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Navigation strategies in patients with vestibular loss tested in a virtual reality T-Maze

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Abstract

During navigation, humans mainly rely on egocentric and allocentric spatial strategies, two different frames of reference working together to build a coherent representation of the environment. Spatial memory deficits during navigation have been repeatedly reported in patients with vestibular disorders. However, little is known about how vestibular disorders can change the use of spatial navigation strategies. Here, we used a new reverse T-maze paradigm in virtual reality to explore whether vestibular loss specifically modifies the use of egocentric or allocentric spatial strategies in patients with unilateral (n = 23) and bilateral (n = 23) vestibular loss compared to healthy volunteers matched for age, sex and education level (n = 23). Results showed that the odds of selecting and using a specific strategy in the T-maze was significantly reduced in both unilateral and bilateral vestibular loss. An exploratory analysis suggests that only right vestibular loss decreased the odds of adopting a spatial strategy, indicating a functional asymmetry of vestibular functions. When considering patients who used strategies to navigate, we observed that a bilateral vestibular loss reduced the odds to use of an allocentric strategy, whereas a unilateral vestibular loss decreased the odds to use of an egocentric strategy. Age was significantly associated with an overall lower chance to adopt a navigation strategy and, more specifically, with a decrease in the odds of using an allocentric strategy. We did not observe any sex difference in the ability to select and use a specific navigation strategy. Findings are discussed in light of previous studies on visuo-spatial abilities and studies of vestibulo-hippocampal interactions in peripheral vestibular disorders. We discuss the potential impact of the history of the disease (chronic stage in patients with a bilateral vestibulopathy vs. subacute stage in patients with a unilateral vestibular loss), of hearing impairment and non-specific attentional deficits in patients with vestibular disorders.

Keywords: vestibular system, labyrinth, spatial navigation, spatial strategies, egocentric, allocentric, reference frame.

1. Introduction

Spatial navigation refers to the ability to accurately orient oneself through the environment, which requires the integration of self-motion and environment information (i.e., gravito-inertial and proprioceptive signals, optic flow, visual, olfactory and acoustic landmarks). Vestibular signals, which provide information about own-body translations and rotations, may thus be pivotal for spatial navigation abilities (Angelaki & Cullen, 2008; Jacob et al., 2014; Yoder & Taube, 2014). Indeed, severe navigation deficits have been reported in animals models with bilateral vestibular deafferentation (Baek et al., 2010; Besnard et al., 2012; Machado et al., 2012; Russell et al., 2003). However, research in patients with vestibular disorders has provided equivocal results as to whether spatial navigation abilities are altered, depending on the clinical population and parameters recorded (reviewed in Smith, 2017). Spatial memory deficits have been reported in patients with a chronic bilateral vestibulopathy (BVP) tested in a virtual adaptation of the Morris water maze task (Brandt et al., 2005; Kremmyda et al., 2016). Others studies found no deficits in BVP patients tested with the Morris water maze task (Dobbels et al., 2020) or in other computer-based navigation and visual memory tasks (Jandl et al., 2015). More clearer deficits have been reported in BVP patients during real-space navigation in a building (Schöberl et al., 2021). The effects of unilateral vestibular loss on spatial navigation abilities are similarly equivocal: while some studies reported altered navigation abilities during triangle completion tasks in a desktop-based setting (Péruch et al., 1999, 2005) others found no consistent alteration in a virtual Morris water maze task (Hüfner et al., 2007). Clearer deficits have been reported in real-space navigation, such as when participants walked along a triangular path (Glasauer et al., 2002) or completed triangular paths (Péruch et al., 2005; Xie et al., 2017), without direct investigation of the spatial navigation strategies used by the patients.

Spatial navigation mainly relies on egocentric and allocentric frames of reference (Burgess, 2006), two operational modes working together to build a coherent representation of the environment (Chen et al., 2014; Gramann et al., 2010; Weniger et al., 2011). Egocentric representations are self-centered and based on subject-object associations. Allocentric representations are instead centered on aspects of the external environment, such as object-object or object-environment associations. While age (e.g., Rodgers et al., 2012) and sex (e.g., Astur et al., 2016) have been shown to influence the use of egocentric and allocentric frames of reference for spatial navigation, little is known about how the vestibular system contributes to these reference frames during navigation. Questionnaires given to 783 adults (aged 18–96 from the general German-speaking population) about their navigation strategies indicated that having experienced vertigo/dizziness during the last 12 months "reduced the scores of both the orientation and the route [egocentric] strategies" (Ulrich et al., 2019). However, frame-dependent strategies during navigation have not been systematically evaluated in humans suffering from vestibular loss using objective measures in well-controlled experimental paradigms.

A convenient way to objectively measure navigation strategies in rodents is the "reverse T-maze paradigm" (Machado et al., 2014; McIntyre et al., 2003), during which animals can use either a spatial strategy based on external landmarks (e.g., visual cues on the walls of or around the T-maze) or a response (egocentric) strategy to find the reward hidden in one arm of the maze. Using the reverse T-maze paradigm in rats, Machado et al. (2014) showed that bilateral vestibular loss affected hippocampal-dependent allocentric strategy (i.e.,

navigation relied less on visual landmarks around the T-maze) and favoured the use of striatum-dependent egocentric strategy (i.e., the ability to remember if the animal turned to the right/left in previous trials). Here, we adapted these procedures for investigations in humans and created a new reverse T-maze paradigm in virtual reality (VR) presented on a computer screen to explore whether unilateral vestibular loss and BVP specifically modify the use of egocentric or allocentric spatial strategies. Although desktop-based settings limit egocentric signals (vestibular, proprioceptive, motor signals), they provide a safe and well-controlled environment and allow patients to allocate most of their attentional resources to the navigation task, instead of to balance and eye movement controls. Navigation deficits have already been demonstrated in desktop-based settings (e.g., Péruch et al., 1999; Brandt et al., 2005), suggesting that vestibular disorders change spatial memory based only on the optic flow generated by virtual space navigation. This is supported by recent behavioural studies in healthy participants showing similar performance when egocentric information (head rotations and locomotion) was present or not during navigation in a virtual space (e.g., Huffman & Ekstrom, 2019).

The aim of this study was to compare the ability to select and use a navigation strategy, and to compare the nature of the navigation strategy selected (egocentric vs. allocentric), in a group of patients with a chronic BVP, a group of patients tested in the subacute stage of a unilateral vestibular neurectomy, and a group of healthy participants carefully matched for age, sex and education level. We also included control tasks for visual recognition memory and visuo-spatial processing speed. As found in rodents (Machado et al., 2014), vestibular loss may favour egocentric spatial frameworks during navigation. Alternatively, vestibular loss may favour the use of visual landmarks for spatial navigation, as showed for postural control and spatial orientation (Lopez et al., 2006).

