onset because the gaze position error increases over time during head impulses in patients with a deficient VOR. Thus, we suggest that the covert saccades are not triggered by a fixed threshold based on the estimated gaze error, but other factors are also important (prediction, other sensory cues, and inherent variability (noise) in threshold triggering mechanisms).

What do we learn from the LATER MODEL and reciprobit plots?

The LATER model (linear approach to threshold with ergodic rate) was first introduced by Carpenter and Williams (26) in order to study distribution of reaction times of saccades in response to a visual stimulus (41-44). They described a simple stochastic model to account for both the random and systematic variation in the saccade latency. When plotted as conventional frequency histogram, the distribution of saccade latencies to the sudden appearance of a new visual target is skewed (26). Thus, when plotted using a reciprocal scale for latency, the distribution becomes relatively symmetrical and Gaussian (Fig. 6, left panel). By plotting our data on a probit scale (y-axis, in effect an inverse error function transformation) and the covert saccade latency on a reciprocal scale (x-axis), we obtained a reciprobit plot which we fitted using two straight lines (Figure 6A, right panel) similar to those proposed by Carpenter & al. (1995). Thus, the LATER model may be also suitable for analysis of early, nonvisual "covert" corrective saccades generated when the VOR is deficient.

In our study, the cumulative probability of early covert saccades in the reciprobit plots was higher with predictable head impulses. Thus this approach provides a way to quantify the effects of various cues, including predictability, that have been previously shown to improve

VOR performance with not only a reduction and clustering of the corrective saccades latencies but also a decrease in gaze error at the end of the first corrective saccades. In the case of predictability, important factors might include prior knowledge and expectation based on timing, direction, movement profile (velocity, size of excursion), and eventually resulting in internally generated movement commands.

Interestingly, the distribution of latencies of covert saccades' on the reciprobit plot showed a similar pattern to the short-latency saccades that occur with visual targets (26). Thus, we hypothesize that nonvisual corrective saccades during head impulses may be initiated by competing stochastic decision mechanisms for signal processing in the brain based on the different available cues, and that the winning mechanism, i.e., the one reaching the threshold sooner, determines when the brain should initiate a corrective saccade. These stochastic mechanisms are important, since sensory input signals are noisy (biological noise) and the brain needs to make an inference about the actual performed head movement and the needed eye correction. We simulated our results with a two decision mechanisms LATER model suggesting that with prediction the threshold for generating early covert saccades is reduced; a change that reflects greater confidence in the predictive mechanism that triggers the earliest corrections. In a Bayesian sense, the threshold was considered a prior and was adjusted accordingly based on stimulus predictability.

What might be the anatomical substrate for these circuits that trigger non-visual early and late covert saccades? In analogy with visually guided saccades, it may be that direct subcortical, mechanisms, perhaps mediated by short-latency visual drives to the superior colliculus account for early visually-guided or even 'express' saccades. The cerebellum, too, has been implicated in the generation of express saccades since asymmetrical lesions of the dorsal vermis abolish express saccades in one direction (45). Saccade (quick phase) related activity for vestibular nystagmus has also been recorded in so-called burster driver neurons in the

medulla (46). How these various circuits relate to generating covert saccades remains to be discovered.

Limitations of the study

We used an automated head impulse device in the attempt to provide a more reproducible vestibular stimulus and so minimize some of the variability of stimulus parameters that might confound the interpretation of corrective saccade timing and amplitude in patients with a deficient VOR. A standardized HIT technique is important when analyzing corrective saccades since gaze error and saccade latency are functions of head velocity and acceleration. Accordingly, variability of the stimulus adds to inherent variability (noise) of the VOR response, which could make statistical inferences more difficult, especially when the number of trials is limited (10). Furthermore, nonlinearities in the ability of an impaired labyrinth to transduce head velocity could make statistical inferences more difficult with a more variable stimulus. Even by using the automated head impulse test, we could not eliminate all variability of head movements because of various factors including neck muscle tension and imperfect coupling of the head to the bite bar. Our results also may not generalize to all patients with loss of vestibular function. We did not study patients with bilateral vestibular loss nor patients with chronic vestibular hypofunction. And there was certainly variability in the degree of vestibular loss when our patients were tested, and the time after onset of illness to time of testing was not the same for all patients allowing recovery and adaptation to take place to different degrees in different patients. Examining larger numbers of patients with more trials might allow a better way to test our model. In addition, we did not use a paradigm, such as *en bloc* rotations, to analyze the influence of neck proprioceptive cues on the VOR response. Other factors that should be considered in future studies including increasing the randomness of the stimulus (more than two velocities, more than two amplitudes, different timings, etc).

CONCLUSIONS

In patients with acute vestibular neuritis, we used an automated system to impose standardized passive head impulses and showed that predictability decreases the latency of corrective saccades, and increases VOR gain. With predictable head impulses the gaze position error after the first corrective saccade, and at the end of the head impulse, is reduced improving the function of the VOR. Using a 'LATER' analysis of distributions of latencies of corrective saccades we were able to see more clearly the patterns shown by covert saccades. We found two subtypes of covert saccades: early (<90ms) and late (>90ms). We propose two rise-to-threshold stochastic decision mechanisms for triggering early and late covert corrective saccades before new visual information becomes available in patients with vestibular hypofunction. Predictability primarily impacts the early mechanism, producing more early covert corrective saccades.

