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Impact of Vestibular Lesions on Allocentric Navigation and Interval Timing: The Role of Self-Initiated Motion in Spatial-Temporal Integration

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Abstract

Bilateral intratympanic sodium arsenate injections (100 mg/ml in isotonic saline) in adult male Long Evans rats produced impairments in allocentric navigation using a 12-arm radial maze procedure as well as a motor test battery designed to evaluate vestibular function. In contrast, no impairments in the accuracy or precision of duration reproduction using 20-s and 80-s peak-interval procedures were observed when both target durations were associated with the same lever response, but distinguished by signal modality (e.g., light or sound). In contrast, an ordinal-reproduction procedure with 800, 3200, and 12,800 ms standards requiring the timing of self-initiated movements during the production phase revealed large impairments in the accuracy and precision of timing for vestibular lesioned rats. These impairments were greater on trials in which self-initiated body movements (e.g., holding down the response lever for a fixed duration) were required without the support of external stimuli signaling the onset and offset of the reproduced duration in contrast to trials in which such external support was provided. The conclusion is that space and time are separable entities and not simply the product of a generalized system, but they can be integrated into a common metric using gravity and self-initiated movement as a reference.

Keywords

Interval timing, time perception, allocentric navigation, cerebellum, dorsolateral striatum, hippocampus, peak-interval procedure, radial-arm maze, magnitude representation, self-initiated movement

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1. Introduction

Neurophysiological evidence suggests that two subcortical structures, the cerebellum and basal ganglia, play a critical role in time perception and motor control (e.g., Allman et al., 2014a; Coull et al., 2011; Gibbon et al., 1997; Harrington et al., 2014; Ivry, 1996; Jones & Jahanshahi, 2014; Lusk et al., in press; Petter et al., in press; Spencer, 2015). Possible connections between these two subcortical structures and the vestibular system have recently become a topic of interest in an attempt to investigate the potential interactions between vestibular function and interval timing (e.g., Barter et al., 2015a, b; Capelli et al., 2007; Fan et al., 2012; Hitier et al., 2014; Jacob et al., 2014; Kim et al., 2014; Lacquaniti et al., 2015; Yin, 2014).

Innervation of the cerebellum by vestibular afferents is a prominent component of the vestibulo–spinal reflex. Lesions of the cerebellar cortex have been shown to produce postural impairments similar to those produced by lesioning vestibular nuclei (Pompeiano, 1974), and the coordinated timing of signals between the vestibular system and the cerebellum is critical for certain types of motor control (e.g., Chaisanguanthum et al., 2014; Colagiorgio et al., 2015; Cullen, 2012; Laurens et al., 2013; Lopez, 2015; Mast & Ellis, 2015). Researchers have also posited a key relationship between the basal ganglia and the vestibular system, particularly in view of the extensive vestibular projections to components of the striatum involved in reflexive motor control (Potegal, 1982; Potegal et al., 1971). Additionally, some investigators have reported connections between the vestibular nuclei and the globus pallidus, characterizing the basal ganglia as a 'vestibular end-station' (Muskens, 1922). Subsequent studies have identified projections from vestibular nuclei to the globus pallidus and putamen, projections traveling through the magnocellular medial geniculate body (e.g., Ebner, 1967; Locke, 1970; Wepsic, 1966). Furthermore, human and animal studies provide evidence that the basal ganglia participate in the motor control of some vestibular reflexes (e.g., Martin, 1967; Raphan & Cohen, 1985; Raphan & Sturm, 1991; Raphan et al., 1992). Behavioral research has demonstrated that, among the components of the basal ganglia, the caudate nucleus is most heavily involved in vestibularly-guided egocentric orientation (Potegal, 1982; Potegal et al., 1971). For example, lesions to the caudate can suppress compensatory movements resulting from experimentally-induced rotations and inhibit some stereotypical behavioral manifestations following labyrinthectomy (Bergouigan & Verger, 1935; Mettler & Mettler, 1940).

Although both the cerebellum and the striatum have been implicated in the perception of durations in the hundredths of milliseconds-to-minutes range (e.g., Gibbon et al., 1997; Meck, 1996, 2005, 2006, a, b, c; Meck & Ivry, in press; Petter et al., in press; Teki et al., 2012) the cerebellum as been specifically associated with sub-second durations (e.g., Ivry & Richardson, 2002; Ivry & Spencer, 2004; Petter et al., in press; Spencer, 2015; Teki et al., 2012), whereas supra-second durations

are thought to be mediated by cortical-striatal circuits (e.g., Allman & Meck, 2012; Gu et al., 2015a; Matell & Meck, 2000, 2004; Matell et al., 2003; Meck, 1988, 1996; Meck et al., 2008; Merchant et al., 2013). Moreover, patients with cerebellar damage showed impairments during accurate timing required for production tasks (e.g., finger tapping), perceptual duration judgment tasks and eyeblink conditioning (e.g., Ivry & Keele, 1989; Mangels et al., 1998; Nichelli et al., 1996; Perrett et al., 1993). Interestingly, the cerebellum receives vestibular and proprioceptive information (Barmack, 2003). Because the cerebellum is involved in both vestibular processing and timing functions, it has been posited by Capelli et al. (2007) that self-motion stimulating the vestibular system could lead to spatial-temporal timing processing perturbations. Only few results are known about time estimation under the vestibular modality. Frankenhaeuser (1960) showed that participants seated at the end of a rotating arm (3g centrifugal acceleration) reproduced temporal intervals systematically shorter than when stationary. Binetti et al. (2010) investigated the effects of rotatory body accelerations on the reproduction of an acoustic isochronous pacing rhythm in a finger-tapping task. The representation of the target frequency varied continuously as a function of changes in vestibular–proprioceptive information. As in the study of Frankenhaeuser (1960), the results showed subjective shortening of target interval in the presence of sinusoidal accelerator rotations along the vertical head-body axis. Semjen et al. (1998) observed a decrease in the accuracy and regularity of timing under microgravity, where the otolith signal reference is missing. Using the Wing and Kristofferson (1973) decomposition of variance analysis, they found an increase of the central timer variance (and not of the motor execution variance) under microgravity. Semjen et al. (1998) proposed that perturbations of the central timer under microgravity are due to reduced vestibular and proprioceptive afferent signals to the cerebellum. These results suggest an influence of vestibular stimulation on timing.

Various studies in rats have demonstrated that lesions in one or both vestibular labyrinths lead to learning and memory deficits in various kinds of spatial maze tasks (for review see Honzik, 1936; Smith et al., 2005, 2010). Although the inclusion of the appropriate visual landmarks can compensate for the observed deficits, in absence of such cues, spatial performance is markedly impaired. These experimental findings are consistent with the deficits in navigational abilities observed in humans with bilateral vestibular dysfunction (e.g., Stackman & Herbert, 2002; Stackman & Taube, 1997; Stackman et al., 2002).

The vestibular contribution to distance estimation and to path integration in darkness has been investigated in a number of studies (e.g., Georges-François et al., 1995; Loomis et al., 2001; Mittelstaedt & Mittelstaedt, 2001). The main findings indicate an overestimation of the travelled distance in darkness. Israël et al. (2004) found that while vestibular information was insufficient to accurately estimate the traveled distance, time estimates were generally used. Furthermore, when the participants were asked to reproduce the previously traveled distance,

the duration of their response was as accurate as the distance (Berthoz et al., 1995). Recently, Glasauer et al. (2007) used a dual-task paradigm during reproduction of travelled distance tasks and showed that both motion distance and duration reproductions were impaired with cognitive load. Thus, self-motion and temporal processing appear to be largely interdependent.

Electrophysiological studies of field potentials in animals have shown that most areas of the striatum respond to electrical vestibular stimulation while human studies isolated responses to vestibular stimulation to the putamen. More recently, tracer studies have identified a pathway between the vestibular nucleus and the striatum via the thalamus, completely bypassing the cortex. Vestibular sensory input is represented in the part of the striatum — the dorsolateral striatum — where fibers from the sensorimotor areas terminate. It is therefore possible that vestibular signals are used, together with other sensorimotor inputs in the striatum, for body and limb control. The combination of electrophysiological results, changes in protein levels and tracer studies have led to the idea that the dorsolateral striatum is likely to be the main input area for vestibular signals in the basal ganglia and these are likely to have an influence on motor control and interval timing (e.g., Hinton & Meck, 1997a, b; Stiles & Smith, 2015).

It has also been argued that the brain utilizes mechanisms that exploit the presence of gravity to estimate the spatial orientation and the passage of time. Several visual and non-visual (e.g., vestibular, haptic, and visceral) cues are merged to estimate the orientation of the visual vertical. However, the relative weight of each cue is not fixed, but depends on the specific task (e.g., Volkening et al., 2014). Using these components a model of the effects of gravity can be combined with multisensory signals to time the interception of falling objects, to time the passage through spatial landmarks during virtual navigation, to assess the duration of a gravitational motion, and to judge the naturalness of periodic motion under gravity (e.g., Lacquaniti et al., 2015). Overall, these issues involve the role of a gravitational reference to mark the timing of actions and perceptions. Considerable work has been carried out in the field of timing and time perception, with a special emphasis on the demonstration of time distortions and what they can reveal about neural timing mechanisms (e.g., Buhusi & Meck, 2005; Harrington et al., 2011; Merchant et al., 2013). By contrast, the idea that the brain constantly strives to maintain accurate time estimates by calibrating them against physical laws from the outside world has received much less attention (e.g., Eagleman, 2004, 2008; Eagleman et al., 2005; Shi et al., 2013; Zago et al., 2011). This hypothesis is especially relevant for the estimates of the duration of a target motion. Thus, the position of a moving object at a given time in the future can be predicted by a forward internal model (e.g., Zago et al., 2004, 2009) and can be compared with sensory feedback to calibrate time estimates and determine spatial location in changing environments such as the Carousel maze (e.g., Bures et al., 1997; Fajnerova et al., 2014; Petrasek et al., 2014; Stuchlik et al., 2001; Svoboda et al., 2015).

