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Vestibulo-ocular responses evoked via bilateral electrical stimulation of the lateral semicircular canals

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Abstract

We investigated the vestibulo-ocular responses (VOR) evoked by bilateral electrical stimulation of the nerves innervating horizontal semicircular canals in squirrel monkeys and compared these responses to those evoked by unilateral stimulation. In response to sinusoidal modulation of the electrical pulse rate, the VOR for bilateral stimulation roughly equals the addition of the responses evoked by unilateral right ear and unilateral left ear stimulation; the VOR time constants were about the same for bilateral and unilateral stimulation and both were much shorter than for normal animals. In response to individual pulse stimulation, the VOR evoked by bilateral stimulation closely matches the point-by-point addition of responses evoked by unilateral right ear and unilateral left ear stimulation. We conclude that, to first order, the VOR responses evoked by bilateral stimulation are the summation of the responses evoked by unilateral stimulation. These findings suggest that – from a physiologic viewpoint – unilateral and bilateral vestibular prostheses are about equally viable. Given these findings, one possible advantage of a bilateral prosthesis is higher gain. However, at least for short-term stimulation like that studied herein, no inherent advantage in terms of the response time constant (“velocity storage”) was found.

Index Terms

vestibular; VOR; neural prosthesis

I. Introduction

We have previously presented the design of a unilateral semicircular canal prosthesis [1,2] and physiological responses evoked by this unilateral prosthesis for guinea pigs [1-3] and squirrel monkeys [4,5]. To convey bi-directional rotation information to the nervous system via unilateral electrical stimulation, our prosthesis used an elevated baseline pulse rate. Data showed that the elevated baseline rate initially evoked large responses, which then dissipated in a day or less [2,3,5]. However, despite the dissipation of the responses evoked by the baseline stimulation, motion-modulated stimulation continued to evoke appropriate motion-modulated electrical vestibulo-ocular reflexes (eVOR) for months after the initial acclimation to the baseline stimulation [5]. Taken together, these findings suggest that the mammalian nervous system can learn to appropriately utilize information provided by a unilateral prosthesis.

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Other research groups have investigated vestibular implants [6,7] but, like us, have not reported responses evoked by bilateral stimulation. Since vestibular information is normally bilateral, we chose to investigate responses evoked by bilateral stimulation. While the push/pull nature of the information provided to the CNS via paired semicircular canals is known [e.g., 8], how bilateral vestibular information is processed by the nervous system is poorly understood. To investigate this question and, more directly, to investigate the potential benefits of bilateral vestibular prosthetics, we measured the eye movements evoked by both unilateral and bilateral stimulation. There are two possible ways that the brain could combine information provided via bilateral electrical stimulation. The brain could sum the signals from the two ears linearly or nonlinearly. For example, the responses from whichever ear was stimulated first or had a stronger signal could predominate. Galiana's model [9] assumed that the bilateral interaction was not simply additive, while Minor et al [10] assumed linear summation of bilateral inputs in their mathematical model of horizontal VOR dynamics. There are some reports of responses evoked by bilateral stimulation. Cohen, Suzuki and colleagues [11] reported that stimulation of the left lateral canal nerve produced a horizontal movement of the eye to the right, while simultaneous stimulation of the right and left lateral canal nerves resulted in a dramatic reduction of the response evoked by either electrode alone. MacDougall et al [12] in their investigation of eye movements evoked by surface galvanic vestibular stimulation of human subjects showed that the magnitude of slow phase eye velocity of response evoked by bilateral stimulation is similar to the sum of the responses evoked by unilateral stimulation. Therefore, based on our own preliminary data as well as the published data, we hypothesized that responses evoked by bilateral stimulation of the two lateral semicircular canals would – to first order – equal the summation of the responses evoked by unilateral stimulation of each of the two canals individually.

To compare the responses evoked by unilateral and bilateral electrical stimulation, two squirrel monkeys were tested extensively using bilateral stimulation of the lateral canals. Testing was performed using modulated stimulation pulses provided for extended periods of time (i.e., hours) as well as single pulse stimulation provided for very brief periods of time (i.e., seconds). Of the roughly 10 squirrel monkeys we have implanted with bilateral ear electrodes in both lateral canals, these were the only two that had bilateral electrodes that both evoked substantial horizontal eye movements in response to electrical stimulation with minimal crosstalk to the facial or other nearby nerves. One monkey (monkey "G") was primarily tested using individual pulse stimulation like the single pulse stimulation utilized for some of our earlier investigations [e.g., 5,15]. Responses during these trials were stable, but the efficacy of the electrode in the left ear changed gradually shortly after we began providing continuous stimulation. Since the responses evoked by continuous stimulation in this animal were not stable, these data are not reported herein other than to report that the data from the first continuous stimulation tests - obtained before the responses began to degrade - mimicked the results from the other monkey. Another monkey (monkey "N") was primarily tested using continuous stimulation with the pulse rates modulated sinusoidally. The modulated stimulation mimicked that provided during our earlier chronic stimulation studies [e.g. 4,5]. Since monkey "N" was primarily prepared for other long-term adaptation experiments, only a limited number of individual pulse tests were conducted (just before the adaptation studies). Specifically, individual pulses were only applied at the current level used for chronic stimulation, and the measured VOR at this single current level mimicked the results from the other monkey.

II. Methods

A brief description of relevant methodologies follows. More detailed methodological descriptions regarding our prosthetic stimulation circuitry and stimulation paradigms have been published [1-5].

