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Rapid acclimatization to baseline stimulation with a multi-canal vestibulocochlear implant

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Abstract

Purpose It is hypothesized that a vestibular implant should re-establish baseline activity of the ampullary nerves. Use of a constant baseline stimulation potentially allows encoding of bi-directional head movements, through the addition of signal modulations. Effective stimulation of the vestibular nerves depends on the ability to acclimate to this baseline signal. This study aims to measure eye movement responses and evaluate patient perception after turning ON and OFF single-canal and multi-canal baseline stimulation with a vestibulocochlear implant.

Methods Nine subjects with a multi-canal vestibulocochlear implant were investigated by turning baseline stimulation ON and OFF. Eye movements were recorded at fixed time points. To quantify acclimatization, both the relative time constant (time until the nystagmus decreases to 37% of its initial maximum value) and the absolute time constant (time until the velocity drops below 5°/s) were calculated. Following each recording, patients' perceptions were collected.

Results A rapid logarithmic decay in response dynamics was observed in all subjects after turning baseline stimulation ON and OFF. Full acclimatization was typically achieved within one minute. The response dynamics were reproducible when tested twice and were comparable when using a stimulation rate of either 100% or 50%. In general, turning baseline stimulation OFF resulted in lower response dynamics compared to ON.

Conclusion The ability to quickly acclimate to step changes in stimulation amplitude level is beneficial and suggests the presence of efficient neuronal processes that aid in the process of dual-state adaptation. Rapid acclimatization paves the way for safe and convenient use of the implant.

Trial registration number and date ClinicalTrials.gov: NCT04918745. Registered 28 April 2021.

Keywords Vestibular implant · Vestibulocochlear implant · Vestibular stimulation · Acclimatization · Adaptation

Introduction

Bilateral vestibulopathy is defined as a severe loss of function of both balance organs. It represents a significant disability, involving substantial balance disturbances, oscillopsia and associated loss of autonomy and quality of life [1–3]. Currently, care for affected individuals is limited to rehabilitation strategies, focusing on compensation, adaptation and substitution [4], as no treatment is available to restore vestibular function. In recent decades, research has increasingly focused on vestibular neuroprostheses. These devices are designed to artificially stimulate the vestibular nerves in patients with vestibular loss. The Geneva-Maastricht group is currently focusing on the application of an investigational intralabyrinthine vestibulo-cochlear implant (VCI) supplied by MED-EL, with the goal of restoring both balance and hearing [5].

In natural vestibular physiology, a baseline neural activity of approximately 90 action potentials per second is generated in the vestibular ampullary nerves. The peripheral vestibular system modulates this nerve rate both upwards and downwards in response to bidirectional movement stimuli. Movement plane specific nerve modulation on top of the baseline signal is crucial for the restoration of bi-directional

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vestibular reflexes, like the vestibulo-ocular reflex (VOR). For example, a head movement in the horizontal plane leads to modulation of the lateral canals, resulting in a compensatory horizontal eye movement. To restore the natural physiology of the semicircular canals, a VCI should establish a continuous vestibular baseline activity in the ampullary nerves. Only after baseline activity is restored, can the implant mimic the natural up and down regulation by using amplitude- and/ or rate modulation of this baseline signal [6–8].

Since vestibular baseline stimulation is a prolonged continuous electrical stimulation of the vestibular nerves, it is expected that the neural activity of the stimulated system will change over time due to neural learning processes. Adaptation and habituation are two independent processes to describe the change induced by prolonged neural activity [9]. Adaptation is defined as a semi-permanent form of associative (context-specific) learning that serves to reduce an error signal elicited by a discrepancy between or within sensory modalities; for example, the asymmetry between two vestibular nuclei after unilateral stimulation onset with a vestibular electrode [8, 10, 11]. Habituation is defined as a form of non-associative (not context specific) learning that leads to a response decline following repeated exposure to a stimulus [8, 12]. For example, exposure to a continuous amplitude stimulation elicited by a vestibular electrode. In the literature, all neural learning mechanisms (both associative and non-associative) have been referred to as 'acclimatization' [8, 10, 13]. Since it is not known if adaptation and/ or habituation is responsible for the responses observed after turning vestibular stimulation ON or OFF in humans, the terminology 'acclimatization' was adopted for subsequent reference in the current paper.

If bi-directional coding of each canal is employed, it is crucial that humans are able to acclimate to baseline stimulation, while maintaining the ability to respond to modulations of stimulation [14]. Moreover, it is of clinical relevance that humans are able to acclimate rapidly without discomfort [15]. If patients would experience prolonged periods of imbalance, dizziness or nausea whenever baseline or modulated vestibular stimulation is turned ON or OFF, comparable to patients with acute unilateral vestibular loss, it would impede the daily use of a vestibular implant.

Previous research in animals showed relatively long acclimatization times to baseline vestibular stimulation [8]. When turning baseline vestibular stimulation ON in guinea pigs, nystagmic eye responses were measured for about 7 days. When stimulation was turned OFF, nystagmus (with lower velocities) reappeared in the opposite direction.

However, time to acclimatization after baseline vestibular stimulation showed species-dependency [7, 8, 16]. The first experiments in a human subject, implanted with one vestibular electrode near the posterior ampullary nerve, showed a much more efficient acclimatization to baseline stimulation compared to animal research [7]. ON–OFF cycles resulted in a progressively shorter duration of the nystagmus response (from > 20 min to < 4 min after turning stimulating ON, and from 3 min to < 1 min after turning stimulation OFF). This finding suggested that dual-state adaptation may be possible in a human subject using a VCI. Dual-state adaptation refers to the phenomenon where a subject adapts to two vestibular input states [11, 17, 18]. The input state, or mode, changes when the baseline is switched ON or OFF.

Currently, only one study described acclimatization to baseline stimulation with a vestibular implant, utilizing multiple electrodes in four subjects. Ocular responses were monitored after onset and showed nystagmus that quickly decayed in 30 min. Intense vertigo was reported by all subjects for less than 5 min immediately upon onset of stimulation [19]. Although these results appear promising in terms of acclimatization to vestibular stimulation, systematic evaluation of eye movements and patient perceptions after turning baseline stimulation ON and OFF in single and multi-channel electrode settings were not reported. Moreover, influence of stimulation parameters such as stimulation rate were not reported.