Extrapolation from data measured in the seconds-to-minutes range for drawing conclusions about the efficacy of interval timing in the msec range is currently considered empirically viable (e.g., Bartholomew et al., in press; MacDonald & Meck, 2004, 2006; Melgire et al., 2005; Merchant et al., 2008, 2013). Consequently, the examination of timing in the supra-seconds range is a reasonable approach towards investigating whether the behavioral deficits caused by vestibular lesions are specific to the spatial domain or concurrently disrupt both temporal and spatial processing. More specifically, the experiments presented here are designed to address the following concerns:

(1) that poor allocentric navigation on the radial-arm maze in vestibular-lesioned rats (e.g., Olton & Samuelson, 1976; Ossenkopp & Hargreaves, 1993; Russell et al., 2003a; Zoladek & Roberts, 1978) is due to faulty vector calculations of distance, dependent on subjective time (i.e., rate × time = distance) as described by Gallistel (1989, 1990);
(2) that cognitive deficits on the radial-arm maze cannot solely be accounted for by the side-effects of surgical error and/or arsenic-induced vestibular dysfunction, including performance deficits related to auditory dysfunction, ataxia (loss of locomotor coordination), hyperactivity, and motivational changes (e.g., Porter, 1991; Porter et al., 1990);
(3) that, separate from the above dead-reckoning theories of navigation (Gallistel, 1990), temporal list theories for navigational deficits are addressed (i.e., timing errors are the explanation for spatial deficits because the subjects do not know 'when to be where' according to a linear time-space vector coding scheme for chaining anticipated start, intermediate, and goal locations (e.g., Cheng, 1986, 1992; Dallal & Meck, 1992; Honig, 1981; Rakitin et al., 1992);
(4) that memory functioning in non-spatial domains should remain intact because these arsenic-induced vestibular lesions do not directly damage the memory structures themselves, but rather deprive these targets of relevant spatial information; and
(5) that disrupted performance in the radial-arm maze in vestibular-lesioned rats may be mediated by affected hippocampal functioning after vestibular lesion (Russell et al., 2006; Smith et al., 2010).

In order to study the role of the vestibular system in radial-arm maze navigation and peak-interval timing (e.g., Buhusi et al., 2013; MacDonald et al., 2007; Meck, 2001; Meck et al., 1984), rats were given intratympanic injections of sodium arsenate to chemically lesion the sensory receptors of the vestibular apparatus. Sodium arsenate injections were intended to destroy the hair cells that transduce changes in angular acceleration (i.e., rotations of the head) in the three orthogonal planes of the bony labyrinths as well as the hair cells that transduce changes in linear

acceleration (i.e., the perception of gravity and forward movements) in the two orthogonal planes of the otolith organs, i.e., the utricle and the saccule (Benson, 1982, 1990; Horn et al., 1981; Taube et al., 1990a, b). Because these inner ear hair cells in the adult rat do not regenerate, the lesions were expected to be physically permanent (Kelley, 1991); however, some functional recovery of behavior might occur (Darlington & Smith, 1991; Vignaux et al., 2012). Given that many previous studies used sodium arsanilate (e.g., Horn et al., 1981; Hunt et al., 1987; Ossenkopp et al., 1992), Dallal (1997) has reported comparable behavioral effects for both sodium arsanilate and sodium arsenate (the drug used in the current study to produce vestibular lesions). Taken together, these experiments allowed us to test theories purporting a common magnitude system for time, space, and number (e.g., Aagten-Murhpy et al., 2014; Walsh, 2003) as well as the role of degeneracy in the recovery of temporal-spatial integration processes following vestibular lesions (e.g., Allman et al., 2014b; Lewis & Meck, 2012; Merchant et al., 2013).

2. Materials and Methods

2.1. Vestibular Lesions (Experiments 1 and 2)

2.1.1. Subjects

The subjects were 40 male Long Evans rats approximately 60 days of age at the beginning of training for Experiment 1 and a group of 20 male Long Evans rats approximately 90 days of age at the beginning of training for Experiments 2.

2.1.2. Surgical Procedures

Rats were anesthetized with intramuscular injections of xylazine hydrochloride (5 mg/kg) and ketamine hydrochloride (45 mg/kg). A random half of the rats (Lesion group) received intratympanic 0.10 ml injections of a sodium araenate solution (100 mg/ml in isotonic saline) — see Dallal, 1997; Horn et al., 1981; Hunt et al., 1987; Nielson, 1991; Plumb, 1991. The remaining rats (Control group) were given bilateral intratympanic injections of an equivalent volume of saline solution. A 22-gauge, 1 ½ in. disposable needle was inserted into the ear through the tympanic membrane until resistance was felt. The araenate solution (warmed to 37° C) was then slowly injected into the middle ear over a period of 3 to 5 s (see Hunt et al., 1987; Ossenkopp et al., 1990). Following surgery rats were returned to the colony room for a 24-h period of recovery in complete darkness. On first exposure to light and visual cues, bilaterally lesions rats should initially navigate backward when placed in a clean cage before adapting to approximations of more normal behavior. Moreover, unilaterally lesioned rats should initially navigate in circles, turning preferentially towards the lesioned or more completely lesioned side (Halmagyi et al., 1988). Rats were evaluated 24-h post-surgery for the effectiveness of the lesions and only rats demonstrating complete lesions were continued in the study.

A random half of the rats in the Control ($n = 20$) and Lesion ($n = 20$) groups were assigned to Squad 1 and the remaining rats were assigned to Squad 2. These two squads were assigned to different orders of behavioral testing. Rats in Squad 1 was evaluated 1-mo post-surgery using a 12-arm radial maze for 45 daily sessions, followed by fixed-interval and peak-interval training for 40 daily sessions. Squad 2 was evaluated 1.5-mo post-surgery using fixed-interval and peak-interval procedures for 40 sessions, followed by 45 daily sessions of 12-arm radial maze training. Both squads received a Motor Test Battery at various time points throughout this experimental period.

Rats were housed individually and maintained at approximately 85% of their *ad libitum* body weights. Water was freely available in their home cages and the light/dark (LD) cycle in the vivarium was set to a 12:12 LD cycle with behavioral evaluation occurring during the light portion of the cycle.

2.2. Experiment 1: 12-Arm Radial Maze Procedures

2.2.1. Apparatus

The apparatus consisted of an elevated radial-arm maze (RAM) with 12 arms radiating equidistantly from a central platform (see Olton, 1979). The RAM had the following dimensions: central disc diameter = 36.5 cm; height above the floor = 80.0 cm; arm length × width = 83.0 cm × 7.6 cm, with edges 1.2 cm high along each side; food well diameter and depth at the end of each arm = 2.5 cm and 0.6 cm, respectively. The maze was placed in a well-lighted roo (4.3 m × 3.0 m) with the global geometry and stable landmark configuration available for viewing by the subjects.

2.2.2. Pre-Training. Sessions 1–2

All rats were shaped to walk down the length of the arms to obtain food pellets from the food wells in groups of 6–8 rats as described by Dallal and Meck (1990).

2.2.3. Radial-Arm Maze Training with Mixed-Baiting Patterns. Sessions 3–47

Each of the rats was then randomly assigned to a particular experimental condition and to a specific mixed-pattern of eight baited (S+) and fourunbaited (S−) arms that remained stable during the experiment. Each of the arms was baited with two 45 mg Noyes pellets. During a test session, an individual rat was placed on the central platform and allowed to select arm on the maze until all baited arms were visited at least once or the rat had made a maximum of 40 choices. A rat must travel at least half of the way down an arm in order for an arm entry to be recorded as a choice. One test session was given per day, five days per week, for a maximum of 45 days at each condition.

2.2.4. Radial-Arm Maze Data Analysis

Radial-arm maze choice data were analyzed in terms of the number of choices required to complete the maze by locating all baited (S+) arms (choices to criterion), working memory errors (arm repeats), reference memory errors (entering an unbaited (S−) arm, choice latency, and turning bias.

2.3. Experiment 1: Peak-Interval Timing Procedures

2.3.1. Apparatus

The apparatus consisted of ten similarly constructed lever boxes. Four of the boxes had inside dimensions of 30.5 × 24.0 × 27.0 cm (length × width × height) and six boxes had inside dimensions of 23.3 × 20.6 × 18.6 cm. The roof and sidewalls of the boxes were transparent acrylic, the front and back walls were aluminum or stainless steel, and the floor was comprised of 16 parallel stainless-steel bars. All lever boxes were house in side of a large insulation-board chamber designed to minimize outside light and sound. These insulation chambers were equipped with a fan for ventilation and a small acrylic window for observation.