A. Animal preparation

The two squirrel monkeys were mature (> 700 grams) males. Each animal underwent three surgeries. Isoflurane was used to provide general anesthesia for all surgeries. During the first surgery an 11 mm diameter 3-turn frontal coil (Cooner Wire #AS632) was implanted on the surface of the sclera and a machined bolt-like structure ("headbolt") was attached to the skull to allow painless head fixation. During the second surgery, one horizontal semicircular canal was plugged by inserting a small piece of fascia into the canal. A stimulating electrode was made from 150 μm diameter platinum wire (Cooner Wire #AS770-34) by stripping 100-200 μm of the Teflon insulation from the tip. This electrode was inserted into the canal toward the ampulla (away from the canal plug). The return electrode was made from the same platinum wire by stripping about 2 mm of the insulation from the tip and was placed superficially beneath the muscle near the ear. An electrical stimulator, specifically a current source, was connected to these electrodes. The stimulation provided during surgery was 600 pps on/off modulated (1 Hz) biphasic current pulses with a pulse width of 200 μs . The eye movements evoked by the stimulation were monitored visually while inserting the electrode toward the ampulla. The insertion depth and angle were adjusted to yield the desired eye movements (i.e., sufficient magnitude, primarily horizontal, little or no facial twitches, etc.). Then two stainless steel screws were inserted into bone near the electrode and dental cement was used to secure the electrode to the bone. The third surgery mimicked the second surgery but was performed on the remaining, previously unaltered, ear.

B. Experiment setup

A Robinson style coil system (CNC Engineering) was used to measure eye movements. The eye position sign convention was defined using the right-hand-rule: positive is to the left and down. Tests were conducted at least four weeks after the third surgery. All the tests were conducted while the animal was awake in the dark, with alertness maintained using low-dose d-amphetamine (0.3 mg/kg), with its head held so that the horizontal canals were roughly parallel with earth-horizontal. The animal was placed such that its eye was very near the center of the search coil frame. The output signals from the search coil system were sampled along with stimulation signals. The ADC card had 16-bit resolution, and the sample rate was 200 Hz for continuous stimulation tests and 18 kHz for individual pulse stimulation tests. (Details describing both tests are provided below.)

C. Electrical stimulation devices and stimulation parameters

The device for individual pulse stimulation had two independently controllable current sources that we developed. During testing, one current source was connected to the electrode implanted in the right horizontal semicircular canal, the other current source to the electrode in the left horizontal canal. A microcontroller (C8051F006, Silicon Laboratories, Inc.) output voltage pulses from its two D/A converters and the two current sources converted the voltage pulses to current pulses. The current pulses of the two channels were synchronized and the timing delay between the current pulses of the two channels was varied between 0 ms and 3 ms.

Three types of individual current pulses were used in this study. The first type was individual biphasic pulses composed of a 200 μs cathodic phase, a 200 μs rest phase, and a 200 μs anodic phase. The magnitudes of cathodic and anodic pulses were always the same. The second type was individual cathodic pulses having only a 200 μs cathodic phase. The third type was individual anodic pulses having only a 200 μs anodic phase. The individual cathodic and anodic pulses were provided by alternating cathodic and anodic pulses every 50 ms. For all three pulse types, the pulses were repeated every 100 ms. For each trial, the electrical stimulation was applied for about 100 seconds so roughly 1000 pulses were delivered.

For continuous stimulation, the bilateral stimulation was controlled by two microcontrollers; each controlled an independent current source that stimulated one electrode inserted in a horizontal canal. An analog signal was sampled by each of two A/D converters (12-bit) located on each of the two microcontrollers. This input signal was then high-pass filtered digitally (time constant 5 seconds) by each microcontroller and was used to modulate the pulse rates of the output current pulse. The modulation sensitivities (change in pulse rate per change in input analog signal) for the two channels were the same. The modulation directions were varied such that the pulse rate of the two channels was either in push/pull mode (pulse rate increased in one ear while it decreased in the other) or in common mode (pulse rate in the two ears always increased/decreased together). For the continuous modulated stimulation studies, the current pulses of the two channels were not synchronized on a pulse-to-pulse basis. The current pulses during continuous stimulation were the same biphasic pulses used for individual biphasic pulse stimulation (200 μ s cathodic stimulation followed by 200 μ s of rest followed by 200 μ s of anodic stimulation). The signals used to modulate pulse rate were sinusoidal (0.01 Hz to 1 Hz).

All electrical stimulation experiments were conducted while the animal's head was stationary. Because the eye movements evoked by individual stimulation pulses were typically small, the largest possible current was used to elicit the largest possible eye movements. The maximal current was limited by stimulation of the facial nerve. The current levels were always maintained below the facial threshold, in part, because facial responses such as eye lid twitches may cause eye movements that interfere with the measurement of eye responses elicited by vestibular stimulation.

D. Methods specific to modulated continuous stimulation

Six experimental conditions were utilized for these investigations. Two of these conditions were rotation experiments conducted without electrical stimulation:

1. "Normal" testing was conducted after the first surgery (headbolt and eye coil surgery), prior to the second surgery (ear surgery). The two ears were intact. The monkey was rotated in the dark at 80 $^{\circ}$ /s sinusoidally.
2. "Plugged" testing was conducted after the third surgery (the surgery on the second ear). The horizontal canals of both ears were plugged. The monkey was tested using the same protocol as when "Normal".

For each of the four remaining conditions, the animal was static in the dark.

3. "Unilateral: R only": only the right ear received electrical stimulation, the left ear was disconnected from the stimulator.
4. "Unilateral: L only": only the left ear received electrical stimulation, the right ear was disconnected from the stimulator.
5. "Bilateral: Push/pull": the instantaneous pulse rate increased in one ear while decreasing in the other ear.
6. "Bilateral: Common mode": the instantaneous pulse rate to the two ears was modulated up and down together, but the individual pulses were not phase-locked on a pulse-to-pulse basis.

For conditions 3 through 6, the electrical stimulation was first turned on with the pulse rate held constant at 200 pps for 30 minutes. Then the pulse rate was modulated sinusoidally - with the pulse rate ranging from 133 pps to 267 pps (around the baseline of 200 pps). This pulse rate modulation was set to be equivalent to the modulation provided in our earlier study [5] for a rotation amplitude 80 $^{\circ}$ /s (modulation sensitivity of 0.9 pps/ $^{\circ}$ /s at rest, time constant 5

seconds). Therefore, we will calculate VOR gains assuming a rotation of 80°/s. The amplitudes of the current pulses to the right ear and left ear were both set at 125 μ A.

