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Research article

Nondestructive and objective assessment of the vestibular function in rodent models: A review

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ABSTRACT

The normal function of the vestibular system is crucial for the sense of balance. The techniques used to assess the vestibular function plays a vital role in the research of the vestibular system. In this article, we have systematically reviewed some popular methods employing vestibular reflexes and vestibular evoked potentials for assessing the vestibular function in rodent models. These vestibular reflexes and vestibular evoked potentials to effective stimuli have been used as nondestructive and objective functional measures.

The main types of vestibular reflexes include the vestibulo-ocular reflex (VOR), vestibulocollic reflex (VCR), and vestibulo-sympathetic reflex (VSR). They are all capable of indicating the functions of the semicircular canals and otoliths. However, the VOR assessment is much more prevalently used because of the relatively stereotypical inputoutput relationship and simple motion pattern of the ocular response. In contrast, the complicated motion pattern and small gain of the VCR response, as well as the undesired component possibly contributed from the acceleration receptors outside the labyrinths in the VSR response, restrict the widespread applications of VCR and VSR in the assessment of the vestibular system. The vestibular evoked myogenic potentials (VEMPs) and vestibular sensory evoked potentials (VsEPs) are the two typical evoked potentials that have been also employed for evaluating the vestibular function. Through exploiting different types of the VEMPs, the saccular and utricular functions can be evaluated separately. The sound-induced VEMPs, moreover, are capable of noninvasively assessing the unilateral vestibular function. The VsEPs, *via* the morphology of their signal waveforms, enable the access to the location-specific information that indicates the functional statuses of different components within the vestibular neural pathway.

1. Introduction

The vestibular function plays an indicative role in understanding and monitoring the physiological status of the vestibular system. Hence, the assessment of the vestibular function is highly demanded in the vestibular research relevant to the fields of pharmacology [1,2], toxicology [3,4], pathology [5,6], and genetics [7,8]. At present, the main methods used for assessing the vestibular function in the preclinical studies include the morphological examinations, gross behavioral tests, and analysis of the vestibular sensory outputs.

The morphological examinations exploit microscopic imaging techniques to characterize the alterations in the structure and composition of the vestibular organs at various scales, from the macro (*e.g.*, hair cells) to the subcellular (*e.g.*, stereocilia) level [9,10]. However, because the morphological examinations typically require animal sacrifice and tissue harvest, its application in the *in vivo* environment is severely limited and even precluded. The gross behavioral tests are usually performed through a test battery, by which the responsive behaviors of the animals can be noninvasively measured [11,12]. However, since the analysis and quantification of the test results largely depend on manual processes, the objectiveness of the method is thus compromised.

The vestibular sensory outputs include the vestibular reflexes and vestibular evoked potentials. Under applied stimuli, these outputs exhibit responses that can serve as objective and quantitative measures to the vestibular function [13–17]. Moreover, some of the responses

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contain location-specific information that indicates the functional statuses of different components within the vestibular neural pathway [18,19]. Therefore, the vestibular sensory outputs are currently considered as excellent tools for assessing the vestibular function *in vivo*. In this article, we have systematically reviewed the applications of the vestibular sensory outputs in assessing the vestibular function of the laboratory animals. As rodent models are the predominant animal models used in the vestibular research [20,21], this review has focused primarily on the studies involving rodents.

2. Vestibular reflexes

The vestibular reflexes consist of the motor- and sympathetic-related reflexes, which act as the bases of the stimulation-evoked responses of the motor systems and sympathetic network, respectively. As the stimuli activating these reflexes include the rotational and linear accelerations, these reflexes are able to examine the functional statuses of the rotational- and linear-acceleration sensors (*i.e.*, the semicircular canals and otoliths) within the vestibular system. The motor-related reflexes employed in the vestibular-function assessment include mainly the vestibulo-ocular reflex (VOR) [13] and vestibulocollic reflex (VCR) [14]. The sympathetic-related reflex used for evaluating the vestibular function is the vestibulo-sympathetic reflex (VSR) [15].

Comparing with the VCR and VSR, the VOR is much more prevalently used in the assessment of the vestibular function. This is because: (1) the input-output relationship of VOR is relatively stereotypical, which significantly reduces the complexity of the data interpretation; (2) the VOR response is attributed to the eye movement, which shows a relatively simple trajectory and thus is easy to record, quantify, and analyze automatically. Due to the complicated motion pattern and small gain of the VCR response, the popularity of the VCR in the vestibular-function assessment is negatively affected. The VSR-based assessment, in addition, suffers the interferences brought by those acceleration-sensitive receptors (*e.g.*, baroreceptors) and reflexes (*e.g.*, cardiopulmonary reflex) outside the labyrinths.

