



## Research Paper

## Vestibular-dependent inter-stimulus interval effects on sound evoked potentials of central origin

N.P.M. Todd <sup>a,\*</sup>, S. Govender <sup>b</sup>, J.G. Colebatch <sup>b</sup><sup>a</sup> Department of Psychology, University of Exeter, Exeter EX4 4QG, UK<sup>b</sup> Prince of Wales Clinical School and Neuroscience Research Australia, University of New South Wales, Randwick, Sydney, NSW 2052, Australia

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## ABSTRACT

Todd et al. (2014ab) have recently demonstrated the presence of vestibular-dependent contributions to auditory evoked potentials (AEPs) when passing through the vestibular threshold as determined by vestibular evoked myogenic potentials (VEMPs), including a particular deflection labeled as an N42/P52 prior to the long-latency AEPs N1 and P2. In this paper we report the results of an experiment to determine the effect of inter-stimulus interval (ISI) and regularity on potentials recorded above and below VEMP threshold. Five healthy, right-handed subjects were recruited and evoked potentials were recorded to binaurally presented sound stimulation, above and below vestibular threshold, at seven stimulus rates with ISIs of 212, 300, 424, 600, 848, 1200 and 1696 ms. The inner five intervals, i.e. 300, 424, 600, 848, 1200 ms, were presented twice in both regular and irregular conditions. ANOVA on the global field power (GFP) were conducted for each of four waves, N42, P52, N1 and P2 with factors of intensity, ISI and regularity. Both N42 and P52 waves showed significant ANOVA effects of intensity but no other main effects or interactions. In contrast both N1 and P2 showed additional effects of ISI, as well as intensity, and evidence of non-linear interactions between ISI and intensity. A source analysis was carried out consistent with prior work suggesting that when above vestibular threshold, in addition to bilateral superior temporal cortex, ocular, cerebellar and cingulate sources are recruited. Further statistical analysis of the source currents indicated that the origin of the interactions with intensity may be the ISI sensitivity of the vestibular-dependent sources. This in turn may reflect a specific vestibular preference for stimulus rates associated with locomotion, i.e. rates close to 2 Hz, or ISIs close to 500 ms, where saccular afferents show increased gain and the corresponding reflexes are most sensitive.

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## 1. Introduction

Acoustic sensitivity of the human vestibular system has long been established and can be demonstrated by means of evoked electromyographic (EMG) signals (Bickford et al., 1964). Such EMG responses can be measured either from muscles of the neck, e.g. the sternocleidomastoid muscle, reflecting the vestibular-collic reflex pathways (the vestibular evoked myogenic potential or VEMP (Colebatch et al., 1994)) or from extra-ocular eye muscles, reflecting activation of the vestibular ocular reflex pathways (ocular VEMP or OVEMP (Rosengren et al., 2005; Todd et al., 2007)).

In the last decade evidence has accumulated from electroencephalographic (EEG) studies in humans that vestibular receptors

may also contribute to sound evoked potentials of central origin. Following a study by de Waele et al. (2001), who showed the existence of short-latency potentials (8–15 ms) in response to electrical stimulation, Todd et al. (2003) demonstrated a similar response to 500 Hz bone-conducted (BC) sound. These acoustically evoked short-latency vestibular evoked potentials (VsEPs) were confirmed to have vestibular origin as they were absent in vestibular patients but present in deaf subjects with intact VEMPs (Rosengren and Colebatch, 2006). Later Todd et al. (2008) used source analysis to confirm that the short-latency VsEPs produced by air-conducted (AC) and BC sound are dominated by the pathways underlying the vestibular-ocular reflex, but also suggested activity in frontal cortex. More recently McNerney et al. (2011) used an alternative source analysis method to suggest that a wider range of vestibular cortical areas contribute to the short-latency potentials activated by sound.

Most recently Todd et al. (2014a) provided evidence that in

\* Corresponding author.

E-mail address: [n.todd@exeter.ac.uk](mailto:n.todd@exeter.ac.uk) (N.P.M. Todd).

addition to short-latency effects there were likely vestibular contributions at longer latencies for AC sound stimulation. These were recognized by systematic changes that took place in morphology and by the intensity dependence of the responses in passing through the vestibular threshold. Of particular interest was a medium-latency deflection, labelled N42/P52, which exhibited a change in slope and latency function, and was absent in an avestibular patient. The long-latency auditory evoked potential (LAEP) N1 also showed some changes in passing through the VEMP threshold. A source analysis indicated a possible contribution of cingulate cortex to both the N42 and N1, as well as temporal lobe, cerebellar and other sub-cortical sources. A follow-up study comparing left vs right stimulation showed that the vestibular-dependent responses indicated a left-ear/right-hemisphere advantage for the long-latency responses (Todd et al., 2014b). Source analysis indicated that these effects may be mediated by a contralateral projection to the right cingulate cortex. In addition we found evidence of a possible vestibular contribution to the auditory T-complex in radial temporal lobe sources.

