A Distinctive Platform System to Study the Effects of a Vestibular Prosthesis on Nonhuman Primate Postural Control

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The purpose of this paper is to describe novel experiments and methodologies utilizing a distinctive balance platform system to investigate postural responses for moderate to severe vestibular loss and invasive vestibular prosthesis-assisted nonhuman primates (rhesus monkeys). For several millions of vestibular loss sufferers in the U.S., daily living is severely affected in that common everyday tasks, such as getting out of bed at night, maintaining balance on a moving bus, or walking on an uneven surface, may cause a loss of stability leading to falls and injury. Aside from loss of balance, blurred vision and vertigo (perceived spinning sensation) are also debilitating in vestibular-impaired individuals. Although the need for vestibular rehabilitative solutions is apparent, postural responses for a broad range of peripheral vestibular function, and for various stationary and moving support conditions, have not been systematically investigated. For the investigation of implants and prostheses that are being developed toward implementation in humans, nonhuman primates are a key component. The measurement system used in this research was unique. Our platform system facilitated the study of rhesus monkey posture for stationary support surface conditions (quiet stance and head turns) and for dynamic support surface conditions (pseudorandom roll tilts of the support surface). Further, the platform system was used to systematically study postural responses that will serve as baseline measures for future vestibular-focused human and nonhuman primate posture studies. [DOI: 10.1115/1.4039140]

Keywords: vestibular loss, pseudorandom stimulus, balance, posture, quiet stance, equilibrium, platform

Introduction

The use of a specialized balance platform, to assess how different levels of vestibular function affect postural control mechanisms on animal models, is a significant contribution toward the investigation, diagnosis, and treatment for balance disorders in humans. In particular, a distinctive animal balance platform is needed to test invasive (balance) prostheses toward human implementation. The focus of this paper is to discuss how a distinctive balance platform made it possible to conduct unique experiments on nonhuman primates with various degrees of vestibular function, for a range of balance test conditions.

People suffering from severe vestibular dysfunction experience equilibrium disorders that can cause unsteady balance in common, daily activities. According to the NIDCD [1], approximately 8 million American adults have chronic balance impairment issues derived specifically from vestibular dysfunction. The odds of balance dysfunction increase significantly with age such that 85% of individuals age 80 and above had evidence of balance dysfunction [2,3]. Postural rehabilitative strategies (such as compensation strategies, balance aids, and invasive vestibular prostheses that aim to partially restore vestibular function) for mild versus marked levels of vestibular dysfunction have not been methodically explored or assessed.

Quiet stance (i.e., stance on a stationary support surface in the absence of external perturbations) is the simplest experimental condition used to evaluate the effects of the visual, somatosensory, and vestibular systems on posture and has been used both in human and animal studies. Humans with severe bilateral vestibular loss have difficulty balancing when visual and somatosensory cues are unavailable or unreliable (e.g., see Ref. [4]). Thus, daily activities, such as standing in dimly lit environments on uneven or compliant surfaces, may prove challenging for individuals suffering from vestibular dysfunction. However, in clinical practice, a broad range in severity of vestibular dysfunction exists and the question remains as to how one may (or may not) be able to compensate for mild to marked vestibular loss.

To systematically probe sensory system contributions, we implemented the following in nonhuman primates (rhesus monkeys): (1) varied the somatosensory cues provided by the platform system's footplates via relatively strong or weak support surface cues (i.e., thin, hard rubber surface or a thick, compliant foam surface, respectively) and (2) varied platform system's mediolateral stance width to provide either a large or small base of support for normal, mild vestibular hypofunction (mBVH) and severe vestibular hypofunction (sBVH) animals [5]. We also employed a more difficult stationary support surface balance task than quiet stance: head turns to illuminated targets.

For both human and nonhuman subjects with severe vestibular loss, maintaining balance while turning the head is difficult [6–8] leading to imbalance and unsteadiness. While previous studies focused on either normal or severe vestibular-loss test subjects, they did not address postural responses to head turns for subjects with various levels of vestibular dysfunction, including a prosthesis-assisted state. We were able to utilize our balance platform to test the effects of a vestibular prosthesis on rhesus monkeys (in a "sBVH + STIM-ON" state). The balance platform system used made it possible to determine the degree to which the

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prosthesis affects posture in a severely impaired animal [9]. This was an initial, but critical, step in documenting the potential benefits of the prosthesis to vestibular-loss humans. A postural task even more difficult for severe vestibular-loss sufferers than the stationary platform conditions described above were dynamic tilts of the support surface.