The following sections provide more detailed information about the applications of these vestibular reflexes in assessing the vestibular function.

2.1. VOR

The VOR, relying upon the vestibular projection to the extraocular muscles, is one of the gaze-stabilizing mechanisms in vertebrates. The retinal slip of the visual image during an acceleration-driven head movement can be minimized by the VOR-induced compensatory eye movement. Therefore, the VOR eye movement is always in an opposite direction of the head movement. Furthermore, the eye-movement amplitude is positively correlated to the head-movement amplitude and thus the stimulus intensity [22,23]. Such a stereotypical relationship between the VOR response and the acceleration stimulus allows straightforward interpretations of the acquired VOR data.

The VOR can be classified as the angular VOR (aVOR) and translational VOR (tVOR), which are respectively activated by the rotational and linear accelerations [24]. The aVOR is more commonly employed since the generation and control of the rotational-acceleration stimuli are practically easier in laboratories [25,26]. The activation of the tVOR is usually conducted by involving the gravity effect into the rotational acceleration stimuli or introducing sufficiently large centrifugal force in an eccentric rotation [27,28].

A typical stimulation setup producing rotational accelerations for the aVOR activation is comprised of a motor, a turntable, and an animal restrainer. The animal is restrained on the turntable in a prone position, with the head located at the rotation centre, to undergo the aVOR generation and acquisition. The motor drives the turntable to rotate about an earth-vertical axis (Fig. 1 A). The rotational acceleration, subsequently, is produced and delivered to the labyrinths of the animal [29,30]. Since no linear acceleration is involved in the stimuli, only the function of the semicircular canals is examined with this setup.

By changing the earth-vertical rotation axis to a horizontal or tilted direction, the gravity effect can be involved during the rotation. In the case that the rotation axis is in the horizontal plane, a pitch (when the rotation axis is perpendicular to the sagittal plane of the animal) or roll (when the rotation axis is perpendicular to the transverse plane of the animal) of the animal may be induced [27,31]. In the case that the rotation axis is neither horizontal nor vertical, an off-vertical axis rotation (OVAR) is conducted [32]. The eccentric rotation of the animal can be exerted by shifting the rotation axis from the centre to the outside of the animal's head. Non-gravity linear acceleration stimuli derived from the significantly elevated centrifugal force, subsequently, will be received by the animal [28]. As all the stimuli provided by the pitch, roll, OVAR, and eccentric rotations have the linear-acceleration component, the indicative information about the otolithic function can be obtained through measuring the VOR responses under these rotations. Recently, an effective simulation of the pure linear acceleration based on the combination of two horizontal rotations in the opposite directions has been reported by Armstrong and the colleagues [33]. With this stimulus, the otolithic function can be specifically examined without activating the semicircular canals.

The intrinsically simple motion pattern of the eye movements makes the automated quantification and analysis of the VOR response practically straightforward. The commonly employed techniques for detecting the VOR response include the video-oculography (VOG) [29,30,34], search-coil method [35,36], and electro-oculography (EOG) [37]. The VOG is capable of tracking the eye movements through the infrared video recording (Fig. 1 A), followed by the automated data analysis based on the video-processing algorithms. The search-coil method is reliant upon the coils implanted in the scleras of the animal, as well as an externally applied electromagnetic field. The eye movements can be characterized by profiling the changes in the induced coil voltage. The EOG, employing multiple subcutaneous electrodes around the eye, tracks the eye movements *via* the measured changes in the cornea-retina potential. Because of the high efficiency and noninvasive nature, the VOG is the most prevalent technique used for the VOR-response detection. The widespread applications of the search-coil method and EOG in detecting the VOR response are restricted mainly by their laborious procedures for placing the electrodes and calibrating the setups.

2.2. VCR

The VCR is another mechanism responsible for the gaze stabilization. *Via* the vestibular projection to the cervical muscles, the VCR is able to trigger the compensatory head movement to stabilize the visual field in the presence of sensible acceleration stimuli [14,38,39]. Similar with the VOR response, the VCR response is generated mainly by the rotational and linear accelerations. Therefore, the stimulation setup for the VCR activation is almost the same as that for the VOR activation. The only difference exists in the animal restrainer. The animal restrainer used in the VCR setup must ensure that the tested animal can freely move the head during the entire experiment; while the animal restrainer used in the VOR setup must guarantee a firmly immobilized animal head [14,40,41].

