Ocular vestibular evoked myogenic potentials to bone conducted vibration of the midline forehead at Fz in healthy subjects

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Abstract

Objective: To provide the empirical basis for using ocular vestibular evoked myogenic potentials (oVEMPS) in response to Fz bone conducted vibration (BCV) stimulation to indicate vestibular function in human subjects. To show the generality of the response by testing a large number of unselected healthy subjects across a wide age range and the repeatability of the response within subjects. To provide evidence that the response depends on otolithic function.

Methods: The early negative component (n10) of the oVEMP to brief BCV of the forehead, in the midline at the hairline (Fz) is recorded by surface EMG electrodes just beneath the eyes. We used a Bruel and Kjaer 4810 Mini-Shaker or a light tap with a tendon hammer to provide adequate BCV stimuli to test a large number (67) of unselected healthy people to quantify the individual differences in n10 magnitude, latency and symmetry to Fz BCV. A Radioear B-71 bone oscillator at Fz is not adequate to elicit a reliable n10 response.

Results: The n10 oVEMP response showed substantial differences in amplitude between subjects, but is repeatable within subjects. n10 is of equal magnitude in both eyes with an average asymmetry around 11%. The average n10 amplitude for Mini Tone Burst BCV is 8.47 μV ± 4.02 (sd), the average latency is 10.35 ms ± 0.63 (sd). The amplitude of n10 decreases and its latency increases with age.

Conclusions: oVEMPs are a new reliable, repeatable test to indicate vestibular and probably otolithic function.

Significance: This study shows the optimum conditions for recording oVEMPs and provides baseline values for individual differences and asymmetry. oVEMPs can be measured in senior subjects without difficulty.

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1. Introduction

Myogenic potentials evoked by air conducted sound (ACS) or bone conducted vibration (BCV) stimuli can be recorded with surface electrodes over contracted sternocleidomastoid muscles (SCM) (Colebatch et al., 1994; Halmagyi et al., 1995; Welgampola, 2008, for a review). Physiological and clinical evidence shows that these...
myogenic potentials are of vestibular origin and so these potentials are called vestibular evoked myogenic potentials (VEMPs). It is now clear that since the vestibular system has projections to many muscle systems, there are many such VEMPs. To specify matters more precisely we propose that the potentials recorded over SCM should be called cervical VEMPs or cVEMPs. cVEMPs are probably generated by otolithic saccular receptors and afferents primarily in the inferior vestibular nerve, since saccular afferents in the cat and guinea pig are located in the inferior vestibular nerve (as in humans (de Burlet, 1929)) and in these species saccular receptors and irregular afferents are activated at short latency by ACS (McCue and Guinan, 1994; Murofushi et al., 1995; Murofushi and Curthoys, 1997). Saccular afferents act via inhibitory neurons in the vestibular nuclei to inhibit cervical motoneurons (Uchino et al., 2005). cVEMPs have become a widely used clinical test of human inferior vestibular nerve and vestibulo-collic function (Welgampola et al., 2003; Welgampola and Colebatch, 2005; Halmagyi et al., 2005) and recent studies in the monkey (Tsubota et al., 2007) have further confirmed the above interpretation.

New physiological evidence has appeared for vestibular and indeed specifically otolithic activation by BCV stimulation. In a study of the responses of 346 primary vestibular afferents in the guinea pig, it was found that BCV at low stimulus levels preferentially activates one class of primary vestibular afferents — irregular otolithic neurons — as opposed to regular otolithic neurons or neurons (regular or irregular) from semicircular canals (Curthoys et al., 2006). It was found that the latter were rarely activated by BCV even up to the maximum stimulus levels used. Irregular otolithic neurons supply predominantly the striola region of the maculae and are sensitive to changes in linear acceleration (jerk) (Fernandez and Goldberg, 1976; Goldberg, 2000). BCV activated some utricular receptors and afferents because some activated neurons were located in the superior vestibular nerve (where all utricular afferents course (de Burlet, 1929)) and tracing of juxtacellular stained neurons which had been activated by BCV showed that some of these activated neurons originated from around the striola of the utricular macula (Curthoys et al., 2006). This highly selective pattern of primary neural activation implies that human responses to BCV indicate otolithic function and, more specifically, the function of otolithic neurons from the striola of the otolithic maculae. Other evidence shows that stimulation of otolithic afferents results in eye movements (Suzuki et al., 1969; Curthoys, 1987).