The challenge for further studies is to discover the circuits that generate covert corrective saccades and the mechanisms by which they are influenced by prediction.

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Figure legends

Fig. 1. Example of recordings in two representative patients (A and B) using the automated HIT device showing fast head impulses and the corresponding eye movements (inverted for comparison). Panel A shows responses to predictable head impulses with covert saccades occurring earlier compared to unpredictable head impulses (Panel B). Panel C shows more covert corrective saccades cluster more with predictable than unpredictable head impulses (Panel D). Note the lower VOR gain with unpredictable head impulses for both patients.

462

463 Fig. 2 Box plot of Gaze Error when *the head stops* considering only *covert saccades* after
464 predictable (Pred) vs. unpredictable (Unpred) head impulses in patients with acute vestibular
465 neuritis. Left: The gaze error in head impulses to the affected side is significantly higher when
466 these are unpredictable. Right: The gaze error in head impulses to the healthy side is also
467 significantly higher when these are unpredictable.

468

469 Fig. 3, left: Box plot of Gaze Error at *the end of covert corrective* saccades after predictable
470 (Pred) vs. unpredictable (Unpred) head impulses in patients with acute vestibular neuritis. The
471 gaze error in head impulses to the affected side is significantly higher when head impulses are
472 unpredictable. Right: Box plot of gaze error at *the end of the first saccade*, considering all
473 trials with a corrective saccade after predictable (Pred) vs. unpredictable (Unpred) automated
474 head impulses. The gaze error between predictable and unpredictable head impulses to the
475 affected side is not significantly different.

476

477 Fig. 4. Left: Box-plot of Gaze Error at the onset of covert saccades in predictable (Pred) vs.
478 unpredictable (Unpred) head impulses. The gaze error at the end of the saccade was
479 significantly higher in unpredictable head impulses to the affected side. Right: Box plot of
480 gaze error at the *onset of the first saccade* in predictable (Predict) vs. unpredictable
481 (Unpredict) automated head impulses. The analysis shows that the gaze error between
482 predictable and unpredictable head impulses to the affected side is significantly different.

483 Fig. 5. Left: Box-plot of all *first covert corrective* saccade latencies in predictable (Pred) vs.
484 unpredictable (Unpred) head impulses. Saccade latency was significantly higher in
485 unpredictable head impulses to the affected side. Right: Box plot of corrective saccade latency
486 considering *the first corrective saccade* in predictable (Predict) vs. unpredictable (Unpredict)

automated head impulses. The analysis shows that the gaze error between predictable and unpredictable head impulses to the affected side is significantly different.

Fig. 6A: The LATER based analysis of *covert corrective saccades* in patients with vestibular neuritis after predictable and unpredictable head impulse tests: Left, frequency histogram (x-axis: Latency; y-axis: Frequency of saccades); right, reciprobit plot: note that the cumulative probability of early saccades in the reciprobit plots was higher with predictable head impulses. Fig. 6B: Simulation of a two decision mechanisms LATER model in the unpredictable (blue) and predictable (red) conditions. Left panel: distribution of saccade latencies predicted by the model in the two conditions. Right panel: reciprobit plot of simulated latency data and their fit. Parameters for unpredictable head impulses: Main unit with τ=1, μ=9, σ=1.1 and Early unit τ_E=1.2, μ_E=0, σ_E=9.2. Parameters for predictable head impulses: Main unit with τ=1, μ=9, σ=1.1 and Early unit τ_E=0.9, μ_E=0, σ_E=9.2.

Fig. 7. Scheme of a two competing saccade triggering mechanisms model: a "Main unit" with parameters μ, σ and τ operates in parallel with a 'maverick' Early unit, whose parameters are μ_E = 0, σ_E. and τ_E. Whichever unit reaches threshold first triggers the response. In both mechanisms the decision signal (blue) starts from an initial level S_0=0.

To simulate the response to unpredictable impulses model parameters for the Main unit were threshold τ=1, a mean rate μ=9 and standard deviation σ=1.1, which made decisions in an average of τ/μ=0.11 seconds. The Early unit of the model had a threshold τ_E=1.2, a mean rate μ=0 and standard deviation σ_E=9.2. To simulate the responses to predictable head impulses, only one change was necessary; the threshold of the Early unit was decreased to τ'_E=0.9.