This study aimed to evaluate eye movement responses and patients' perceptions after turning single- and multi-canal baseline stimulation ON and OFF. The effect of stimulation rate was evaluated during single-canal baseline stimulation. Based on previous research [7, 8], it was hypothesized that turning baseline stimulation ON would result in larger response dynamics (higher slow-phase velocity (SPV) of the nystagmus and more intense patients' perceptions) as well as a longer acclimatization time, compared to responses after turning baseline stimulation OFF. Acclimatization times were hypothesized to extend up to 30 min after turning ON [19] and up to 15 min after turning OFF baseline stimulation [7]. Secondly, it was hypothesized that higher SPV of nystagmus is correlated with a longer time to acclimate. Thirdly, it was hypothesized that simultaneously stimulating all three semicircular canal electrodes using baseline stimulation, elicits greater response dynamics in comparison to only one electrode/canal at a time. Lastly, no difference was expected between different stimulation rates.

Materials and methods

Subjects and preparations

Nine patients were enrolled in this study. All subjects were subjects in the VertiGO! Trial, which was extensively described in [5]. In brief, the VertiGO! Trial cohort comprised individuals with both bilateral vestibulopathy and severe-to-profound neurosensory hearing loss on at least

the implanted side. Patient characteristics are summarized in Table 1. Each subject was implanted with a multi-canal VCI. Electrodes were surgically inserted in the semicircular canals using an intralabyrinthine surgical approach, close to the ampullary nerves, as previously described [20].

Study design

All experiments were conducted as part of a 4-day study period, dedicated to analyzing multiple variables related to fitting the vestibular electrodes. Single-canal experiments were conducted, in which the lateral ampullary nerve (LAN), superior ampullary nerve (SAN) and posterior ampullary nerve (PAN) were individually stimulated. Each single-canal experiment was performed three times: twice at the 100% stimulation rate and once at 50% of the maximum stimulation rate. Multi-canal experiments (using continuous interleaved stimulation of all three vestibular electrodes) were performed once on the fourth day. Therefore, the study period consisted of ten ON/OFF cycles in total (see Fig. 1). During each cycle, a minimum duration of 90 min of continuous baseline stimulation was ensured before stimulation was turned OFF. The subject was seated in a chair in a room with dimmed light. During the 30-min period following the initiation of stimulation and the 15-min period following the cessation of stimulation, eye movements were recorded with video goggles and subjects' perceptions were collected (see below).

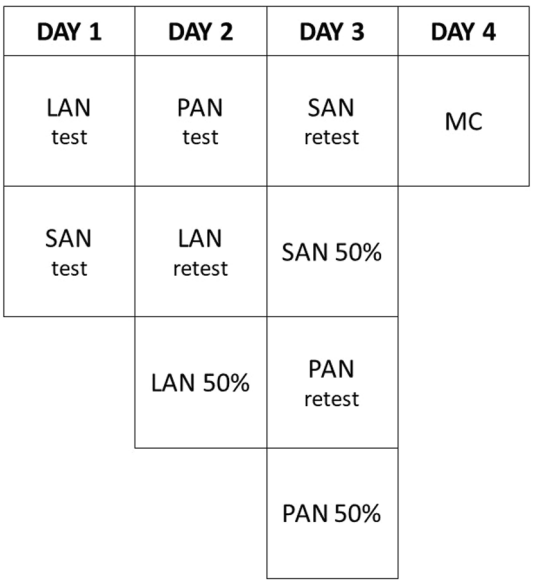

Fig. 1 Schedule of experiments per subject. Each block represents one experiment, containing one baseline ON/OFF cycle with at least 90 min in between ramping up and down. Single-canal experiments were performed twice; one test, one retest. *LAN* Lateral Ampullary Nerve stimulation, *SAN* Superior Ampullary Nerve stimulation, *PAN* Posterior Ampullary Nerve stimulation, *MC* Multi-canal stimulation. 50% indicates that baseline stimulation rate was reduced to 50% of the initial stimulation rate

Baseline stimulation parameters

Baseline stimulation with a constant rate and at a constant current level was applied using dedicated research software (*AmpFit, supplied by MED-EL, Innsbruck, Austria*). Stimulation was turned ON using a five second linear ramping up period, and turned OFF with a five second ramping down period to limit potential discomfort. Baseline stimulation was administered using biphasic charge-balanced, cathodic-first current pulses with a duration of 200 µs per phase and an interphase gap of 2.1 µs. The amplitude was subject-specific, set at 50% of the electrical dynamic range, identified for each electrode. The dynamic range was determined before every stimulation cycle as the interval between threshold (i.e. first percept and/or eye movement) and the upper comfortable level (i.e. level directly below discomfortable percept or facial nerve stimulation). Stimulation rate was consistent across electrodes but varied among subjects, as it was dependent on the individual's cochlear implant fitting. Therefore, the maximum stimulation rate ranged between 322 and 400 pulses per second (pps). Single-canal cycles with 50%

Table 1 Subject characteristics

Subject ID	Sex	Age at implantation (years)	Etiology BV	Duration BV symptoms (years)	Implant side
VCI-1	Female	54	DFNA-9	7	R
VCI-2	Male	65	Auto-immune (CREST)	21	R
VCI-3	Male	52	DFNA-9	30	L
VCI-4	Male	66	DFNA-9	10	R
VCI-5	Male	28	Idiopathic	4	R
VCI-6	Male	66	M. Meniere	25	R
VCI-7	Female	62	DFNA-9	6	L
VCI-8	Male	63	Skull base fracture	< 1	R
VCI-9	Female	62	Skull base fracture	< 1	R

rate (LAN50%, SAN50% and PAN50%, see Fig. 1) consequently ranged between 161 and 200 pps.

Eye movement recordings and subjects' perception

Movements of the left eye were recorded using 2-dimensional binocular video-oculography at 50 samples per second (*525b VisualEyes, Interacoustics, Middelfart, Denmark*). Before the start of measurements, a 20 s recording of the eyes was performed to check for the presence of spontaneous nystagmus. The lid of the video-oculography system was put on during each eye recording measurement, resulting in complete darkness to eliminate gaze fixation. To minimize artifacts resulting from spontaneous eye movements or blinking during each measurement window, subjects received a tactile feedback signal prompting them to open their eyes and maintain their gaze in the same position. In between measurements, the lid was removed to allow subjects to freely choose their earth-fixed targets within the light-dimmed room.