Recently, Rosengren et al. (2005) and Todd et al. (2007) reported that in some selected subjects small, short latency (10 ms), negative evoked myogenic potentials can be recorded by surface electrodes around the eyes in response to BCV of the mastoid by short tone bursts (7 ms, 500 Hz) delivered by a standard clinical bone oscillator (a Radioear B-71, New Eagle Pennsylvania). They termed these potentials oculomotor vestibular evoked myogenic potentials (oVEMPs). The oVEMP to a brief stimulus consists of a number of potentials but it is the earliest negative peak, at around 10 ms, (n10) which is of greatest interest. Rosengren et al. (2005) found that this n10 component is present in patients without hearing and absent in patients with hearing but without vestibular function. The latter components of the oVEMP can be affected by instructions, so greatest interest has focussed on the n10 component. Since the n10 component to mastoid stimulation is negative it reflects excitation (Colebatch and Rothwell, 2004), and this is probably caused by peripheral vestibular stimulation resulting in activation of eye muscles because the myogenic potentials occur before the eye starts to move (Todd et al., 2007).

Iwasaki et al. (2007) reported oVEMPs from unselected subjects measured by surface electrodes under the eyes to relatively powerful BCV at Fz, using a tendon hammer or a Bruel and Kjaer 4810 Mini-Shaker to deliver the stimuli. They reported that if the forehead of a subject who is lying supine and looking upwards (toward the top of their head) is given Fz BCV stimulation then short latency (8-10 ms) negative surface potentials (n10) similar to those reported by Rosengren et al. (2005) are recorded from beneath the eyes. In the few healthy control subjects reported by Iwasaki et al. (2007), the n10 to Fz BCV stimuli were about equal in amplitude and latency for both eyes, but results from only 9 subjects were reported and one aim of the present study was to quantify the magnitude of the average n10 response and its symmetry in the two eyes of a large number of unselected healthy subjects.

Importantly, when Fz BCV stimulation is given to patients with known unilateral vestibular loss (UVL patients) the n10 component indicates the side of loss: n10 is absent or greatly reduced beneath the eye on the side contralateral to the unilateral vestibular loss (Iwasaki et al., 2007). Other studies had earlier reported that oculomotor potentials to bone conducted stimuli may indicate the side of unilateral vestibular loss (Jombik and Bahyl, 2005a,b).

In this study, we sought to provide the empirical basis for using oVEMPs in response to Fz BCV stimulation to indicate vestibular, and indeed otolithic, function in human subjects and patients. For Fz BCV, we sought to establish the optimum conditions for recording the n10 potential of the oVEMP and to provide evidence: (1) that the 4810 Mini-Shaker does elicit a usable n10 potential in all subjects without selection, (2) that the n10 to Fz BCV stimulation is repeatable within a subject, (3) to provide baseline data concerning the extent of individual differences in n10 magnitude, latency and asymmetry and the dependence of these on age, (4) to further confirm that n10 is of vestibular origin, and (5) to identify the optimum conditions for recording oVEMPs. The asymmetry ratio (AR) for the n10 to Fz BCV stimuli in a large group of healthy asymptomatic subjects was calculated by comparing the magnitude of the n10 response in the left and right eyes (using the standard formula for a vestibular asymmetry ratio = ((larger – smaller)/(larger + smaller)) × 100). To verify further
that n10 to Fz BCV was vestibular we tested patients without vestibular function, but remaining hearing and normal facial nerve functioning. Following Rosengren et al. (2005) we hypothesized that it is probably mainly the inferior oblique which generates the n10 to Fz BCV stimulation. That hypothesis was tested by measuring n10 to Fz BCV stimuli but with different eye positions; looking up, straight ahead and down. Looking up acts to bring the belly of the inferior oblique close to the surface electrodes beneath the eyes and so we expected larger oVEMPs looking up compared to looking straight ahead or looking down.

Since the optimum stimulus waveform for Fz BCV to elicit n10 is still not clear, we used a number of stimulus waveforms; a tap at Fz with a reflex hammer (Tendon Hammer Tap = TH tap), a condensation pulse (Mini Tap+), a short tone burst of 500 Hz lasting 6 or 7 ms (Mini Tone Burst MTB). A rarefaction pulse (Mini Tap−) was also used but the n10 in response to the MT-stimulus includes an additional delay due to the mechanical operation of the 4810. Reversing the polarity of the command voltage adds a significant mechanical delay while the metal armature in the 4810 is first withdrawn and then driven towards the skull. This mechanical delay is of the order of milliseconds and so the latency of n10 for MT− stimuli appears to be much longer than latencies for MT+. Because of this mechanical delay we have not included latency data from MT−. The command voltage for the pulses was an 0.1 ms square wave. Small lightweight (1 g) custom-made triaxial linear accelerometers (ADXL311) were used to measure the linear acceleration at the mastoids.

