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Influence of stimulus interval on the habituation of vestibulo-ocular reflex and sensation of rotation in humans

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HIGHLIGHTS

- Time interval between velocity steps influences vestibular habituation of nystagmus.
- VOR habituates only when steps are delivered after the primary phase nystagmus.
- Perception of self-rotation habituates irrespectively of stimulus interval.

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ABSTRACT

Previous studies in cats revealed that vestibular habituation of the vestibulo-ocular reflex (VOR) only occurs when velocity steps are delivered during the secondary phase nystagmus, suggesting that the presence of anti-compensatory slow phases may trigger the habituation process. We verified this property in humans by comparing vestibular habituation of VOR and sensation of rotation when steps were delivered either immediately after the perception of self-rotation had stopped, which is shortly before the nystagmus reverses direction; or when steps were delivered 60 s later, i.e. during the secondary phase. Vestibular habituation of the VOR occurred in both instances. However, the decrease in VOR peak slow phase velocity and time constant was larger when steps were delivered after nystagmus reversal compared to before nystagmus reversal. The duration of the perception of self-rotation habituated equally for both conditions. These results confirm that VOR habituation fully develops only when velocity steps are delivered after the primary phase nystagmus. This finding may be helpful for minimizing the impact of repetitive vestibular stimuli in protocols using crossover design for drug studies, testing recovery in vestibular patients, or training people for different gravitoinertial environments.

Vestibular habituation is characterized by a progressive decrease in the gain and time constant of the vestibulo-ocular reflex (VOR) during repeated exposure to angular velocity steps, and the retention of this decrease from one exposure series to the next (see [10] for review). One important feature of vestibular habituation is that the decrease in the VOR is limited to the direction of the stimulus used during the habituation series [4]. In humans, vestibular habituation by repeated rotational stimulation induces not only a decline in the VOR, but also in the perception of self-rotation (PSR) [9,14,15,30]. When humans are exposed to repeated velocity steps in the same direction, habituation of the VOR takes place mostly for that direction of stimulation, but the PSR habituates for both directions of stimulation [6].

Following a velocity step in yaw, after the original (primary) nystagmus dies out, a secondary phase nystagmus may develop with slow phases (SP) in the opposite direction, i.e. in the same direction as head rotation [1]. Previous studies in cats revealed that habituation of the VOR only occurred when velocity steps were delivered after the nystagmus reversal. For example, the VOR with SP to the right did not habituate when steps in the counterclockwise (CCW) direction were delivered during the primary phase nystagmus, but the VOR with SP to the left progressively decreased when steps in the clockwise (CW) direction were given during the secondary phase nystagmus [11]. The objective of this experiment was to verify if the same was true in human subjects. Indeed, protocols generating repeated velocity steps are routinely used for testing drug efficacy or tracking recovery in vestibular patients. Adjusting the timing between two successive velocity steps might prove useful to limit the influence of vestibular stimuli repetition on the responses being tested.

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In cats the intensity of the secondary phase nystagmus is approximately one-half of that of the preceding response, whereas in humans it is closer to one-fifth [8]. The exact moment when the slow component of the vestibular nystagmus reverses direction in humans is therefore quite difficult to detect in real time. By contrast, the end of the PSR is easy to detect and previous studies have shown that PSR has shorter duration than the primary phase nystagmus [2,6,17]. Therefore, in the present study we have used the end of the PSR as a precursor to the nystagmus reversal.

Six healthy subjects (2 females, 4 males) aged 20–61 (mean 36.2) were exposed to 200 angular velocity steps in yaw directed alternatively in the CW and CCW directions during 10 sessions (called A–J) over a 5-day period. Previous studies in animals had suggested that vestibular habituation had different characteristics when the velocity steps generated post-rotatory nystagmus or per-rotatory nystagmus [10]. To avoid this possible confounding factor, our protocol included an equal number of per-rotatory and post-rotatory responses.

Each session included two series of 10 steps. In the first series (Fig. 1A), subjects were rotated CW from 0°/s to 80°/s with an acceleration of 80°/s^2, generating a per-rotatory horizontal nystagmus with SP to the left and a PSR to the right. When the subjects reported that they no longer had a sensation of rotation, the chair was stopped with a deceleration of 80°/s^2, producing a post-rotatory nystagmus with SP to the right and a PSR to the left. After this PSR had stopped, we waited for 60 s before the chair was rotated CW again. The 60-s duration was long enough for the CW steps to be delivered after nystagmus reversal, based on previous data [2,6] and a validity check performed in the present study (see Fig. 2D). The same procedure was repeated five times, after which the chair was stopped for about 1 min.

In the second series (Fig. 1B), subjects were rotated CCW, generating a per-rotatory nystagmus with SP to the right and a PSR to the left. After this PSR had stopped and 60 s had elapsed, the chair was stopped, generating a post-rotatory nystagmus with SP to the left a PSR to the right. Immediately after this PSR vanished, the chair was rotated again. This procedure was repeated five times. The duration of each session was about 30 min.