2. Methods

2.1. Participants

Forty-six patients with a vestibular failure took part in the study. Among them, 45 participants were right-handed and one was left-handed based on the Edinburgh Handedness Inventory (Oldfield, 1971). Twenty-three patients presented a severe BVP (*BVP group*: 11 females; mean age ± SD: 58.9 ± 14.1 years) according to the diagnostic criteria from the Bárány Society (Strupp et al., 2017). The BVP was idiopathic in all patients, which have been described elsewhere (Deroualle et al., 2017; Nakul et al., 2020). Patients were tested during the chronic stage of the BVP. Twenty-three patients had a unilateral vestibular loss (*UVL group*: 11 females; 58.6 ± 11.4 years) due to an acute unilateral vestibulopathy (AUVP; vestibular neuritis and labyrinthitis, $n = 9$) or a unilateral vestibular neurectomy (UVN; neuroma and Menière's disease, $n = 14$). Patients with AUVP were tested 1−7 days after hospitalization (3.6 ± 1.7 days) and patients with UVN were tested 2−8 days (6.3 ± 1.4 days) after surgery, depending on their fatigue level. All patients tested in the acute or subacute phase of the UVL were included in the study only if they were able to sit upright with their head and trunk straight and motionless at the time of the test, and if they reported no severe fatigue, and experience no severe nausea, vertigo and dizziness the day of the test. Nausea and vomiting were non-inclusion criteria.

Patients underwent standard otoneurological examinations, including the bithermal caloric test with water at 44°C and 30°C, and the video head impulse test. Some patients underwent cervical and/or ocular vestibular-evoked myogenic potentials recordings. Clinical data are summarized in **Table 1** and **Tables S1-S2**. Both groups of patients were compared to 23 volunteers without history of otoneurological disorder (*Control group*: 11 females, 58.1 ± 13.5 years). All controls were right-handed based on the Edinburgh Handedness Inventory (Oldfield, 1971). Although controls did not receive otoneurological examination, they showed subjective visual vertical within the normal range. The three groups of participants did not differ in terms of age, sex, education level, and game experience (**Table 1**). Participants were informed about the study and gave their written informed consent. Procedures were approved by the local Ethics Committee (CPP Sud-Méditerranée II) and followed the Declaration of Helsinki.

2.2. Visuo-spatial tasks

The virtual environments were designed using the VRmaze RESEARCH software (InMind-Vr ®), previously reported with a learning spatial task in healthy participants (Machado et al., 2019) and displayed on a 24'' computer screen (Iiyama ProLite XUB2493HSU-B1). We used a large screen non-immersive VR environment rather than 3D immersive VR, in order to prevent cybersickness, a common complaint of exposure to VR googles (LaViola, 2000). Participants navigated through the virtual environments by using three arrows on a keyboard: "up" to move forward; "right" and "left" to rotate their viewpoint in the clockwise and counter-clockwise direction, respectively. It was not possible to navigate backwards, neither to move the viewpoint upward or downward.

2.2.1. *Virtual reverse T-Maze task*

Participants were instructed that they would find themselves in a virtual maze located at the centre of a room. The VR environment gave a first-person viewpoint and contained salient landmarks, i.e., coloured geometric symbols (**Figure 1a**). The T-maze was composed of two opposite arms extending from the middle one, in which participants were initially placed. Each arm ended with a wall, behind which there may or may not be a target, which participants could not see. Before the first trial, participants were instructed that only one of the two opposite arms contained a target and that they had to retrieve it. When they reached the target, the text "Found" was displayed on the screen and the trial was over. There was no time limit to complete a trial. Then, participants were relocated to the starting point and asked to find the target again. A total of 5 trials were administered. For the first four trials (T1–T4), the target was always located in the same arm (right or left arm, counterbalanced across patients) in order to make it possible to create a spatial association between the target and the visual landmarks (allocentric reference), or between the target and the arm side with respect to the subjective, egocentric viewpoint. On trial 5, referred to as the *probe* trial, the T-maze was rotated by 180°, so that visual landmarks were inverted front/back and right/left) as classically done in animal studies (Machado et al., 2014) (**Figure 1b**). In the probe trial, both arms contained a target.

After they completed the probe trial, participants were asked to explain which strategy they used during this last trial. For coding the navigation strategy, we followed procedures adapted from previous T-maze studies (Astur et al. 2016):

- When participants answered they turned in the same right/left arm of the T-maze (with respect to their viewpoint) where they remembered they found the target previously, and thus ignored the rotation of the visual environment, we recorded an *egocentric strategy*.
- When participants reported they followed the visual landmarks (coloured geometrical symbols) that were rotated, we recorded an *allocentric strategy*.
- When participants reported to have followed no particular strategy, *No-Strategy* was recorded.

Verbal reports were compared to behavioural data and corrected to "No-Strategy" if incongruent, as in this case participants failed to use and report a clear navigation strategy. For example, if participants reported that they followed the rotation of visual landmarks (allocentric strategy), but the behavioural data showed that they turned on the same side where they found the target during the previous trials (egocentric strategy), we corrected to "No-Strategy". This correction was applied in only 3 out of 69 participants (2 patients, 1 control) and it was confirmed that the overall results were not affected by this correction.

2.2.2. Control for visuo-spatial processing speed

Participants were virtually placed at the centre of a neutral circular area. They were instructed to locate a circular red target, which could be on their back, front, or side, and to retrieve it as quickly as possible by rotating their viewpoint and moving forward towards the target. When participants reached the target, the text "Found" appeared on the screen and participants were repositioned at the centre of the circular area. The location of the target changed in each trial in a pseudorandomized order. Eight trials were administered, for which the time to retrieve the target was recorded.

2.3. Control for visual recognition memory

To control that navigation strategy was not modulated by altered visual recognition memory in patients, we used a computer-based adaptation of the Doors Test (Baddeley et al., 2006) following procedures from previous studies on spatial navigation abilities (Brandt et al., 2005; Hüfner et al., 2007). The test was presented on a computer screen using PsychoPy (Peirce et al., 2019) and consisted of two parts: Part A and Part B. Each part was composed of a presentation and a response phase. In the 'presentation phase', participants were presented with a sequence of 12 different types of doors for 3 s each. In the 'response phase', a same *target* door of the presentation phase was displayed in a 2 × 2 array together with three distractors. The whole phase was composed of 12 arrays in which participants were asked to identify the target door without time limit. In Part A, the distractors were different categories of doors than the target door (e.g., a garage door, a garden door), whereas in the more difficult Part B, the distractors were the same type of door with a few different details (e.g., different doorbells). One point was awarded for each correct response and only those participants who obtained at least a score of 8 in Part A were administered Part B.

2.4. Experimental procedures

Participants were tested while comfortably sitting in front of a desk with the lights switched off in the room to minimize the influence of peripheral visual signals from the experimental room. They first received instructions about the virtual T-Maze task, after which they completed a minimum of 8 training trials with no maze to become familiar with procedures to navigate in the VR environment. During the training, participants were asked to move into a virtual open space in order to retrieve a circular red target. When the training was over, the T-Maze task started, and participants were asked to report the strategy they used. Participants then performed the control task for visuo-spatial processing speed and the Doors Test. Participants took short breaks between tasks and they were instructed to stop if they felt nauseous, dizzy or experienced any kind of discomfort. No patient had to stop the experiment due to any of these symptoms. Several pilot tests were conducted to develop a sequence of cognitive tasks in VR (including the T-Maze task) which reduced as much as possible the duration of VR exposure to avoid the occurrence of nausea, fatigue and lack of comfort. The whole experiment lasted not more than 30 minutes on average.

