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Finding Physiological Responses in Vestibular Evoked Potentials

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Abstract—**Vestibular prostheses are regarded as a promising tool to restore lost sensation in patients with vestibular disorders. These prostheses often electrically stimulate the vestibular nerve and stimulation efficacy is evaluated by measuring the vestibulo-ocular reflex (VOR). However, eye movement recording as intuitive metric of vestibular functionality is difficult to obtain outside the laboratory environment, and hence not available as an error signal in a closed-loop prosthesis. Recently we investigated vestibular evoked potentials (VEPs) by stimulating and recording in the same semicircular canal of a guinea pig. Here we studied the correlation between VOR and one region of VEP. We further analyzed a second portion of VEP, where vestibular nerve activity should occur using rectified bin integration (RBI). To this end, stimulation artifact was significantly reduced by hardware and software approaches. We found a high VEP-VOR correlation (R-squared=0.86), suggesting that VEP could substitute VOR as metric of vestibular function. Differences between below and above vestibular threshold stimulation were seen for the second portion of VEP. Further investigations are required to determine the specific parts of VEP that accurately represents vestibular function(s).**

I. Introduction

VESTIBULAR organs in the inner ear consist of three semicircular canals (horizontal, superior and posterior) that measure head rotation, and two otolith organs that measure linear acceleration of the head [1]. Vestibular disorders deteriorate gaze, postural control and spatial orientation; current therapies such as medication and rehabilitation often fail to treat these disorders satisfactorily. To restore functionality, vestibular prostheses often stimulate the vestibular nerves electrically, using modulation of stimulation parameters (e.g., pulse frequency) to encode relevant information such as head angular velocity (Merfeld et al. [2,3], Della Santina et al. [4,5]). Devices designed thus far operate in open-loop control; electrical stimulation is activated and reflexive eye movements (i.e. vestibulo-ocular reflex (VOR)) are observed as functional output. However, this output is not fed back to tune the stimulation.

In earlier work, we highlighted the necessity for a closed-loop vestibular prosthesis and investigated vestibular evoked potentials (VEPs) as useful metric of stimulation efficacy [6,7]. VEP is a more direct metric of vestibular function compared to VOR and vestibular evoked myogenic potential (VEMP)—which both involve several synapses and are difficult to obtain outside a lab environment. In our previous paper [7], VEPs induced by electrical stimulation of the horizontal canal in a guinea pig were analyzed in the time domain using stimulation-triggered averaging and rectified bin integration (RBI). Stimulation and recording were done with the same implanted electrode array. Evidence was found that these measurements contained relevant information beyond stimulation artifact expressed in differences between below and above vestibular threshold stimulations.

Here, we push the analysis of VEP further to uncover the relationship with vestibular function. In the following sections, animal preparation and experiment setup are described. We then test a correlation between VEP and VOR, and continue with artifact reduction via electrode site selection and template subtraction. This allows calculation of RBI over other parts of VEP that previously have been contaminated by stimulation artifact—specifically the portion of VEP where vestibular nerve activity should be present. The RBIs are then compared, and differences between below and above threshold stimulation are manifested in this analysis.

These results are another step in VEP characterization, and will help design a closed-loop prosthesis. But they are not yet an attempt to reproduce vestibular system dynamics, natural firing rates, or responses to natural movement. These cannot be addressed with single stimulation pulses.

II. Methods

A. Animal Preparation

A male, mature guinea pig was prepared for these experiments with three surgeries (details in [3,7]). All experiments were approved by the institutional animal care and use committee and were in accordance with US Dept. of Agriculture guidelines. In brief, the animal was initially instrumented with a fiberglass-composite, bolt-like structure ("headbolt"). A container for stimulation circuitry and connectors ("headcap") was semi-permanently attached to the headbolt. Afterwards, a 3-turn stainless steel eye coil was inserted for VOR measurements. Finally, a double-sided electrode array with eight sites [8] was implanted into the ampulla of the left horizontal canal. Electrode placement was improved by using a micromanipulator and a portable stimulation device as well as monitoring eye movement to cyclic stimulation of electrode sites during surgery.

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B. Experiment Setup

Details can be read in [7], two aspects are highlighted herein. For VEP measurements, the implanted electrode and Tucker-Davis Technologies (Alachua, FL, USA) devices were used (Medusa Base Station (24.4 kHz sampling rate), preamplifier (RA16PA) that included analog bandpass filtering between 2.2–7,500 Hz, and buffer (RA4AC)).