For each of the six experimental conditions listed above, the animal was tested using seven modulation (or rotation) frequencies, they were 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, and 1 Hz. Each trial included between 2 and 20 sinusoidal cycles (fewer cycles were used for low frequency tests).

Data analysis was described in details in our previous publication [5]. In brief, the eye velocity was computed from eye position data recorded originally during tests, and then the fast phases were removed to keep only the slow phase velocities (SPV). For each sinusoidal cycle, the SPV data, as well as the modulation signal (for electrical stimulation tests) or rotation velocity (for rotation tests), were fit to both sine and cosine waves using linear regression. The average of the sine and cosine components were calculated across cycles for a given trial and the mean

amplitude ($A = \sqrt{A_s^2 + A_c^2}$) and phase ($\phi = \arctan(A_s / A_c)$) were then calculated from these average values. The standard error (SE) of the mean was found by calculating the covariance ellipse for the sine and cosine components. The VOR gain was defined as the amplitude of SPV divided by 80°/s, which was the peak angular velocity (or the peak angular velocity simulated via the prosthesis). The phase of VOR was defined relative to the modulation signal for electrical stimulation trials or rotational velocity for motion trials. For each experiment, a first-order high-pass transfer function was fit to the average data across each of the seven frequencies to compute the fitted transfer function gain constant and time constant.

E. Methods specific to single pulse stimulation

The relationship between eVOR evoked by unilateral and bilateral individual pulse stimulation was investigated under three conditions:

1. It was reported that the amplitude of the VOR evoked by acoustic clicks [13] and rotation [14] varies with eye position. Therefore, we examined the effect of eye position on responses evoked by bilateral and unilateral electrical stimulation;
2. The VOR evoked by unilateral electrical stimulation increases with the strength of stimulation [1,5]. To investigate how the VOR changes with bilateral electrical stimulation with current level, we designed two experiments:
 - a. The current levels to the right ear and the left ear were selected so that they evoked nearly equal size eye responses for unilateral stimulation;
 - b. The current levels to the right ear and the left ear were selected so that they evoked substantially different eye responses for unilateral stimulation;

In both of the above experiments, the current pulses applied to the two sides were synchronized and in phase.
3. We investigated the effect of timing delays between the pulses to the right ear and the pulses to the left ear.

Figs. 1A and 1B show examples of the horizontal eye movements elicited by individual biphasic pulses applied to the right ear at a current magnitude of 300 μ A. The eye movements evoked by the stimulation pulses summed with a small (circa 2-3°/s), but consistent, nystagmus. In Fig. 1A, the small electrically-evoked responses are barely noticeable. Fig. 1B expands the data inside the small rectangle in Fig. 1A, and Fig. 1C shows the corresponding biphasic current pulses. The background noise is clearly noticeable in Fig. 1B. At lower current levels (e.g., 60 μ A), the magnitudes of the responses were smaller (the magnitude of the response was roughly proportional to stimulation current pulse level) such that the response magnitude became

comparable to the background noise. To increase the signal-noise ratio, the evoked responses were processed as follows.

First the falling edge of each cathodic phase of the current pulse was found. The data between 10 ms prior to that edge and 90 ms after that edge was defined as a cycle. Then the peak-to-peak magnitude of each cycle of eye movement was calculated and the median of these peak-to-peak values times 1.3 was used as a threshold. To reject cycles that included fast phases or saccades, any cycle with a peak-to-peak magnitude smaller than the threshold was labeled as a “good cycle” for further processing. The threshold was chosen through trial and error to include as much data as possible while maintaining good data quality. The top trace in Fig. 1D (the gray trace) shows the result of averaging of “good cycles” for the data shown in Fig. 1A (only for data in the -1 degree eye position group, see section III.B.1 for detail). This trace is the averaging of 10 cycles of data and only the part of data from 10 ms prior to and 30 ms after the falling edge of the cathodic phase is shown. Fig. 1E indicates the corresponding biphasic pulse.

As shown in Fig. 1A, 1B, and 1D, the nystagmus yields a leftward (positive) change in eye position for this animal. This complicates measures of the amplitude and latency of the response. To minimize the influence of the nystagmus, the data 10 ms prior to the falling edge of the cathodic pulse were fit with a line segment, and the slope of this line was projected for the remaining 90 ms of each data cycle. Then this slope was subtracted from the data. The bottom trace in Fig. 1D (the black trace) shows the response after this nystagmic slope removal.

To compute the amplitude of the response, we first found the time of the peak response and defined the average of the data within 1 ms (0.5 ms prior and after the peak time) as the average peak response. The average taken 10 ms prior to the falling edge of the cathodic phase was defined as the base value. The amplitude of the response evoked by stimulation was defined as the difference between the peak and base.

III. Results

A. Responses evoked by modulated continuous stimulation

All modulated pulse rate continuous stimulation test data shown in this section (Section A, Figs. 2 and 3) were obtained from monkey “N”. As examples, the leftmost column of Fig. 2 shows a signal representing the electrical modulation at 0.1 Hz (Fig. 2A) as well as the horizontal eVOR evoked by continuous stimulation for different testing conditions (Fig. 2B, C, D and E). The second column shows mathematical summation (Fig. 2G) and mathematical subtraction (Fig. 2H) of the eVOR evoked by unilateral stimulation. The third column shows the VOR (Fig. 2J and K) evoked by sinusoidal rotation (Fig. 2I) at 0.1 Hz.

When the response evoked by “Unilateral: R only” stimulation (Fig. 2D) is added to the response evoked by “Unilateral: L only” stimulation (Fig. 2E), this summation (Fig. 2G, “R only + L only”) yields a response much like that evoked by “Bilateral: Push/pull” stimulation (Fig. 2B). And when the response evoked by “Unilateral: L only” stimulation is subtracted from the “Unilateral: R only” response, the resultant trace (Fig. 2H, “R only - L only”) mimics the response evoked by “Bilateral: Common mode” stimulation (Fig. 2C). Both of these example findings are consistent with the hypothesis that responses evoked by bilateral stimulation roughly equal the linear combination (summation or subtraction) of the responses evoked by unilateral stimulation. This finding is investigated more thoroughly across frequencies in Fig. 3.