2.5. Data Analysis

The navigation strategy (Allocentric *vs*. Egocentric) or absence of strategy (No-Strategy) reported for the probe trial was coded as a categorical variable. To analyse the predictors of the navigation strategy, we calculated several logistic regressions (SPSS 26, IBM, USA). Outcomes were either the presence of a navigation strategy (Strategy *vs*. No-Strategy) or the type of strategy (Allocentric *vs*. Egocentric). In patients with unilateral vestibular loss, we also conducted two exploratory analyses regarding (1) the type of UVL, *i.e.* patients with AUVP tested in the acute stage of the disorder *vs*. patients with UVL tested in the acute stage after the neurectomy but during the chronic stage of a neuroma or a Menière's disease; (2) the influence of left *vs*. right vestibular lesion, irrespective of the type of UVL. Depending on how participants were stratified, predictors in the logistic regression were the Group (BVP, UVL, Controls), Type of UVL (AUVP *vs*. UVN) and/or Side of UVL (left *vs*. right UVL), with the Sex and Age as covariates.

For each participant and each trial in the T-Maze, we measured the time and path length to retrieve the target. For each participant, we calculated the mean time to reach the target in the control task for visuo-spatial processing speed. As the Shapiro-Wilks test showed that most of these data were not normally distributed, we ran non-parametric procedures in SPSS 26 (IBM, USA). Within-group analyses were carried out using Friedman's tests with the trials (T1–T4) as a within-subject factor and post-hoc comparisons were performed using the Wilcoxon test with a Bonferroni correction. Between-group analyses were carried out using the Kruskal-Wallis test. Differences were considered significant for $p < 0.05$ unless alpha level was corrected for multiple comparisons.

3. Results

3.1. Spatial strategies in the VR T-Maze

Although 65% of the controls reported having used a navigation strategy (whether allocentric or egocentric), only 35% of BVP patients and 30% of UVL patients used one (**Figure 2a**). A first logistic regression indicated that the ability to use a navigation strategy with respect to No-Strategy was significantly predicted by the Group ($\chi^2 = 7.59$, $p < 0.05$) and Age ($\chi^2 = 10.04$, $p < 0.01$). The odds to use a navigation strategy *vs*. No-Strategy were significantly reduced in BVP patients (odds ratio [OR]: 0.23; 95% confidence interval [CI]: 0.06−0.89; $p = 0.033$) and in UVL patients (OR: 0.19; CI: 0.05−0.73; $p = 0.016$) when compared to controls (**Table 2**). In other words, the odds of controls to use a navigation strategy compared to No-Strategy were 4.4 times more than that for BVP patients and 5.3 times more than that for UVL patients. Age was significantly associated with a reduction in the odds of using a strategy with respect to No-Strategy (OR: 0.93; CI: 0.88−0.98; $p = 0.005$). Sex was not a significant predictor ($p = 0.893$) (**Table 2**).

In a first exploratory analysis, UVL patients were stratified in AUVP and UVN (**Figure S1** and **Table S3**). A logistic regression showed that the odds to use a navigation strategy vs. No-Strategy were significantly reduced in patients with UVN ($p = 0.008$) when compared to controls, whereas this was not the case in AUVP ($p = 0.348$). The odds of controls to use a navigation strategy compared to No-Strategy were 11.1 times more than that for patients with UVN.

In a second exploratory analysis, patients were stratified according to the side of the vestibular loss. A logistic regression analysis indicated that only right UVL reduced significantly the odds to use a navigation strategy vs. No-Strategy when compared to controls ($p = 0.015$) (**Figure S2** and **Table S4**). This was not the case in patients with left UVL ($p = 0.204$). The odds of controls to use a navigation strategy were 20 times more than that for patients with right UVL.

In a last multivariate logistic regression analysis, Group ($\chi^2 = 18.6$, $p < 0.001$) and Age ($\chi^2 = 16.84$, $p < 0.001$) were significantly associated with the odds of using specifically an egocentric or an allocentric navigation strategy when compared to No-Strategy (**Figure 2a**). **Table 3** shows that UVL patients had a significantly lower chance of using an egocentric strategy when compared to No-Strategy than controls ($p < 0.05$), whereas this was not the case of BVP patients ($p = 0.20$). Conversely, BVP patients had a significantly lower chance of using an allocentric strategy when compared to No-Strategy than controls ($p < 0.05$). This was not the case of UVL patients ($p = 0.23$). Altogether, this indicates a reduced use of allocentric strategies in BVP patients and a reduced use of egocentric strategies in UVL patients. The analysis also indicates that Age was significantly associated with a reduced odds of using an allocentric strategy when compared to No-Strategy ($p = 0.001$). By contrast, Age was not significantly associated with the odds of using an egocentric strategy rather than No-Strategy. Sex was neither related to the odds of using an egocentric or an allocentric strategy when compared to No-Strategy.

3.2. Time and path length to retrieve the target

Friedman's tests showed that the time to retrieve the target significantly changed from T1 to T4, indicating improved ability to navigate in the T-Maze in all groups of participants (Controls: $\chi^2_{(3)} = 13.07$, $p = 0.004$; BVP: $\chi^2_{(3)} = 10.77$, $p = 0.013$; UVL: $\chi^2_{(3)} = 21.37$, $p < 0.001$) (**Figure 2b**). Friedman's tests showed that the path length did not significantly change from T1 to T4 for Controls ($\chi^2_{(3)} = 4.47$, $p = 0.215$) and UVL patients ($\chi^2_{(3)} = 3.26$, $p = 0.353$), but the change was significant for BVP patients ($\chi^2_{(3)} = 8.48$, $p = 0.037$) (**Figure 2c**). Followed up tests for the BVP group showed that the path length decreased between T1 and T4 (Wilcoxon test, $p = 0.026$), and between T2 and T4 ($p = 0.009$), however the differences were not statistically significant after Bonferroni correction (corrected $\alpha = 0.0083$). Kruskal-Wallis tests indicated no significant effect of the Group for T1 to T4 regarding the time (all $H_{(2)} < 5.19$ and $p > 0.075$) and the path length (all $H_{(2)} < 5.0$ and $p > 0.082$). For the probe trial, there was no significant effect of the Group for the time ($H_{(2)} = 1.54$, $p = 0.464$) and the path length ($H_{(2)} = 1.17$, $p = 0.917$).

3.3. Controls for visuo-spatial processing speed and visual recognition memory

The time to retrieve the target in the control task did not differ between groups (Kruskal-Wallis test: $H_{(2)} = 3.67$, $p = 0.159$; **Figure 2d**), indicating similar abilities to locate visual targets and to navigate the virtual environment between groups.

Participants from the three groups recollected a similar number of items in the Doors Test, indicating no significant effect of vestibular loss on visual recognition memory ($H_{(2)} = 5.46$, $p = 0.065$; **Figure 2d**).

4. Discussion

4.1. Vestibular loss decreases the odds of using a navigation strategy

General effect of vestibular loss on the odds of using a navigation strategy

We found that patients with chronic BVP and patients with a UVL in the acute/subacute stage of a vestibular loss failed to select and use a specific strategy to orient themselves in a VR T-maze. Our finding is congruent with results from a recent survey revealing that vertigo/dizziness in the last 12 months decreases the odds that individuals report using either an egocentric or an allocentric strategy (Ulrich et al., 2019). Such a failure to select and use a proper navigation strategy is consistent with studies indicating that vestibular disorders impair performances in spatial memory tasks during navigation in VR (i.e. based only on optic flow and allocentric references, Brandt et al., 2005; Kremmyda et al., 2016; Péruch et al., 1999), as well as during novel route recombination (Schöberl et al., 2021) and triangle completion (Glasauer et al., 1994; Péruch et al., 2005) in VR and real space navigation (i.e. using egocentric references) tasks/settings. Other studies did not find significant effect of BVP and UVL on navigation performance (Dobbels et al., 2020; Jandl et al., 2015).