Nonhuman animal studies that used white-noise approximated (or "pseudorandom") roll-tilt stimuli to perturb posture were not encountered by the authors of this paper. Previous cat studies [10–14] involved the use of balance platforms that allowed for only ramp-hold translations and rotations for unimpaired balance, as well as the effects impaired balance caused by spinal cord injury and severe vestibular loss. As opposed to ramp-hold stimuli, to investigate postural responses to support surface tilts as a function of amplitude (and frequency), a pseudorandom input platform tilt has been applied in several human studies (as in Refs. [15–17]). Peterka [17] showed that normal human subject's stimulus–response curves (i.e., root-mean-square center-of-mass body sway as a function of platform tilt amplitude) saturated as platform tilt increased. As tilt amplitude increases, the normal human orients more with earth-vertical and less with the tilting platform. However, human subjects with severe bilateral vestibular loss do not exhibit this characteristic and instead oriented increasingly more with the support surface, likely due to their severe vestibular impairment; this response resulted in instability and falls.

The balance platform described here made it possible to input a bandwidth of frequencies simultaneously as roll-tilt stimuli. We were able to utilize our balance platform to test our hypothesis that the animal's trunk response to platform tilt would exhibit varied degrees of saturation in trunk sway depending on the level of vestibular function [18]. This type of stimulus was advantageous in that several frequencies at nearly equal power, and for various tilt amplitudes, could be presented to the animal at once. Pseudorandom tilt stimuli are advantageous as input stimuli in that, if one assumes a linear-approximated system, one can obtain the (postural control) system transfer function. Such balance stimuli are invaluable to characterizing postural control in animals other than, or in parallel to, humans.

Methods

We investigated the effects of the degree of vestibular function on the postural response to various balance platform experimental test conditions (Fig. 1). For our experiments, two juvenile female rhesus monkeys were used: monkey S (7.9 kg) and monkey M (6.7 kg). However, more animals may be used in future studies. Experiments were approved by the Institutional Animal Care and Use Committee and were in accordance with USDA guidelines. For the two rhesus monkeys studied, vestibular function ranged from normal, mBVH, sBVH, and severe bilateral vestibular hypofunction + prosthetic stimulation (or sBVH + STIM-ON). Vestibular ablation was accomplished by intratympanic gentamicin and systemic intramuscular streptomycin injections. The details of the vestibular ablative procedures using aminoglycosides [19] and the prototype prosthesis (a one-dimensional, right posterior semicircular canal prosthesis) are described in Ref. [18].

Animal Justification. An advantage to using animal models (rhesus monkeys) as test subjects for the experiments described was that they had the potential to serve as their own control, as opposed to human studies where normal and severe vestibular-loss patients would typically be different individuals. By investigating the posture of animals in normal, mBVH, and sBVH, as well as a sBVH + STIM-ON states using the balance platform system described, it would allow the establishment of a database on the effects of different levels of vestibular function on posture for nonhuman primates, ultimately facilitating future human studies, including those investigating the use of rehabilitative solutions, such as the invasive vestibular prosthesis.

Although human testing would be the most direct path to characterization of an invasive vestibular prosthesis, the use of nonhuman primate test subjects allowed for more degrees-of-freedom in that a broader and more extensive range of the research experiments could be conducted leading up to/in conjunction with human investigations of the vestibular prosthesis. Utilizing the rhesus monkey allowed the characterization of postural responses for varied levels of vestibular function. It also allowed the further development of the prosthesis itself, prosthesis implantation procedures, and postural characterization of the prosthesis [18]. Development of this knowledge base in nonhuman primates enhances the potential benefits associated with current and future implementation of the invasive prosthesis in humans.