2. Methods

All procedures were in accordance with the Helsinki declaration and were approved by the University of Sydney Human Ethics Committee or the University of Tokyo Human Ethics Committee. A total of 67 normal healthy subjects were tested with informed consent: 26 male, 41 female; age range 20–83 years, average age 47 years. None of the normal subjects reported any auditory, vestibular, neurological or visual problems (apart from standard refractive errors).

Five patients with bilateral vestibular loss, including three patients with vestibular loss due to systemic gentamicin and two with idiopathic vestibular loss, were tested. The patients had little or no caloric responses, and showed corrective saccades to positive horizontal head impulses, had absent cVEMPs and so it was presumed that most vestibular receptors had been rendered dysfunctional.

Subjects lay supine on a bed with their head supported on a pillow but positioned so that the head was horizontal or pitched slightly nose down. After thorough cleaning of the skin beneath the eyes with alcohol wipes, surface EMG type electrodes were applied to record the responses from beneath both eyes. For each eye, the active (+) self-adhesive recording electrode (Cleartrace 1700-030, Con-
recordings and so asymmetric oVEMPs. It was important that the magnitude of the EMG was equal in both eyes. If these conditions were not met the electrodes were removed and the skin was re-cleaned and the electrodes replaced.

2.2. Stimuli

The stimuli were either (1) tendon hammer (TH) taps delivered manually at Fz by a small tendon reflex hammer with a flexible shaft (Keeler, London) at a rate of about 1 per 2 s. The hammer was fitted with an inertial micro-switch which triggered the sweep of the averager, or (2) tone bursts lasting 6 ms delivered either by a Radioear B-71 bone conduction oscillator (Radioear, New Eagle, Pennsylvania) or (3) stimuli by a hand-held Bruel and Kjaer (Naerum, Denmark) Mini-Shaker 4810, fitted with a short bolt (2 cm long, M4) terminated in a bakelite cap 1.5 cm in diameter which was the contact point for the stimulator on the subject’s forehead at Fz. The 4810 was driven by computer-generated signals (condensation square waves of 0.1 ms duration (Mini Tap+ = MT+)) or brief shaped 500 Hz tone bursts, lasting a total of 7 ms including a 2 ms rise and 2 ms fall with a zero crossing start (Mini Tone bursts = MTB). In some cases, tone bursts of 6 ms duration were used without any detectable difference. The peak acceleration was about 20 g and the repetition rate was 3/s. To ensure subject safety, the subject always felt the stimulus with their finger prior to having the stimulator placed on their forehead and agreed to the stimulus being applied. The stimuli were small and no subject declined a stimulus, but it was not possible to test all subjects with all stimuli. The Mini-Shaker weighs approximately 1 kg and the weight of the shaker was used to standardize the force used in all subjects. It was hand-held but the operator simply maintained its near-vertical orientation, and did not force the shaker against Fz. To minimize electrical artifacts, the case of the Mini-Shaker was shielded and the Mini-Shaker signal leads were shielded and connected to power ground. Flexible shielded cable was used for the electrode leads and these latter shields were led to the ground electrode on the subject.

The tendon hammer (TH) was fitted with an inertial microswitch that produced a pulse for triggering the averager after a delay of about 3.5 ms from the moment that the hammer made contact with the head (as shown by separate measurements of the TH tap stimulus by a miniature accelerometer bonded to the hammer). Because of that delay, the latencies of the raw recorded responses appear to be shortened by 3.5 ms. In the figures, we have shifted the records for the TH taps later by the 3.5 ms so that the latencies of the responses to TH taps can be compared directly to the responses to the other stimuli.

In some experiments we measured the linear accelerations at both mastoids using two custom-made triaxial miniature linear accelerometers. Each one was comprised of two dual axis Analog Devices ADXL311 miniature sur-

face mount accelerometers, cemented together and embedded in Araldite to make a package 9 mm × 8 mm × 11 mm and weighing 1 g. This triaxial accelerometer had broad bandwidth (dc-6 kHz). The triaxial accelerometers were taped to the person’s mastoid at approximately 2.5 cm above and 3 cm posterior to the acoustic meatus, approximately level with the top of the pinna using double-sided tape and then held in place using medical adhesive tape. We also used similar single axis or double axis Analog Devices accelerometers to measure the acceleration of the tendon hammer and the Mini-Shaker, respectively.