A liquid dipper (Lafayette Instruments) delivered 0.01 cc of corn oil through an opening centered in the front wall of the lever box. The dipper cup was located approximately 2.5 cm above the grid floor. All of the lever boxes contained a stainless-steel response lever to the right of the dipper opening. In four of the boxes the lever was 1.0 × 2.8 × 2.2 cm (height × length × width) located 2.5 cm above the grid floor and in the remaining six boxes the lever was 0.5 × 3.5 × 1.5 cm (height × length × width) located 3.0 cm above the grid floor. The levers in all boxes were stationary and did not retract.

Each lever box had an evenly spaced left-to-right series of red, white, and green jewel lights (Type 24E, 1.5 cm in diameter) located approximately 8.0 cm above the grid floor and centered over the

response lever. A 4.5 KHz tone module containing a SONALERT tone generator, set to register 70–80 dB above background, was centered on the front wall of each lever box, approximately 4.5 cm from the ceiling. A 20-w houselight was centered on the back wall of the lever box, approximately 4.5 cm from the ceiling. A DOS/Windows-based computer using custom designed software controlled the experimental equipment and recorded the raw response data with a sampling rate of 16 Hz.

2.3.2. Pre-Training. Sessions 1–5

A shaping procedure was used for five daily sessions in order to establish lever pressing for corn oil reinforcement. Each lever press was rewarded on a continuous reinforcement schedule. In addition, the cue lights directly above the lever came on simultaneously for 3 s, followed by a dipper delivery of corn oil every 60 s, independent of responding. The houselight illuminated the lever box for the entire session which lasted for a maximum of 2 h or until the rat made 60 lever presses.

2.3.3. Fixed-Interval Training. Sessions 6–15

Following lever shaping, the rats were introduced to a fixed-interval (FI) schedule of reinforcement. In this procedure, 20-s FI trials were signaled by either the combined illumination of the three cue lights or the activation of the SONALERT (counterbalanced across lever boxes and treatment groups) and 80-s FI trials were signaled by the remaining signal (light or sound). Reinforcement was made available on all trials at the target duration matching the signal modality (e.g., light = 20 s and sound = 80 s or vice versa). The first lever press after the appropriate target duration activated the dipper and terminated the signal. All trials were separated by a 100 s intertrial interval (ITI). The houselight illuminated the lever box for the entire session, which lasted 2.5 h and were conducted at approximately the same time each day for five days/week.

2.3.4. Peak-Interval Training. Sessions 16–45

Once FI training was completed, the peak-interval (PI) procedure was implemented by the inclusion of unreinforced probe trials. During these sessions, 20-s FI and associated probe trials were randomly alternated with 80-s FI and associated probe trials. Probe trials were the same as their associated FI trial with the exception that reinforcement wasn't primed at the target duration and the signal remained on for three times the FI value plus a random duration of approximately 40 s (normally distributed) at which point the signal was terminated independent of responding and an ITI began (see Buhusi & Meck, 2010; Cheng & Meck, 2007; Church et al., 1994; Paule et al., 1999; Yin et al., in press). Each of the four trial types had an equal probability of occurring on each trial (25%). The houselight illuminated the lever box for the entire session, which lasted 2.5 h and were conducted at approximately the same time each day for five days/week.

2.3.5. Peak-Interval Data Analysis

Responses occurring on unreinforced probe trials were averaged across sessions and analyzed as a function of signal duration for individual rats. These response rate functions were fit using PeakFit (Systat Software), which provided measures of peak time, peak rate, spread, and coefficient of variation (CV — spread/peak time). Individual peak functions were then normalized, averaged across rats, and renormalized. Additional details concerning single-trials analysis and superimposition plots are provided in Dallal (1997) — see also Cheng & Meck, 2007; Church et al., 1994; Matell et al., 2003; Yin et al., in press.

2.4. Experiment 1: Motor Test Battery

Rats were tested six times using a motor test battery at regular intervals over a 2-month period in order to evaluate the degree of vestibular loss. Rats' performances were ranked on a scale from 1–4 where 1 = normal behavior and 4 = severely impaired behavior by the combined scores of two independent raters.

2.4.1. Measure 1 — Loss of Righting

The rat was dropped from a height of approximately 30–45 cm, from the base of its tail; nose downward onto an open field apparatus (an elevated, stable surface 0.90 m high × 1.40 m long × 0.75 m wide × 0.10 m deep). Normal performance is to land balanced, with weight distributed relatively evenly among all four paws upon complete contact with the ground. Impaired performance involves a lack of balance and/or contact with the ground with body parts other than the bottoms of the paws (and the tail). This test of loss of righting was used in favor of ones that require the rat to respond to a quickly inclined plane or ones that require the rat to maintain its balance on a rotating horizontal pole (Horn et al., 1981).

2.4.2. Measure 2 — Ataxia

Released onto the same open field apparatus, normal rats will walk forward and turn infrequently to explore the space. Impaired rats, when bilaterally lesioned, will back up and circle in both directions during much of the exploratory period, sometimes tucking their heads underneath their chests (Dallal, 1997; Nielson, 1991). If the deficit is somewhat stronger on one side, the rat will tend to turn in the direction ipsilateral to the more damaged side (Porter, 1991). This unidirectional circling behavior, presumably under nigrostriatal control, is readily potentiated in normal rats by small hemispheric imbalances in dopamine levels (e.g., Crowne et al., 1991). Additionally, bilaterally impaired rats tend to flatten their bodies while locomoting (e.g., Hunt et al., 1987; Nielson, 1991) and tend to rear up less often (Porter, 1991).

2.4.3. Measure 3—Head Tilt or Bobbing

While on the open field apparatus, normal rats will maintain an even head posture, interrupted infrequently by smooth head turn. Impaired rats, when bilaterally lesioned, may habitually tip or bob their heads backward. If the deficit is somewhat stronger on one side, the rat will often adopt a static head tilt in the direction ipsilateral to the more damaged side (Hunt et al., 1987).

2.4.4. Measure 4 — Hyperactivity

Impaired versus normal rats will show a heightened level of activity and behavioral stereotypy on the open field apparatus (Porter et al., 1990).

2.4.5. Measure 5 — Swimming

Impaired versus normal rats will show an inability to orient correctly when dropped from a height of approximately 10–20 cm into a sink (60 cm long × 45 cm wide × 45 cm deep) filled with cold water to a depth of at least 35 cm. Normal rats will readily come to the surface and swim easily. Impaired rats will thrash about and spend time circling randomly under water (Dallal, 1997; Horn et al. 1981).

2.4.6. Data Analysis — Composite Motor Score

The mean score for each of the five measures was computed, and then the sum of the means was taken to derive the Composite Motor Score. This calculation was chosen in order to normalize for the possibility of uneven measurements taken between studies and to give equal weighting to each of the five measures in the Motor Testing Battery. A normal rat, under this scoring scheme should rate a 5 on the Motor Test Battery. Rats with motor scores greater than 5 will show graded impairment relative to normal rats. Repeated measures ANOVAs conducted on these data indicated that no significant improvement was observed in the lesion or control group during the course of the study, p's > 0.05. Finally, the mean Composite Motor Scores for individual rats were correlated with these rats' steady-state RAM performance (i.e., mean choices to criterion) during the last nine sessions of testing and with selected measures (e.g., peak time, mean rate, and discrimination index) from the last 10 sessions of 20-s and 80-s PI training.

2.5. Experiment 2: Ordinal-Reproduction Timing Procedures

2.5.1. Surgical Procedures

Rats received vestibular lesions with bilateral intratympanic sodium arsenate injections (100 mg/ml in isotonic saline) and were evaluated with the motor test battery as described in Experiment 1. Ten control rats and 10 rats with bilateral vestibular damage (confirmed by the motor test battery) completed the experiment.

2.5.2. Apparatus

The apparatus consisted of 10 standard lever boxes built of aluminum front/back walls and two Plexiglas slide walls and ceiling. The floor was constructed of stainless steel parallel bars with a drop tray underneath. A response lever was located on the left side of the front wall, 10 cm above the grid floor. A pellet dispenser delivered 45-mg food pellets (Research Diets, Inc., New Brunswick, NJ) to a food cup located in the middle of the front wall and to the right of the lever. A 6-W house light was mounted near the top of the front wall of the lever box and provided general illumination. Red, green, and yellow LED cue lights were horizontally arranged immediately above the lever. A speaker located in the back of the box was used to deliver white noise. Each lever box was housed inside a light and sound insulated chamber, and was equipped with a ventilation fan and an eyepiece viewer for observation. An IBM-PC-compatible computer attached to a MED–PC interface box was used to control the experimental equipment and record the behavioral responses.

2.5.3. Pre-Training. Sessions 1–5

A shaping procedure was used for five daily sessions in order to establish lever pressing for food pellets. Each lever press was rewarded on a continuous reinforcement schedule. In addition, the cue lights directly above the lever came on simultaneously for 3 s, followed by a food pellet delivery every 60 s, independent of responding. This procedure continued for a maximum of 2 h or until the rat made 60 lever presses.

