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Cortical modulation of nociception by galvanic vestibular stimulation: A potential clinical tool?

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ABSTRACT

Objective: Vestibular afferents converge with nociceptive ones within the posterior insula, and can therefore modulate nociception. Consistent with this hypothesis, caloric vestibular stimulation (CVS) has been shown to reduce experimental and clinical pain. Since CVS can induce undesirable effects in a proportion of patients, here we explored an alternative means to activate non-invasively the vestibular pathways using innocuous bi-mastoid galvanic stimulation (GVS), and assessed its effects on experimental pain.

Methods: Sixteen healthy volunteers participated in this study. Experimental pain was induced by noxious laser-heat stimuli to the left hand while recording pain ratings and related brain potentials (LEPs). We evaluated changes of these indices during left- or right-anodal GVS (cathode on contralateral mastoid), and contrasted them with those during sham GVS, optokinetic vestibular stimulation (OKS) using virtual reality, and attentional distraction to ascertain the vestibular-specific analgesic effects of GVS.

Results: GVS elicited brief sensations of head/trunk deviation, inoffensive to all participants. Both active GVS conditions showed analgesic effects, greater for the right anodal stimulation. OKS was helpful to attain significant LEP reductions during the left-anodal stimulation. Neither sham-GVS nor the distraction task were able to modulate significantly pain ratings or LEPs.

Conclusions: GVS appeared as a well-tolerated and powerful procedure for the relief of experimental pain, probably through physiological interaction within insular nociceptive networks. Either isolated or in combination with other types of vestibular activation (e.g., optokinetic stimuli), GVS deserves being tested in clinical settings.

Introduction

The insula is known as a multisensory processing area of the brain. While its posterior granular part has attracted attention as a key region in the initial stages of nociceptive processing [1–3], the posterior insula is a multimodal area receiving input from diverse sensory systems [4–6], the vestibular system being a prominent part of such converging input [7]. The parietoinsular vestibular cortex (PIVC), a transitional region comprising parts of the posterior granular insula and retroinsular cortex, has increasingly been recognized as a core region for cortical vestibular processing [8–12]. While early data on PIVC mostly derived from animal studies in non-human primates [a review in Ref. [13]], a significant body of evidence has accumulated over the last decade, underpinning the existence of this region in humans. Meta-analyses on functional imaging data in humans demonstrated that the posterior insula, parietal operculum and retroinsular region were consistently activated by different modes of vestibular stimulation, including both caloric (CVS) and galvanic vestibular (GVS) stimulations [14,15]. Vertigo of cortical

Abbreviations: CVS, caloric vestibular stimulation; GVS, galvanic vestibular stimulation; LEPs, laser-evoked potentials; Nd:YAP, neodymium-doped yttrium-aluminum-perovskite; OKS, optokinetic stimulation; PIVC, parietoinsular vestibular cortex.

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origin due to acute ischemic stroke has been associated with PIVC [16], and direct electrical stimulation of the posterior insula using intracortically-implanted electrodes was able to induce vestibular sensations [17]. Furthermore, a recent functional-connectivity MRI analysis combined with diffusion tensor imaging demonstrated congruent functional and structural connections between the vestibular nuclei and the posterior insula [18].

Of particular interest in pain research is whether convergence between the nociceptive and vestibular systems can be utilized as an alternative analgesic strategy. Ramachandran et al. [19] introduced the concept that vestibular activation is theoretically able to reduce pain by interfering with nociceptive afferents at their arrival to the posterior insula. Indeed, there exists overlap between the posterior insular sectors where direct insular stimulation in humans can elicit vestibular and nociceptive responses [17], and prior studies using CVS have reported pain relief in several clinical pain conditions, including post-stroke pain [19–22], phantom limb pain [23], spinal cord lesions [24,25], complex regional pain syndrome [26] and migraine [27]. Similar CVS methods applied in healthy volunteers were able to reduce both subjective pain sensation and nociceptive laser-evoked potentials [28,29]. However, CVS performed by administrating cold/warm water into the external ear canal can in a proportion of patients trigger undesirable effects such as nausea and vomiting [21,26,30,31]. This may limit its use in some patients even if it attenuates their pain [21], although the majority of pain patients would likely be more tolerant of the transient unpleasant effects than dizziness patients who undergo CVS as a diagnostic procedure (e.g. Ref. [31]). In addition, distinction between vestibular-specific effects and non-specific/placebo ones is still a matter of debate, since prior studies often did not use perceptually-indistinguishable sham/control conditions but only distinguishable ones (e.g., ice-pack simulating only cold sensation to CVS [20,21,26]; a comparison with CVS effects on tactile thresholds [28]). In particular, control/sham conditions were lacking in the single previous study that recorded cortical nociceptive-evoked potentials [29]. A more recent report using a 'natural' mode of vestibular activation via head motion stimuli was unable to induce greater analgesic effects than control conditions, and suggested that previous studies may have suffered from non-specific effects, plausibly linked to distraction [32]. Given the current situation in pain clinics where the vestibular-mediated analgesic strategy is rarely practiced, further instrumental efforts are also required to enhance its clinical application.