The amplitudes of all myogenic potentials were measured from baseline to peak. The onset of the response is shown in some of the figures by a short vertical dashed line. The values are expressed below as mean ± standard deviation or ±two-tailed 95% confidence intervals (Winer et al., 1991). The significance level was set at 0.05.

3. Results

3.1. oVEMPs to Fz BCV for different stimulus waveforms

All healthy subjects tested showed oVEMPs in response to Fz BCV stimulation by the tendon hammer or the 4810 Mini-Shaker (see Fig. 2). The BCV from the tap by a reflex hammer or a Brue1 and Kjaer Mini-Shaker 4810 elicits negative/positive EMG responses from both eyes with a latency of around 6–8 ms to the foot of the first negative-going EMG response (n10). The superimposed responses from all 67 subjects are shown in Fig. 2. However, measurable n10 responses were not observed with Fz BCV stimulation in patients with remaining hearing but bilateral vestibular loss (Fig. 3). The Radioear B-71 bone oscillator at Fz is not an adequate stimulus to elicit n10 responses reliably and the tendon hammer TH is not sufficiently controlled, so the following reports focus on the results for stimuli delivered by the Mini-Shaker. All oVEMP responses were of equal amplitude and similar in shape (Fig. 2) under each eye, although the amplitudes varied very considerably from person to person (see Fig. 4). oVEMPs always began with an initial negative–positive wave (n10). The latencies and the amplitudes of each response are shown in Table 1.

3.2. Effect of bilateral vestibular loss

Five patients with bilateral vestibular loss were tested. These patients had no evidence of vestibular function on other tests (ice-water calorics, angular acceleration tests, head impulses, cVEMPs) although they had remaining hearing in both ears and normal blinks. On the basis of this evidence we presumed these patients had probably lost all peripheral vestibular function bilaterally. During the calibration saccades the responses were of normal amplitude and equal in the two eyes but the patients had no detectable oVEMP responses to BCV (Fig. 3). This confirms Rosen-
suggests that oVEMPs are not of auditory origin and are not due to blinks.

### 3.3. Amplitude of n10

Individual records for 3 subjects in response to the stimuli applied at Fz are shown in Fig. 4.

As can be seen in Figs. 2 and 4, the n10 responses were symmetrical in the two eyes and the latencies of the onset of the stimulus were consistent among subjects. In measuring n10 amplitude we sought to be conservative and so we focussed on the very earliest stimulus-locked response and that is from the baseline to the initial peak (n10). Until further work is conducted we cannot be sure about how other factors may affect the much later trough and so contaminate a peak-to-peak measure. Whilst the n10 was present in all subjects, there were considerable differences between subjects in the amplitude of the n10 responses as shown by the individual records for 3 subjects in Fig. 4. The largest amplitude responses were about five times greater than the smallest responses.

Table 1 shows the average amplitude and latency to peak for Mini Tap+, Mini Tone Burst and Tendon...
Hammer Taps. It also shows the range between the smallest and the largest values recorded in healthy subjects. The different stimulus waveforms cause differences in n10 amplitude and latency. For Mini Tap+ the average amplitudes of the n10 potential was 7.68 μV. The average amplitude with the MTB was slightly but significantly larger at 8.47 μV. The average latency to peak for Mini Tap+ was 8.99 ms ± 0.45 (sd) and the average latency to peak for Mini Tone Burst was slightly but significantly longer at 10.35 ms ± 0.63 (sd). The average latency difference to peak between the two eyes was 0.19 ms.

3.4. Repeatability

To examine the within-subject repeatability, oVEMPs in response to Mini-Shaker stimulation were recorded on two occasions. Fig. 4 shows examples from 3 subjects: a female, 25, tested 3 months apart; a female, 39, tested 1 week apart; and a male, 64, tested 2 days apart. The responses are repeatable: in both the first and the second recording sessions the n10 responses were similar in shape and there were no major differences in the amplitudes and latencies of the early negative potentials between them from one occasion to the next, even allowing for the different electrode placements, different stimulator placement and variation in eye muscle tension between tests and during the test.