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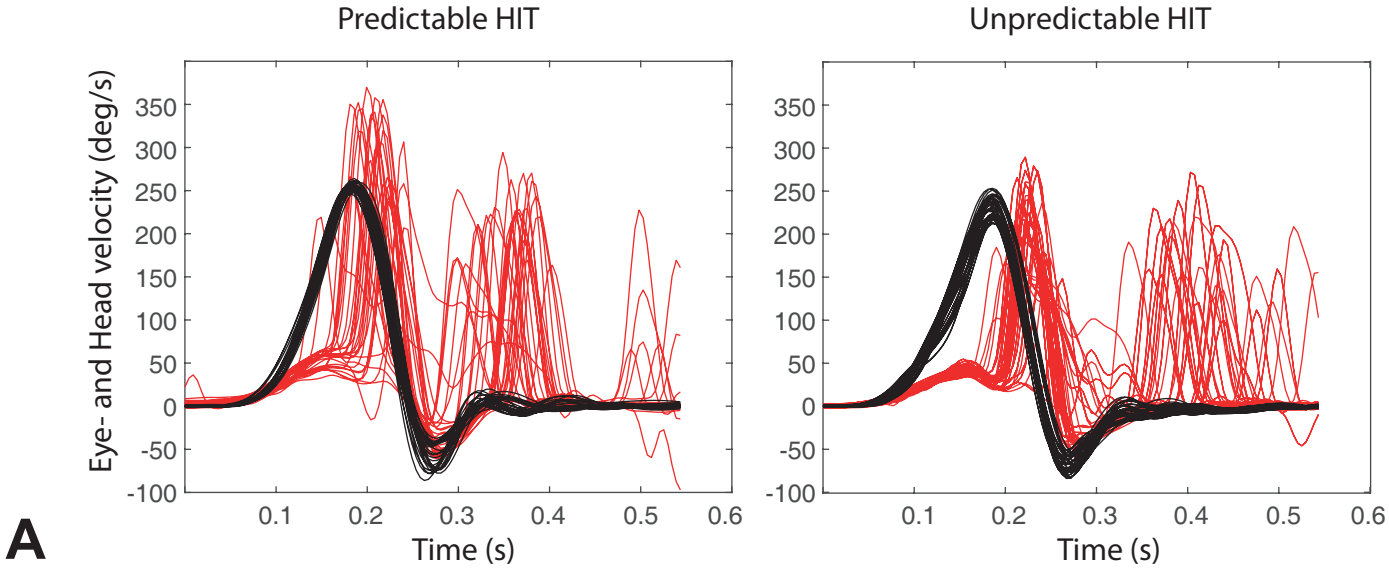