In search of alternative means for vestibular-mediated analgesia, we assessed the pain-relieving potentialities of innocuous galvanic (direct current) stimulation applied to the mastoids (GVS), a technique that has been proven to activate the vestibular projections in the posterior insula [33–36]. This technique safely enables adequate vestibular stimulation [36], and (like CVS) its therapeutic potentialities have been suggested in several neurological conditions (see Refs. [37–40] for reviews). The objectives of current study were threefold and aimed to assess (1) whether vestibular activation using GVS could reduce nociceptive sensations and related cerebral responses; (2) whether such effects could be reproduced and/or enhanced by combining two modalities of vestibular activation (i.e., GVS plus optokinetic stimulation (OKS)), and (3) whether the modulation of nociceptive responses was specifically related to vestibular input, rather than to non-specific effects due to distraction.

Methods

Participants

Sixteen (16) healthy naive volunteers (mean age 28.7 ± 10.1 years old, 6 females, 1 left-handed) were recruited, and all but one completed the study. None of the participants had prior histories of pain-related conditions, vestibular diseases, neurological disorders, or traumatic/orthopedic problems involving head, neck or upper limbs. All the participants provided written informed consent and received compensation for their participation. Experimental procedures concerning the non-invasive cortical stimulation were approved by the Local Ethics Committee (CPP-Sud Est IV; Ref A-16 144, Identification n° 2016-A00022-49, CHU PROM 1308172). The use of laser stimulation was also approved by the Local Ethics Committee (CPP approval 01/06/2017, Code 69HCL 16_0644, n° Clinical trial: NCT03094312)).

Stimuli and recording methods

Nociceptive stimuli

Radiant heat pulses from a neodymium-doped yttrium-aluminum-perovskite laser (Nd:YAP 1340, El.En.®, Florence, Italy) were used to induce nociceptive sensations and related cortical potentials (i.e., laser-evoked potentials, LEPs). The laser stimuli were delivered to the left hand dorsum (C6 spinal segment) at intensities ranging from 60 to 100 mJ/mm^2 (wavelength 1.34 μm; 4 mm beam diameter; pulse duration 5 ms), which have been demonstrated to induce Aδ-selective LEPs in previous scalp and intracranial evoked potential studies [41–44]. Prior to the experiment, a few test stimuli were delivered in order to determine the "pain threshold", defined as the intensity that evoked nociceptive sensations corresponding to 4/10 on a verbal numerical scale where 0 = no sensation; 1 = light touch or barely pricking sensation (sensory threshold); 2 = pricking, easily noticeable; 3 = clearly pricking but still not painful; 4 = painful (reminiscent of pulling a hair or a drop of boiling hot water); 5 = painful and prompting to rub the skin; from 6 to 10 = strongly painful and unpleasant, up to worst imaginable pain [41–43]. The laser pulses were delivered at this fixed intensity throughout the experiment.

GVS

The GVS was performed by applying direct currents to bilateral mastoids [a review in Ref. [36]] using Starstim® wireless transcranial direct-current neurostimulator and Pistim® Ag/AgCl electrodes with 1-cm radius (Neuroelectrics®, Barcelona, Spain). Following skin preparation to reduce impedance (<5 kΩ), anodal and cathodal electrodes were positioned over the mastoids, posterior and inferior to the ears (each recording condition with GVS is mentioned in reference to the side of anodal stimulation (e.g., right-anodal GVS) in the following text). The stimulus intensity was set to 2 mA for all the participants, which was determined in accordance with previous studies [35,45,46] and after a pilot study that assured the participants' tolerance for this intensity. Active GVS lasted for 7 min edged by 3-s initial and final linear ramps, whereas sham GVS consisted of the linear ramps only (see below for details of experimental procedure). Concerning the active GVS, both left-anodal and right-anodal montages were evaluated in this study.