Eye movement recordings were performed continuously during the first 60 s after baseline ON or OFF. Thereafter, eye movements were recorded for 20 s at fixed time intervals: 3, 5, 10, 20 and 30 min. Given the assumption that acclimatization following baseline OFF is quicker in comparison to turning baseline ON, the measurement time points after cessation of baseline were reduced to 2, 5, 10 and 15 min.

After each eye movement recording, each subject's perception was assessed in terms of intensity, quality and duration. First, the intensity of perception was evaluated by presenting a printed visual analog scale ranging from 0 to 10 to the subject, with 0 representing no perception and 10 representing perception that was too intense (uncomfortable). Second, the quality of perception was queried by asking what they felt, if they felt a sensation of movement (and if so, whether there was a specific direction), and if they heard any sounds. Third, if perception was no longer present at the end of the eye movement recording, the duration of the perception (in seconds) was timed.

Data analysis

Nystagmus was quantified by measuring the 2D SPV (°/s) using custom-made software (*KingsLab 1.8.8, Maastricht University, Maastricht, The Netherlands*). The horizontal and vertical eye movements were recorded. From these traces the 2D vector of the eye velocity was calculated. Velocity was considered to be zero when no nystagmus could be detected within the measurement frame. No consistently present spontaneous nystagmus was detected with a slow phase velocity ≥ 2 °/s before baseline stimulation. Therefore, no response corrections were implemented. This would compromise reliability due to incorrect (alignment) correction, leading to inaccurate vector summation.

All SPV and 2D vectors of the nystagmus were collected continuously within each recording frame. The timing of each SPV was defined as the center of the slow-phase eye position trace. Nystagmus beats collected during ramping up were deleted, such that further analysis primarily focused on the effect directly after ramping up or down of baseline stimulation. The highest SPV was selected as the SPV_{max}.

The peak eye velocities recorded during the first 60 s were plotted per subject and per experiment, as a function of time. Following visual inspection of the plotted data, it was decided to fit three curves through each plot: a logarithmic fit, an exponential fit and a second degree polynomial fit. The fitted curve showing the smallest R^2 score was chosen as the best fitting function for that particular experiment/subject.

To quantify acclimatization to baseline stimulation, two methods were used. First, the relative time constant (rTc) was calculated based on exponential decay, defined as the time in seconds for the SPV to decrease to 37% (one divided by e) of the SPV_{max} [21]. Second, the absolute time constant (aTc) was estimated, defined as the time in seconds until eye movements showed an SPV of less than 5°/s [22]. The aTc was only calculated if the SPV_{max} was greater than 5°/s. Both rTc and aTc were calculated using the formula of the best fitting function (i.e. logarithmic/ exponential or second degree polynomial).

The difference in outcomes (SPV_{max}, rTc, aTc, perception) between two similar single-canal baseline stimulations (test–retest) was investigated. This comparison aimed to assess the reproducibility of acclimatization patterns. Moreover, the SPV_{max} difference between 50 and 100% stimulation rates was investigated. Given the small sample size, it was anticipated that the assumptions for normality would not be met. Consequently, the non-parametric Friedman test was used to analyze the significance of the differences in SPV_{max}, rTc, aTc and perception derived from the different single-canal baseline stimulation experiments. These experiments were considered as three group variables (cfr. Figure 1). This study did not aim to investigate the variation in acclimatization between LAN, SAN and PAN electrodes.

Since the amplitude of baseline stimulation could differ between the two similar single-canal measurements (minor dynamic range difference in test–retest), the related samples were analyzed separately and it was decided to not combine the measurements regardless of the outcome of the test–retest difference. Summary values were reported as median values, followed by the range.

To analyze potential differences in response dynamics (SPV_{max}, 2D vector, aTc, rTc, subjects' perceptions) between baseline stimulation ON versus OFF, the within-subject change was calculated. The change in SPV_{max} vector was

defined by the convex angle between the ON vector and the OFF vector. The area under the fitted curve (AUC) was computed as a summary statistic to compare the ON and OFF best fitting functions. The Wilcoxon signed-rank test was applied to test for significant differences between the ON and OFF condition.

The same approach was used to analyze the difference in response dynamics between single-canal baseline stimulation and multi-canal baseline stimulation. The within-subject change was calculated as the multi-canal outcome minus each single-canal outcome (MC-LAN, MC-SAN, MC-PAN). To investigate whether a monotonic relationship existed between SPV_{max} and aTc/rTc, the Spearman's rank correlation coefficient was calculated. To ensure validity of the test and to check for potential Simpson's paradox, the data was first analyzed separately for each group (electrode). All statistical tests were conducted using a significance level of $\alpha = 0.05$.

The quality of perception was analyzed by two researchers (BLV, BV). In case a perception of movement was reported by the subject, the alignment was evaluated in consensus between these two researchers. This evaluation involved comparing the movement direction reported by the subject with the expected movement direction according to the plane of the stimulated canal.

Ethical considerations

The VertiGO! Trial protocol was approved by the local medical ethical committee of the Maastricht University Medical Center (MUMC+), registered in Clinical Trials.gov (NCT04918745). It was conducted in accordance with the Declaration of Helsinki. Subjects provided written informed consent prior to participating in the trial and were compensated for their travelling and accommodation costs [5].

Results

Overview

Baseline stimulation: maximum slow-phase velocities of nystagmus

Eye movement responses and subjects' perceptions as a result of turning baseline stimulation ON and OFF, are presented in Table 2. Additionally, this table illustrates the electrode specific stimulation amplitudes and pulse rates.

Turning baseline stimulation ON elicited a nystagmus in 8 out of 9 subjects, in all single-canal and multi-canal conditions. Subject VCI-3 did not show any eye movements. The median SPV after turning ON baseline stimulation (single-canal and multi-canal taken together) was 11.1 °/s (range 0–38.1), with subject VCI-9 showing a remarkably high eye movement response of 38.1 °/s after turning ON LAN single-canal baseline stimulation. Turning single-canal baseline stimulation OFF elicited a nystagmus in 6 subjects for LAN, 6 for SAN and 7 for PAN. Turning multi-canal baseline stimulation OFF elicited a nystagmus in the same 6 subjects. Median SPV_{max} after turning OFF baseline stimulation (single-canal and multi-canal combined) was 6.1 °/s (range 0–26).

