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# Latency and Initiation of the Human Vestibuloocular Reflex to Pulsed Galvanic Stimulation

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Aw, Swee T., Michael J. Todd, and G. Michael Halmagyi. Latency and initiation of the human vestibuloocular reflex to pulsed galvanic stimulation. J Neurophysiol 96: 925-930, 2006; doi:10.1152/jn.01250.2005. Cathodal galvanic currents activate primary vestibular afferents, whereas anodal currents inhibit them. Pulsed galvanic vestibular stimulation (GVS) was used to determine the latency and initiation of the human vestibuloocular reflex. Three-dimensional galvanic vestibuloocular reflex (g-VOR) was recorded with binocular dual-search coils in response to a bilateral bipolar 100-ms rectangular pulse of current at 0.9 (near-threshold), 2.5, 5.0, 7.5, and 10.0 mA in 11 normal subjects. The g-VOR consisted of three components: conjugate torsional eye rotation away from cathode toward anode; vertical divergence (skew deviation) with hypertropia of the eye on the cathodal and hypotropia of the eye on the anodal sides; and conjugate horizontal eye rotation away from cathode toward anode. The g-VOR was repeatable across all subjects, its magnitude a linear function of the current intensity, its latency about 9.0 ms with GVS of  $\geq 2.5$  mA, and was not suppressed by visual fixation. At 10-mA stimulation, the g-VOR [x, y, z] on the cathodal side was  $[0.77 \pm 0.10, -0.05 \pm 0.05, -0.18 \pm 0.06^{\circ}]$ (mean  $\pm$  95% confidence intervals) and on the anodal side was  $[0.79 \pm 0.10, 0.16 \pm 0.05, -0.19 \pm 0.06^{\circ}]$ , with a vertical divergence of 0.20°. Although the horizontal g-VOR could have arisen from activation of the horizontal semicircular canal afferents, the verticaltorsional g-VOR resembled the vestibuloocular reflex in response to roll-plane head rotation about an Earth-horizontal axis and might be a result of both vertical semicircular canal and otolith afferent activations. Pulsed GVS is a promising technique to investigate latency and initiation of the human vestibuloocular reflex because it does not require a large mechanical apparatus nor does it pose problems of head inertia or slippage.

### INTRODUCTION

Galvanic vestibular stimulation (GVS) has been used to study the human vestibular system for >150 yr (Fitzpatrick and Day 2004). Animal studies with implanted stimulating electrodes show that cathodal GVS activates primary, especially irregularly discharging, vestibular afferents from all the vestibular endorgans, whereas anodal stimulation inhibits them, believed to be acting on their spike-trigger zones (Goldberg et al. 1984; Minor and Goldberg 1991).

Previous human studies show that maintained bilateral bipolar GVS of 0.5–10 mA, for 4–240 s, elicits static ocular torsion and a torsional–horizontal nystagmus away from the cathode toward the anode (MacDougall et al. 2002, 2003, 2005; Schneider et al. 2002; Watson et al. 1998; Zink 1997). Similarly in monkey, maintained GVS of 0.1 mA with implanted electrodes generates a torsional–horizontal nystagmus (Minor et al. 1996). Although nystagmus responses to GVS are

consistent in each subject at different times, they vary considerably between subjects (MacDougall et al. 2002). Using near-threshold GVS of 0.1–0.9 mA maintained for 4 s, a VOR latency of about 46 ms was reported (Severac Cauquil et al. 2003).

Although the nystagmus response to GVS is reproducible within subjects, its usefulness is hampered by the substantial variability between subjects, both in direction and magnitude (MacDougall et al. 2002). We therefore wondered whether using brief (100-ms pulses) rather than maintained GVS would generate a more consistent galvanic vestibuloocular reflex (g-VOR) because the initial vestibuloocular reflex in the first 100 ms should not be influenced by saccades, vision, or adaptation. Because of the low signal-to-noise ratio of the initial g-VOR when using near-threshold GVS, we also wondered whether suprathreshold pulsed GVS could give a definitive value for g-VOR latency. The objective of this study was to determine the latency and initiation of the human vestibuloocular reflex in response to pulsed GVS.