For VOR measurements, the implanted wire coil was connected to a National Instruments DSP (Austin, TX, USA). A LabVIEW program measured induced currents and computed eye movement with a sampling rate of 25 kHz and a low-pass RC filter of 3 kHz. All data was processed with Matlab (Mathworks, Natick, MA, USA).

C. Stimulation and Recording Paradigm

Different sites of the electrode array were used for stimulation and recording after threshold testing 2-3 weeks post surgery [7]. Briefly, these tests found two critical thresholds: *facial* and *vestibular*. Stimulating at the former results in facial nerve twitching, it is thus the upper limit. The latter is the lower limit, stimulating above the vestibular threshold will cause VOR, a major functional output of the vestibular system. We assume that a lack of VOR implies that the vestibular nerve is not sufficiently excited.

To record VEP, measurements with this electrode array were made during and after charge-balanced, symmetric, biphasic pulses consisting of a cathodic phase, an interphase gap (IPG) and an anodic phase. We used pulses with 200 µs each for cathodic, anodic phase and IPG at 5 pulses per second (pps). Two current amplitudes below and above vestibular threshold were applied.

VOR was measured for stimulation pulses with 200 µs phase durations using the coil system described in the prior section. However, VOR and VEP were not measured simultaneously as the coil system introduced inordinate noise to the VEP recordings. In all trials (VEP and VOR), stimulation lasted 40 s. Afterwards, time traces were analyzed and average responses were computed.

D. Artifact reduction

Both a hardware and software approach were pursued to reduce stimulation artifact which would hamper analysis. In terms of hardware, electrode sites were chosen for recording based on the observed reduction of artifact. While stimulation occupied two sites, recording required at least three sites: one or more recording, a reference and a ground. The recording and reference sites were differentially amplified.

Artifact was further reduced by template subtraction. A template was inferred from below vestibular threshold stimulation and a multiple was subsequently subtracted from a recording above vestibular threshold. The appropriate multiplication factor corresponded to the ratio of the two current amplitudes for below and above threshold stimulation [9].

E. Rectified bin integration

RBI values are computed from filtered signals that are rectified and integrated. Specifics are in [10]. Conceptually it is a measure of signal power inside a specific time-bin.

III. Results

A. Correlation of VEP and VOR

The average VEP response to above threshold stimulation (60 µA) showed a characteristic "bump" after the large spike. This bump in the VEP shared characteristics with the average horizontal eye movement response recorded in a separate trial to the same stimulation pattern. Specifically, the average VOR response rose to a positive peak at approx. 15 ms, while average VEP decreased to a negative peak at ca. 16 ms. Both signals then returned slowly to baseline (Fig. 1). Importantly, this bump was solely evident for above threshold stimulation (threshold at 30 µA); stimulation below threshold at 10 µA did not exhibit such a bump and also did not elicit any eye movement.

Correlation analysis evaluated a maximum correlation of R-squared=0.86 between the average VOR response (0-54 ms) and part of the average VEP response (1.6-55.6 ms) shown in Fig. 1. Time point 0 indicated stimulation onset.

B. Artifact reduction

The stimulation and recording setup illustrated in Fig. 2(A,B) (and similar orientations) resulted in amplifier saturation, whereas positioning both recording and reference sites to be approximately equidistant to the stimulation site succeeded in avoiding amplifier clipping (Fig. 2C,D). The nominal range of the preamplifier was +/-4 mV and saturation was most likely due to stimulation artifact.

To reduce stimulation artifact further, template subtraction was applied. The average VEP response of below threshold stimulation (10 µA) was used for the template. This was scaled by six and then subtracted from the average response of above threshold stimulation (60 µA, Fig. 3A).

In Fig. 3(B) the first peaks of the scaled template (dashed line) aligned well in time and amplitude with the average response for 60 µA (solid line). The subtraction finally led to Fig. 3(C) with only residual peaks till 0.5 ms, where three regions of interest in VEP were defined: i) cathodic response

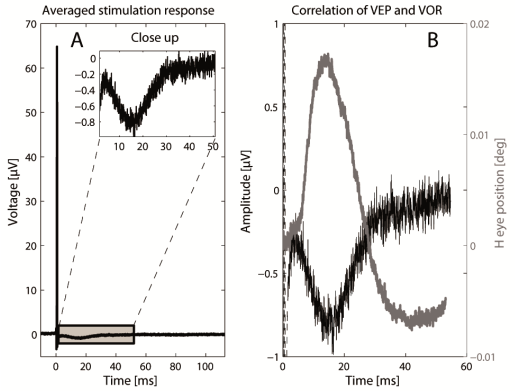

Fig. 1. (A) Average stimulation response to stimulation at 60 µA and 200 µs phase durations and IPG. Inset shows a magnification of the "bump" after the large spike (grey shaded box). This bump was only evident in above threshold stimulation. (B) Correlation of average VEP (black) and average horizontal VOR (grey). The peak of VOR leads the VEP peak by 1.6 ms, the length of the correlation window was 54 ms (R-squared=0.86).