2.5.4. Ordinal-Reproduction Training (with Lever Insertion/Retraction) Sessions 6–15

Following lever shaping, the rats were introduced to the ordinal-reproduction procedure where a standard signal is first presented, following which the rat has to reproduce the interval in order to earn reinforcement. Standard signal durations (e.g., 800, 3200, and 12800 ms) of cue lights + white noise are followed by a 1-s inter-stimulus interval (ISI) and then the insertion of the response lever. For one trial type (filled trials), a subsequent lever press turns on the cue lights + white noise and initiates (start time) the reproduction interval and the cue lights + white noise stays on as long as the lever is depressed. Release of the lever terminates the reproduced interval (stop time), turns off the cue lights + white noise, and retracts the lever. Another trial begins following an intertrial interval (ITI) of 20 s plus a random amount of time with a mean of 20 s, randomly distributed. In the second trial type (unfilled trials), a subsequent lever press following the presentation of the standard signal duration initiates the reproduction interval (but no external signal) that continues until the lever is released. Both trial types (filled or unfilled by an external stimulus) occur randomly with equal probability. In both trial types, reinforcement is delivered at the release of the lever if the reproduced duration is equal to or greater than the standard signal duration presented on that trial. This ordinal-reproduction procedure has some properties of the differential reinforcement of low (DRL) rates procedure (e.g., Cheng et al., 2006, 2008; Gu, 2014) as well as the ordinal comparison and duration bisection procedures (e.g., Cordes & Meck, 2014; Gu, 2014; Meck, 1983). Sessions lasted approximately 2.5 h and were conducted near the same time each day for seven days/week.

2.5.5 Ordinal-Reproduction Training (without Lever Insertion/Retraction). Sessions 16–45

Once rats are performing well on both trial types (filled and unfilled by external cues), the lever was inserted at the beginning of the session and remained there at all times, but only recorded responses at the offset of the ISI following the presentation of the standard signal duration. This change in

procedure eliminated lever insertion and withdrawal as potential cues for the start and stop times of the reproduced interval.

3. Results

3.1. Radial-Arm Maze Choices to Criterion

A comparison of the mean choices to criterion between control and lesioned rats was conducted using a repeated-measures ANOVA. While both treatment groups improved in choice performance over blocks of three days, $F(1, 14) = 18.45$, $p < 0.01$ as illustrated in Fig. 1, there was a significant effects of treatment such that the lesioned rats consistently took more choices to complete the maze than control rats, $F(1, 34) = 30.38$, $p < 0.01$ and learned the maze at a slower rate according to a significant Treatment × Choices interaction, $F(14, 476) = 3.33$, $p < 0.01$.

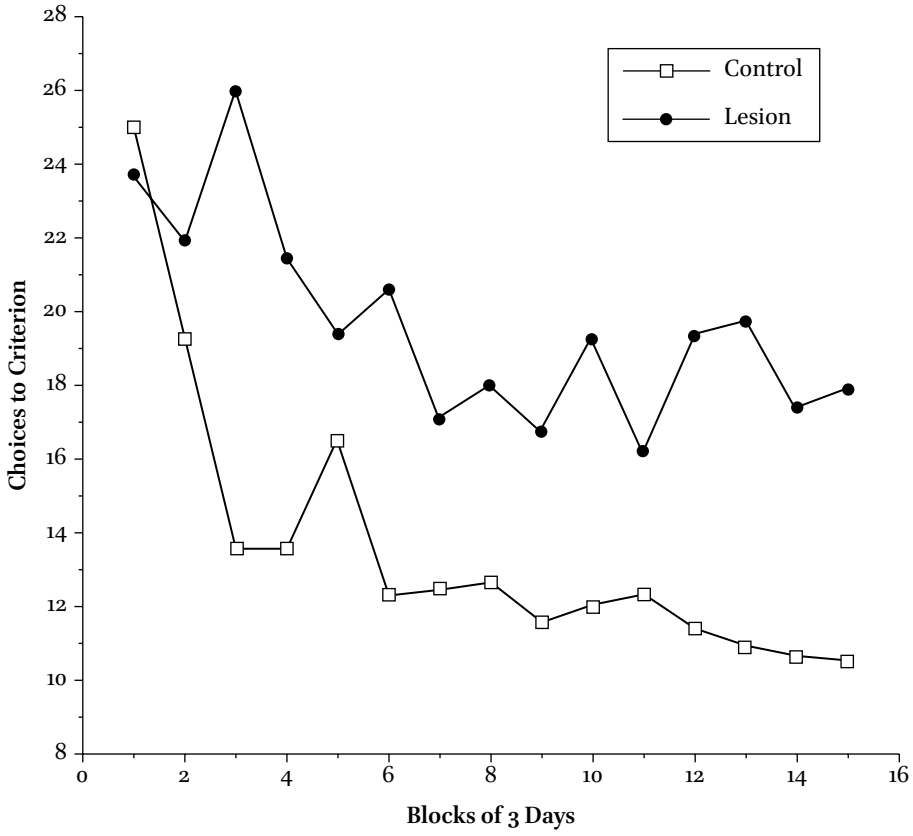

Figure 1. Mean number of choices required to find the eight baited locations in the 12-arm radial maze as a function of blocks of three daily sessions. The choices to criterion measure is composed of both working memory errors (e.g., repeating an arm) and reference memory errors (e.g., entering an arm that is never baited in the 8 S+, 4 S− baiting pattern).

3.1.1. Working and Reference Memory Errors

Significant treatment effects for working memory, $F(1, 34) = 28.52$, $p < 0.01$ and reference memory, $F(1, 34) = 21.08$, $p < 0.01$ are indicated by the increased error rates illustrated in Fig. 2. While both working and reference memory errors increased following vestibular lesions, working memory errors increased proportionally more than reference memory errors as revealed by a significant effect of treatment for working memory errors, $(F, 34), = 41.08$, $p < 0.01$ and a non-significant effect of the proportion of choices resulting in reference memory errors, $F(1, 34) < 1, p > 0.05$.

3.1.2. Turning Bias

During the first half of training, control rats exhibited a preference to consistently turn two or three arms to the left or right of the arm just exited, whereas vestibular

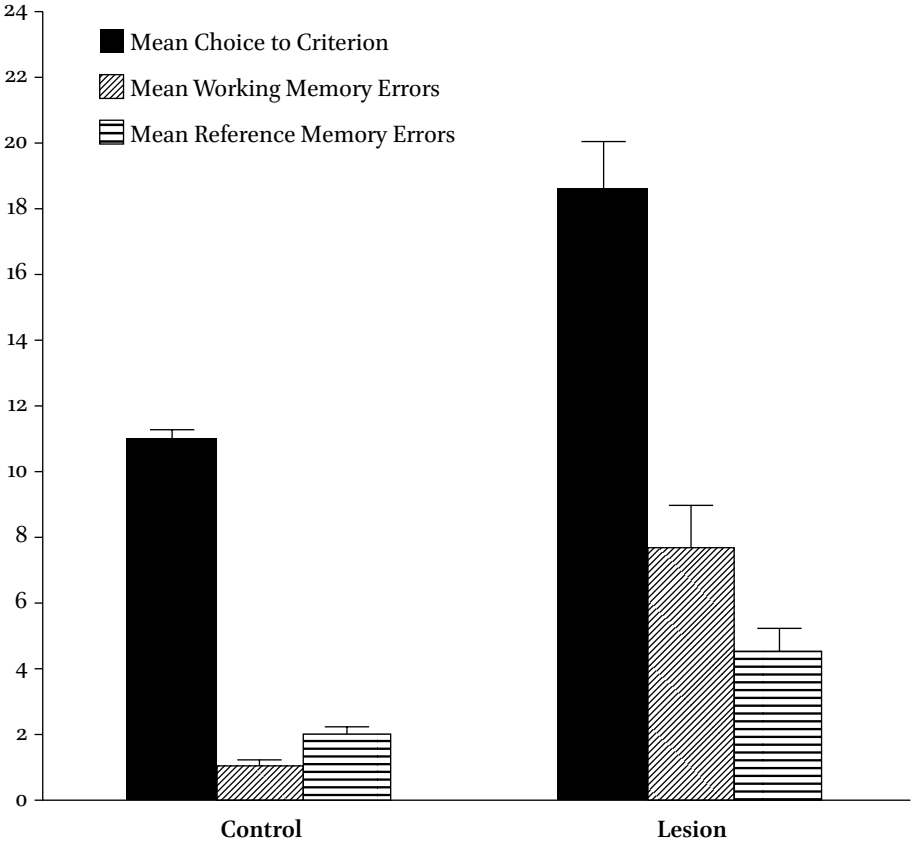

Figure 2. Mean ± SE choices to criterion (total choices required to find the eight baited S+ arms), working memory errors (arm repeats), and reference memory errors (entering an unbaited S− arm) during the last three blocks of post-surgical training (nine sessions) on the radial-arm maze (RAM) procedure.

lesioned rats distributed their choice with less bias and an unusually compelling tendency for revisiting the arm just exited (data not shown — see Dallal, 1997; Ossenkopp & Hargreaves, 1993). Repeated measures ANOVAs of turning biases for trials 1–21 revealed significant effects of treatment for both squads of rats; $F(1, 18) = 8.46$, $p < 0.01$, $F(1, 14) = 10.08$, $p < 0.01$, significant effects of Position; $F(1, 6) = 10.78$, $p < 0.01$, $F(1, 6) = 14.46$, $p < 0.01$, and significant effects of the Treatment x Position interaction; $F(6, 108) = 5.37$, $p < 0.01$, $F(6, 84) = 2.56$, $p < 0.05$.