Equipment Descriptions. Animals were trained to freely stand on the balance platform in order to receive juice reward. The setup surrounding the platform was black foam board and black tarp. Balance platform fabrication methods are not discussed here; however, the platform itself was constructed with aluminum 80/

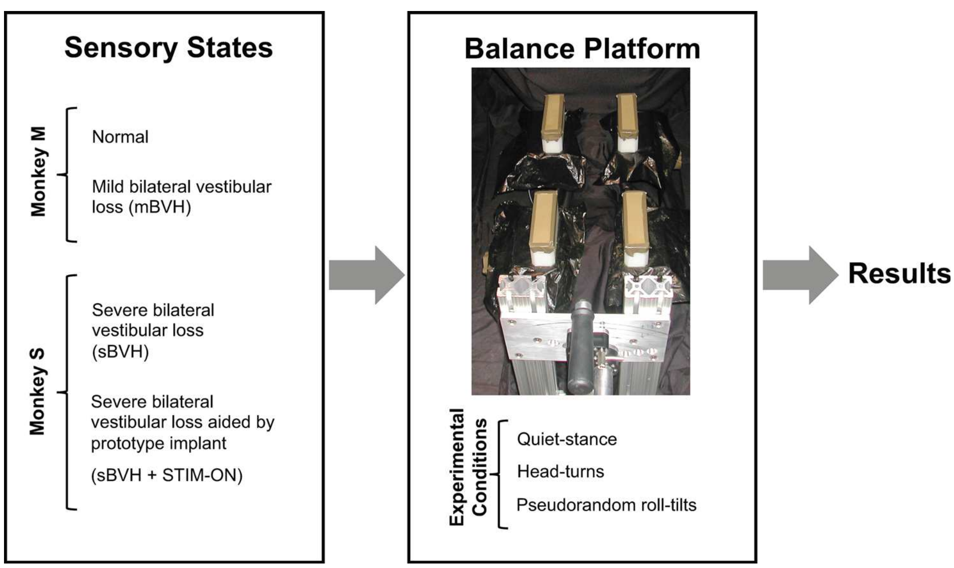

Fig. 1 Sensory states for rhesus monkey balance experiments; experimental conditions using the balance platform and actual balance platform are also shown

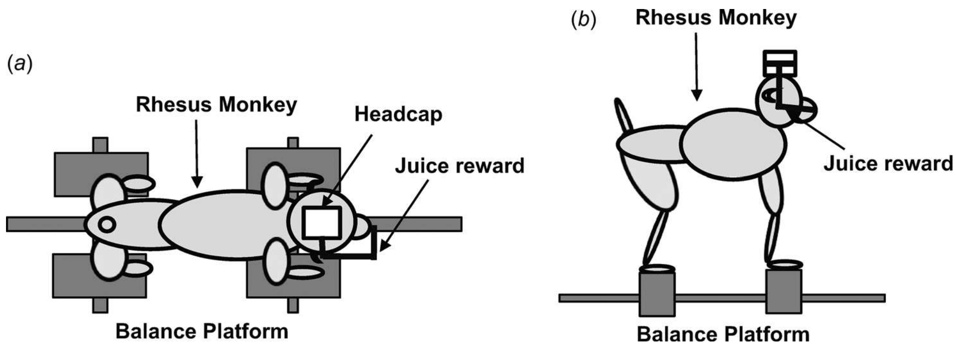

Fig. 2 Schematic of quiet stance test setup: (*a*) top view and (*b*) side view

20 stock (as shown in Fig. 1), and each of the platform's four footplates was made out of acrylic. The rhesus monkey balance platform used for this research consisted of four platform footplates that were equipped with tri-directional force sensors (ME-Meßsysteme GmbH, KD24S, Hennigsdorf, Germany) used to quantify ground reaction footplate forces. Force data were sampled at 200 Hz for the quiet stance and head-turn experimental conditions and at a rate of 600 Hz for the pseudorandom tilt experimental condition, using LabVIEW (National Instruments Corp., Austin, TX). To measure the motion of the head, foretrunk, and hind trunk of the animal, three, six-degree-of-freedom sensors (miniBIRD, Ascension Technology Corporation, Milton, VT) were sampled at 100 Hz for the quiet stance and head-turn experiments and at 150 Hz for the pseudorandom platform tilt experiment.