It has been well-established that the LAEPs and their magnetic equivalents are highly dependent on the inter-stimulus interval (ISI) (Picton et al., 1974; Hari et al., 1982; Lü et al., 1992; Sams et al., 1993; Carver et al., 2002; Snyder and Large, 2005). In the above studies by Todd et al. (2014a,b), however, the ISIs were limited to a narrow range between 600 and 1000 ms but any possible vestibular interactions with the ISI dependency are unknown. We wished in the present study, therefore, to investigate the effects of ISI and regularity on the vestibular-dependent changes in sound evoked potentials, and in particular the N42/P52, N1 and P2 waves. The presence of a vestibular interaction with ISI would be of considerable theoretical interest, for example with respect to suggested vestibular contributions to rhythm perception (Trainor et al., 2009; Todd and Lee, 2015a,b). Knowledge of such an interaction may also have benefit for clinical usage of VsEPs and for determining optimal stimulus rates.

## 2. Material and methods

### 2.1. Subjects

Five healthy subjects were selected for this study (2 females and 3 males, age range 22–53). All subjects were first screened for any hearing impairment using a standard screening audiometer (frequency range 250 Hz to 8 kHz) in order to check that their hearing thresholds were in the normal range. Prior to any testing, all participants gave written informed consent according to the Declaration of Helsinki.

### 2.2. Stimuli

The experimental stimuli employed for obtaining vestibular responses were AC 2-ms, 500-Hz, single cycle tone pips. AC stimuli were delivered by insert earphones (3A insert earphone, E-A-RTone Gold, Guymark UK Limited). Stimulus calibration was carried out using a GRAS IEC711 Coupler (RA0045) and a pressure-field microphone (Model 4134) with a 2260 Investigator (Brüel and Kjær, Naerum, Denmark). The stimuli were generated using customised software with a laboratory interface (power 1401, Cambridge Electronic Design, Cambridge, UK) and a commercial or custom amplifier. Two intensities were employed, i.e. +6–9 dB re 1 V peak (133–136 dB pk SPL) and –30 dB re 1 V pk, arranged so that the high intensity stimulus was above vestibular threshold and the low intensity stimulus below threshold, as is commonly assumed in vestibular research (e.g. McNerney et al., 2011).

### 2.3. Vestibular responses

As only two intensities were employed in the present study we did not measure exact vestibular thresholds, but checked prior to conducting EEG that VEMPs were present and absent for the two intensities. Subjects were tested lying supine on a couch, with the backrest tilted to approximately 30–45° from the horizontal, and required to lift their heads against gravity to activate the sternocleidomastoid (SCM) muscles. Surface EMG was measured from the ipsilateral SCM using self-adhesive Ag/AgCl electrodes. Active surface electrodes were placed over the middle of the SCM muscle belly and were referred to electrodes placed on the medial clavicle. EMG was amplified, bandpass filtered (5 Hz–1 kHz) and sampled using a Power1401 interface (CED Ltd., Cambridge, UK). The EMG was sampled at a rate of 5 kHz, starting 10 ms before to 80 ms following stimulus onset, and averaged. Up to 200 stimuli were presented at a stimulus rate of about 5 Hz. The presence or absence of a VEMP was determined by visual inspection.

### 2.4. VsEPs

VsEPs were recorded with subjects comfortably seated with their gaze directed straight ahead to picture card at a viewing distance of 100 cm. AC pips were presented binaurally at seven stimulus rates with ISIs of 212, 300, 424, 600, 848, 1200 and 1696 ms. The inner five intervals, i.e. 300, 424, 600, 848, 1200 ms, were presented twice in both regular and irregular conditions. In the irregular conditions stimuli had ISIs randomly varying with a uniform probability distribution between adjacent intervals, thus for the 300 ms irregular condition the ISIs varied randomly between 212 and 424 ms. Evoked potentials (EPs) were recorded for the two intensities. EEG was recorded using a 64-channel EEG system (Biosemi, Inc., USA). Additional electrodes were also placed below each eye (i.e. infra-ocular electrodes, IO1 and IO2), at deep frontal (F9 and F10) and at ear-lobe locations (A1 and A2). Electrode offset (i.e. running average of the voltage measured between CMS and each active electrode) was maintained below 20  $\mu$ V. Recordings were made with a band-pass of between 0.16 Hz and 1 kHz. Artefact elimination, epoching and averaging of EPs were carried out using the BESA 5 software. Epochs were 350 ms in length, from 50 ms before to 300 ms following the stimulus onset. After collection, EPs were filtered at 1–300 Hz and referenced either to linked ear-lobe electrodes or to an average reference using Scan software (v4.3, Neuroscan, USA). All subsequent analyses were conducted using the average reference.

### 2.5. Source analyses

BESA software (version 5.3 MEGIS Software GmbH, Germany) was used for dipole modelling. The standard four-shell elliptical head approximation was employed with the following parameters. The radial thickness of the head, scalp, bone and CSF were 85, 6, 7 and 1 mm, respectively, with conductivities set to 0.33, 0.33, 0.0042 and 1.0, respectively. We adopted a modelling strategy from previous occasions of using pairs of regional sources and dipoles (Todd et al., 2008, 2014a, b). This approach had been arrived at after extensive modelling using different strategies. Ocular sources and temporal lobe sources are ubiquitous for the stimuli employed and two pairs locate without fail to these areas, irrespective of starting conditions. Regional sources are appropriate to model the complexity of the (known) activation of the bilateral extra-ocular eye muscles (EOM) in conjunction with the retinal corneal dipole (RCD) associated with eye movement, and for activity in bilateral temporal cortex, which includes independent radial and tangential components (Scherg et al., 1989; Näätänen and Picton, 1987). For

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