Fig. 3A shows eVOR gain versus frequency for electrical stimulation trials and VOR gain for rotation trials, Fig. 3B shows phase versus frequency for the same data, and Table 1 shows the

fitted gain constants and time constants for each condition shown in Fig. 3. The normal gain constant for this animal was 0.26. This relatively low gain might be because this animal was quite old for a squirrel monkey – circa 15 years of age at the time of the normal testing. Despite this relatively low gain, the fitted time constant was about 15.6 s, which is not abnormally low. Following canal plugging the VOR gain (0.002) dropped substantially and was indistinguishable from noise.

Unilateral electrical stimulation to either the right ear or the left ear evoked a substantial eVOR that was roughly half the magnitude of the normal VOR. As demonstrated in Fig. 3A as a function of frequency, the eVOR evoked by bilateral push/pull electrical stimulation was roughly equal to the linear summation of unilateral right ear and unilateral left ear stimulation and demonstrated a gain constant of 0.24, which was, coincidentally, about the same as for the normal condition (0.26). The eVOR evoked by bilateral common mode stimulation was roughly equal to the linear subtraction of unilateral right ear and unilateral left ear stimulation and was similar to that for the plugged condition.

To quantify the correlation demonstrated in Fig. 3A between responses evoked by bilateral push/pull electrical stimulation and the summation of responses evoked by unilateral stimulation, we calculated the correlation coefficient between these two data sets, which was 0.9947, and the square of the correlation coefficient, which was 0.9895. The squared correlation coefficient is also known as the coefficient of determination and sometimes called “r-squared”. A squared correlation coefficient of 0.9895 indicates that 98.95% of the response variation observed during bilateral push/pull stimulation can be explained by the correlation with the sum of the unilateral responses. Since the squared correlation coefficient represents the percentage of variation in one variable explained by the correlation with the second variable, for the remainder of the paper, we will only present the squared correlation coefficient.

Fig. 3B shows that the phases were very similar for all conditions except for the normal responses. Table 1 shows the fitted time constants for all conditions where the response amplitude was large enough to yield a reliable time constant estimate. Consistent with the phase data shown in Fig. 3B, the time constants of eVOR responses to bilateral push/pull stimulation, unilateral stimulation, and the summation of unilateral stimulation were close to each other (~3 seconds), which is shorter than the five second time constant of the prosthesis and much shorter than the time constant for the normal animal (15.6 seconds).

B. Responses evoked by individual pulse stimulation

All individual pulse stimulation data reported in this section (Section B, Figs. 4-8) were from monkey “G”.

1. Effect of eye position—During the individual pulse stimulation tests, we observed that the amplitude of responses evoked by pulsatile stimulation varied with eye position. To quantify this observation, we grouped the response cycles according to the absolute average horizontal eye position for the 10 ms just before the current pulse was provided. Specifically, eye position prior to stimulation was measured to always be between $\pm 20^\circ$. Therefore, we grouped the responses into 40 bins each having a width of 1° ($\pm 0.5^\circ$). The vast majority (> 95%) of the data fell between $\pm 5^\circ$. All the responses in each bin were processed as explained in section II. E, i.e., all “good cycles” were added together on a point-to-point basis, and the sum was divided by the number of responses in this bin. Bins that contained fewer than 10 responses were discarded.

In the first test (“R only”), the current level of biphasic pulses to the right ear was 300 μA , and the left ear was not stimulated. In the second test (“L only”), the current level to the left ear was 110 μA and the right ear was not stimulated. The current level of 110 μA was used so that

the magnitude of eye movement responses evoked by left ear stimulation was roughly equal to that evoked by right ear stimulation at 300 μA , though in the opposite direction. In the third test ("Bilateral"), 300 μA current pulses were applied to the right ear and 110 μA current pulses were applied to the left ear. For all data in this section, the stimulation to the left and right ears was provided simultaneously (i.e., 0 ms timing delay between the current pulses provided to the right and left ears).

Fig. 4A shows the average horizontal eye responses evoked by individual biphasic current pulses at different eye positions. Fig. 4B shows the amplitudes of the traces shown in Fig. 4A vs. horizontal eye position. The magnitudes of responses to "L only" stimulation changed significantly with eye position, while the responses evoked by "R only" stimulation were relatively insensitive to eye position. In "Bilateral" stimulation, the change in the response with eye position was clearly evident, since the direction of the eye response changed with eye position. In other words, the exact same stimulation evoked a leftward eye response when the eye was positioned to the left but evoked a rightward response when the eye was positioned to the right. Although the changes with eye positions were different for the three stimulation configurations, the responses to the "Bilateral" stimulation roughly match the summation of responses to "R only" and "L only" stimulation as shown in Fig. 4. This is supportive of the hypothesis that responses evoked by bilateral stimulation result from a summation of the "R only" and "L only" responses. The squared correlation coefficient between the "Bilateral" and "R only + L only" was 0.99.

Similar tests were conducted using individual cathodic pulses at current levels of 320 μA to the right ear and 120 μA to the left ear. The results (not shown) were similar to those reported above. The squared correlation coefficient between the "Bilateral" and "R only + L only" data was 0.98.

2. Effect of bilateral current levels

Cancellation condition: As can be seen from Fig. 4B, around the eye position of -3 degrees (the average eye position for the tests shown was -2.7 degrees), the responses to "R only" and "L only" unilateral stimulation evoked responses having roughly the same magnitude but opposite direction, while the response evoked by "Bilateral" stimulation was nearly zero. This was the case because the current levels were chosen to yield this near-cancellation. More specifically, the evoked responses canceled each other during bilateral stimulation at that selected current level pair (300 μA for right ear, 110 μA for left ear). Although for a certain current level pair the cancellation could be best achieved at a specific eye position (as shown in Fig. 4B), for the remainder of this paper the responses at all eye positions were included in data analysis. (The outcome would be almost the same but slightly "better" if only the responses at certain eye position, for example around the average eye position of each test, were included in data analysis). In this section, nine biphasic pulse current level pairs were used to further examine such cancellation, they were (for right ear/left ear): 60/30, 90/40, 120/50, 150/60, 180/70, 210/80, 240/90, 270/100, and 300/110 ($\mu\text{A}/\mu\text{A}$). The minimum current level was chosen so that the eye responses evoked by unilateral individual biphasic pulse stimulation were just noticeable.