In order to limit visual cues, all test sessions were conducted in dim lighting with a black tarp surround. When recording test sessions, infrared illuminators (48-LED Illuminator Light Cctv Ir Infrared Night Vision) were used in conjunction with a pair of Kodak (movie) cameras with infrared lenses. The cameras were positioned to image the front side of the animal to record: (1) animal behavior and (2) human handling artifacts within a given test session.

Experimental Test Conditions. The stationary platform allowed for changes of the base of support and also of the support surface material (quiet stance experiment); e.g., foam could be attached to the footplates. The stationary platform was also used in conjunction with illuminated targets placed on the surround to evoke animal head movements (head-turn experiment). Furthermore, the platform allowed for dynamic tilts in the roll axis (pseudorandom stimulus experiment).

Quiet Stance. The quiet stance condition is the simplest condition used to evaluate the effects of the three main sensory systems (i.e., visual, somatosensory, and vestibular systems) on postural control by measuring ground reaction forces and head and trunk motion while the animal attempted to stand still (Fig. 2). The platform surface characteristics were varied to produce levels of increasing task difficulty level: gum-wide, gum-narrow, foam-wide, and foam-narrow. A gum-wide condition provided a hard support surface (i.e., strong footplate cues) and wide (18 cm) stance width that yielded a large base of support, while a foam-narrow condition provided a complaint foam support surface (i.e., weak footplate cues) and narrow (9 cm) stance width that yielded a small base of support.

Head Turns to Illuminated Targets. A stationary platform condition more difficult than quiet stance was head turns to illuminated targets (Fig. 3). In this research, the effects of four different levels of head-in-space (vestibular) information on trunk sway were investigated while the animal turned its head toward illuminated targets. The two animals were tested in normal, mBVH, sBVH, and sBVH + STIM-ON states. Targets were placed counterclockwise in yaw (at 0 deg (or straight ahead), 40 deg, 60 deg, 90 deg) and ∼40 deg oblique (i.e., in the plane of the

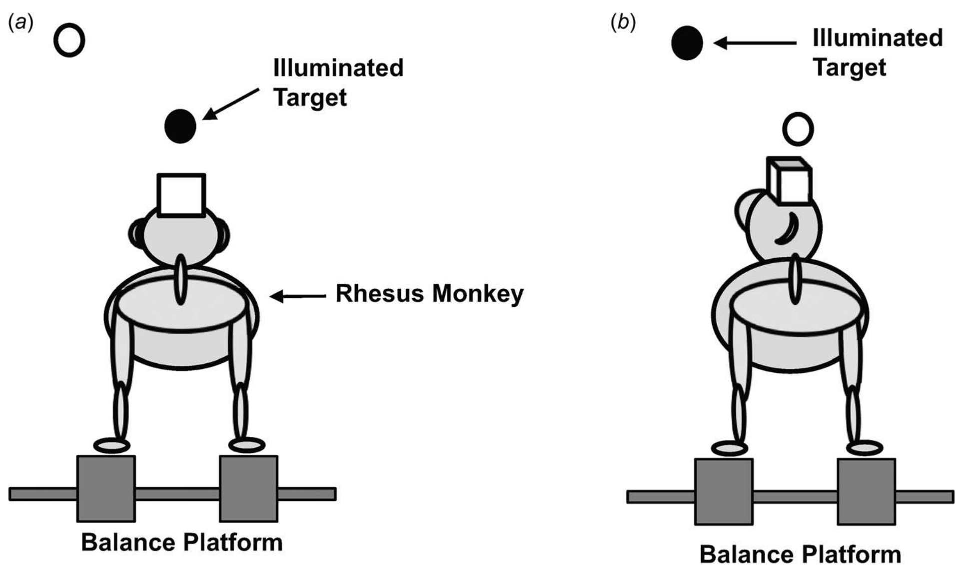

Fig. 3 Schematic of head turn experiment: (*a*) animal fixates on the target straight ahead and (*b*) offset target is illuminated and animal turns it head to fixate on the target