OKS and visual distraction task

The OKS was delivered via a virtual reality head set (Oculus Rift DK2®, Oculus VR, LLC, Menlo Park, CA, USA) (http://www.oculusvr.com/)) in accord with previous studies suggesting this tool as a potent means to investigate visuo-vestibular processing [47,48]. The visual stimuli consisted of multiple small randomly-distributed white dots moving coherently in a 3D-spherical space —a method that has been shown to produce vection (i.e., self-motion perception) more efficiently than does conventional 2D presentation [47]. Here we presented left-downward OKS, in which the white dots

move as if they were attached to a sphere that rotates about an oblique axis at an angular velocity of 20°/s in the diagonal leftward direction as employed by Chiarovano et al. [47]. No other directions were employed in this study so as not to orient spatial attention away from the stimulated hand (otherwise distraction rather than visuo-vestibular effects may prevail). The stimulus duration of OKS was identical (i.e., 7 min) to those of GVS conditions (see below for the experimental procedure).

Concerning the non-vestibular visual distraction task, participants were instructed to detect and count red dots intermingled with white dots, which do not move continuously but changed randomly their position every 5–10 s. The same number and size of dots were presented as in OKS through the virtual reality eyeglasses for 7 min. The participants reported a total number of red dots after the recording.

Evoked potential recordings

The scalp EEG recordings were performed with Ag/AgCl electrodes disposed on a head cap (32-channel Quick-Cap®) designed for the extended International 10–20 System. A reference electrode and a ground electrode were placed on the nose and mid-forehead, respectively. Scalp-electrode impedance was lowered to less than 5 kΩ. The EEG signals were acquired by asalab® software and amplifiers (ANT Neuro, Enschede, Netherlands) at a sampling rate of 512 Hz. A band-pass filter of 0.1–100 Hz and a notch filter of 50 Hz were applied for online surveillance of vigilance, eye blinks and other movement-related artefacts. Only continuous raw EEG signals were stored for offline LEP analysis.

Experimental design and tasks

The participants sat upright on a comfortable armchair with a headrest during all experimental procedures. After the preparation of EEG and GVS, and the determination of laser-pulse intensity, LEP recordings and online assessment of nociceptive sensations (i.e., the verbal numerical rating) were performed under GVS conditions (left-anodal and right-anodal montages), control conditions (LEP recordings without any concomitant stimulation), active-control conditions (sham-GVS, OKS, attentional distraction) and a combination of left-anodal GVS and OKS. The last condition was added to test possible enhancement of effects by the combination of two vestibular activation procedures. The left-anodal choice was guided by a pilot study having shown only modest effects for this montage.

Since the duration of possible GVS effects could not be anticipated, the right- and left-anodal conditions were performed on separate days (>3 weeks apart) and as the last session for each day to prevent any carry-on effects. The baseline conditions were thus repeated for each day. The orders of the conditions were as follows (see also Fig. 1):

- 1st series of recording (S1): initial baseline (Baseline-i-S1) → sham GVS → left-anodal GVS → left-anodal GVS + OKS → final baseline (Baseline-f-S1)
- 2nd series of recording (S2): initial baseline (Baseline-i-S2) → OKS or Distraction → Distraction or OKS → right-anodal GVS → final baseline (Baseline-f-S2)

The session order between the OKS and distraction conditions were randomized across the participants to counteract possible effects of condition order. The final baseline conditions (i.e., Baseline-f-S1 and Baseline-f-S2) were recorded 40 min after the preceding conditions in order to assess spontaneous recovery. For the rest of intervals between conditions, we waited at least 3–4 min so that there weren't any remaining sensations before starting each condition.

The laser stimulus was delivered 10 times per each condition. To minimize habituation, the 10 stimuli were divided into three blocks (3-3-4 stimuli) separated by 90-s breaks. Inter-stimulus interval within each block was 8–10 s. We displaced the stimulus site by at least 5 mm after each stimulus to avoid nociceptor fatigue and sensitisation. The left hand was stimulated in all subjects, since some neuroimaging studies in humans have suggested stronger activation of the right PIVC than its left counterpart during vestibular processing [11,35,49,50]. The participants were instructed to avoid eye blinks within 1–2 s following each stimulus, and then provided pain ratings using the verbal numerical scale. Except for the baseline conditions during which no concomitant stimulation was presented, the LEP recording was started at 2 min after the initiation of vestibular stimulation/distraction task (i.e., GVS, OKS, GVS + OKS, or distraction) in order to avoid the initial period with possible effects of attentional distraction due to the initiation of the concomitant stimulation. The experimenter operating the GVS and OKS was not involved in the laser stimulation, so as to avoid any examiner bias in obtaining expected results. Both the participants and experimenters wore eye protections against laser beam, except during the OKS, GVS + OKS and distraction conditions, during which the participants wore the virtual reality headset.

Data analysis

Data processing

A mean value of pain ratings (verbal numerical scales) was obtained for each condition per participant, and was used for later statistical comparisons between conditions.