### METHODS

### Subjects

Eleven normal subjects (range: 23-65 yr;  $38.7 \pm 4.9$  yr, mean  $\pm 1$  SE) were tested with GVS after giving informed consent. The protocol was approved by Royal Prince Alfred Hospital Ethics Committee in accordance with the Helsinki II Declaration (BMJ 1991; 302: 1194).

### Recording system

Binocular three-dimensional (3D) eye positions in response to pulsed GVS were recorded using the search coil technique. Each subject was supine during the recording with head secured to a head-holder to prevent any motion artifact and in darkness viewing a 2-mm-fixation LED located 600 mm away. Binocular eye positions in three axes—horizontal, vertical, and torsional—were recorded with dual-search coils (Skalar, Delft, The Netherlands), precalibrated to determine the search coil gains and offsets. During recording, the search coil signals obtained after preamplification and phase detection (CNC Engineering, Cleveland, OH) and the computer-controlled current switch voltage were sampled with 24-bit resolution at 5 kHz using LabVIEW (National Instruments, Austin, TX) on a Win2000based PC (Microsoft, Redmond, WA). Resolution of the eye movement recording system was < 0.1 min of arc. Maximum errors and cross-coupling were < 2% (Aw et al. 2003).

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FIG. 1. Time series recording of the binocular three-dimensional (3D) eye positions and derivative of the initial torsional eye positions from a normal subject in response to bilateral, bipolar 5-mA, 100-ms rectangular pulse of galvanic vestibular stimulation (GVS) in the left-cathode/right-anode configuration. Galvanic vestibuloocular reflex (g-VOR) latency was determined by an automated software algorithm as the interval between the GVS onset and the point when the initial torsional eye velocity exceeded 1 SD of its baseline noise. Horizontal, Hor; vertical, Ver; torsional, Tor.

### Galvanic vestibular stimulation

The galvanic stimulus was a bilateral, bipolar 100-ms rectangular pulse of current at preset intensities (0.9–10 mA) delivered by 4-cm<sup>2</sup> transmastoid surface electrodes (Neutralect, MSB Limited, London, UK). It was generated by a battery device and delivered through an isolated computer-controlled switch at a repetition rate of one/s for 60 repetitions. Eleven subjects were tested with 5-mA current intensity in both left-cathode/right-anode and right-cathode/left-anode configurations. Eight of these subjects were also tested with current intensities of 0.9 (near-threshold), 2.5, 7.5, and 10 mA.

### Data analysis

Data were analyzed off-line using LabVIEW software. Binocular eye positions in space-fixed coordinates were computed in 3D as rotation vectors and Euler's angles. Any trials with blinks were manually excluded. Leftward, downward, and clockwise (CW) direc-

TABLE 1. Latencies and peak eye positions of the gVOR

tions from the subject's view were positive for horizontal (z), vertical (y), and torsional (x) eye rotations, respectively. Rotation of the upper pole of the eye toward the subject's right was CW and toward the subject's left was counterclockwise (CCW). The torsional and horizontal data obtained for the right-cathode/left-anode configuration were inverted before pooling with data from the left-cathode/right-anode configuration. Magnitude of the g-VOR ( $\sqrt{x^2 + y^2 + z^2}$ ) was determined from horizontal (z), vertical (y), and torsional (x) eye velocities derived in 3D at peak eye positions (Haslwanter 1995).

Latency of the g-VOR was determined using an automated software algorithm. It was defined as the interval between the GVS onset (i.e., onset of the computer-controlled current switch) and the point where the derivative of the torsional eye position (i.e., eye velocity) first exceeded 1 SD of its baseline noise (Aw et al. 2003). Because the torsional, vertical, and horizontal onsets were the same, the largest of the three components—the torsional component—was used to determine the latency (Fig. 1).

### Statistical analysis

Means  $\pm$  1 SE of the binocular g-VOR for each current intensity were determined from >30 GVS repetitions in each subject. At each current intensity (0.9, 2.5, 5.0, 7.5, and 10 mA) group means  $\pm$  95% confidence intervals (95%CI) were determined from eight subjects. Student's *t*-test for differences between two means of dependent observations was used to test for differences between the eye positions on cathodal and anodal sides. A significance level of P = 0.05 was used in the statistical analysis.