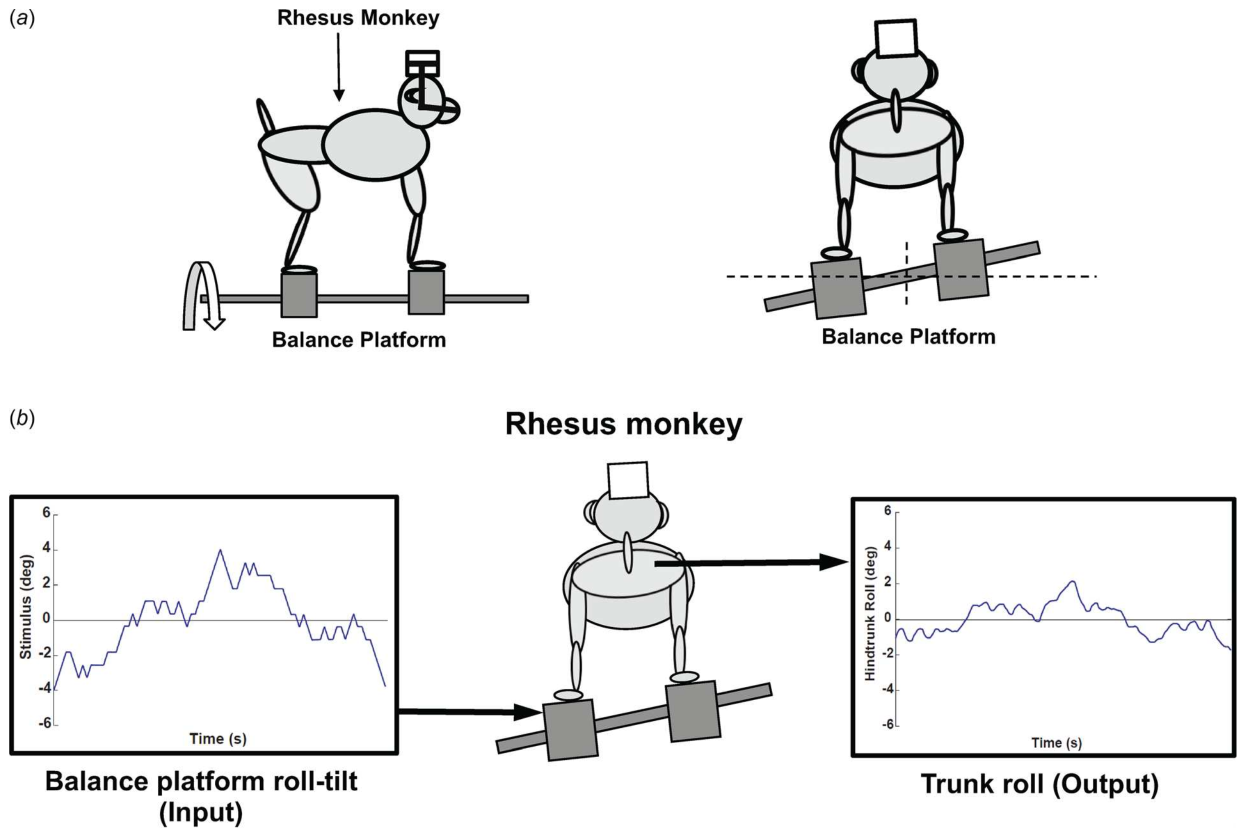

Fig. 4 (*a*) Schematic of pseudorandom roll-tilt test setup and (*b*) PRTS balance platform input (left), animal (middle), and trunk roll output (right)

prosthesis-implanted, right-posterior canal). Measured output responses were the head and trunk movements of the animal.

Pseudorandom Roll-Tilt Stimulus. Stabilizing on a tilting balance platform was a test condition even more difficult than the stationary platform conditions above (Fig. 4). Pseudorandom stimuli are beneficial in that they: (1) are white noise approximated stimuli that are unpredictable to the test subject, (2) excite a bandwidth of frequencies (as opposed to one discrete frequency) at approximately equal power, and (3) allow for determination of the impulse response, or the system transfer function, which completely characterizes the linear approximated system. A white noise approximated signal (pseudorandom ternary sequence (PRTS) stimulus) has been used as an input perturbation stimulus for human normal and vestibular-loss subjects (first shown in Ref. [17]). However, previous posture studies in animals, other than humans, have not utilized pseudorandom roll-tilt stimuli. Such stimuli are valuable in characterizing an animal's posture in that they are unpredictable to the animal, their duration can be customized to accommodate attention and behavioral focus in animals. Further, this stimulus allowed a bandwidth of frequencies (0.0625–2.23 Hz) to be input to the balance platform simultaneously at nearly equal power. The utilization of the PRTS (platform) roll tilts was a unique opportunity to investigate the monkey's trunk response for different levels of vestibular function. From the measured trunk responses, the frequency response (or system transfer function) as well as trunk orientation as a function of stimulus amplitude could be determined for platform roll-tilt amplitudes of 0.5 deg, 1 deg, 4 deg, 6 deg, and, 8 deg peak to peak.