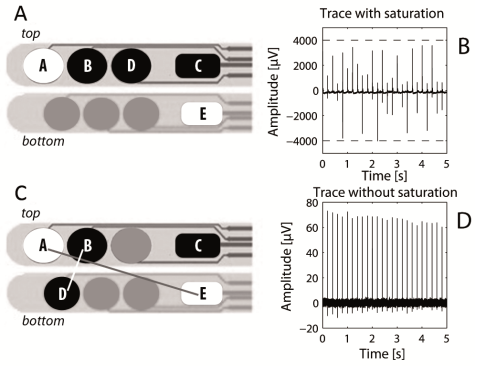

Fig. 2. (A) An example of electrode configuration where amplifier clipping occurred. White sites A and E were stimulation electrodes, black sites B, D and C were recording electrodes (recording, reference and ground, respectively). Clipping was evident in the measurement (B). The nominal range of the preamplifier is indicated by horizontal dashed lines. (C) Recording setup rejecting large stimulation artifact. Recording reference was moved beneath site A. This formed an approximate right angle between recording path (white line between sites B and D) and stimulation path (grey line between sites A and E). (D) Note the magnitude difference between (B) and (D) for recordings with identical stimulation pattern (200 µs phase durations and IPG, 60 µA at 5 pps).

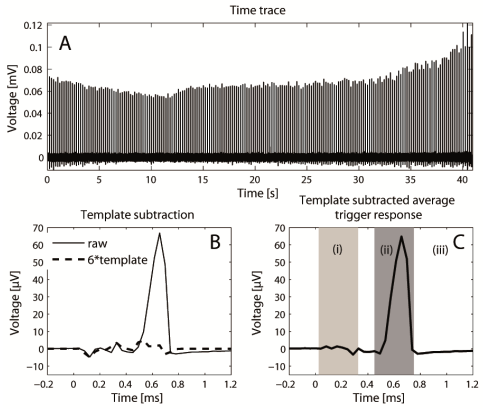

Fig. 3. (A) Time trace of 200 µs stimulation at 60 µA. (B) From the average trigger response of below threshold stimulation at 10 µA, a template was calculated, scaled (dashed line), and then subtracted from the average trigger response of 60 µA stimulation (solid line). This reduced stimulation artifact and yielded the response in (C). We defined labels (i) through (iii) in the differently shaded regions (see text for details).

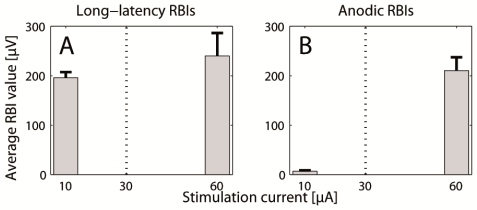

Fig. 4. Comparison of long-latency and anodic RBIs. Vertical dotted lines represent vestibular threshold. (A) Long-latency RBI for 200-200-200 µs stimulation. Significant difference between 10 and 60 µA (2-sample KS test, α=0.01). (B) RBI computed over the anodic response, augmented this difference between below and above threshold.

(25-325 µs), ii) anodic response (450-750 µs), and iii) long latency response (0.75-30 ms). Anodic RBI was determined from 450-750 µs, long-latency RBI from 0.75-10.75 ms. These three regions are temporal associations to parts of the stimulation pulse and are not necessarily causal. Yet neural activation should occur during the anodic response.

C. RBI below and above threshold

After template subtraction, RBI was calculated for both long-latency *and* anodic response to stimulation with two current amplitudes. As in [7], there were statistical differences between below and above threshold stimulation for the long-latency RBIs (Fig. 4A).

However, these differences were hardly discernible. Computing RBIs over anodic region emphasized the differences between 10 and 60 µA stimulation (Fig. 4B). No correlation was found between anodic and long-latency RBI (R-squared<0.05).

Furthermore, RBIs of the anodic and cathodic response were evaluated to explain the initial decreasing and later increasing trend of the spike amplitude in Fig. 3(A). Cathodic RBIs remained constantly low over the course of the trial, whereas anodic RBIs displayed a higher mean and more variability.