Baseline stimulation: subjects' perception

When baseline stimulation was turned ON, all subjects reported a comfortable perception, with a median VAS score of 3 (range 1–5). The median duration of this perception was 15 s (range 2–60 s).

When baseline stimulation was turned OFF, no perception was reported in 6 out of 9 subjects. However, subjects VCI-5, VCI-8, and VCI-9 reported a maximum VAS score of 3 out of 10. The median duration of this perception was 7 s (range 0–30 s).

Three subjects (VCI-5, VCI-8, VCI-9) reported a clear motion perception for baseline stimulation in both multi-canal and single-canal conditions. During multi-canal stimulation, all subjects (implanted on the right side) reported rightward spinning when baseline stimulation was turned ON. Leftward spinning around the same axis was reported when turning baseline stimulation OFF. During single-canal stimulation, results varied. LAN stimulation evoked a motion percept approximately aligned with the yaw axis in all three subjects. However, during SAN stimulation, the motion percept was not aligned with the canal and was perceived as yaw instead of the expected pitch. PAN stimulation resulted in a variety of motion percepts, including roll, pitch and upward translation.

Two subjects (VCI-4, VCI-6) reported an auditory percept, described as a high frequency noise with a duration less than 60 s. No negative symptoms were reported, such as disorientation or nausea.

Logarithmic acclimatization pattern of eye movement responses

To examine acclimatization patterns in eye movement responses in more detail, the SPVs observed during the first 60 s were plotted for each experiment and each subject. Figure 2 provides a representative example (VCI-5) of this eye movement analysis after turning multi-canal baseline stimulation ON (green) and OFF (red). The logarithmic trendline shown in Fig. 2 provided the most representative fit.

Best fitted eye movement acclimatization patterns after turning single-canal baseline stimulation ON (green) and OFF (red) per subject can be found in Supplementary

Table 2 Overview of eye movement responses, subjects' perception outcomes, and electrode specific stimulation settings per subject

Part 1.1 Single-canal baseline stimulation, test, 100% rate									
Subject ID	Eye movement responses				Subjects' perception			Baseline stimulation	
	SPV_{max}(°/s)	Angle (°)	rTc (sec)	aTc (sec)	Duration (sec)	Intensity (VAS)	Motion/ Audio sensation	Level (μAmp)	Rate (pps)
A. LAN single-canal baseline stimulation (ON)									
VCI-1	5.8	75	140	–	30	3	–	200	343
VCI-2	13.6	23	152	100	20	2	–	175	400
VCI-3	–	–	–	–	6	2	–	250	322
VCI-4	2.1	102	12	–	30	3	–	162.5	388
VCI-5	14.5	355	25	28	10	3	Rightward Yaw	150	387
VCI-6	18.9	92	39	58	40	3	–	112.5	354
VCI-7	12.3	164	15	12	25	3	–	200	362
VCI-8	19.2	356	240*	240*	20	1	Rightward Yaw	300	350
VCI-9	38.1	7	240*	240*	50	2	Rightward Yaw	262.5	360
B. LAN single-canal baseline stimulation (OFF)									
VCI-1	4.3	93	6	–	0	0	–	200	343
VCI-2	11.7	200	3	3	0	0	–	175	400
VCI-3	–	–	–	–	0	0	–	250	322
VCI-4	–	–	–	–	0	0	–	162.5	388
VCI-5	12	195	35	102	10	1	–	150	387
VCI-6	14	222	16	17	0	0	–	112.5	354
VCI-7	–	–	–	–	0	0	–	200	362
VCI-8	8.6	290	24	12	3	1	Leftward Yaw	300	350
VCI-9	6.2	176	30	6	30	2	Leftward Yaw	262.5	360
C. SAN single-canal baseline stimulation (ON)									
VCI-1	7.6	98	42	8	NA	1	–	150	343
VCI-2	21	88	39	58	15	3	–	175	400
VCI-3	–	–	–	–	5	4	–	262.5	322
VCI-4	2.3	100	4	–	15	4	–	175	388
VCI-5	21.4	99	28	54	60	5	Rightward Yaw	137.5	387
VCI-6	18.9	68	19	36	40	3	–	112.5	354
VCI-7	8.4	91	10	4	20	3	–	225	362
VCI-8	12	71	23	19	15	1	Rightward Yaw	312.5	350
VCI-9	12.4	97	78	66	20	3	–	262.5	360
D. SAN single-canal baseline stimulation (OFF)									
VCI-1	–	–	–	–	0	0	–	150	343
VCI-2	11	252	18	4	0	0	–	175	400
VCI-3	–	–	–	–	0	0	–	262.5	322
VCI-4	–	–	–	–	0	0	–	175	388
VCI-5	17.9	263	70	135	5	1	–	137.5	387
VCI-6	10.2	189	12	9	0	0	–	112.5	354
VCI-7	7.5	260	2	2	0	0	–	225	362
VCI-8	9.9	349	1	1	5	1	–	312.5	350
VCI-9	6.2	340	54	20	10	2	–	262.5	360
E. PAN single-canal baseline stimulation (ON)									
VCI-1	7.5	102	11	1	NA	1	–	200	343
VCI-2	16	267	37	48	0	0	–	237.5	400
VCI-3	–	–	–	–	10	1	–	275	322
VCI-4	2.2	103	5	–	10	4	High freq noise	200	388
VCI-5	11.1	248	160	75	30	3	Upward Translation	175	387

Table 2 (continued)

Part 1.1 Single-canal baseline stimulation, test, 100% rate

Subject ID	Eye movement responses				Subjects' perception			Baseline stimulation	
	SPV_{max}(°/s)	Angle (°)	rTc (sec)	aTc (sec)	Duration (sec)	Intensity (VAS)	Motion/ Audio sensation	Level (μAmp)	Rate (pps)
VCI-6	15.4	115	9	7	5	2	High freq noise	100	354
VCI-7	4.7	277	171	–	20	2	–	287.5	362
VCI-8	17.8	332	24	90	10	1	Rightward Roll	450	350
VCI-9	11.7	250	4	3	25	3	–	162.5	360
F. PAN single-canal baseline stimulation (OFF)									
VCI-1	4.6	86	14	–	0	0	–	200	343
VCI-2	8.6	70	3	2	0	0	–	237.5	400
VCI-3	–	–	–	–	0	0	–	275	322
VCI-4	–	–	–	–	0	0	–	200	388
VCI-5	7.6	126	19	7	0	0	–	175	387
VCI-6	11.8	120	71	42	0	0	–	100	354
VCI-7	2.3	100	3	–	0	0	–	287.5	362
VCI-8	10.6	293	37	27	0	0	–	450	350
VCI-9	15.7	89	46	51	25	3	Leftward Pitch	162.5	360