3.5. Effect of head stabilization

The effect of head stabilization on the n10 was tested on three subjects. It is possible that the stimuli to Fz may generate the oVEMP response by virtue of stimulation of the semicircular canals, for example, if the head were free to move and rotate in pitch around an interaural axis. In this case, a TH tap to the forehead would cause an initial backward angular head rotation in pitch which would activate vertical semicircular canals, resulting in a short latency downward eye movement response. Directly against this possibility is the result that the direction of the eye movement related response which we observed was upward, not downward (Fig. 2). We further tested the idea that canal stimulation is involved by measuring in 3 subjects the n10 to Fz BCV while the subject was restrained by having their head firmly fixed by a board and comparing that

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Amplitude (μV)</th>
<th>Latency (ms)</th>
<th>Differences (ms)</th>
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</thead>
<tbody>
<tr>
<td>Mini Tap+ n = 47</td>
<td>Average 7.68 ± 3.68</td>
<td>8.99 ± 0.45</td>
<td>Range 2.00–18.54</td>
</tr>
<tr>
<td>Mini Tone Burst n = 64</td>
<td>Average 8.47 ± 4.02</td>
<td>10.35 ± 0.63</td>
<td>Range 2.23–19.37</td>
</tr>
<tr>
<td>Tendon Hammer Tap n = 15</td>
<td>Average 7.44 ± 3.78</td>
<td>9.83 ± 0.61</td>
<td>Range 2.46–16.4</td>
</tr>
</tbody>
</table>
to the n10 with the head free. The n10 responses are almost identical head fixed or head free (Fig. 5A), so we consider that canal activation due to angular head rotation is not likely. Furthermore, with head free the same n10 waveform is found for TH stimulation at Fz and also at the inion (the point at the back of the head diametrically opposite Fz). If the n10 had been due to head rotation and so canal activation, these two opposite points of stimulation should have produced oppositely directed head rotations and so presumably different n10s. In fact, the n10s were almost identical for Fz and inion stimulation (Fig. 5B).

3.6. Gaze direction

The effect of vertical gaze direction on the size of the oVEMP response to Fz BCV was tested on five subjects using TH tap, Mini Tap+, Mini TB. For all modes of stimulation changing the direction of gaze markedly affected the amplitude and latencies of the responses in the same way (Fig. 6). Looking upward resulted in a significant increase of the amplitude of the n10 component compared to looking straight ahead ($p < 0.01$). Looking downward markedly decreased or almost abolished the n10 response. For most subjects, the n10 with gaze straight ahead was just detectable above noise level, but by changing gaze position to be looking up, a clear n10 response could be detected (Fig. 6).

3.7. Age

We measured the amplitude of n10 and the latency to peak for each mode of stimulation and the average amplitudes decreased with age and average latency (to peak) increased with age (Fig. 7). However, even in the oldest subject tested (83) a clear n10 was observed and they were symmetrical.

3.8. Symmetry

For healthy subjects, the amplitude of the n10s under the two eyes in response to the Fz stimulus was symmetrical. We used the standard way of calculating an asymmetry ratio ($AR = ((\text{largest} - \text{smallest})/(\text{largest} + \text{smallest})) \times 100$) and for each subject this was calculated for each of the four stimulus modes (MTB, MT+, MT−, TH). The ARs were very similar and so they were averaged and Fig. 8 shows the average AR values for all 67 healthy subjects tested, together with the 95% confidence intervals, the median ratio.
3.9. Measurement of the linear accelerations of the stimulus

3.9.1. At the stimulator

The accelerometer on the tendon hammer showed that a single tap to Fz generated an acceleration, which reached 40g peak in about 2 ms (Fig. 9). Both Mini Tap+ and Mini Tap− generated damped oscillations whose peak amplitudes were about 27g and 21g, respectively. Both the oscillations were damped within 8 ms, which were much longer than the command voltages (0.1 ms). The oscillations generated by Mini Tone Burst lasted for about 12 ms and 9 ms, respectively, which were also longer than the durations of the command stimuli (7 ms) (Fig. 9).

3.9.2. At the mastoids

The peak linear accelerations measured at the skin over the mastoids for Fz stimulation were much smaller than those measured on the stimulators, by a factor of about 100 (Fig. 9). These accelerometers were very securely fixed to the head. In some cases they were cemented to the skin over the mastoid by cyanoacrylate glue (“supaglue”) to ensure very secure fixation. The oscillations in response to the minitaps are due in part to the ringing in the stimulator itself as shown by the accelerometer records from the minishaker shaft, but also from the ringing of the skull.