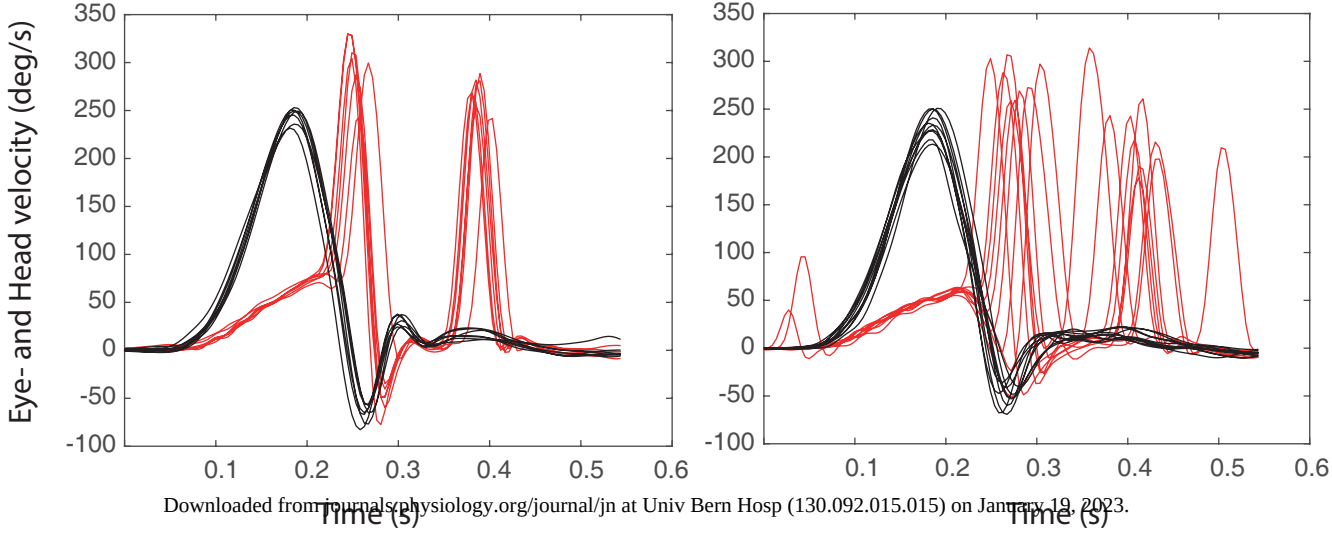
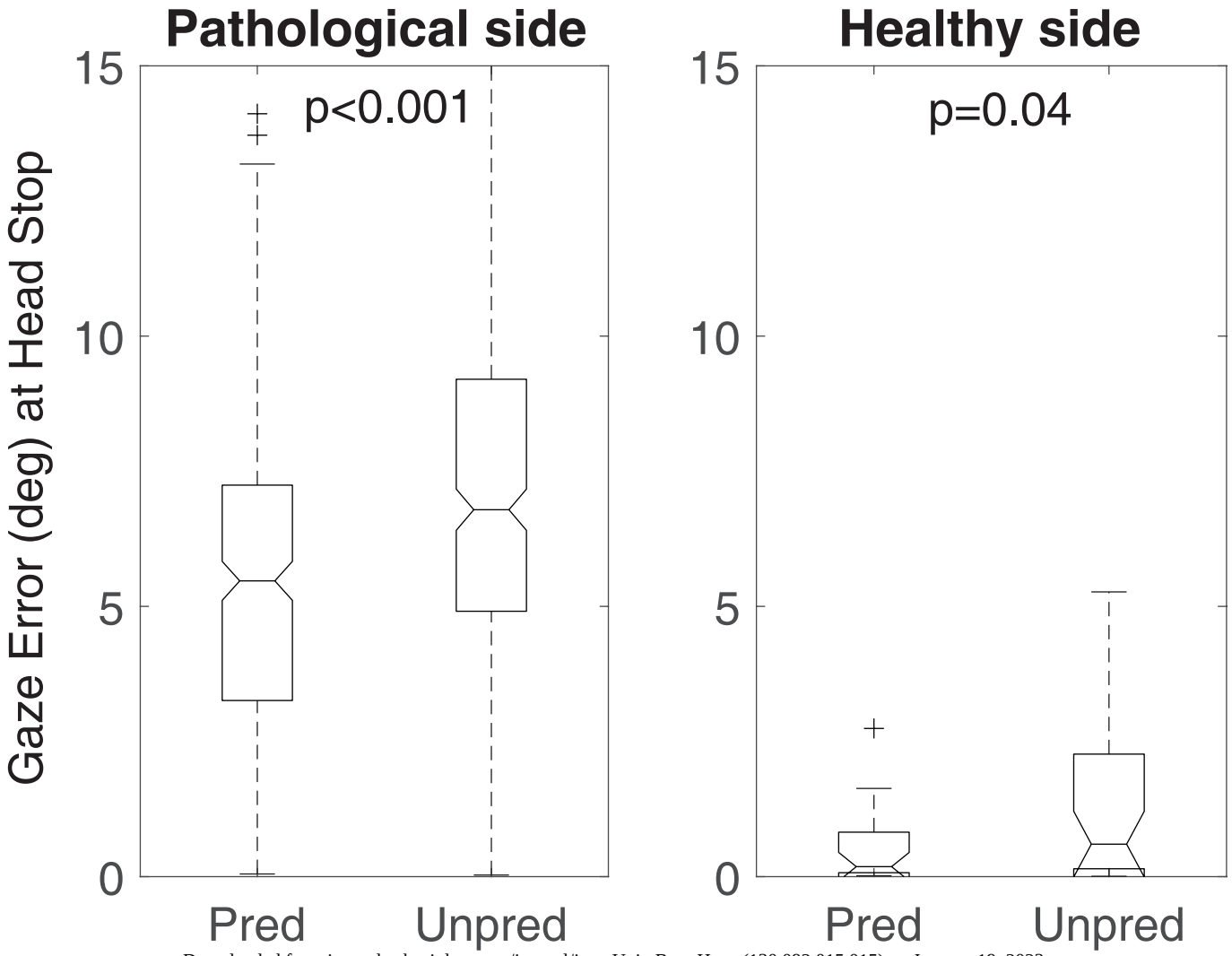
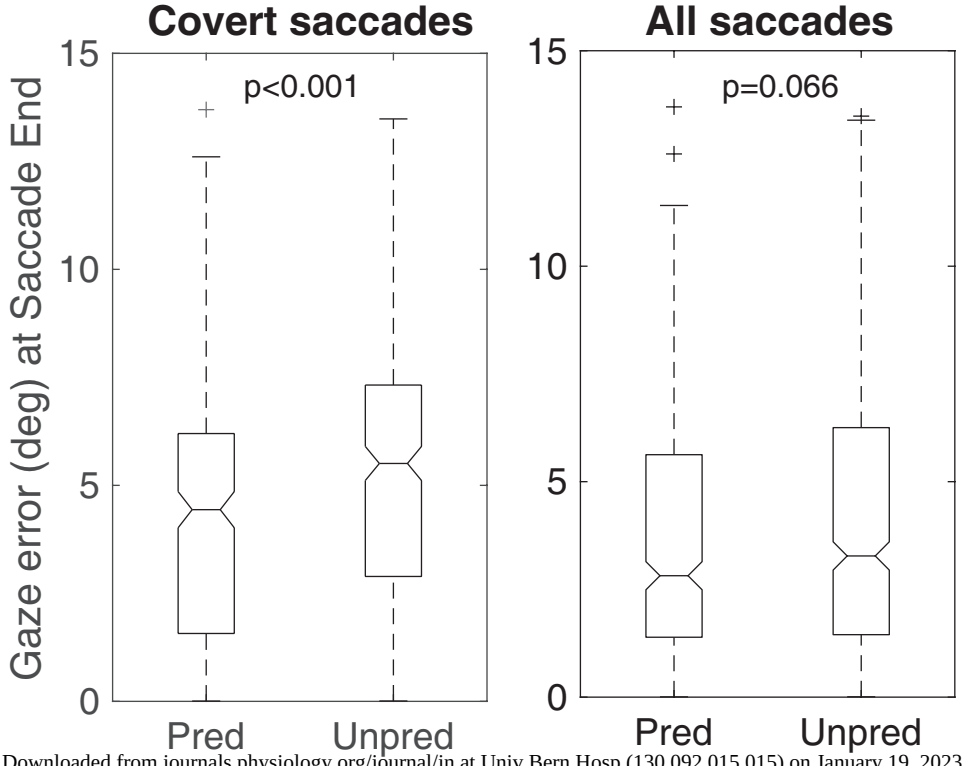