3.1.3. Choice Latency

In terms of choice latency, as measured by a repeated measures ANOVA of the combined data of Squads 1 and 2, there was a significant effect of Treatment; $F(1, 34) = 10.22$, $p < 0.01$, no significant effect of Choice Number; $F(1, 5) < 1$, $p > 0.05$, and a significant effect of the Treatment × Choice Number interaction; $F(5, 170) = 6.19$, $p < 0.01$. These data (not shown) were analyzed for choices 3–8, omitting choices 1 and 2 because of the excessive disruption to the vestibular lesioned rats of initially being released onto the maze. Control rats show the normal increase in choice latency as memory load increases (e.g., Brown & Cook, 1986; Cook et al., 1985). Lesioned rats, conversely, show a decrease in choice latency as the trial progresses. Based on arguments presented by Brown and Cook (1986), this deviation from the prototypical choice latency function might suggest that lesioned rats prospectively (versus retrospectively) code navigation information in working memory, and the progressively shorter latencies are a reflection of the decreasing demands on working memory over this portion of the trial. A less dramatic and more plausible interpretation, given the level of observed hyperactivity in lesioned rats, is that progressively decreasing latencies are more likely the result of a reduction in fear and an increased interest in more efficiently finding the food hidden on the maze. See Dallal (1997) for additional analysis of choice latency and turning bias data.

3.2. Peak-Interval Response Measures

3.2.1. Peak Time

PeakFit analyses obtained from the individual 20-s peak functions provided a mean peak time of 22.08 s ± 3.6 for controls and 18.48 s ± 3.3 for lesioned rats, which was significantly different; $F(1, 35) = 4.85$, $p < 0.05$. There was a non-significant effect of Modality on peak time, $F(1, 35) < 1$, $p > 0.05$, and a non-significant effect of the Treatment × Modality interaction, $F(1, 35) < 1$, $p > 0.05$.

A similar PeakFit analysis obtained from the individual 80-s peak functions provided a mean peak time of 77.08 s ± 6.2 for controls and 66.86 s ± 6.5 for lesioned rats, indicating a non-significant effect of Treatment, $F(1, 35) = 2.09$, $p > 0.05$, a non-significant effect of Modality, $F(1, 35) < 1$, $p > 0.05$, and a non-significant effect of the Treatment × Modality interaction, $F(1, 35) = 3.28$, $p > 0.05$. Overall, there was a tendency for vestibular lesioned rats to have earlier peak times than control rats, but this was only significant for the 20-s target duration. Peak functions for control and vestibular lesioned rats plotted as a function of time for 20-s and

80-s target durations in terms of absolute and relative response rate are shown in Figs 3 and 4, respectively.

3.2.2. Peak Rate

PeakFit analyses obtained from the individual 20-s peak functions provided a mean peak rate of 42.5 resp/min ± 4.4 for controls and 77.5 resp/min ± 7.1 for lesioned rats, a significant difference of Treatment; $F(1, 35) = 34.85$, $p < 0.01$. There was a non-significant effect of Modality on peak rate, $F(1, 35) < 1, p > 0.05$, and no significant effects of any of the interactions, F's$(1, 35) < 1$, p's > 0.05.

A similar PeakFit analysis obtained from the individual 80-s peak functions provided a mean peak rate of 32.4 resp/min ± 5.3 for controls and 22.1 resp/min ± 4.8 for lesioned rats, indicating a non-significant effect of Treatment, $F(1, 31) < 1$, $p > 0.05$. There was a non-significant effect of Modality on peak rate, $F(1, 31) < 1$, $p > 0.05$, and no significant effects of any of the interactions, F's$(1, 31) < 1$, p's > 0.05. Overall, there was a tendency for vestibular lesioned rats to have higher peak rates than control rats, but this was only significant for the 20-s target duration.

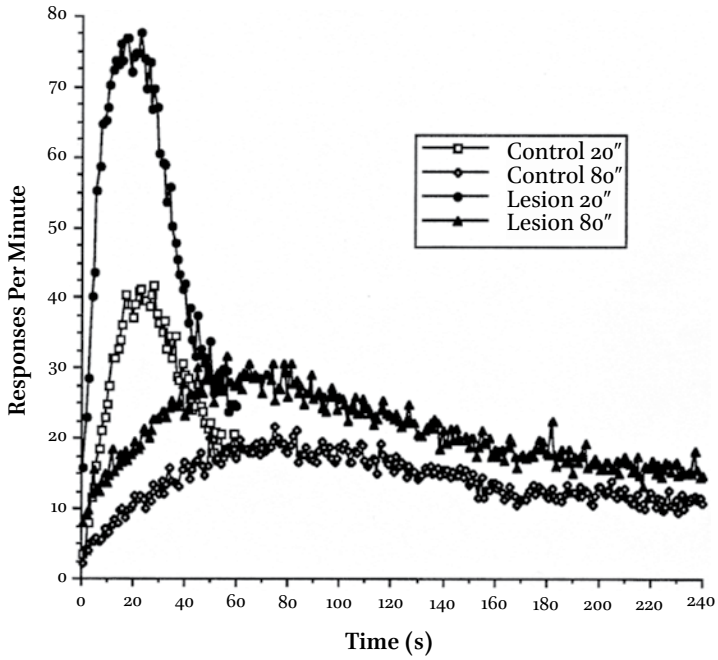

Figure 3. Mean number of responses per minute plotted as a function of time since the onset of the signal (light or sound) for vestibular lesioned and control rats trained with 20-s and 80-s target durations in the peak-interval (PI) procedure. These post-surgical data are taken from the last ten sessions of PI training.

3.2.3. Coefficient of Variation

The coefficient of variation (CV) was defined as the spread at the 75% maximal response rate divided by the peak time as determined by the PeakFit application. For the control group, the CV was 0.49 ± 0.06 and 0.52 ± 0.04 for the 20-s and 80-s target durations, respectively. For the vestibular lesion group, the CV was 0.47 ± 0.03 and 0.48 ± 0.03 for the 20-s and 80-s target durations, respectively. ANOVAs conducted on the CV measures revealed a non-significant effect of Treatment; $F(1, 35) = 1.23$, $p > 0.05$, non-significant effects of Modality and Duration; F's$(1, 35) < 1$, p's > 0.05, a non-significant effect of the Treatment × Modality interaction, and a significant Treatment × Modality × Target Duration interaction; $F(1, 35) = 13.37$, $p < 0.01$ — indicating a trend for vestibular lesioned rats to have lower CVs for 20-s visual signals and control rats to have lower CVs for 80-s auditory signals. These data show that, as expected, the CV was relatively constant across the 20-s and 80-s target durations used in the PI procedure (e.g., Cheng & Meck, 2007; Church et al., 1984).

3.3. Motor Test Battery

For the purposes of this study, the motor test battery presented here is a more efficient solution for measuring the functional, and implied structural, extent of

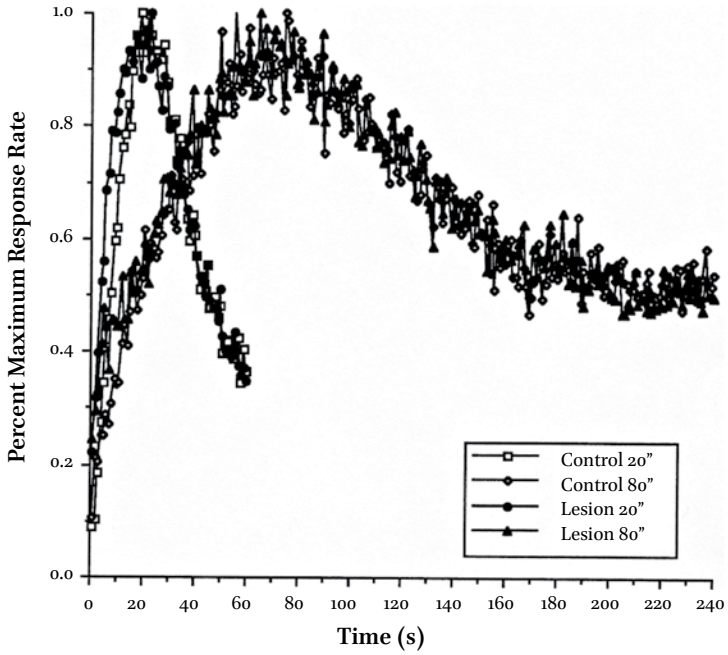

Figure 4. Percent maximum response rate plotted as a function of time since the onset of the signal (light or sound) for vestibular lesioned and control rats trained with 20-s and 80-s target durations in the peak-interval (PI) procedure. Post-surgical data are taken from the last ten sessions of PI training.

damage to the vestibular system than procedures designed to detect finer variations in the extent of structural damage alone (Rubel et al., 1995). Moreover, electron microscopic inspection of the hair cells and endolymph was rejected on the basis that the damage detectable by these methods is not directly translatable into specific measures of behavioral dysfunction investigated in the current study (e.g., Anniko & Wersall, 1975, 1977; Riccio et al., 1967). As a consequence, a behavioral test battery based on the human clinical literature was developed. This Motor Test Battery included measures of loss of righting, ataxia, head tilt or bobbing, hyperactivity, and disorientation during swimming that were combined into a composite motor score for further analysis. Taken together, this measure is likely to be the best predictor of an individual rat's spatial aptitude at any one time during training as each of the individual measures and each of the individual rats has its own time-course for recovery following lesioning.