Part 1.2: Multi-canal baseline stimulation

Subject ID	Eye movement responses				Subjects' perception			Baseline stimulation			
	SPV_{max}(°/s)	Angle (°)	rTc (sec)	aTc (sec)	Duration (sec)	Intensity (VAS)	Motion/ Audio sensation	Level (μAmp) LAN	SAN	PAN	Rate (pps)
A. Multi-canal baseline stimulation (ON)											
VCI-1	5.4	84	20	4	40	3	–	175	150	200	343
VCI-2	19.5	342	55	47	10	3	–	175	187.5	237.5	400
VCI-3	–	–	–	–	12	3	–	250	256	169	322
VCI-4	3	249	7	–	7	3	High freq noise	162.5	187.5	200	388
VCI-5	23	67	21	27	15	5	Rightward Yaw	156	144	175	387
VCI-6	15.9	240	23	44	15	4	High freq noise	112.5	112.5	162.5	354
VCI-7	8.7	186	107	–	20	2	–	187.5	225	275	362
VCI-8	26	320	84	200	15	1	Rightward Yaw	300	312.5	450	350
VCI-9	26	341	72	162	15	3	Rightward Yaw	232	245	156	360
B. Multi-canal baseline stimulation (OFF)											
VCI-1	3.3	115	13	–	0	0	–	175	150	200	343
VCI-2	12.2	221	71	38	0	0	–	175	187.5	237.5	400
VCI-3	–	–	–	–	0	0	–	250	256	169	322
VCI-4	–	–	–	–	0	0	–	162.5	187.5	200	388
VCI-5	24.2	208	16	49	10	2	Leftward Yaw	156	144	175	387
VCI-6	15.6	181	2	4	0	0	–	112.5	112.5	162.5	354
VCI-7	–	–	–	–	0	0	–	187.5	225	275	362
VCI-8	10.7	46	5	4	5	1	Leftward Yaw	300	312.5	450	350
VCI-9	11	135	13	10	20	3	Leftward Yaw	232	245	156	360

The maximum slow-phase velocity of the nystagmus (SPV_{max}) was defined as the maximum eye velocity after ramping up/down. The angle represents the 2D eye movement angle on a polar plot, where 0° corresponds to a leftward eye movement and 90° corresponds to an upward eye movement. The relative Time constant (rTc) and absolute Time constant (aTc) were both mathematically derived from the fitted trendlines. The maximum intensity was scored on a visual analog scale (VAS) ranging from 0 to 10

Freq frequency, *NA* missing data

*Time constant was set to 240 s, which is the midpoint between the 3 and 5 min measurement

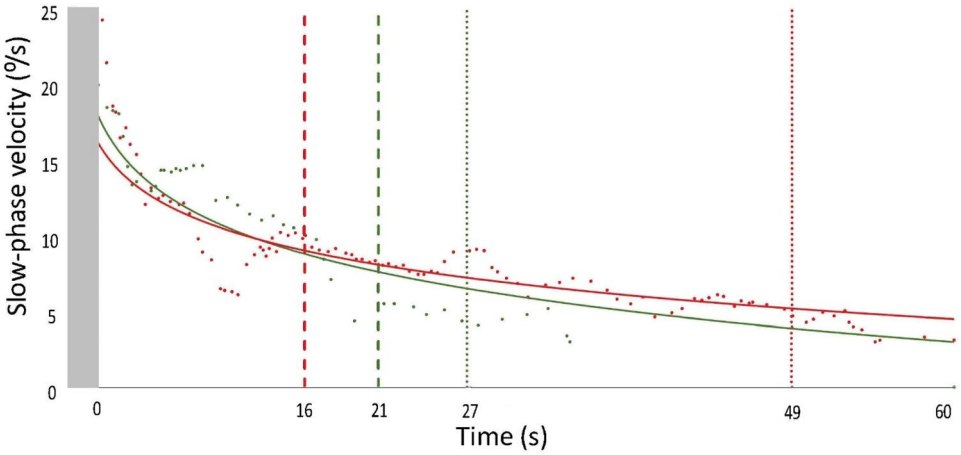

Fig. 2 Slow-phase velocities of the left eye observed during the first 60 s after multi-canal baseline stimulation ON (green) and OFF (red) in subject VCI-5, implanted with a VCI on the right side. The initial ramping up phase is displayed in grey. A logarithmic fit was applied (solid lines), from where the time constants were calculated. Furthermore, the absolute time constants (dashed lines) and relative time constants (dotted lines) are displayed. The 2D vector of the SPV differs between the ON and OFF condition, as illustrated in Fig. 3b

Information (SI 1) (first test only). Figure 3a demonstrates these patterns for the multi-canal condition. Figure 3b displays the 2D vector points of the maximum SPV collected during this 60 s acclimatization. Across all subjects and conditions, acclimatization patterns showed the best fit (i.e. lowest R^2 value) when fitted with a logarithmic function, with a median R^2 value of 0.87 (range 0.75–0.97). Hereby, a rapid decay in eye movement responses was observed, as no eye movements were detected at the 3 min measurement interval in almost all experiments. Exceptions were noted after turning baseline stimulation ON for subject VCI-8 in the multi-canal and the LAN condition, as well as for subject VCI-9 in the LAN condition. In these instances, eye movements ceased in between the 3 and 5 min measurement intervals. Due to these specific observations, it was not possible to calculate the time constants for subjects VCI-8 and VCI-9 in the LAN condition. Therefore, it was decided to set the time constants in these cases to a maximum of 240 s (midpoint of the 3 and 5 min measurement) (Table 2). The median rTc after turning ON baseline stimulation (single-canal and multi-canal taken together) was 26.5 s (range 4–240), and 47 s for aTc (range 1–240). The median rTc after turning baseline stimulation OFF was 16 s (range 1–71). The median aTc was 10 s (range 1–135).