### RESULTS

### Latency

The latency of the g-VOR was about 9 ms with a GVS of  $\geq 2.5$  mA (Fig. 1). Group means  $\pm 95\%$ CIs of the pooled g-VOR latency (for left-cathode/right-anode and right-cathode/left-anode configurations) are displayed in Table 1. However, when the GVS was near-threshold at 0.9 mA, the g-VOR latency was prolonged to about 32 ms. Latency of the g-VOR for the eye on the cathodal side was not significantly different (P > 0.05) from the eye on the anodal side.

### Directions

The binocular g-VOR evoked by bilateral, bipolar GVS consisted of three components: conjugate torsional eye rotations approximately equal in amplitude and rotated away from the cathode toward the anode; vertical divergence (skew deviation) with the intorting eye hypertropic on the cathodal side and the extorting eye hypotropic on the anodal side; and

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	Cathodal Side				Anodal Side				
Current Intensity, mA		Peak Eye Position,°				Peak Eye Position,°			<b>C1</b>
	Latency, ms	Torsional	Vertical	Horizontal	Latency, ms	Torsional	Vertical	Horizontal	Skew Deviation,°
0.9	$31.2 \pm 1.8$	$0.05 \pm 0.01$	$-0.01 \pm 0.01$	$-0.01 \pm 0.01$	$32.2 \pm 2.3$	$0.05 \pm 0.01$	$0.01 \pm 0.01$	$-0.01 \pm 0.01$	0.02
2.5	$9.3 \pm 0.7$	$0.16 \pm 0.02$	$-0.02 \pm 0.01$	$-0.03 \pm 0.01$	$9.1 \pm 0.5$	$0.17 \pm 0.02$	$0.04 \pm 0.01$	$-0.03 \pm 0.01$	0.06
5.0	$9.0 \pm 0.3$	$0.36 \pm 0.05$	$-0.03 \pm 0.02$	$-0.12 \pm 0.03$	$8.9 \pm 0.3$	$0.38 \pm 0.04$	$0.09 \pm 0.03$	$-0.12 \pm 0.03$	0.12
7.5	$9.0 \pm 0.4$	$0.58 \pm 0.08$	$-0.03 \pm 0.04$	$-0.15 \pm 0.06$	$9.0 \pm 0.4$	$0.59 \pm 0.08$	$0.12 \pm 0.04$	$-0.14 \pm 0.04$	0.15
10.0	$9.0 \pm 0.7$	$0.77\pm0.10$	$-0.05\pm0.05$	$-0.18\pm0.06$	$9.0\pm0.4$	$0.79\pm0.10$	$0.16\pm0.05$	$-0.19\pm0.06$	0.20

Values are group means  $\pm$  95% confidence intervals (95%CI) of the latencies and peak eye position from pooled g-VOR responses (torsional, vertical, and horizontal) for left-cathode/right-anode and right-cathode/left-anode configurations from pulsed GVSs of 0.9, 2.5, 5.0, 7.5, and 10.0 mA.



FIG. 2. A: time series recording of binocular 3D eye positions from a normal subject in response to 2 repetitions of bilateral, bipolar 5-mA 100-ms rectangular pulses of GVS of left-cathode/right-anode configuration and 2 of right-cathode/left-anode configurations. B: time series of the group means  $\pm$  SE of binocular 3D eye positions from 8 subjects to pulsed GVS of [0.9, 2.5, 5.0, 7.5, 10] mA in the left-cathode/right-anode and right-cathode/left-anode configurations. Initial g-VOR increased linearly with current intensity. Binocular 3D eye positions are displayed as eye movements from the cathodal and anodal sides.

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conjugate horizontal eye rotations also approximately equal in amplitude and rotated away from the cathode toward the anode (Fig. 2, *A* and *B*). Figure 2*A* shows a typical binocular 3D eye position time series recording from a normal subject illustrating these patterns of eye movements in response to two 5-mA pulsed GVSs of left-cathode/right-anode and two of right-cathode/left-anode configurations. When the current intensity was increased from 0.9 (near-threshold) to 2.5, 5.0, 7.5, and 10.0 mA, the patterns of 3D eye movement responses of the g-VOR remained consistent, as shown by the means  $\pm$  1 SE of eye positions from eight subjects in Fig. 2*B*.