After a postoperative test period of 24 h, the motor test battery indicated a 100% hit rate (i.e., successful bilateral vestibular lesioning). The composite motor scores correlated highly with spatial performance as measured by choices to criterion on the RAM at steady-state levels of choice performance. Conversely, the degree to which motor and temporal indices (e.g., peak time, peak rate, and CV) were correlated was negligible. A correlation matrix for these measures is shown for control ($n = 20$), vestibular lesioned ($n = 20$), and all rats ($n = 40$) in Tables 1, 2, and 3, respectively. In addition, a correlation matrix for choices to criterion, individual motor scores, and composite motor scores is shown for all rats ($n = 40$) in Table 4. Overall, these results show a high degree of correlation among the different motor scores and a high degree of correlation between the composite motor score and RAM performance, but not interval timing measures. The composite motor scores and their correlations remained stable throughout the course of the experiment (see Dallal, 1997).

3.4. Ordinal-Reproduction Timing

Distributions for the reproduced durations at each of the three standard durations (800, 3200, and 12800 ms) during the last 10 sessions of training on the ordinal-reproduction procedure without lever insertion/retraction were analyzed using PeakFit as previously described. The mean response functions are plotted in Fig. 5 for rats in the control (top panel) and vestibular lesioned (bottom panel) groups.

3.4.1. Peak Time

Rats in the control and vestibular lesion groups revealed significant effects on the modes of the response distributions (peak time) for Treatment, Standard Duration, and Trial Type; $F(1, 18) = 11.35$, $p < 0.01$; $F(2, 36) = 1.746\text{E}4$, $p < 0.0001$; and $F(1, 18) = 226.55$, $p < 0.0001$, respectively. There were also significant effects of the Trial Type × Treatment and the Standard Duration × Trial Type interactions; $F(1, 18) = 29.46$, $p < 0.0001$ and $F(2, 36) = 13.29$, $p < 0.001$, respectively. In contrast,

Table 1.
Control rats ($n = 20$). Correlation matrix for radial-arm maze, composite motor score, and peak-interval timing measures

	Choices	Motor	20' Time	80' Time	20' Rate	80' Rate	20' CV	80' CV
Choices	1.000**							
Motor	—	1.000**						
20' Time	−0.086	—	1.000**					
80' Time	0.098	—	0.296	1.000**				
20' Rate	0.146	—	0.270	0.533*	1.000**			
80' Rate	0.172	—	0.533*	0.506*	0.921**	1.000**		
20' DI	−0.111	—	0.048	0.015	−0.336	−0.323	1.000**	
80' DI	−0.179	—	0.017	0.021	−0.482*	−0.495*	0.150	1.000**

Choices = choices to criterion in the 12-arm radial maze procedure; Motor = Composite Motor Score from the motor test battery; Time = peak time during unreinforced probe trials in the peak-interval procedure; Rate = average response rate during unreinforced probe trials in the peak-interval procedure; CV = coefficient of variation; * = $p < 0.05$; ** = $p < 0.01$.
Note 1: The Composite Motor Score of the control group has a variance of 0 and correlations with this measure can't be computed.
Note 2: Given the observation of superimposition for 20-s and 80-s target durations, the spread for peak functions would be expected to increase as a function of average response rate. This relationship would be expected to lead to a significant correlation between the Time and Rate measures, whereas the maximum response rate (peak rate) and other motor factors should be independent of peak time (Cheng & Meck, 2007; Yin et al., in press).

Table 2.
Vestibular lesioned rats ($n = 20$). Correlation matrix for radial-arm maze, composite motor score, and peak-interval timing measures

	Choices	Motor	20' Time	80' Time	20' Rate	80' Rate	20' CV	80' CV
Choices	1.000**							
Motor	0.602**	1.000**						
20' Time	0.019	0.554*	1.000**					
80' Time	0.360	0.311	0.110	1.000**				
20' Rate	−0.123	0.110	0.389	0.337	1.000**			
80' Rate	−0.188	−0.065	0.161	0.207	0.877**	1.000**		
20' DI	0.315	0.136	−0.070	0.282	−0.197	−0.179	1.000**	
80' DI	0.121	−0.080	−0.284	−0.110	−0.037	−0.002	0.409	1.000**

Choices = choices to criterion in the 12-arm radial maze procedure; Motor = Composite Motor Score from the motor test battery; Time = peak time during unreinforced probe trials in the peak-interval procedure; Rate = average response rate during unreinforced probe trials in the peak-interval procedure; CV = coefficient of variation; * = $p < 0.05$; ** = $p < 0.01$.

Table 3.
All rats ($n = 40$). Correlation matrix for radial-arm maze, composite motor score, and peak-interval timing measures

	Choices	Motor	20' Time	80' Time	20' Rate	80' Rate	20' CV	80' CV
Choices	1.000**							
Motor	0.775*	1.000**						
20' Time	0.051	0.250	1.000**					
80' Time	0.213	0.162	0.202	1.000**				
20' Rate	0.102	0.192	0.314	0.415*	1.000**			
80' Rate	−0.027	−0.008	0.427*	0.351	0.889*	1.000**		
20' DI	0.101	0.048	0.015	0.133	−0.280	−0.276	1.000**	
80' DI	−0.019	−0.081	−0.083	−0.045	−0.305	−0.309	0.244	1.000**

Choices = choices to criterion in the 12-arm radial maze procedure; Motor = Composite Motor Score from the motor test battery; Time = peak time during unreinforced probe trials in the peak-interval procedure; Rate = average response rate during unreinforced probe trials in the peak-interval procedure; CV = coefficient of variation; * = $p < 0.05$; ** = $p < 0.01$.
Note 1: The Composite Motor Score of the control group has a variance of 0 and correlations with this measure can't be computed.
Note 2: Given the observation of superimposition for 20-s and 80-s target durations, the spread for peak functions would be expected to increase as a function of average response rate. This relationship would be expected to lead to a significant correlation between the Time and Rate measures, whereas the maximum response rate (peak rate) and other motor factors should be independent of peak time (Cheng & Meck, 2007; Yin et al., in press).

Table 4.
All rats ($n = 40$). Correlation matrix for choices, individual motor scores, and composite motor scores

	Choices	LOR	Ataxia	HTB	Hyperactivity	Swim	Composite
Choices	1.000**						
LOR	0.678**	1.000**					
Ataxia	0.774**	0.898**	1.000**				
HTB	0.508**	0.760*	0.794**	1.000**			
Hyperactivity	0.658**	0.769**	0.899**	0.874**	1.000**		
Swim	0.655	0.914**	0.913**	0.890**	0.903**	1.000**	
Composite	0.683**	0.913**	0.947**	0.925**	0.944**	0.983**	1.000**

Choices = choices to criterion in the 12-arm radial maze procedure; LOR = loss of righting; HTB = head tilt or bobbing; Composite = Composite Motor Score; * = $p < 0.05$; ** = $p < 0.01$.

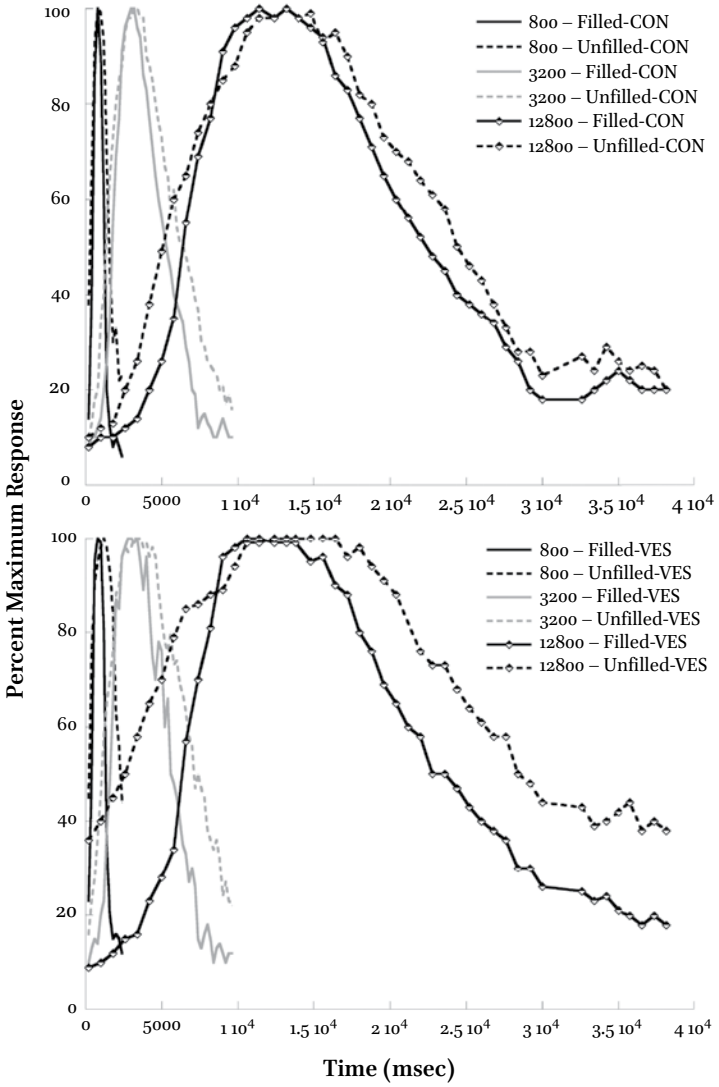

Figure 5. Ordinal-reproduction timing data for control (top panel) and vestibular lesioned rats (bottom panel). Reproduced durations for each of the three standard durations (800, 3200, and 12800 ms) are plotted in terms of percent maximum response as a function of the distribution of reproduced durations for trials demarcated by the cue lights + white noise (filled; solid lines) and trials demarcated only by self-initiated responses (unfilled; broken lines).