Reproducibility of single-canal experiment results and stimulation rates

The Friedman signed rank tests did not reveal any significant differences between the three groups of measurements (test, retest, test at 50% stimulation rate). An overview of the exact statistics of all comparisons can be found in the Supplementary Information (SI2). Consequently, only the first single-canal test result was used for the analysis.

Baseline ON versus OFF

Analysis at group level

At group level, a statistically significantly larger SPV_{max} was observed after turning baseline stimulation ON versus OFF, except for the PAN single-canal experiments (Fig. 4a). The median differences in SPV_{max} between ON and OFF ranged from 3.55 to 5.15 °/s. Similarly, a significant difference in 2D angle was found when ON and OFF were compared (Fig. 4b). The median angle differences (convex angle) between the ON and OFF conditions ranged from 103 to 145°, indicating a drift of the eyes in the opposite direction. However, no significant differences were observed in acclimatization time: both rTc and aTc were comparable (Fig. 4c and d). See Supplementary Information (SI3), for an overview of the exact statistics of all comparisons.

Analysis at individual level

At the individual level, a significant difference in logarithmic decay was observed across all subjects. By comparing the AUC of the logarithmic functions illustrated in Fig. 3a, it was found that the ON responses showed significantly higher AUC values compared to OFF responses in all subjects ($p < 0.001$), except for VCI-5. In this subject, a significant smaller AUC was recorded during ON versus OFF ($p < 0.001$). The Supplementary Information (SI1) provide an overview of the significant differences in logarithmic decay observed during single-canal baseline stimulations.

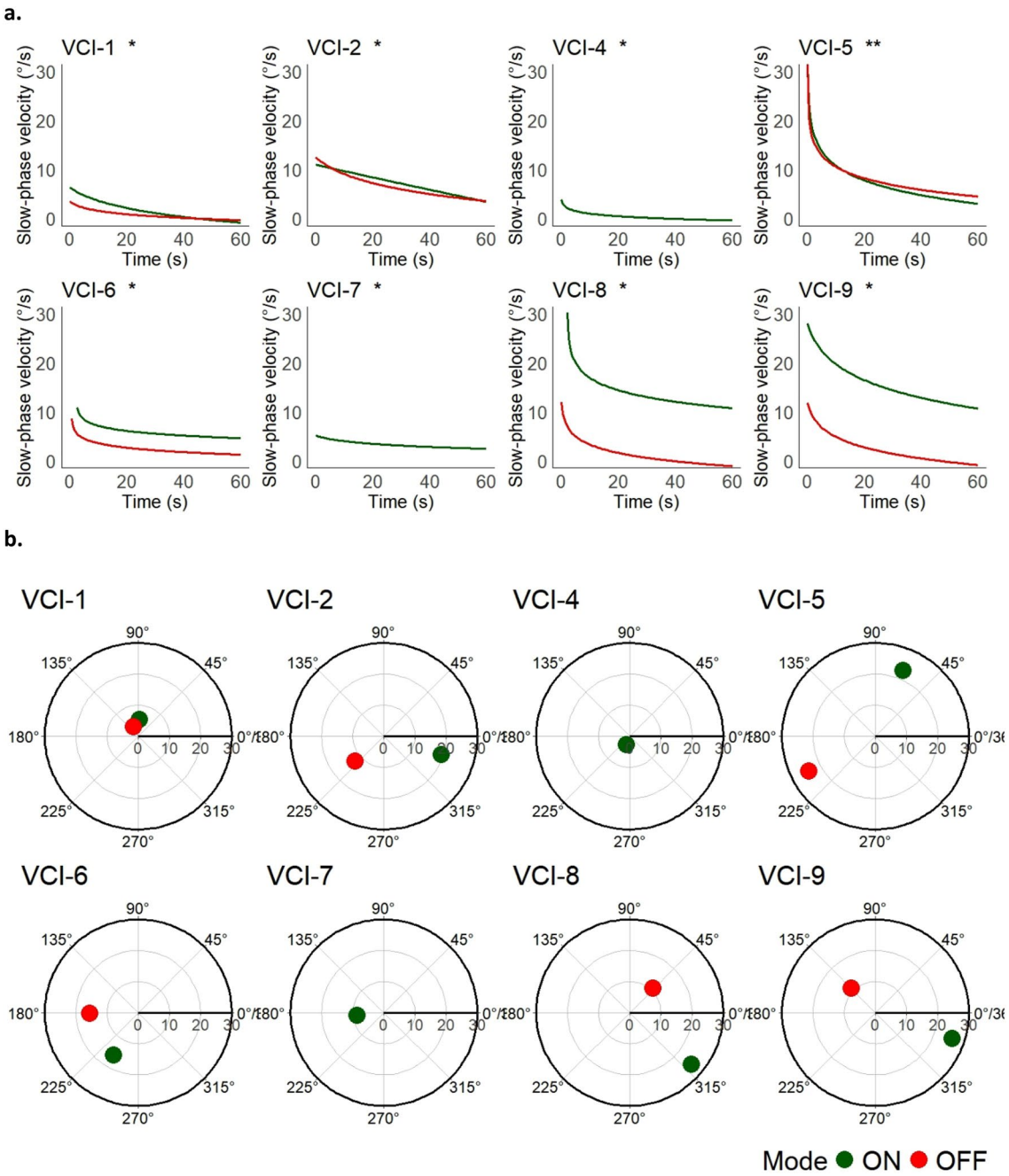

Fig. 3 Best fit of slow-phase velocities of all nystagmus observed during the first 60 s after turning multi-canal baseline stimulation ON (green) and OFF (red). *The area under the curve is significantly larger during ON versus OFF, $p < 0.001$. **The area under the curve is significantly smaller during ON versus OFF, $p < 0.001$ (**a**). Polar plots displaying the 2D vector points of the maximum slow-phase velocity of nystagmus (SPVmax) at multi-canal baseline stimulation ON (green) and OFF (red), where 0° corresponds to a leftward eye movement and 90° corresponds to an upward eye movement (**b**). N.B. The absence of a fitted line (**a**) or displayed point (**b**) represents no eye movement responses

Turning OFF baseline stimulation resulted in almost no perception. Therefore, no statistical comparisons between the ON and OFF conditions were conducted regarding outcomes of perception.