### Amplitude, magnitude, and slope

The amplitudes of the torsional, vertical, and horizontal components of the g-VOR increased with current intensity from 0.9 to 10 mA (Fig. 2*B*). The peak g-VOR eye positions [x, y, z] pooled from left-cathode/right-anode and right-cathode/ left-anode configurations are displayed in Table 1. The magnitude of the g-VOR scaled linearly with the current intensity (Fig. 3), showing that the total g-VOR output, and not just its individual components, increased linearly with current intensity from 0.9 to 10 mA. The slope of g-VOR magnitude versus

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the current intensity on the cathodal side was  $0.94^{\circ} \cdot s^{-1} \cdot mA^{-1}$  and on the anodal side was  $0.92^{\circ} \cdot s^{-1} \cdot mA^{-1}$  (mean square error = 0.02).

The torsional component was about fourfold larger than either the vertical or the horizontal component. Binocular torsional eye rotations (away from cathode toward anode) were conjugate, approximately equal in amplitude and not significantly different (P > 0.05), and increased with current intensities between 0.9 and 10 mA. The peak torsional eye position at 10 mA was about  $0.8^{\circ}$  (Table 1 and Fig. 2B). Vertical divergence (skew deviation) also increased with current intensity. The hypertropic eye on the cathodal side was significantly different (P < 0.05) from the hypotropic eye on the anodal side for all current intensities between 0.9 and 10 mA. At 10 mA, the vertical divergence was 0.20°. Horizontal eye rotations also increased with current intensity. Binocular horizontal eye rotations, away from the cathode toward the anode, were conjugate, approximately equal in amplitude, and were not significantly different (P > 0.05) from each other for all current intensities between 0.9 and 10 mA. The peak horizontal eye position at 10 mA was about 0.2°.

### DISCUSSION

The initial g-VOR consisted of three components: conjugate torsional eye rotation away from cathode toward anode; significant vertical divergence (skew deviation) with hypertropia of the intorting eye on the cathodal side and hypotropia of the extorting eye on the anodal side; and conjugate horizontal eye rotation away from the cathode toward the anode. The torsional component was nearly fourfold larger than the horizontal or vertical components.



FIG. 3. Relationship between the peak binocular g-VOR magnitude and the current intensity. Magnitude of g-VOR scaled linearly with the pulsed GVS current intensity.

GVS most likely stimulates the vestibular afferents from the semicircular canals (Goldberg et al. 1984; Kim and Curthoys 2004; Minor and Goldberg 1991) and otoliths (Suzuki et al. 1969) in a pattern that has no real rotational or translational equivalent (Fitzpatrick and Day 2004). Bilateral bipolar GVS will increase the firing rate of the semicircular canal and otolithic afferents by depolarization on the cathodal side and decrease their firing rate by hyperpolarization on the anodal side, regardless of their directional activation specificity to generate a net vestibuloocular output from the vectorial summation of the ocular responses.

The initial g-VOR could be explained by considering the total effect of bilateral bipolar GVS on all semicircular canals (Day and Fitzpatrick 2005) and otoliths (Watson et al. 1998; Zink et al. 1997). GVS would activate homolateral vertical semicircular canals to generate a skew-torsional VOR, with cancellation of some of the vertical components, in a pattern similar to that produced by roll-plane head rotations about an Earth-vertical axis (Kori et al. 2001; Schmid-Priscoveanu et al. 2000). GVS of the horizontal canals would generate net horizontal eye rotation away from the cathode toward the anode, similar to that produced by yaw-plane head rotation about an Earth-vertical axis. Bilateral bipolar GVS would result in unopposed activation of the two utricles and also generate skew torsion. Unilateral GVS of the utricular nerve induces skew-torsion and small contraversive horizontal rotation (Suzuki et al. 1969), a response pattern similar to the initial g-VOR. Natural static skew torsion [i.e., conjugate ocular torsion (counterroll) with skew deviation] is an otolith-ocular reflex in response to roll-plane head tilt about an Earthhorizontal axis (Glasauer et al. 1999; Kori et al. 2001). Pathological static skew torsion, part of the ocular tilt reaction, is present in lesion of the peripheral vestibular, probably utricular, pathways (Halmagyi et al. 1979). In contrast, GVS of the saccular nerve elicits depolarizing and/or hyperpolarizing postsynaptic potentials in only about 30% of ipsilateral and contralateral superior and inferior recti and contralateral superior oblique motorneurons, suggesting a reduced role of sacculoocular reflex (Isu et al. 2000) and upward or downward vertical eye movements (Goto et al. 2004). GVS of the saccular macula elicits variable upward and contraversive torsional eve rotation in the ipsilateral eye (Curthoys 1987).