Fig. 5A shows the average of horizontal eye responses induced by individual biphasic pulses at different current levels. Fig. 5B shows the amplitudes of the traces in Fig. 5A vs. current levels. The magnitudes of response evoked by unilateral stimulation increased with current level. The responses to "R only" and "L only" stimulation were roughly equal in magnitude but opposite in direction, and the summation was near zero. The responses to bilateral stimulation were very small and roughly match the summation of unilateral stimulation responses.

Non-cancellation condition: In this experiment, the current levels were not tailored to yield cancellation. First the biphasic pulses current to the left ear was set at 70 μA (the median of the current levels for the left ear in the cancellation condition), and the current to the right ear was the same nine current levels as for the cancellation condition, i.e., the current level pairs were (for right ear/left ear): 60/70, 90/70, 120/70, 150/70, 180/70, 210/70, 240/70, 270/70, and 300/70 ($\mu\text{A}/\mu\text{A}$). Then the current to the right ear was set at 180 μA (the median of the current levels for right ear in the cancellation condition), and the current to the left ear were the same nine levels as in the cancellation condition, i.e., the current level pairs were (for right ear/left ear): 180/30, 180/40, 180/50, 180/60, 180/70, 180/90, 180/100, and 180/110 ($\mu\text{A}/\mu\text{A}$).

Fig. 6A shows the average horizontal eye responses evoked by individual biphasic pulses at different current levels when the current to the left ear was set at 70 μA constant. Fig. 6B shows the amplitudes of responses shown in Fig. 6A vs. current level. Not surprisingly, the responses to the “R only” stimulation were similar to those shown in Fig. 5, and the responses to the “L only” stimulation were about the same as those shown in Fig. 5 at 70 μA . The response to “Bilateral” stimulation increases with current level and match closely the summation of the response to “R only” and “L only” stimulation. The squared correlation coefficient for the data shown in Fig. 6B was 0.98. Similar tests were conducted using individual cathodic pulses (not shown) and the results were similar to that of the biphasic pulse stimulation with a squared correlation coefficient of 0.96.

Fig. 6C shows the amplitudes vs. current level for responses evoked at different current levels when the current to the right ear was 180 μA constant. The squared correlation coefficient was 0.96. For a similar experiment (not shown) using cathodic pulses, the squared correlation coefficient was 0.95.

3. Effect of timing delay—In the previous experiments, the current pulses delivered to the two ears were delivered synchronously, which is the same as saying that the timing delay between pulses applied to left and right ears was 0 ms. In this experiment, we delayed the current pulses applied to one ear with respect to the current pulses delivered to the other ear. Delays were 0.0, 0.6, 1.0, 1.5, 2.0, 2.5, and 3.0 ms. The current level was 300 μA for the right ear and 110 μA for the left ear, which was the same as the previously presented cancellation condition.

Fig. 7A shows the average horizontal eye response evoked by individual biphasic pulses when the current pulse to the left ear leads the pulse to the right ear. The summation (“R only + L only”) traces were made via a point-by-point addition of the responses evoked by “L only” stimulation with the responses evoked by “R only” stimulation delayed by 0.0, 0.6, 1.0, 1.5, 2.0, 2.5, and 3.0 ms, to match the relative delivery of the pulses to the right ear during “Bilateral” stimulation. Fig. 7B shows the response amplitudes shown in Fig. 7A vs. delay time. The response magnitude to bilateral stimulation was near zero when the delay was 0 ms (near cancellation at selected current level), and increased when the delay became bigger because the cancellation was less effective. The responses to bilateral stimulation matched the summation of the responses to unilateral stimulation. The squared correlation coefficient was 0.93 for data shown in Fig. 7B. Similar testing with cathodic pulses (not shown) demonstrated a similar outcome with a squared correlation coefficient of 0.95.

Fig. 7C shows the amplitudes of responses when the current pulse to the right ear leads the pulse to the left ear. The squared correlation coefficient was 1.00 (0.9975). For similar testing using cathodic pulses, the results were similar (not shown); the squared correlation coefficient was 0.98.

4. Comparison of responses to anodic, cathodic and biphasic pulses—Fig. 8A shows responses to individual anodic and cathodic pulses as well as biphasic pulse stimulation to the right ear. The current amplitudes used for anodic pulses and cathodic pulses were 96, 128, 160, 192, 224, 256, 288, 320 μ A; the current amplitudes used for biphasic pulses were 90, 120, 150, 180, 210, 250, 270, 300 μ A. Fig. 8B shows the magnitude of the responses shown in Fig. 8A. Fig. 8C shows responses evoked by stimulation of the left ear. The current level for anodic pulses, cathodic pulses and biphasic pulses were 40, 50, 60, 70, 80, 90, 100, 110 μ A. Fig. 8D shows the magnitude of responses shown in Fig. 8C.

While quantitative differences are clearly evident, individual biphasic, cathodic, and anodic pulses elicited qualitatively similar eye movement patterns. The magnitude of responses to biphasic pulse and cathodic pulse were about the same, while responses to anodic pulses were significantly smaller, which is consistent with an earlier report [15]. For biphasic stimulation, the cathodic stimulation phase is generally considered the one that elicits neural responses, while the anodic phase is generally used for charge balancing. Responses to anodic pulse were not reported in previous sections, because at low current levels the responses elicited by individual anodic pulses were very small and often barely detectable. Nonetheless, as noted before and shown herein, anodic pulses can and do evoke action potentials when the current levels are high enough, and the neuron is not in a refractory period.