SPV_{max} versus time constant

A positive association between SPV_{max} and acclimatization time was found, with a statistically significant positive

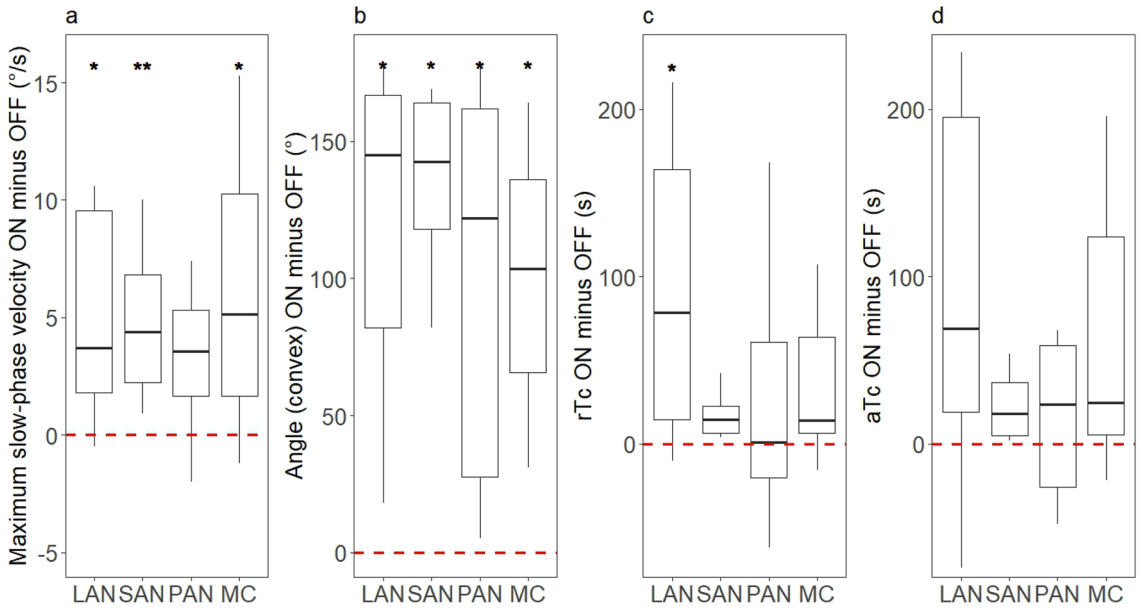

Fig. 4 Boxplots representing the within-subject change in ON minus OFF for slow-phase velocity of the nystagmus (SPV_{max}) (**a**), Angle difference (convex angle) (**b**), relative time constant (rTc) (**c**), absolute time constant (aTc) (**d**). *p < 0.05 ** p < 0.01. The red dashed line represents no difference

correlation between SPV_{max} and aTc for the baseline ON condition (Spearman's $\rho = 0.69$, $p < 0.001$). For the OFF condition, the correlation between SPV_{max} and aTc was also positive and significant (Spearman's $\rho = 0.56$, $p = 0.008$). No significant correlation was observed between SPV_{max} and rTc. Time constant and SPV_{max} are displayed in the Supplementary Information (SI4).

Multi-canal versus single-canal stimulation

No significant median within-subject difference in SPV_{max}, rTc, aTC or VAS was found when comparing multi-canal to single-canal measurements (Fig. 5a–d). This applied for all three multi-canal-single-canal comparisons. See

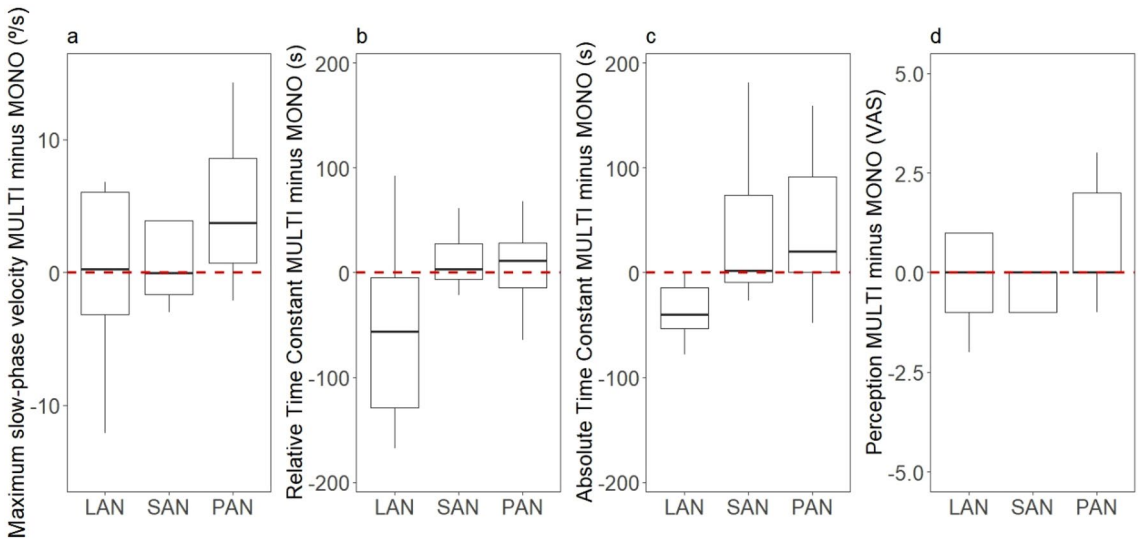

Fig. 5 Boxplots representing the within-subject difference between multi-canal minus single-canal (LAN, SAN, PAN) baseline stimulation in maximum slow-phase velocity (SPV) of the nystagmus (**a**), relative time constant (rTc) (**b**), absolute time constant (aTc) (**c**), VAS score (**d**). The red dashed line represents no difference

Supplementary Information (SI3), for an overview of the exact statistics of all comparisons.

Discussion

This study demonstrated a rapid decay in elicited eye movement responses and subjects' perceptions after turning baseline stimulation ON and OFF, using a VCI in humans. Significant acclimatization after ramping up or down baseline stimulation was typically achieved within one minute and was reported as comfortable. The response dynamics were reproducible when tested twice in single-canal settings and were comparable when using either a 100% or 50% stimulation rate. In general, turning baseline stimulation ON resulted in higher SPVs (SPV_{max} and SPVs collected during the first 60 s). All subjects report a comfortable perception after turning baseline stimulation ON. Most subjects did not report any perception after turning baseline stimulation OFF. No significant differences were observed between single-canal and multi-canal baseline stimulation. Consistent with previous research in subjects implanted with a VCI, a large response variability was observed between individuals.