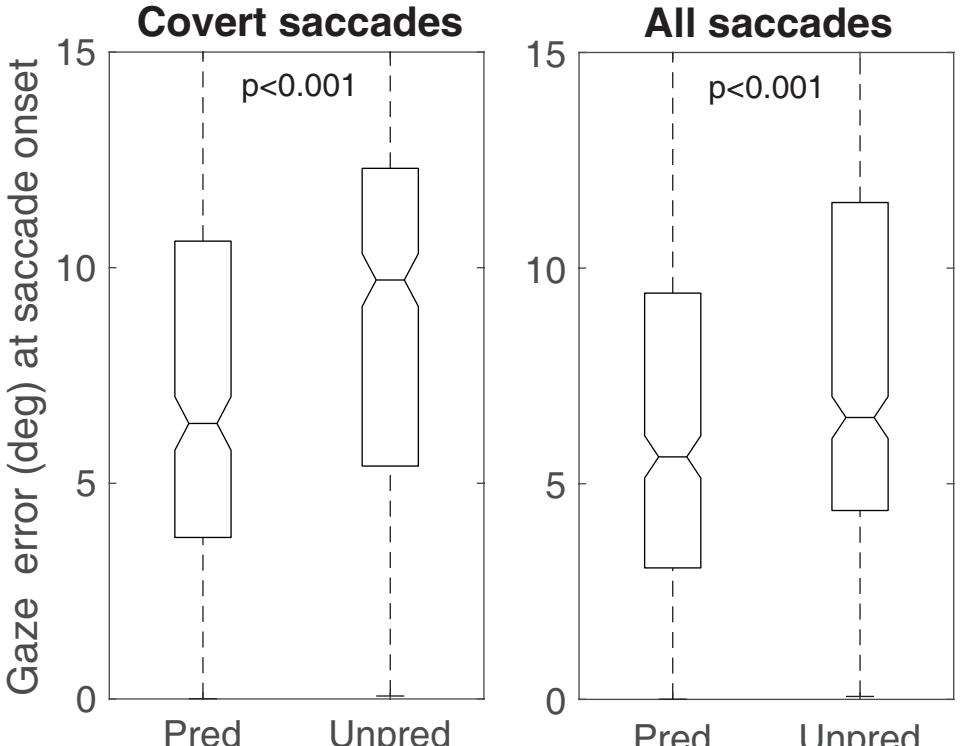
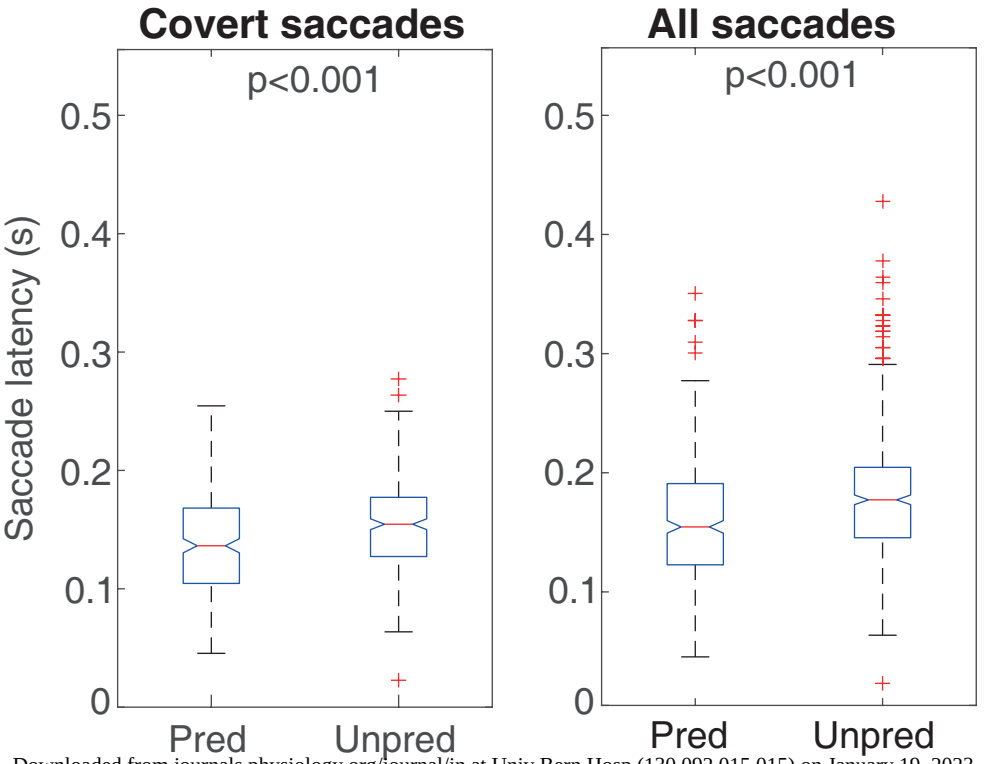