5. VOR latency to individual pulses stimulation—The responses evoked by individual pulses were processed using the signal averaging techniques and slope removal described earlier. To compute the latency, we first found the peak of the response, then fit a line segment to the portion from 1/3 to 2/3 of the peak of the first leg of the response, and fit another line segment for the 10 ms “baseline” data prior to the start edge, and defined the time between the start of the stimulation and the time of the intersection of the two line segments as the latency. The latency was about 5 ms and was independent of whether the pulse was anodic, cathodic, or biphasic. While movement of the left eye was always measured, we did not find a significant difference in the VOR latency when the left or right ear was stimulated.

IV. Discussion

A. VOR response evoked by bilateral stimulation is primarily explained by a linear combination of responses evoked by unilateral stimulation

For modulated continuous stimulation ranging from 0.01 Hz to 1 Hz, the eVOR evoked by bilateral push/pull electrical stimulation roughly matched the linear addition of the eVOR evoked by unilateral right ear stimulation and that evoked by unilateral left ear stimulation, and the eVOR gains evoked by bilateral common mode stimulation roughly matched the eVOR gains resulting from the linear subtraction of the unilateral responses (Fig. 3A). The fitted eVOR gain constants also indicate that the responses evoked by bilateral stimulation were to first order well modeled as the linear summation of responses evoked by unilateral stimulation (Table 1). The eVOR phases of bilateral and unilateral stimulation were essentially the same, as shown in Fig. 3B, and the time constants of the responses evoked by bilateral and unilateral stimulation were all around 3 s, as shown in Table 1. These findings are consistent with hypothesis that the responses evoked by bilateral stimulation were due to a linear summation of responses evoked by unilateral right ear and unilateral left ear stimulation.

The individual pulse stimulation experiments reveal more details of eVOR evoked by bilateral and unilateral stimulation. Fig. 4 indicates that although the amplitude of eVOR evoked by unilateral individual pulse stimulation changes with eye position, the responses evoked by bilateral individual pulse stimulation were roughly the linear summation of the responses evoked by unilateral right ear and unilateral left ear stimulation across all eye positions.

The magnitude of the eVOR evoked by unilateral right ear and unilateral left ear individual pulse stimulation increases with current level (Fig. 5). As long as the magnitudes of responses evoked by unilateral stimulation of each ear were nearly equal, bilateral stimulation evoked very small responses. The effects of stimulation on the two ears canceled each other during bilateral stimulation over a broad current level range; cancellation being a special case of linear combination, of course.

Even when the magnitudes of the responses evoked by unilateral stimulation of the two ears were significantly different, the responses evoked by bilateral stimulation roughly matched the linear summation of the responses evoked by unilateral right ear and unilateral left ear stimulation (Fig. 6). It is worth noting that in this animal (monkey "G"), the current levels needed to evoke roughly equal magnitude eVORs for the two ears were substantially different. This indicates that although the efficacy of the electrode-nerve system of the two ears was different, the responses to bilateral electrical stimulation were a linear summation of responses evoked by unilateral stimulation while neither ear was predominant over the other.

Even when there was a timing delay between the current pulses for the two ears, the assumption that the response evoked by bilateral stimulation is a linear summation of the responses evoked by unilateral right ear and unilateral left ear stimulation still held true (Fig. 7). No matter which ear received the current pulse first, neither ear was predominant, since the response roughly equaled the linear summation of the response evoked by the unilateral stimulation.

Quantitatively supporting the conclusions presented in the previous five paragraphs, the squared correlation coefficients between the response evoked by bilateral stimulation and the linear summation of the responses evoked by unilateral right ear and unilateral left ear stimulation were equal or greater than 0.95 with just one exception (0.93, Fig. 7B). Therefore, we conclude that, to first order, the VOR responses evoked by bilateral stimulation are consistent with a linear summation of the responses evoked by unilateral stimulation.

B. Bilateral prosthesis is feasible and has advantage of higher gain

Although the vestibular system is bilateral in nature, so far only unilateral prostheses have been actually tested on animal models and proven feasible [1-5,7]. Based on our findings that responses evoked by bilateral stimulation are more-or-less the linear summation of the responses evoked by unilateral stimulation, we predict that a bilateral prosthesis is very likely to prove feasible. Bilateral vestibular prostheses could have the advantage of higher sensitivity, since the VOR evoked by bilateral stimulation is roughly twice that evoked by unilateral stimulation (all else equal). Another potential advantage of a bilateral vestibular prosthesis relates to baseline stimulation and associated adaptation. For a unilateral vestibular prosthesis to convey bi-directional rotational information, the baseline stimulation pulse rate needs to be elevated, and the animal needs to take a day or so to adapt to the elevated baseline [2,3]. Bilateral prostheses might be able to avoid using an elevated baseline, and so this phase of adaptation may be easier or even unnecessary.

A bilateral prosthesis could have other advantages over a unilateral prosthesis. For example, in the unilateral prosthesis study we didn't see the VOR gain change significantly - even over periods of months [5]; and the effect of velocity storage was not evident either [5]. A bilateral prosthesis might be more natural, so the animal may be able to adapt more easily. However, at least for acute stimulation, bilateral stimulation didn't show a longer time constant than unilateral stimulation. While this doesn't mean that velocity storage might not be regained with chronic bilateral stimulation, it certainly does not suggest that restoration of velocity storage will occur simply because bilateral stimulation is provided instead of unilateral stimulation.

C. Cathodic and biphasic stimuli were equally efficacious, while anodic stimuli was less effective to evoke eVOR

Three additional findings deserve mention. First, we reported that cathodic stimuli and biphasic stimuli were equally efficacious in evoking eye responses (Fig. 8). Second, confirming an earlier report [15], data presented herein (Fig. 8) showed that anodic stimulation, though less effective than cathodic or biphasic stimuli, can evoke eye responses. This is also consistent with the finding that vestibular afferent responses evoked via anodic pulses have substantially greater thresholds than those evoked by cathodic pulses; this was true for both regular and irregular afferent neurons [16]. Third, we found a latency of about 5 ms from the leading edge of each stimulation pulse to the first noticeable eye position change evoked. This held true for anodic, cathodic, and biphasic pulses for both ears. Taken together, these three findings provide several insights that are discussed briefly below.