Results from the present study and results from virtual adaptations of the Morris water maze task are difficult to compare directly, as we focused on self-reports about navigation strategies instead of performance

in terms of response time, path length and heading errors as in previous navigation studies (Brandt et al., 2005; Kremmyda et al., 2016; Péruch et al., 1999). Here, we chose to focus on the navigation strategy following procedures from a classical behavioural task in rodents (Machado et al., 2014). Being able to exactly record the participant's experience and strategy (following the landmarks that have rotated in the environment, or remembering the motion with respect to the egocentric viewpoint) and to compare it with the behaviour (recording of the path in the virtual T-maze) is a clear advantage with respect to animal studies. In particular, it avoids confusion between random exploration of either arm of the T-maze and explicit, deliberate exploration of a given arm of the T-maze based on a clear spatial strategy.

Only 5 trials were applied in the present task, and it is possible that patients with a BVP or UVL require a larger number of trials before being able to select and report a proper navigation strategy, instead of searching randomly into one arm of the T-maze or the other. The dramatic decrease in the odds of selecting and using a navigation strategy (with respect to No-Strategy) in both groups of patients with vestibular disorders can be accounted for by specific influence of vestibular disorders on the function and structure of the brain network involved in spatial navigation (review in Smith, 2017) and/or by unspecific effects of the vestibular loss on attention, fatigue and ability to explore and remember visual landmarks (see below). The lower ability to select and use navigation strategies in patients with vestibular disorders indicates that vestibular signals about own-body rotations and translations are in general important for spatial memory and wayfinding strategies (Ulrich et al., 2019). Alternatively, it can indicate that vestibular disorders have general effects on cognition reaching beyond spatial navigation, as suggested by recent epidemiological studies (Bigelow et al., 2016; Harun et al., 2016; Semenov et al., 2016).

Measures taken to reduce unspecific effects of vestibular loss on fatigue and attention

There is a large body of evidence showing that patients with a BVP, and to a lesser extent patients with a UVL, can complain about a lack of attention, difficulty to focus and fatigue (Bigelow et al., 2016; Popp et al., 2017). As the experiment lasted about 30 min, fatigue may have installed, especially for patients who underwent surgery and general anaesthesia several days before the T-Maze task. Several measures were taken to reduce these effects. The T-Maze task was administered first during the experiment in order to limit the effects of fatigue on navigation performance. In addition, participants were tested while sitting on a chair in front of a computer screen in order to have most of their attentional resources allocated to the navigation task, instead of to keeping balance control and stabilizing gaze (see below). Overall larger attentional deficits in patients with BVP and stronger fatigue in UVL patients who underwent surgery may have decreased the attention paid to visual landmarks. Although there was no eye movement recording in the present experiment to measure exploration of visual landmarks, there is evidence to suggest that BVP patients exhibit different visual exploration than healthy participants, including fewer object fixations during real-space navigating (Schöberl et al., 2021).

It is important to note that the lack of group difference in the control task for navigation speed indicates that the decrease in the likelihood to select and use a navigation strategy cannot be accounted for by a decrease

in processing speed or in the ability to navigate through the VR environment. In addition, the absence of group difference in the Doors Test rules out an influence of altered visual recognition memory on the difference in navigation strategies. Although the Doors Test did not control for visual memory in the T-Maze task directly, it provides congruent findings with previous investigations in BVP patients (Brandt et al., 2005; Kremmyda et al., 2016) and indicates that general mechanisms of visual memory and attention remained unaltered in chronic BVL and in UVL patients tested in the subacute phase of the surgery for UVN and hospitalization for AUVP. Finally, the careful matching of the groups also excludes an effect of age, education level or computer/game expertise on the reported differences in the navigation strategies.

Impact of hearing impairment

Another factor that may partly explain differences between the groups of patients is a concomitant hearing impairment (reviewed in Smith, 2022). Recent studies suggest that cognitive dysfunctions previously reported in patients with vestibular disorders may be related to hearing loss (Dobbels et al., 2019, 2020). Dobbels et al. (2019) used a battery of cognitive tests in 64 BVP patients and 83 controls and found that the hearing status was significantly related to performance in the immediate memory (remembering a list of words) and language, but hearing loss was not significantly related to visuo-spatial functions, which are at stake in the present study. In another study using the virtual Morris water maze in BVP patients, the degree of hearing loss was significantly related to the time to reach the hidden platform, and inversely related to the time participants spent searching in the right quadrant of the water maze (Dobbels et al., 2020). There was no significant relation with the path length and the heading error. By contrast, other studies found no correlation between hearing loss in UVL patients (after neurectomy for neuroma and Menière's disease) and performance in egocentric and allocentric mental rotation (Deroualle et al. 2019), and found no difference between deaf signers and hearing nonsigners engaged in visuo-spatial perspective-taking, 3D object mental rotation and spatial orientation tasks (Secora & Emmorey, 2019). As pointed out in a recent comprehensive review of the topic (Smith, 2022), understanding the respective contributions of hearing impairment and vestibular loss on spatial cognition will require large scale prospective studies comparing navigation strategies in patients with only a vestibular loss (BVP or UVL), patients with only hearing impairment, patients with vestibular and hearing loss, and carefully matched control participants. At the moment, we cannot exclude that a sensorineural loss, including both vestibular and auditory dysfunctions, is responsible for the reported decrease in the odds of using a navigation strategy.

4.2. Exploratory analysis of the effect of the type of unilateral vestibular loss on the odds of using a navigation strategy

An exploratory analysis suggests that patients with UVN, but not patients with AUVP, had lower chance to select and use spatial strategies. This result should be taken with caution because of the small sample size when patients were stratified according to their type of UVL. It is important to note that the chronic/acute stage of the vestibular loss differs strongly in both subpopulations of patients. UVL patients tested in the chronic stage

of a neuroma or Menière's disease present a similar reduction in the odds of using a navigation strategy as patients with a chronic BVP. The vestibular loss in the patients was probably already important before the neurectomy, and vestibular compensation was probably well developed before neurectomy, as indicated by moderated subjective visual vertical deviation after the UVN (**Tables S1-S2**). By contrast, patients tested in the acute stage of AUVP do not show this reduction in the odds of using a navigation strategy, despite larger subjective visual vertical deviations (**Tables S1-S2**).

We speculate that the decrease in the odds of using a navigation strategy is not an immediate effect of the UVL but reflects the chronic stage of a vestibular loss. While a vestibular neurectomy after a chronic Menière's disease or neuroma creates a total and enduring deafferentation affecting spatial perception and cognition durably (Borel et al., 2008; Devèze et al., 2015; Lopez et al., 2007; Vibert & Häusler, 2000), AUVP may preserve part of the vestibular function, patients may recover within a couple of days (Halmagyi et al., 2010; McGarvie et al., 2020), and its impact on cognition may depend on the disease severity. There is indeed evidence to suggest that both hippocampal functions and structure depend on vestibular reflexivity and the degree of clinical impairment (Göttlich et al., 2016; Jacob et al., 2020; Kamil et al., 2018; Seo et al., 2016).