Fig. 6. Lowering gaze reduces n10 amplitude. The figures show the oVEMPs in response to each mode of the BCV stimulus (TH taps, MT+ and MTB) for a single healthy subject for various directions of gaze: upward (Up), straight ahead (St) and downward (Down). The reduction in n10 amplitude on lowering gaze is found for all Fz BCV stimuli. The dashed vertical lines indicate the foot of the n10 response.

Fig. 7. For MTB there is a significant decrease in n10 amplitude with age (left panel) although the amplitude of n10 in senior subjects is still usable and the test is not at all difficult or taxing on the subject. The significant regression line is shown. Similarly there is a significant increase in n10 latency with age (right panel). For simplicity these figures show the results for MTB but similar results were found for MT+ stimuli. The figures show the means and 95% confidence intervals and the box and whisker plots (right axes) show the median and the quartiles.
They are not due to the accelerometers being insecurely fixed. Measures on 7 different subjects showed differences in amplitude and latency between individuals, but the overall temporal pattern and pattern of relative amplitudes of the X, Y and Z components were similar and mostly symmetrical. For Fz stimuli, the largest and earliest components were in the interaural direction. So a TH tap at Fz causes both mastoids to accelerate outwards simultaneously (Fig. 9) in agreement with earlier observations of bone conducted vibrations (von Békésy, 1960). The attenuation from Fz to the mastoid is about a factor of 100 from Fz \((/C_{24}^{40} \text{g peak})\) to the magnitudes recorded at the mastoid \((/C_{24}^{0.4} \text{g})\), and that attenuation is close to the value found by von Békésy (1960).

4. Discussion

We emphasize that using our moderate intensity Fz BCV stimuli, we could evoke oVEMPs in all normal subjects tested – no selection was necessary. The regular presence of n10 in all unselected healthy subjects we have tested and its high repeatability in response to BCV at Fz within subjects (Fig. 4), given the conditions we have described, shows that the n10 component is repeatable and is a suitable candidate response for a clinical test of otolith function.

In all healthy subjects tested, short duration Fz BCV stimulation elicited short latency potentials from surface EMG electrodes on the skin just beneath the lower eyelids. To optimize the recording of these oVEMPs a powerful stimulator was used and the response was maximized by requiring the subjects to look upward during stimulation.

It is likely that the major contributor to n10 is the inferior oblique because of the electrode placement just beneath the eyes and because looking upward increased the amplitude of the n10 compared to looking straight ahead or down. oVEMPs were repeatable for any given subject, although there was large variability in n10 amplitude across subjects. Given the very considerable differences in skull size, shape, mass and the effect that those parameters must have on the transmission of the vibration, the variability between people is not at all surprising.

4.1. Vestibular origin

Is the n10 to Fz BCV necessarily of vestibular origin? oVEMPs are not due to auditory function because the n10s were found to be present in patients with no hearing but residual vestibular function (Rosengren et al., 2005). That result also excludes the possibility of the n10 being due to the auditory post auricular muscle response (O’Beirne and Patuzzi, 1999). Further confirming the vestibular origin is the result that patients with bilateral vestibular loss, but preserved cochlear function showed no oVEMP response. Although these patients had clear eye movement response to the calibration stimuli, they had no detectable n10 oVEMP responses to Fz BCV (Fig. 3).

Testing control patients confirmed the likely vestibular origin of the n10 to Fz BCV. Just as has been found with mastoid B-71 stimulation, patients with bilaterally absent vestibular function had no measurable n10 to Fz BCV, whereas patients with vestibu lar function but no hearing had oVEMPs (Rosengren et al., 2005).

The n10 is unlikely to be of semicircular canal origin since it is the opposite direction for a probable compensatory eye movement to any backward head angular rotation which would be caused by a tendon hammer tap to Fz. The calibration markers in Figs. 2 and 3 show that it is an upward eye movement which causes a negative potential, whereas the most probable direction for an eye movement to compensate for a head rotation is downward.

These facts

- that the polarity of the n10 corresponds to an upward rather than a downward eye movement (as would be expected from semicircular canal activation)
- the absence of any detectable effect of head stabilization on n10
- and the fact that opposite stimulation points on the head produce the same n10

argue strongly against the possibility that n10 arises from semicircular canal stimulation. These results from human subjects pointing to otolithic origin are in accord with the physiological evidence showing that in the guinea pig bone conducted vibration is an ineffective stimulus for primary semicircular canal afferents, whereas most primary otolith irregular neurons respond vigorously to bone conducted vibration.
The n10 to Fz BCV is not caused by actual vibration of the eye ball (Garcia-Perez and Peli, 2003) because n10 occurs after the end of the vibration stimulus and in patients without vestibular function any vibration of the eyeball would be expected to be similar to that in normal subjects. However, patients with no vestibular function showed no n10 response. It is unlikely that the oVEMP is a tendon reflex of the inferior oblique muscle elicited by the vibration because patients with bilateral loss of vestibular function showed no n10 although their eye muscles were fully functional and they executed the calibration saccades correctly.