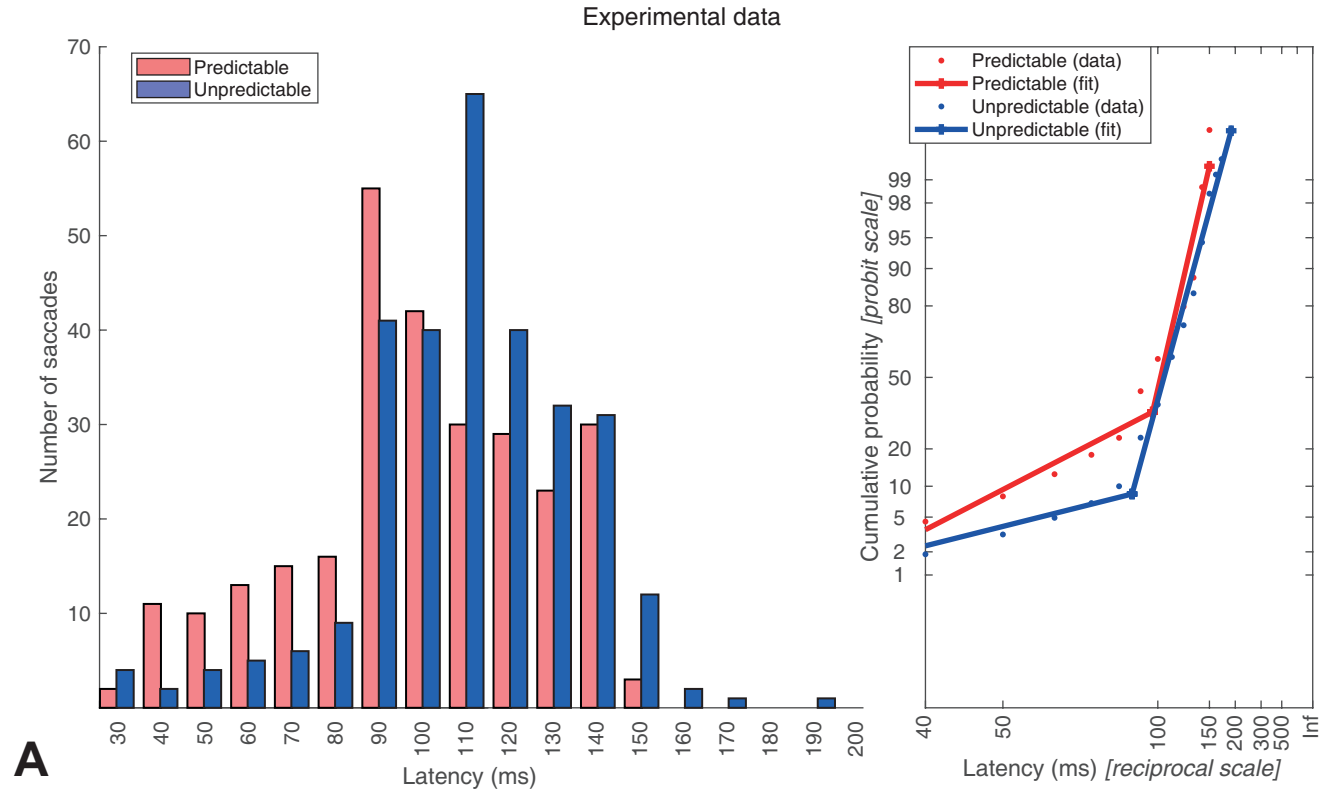


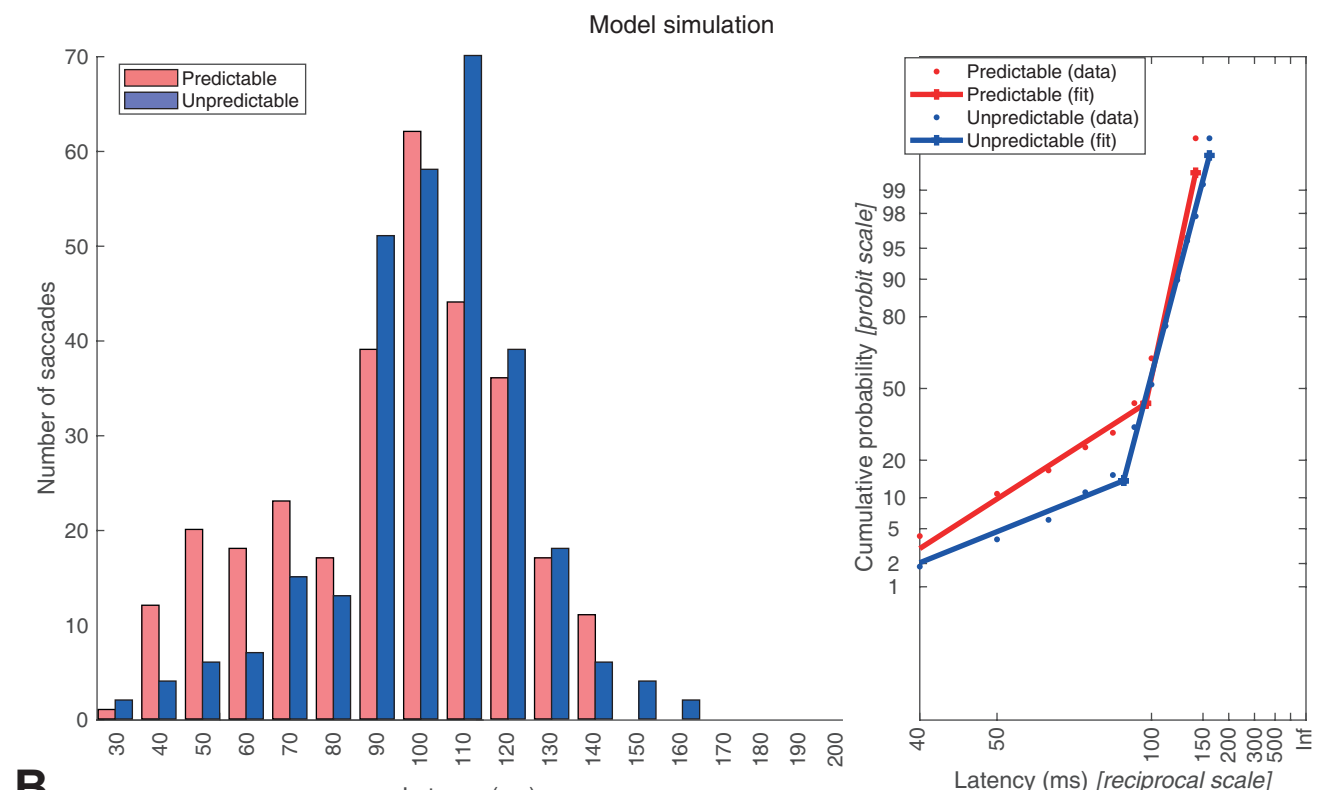


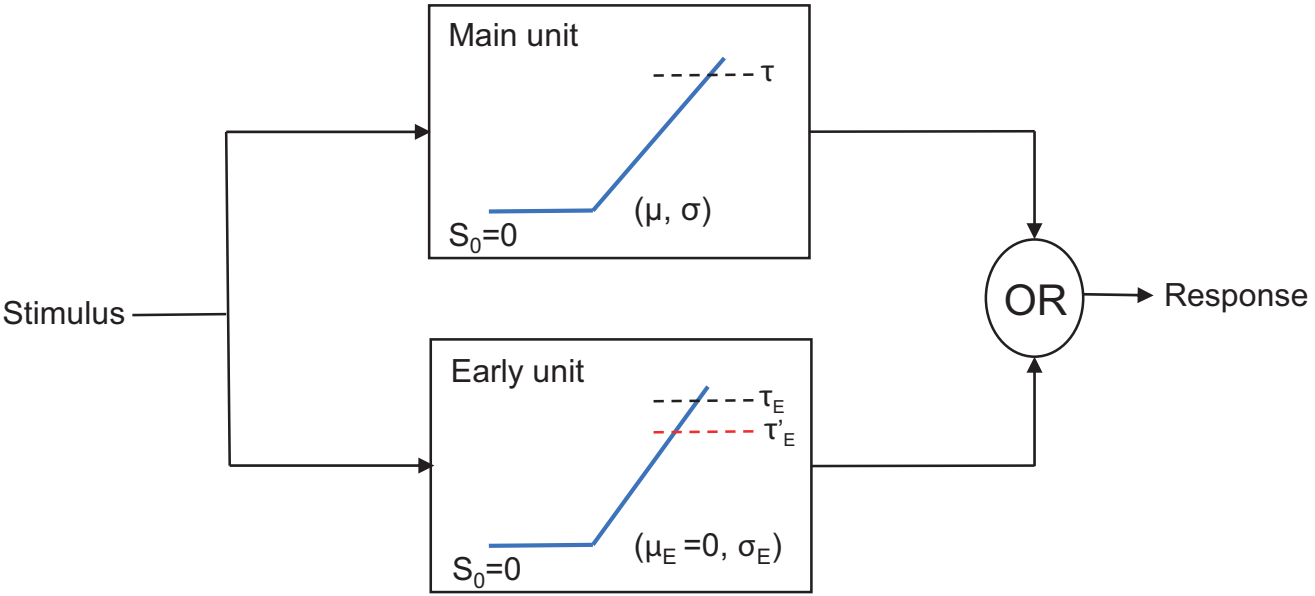




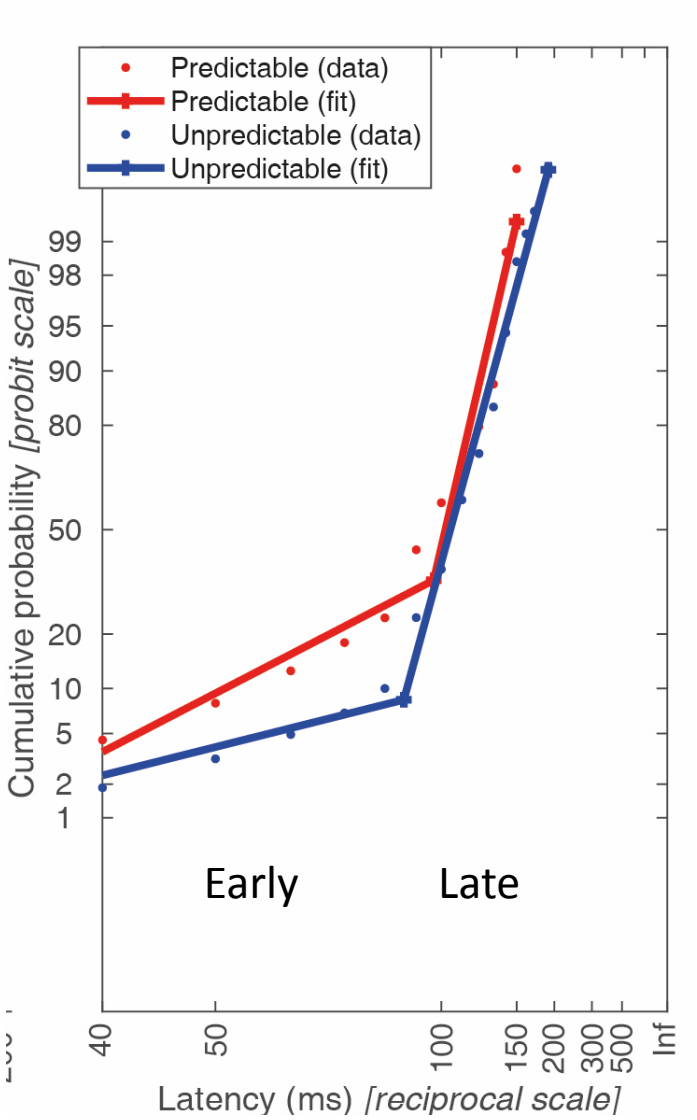