Another important difference between the groups is that UVN patients, but not AUVP and BVP patients, were evaluated shortly after a surgery under general anaesthesia. General anaesthesia may have influenced performance because of its well-known effects on cognition (Belrose & Noppens, 2019). A recent study isolated the specific effect of general anaesthesia on cognition. Cognitive abilities, such as spatial memory and attention, recovered within 3 hours of return of consciousness after general anaesthesia (Mashour et al., 2021). This study was conducted in healthy participants and the effect of anaesthesia on cognition in patients with a chronic UVL may be different. Animal studies showed that anaesthesia can modify the time course of vestibular compensation (reviewed in Gliddon et al., 2004) and anaesthesia may even reduce pre-existing compensation in patients with Menière's disease and neuroma. Although the influence of anaesthesia cannot be excluded in the present study, our control cognitive tasks revealed no significant difference in visual processing speed and visual recognition memory between UVN patients and the two other groups.

4.3. Exploratory analysis of the effect of the side of unilateral vestibular loss on the odds of using a navigation strategy

Our exploratory analysis suggests that only right UVL decreased the probability to select and use spatial strategies. This result should be taken with caution because of the small sample size when patients were stratified according to their lesion side, and because of the different sizes of the two groups. The limited sample size in the present study, as well as in previous studies, may account partly for the equivocal results reported in the literature comparing the effects of left *vs*. right vestibular disorders on perception and cognition. In line with the present findings, Hüfner et al. (2007) showed a trend to perform worse in a VR navigation task only in patients with right UVL. This result and our results are in line with neuroimaging studies highlighting a dominance of the right cerebral hemisphere in right-handed participants (Dieterich et al., 2003, 2017; Dieterich & Brandt, 2018). Importantly, the neural network involved in visuo-spatial attention has been located mainly

in the right cerebral hemisphere (Dieterich & Karnath, 2006), and right UVL (in right-handed participants) may disorganize the functions of this visuo-spatial attention network. In contrast with the present findings, studies have assessed no differences between right and left UVL with respect to cognitive performance (Ayar et al., 2020; Popp et al., 2017), or found that only left UVL altered the perceived straight ahead (Saj et al., 2013) and own-body mental imagery (Deroualle et al., 2019). How the side of the vestibular loss influences cognition requires further investigations in much larger samples of participants, especially with respect to spatial navigation abilities.

4.4. Effect of BVP and UVL on egocentric vs. allocentric navigation strategies

To the best of our knowledge, this is the first systematic comparison of spatial strategies during navigation in humans with unilateral and bilateral vestibular loss.

Our results indicate that a chronic BVP dramatically decreased the odds of using an allocentric navigation strategy. Our findings in humans are fully compatible with observations in rats with a bilateral vestibular loss also tested in a reverse T-maze (Machado et al., 2014): bilateral vestibular loss affected hippocampal-dependent allocentric strategy and favoured the use of striatum-dependent egocentric strategy. Allocentric coding has been associated with activation of the hippocampus and/or the entorhinal cortex during visually guided navigation in VR (Bohbot et al., 2012; Guderian et al., 2015; Jacobs et al., 2013; Maguire, 1998; Sherrill et al., 2013). Interestingly, there is evidence to suggest that the volume of the hippocampus is reduced in patients with a total and chronic BVP (patients with neurofibromatosis 2; Brandt et al., 2005) and in patients with a partial BVP (Kremmyda et al., 2016) when compared to healthy controls. This hippocampal atrophy remains controversial as it was not confirmed in other groups of patients with chronic and partial BVP (Cutfield et al., 2014; Göttlich et al., 2016). Furthermore, BVP patients showed lower activation in the right anterior hippocampus and bilateral insula during real navigation, which correlated with higher error rates on recombined novel routes (Schöberl et al., 2021). In the same study, patients with a complete BVP showed higher activations in the caudate nucleus when compared to patients with incomplete lesion (Schöberl et al., 2021). Another fMRI study, using a computer-based spatial navigation task, indicated that cerebellar activity was higher in BVP patients when compared to controls (Jandl et al., 2015), especially in a cerebellar region known to be involved in sequence-based navigation (Iglói et al., 2015). Altogether, these results suggest that BVP increases the odds of shifting from an allocentric strategy to a striatum-dependent (i.e., egocentric) navigation strategy.

On the contrary, we found that UVL decreased the odds of using an egocentric navigation strategy. The vestibular system has been proposed to be strongly connected to a multisensory fronto-parieto-temporal network in the right cerebral hemisphere underlying visuo-spatial processing and attention in an egocentric frame of reference (Bottini et al., 2001; Fink et al., 2003; Saj et al., 2014). As summarized in Dieterich & Karnath (2006), data from patients with stroke and neuroimaging studies show a right hemisphere dominance and common areas for both visuo-spatial neglect and vestibular information processing. There is evidence to suggest distortions of the egocentric reference frame in patients with unilateral vestibular disorders tested either

in the chronic stage after a total vestibular neurectomy (Saj et al., 2013), or in the chronic stage of a partial unilateral vestibulopathy (Saj et al., 2021), as patients present with deviations of the subjective straight ahead. A study from our group in patients with UVL, operated on for schwannoma and Menière's disease as in the present study, indicates deficits for spatial imagery in an egocentric reference frame, whereas spatial imagery in an allocentric reference frame was unaffected (Deroualle et al. 2019). Similarly, studies in healthy participants indicate that caloric, galvanic and magnetic vestibular stimulation can change egocentric space perception (Hamann et al., 2009; Lindner et al., 2021; Pavlidou et al., 2018). In addition to interfering with the brain network underlying egocentric representations, UVL can affect the function and structure of the visuospatial attention network (Corbetta et al., 2008), such as altered responses in the intraparietal sulcus (Helmchen et al., 2014), or gray matter volume reduction in the right superior temporal gyrus (zu Eulenburg et al., 2010) and supramarginal gyrus (Hüfner et al., 2009). Consistently, recent measures of visuospatial attention in microgravity showed enhanced stimulus-driven attentional capture to the detriment of endogenous attention (Salatino et al., 2021). A neuroimaging study after short-term acute exposure to microgravity showed a decreased functional connectivity at the right temporo-parietal junction/angular gyrus (Van Ombergen et al., 2017), a core area within the right attentional network and deemed crucial for self and own-body consciousness (Ionta et al., 2011). Acute exposure to microgravity creates mismatches between visual, proprioceptive and vestibular inputs (Van Ombergen et al., 2017), which can disorganize networks supporting visuospatial processing and attention in a body-centred reference frame. We speculate that similar disorganization may occur in UVL patients tested in the acute or subacute stage of a neurectomy or AUVP.

The different patterns observed in patients with BVP and UVL can be accounted for by other factors than the extent of the vestibular loss. One crucial difference is that BVP patients were tested in the chronic stage of their vestibular loss, whereas UVL patients were tested in the acute/subacute stage of the vestibular loss. Accordingly, the brain mechanisms that are in place at the time of the cognitive tests in patients with chronic BVP and in patients with acute UVL may be very different.

