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A NOVEL PLATFORM-SYSTEM TO STUDY THE EFFECTS OF A VESTIBULAR PROSTHESIS ON NON-HUMAN PRIMATE POSTURAL CONTROL

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ABSTRACT

For the several millions of vestibular loss sufferers nationwide, 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 loss of stability leading to falls and injury. Aside from loss of balance, blurred vision and vertigo (perceived spinning sensation) are also extremely debilitating in vestibular impaired individuals. For the investigation of implants and prostheses that are being developed towards implementation in humans, non-human primates are a key component.

The purpose of our study was to implement a distinctive balance platform-system to investigate postural responses for moderate to severe vestibular loss and invasive vestibular prosthesis-assisted non-human primates (rhesus monkeys) for test balance conditions of various task-difficulty levels. 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.

The measurement system used in this research was unique in that it allowed us to conduct animal experiments, not investigated previously; such experiments are necessary towards the development on an invasive vestibular prosthesis to be used in humans suffering from vestibular loss. Our platform-system facilitated the study of rhesus monkey posture for stationary support surface conditions (i.e., quiet stance and head turns; more versus fewer footplate cues and large versus small base-of-support) and for dynamic support surface conditions (i.e., 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 non-human primate posture studies.

INTRODUCTION

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].

In clinical practice, a broad range in severity of vestibular dysfunction exists across vestibular-loss sufferers. Despite its public health importance, previous studies have focused predominantly on quantifying the imbalance of subjects suffering from severe vestibular dysfunction. However, postural rehabilitative strategies (e.g., compensation strategies, balance aids, versus 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. An understanding of how different levels of vestibular function affect the postural control mechanisms used for various balance test conditions, will ultimately aid the physician in determining the most beneficial rehabilitative solution for the patient.

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. Horak et al. [4] have shown that (bipedal) humans with bilateral vestibular loss are able to maintain sway within normal range as long as they receive cues from visual or somatosensory systems. However, it has been shown that humans with bilateral vestibular loss have difficulty balancing when visual and somatosensory cues are unavailable or unreliable (e.g., [4]). Thus, daily activities, such as standing in dimly-lit environments on uneven or compliant surfaces, may prove challenging for those suffering from vestibular dysfunction.

We implemented the following: 1) varied the somatosensory cues provided by the platform-system's footplates by providing 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. We hypothesized that an animal with mild bilateral vestibular hypofunction (mBVH) would be able to compensate for its loss and a severe bilateral vestibular hypofunction (sBVH) animal would be unable to compensate and have increases in sway. We also employed a more difficult stationary support surface balance task than quiet stance: head turns to illuminated targets.

For both human and non-human subjects with severe vestibular loss, maintaining balance while turning the head is difficult [5-7] leading to imbalance/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. The effect of partially restored vestibular information (via a vestibular prosthesis) on an animal's posture while undergoing head turns has not previously been studied and furthered understanding could have implications for humans with severe vestibular loss. The degree to which the prosthesis affects posture in a severely impaired animal is an initial, but critical, step in documenting the potential benefits of the prosthesis to vestibular-loss humans. We hypothesized that a sBVH animal receiving electric stimulation provided by an invasive vestibular prosthesis would be able to stabilize itself better than a sBVH animal not receiving these cues during head turns. 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.

To investigate human 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 (e.g., [8-10]). Peterka [10] showed that normal human subject's stimulus-response curves (i.e., root-mean-square (RMS) center-of-mass (COM) body sway as a function of platform tilt amplitude) saturates as platform tilt increases. The saturation of the normal subject's response as stimulus amplitude increases is attributed to the normal test subject's ability to increase orientation to earth-vertical as opposed to the platform surface. The sway saturation described can be observed in stimulus-response curves and also transfer function (trunk-to-platform) gain. This orientation to earth-vertical prevents normal humans from falling at the larger amplitude tilts in both the sagittal and frontal planes [8], [10]. 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 orient increasingly more with the support surface, likely due to their severe vestibular impairment [10]. At larger amplitudes, this response results in instability and falls.

Postural responses to pseudorandom tilt stimuli are advantageous in characterizing the postural control system in that, if we assume a linear-approximated system, we can obtain the (postural control) system transfer function. However, this stimulus, and hence the determination of a postural control system transfer function, have not been published for quadrupeds. Instead, ramp and hold rotations [11] and discrete sinusoidal inputs (e.g., [12, 13]) have been used. Macpherson et al. [11] examined bilateral vestibular-loss cats during ramp and hold pitch and roll rotations of the support surface (~ 6°). Similar to Peterka's [10] study in humans, the large body sway for vestibular-loss cats in response to platform tilt suggests that muscle activation patterns were opposite those of normal subjects (i.e., abnormal response magnifies body sway leading to destabilization) and consequently the lesioned animal became unstable. We hypothesized 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.