As the VCR involves highly sophisticated circuitry and musculature, the VCR response shows a more complicated motion pattern than the VOR response. As a result, the video-recording techniques become insufficient for accurately capturing the VCR response. Instead, the search-coil method is considered as the most preferable head-tracking technique for the VCR-response detection. With the coils affixed on the animal's scalp and the external electromagnetic field, the responsive head movement can be profiled by the varying induced coil voltage [40,42].

The VCR responses acquired from rodents usually have very small

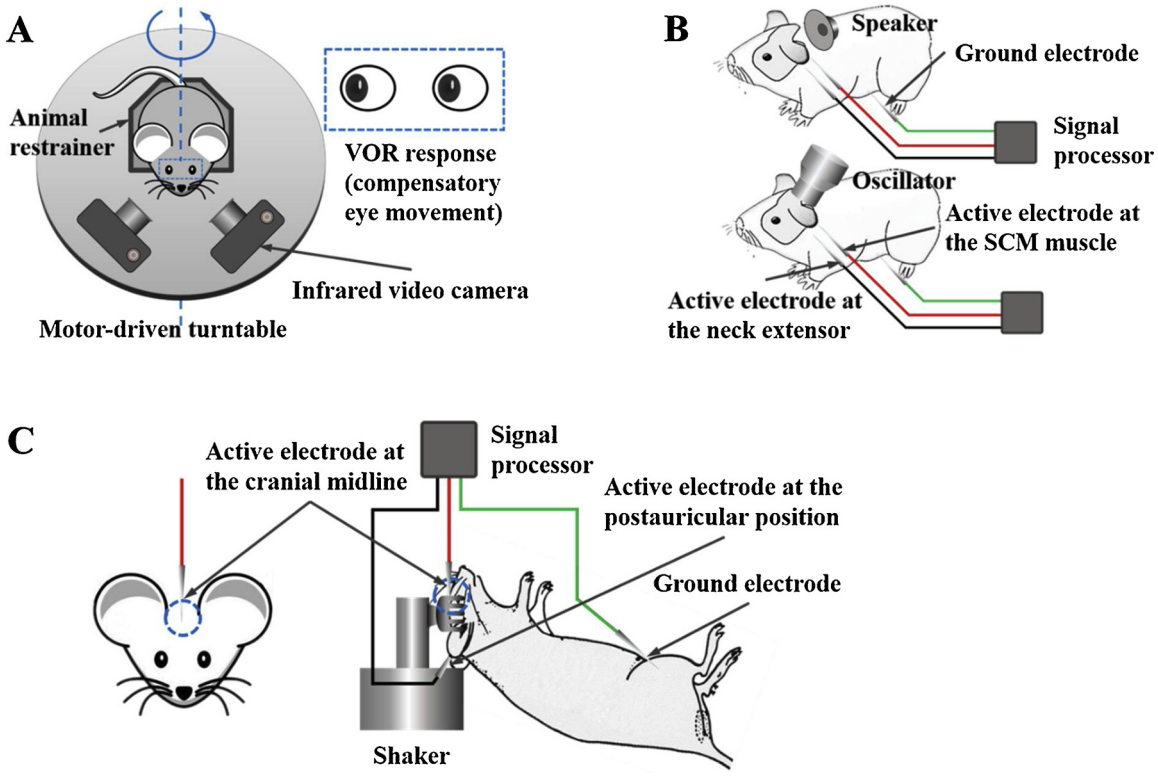

Fig. 1. (A) The setup for generating and detecting the VOR (specifically, aVOR) response in rodents (mice). The stimulus is the rotational acceleration in the horizontal plane; the detection method is the VOG. **(B)** The setup for evoking and collecting the VEMPs in rodents (guinea pigs). The stimuli are ACS (delivered by the speaker) and BCV (delivered by the oscillator). The collection is performed with the electrodes. SCM: sternocleidomastoid. **(C)** The setup for evoking and collecting the VsEPs in rodents (adopted from the Fig. 1 in [19] with permission). The stimulus is the linear acceleration (delivered by the shaker). The collection is performed with the electrodes.

gains. Therefore, the sensitivity and reliability of the vestibular-function assessment using the VCR in rodents are significantly reduced. Two possible reasons leading to the small VCR-response gains in rodents have been proposed. The first one is the intrinsically greater inertia of the rodent head than the eyes. The second one is the much more robust ocular motility in mammals, including the rodents. Such robust ocular motility results in a remarkable suppression of the VCR response by the concurrently induced but more predominant VOR response under the acceleration stimuli [14,40,41,43,44].