4.5. Effect of age on navigation strategies

Age was significantly associated with an overall lower chance to adopt a navigation strategy and a decrease in the odds of using an allocentric strategy. These results are consistent with previous studies that pointed out an association between the age-related decline of the vestibular function and spatial orientation accuracy (Anson et al., 2021). Moreover, other studies highlighted the use of an allocentric frame of reference in younger compared to older adults during navigation (Bohbot et al., 2012; Li & King, 2019) and the increased odds of using an egocentric than an allocentric spatial strategy in older adults (Irving et al., 2018; Rodgers et al., 2012). For example, individuals tested in a homing task requiring to combine self-motion signals and visual landmarks revealed that "older adults did not place as much influence on visual information as would have been optimal" for accurate spatial representations (Bates & Wolbers, 2014). However, studies of real-space navigation revealed that older participants make more saccades and search saccades when navigating (Irving et al., 2018). Many factors can explain the effect of age on navigation strategies and performance, including decline in the

visual, proprioceptive and vestibular sensory systems, or changes in the entorhinal-hippocampal network (reviewed in Lester et al., 2017). Functional neuroimaging revealed that activity in the hippocampus decreases with age whereas activity in the cerebellum and right putamen increases with age, in line with a shift from predominantly allocentric to egocentric navigation strategies (Irving et al., 2018).

4.6. Effect of sex on navigation strategies

We did not observe any sex difference in the ability to select and use of specific navigation strategy. This results seems in contrast with results from a recent survey in healthy participants (Ulrich et al., 2019), results from navigation tasks (Astur et al., 2016; Mueller et al., 2008) and data from neuroimaging suggesting that men and women use different strategies and activate different brain areas during navigation (Grön et al., 2000; Irving et al., 2018). However, our results are consistent with other studies that did not observe any sex-related difference in the use of navigation strategies in virtual radial mazes and T-mazes (Levy et al., 2005; Schmitzer-Torbert, 2007). Our results are also consistent with a lack of differences in navigation performance and visual exploration parameters reported in a recent study using real-space navigation (Irving et al., 2018). Many reasons could explain these differences. For example, as highlighted by Astur and colleagues, previous administered tasks may influence strategy selection of the subsequent spatial tasks (Astur et al., 2016). Contrary to previous works (Astur et al., 2016; Levy et al., 2005), the current study administered no other spatial tasks before the T-Maze, preventing any bias toward egocentric or allocentric strategies. A second possible issue concerns the different male and female reliance on visual information for navigation. As previously demonstrated, females generally spend more time looking at surrounding landmarks and show impaired performance when no landmarks are available (Andersen et al., 2012; Sandstrom et al., 1998), while males typically show an advantage in time performance as they are more prone to use additional information from the environment, such as room geometry or Euclidian coordinates. Although this is not correlated to the use of a spontaneous spatial strategy during navigation (Andersen et al., 2012), most of the previous findings that revealed an effect of sex resulted from the analysis of the time and accuracy to navigate (Grön et al., 2000; Mueller et al., 2008) and not from a direct comparation of behavioural data and verbal reports. Indeed, a third point concerns the methodology used to determine the strategies. In contrast with other studies (Astur et al., 2016; Levy et al., 2005), participants of the present study were asked to explain which strategy they used during the probe trial, making it possible to correct the behavioural data if inconsistent and to record the No-Strategy option. The evidence on sex-related differences for spatial strategies are therefore equivocal. Further researches are needed to address the influence of sex in adopting a specific spatial strategy during navigation.

4.7. Time and path length to retrieve the target in the virtual T-maze

The data indicate that overall, there was no difference between groups regarding the time and the path length to retrieve the target in the T-maze. This indicates that the ability to navigate through a virtual maze using a keyboard was equivalent across groups and that differences in performances were mostly related to differential use of spatial navigation strategies. We note a significant effect of the trial on the path length only in patients

with BVL, suggesting that these patients improve their ability to navigate in the VR-maze over the trials repetition. Such an effect might be related to the fact that BVL patients showed delayed spatial learning when required to find a hidden platform in the VR Morris water maze (Kremmyda et al., 2016), and present the strongest cognitive impairments among patients with a vestibular loss, including deficits of visuo-spatial attention, speed processing and executive functions (Popp et al., 2017).

4.8. The virtual reversed T-maze task to measure navigation strategies in patients with vestibular disorders and healthy controls

We used a large screen, VR environment in sitting participants rather than a 3D immersive environment or real-space navigation. The approach, which is common in cognitive neuroscience, has several advantages. First, it aimed at reducing cybersickness, which is common during immersion in VR (LaViola, 2000). Second, a desktop-based setting allows to better control the sensory stimuli between groups of participants. Third, it avoids the confounding factors related to the different abilities of controls, BVP and UVL patients to perform head rotations and to stabilize images on the retina when exploring the environment. Fourth, as patients with vestibular disorders can have attentional deficits, performing the task while sitting in front of a computer screen ensures that most of the attentional resources are allocated to the navigation task, instead of to balance control.

Several authors suggested that navigation in desktop-based settings loses ecological validity compared to real-space navigation and immersive VR using googles (e.g., see review in Taube et al., 2013). Navigating in a 3D environment is much more complex than in a 2D environment (Brandt et al., 2017), especially with respect to the multisensory processing of vestibular and proprioceptive inputs, as well as auditory and olfactory stimuli (Schöberl et al., 2020). Desktop based-settings impoverish sensory feedback from motion-sensitive systems (vestibular, motor, proprioception) as there is no locomotion. The lack of sensory feedback related to locomotion and exploration may have decreased the use of egocentric navigation strategies in all groups of participants tested in the virtual T-maze task. However, recent behavioural and neuroimaging studies in healthy participants suggest that there is a modality-independent brain network underlying spatial memory and that removing egocentric signals does not change navigation performance (Huffman & Ekstrom, 2019). In line with this idea, early studies in patients with vestibular disorders found no difference between real-space and VR navigation (Péruch et al., 1999).

The fact that in our study participants were tested sitting on a chair while looking straight to the screen in from of them may have impacted performance with respect to real navigation. This posture decreases the difficulty of the task for patients with BVP and UVL when compared to real navigation because the cognitive load related to balance control (Bessot et al., 2012; Redfern et al., 2004) is reduced in this non-challenging posture. It is therefore possible that this setting decreases the deficits in spatial cognition when compared to the disorders that patients may experience in their daily life when navigating in real space, especially when they are involved in multiple tasks. In our setting, the main sensory feedback about self-motion in the VR environment comes from the optic flow on the screen and there is evidence to suggest that vestibular disorders change the ability to encode navigation based on optic flow only (Péruch et al., 1999).

We chose to have no time limit for maze exploration to match procedures from the T-Maze in rodents with a BVL (Machado et al., 2014). There are several advantages of having no time limit to retrieve the target, including a time that participants judge necessary to navigate without experiencing nausea from fast motion in the VR, or a time necessary to explore the visual environment and to pay attention to the visual cues in the VR T-maze. Having no time limit to search for the target in the T-Maze may favour the use of navigation strategy based on the visual exploration of landmarks in all groups of participants.