Results and Discussion

This paper focuses on the unique methodology and distinctive platform system used as a means to capturing and evaluating the animals' balance performance. For this reason, the paper does not focus on the balance platform system evaluation without the animal. Instead, it focuses on the novel diagnostic system, methodologies, and procedures used.

The detailed results from these sets of experiments are discussed in our published works for quiet standing in the normal (un-impaired), mBVH, and sBVH states [5], for head turns in the normal, mBVH, sBVH, and sBVH + STIM-ON states [9], and for postural responses to the PRTS stimulus [18]. However, a summary of the results of each is described briefly below.

Through use of the quiet stance condition, the severity of the vestibular dysfunction was observed to affect postural compensation. For stationary support surface conditions (quiet stance and head turns described here), a mBVH animal had decreased sway compared to normal but that a sBVH animal had increased sway relative to both the mBVH and normal states. The quiet stance results suggest that the animal may have been able to compensate for the mild level of vestibular dysfunction using a "stiffening" strategy to reduce its trunk sway. However, for the sBVH animal, this stiffening strategy was ineffective and the animal had increased trunk sway (instability). Further, we were able to characterize postural control mechanisms used to compensate for different levels of vestibular function via a feedback controller model [5], previously only applied to human posture.

From the head-turn experimental condition, for both normal and mBVH states, the monkey could stabilize its trunk during head turns, but that this was not possible when vestibular damage was severe (i.e., in the sBVH state). However, trunk sway was reduced (stability increased) for the sBVH + STIM-ON state [9]. For the head turn condition, the observation that trunk sway stability was increased in the sBVH + STIM-ON state compared to the sBVH state indicates that further human and nonhuman primate investigations utilizing prosthetic stimulation (via a prototype vestibular prosthesis) should continue. This observation leads one to project that an invasive vestibular prosthesis could potentially pose as a rehabilitative solution for partial balance restoration in severe vestibular loss humans.

For the tilting support surface, the normal animal had trunk sway less than the platform tilt amplitude at larger platform tilts (i.e., exhibited saturation of the stimulus–response curve similar to that seen in humans). Although the mBVH animal also demonstrated this finding, the sway was generally elevated from normal. For the pseudorandom roll tilts, we attributed saturation of the stimulus–response curve to the normal animal being able to align more with earth-vertical and less with the platform, compared to the mBVH animal, as amplitudes increased. We were able to successfully utilize a feedback controller model (previously only applied to human data) to further explore the idea of sensory reweighting in a nonhuman primate animal model [18]. This finding was important in that similar stimuli could be used to characterize the effects of the prosthesis, or invasive balance devices, that are being developed toward human implementation.

Conclusion

The platform system and methodology discussed here aids in establishing the baseline measures of nonhuman primate postural responses to a wide variety of test situations and in different vestibular states necessary for the investigation of rehabilitative solutions, including invasive prototype vestibular prostheses. The main purpose of this paper was to display an overview of the utility and importance for studying nonhuman primate postural control for different levels of vestibular function using our platform system. The use of this system allows the establishment of a baseline database of primate postural responses to a wide variety of test situations for different levels of vestibular impairment. These results will serve a metric against which rehabilitative techniques (e.g., posture mechanisms used to compensate and invasive prototype vestibular prostheses) can be evaluated. The effect of partially restored vestibular information (via a vestibular prosthesis) on an animal's posture while undergoing head turns had not previously been studied and furthered our understanding of the prosthesis' implications for humans with severe vestibular loss. Further, the platform and techniques used were for rhesus monkey standing on four limbs, but could be applicable toward similar sized animals for other experiments studying balance.

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