Rapid acclimatization to baseline

Acclimatization times obtained in this study, were much shorter than the previously reported times for decay. In this study, median time constants below 1 min were found, compared to nearly 30 min decay time in the literature [7, 19]. A comparison of SPV_{max} and aTc revealed a positive association, indicating that higher SPV_{max} values are associated with longer fade-out times. The association between SPV_{max} and rTc was less clear, which supports the idea that eye movement decay is a relative process. In other words, stronger initial responses may result in a more prolonged decay, but the rate at which it decays is generally the same for all responses [23]. Although no analysis was previously reported on the association between SPV and time constant [7], it appears that subjects with lower SPV_{max} also tend to experience shorter durations of evoked nystagmus.

The rapid acclimatization demonstrated in this study might be induced by a reduction in the synaptic efficacy of the electrically stimulated neurons, as previously hypothesized [8]. In theory, the efficacy of modulation of the baseline signal would also decline as a result of this reduced synaptic efficacy. In practice, however, strong eye movements were observed when modulating the baseline stimulation using block and sinusoidal stimulation (previous research reviewed in [24, 25]).

No discomfort was mentioned by the subjects during baseline stimulation. Classification of types of perception was excluded from the scope of this study and will be published in a separate study (*under revie*w).

ON versus OFF & MULTI versus SINGLE

As expected, eye movements and perceptual responses were larger (in almost all patients and in most electrodes) when baseline stimulation was turned ON compared to when it was turned OFF. The difference in eye movements and perceptual responses between turning the implant ON and OFF may be attributed to the fact that transitioning from ON to OFF represents a return to the familiar, unstimulated state. This change might be more easily acclimated by the brain, although these processes are complex [26]. Furthermore, a type of high-pass filtering could explain the more decreased responses observed with baseline OFF compared to baseline ON [27].

The range of vector angle change of 103 to 145° indicated that bidirectional eye movement responses were evoked. The change in vector towards the other side, or reversal of eye responses, aligns with previous findings that acclimatization contributes to the resolution of nystagmus during prolonged stimulation [7, 11]. In fact, the reversal of the error signal caused by turning baseline stimulation OFF induces reversal eye responses, commonly known as 'nystagmus after effects' [8, 10]. This implies that the central nervous system acclimated to the new situation of unilateral stimulation. The phenomenon, where spontaneous nystagmus occurs even in the absence of input to both vestibular nuclei, is known as Bechterew's phenomenon [28]. The potential for reversal of eye movements after turning baseline stimulation OFF, reaffirms the importance of utilizing a baseline to facilitate bidirectional information with unilateral implantation [19, 29].

Multi-canal stimulation did not result in a linear sum of single-canal stimulation effects on eye movement responses and/ or perceptions. This is clinically relevant because the implant is designed to simultaneously stimulate all three canals. Further analysis of the vector summation of SPV vectors was beyond the scope of this study.

Dual-state adaptation

The potential of dual-state adaptation might influence the response dynamics. This implies that after several baseline ON and OFF transitions, acclimatization could happen more quickly. The design of this study did not allow for the analysis of the effect of more than 10 transitions. Since single-canal ON- and OFF-cycles were conducted on the first three days and the multi-canal ON/OFF cycle was consistently conducted on the fourth day, acclimatization to multi-canal baseline stimulation might be influenced by the measurements from the previous days. This could lead to a cumulative underestimation of response dynamics over the 4-day

testing period. However, no differences were found between the three single-canal measurements that were performed over time. Due to the stable responses during the first three days, a significant increase in dual-state adaptation within just ten ON/OFF cycles over 4 days was considered unlikely.

Limitations

First, the analyses should be interpreted with caution due to the limited sample size within this translational research project. While a population of nine subjects with different etiologies of bilateral vestibulopathy is of considerable size in this emerging field, measurement comparisons within and between subjects should be interpreted cautiously. Hence, it is most valuable to analyze graphs on an individual patient basis rather than relying solely on summarized models across the entire sample. Similar to findings from earlier studies involving VI recipients, substantial variability was observed across patients and across electrodes. This variability may be attributed to several factors, such as etiology and duration of bilateral vestibulopathy. In this trial, the effect of electrode positioning on responses was most likely minimal, since the surgical protocol did not change between subjects and the electrode positioning was strictly monitored and analyzed [30]. Furthermore, electrode impedances remained relatively constant over time.

Second, precise 3D measurement of eye movements (including torsion) could have been valuable. However the data collection method in this study did not allow for 3D recording. Nevertheless, based on observations of the eye movements, it should be noted that the torsional component would not significantly impact SPV measurements during LAN and SAN stimulations.

Implications, relevance and future directions

This study indicates that turning baseline stimulation ON and OFF does not induce substantial negative symptoms. This is crucial as comfortable and rapid acclimatization supports the safe integration of vestibular stimulation into daily life use, where frequent ON/OFF cycles are necessary for tasks like changing batteries, sleeping and showering, and large responsivity to the OFF condition might lead to accidents. The ability to quickly acclimate to changes in stimulation is beneficial and suggests the presence of efficient neuronal processes that aid in the potential of dual-state adaptation [11, 18]. Acclimatization also sets the stage for implementing motion-modulated electrical stimulation. Further exploration is required to determine whether this rapid and comfortable acclimatization will result in a low risk of failure when using the VCI in daily life.

Conclusion

The results shown here demonstrate that eye movement responses and patients' perceptions rapidly acclimatized to baseline stimulation (to both ON and OFF conditions), typically within one minute and without discomfort. This quick acclimatization represents a notable improvement over the previously anticipated 30 min timeframe. Response dynamics proved reproducible across repeated tests under single-canal conditions and were similar at both 100% and 50% stimulation rates. Turning baseline stimulation OFF resulted in lower response dynamics compared to the ON condition. The rapid acclimatization observed in this study cautiously paves the way for safe and convenient use of the VCI in daily routines.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by B.L.V, S.C.J.v.B and B.V. The first draft of the manuscript was written by B.L.V and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Not yet available.

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