METHODS

For our experiments, two juvenile female rhesus monkeys were used: monkey S (7.9 kg) and monkey M (6.7 kg). Experiments were approved by the Institutional Animal Care Committee and were in accordance with USDA guidelines.

We investigated the effects of the degree of vestibular function on the postural response to head turns. For the two rhesus monkeys we studied, vestibular function ranged from normal, mBVH, sBVH, and severe bilateral vestibular hypofunction + prosthetic stimulation (or sBVH + STIM-ON). Vestibular ablation was accomplished by intra-tympanic (IT) gentamicin and systemic intramuscular (IM) streptomycin injections. Because the main focus of this paper is the platform-system and experimental conditions used, details of the vestibular ablative procedures using aminoglycosides [14] and the prototype prosthesis (a one-dimensional, right posterior semicircular canal prosthesis) described in [16].

A. Animal Justification

The advantage to using animal models/test subjects (e.g., rhesus monkeys) for the experiments described were that they had the potential to serve as their own control, as opposed to human studies where normal and severe vestibular-loss patients were different individuals. By investigating the posture of animals in normal, mBVH, and sBVH, as well as a sBVH + STIM-ON states, it would allow us to establish a database on the effects of different levels of vestibular function on posture for non-human 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 non-human primate test subjects allowed for more degrees-of-freedom in that 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 us to characterize postural responses for varied levels of vestibular function. It also allowed us to further develop the prosthesis itself, prosthesis implantation procedures, and postural characterization of the prosthesis [16]. By developing this knowledge base in non-human primates, this decreases the possible risks and enhances the potential benefits associated with current/future implementation of the invasive prosthesis in humans.

B. Equipment Descriptions

Animals were trained to freely-stand on the balance platform in order to receive juice reward. 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 hindtrunk 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 and side of the animal to record: 1) animal behavior and 2) human handling artifacts within a given test session.

C. Experimental Test Conditions

The stationary platform allowed for changes of the base-of-support and also of the support surface material (quiet stance experiment). 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).

<u>Quiet stance:</u> 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. 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.

<u>Head turns to Illuminated Targets:</u> A stationary platform condition more difficult than quiet stance was head turns to illuminated targets. In this research, we investigated the effects of four different levels of head-in-space (vestibular) information on trunk sway 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 counter-clockwise in yaw (at 0 (or straight ahead), 40, 60, 90^{o}) and ~40^{o} oblique (i.e., in the plane of the prosthesis-implanted, right-posterior canal). Measured output responses were the head and trunk movements of the animal.

<u>Pseudorandom Roll-Tilt Stimulus:</u> Stabilizing on a tilting balance platform was test condition even more difficult than the stationary platform conditions above. 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 (e.g. pseudorandom ternary sequence (PRTS) stimulus), has been used as an input perturbation stimulus for human normal and vestibular-loss subjects (e.g., [10]). 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/behavioral focus in animals, and also allow a bandwidth of frequencies (in our case 0.0625-2.23 Hz) were tested 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, 1, 4, 6, and, 8^{o} p-p.

RESULTS & DISCUSSION

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 [15], as well as for head turns in the normal, mBVH, sBVH, and sBVH + STIM-ON states [16]. The animal's postural responses to the PRTS stimulus are currently submitted and under review. However, we summarize the results of each briefly below.

Through use of the quiet stance condition, we observed that the severity of the vestibular dysfunction affects postural compensation. For stationary support-surface conditions (e.g., quiet stance and head turns), we observed that 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 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 [15].

From the head turn experimental condition, we observed that for the 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, we observed that trunk sway was reduced (stability increased) for the sBVH + STIM-ON state [16]. For the head turn condition, the observation that trunk sway stability was increased in the sBVH + STIM-ON state compared to the sBVH state indicate that further human and non-human 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 non-human primate animal model. 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 towards human implementation.

CONCLUSION

The main purpose of this paper was to display an overview of the utility and importance for studying non-human primate postural control for different levels of vestibular function using our newly-developed platform-system techniques. The use of this system allows us to begin to establish the 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 platform-system discussed here aids in establishing the baseline measures of non-human 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.

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