Finally, the presentation of the task on a screen, instead of in head-mounted VR googles, allowed participants to see visual cues in their peripheral visual field. The number of visual stimuli in the room was kept to a minimum, tests were performed in a dim room, and participants were asked to keep their heads still in front of a large screen, minimizing the influence of the peripheral visual cues on navigation strategies.

4.9. Main limitations of the study

As detailed above, a predominant limitation of the study is that navigation strategies were collected in patients with a very different history of vestibular disorders: patients with a BVP had a chronic condition, UVL patients with a Menière's disease or a neuroma had a chronic condition but were tested during the acute stage of a vestibular neurectomy, whereas patients with AUVP (neuritis) were tested in the acute stage of their disease. Taken together, the results indicate that BVP and UVL patients show a decrease in the odds of using a navigation strategy, but comparisons between groups will require confirmation in larger groups of participants all tested in the chronic stage of their disease. The impact of hearing impairment on spatial memory and cognition in general will also need to be taken into account more systematically in future studies. Finally, the vestibular function was not measured in the control group. This prevented us from carrying out a comprehensive analysis of the connection between the vestibular system reflexivity and behavioural performance.

4.10. Conclusions

In conclusion, findings of the present study shed light on the specific contributions of vestibular inputs on the frame-dependent spatial coding. Overall, an impairment of vestibular system has been showed to prevent adopting spatial strategies during virtual navigation. When considering patients who used strategies to orient themselves in the VR environment, we showed that a bilateral vestibular damage decreases the use of allocentric strategy, while a unilateral impairment decreases the use of an egocentric strategy. Further studies are needed to confirm these results using real-space navigation tasks and using functional neuroimaging, and to determine whether and to what extent these deficits impair the patients' daily life.

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Conflicts of interest

S. Besnard and M.L. Machado have or had financial relationships with InMind-VR and have been involved in the development of the VRMaze software.

Figure Legends

Figure 1. (A) Example of visual landmarks as seen from the first-person perspective at the starting point in the T-maze. (B) Top view of the virtual T-maze in the first four trials (T1–T4) and in the probe trial after the T-maze was rotated by 180°.

Figure 2. (A) Percentage of participants that reported No-Strategy or a specific spatial strategy (egocentric or allocentric) to retrieve the target in the probe trial of the T-Maze task. (B) Box-and-whisker plots showing the time and the path length (C) to retrieve the target in first four trials of the T-Maze task. Means are shown as +. The solid line inside the box is the median and boxes cover the interquartile range (5–95). (D) Box-and-whisker plots showing the number of correct items recalled in the Doors Test and the time to find the target in the control task for visuo-spatial processing speed. BVP = Bilateral vestibulopathy; UVL = Unilateral vestibular loss.

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Figure1

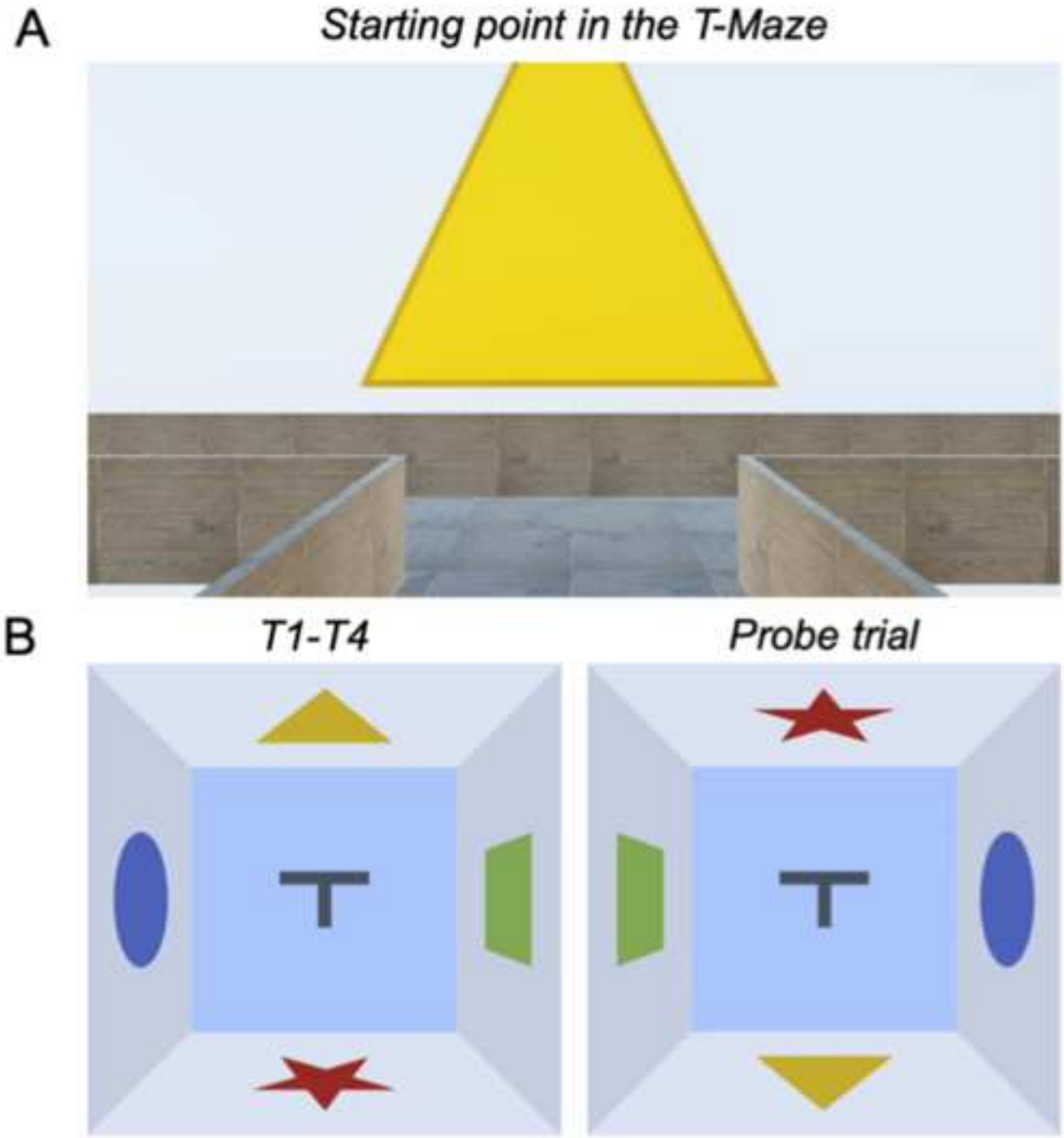
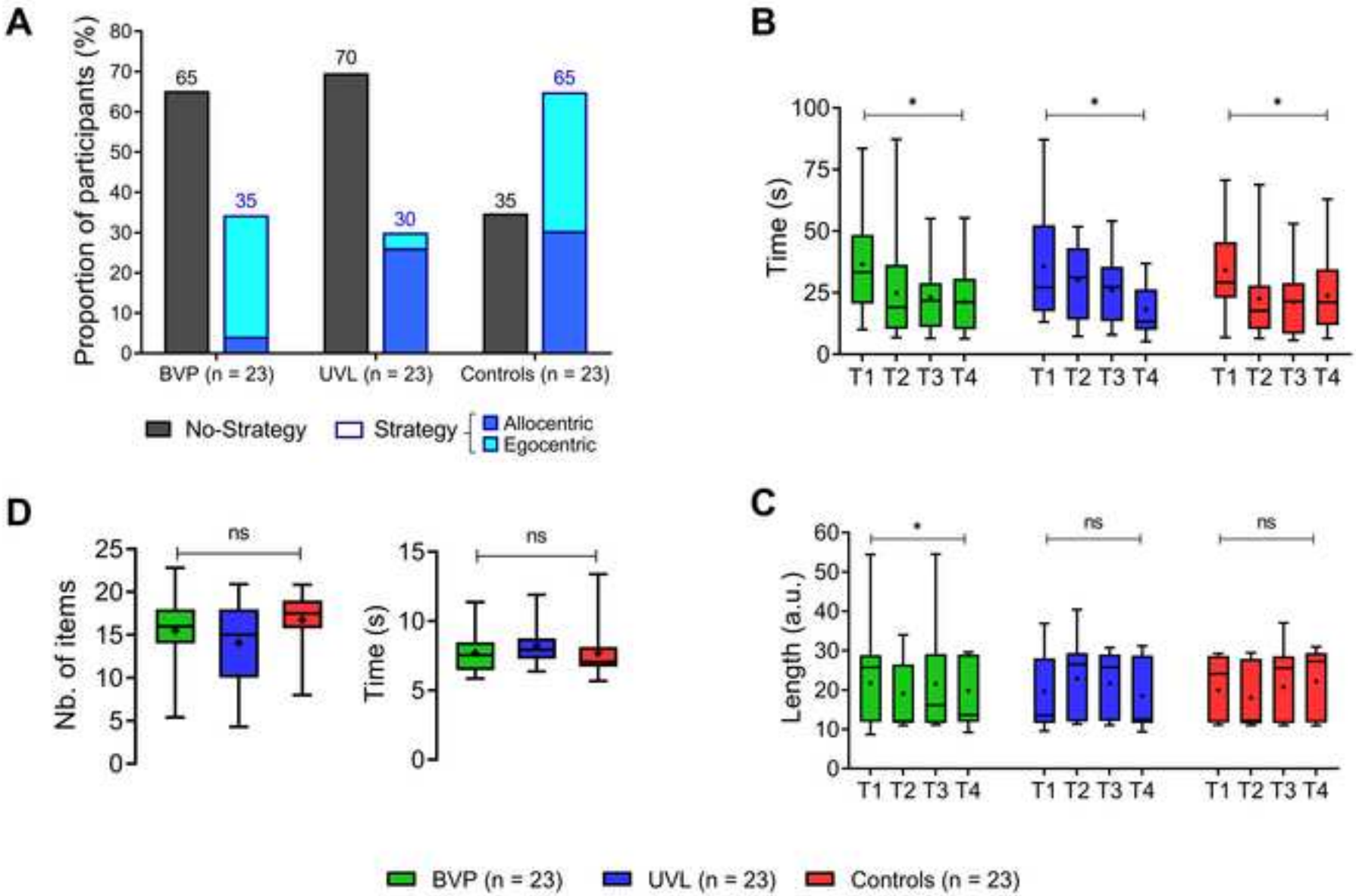