2.3. VSR

The VSR plays an important role in maintaining steady levels of the blood pressure, heart rate, and respiratory frequency during body motions. When the vestibular sensors are effectively stimulated, the VSR is systematically triggered to regulate the responsive activities of the relevant muscles in the circulation and respiration systems [45–48]. The functional statuses of the vestibular sensors can be examined through studying the detectable sympathetic responses.

When using the accelerations to activate the VSR, some sympathetic-related receptors (*e.g.*, baroreceptors) and reflexes (*e.g.*, cardiopulmonary reflex) outside the labyrinths are also concurrently activated [49–52]. As a result, the detected sympathetic responses may contain undesired non-vestibular contributions. By comparing the detected results before and after the deactivation of the vestibular systems, the interference from these non-vestibular sympathetic responses can be eliminated. For doing this, however, invasive and laborious surgical operations are then necessary [53–55].

Electrical stimulations (*e.g.*, galvanic vestibular stimulation, GVS) are also capable of giving rise to the VSR responses [56,57]. In comparison to the accelerations, the electrical stimuli evoke mainly the vestibular ascending pathway instead of the vestibular organs. Hence, the electrical stimulation methods are practically capable of testing the function of the vestibular ascending pathway. However, denervation surgeries are required to block the non-labyrinthine inputs under the electrical stimuli [51]. Moreover, the vestibular afferents responsible for the accelerations in various directions are always simultaneously activated when the electrical stimuli are employed [53]. This leads to a poor directional specificity of the VSR responses resulted from the electrical stimuli.

The VSR response in rodents can be detected through measuring either the changes in the blood pressure or the activities of the sympathetic nerves. The blood-pressure measurement is usually performed by inserting a catheter probe into the abdominal or femoral artery of the animal [52,58]. The measurement of the sympathetic-nerve activities requires microsurgeries to isolate the nerve endings and place the recording electrodes. In addition, it is usually required to measure the sympathetic-nerve activities from a variety of sites all over the body for an integrated analysis. This is because the VSR responses are anatomically patterned [53].

3. Vestibular evoked potentials

The main types of the vestibular evoked potentials include the vestibular evoked myogenic potentials (VEMPs) and vestibular sensory evoked potentials (VsEPs). The VEMPs are generated *via* the vestibular projections to the motor nuclei in particular skeletal muscles; while the VsEPs are derived from the vestibular projections to the specific sites of the nervous system [59–63]. Both of the potentials are commonly employed for assessing the vestibular function in preclinical vestibular research.

The VEMPs, when employed as an assessment tool, possess two

substantial advantages: (1) the functions of the two types of otoliths (*i.e.*, the saccules and the utricles) can be separately evaluated using the VEMPs; (2) noninvasive unilateral examination of the otolithic function can be enabled by the VEMPs [59,60]. The VsEPs are particularly useful when probing the functional statuses of different components within the vestibular neural pathway, as the location-specific information can be revealed from the waveforms of the VsEP signals [18,19].

The applications of the VEMPs and VsEPs in the assessment of the vestibular function are presented and discussed in the following sections.

3.1. VEMPs

The cervical VEMPs (cVEMPs) and ocular VEMPs (oVEMPs) are two main types of the VEMPs. The cVEMPs are the events of the VCR pathway and collected from the sternocleidomastoid muscles; in comparing, the oVEMPs are the events of the VOR pathway and collected from the extraocular muscles [59,64,65]. Physiological studies have shown that the cVEMPs and oVEMPs are evoked by the activations of the saccule and utricle, respectively [60,66,67]. Therefore, the saccular and utricular functions can be separately evaluated through analyzing the evoked signals of the corresponding type of VEMPs.

Although the accelerations and GVS are also capable of evoking VEMPs [68,69], the major types of the stimuli employed to generate VEMPs in laboratories are the air-conducted sound (ACS) and bone-conducted vibration (BCV) (Fig. 1 B). Because the BCV-evoked VEMPs are more robust than the ACS-evoked ones, the BCV is usually more preferable than the ACS, especially when the vestibular hypofunction potentially exists. However, when specifically evaluating the saccular function using the cVEMPs, the ACS is the better stimulus because the BCV may introduce undesired activation of the utricle [70,71]. In addition, the ACS allows noninvasive unilateral stimulation since the stimulating sound can be delivered separately and asymmetrically to the bilateral labyrinths. This merit of the ACS-evoked VEMPs enables unilateral assessment of the otolithic function [72,73].