It is not surprising that cathodic and biphasic pulses yield indistinguishable responses, since the cathodic phase of the biphasic pulse comes first and since the cathodic phase of biphasic stimulation is generally considered the phase that evokes neural activity most efficiently. This confirms that the 200 μ s rest phase between cathodic and anodic pulses is enough to eliminate any measurable inhibition of slowly developing action potentials by the anodic charge recovery pulses but does not inform us regarding how short the rest phase can be.

The finding that anodic pulses can evoke neural responses (though less effectively than cathodic and biphasic pulses) is often forgotten. The fact that the responses evoked by anodic stimulation were in the same direction as those evoked via cathodic and biphasic stimuli is important because it shows that the stimuli are activating afferent neurons and not the hair cells, since anodic stimulation of hair cells would evoke graded responses in the direction opposite those evoked by cathodic stimulation.

Activation of neurons via anodic stimuli can occur via two mechanisms – sometimes called virtual cathode and anodic break mechanisms [17]. Anodic break mechanisms can be ruled out for this application because such mechanisms are substantially slower [17], while we found that the VOR latency for anodic stimuli was no different than for cathodic stimuli. Therefore, the responses evoked via anodic pulses are probably due to the virtual cathode mechanism, which simply refers to the fact that any current entering the neuron must also exit the neuron. When the current density exiting the neurons reaches threshold, an action potential is evoked [17]. The threshold to action potentials via anodic stimuli is greater than for cathodic stimuli, which explains why the responses evoked by anodic stimuli are smaller than for cathodic stimuli.

D. Effect of eye position on amplitude of eVOR

Fig. 4 shows the magnitudes of horizontal eVOR evoked by individual biphasic current pulses in monkey “G”. The search coil was implanted on the left eye of this animal. When the left ear was stimulated (“L only”), the amplitude of the eVOR changed significantly with eye position. The amplitude was bigger if the eye turned to right (negative on x-axis). This phenomenon was not so obvious if the stimulation was applied to the right ear (“R only”). Our finding agrees with a recent paper on acoustic stimulation of the vestibular system. Zhou et al [13] applied acoustic click stimulation to monkeys' ears while the animals fixated on visual targets at varying eccentricities. They reported that the amplitudes of the first horizontal eye velocity peaks were correlated with gaze eccentricity. The effect of gaze eccentricity on the amplitude was bigger for the ipsilateral eye than for the contralateral eye. The amplitude increased if the eye moved in the contralateral direction from the stimulated ear. They speculated that the eye position may change the excitabilities of vestibular interneurons by shifting their resting firing rate, and/or the excitabilities of the extra-ocular motoneurons so that the amplitude of eye movement

changed. Snyder et al [14] observed that in monkeys the steady state amplitude of the VOR response induced by brief rotation about a vertical axis during the execution of vergence eye movements was linearly related to vergence angle. They believe that this can stabilize retina images against eye translation because the axes of rotations of head and eye are different.

Fig. 4 also shows that the direction of the eye response changed with eye position in “Bilateral” stimulation. This can be explained by our “linear summation” hypothesis. The direction of eVOR evoked by left ear and right ear were opposite. The change of amplitudes of eVOR with eye position was significant for the left ear stimulation but it was not so obvious for the right ear stimulation. The summation of responses evoked by the two ears changed amplitude and direction with eye position, and the responses to bilateral stimulation mimicked the summation.

E. Conclusions

Our findings show that the eVOR evoked by bilateral electrical vestibular stimulation is about the same as the linear summation of the VORs evoked by unilateral stimulation applied independently to the right ear and left ear. This was true for a number of different stimulation combinations. Based on these findings with short-term stimulation, we predict that a bilateral vestibular prosthesis, which holds potential advantages over a unilateral prosthesis, is physiologically feasible. It is important to note that our conclusions regarding bilateral stimulation are based on responses evoked by acute stimulation only. The differences between bilateral and unilateral prostheses with chronic stimulation remain to be investigated. In addition, we recognize that a bilateral prosthesis would be more complex and more costly and would involve greater risk. A risk/benefit analysis of bilateral versus unilateral vestibular implants is probably premature.

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Fig. 1.

(A) Horizontal eye responses of monkey “G” evoked by individual biphasic pulse stimulation (300 μ A) of the right ear lateral semicircular canal. The evoked responses “piggybacked” on a small (circa 2-3°/s) baseline nystagmus in the dark. (B) Enlargement of content in the small rectangle in (A). Note the background noise and the slope caused by nystagmus. (C) Biphasic current pulses corresponding to (B). (D) The top trace (gray) shows the result of averaging for the data shown in (A) in the -1 degree eye position group. The bottom trace (black) is the response after removal of the slope (slow phase of nystagmus). The vertical line indicates the response peak. (E) A biphasic current pulse corresponding to (D). For eye movement responses, left is positive.

Fig. 2.

Horizontal eye responses of monkey “N” evoked by modulated electrical stimulation and rotation. The top plot in the leftmost column shows the modulation signal (A) that modulated the pulse rate ranging from 133 pps to 267 pps around the baseline of 200 pps, which was equivalent to the modulation provided in our earlier study [5] for a rotation amplitude 80 °/s. The example shown is for 0.1 Hz. The rest of the column shows the eVOR slow phase velocity (SPV) evoked by the modulated continuous electrical stimulation of bilateral push/pull (B), bilateral common mode (C), the right ear (D), and the left ear (E). The second column show the summation (G) and subtraction (H) of the responses to the right and left ear electrical stimulation. The third column shows the responses to yaw rotation (I) when the animal was normal (J) and when both of the horizontal canals were plugged (K). For electrical stimulation, the amplitudes of the current pulses to the right ear and left ear were both set at 125 μ A.

Fig. 3.