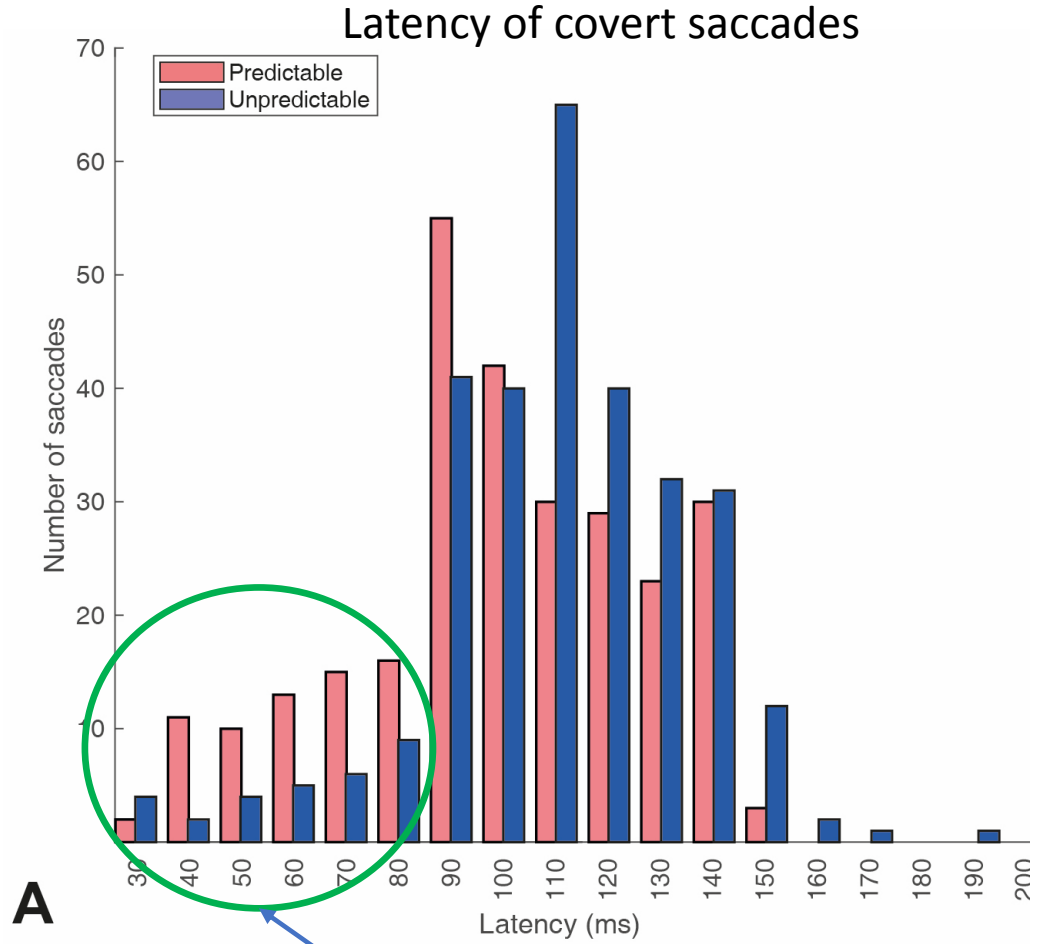






LATER analysis of covert saccades during predictable and unpredictable head impulses identifies two distributions for covert saccades in acute vestibular neuritis patients, produced by two competing decision mechanisms, which we called early and late covert saccades





A

Predictable head impulses show more early covert saccades than unpredictable ones.