There are two methods reported in the literatures for detecting the VEMP signals in rodents. The first one is to measure the myogenic potentials from specific muscles (*i.e.*, sternocleidomastoid or extraocular muscles). The second one is to record and analyze the action potentials from single neurons. The measurement of the myogenic potentials may be performed on either alert or anaesthetized animals [74–78]. Because such a measurement requires a constantly contractive status of the corresponding muscles, it is necessary to firmly restrained the animal in a prone position with its head elevated and neck hyperextended when performing this measurement on an alert animal [74]; while decerebration of the animal at the intercollicular level is needed when performing this measurement on an anaesthetized animal [75]. The single-neuron spikes are recorded extracellularly using the microelectrodes, followed by the computational analysis. Microsurgery is required for the precise placement of the microelectrodes over the vestibular afferents.

3.2. VsEPs

The VsEPs, as an analogue to the acoustic brainstem responses, are sourced from the nuclei of the ascending vestibular pathway. The functional status of each component within the pathway can be indicated through the morphological features of the VsEP signal waveforms. In the short-latency VsEPs acquired from mammals and avians, for instance, the first positive and negative peaks represent the activity of the vestibular nerve. Hence, the peripheral vestibular function can be indicated by the amplitudes and latencies of these two early peaks. The second positive peak carries the information of both the peripheral and central vestibular functions. The later peaks are primarily attributed to the neural activities within the central relays [18,19,79,80]. The waveforms of the middle- and long-latency VsEP signals also contain the location-specific information. However, they are not used very often in current vestibular research, owing to a lack of thorough understanding of the physiological significance of the waveform components [81–83].

Both the rotational and linear accelerations are capable of evoking the VsEPs. Therefore, the VsEPs are used for assessing the functions of both the otoliths and semicircular canals. Furthermore, because the VsEP signals are typically collected from animals under anaesthesia, the immobilization status of the animals makes the VsEP measurement practically easier. The linear accelerations for evoking the VsEP signals are usually provided by a shaker, which is connected with the animal's head to deliver the stimuli (Fig. 1 C) [19,84]. The rotational accelerations are often produced using a motor-driven turntable that carries the animal during the experiment [81,85,86]. Besides the accelerations, the ACS and BCV have been also employed as effective stimuli for evoking VsEPs [87,88]. The VsEP signals are, typically, collected *via* the subcutaneous electrodes placed on the animal's scalp (Fig. 1 C).

4. Conclusion

This article systematically reviewed the preclinical applications of the vestibular sensory outputs for assessing the vestibular function. Through analyzing the vestibular-reflex responses and/or vestibular evoked potentials under stimulation, the vestibular function can be objectively and quantitatively evaluated *in vivo*. Among the vestibular reflexes, the VOR is more prevalently employed than the VCR and VSR in the assessment of the vestibular function due to two merits of the VOR: (1) the relatively stereotypical input-output relationship; (2) the simple motion pattern of its response. The VEMPs and VsEPs are the main types of the vestibular evoked potentials used for the vestibular-function examination. With the VEMPs, the saccular and utricular functions can be separately evaluated by measuring the cVEMPs and oVEMPs, respectively. The ACS-induced VEMPs, specifically, are capable of noninvasively examining the unilateral vestibular function. The VsEPs, *via* the morphology of their signal waveforms, are able to offer the location-specific information indicating the functional statuses of various components within the vestibular neural pathway. The advantages and disadvantages of these assessment tools have been summarized in Table 1.

Table 1
The advantages and disadvantages of the vestibular sensory outputs in assessing the vestibular function.

	Advantages	Disadvantages
VOR	(1) Stereotypical input-output relationship; (2) Simple motion pattern of the response;	
VCR		(1) Complicated motion pattern of the response; (2) Small gain of the response;
VSR		Interferences from the non-vestibular inputs;
VEMPs	(1) Separate assessment of the saccular and utricular functions; (2) Noninvasive assessment of the unilateral vestibular function;	
VsEPs	Access to the location-specific information indicating the functional statuses of different components within the vestibular neural pathway;	

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