The experiment was performed in the Neuro-Ophthalmology Unit of the Hôpital Neurologique in Bron, France, with the understanding and written consent of each subject. The test procedures were approved by the local ethical committee on human experimentation (CCPRB Lyon B, n° 2004/087B) in agreement with French law (March 2, 2002) and the Declaration of Helsinki. Normal visual oculomotor control (optokinetic nystagmus, smooth pursuit, saccades), normal vestibular nystagmus induced by sinusoidal profiles, and the absence of pathologic nystagmus (spontaneous, gaze-evoked) prior to the habituation session series suggested that all subjects had putatively normal vestibular function.

Subjects were seated on a servo-controlled rotating chair with the head in a natural head-erect position. A goggle with an infrared light and video camera (VNG Ulmer, Synapsys SA, Marseille, France) was mounted in front of the subject's right eye to record horizontal eye movements. Pre- and post-test eye measurement calibrations were made by having subjects sequentially fixate a series of visual targets (1°) positioned 15° apart at a distance of 1.8 m with their left eye uncovered. During the habituation series, subjects were instructed to keep their eyes open in the dark and to look straight ahead at an imaginary horizon. They were also instructed to report verbally when their PSR had stopped.

Eye images were digitized (50 Hz) and eye position was computed in a head frame of reference using a commercial off-the-shelf software (VNG Ulmer, Synapsys SA, Marseille, France). Fast phase components of the eye movements were identified using acceleration and velocity thresholds and excluded from the analysis. The slow cumulative eye position of post-rotatory nystagmus was reconstructed by making an appropriate polynomial interpolation in position between SP according to the method described in Torte

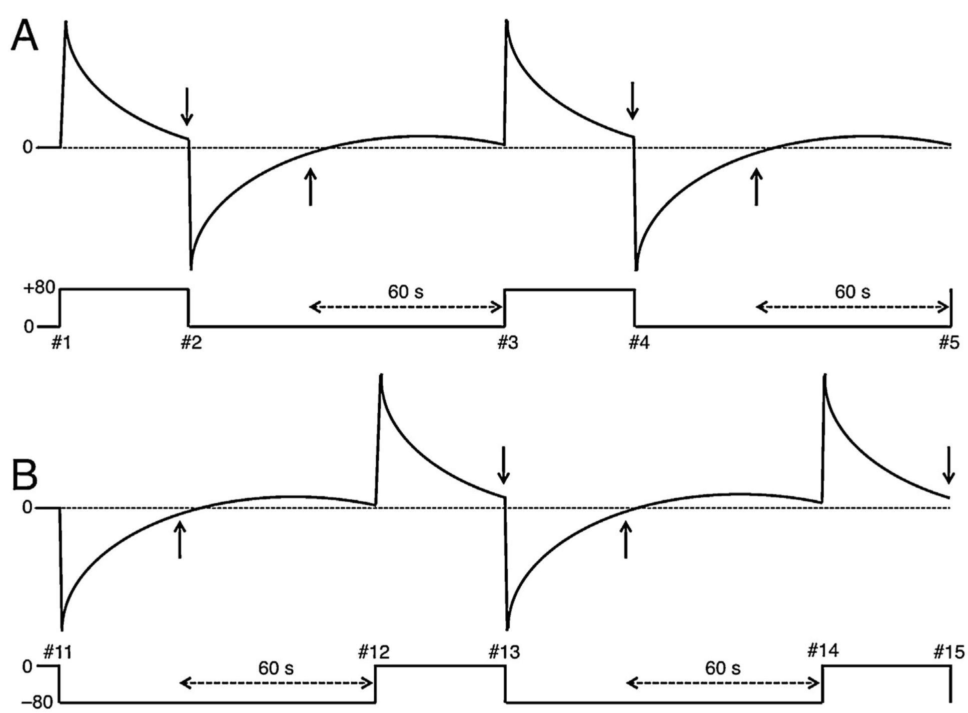

Fig. 1. Schematic of the VOR horizontal slow phase velocity during the first five velocity steps of the two series within a session. (A) Per-rotatory nystagmus to velocity steps directed CW (0 to +80°/s) followed by post-rotatory nystagmus to velocity steps directed CCW (+80°/s to 0). (B) Per-rotatory nystagmus to velocity steps directed CCW (0 to −80°/s) followed by post-rotatory nystagmus to velocity steps directed CW (−80°/s to 0). In both series, the steps directed CCW (e.g. #2, #4, #13, #15) were delivered immediately after the PSR during the preceding stimulation had stopped (arrows). The steps directed CW (e.g. #3, #5, #12, #14) were delivered 60 s after the PSR had stopped. The crossing of the VOR SPV with the dotted line (0°/s) corresponds to nystagmus reversal.