Bode plots of horizontal eye responses of monkey "N". (A) Gain and (B) phase of horizontal VOR evoked by modulated electrical stimulation of the right ear (▷), the left ear (◁), bilateral push/pull (◊), bilateral common mode (◻), the summation (◆) and subtraction (■) of the responses to the right and left ear electrical stimulation, the responses to yaw rotation when the animal was normal (○), and when the canals were plugged (×). Standard error of the mean (SEM) is shown as vertical bars. Phases are not shown for bilateral common mode stimulation, subtraction of unilateral stimulation, and rotation after plugging because the VOR amplitudes were too small to compute phase information reliably.

Fig. 4.

(A) Average horizontal eye responses of monkey “G” evoked by individual biphasic pulses (after slope removal) at different eye positions. The first column (from left) is for the “R only” stimulation, the second column is for the “L only” stimulation. The traces in the third column are the point-to-point addition of the “R only” and the “L only” responses. The fourth column shows responses evoked by “Bilateral” stimulation. In each column, the traces (from bottom to top) show the response average at eye positions from -5 degrees to 0 degree. The spaces between traces in each column are only to separate the traces and do not represent absolute eye position. The traces start 10 ms prior to the current pulse, which is not shown. (B) Peak amplitudes of the traces shown in (A). The responses evoked by bilateral stimulation ($\diamond$) match the mathematical addition ($\blacklozenge$) of the “R only” ($\triangleright$) and “L only” ($\triangleleft$) responses.

Fig. 5.

(A) Average horizontal eye response of monkey “G” evoked by individual biphasic pulses (after slope removal) at different current levels designed to yield near-cancellation of the evoked responses. The first column (from left) is for the “R only” stimulation, the second column is for the “L only” stimulation. The traces in the third column are the point-to-point addition of the “R only” and the “L only” responses. The fourth column shows responses evoked by “Bilateral” stimulation. In each column, the traces (from bottom to top) show the response average for current levels from 60 μA to 300 μA for right ear and 30 μA to 110 μA for left ear. The spaces between traces in each column are only to separate the traces and do not represent absolute eye position. The traces start 10 ms prior to the current pulse. (B) Peak amplitudes of the traces shown in (A). The responses evoked by bilateral stimulation ($\diamond$) match the mathematical addition ($\blacklozenge$) of the “R only” ($\triangleright$) and “L only” ($\triangleleft$) responses.

Fig. 6.

(A) Average horizontal eye response of monkey “G” evoked by individual biphasic pulse (after slope removal). The first column (from left) is for the “R only” stimulation, the second column is for the “L only” stimulation. The traces in the third column are the point-to-point addition of the “R only” and the “L only” responses. The fourth column shows responses evoked by “Bilateral” stimulation. In each column, the traces (from bottom to top) show the response average for current levels from 60 μA to 300 μA for the right ear and 70 μA for the left ear. The spaces between traces in each column are only to separate the traces and do not represent absolute eye position. The traces start 10 ms prior to the current pulse. (B) Peak amplitudes of the traces shown in (A). The responses evoked by bilateral stimulation ($\diamond$) match the mathematical addition ($\blacklozenge$) of the “R only” ($\triangleright$) and “L only” ($\triangleleft$) responses. (C) Peak amplitudes of the responses evoked by individual biphasic pulse when the current level applied to the right ear was fixed at 180 μA while the current to the left ear varied between 30 μA and 110 μA . The responses evoked by bilateral stimulation ($\diamond$) match the mathematical addition ($\blacklozenge$) of the “R only” and “L only” ($\triangleleft$) responses.

Fig. 7.

(A) Average horizontal eye response of monkey “G” evoked by individual biphasic pulse (after slope removal) with the current pulse to the right ear delayed relative to the left ear stimulation. The first column (from left) is the response to the right ear at 300 μ A, the second column is the response to the left ear at 110 μ A. The traces in the third column show the point-to-point addition of the “R only” and the “L only” responses when the response to the “R only” was shifted in time by 0, 0.6, 1, 1.5, 2, 2.5, and 3 ms (for traces from top to bottom). The fourth column shows the responses evoked by “Bilateral” stimulation. The traces (from top to bottom) are the responses to the stimulation pulse with the pulse to the right ear delayed 0, 0.6, 1, 1.5, 2, 2.5, 3 ms. Spaces between traces in each column only separate the traces and do not represent absolute eye position. The traces start 10 ms prior to the current pulse to the left ear. (B) Peak amplitude of the traces shown in (A). The responses evoked by bilateral stimulation ($\diamond$) match the mathematical addition ($\blacklozenge$) of the “R only” and “L only” responses. (C) Peak amplitudes of the responses when the current to the left ear was delayed. The responses evoked by bilateral stimulation ($\diamond$) match the mathematical addition ($\blacklozenge$) of the “R only” and “L only” responses.

Fig. 8.

(A) Average horizontal eye response of monkey “G” to individual pulses to the right ear at current levels (from bottom to top) from 96 μA to 320 μA for anodic and cathodic pulses and from 90 μA to 300 μA for biphasic pulses. (B) Peak amplitudes of the responses evoked by right ear stimulation via anodic ($\blacktriangleright$), cathodic ($\blacktriangleleft$), and biphasic ($\blacktriangleright$) pulses. The responses evoked by cathodic and biphasic pulses are indistinguishable, while those evoked by anodic pulses are smaller. (C) Average horizontal eye response to individual pulses applied to the left ear at current levels (from bottom to top) from 40 μA to 110 μA for anodic, cathodic, and biphasic pulses. (D) Peak amplitude of responses evoked by left ear stimulation via anodic ($\blacktriangleleft$), cathodic ($\blacktriangleright$), and biphasic ($\blacktriangleleft$) pulses. The responses evoked by cathodic and biphasic pulses are indistinguishable, while those evoked by anodic pulses are smaller.

Table 1

VOR gain constant and time constant

	Gain constant	Time constant (s)
Unilateral : R only	0.096	3.30
Unilateral : L only	0.127	2.72
Bilateral : Push/Pull	0.236	3.28
Bilateral : Common mode	0.021	
R only + L only	0.222	3.00
R only - L only	0.037	
Normal	0.260	15.57
Plugged	0.002	