Concomitant stimulation of all the semicircular canals and otoliths with bilateral bipolar GVS might explain why the torsional component of the g-VOR is fourfold larger than the horizontal or vertical components. In humans, the torsional component of the VOR is about the same amplitude as the vertical component from single posterior canal activation, about 40% of the vertical component with single superior canal, and about 40% of the horizontal component with single horizontal canal activation (Aw et al. 2005). Also the gain of static torsion from only otolith stimulation is less than half the gain of dynamic torsion from combined vertical canal and otolith stimulation (Kori et al. 2001). The torsional components from all five vestibular end organs on one side when activated simultaneously by GVS are synergistic, although the vertical components from superior and posterior canals are antagonistic and therefore smaller. The horizontal components from the horizontal canal and utricular activations would be synergistic (Suzuki et al. 1969), but antagonistic with the small horizontal component from posterior canal activation (Aw et al. 2005).

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With a GVS of  $\geq 2.5$  mA, the latency of the human g-VOR is about 9 ms. Because GVS activates the semicircular canals and otoliths together, this suggests that the angular and linear VOR may have a similar latency, about 9 ms, a value similar to the human (Aw et al. 1996; Collewijn and Smeets 2000) and monkey (Minor et al. 1999) angular VOR latency, and monkey (Angelaki and McHenry 1999) linear VOR latency. Because GVS simultaneously activates semicircular canals and otoliths, both angular and linear VOR contribute to the torsional component of the g-VOR. Our data show a linear torsional position curve during the entire 100-ms rectangular pulse of GVS (Figs. 1 and 2); if the otoliths responded later than the semicircular canals, then the slope of the torsional position curve would change at the point the otolith response appeared. However, linear VOR latency was previously reported to be much longer in humans (>30 ms) (Aw et al. 2003; Bronstein and Gresty 1988; Crane and Demer 1998; Wiest et al. 2001) than in monkeys (8-12 ms) (Angelaki and McHenry 1999). This discrepancy might be explained by the difficulty of delivering transient linear high accelerations to humans as opposed to monkeys. Irregular vestibular afferents that are shown to be more sensitive to high-frequency stimuli (Hullar et al. 2005) are also much more sensitive to the galvanic currents (Goldberg et al. 1984). We suggest that g-VOR latency perhaps reflects the linear VOR latency when predominantly irregular afferents are activated and is similar to the angular VOR latency in response to the high-acceleration head rotations (Aw et al. 1996; Collewijn and Smeets 2000; Minor et al. 1999). With near-threshold GVS (0.9 mA), the g-VOR latency was prolonged to about 32 ms, similar to the nearly 46 ms reported (Severac Cauquil et al. 2003). We suggest that this prolongation could be the result of a lower signal-to-noise ratio of the initial g-VOR when GVS is near-threshold.

The magnitude of the g-VOR (i.e., the total g-VOR output) was found to increase linearly with cathodal current intensity (Fig. 3). Cathodal galvanic current in the perilymphatic or endolymphatic space was shown to increase vestibular afferent firing (Goldberg et al. 1994), probably from increased transepithelial polarization by mechanotranduction channels in the hair cells (Norris et al. 1998). We speculate that the GVS range of 0.9–10 mA used in our study may have stimulated the hair cells within the linear range of transduction (Hudspeth and Corey 1977), thus resulting in a linear increase in g-VOR magnitude.

In contrast to the nystagmus evoked by maintained GVS, which shows large intersubject variability but within-subject reproducibility (MacDougall et al. 2002), the initial g-VOR evoked by pulsed GVS shows a high level of intersubject repeatability (Fig. 2*B*), probably because there is not enough time for the indirect vestibuloocular pathways in the brain stem and cerebellum, such as those responsible for velocity storage and adaptation, to become involved.

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### G R A N T S

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