there were non-significant effects of the Standard Duration × Treatment and the Standard Duration × Trial Type × Treatment interactions; $F(2, 36) = 1.56$, $p > 0.05$ and $F(2, 36) = 1.37$, $p > 0.05$. Taken together, these findings indicate that reproduced durations were significantly longer for the vestibular lesioned rats

than for the control rats and that trial-type also affected timing performance with reproductions during unfilled trials being significantly longer than on filled trials which tended to be centered close to the standard durations of 800, 3200, and 12800 ms. The significant Standard Duration × Trial Type interaction indicated that the effects of trial type increased as a function of the standard durations in a proportional rather than an absolute manner (e.g., Lake and Meck, 2013; Meck, 1983, 2002; Meck & Angell, 1992; Meck & Church, 1987; Penney et al., 1996).

3.4.2. Peak Spread

Rats in the control and vestibular lesion groups revealed significant effects on the spread of the response distribution at 75% maximal (peak spread) for Treatment, Standard Duration, and Trial Type; $F(1, 18) = 294.58$, $p < 0.001$; $F(2, 36) = 5{,}647.06$, $p < 0.0001$; and $F(1, 18) = 131.49$, $p < 0.0001$, respectively. There were also significant effects of the Trial Type × Treatment, Standard Duration × Trial Type, Standard Duration × Treatment, and the Treatment × Standard Duration × Trial Type interactions; $F(1, 18) = 43.70$, $p < 0.0001$, $F(2, 36) = 32.96$, $p < 0.001$, $F(2, 36) = 80.42$, $p < 0.0001$, and $F(2, 36) = 16.71$, $p < 0.0001$. Taken together, these findings indicate that reproduced durations were significantly more variable (hence demonstrating greater spread) for the vestibular lesioned rats than for the control rats and that type-type also affected timing performance with reproductions on unfilled trials being significantly more variable than on filled trials. The various interactions indicated that the spread effects increased with standard duration, but particularly so for the vestibular lesioned rats at 12800 ms on unfilled trials, i.e., trials requiring the timing of self-initiated movements without external cuing.

3.4.3. Coefficient of Variation

An analysis of the coefficient of variation allows an evaluation of vestibular lesion and trial-type effects relative to the standard durations (800, 3200, and 12800 ms). Such an analysis is critical to understanding these effects due to the scalar property of interval timing, which indicates that the standard deviation increases proportionally with the mean of the target duration (e.g., Gibbon et al., 1984, 1997). The question here is whether the scalar property holds across the various experimental conditions or is violated by them. ANOVAs revealed a significant effects of Treatment and Trial Type, indicating that CVs were significantly higher for vestibular lesioned rats than control rats; $F(1, 18) = 221.71$, $p < 0.0001$ and significantly higher for unfilled trials than for filled trials, $F(1, 18) = 88.99$, $p < 0.0001$. Interestingly, the effect of Standard Duration was non-significant, although the Treatment × Standard Duration × Trial Type interaction was significant, $F(2, 16) = 1.38$, $p > 0.05$ and $F(2, 36) = 9.57$, $p < 0.001$, respectively. This result implies that the scalar property (constant coefficient of variation) held across all conditions except for the vestibular lesioned rats during the unfilled trials, indicating that vestibular lesioned rats violated the scalar property during the timing of self-initiated movements as illustrated in Fig. 6.

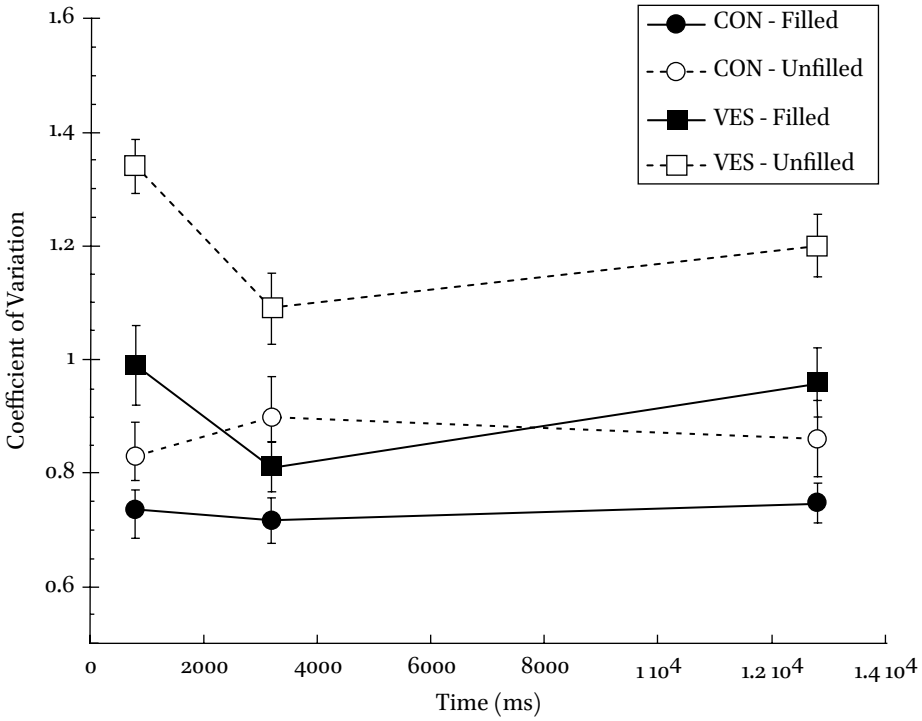

Figure 6. Mean (± SE) coefficient of variation of the reproduced duration distributions plotted as a function of time for the three standard durations (800, 3200, and 12800 ms) for the control (circles) and vestibular lesioned rats (squares). Functions are presented separately for trials demarcated by the cue lights + white noise (filled; solid lines) and trials demarcated only by self-initiated responses (unfilled; broken lines).

4. Discussion

The data presented here clearly demonstrate that loss of vestibular function in adult rats produces a high degree of behavioral dysfunction in terms of the rats' ability to locate hidden food items in space although latency to make choices was similar to control rats. These results are in close agreement with previous findings (e.g., Russell et al., 2003a; Smith & Zheng, 2013; Smith et al., 2005, 2015). The conclusion is that the disruption of egocentric orientation inputs to the cognitive mapping system (presumably mediated by the hippocampus; O'Keefe and Nadel, 1978) interferes with the rat's ability to form and/or use an abstract representation of space while other cognitive/memory functions are spared. Rats receiving lesions to their vestibular system during adulthood, either prior to or following RAM training, are permanently impaired in their ability to efficiently navigate (Dallal, 1997). Taken together, the implication of these experiments is that while the ability to form an allocentric cognitive map may be impaired by a vestibular

lesion in adulthood, the ability to use that representation (even when previously formed under optimal conditions) to guide behavior is perhaps more substantially affected. In contrast, lesions of the vestibular system during early development are apparently functionally compensated for by other behavioral and/ or neural mechanisms (Dallal, 1997). Interestingly, other inputs to egocentric/ idiothetic navigation (truncal receptors, proprioceptors, efference copies, etc.) cannot fully compensate for this deprivation nor can allocentric navigation, at least within the time frame studied. Subsequent functional recovery of normal navigational strategies and spatial memory efficacy may be due to the substitution of visual, motoric, and/or other proprioceptive cues for vestibular cues when the rat is learning to coordinate egocentric/dead-reckoning information (e.g., angles and distances traveled over time) with observer-independent spatial representation (see McNaughton et al., 1991; Wallace et al, 2002). It is also conceivable that the navigational systems in the brain re-organize themselves and eventually allow the animal to navigate without vestibular input. Again, while these ideas pertaining to one or more sensitive periods of neural plasticity and the selective strengthening of dominant neural pathways during development are theoretically compelling, they have not yet been experimentally documented for the bio-behavioral development of vestibular processing or of cognitive mapping and interval-timing strategies (Smith et al., 2015). Moreover, it is unclear to what extent functional recovery may have occurred due to degeneracy (e.g., Lewis & Meck, 2012; Merchant et al., 2013).

In both the present study and a previous one (Ossenkopp & Hargreaves, 1993) with bilaterally labyrinthectomized rats, spatial working memory performance was shown to be dramatically impaired. Loss of vestibular input thus seems to deprive subjects of key sensory information needed for orientation in a complex spatial environment such as the RAM, but not a simpler spatial task such as the Y-maze for which information from other sensory modalities provided an adequate substitute (Dallal, 1997). Previous research, also consistent with the present study, shows that specific experimentally-produced rotational vestibular cues can be used by rats on a RAM in locating a reward spatially fixed relative to the global geometry and stable landmarks of the test environment; performance in these tasks is disrupted by irregularites in the angular placement of maze arms (Grobety & Schenk, 1992) and by vestibular dysfunction (Matthews et al., 1989).