Figure2REVISED



	BVP (*n* = 23)	**UVL** (*n* = 23)	**Controls** (*n* = 23)
Age (years)	59.3 ± 14.2	58.7 ± 11.4	58.1 ± 13.3
Females/Males	14/9	14/9	14/9
Handedness (laterality quotient, %)	22 right-handed: 85.7 ± 14.0% 1 left-handed: –58%	23 right-handed: 85.6 ± 14.6%	23 right-handed: 89.4 ± 10.2%
Highest education level (%)			
Level 1	21.4%	13.04%	0%
Level 2	0%	17.3%	8.6%
Level 3	7.1%	30.4%	21.7%
Level 4	42.8%	13.04%	30.4%
Level 5	28.5%	26.08%	39.1%
Employment status (%)			
Employed	65.2%	56.5 %	65.2%
Student	0%	0%	4.3%
Retired	34.7%	43.4%	30.4%
Unemployed	0%	0%	0%
Marital status (%)			
Single	0%	0%	13.04%
Married/couple	82.6%	78.2%	82.6%
Divorced/widowed	17.3%	17.3%	4.3%
Game experience			
Keyboard expertise	5	5	5
3D videogames skills	0	0	0
2D videogames skills	0	0	0
Videogaming (childhood)	0	0	0
Videogaming (last year)	0	0	0
SVV (°)	2.3 ± 1.9	Left UVL: –3.6 ± 4.6 Right UVL: 4.0 ± 6.6	1.3 ± 1.6

BVL = Bilateral vestibulopathy; UVL = Unilateral vestibular loss; SVV = Subjective visual vertical.

Table 1. Demographic data of patients with vestibular disorders and healthy participants. Mean ± SD is reported for age and SVV, median is reported for Game Experience, percentage of participants is reported for education level, employment and marital status. Education level is based on the French education system: *Level 1* (before high school), *Level 2* (accomplished high school), *Level 3* (two years after high school), *Level 4* (Bachelor's degree), *Level 5* (Master's degree, Engineering degree, PhD, MD). Game experience score was rated using a six-point Likert scale (1: *never*, 2: *sometimes*, 3: *every month*, 4: *every week*, 5: *almost every day*, 6: *every day*). Negative signs indicate counterclockwise tilt of the SVV; positive signs indicate clockwise tilt of the SVV.

Table2

	Strategy vs. No-Strategy		
	β	Odds ratio (95% CI)	p
Intercept	4.96		***0.003***
Age	−0.07	0.93 (0.88−0.98)	***0.005***
Group			
BVP	−1.46	0.23 (0.06−0.89)	***0.033***
UVL	−1.66	0.19 (0.05−0.73)	***0.016***
Controls	Ref	Ref	
Sex			
Female	0.08	1.08 (0.36−3.27)	0.89
Male	Ref	Ref	

Table 2. Results from the logistic regression. $R^2 = 0.22$ (Cox−Snell), 0.29 (Nagelkerke). Model fitting: $\chi^2(4) = 16.83$, $p = 0.002$.

Table3

	Egocentric strategy vs. No-Strategy			Allocentric strategy vs. No-Strategy		
	β	Odds ratio (95% CI)	*p*	*β*	Odds ratio (95% CI)	*p*
Intercept	1.96		0.33	7.34		***0.002***
Age	−0.04	0.97 (0.91−1.02)	0.23	−0.13	0.88 (0.82−0.95)	***0.001***
Group						
BVP	−0.92	0.40 (0.10−1.60)	0.20	−3.63	0.03 (0.00−0.46)	***0.013***
UVL	−2.87	0.06 (0.01−0.55)	***0.013***	−1.03	0.36 (0.07−1.89)	0.23
Controls	Ref	Ref		Ref	Ref	
Sex						
Female	0.48	1.62 (0.43−6.09)	0.48	−0.26	0.77 (0.17−3.59)	0.74
Male	Ref	Ref		Ref	Ref	

Table 3. Results from the multinomial logistic regression. $R^2 = 0.39$ (Cox−Snell), 0.45 (Nagelkerke). Model fitting: $\chi^2(8) = 33.79$, $p < 0.0001$.