4.2. Blinks

The n10 to Fz BCV is not caused by actual vibration of the eye ball (Garcia-Perez and Peli, 2003) because n10 occurs after the end of the vibration stimulus and in patients without vestibular function any vibration of the eyeball would be expected to be similar to that in normal subjects. However, patients with no vestibular function showed no n10 response. It is unlikely that the oVEMP is a tendon reflex of the inferior oblique muscle elicited by the vibration because patients with bilateral loss of vestibular function showed no n10 although their eye muscles were fully functional and they executed the calibration saccades correctly.

4.2. Blinks

The n10 is not a blink or the precursor to a blink. The early component of a blink response (R1) evoked by tendon hammer taps to the glabella has an onset latency of 12.5–14.4 ms (Kimura et al., 1985; Sunohara et al., 1985). The onset latency of the n10 oVEMP response evoked by MT+ or tendon hammer taps to Fz is much shorter at 6.75 ms (see Fig. 5), i.e., about 6 ms earlier than the early R1 component of the blink response. Kugelberg (1952) described how both components of the blink reflex are well developed when tendon hammer taps are applied to the glabella. He reported that when tendon hammer taps are applied to the upper part of the forehead the threshold for evoking a blink response is raised, especially for the early component (R1), and the amplitude of this response is diminished. Taps applied even further away from the eyes to the top of the skull evoke a late component (R2), but the early response (R1) is absent (Kugelberg, 1952). These results explain why we rarely saw blinks or blink-related potentials and they did not affect our measures of
n10. In patients with bilateral vestibular loss the n10 component was greatly reduced or absent (Fig. 3), however, these patients showed normal blink reflexes evoked by tendon hammer taps to the glabella.

Similar considerations negate the possibility that the n10 is due to a reflex of facial muscles; the patients with bilateral vestibular loss had full facial muscle functioning but the n10 was bilaterally absent in patients with bilateral vestibular loss (Fig. 3).

4.3. Later components of the oVEMP

As can be seen in most figures, in addition to the n10 potential, several positive-negative waves occurred at long latencies. Whilst these later waves may also reflect vestibular activation to some extent, we concentrated on the n10 potentials for a number of reasons: (1) in healthy subjects, instructions (“try not to blink”) changed the later potentials but had no detectable effect on n10, (2) because of the likelihood that the later responses could be due affected by other brainstem reflexes, such as cervico-ocular reflex, jaw closure reflex, blink reflex, or postauricular muscle response. The pathways for cervico-ocular reflex and jaw reflexes are polysynaptic and the latencies were much longer than n10 (Desmedt, 1983; Popov et al., 1999).

4.4. The stimulus: linear acceleration caused by BCV

A vibration or tap applied to the head causes waves to travel around and through the head, analogous to seismic waves produced by an earthquake. In the case of the head these waves result in a complex time varying pattern of X, Y and Z accelerations of the head including accelerations outward (Y) at each mastoid (as shown in von Békésy, 1960, p. 130–131, Figs. 6.2, 6.3, 6.4). This is shown by measurements of linear acceleration at the mastoids using subminiature triaxial linear accelerometers in response to taps and vibrations at Fz. These linear accelerations will cause vestibular receptor hair cells to be bent and so activate vestibular afferent neurons. Recordings from primary afferent neurons in the guinea pig show that bone conducted vibration at moderate intensities, indeed selectively activates the neurons responsive to linear accelerations, the otolithic afferents, from both saccular and utricular maculae (Curthoys et al., 2006) whereas bone conducted vibration is ineffective in activating neurons responsive to angular accelerations – the semicircular canal afferents.