IV. Discussion

A. Correlation of VEP and VOR

The high correlation (R-squared=0.86) between parts of average VOR and long-latency VEP indicated that an eye movement artifact was likely recorded (Fig. 1). The long-latency bin includes the 1.5 ms latency between vestibular afferents and abducens neurons (in primates) reported in [11]. These neurons innervate the lateral rectus muscle that controls abduction of the eye. Another time delay of ca. 4 ms is then added for the transformation of abducens neurons firing into eye movement. The total delay (5.5 ms) corresponds to the first inflection points of the eye position and VEP curves (Fig. 1B). Thus it is conceivable that the correlated part of VEP is an eye muscle/movement artifact. Further, the exact cause of the 1.6 ms difference between signal peaks in VEP and VOR is unknown (Fig. 1B). The high-pass filter on the TDT system may introduce up to 1 ms delay where the VOR recording system had no high-pass filter (TDT, *pers. comm.*, March 2011).

In terms of control, however, both VOR and the correlated long-latency response are too slow (54 ms) to be measured at normal stimulation rates (e.g., 250 pps baseline [3]). Therefore we were interested, whether the anodic response also contained any relevant vestibular information, since anodic RBI can be calculated in a shorter bin than long-latency RBI. Thus, anodic RBI would permit high stimulation rates (e.g., up to 400 Hz [5]). Artifact reduction was used to access the anodic period response.

B. Artifact reduction

Choosing favorable recording sites on the electrode array avoided amplifier saturation. Interestingly, these two electrode sites for recording and reference were the closest to the stimulation electrode and moreover they formed a right angle to the stimulation path (Fig. 2B). We believe that thus both sites were exposed to similar stimulation artifacts, which were nearly canceled out by the differential recording. We therefore propose this recording setup for multi-site electrode arrays near the vestibular nerve.

Since we wanted to study vestibular nerve activity in VEP, remaining artifacts had to be diminished further. This was achieved with template subtraction (Fig. 3). However, template subtraction may not be suitable for a chronic prosthesis if the template changed over time. For chronic prosthesis we will use the masker-probe method, which is vastly used in cochlear implants [12].

C. RBI below and above threshold

Having reduced the artifact, we tried to find a correlation between anodic and long-latency response that we have shown is correlated to VOR. The mean and standard deviation of anodic and long-latency RBIs were compared.

From our earlier contribution we were aware of the statistical differences between below and above threshold long-latency RBI (Fig. 4A). These differences were affirmed by the RBIs for the anodic response. We assume that the anodic response represents vestibular nerve activity, which would render RBI clearly different for below and above threshold stimulation. Furthermore, we conjecture that the long-latency response relates to eye-movement. The small differences in long-latency RBI may be due to the minuscule eye movement (peak of 0.015 deg) recorded to stimulation with 60 μA at 5 pps. In comparison, [3] recorded stronger eye movement to pulsatile stimulation and higher current amplitude (0.12 deg at 250 pps and between 60 and 125 μA).

There was no correlation between the mean anodic and long-latency RBIs. Long-latency RBI might have been not sensitive enough, especially in view of the minute eye movements caused. This motivates further experiments with stimulation bursts and higher amplitudes.

RBI was then also used to examine the trend observed in Fig. 3(A). This varying trend was due to variations of the anodic RBI, while the RBI of the cathodic response stayed constantly low. If the response variation were caused by uncorrected stimulation artifact, we would expect to see it in all RBIs. We think that the cathodic region does not contain any neural responses since we expect these not to develop before 300 μs after stimulation onset [13, Chapt. 3].

V. Conclusions and Future Work

We have discovered a high correlation between the long-latency response of VEP and VOR. Encouraged by this we also examined the anodic response, which most likely represents vestibular nerve activity.

To study the anodic region, stimulation artifact was reduced substantially by favorable recording site selection. We propose to record in a 90 deg angle from the stimulation path, with electrode sites equally distanced and as close as possible to the stimulation electrode.

Calculation of RBI for the anodic region manifested a stronger separation of below and above threshold stimulation than for the long-latency region. But no correlation was found between both regions. This might be due to very small eye movements elicited, therefore more experiments are required to improve eye movement. Additionally, VEP should be recorded not only to single pulses, but also to natural movement. This correlation between VEP and VOR is important as the latter is the gold standard for evaluating vestibular functionality. Such a measure for functionality is instrumental in a closed-loop vestibular prosthesis and should be readily available.

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