The ratio of sequential adjacent arm entries to total arm entries is a measure of response stereotypy (praxis; algorithmic responding) previously observed in rats tested in a RAM task (e.g., Dale, 1986; Dale & Innis, 1986; Meck et al., 1988, 1989; Williams et al., 1990). Efficient learning of the RAM task does not require such stereotypic adjacent-arm entries (Olton & Samuelson, 1976) and is often prevented in experimental practice by guillotine doors separating the platform from each of the arms. Here it is interesting to note that vestibular lesioned rats in the present study showed significantly less turning bias during the first half

of training (Dallal, 1997). These findings suggest that loss of vestibular information may have impaired the rat's ability to identify an arm that had just been entered or an adjacent arm (despite the availability of visual cues), thereby disrupting algorithmic responding as a compensatory mechanism for deficiencies in spatial memory.

Given the importance attached to angular velocity signals from the vestibular system in landmark learning and sense of direction (e.g., McNaughton et al., 1991), the observation that the deficits in vestibular-lesioned rats occur in the presence of reliable visual cues is consistent with such an argument. However, it should be noted that the labyrinthectomized rats probably had compromised visual input, due to loss of the vestibulo-ocular and vestibulo-collic reflexes. The present findings do not clarify the relative importance of visual and vestibular cues in cognitive mapping. Future studies will need to examine the use of dark room or another obscured global geometry condition and randomized landmarks test manipulations to comparatively examine the relative contributions of visual and vestibular cues throughout RAM acquisition by both rats lesioned as adults and rats lesioned neonatally. The value of such proposed extensions of the present work would be further enhanced if potential gender influences on the relative roles of visual and vestibular cues were systematically investigated and confirmed for pigmented versus albino rat strains (e.g., Buhusi et al., 2005; Pleil et al., 2011; Williams et al., 1990).

In comparison with the spatial navigation data following lesions to the hippocampus (the putative site of the cognitive map — Meck et al., 1984, 2013; O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978; Olton et al., 1979) and lesions of the caudate nucleus, putamen, and frontal cortex (which presumably affect temporal integration and egocentric orientation — Dallal & Meck, 1993; Dallal et al., 1993; Li et al., 2001; Meck, 2006a, b, c; Meck & Benson, 2002; Meck et al., 1986, 1987; Olton et al., 1988; Potegal, 1969, 1982; Potegal et al., 1971), vestibular lesions produce behavioral effects that, to a first approximation, appear more like lesions to the hippocampus than to the caudate nucleus (Dallal, 1997). This is consistent with the hypothesis that vestibular lesions modulate hippocampal functioning (e.g., Russell, 2006; Smith et al., 2009, 2010) and prevent vital spatial information from reaching the hippocampus and, thereby, interfere not only with self-motion related cues, but also with spatial decisions and cognitive mapping strategies (e.g., Nekovarova et al., 2006, 2009; Stuchlik et al., 2012; Wallace et al, 2002; Yoder et al., 2015). Moreover, these effects are consistent with data showing that the hippocampus is essential for processing sequential information, e.g. anticipatory selection of maze arms experienced in a temporal sequence (e.g., DeCoteau & Kesner, 2000). In this regard, the points to be made from the current work are fairly straightforward: (a) Vestibular lesions have basically no effect on temporal processing unless an explicit spatial component is added to the timing task. (b) Rather, they increase responsiveness overall (by about the same factor for

20-s and 80-s target durations in the PI procedure), but without impairing either the accuracy or the precision of timing as shown in Figs 2 and 3. The additional dual- versus single-threshold analyses determining when rats start (S1) and stop (S2) responding and how these are correlated with the width and mid-point of that interval (see Church et al., 1994; Matell et al., 2006) were inconclusive in showing that lesioned rat were more likely to use separate S1 and S2 thresholds for responding (Dallal, 1997). This is an important observation because mechanisms controlling the initiation and termination of responding have sometimes been shown to be distinguishable in terms of vestibular input (e.g., Cohen et al., 1992) and the striatal control of timed response patterns (e.g., Agostino et al., 2013; MacDonald et al., 2012).

Correlations with motor indices of vestibular damage (see Table 1) confirm the role vestibular inputs play in spatial versus temporal processing and support the idea that vestibular projections relevant to dead reckoning are likely to pass through areas of the basal ganglia other than the caudate. Taken together, then this series of experiments indicates the specificity of vestibular inputs to allocentric spatial navigation and the cognitive mapping of angles and distances. Our view is that the real novelty in thinking about spatial navigation and linking it with prospective and retrospective timing (see MacDonald, 2014; MacDonald et al., 2014) is the notion that the cognitive mapping process for time and space is specialized to translate multisensory information into a 'common language,' an abstraction accessible to all the sensory systems as they are used independently, or in a coordinated fashion, to solve complex tasks (Yin & Troger, 2011). This 'common language,' hypothetically in the form of non-modality specific computational geometry, ideally allows the guidance systems that put together the information on where you are and when you were there to inform other systems where you would like to go, how to get there, and when you should arrive and depart based on past experience and current environmental conditions. Various studies have shown the importance of the hippocampus in coordination of spatial-temporal information (e.g., Howard et al., 2014; Pastalkova et al., 2008). More simply put, this 'common language' for spatial and temporal information is what allows someone to put milk in the icebox after work while the lights are on and effectively retrieve that milk, upon waking at a predetermined time in the middle of the night and choosing to leave the lights off, by feeling around for remembered obstacles and landmarks in order to orient the spatial and temporal maps that guide the way to the icebox. This recognition of a 'common language' for cognitive mapping shares some characteristics with theories of magnitude representation such as A Theory Of Magnitude (ATOM) which posits that time, space and quantity are part of a generalized system (Cordes et al., 2007; Walsh, 2003), but also stresses the independence of such systems (e.g., Aagten-Murphy et al., 2014; Dallal & Meck, 1993; Lake et al., 2014; Matthews & Meck, 2014; Matthews et al., 2014; Meck et al., 1984, 2013; Rakitin et al., 1992; Svoboda et al., 2015).

Correlations among choice performance in the RAM and the accuracy and precision of interval timing in the PI procedure would also be expected based on shared similarities in the memory and decision stages (e.g., Meck, 2001; Meck et al., 2012). The findings from the ordinal reproduction procedure used in Experiment 2, however, argue for a deeper integration of space and time as a function of attention, beat induction, and clock speed (e.g., absolute vs. proportional shifts in the psychometric functions and the metrical representation of time — Meck, 1983; Penney et al., 1996; Todd & Lee, 2015) and the representation (what and when) of self-initiated movements that can be accounted for by an accumulator model of spontaneous neural activity (e.g., Hoffstaedter et al., 2012; Schurger et al., 2012). The observation that the scalar property of interval timing was violated in rats with vestibular lesions during unfilled, but not filled, trials indicates that the vestibular system is crucial to the timing of self-initiated movements without external stimulus support. Moreover, this finding suggests that internal models of target motion for self-initiated movements are also scalar, i.e., the standard deviation grows proportional to the mean of the reproduced target (motion or duration) and response distributions for different targets superimpose on a relative time scale = constant CV (e.g., Buhusi et al., 2009; Gibbon et al., 1984; Russell et al., 2003b, 2006). Successful performance on unfilled/self-initiated trials requires the integration of both self-initiated movement and temporal signals (e.g., Barnett-Cowan, 2013; Barnett-Cowan & Harris, 2009; Barnett-Cowan et al., 2012; Soyka et al., 2013; Zago et al., 2004). Decreased sensitivity to self-initiated movements would be expected to increase both the variability and the latency to initiate the timing of the reproduced durations in Experiment 2. This prediction is supported by increased peak times and CVs depicted in Figs 5 and 6, respectively. Disruptions in spatial-temporal performance would also be expected to occur in the hybrid RAM procedure developed by Buhusi et al. (2013) which included a temporal criterion for the amount of time mice are held in the central platform following each arm choice. Mice deficient in the Close Homolog to L1 cell adhesion molecules (CHL1) tested in this RAM procedure exhibited impairments in spatial-temporal integration similar to the vestibular lesioned rats in the self-initiated trials of the ordinal reproduction procedure reported here. Future studies are needed to determine whether CHL1 mice have impairments in vestibular function and whether vestibularly lesioned animals would show similar levels of impairment in both the hybrid RAM and self-initiated component of the ordinal reproduction timing procedure.

Finally, the results from the ordinal reproduction share some similarity with the pattern of timing dysfunctions observed in Parkinson disease patients who exhibit violations of the scalar property and alterations in peak time when tested OFF, but not ON their dopaminergic medication (e.g., Gu et al., 2015b; Malapani et al., 1998; Shi et al., 2013). The logical conclusion being that neural noise induced in either

vestibular or motor systems distorts the perception of self-initiated movement and thereby alters the perception of time in various contexts (e.g., Barter et al., 2015a, b; Binetti et al., 2010; Cheng et al., 2011; Jahanshahi et al., 1995; Jones and Jahanshahi, 2014, 2015; Mello et al., 2015; Rancz et al., 2015; Stiles and Smith, 2015; Yin, 2014).

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