The linear accelerations at the mastoids measured using two tri-axial linear accelerometers showed that the accelerations caused by the BCV at Fz were caused by symmetrical acceleration at both mastoids with the largest component being in the interaural direction. During a tap at Fz, the peak acceleration of the reflex hammer is around 40g in 2 ms which is a change in linear acceleration (a peak jerk) of 20,000g/s. Measures with triaxial linear accelerometers on the mastoids showed that there is a considerable attenuation of the force of the hairline tap; only around 1% of the acceleration at the tap location is measured at the skin over the mastoid. When the tap is on the midline our measures showed that both mastoids are stimulated about equally. This is an unusual otolithic stimulus: other linear accelerations do not produce such a stimulus pattern – so, for example, a roll-tilt around a nazo-occipital axis gravity acts to drag otoconia laterally on the otoliths of one ear and medially on the otoliths of the other.

The variability in n10 between subjects is to be expected given the normal range of skull shapes, size, and masses (Tonndorf, 1972). In this study, oVEMPs were symmetrical when stimulating at Fz, in agreement with previous measures of head acceleration which have shown that vibration applied at the midline of the skull spread symmetrically to both temporal bones, while stimulation applied at the temporal bone transmits asymmetrically (von Békésy, 1932; Stenfelt and Goode, 2005). The linear acceleration measured at the mastoid in response to BCV showed high variability in absolute amplitudes but the relative amplitudes of the X, Y and Z components were basically similar across subjects (Fig. 9). This variability of the acceleration may affect the variability of oVEMPs. Anatomical variability of the labyrinth within the skull (Blanks et al., 1975) might also contribute to these variable responses since linear accelerations directed along different axes of the maculae cause different directions of eye movement responses (Hess and Dieringer, 1991).

4.5. oVEMPs and eye movements

In light of these results and in light of recent neural evidence showing the specific activation of otolithic afferents by bone conducted vibration (Curthoys et al., 2006), we suggest that the n10 reflects activation of otolithic receptors of both the utricular and saccular maculae resulting in activation of the contralateral inferior obliques (Iwasaki et al., 2007). The reason for that suggestion is as follows.

We suggest that the Fz BCV stimulus activates specific regions of the otolithic maculae and so results in the oVEMP response. Suzuki et al. (1969) found that unilateral utricular nerve stimulation by high frequency electrical stimuli caused excitatory activity in the contralateral inferior oblique and inferior rectus muscles and in the ipsilateral superior oblique and superior rectus muscles, resulting in conjugate eye movements by both eyes. The placement of our recording electrodes beneath the eyes preferentially enhances potentials from the inferior obliques and inferior recti of both eyes, but it is clear from Suzuki's results that other eye muscles will also be activated by otolithic stimulation. oVEMPs recorded by electrodes under the eyes cannot be used to infer the direction of any stimulus-locked eye movement response since the movement will be the outcome of the action of all eye muscles.
4.6. Conclusion

It appears that the one stimulus, the BCV at Fz, can test both vestibulo-collic (Halmagyi et al., 1995) and vestibulo-ocular pathways, (Rosengren et al., 2005; Iwasaki et al., 2007). cVEMPs and oVEMPs complement each other – cVEMPs test primarily ipsilateral sacculo-ocular pathways whereas oVEMPs to Fz BCV primarily test crossed otolith-ocular (which probably include utriculo-ocular) pathways. However, testing with cVEMPs and oVEMPs has very different requirements, because the p13 of the cVEMP is an inhibitory response, whereas the n10 of the oVEMP is an excitatory response. In the case of cVEMPs it is necessary to ensure there is adequate muscular contraction to generate the excitation required to be able to detect the inhibitory p13 response. In sharp contrast, the n10 of the oVEMP is an excitatory response. It is quantifying an increase in EMG activity (excitation) in response to the BCV stimulus. The absolute magnitude of the EMG for the oVEMP will depend on many factors such as electrode location, skull characteristics, height of fixation point above straight ahead (as we ourselves show here), but the Fz BCV stimulus is eliciting an excitatory response, not inhibiting an ongoing excitatory response as is the case with p13 of the cVEMPs.

A clinical test using BCV at Fz would test both saccular and utricular function. However other evidence from patients with identified lesions is needed to establish that matter conclusively in humans. For clinical use, the oVEMP has many advantages: for oVEMPs the measurement interval only lasts about 20 s or less and we have found that most people lying supine on a bed can look upward for such a short interval without difficulty. This is in stark contrast to cVEMPs where tensing the neck muscles for the measurement interval can be so fatiguing that senior patients are rarely tested. If there is any doubt or question about n10 it is quick and simple and undemanding to re-run the 20-s test.

Note added in proof

Bruel and Kjaer recommend that the weight of the 4810 be supported by the operator or by a separate stand so that the vibrator tip rests lightly against Fz.

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References