Pre-averaging signal processing and averaging of LEPs were performed with Matlab® (The Mathworks, Inc.). The raw EEG was filtered at 0.1–30 Hz, and then segmented into 700-ms epochs, consisting of 100-ms pre-stimulus and 600-ms post-stimulus periods, for each condition. Epochs contaminated by eye blinks or

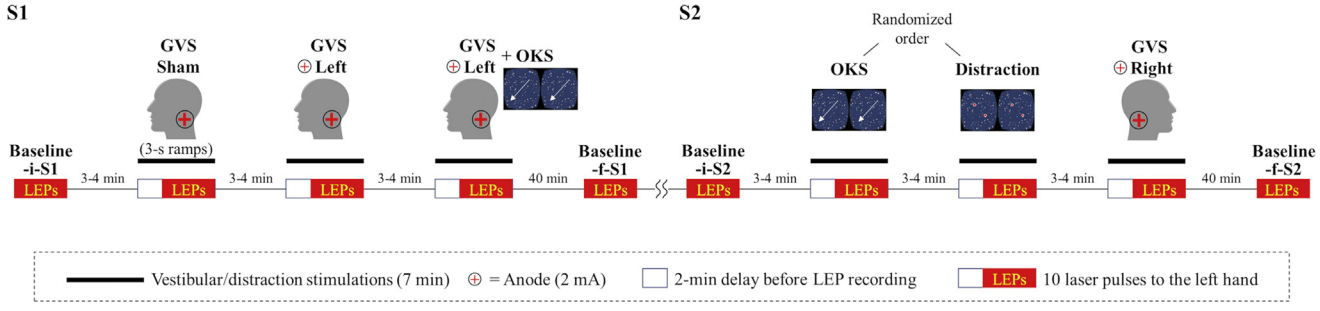

Fig. 1. Experimental paradigm. Baseline-i, initial recording of laser-evoked potentials (LEPs) and subjective sensations; Baseline-f, final recording of LEPs and subjective sensations; GVS, galvanic vestibular stimulation; OKS, optokinetic stimulation; S1, the first series of recording; S2, the second series of recording.

other movement-related artefacts were visually identified and rejected from later processing. Average waveforms were calculated separately for each condition, and the largest negative–positive deflections (i.e., N2–P2 waves) were identified at the vertex (Cz) in latency rages of 180–280 ms and 310–410 ms, respectively [41,51,52]. A baseline correction using the pre-stimulus period and a DC-detrending operation were applied to each single epoch prior to averaging. Group-level scalp topographies were computed at the peak latencies of N2 and P2 waves (see Table S1) using FieldTrip (http://fieldtrip.fcdonders.nl/), an open-source MATLAB-based toolbox [53].

Statistical analysis

Statistical analyses for pain ratings (verbal numerical scales) and LEPs (i.e., N2/P2 latencies, N2–P2 amplitudes) were performed by using JMP® (version 13: SAS Inc., Cary, USA). Sample size was determined using G*Power® [54], while considering the following parameters: one participant group, 8 repetitions, an alpha error probability of 0.05, power (1-β error probability) of 0.9, and 0.7 for correlation among repeated measures, which yielded a minimum of 13 participants to obtain a moderate effect size of 0.25. Repeated measures analysis was conducted with a linear mixed model, in which the LEP recording condition was treated as a fixed effect while the participant was included as a random effect [a review in Ref. [55]] (briefly, the random effect approach allows to extrapolate estimates of the fixed effect to a larger population beyond the study sample). Tukey's Honestly Significant Difference post-hoc correction was employed for multiple comparisons. A corrected $P < 0.05$ was considered significant throughout the statistical comparisons. Results are expressed as the mean ± standard deviation unless stated otherwise.

Results

GVS was well tolerated by all the participants and only induced transient light-headedness or subjective sensations of head/trunk deviation. These sensations were perceived only briefly at the beginning and the end of the 7-min stimulation, and hence the participants were unable to distinguish between the sham-GVS and active GVS conditions. Indeed, during post-session debriefing none of them reported having recognized the existence of the sham-GVS session. Upon specific questioning, no adverse effects such as nausea, vomiting, vertigo and skin lesions were reported by any of participants throughout or after the experiments. The OKS also did not induce any adverse effects but only slight percept of left-downward motion. Unexpectedly, one participant did not tolerate the virtual reality eyeglasses, which induced claustrophobic sensation. Condition-dependent changes in subjective pain ratings and LEP amplitudes are summarized in Table 1 and displayed in Fig. 2.

Table 1
Pain ratings (verbal numerical scales) and LEP amplitudes.

Conditions	Verbal numerical ratings	LEP amplitudes (μV)
Baseline-i	3.2 ± 0.9	40.4 ± 16.9
Sham-GVS	2.9 ± 0.9	39.2 ± 18.7
Left-anodal GVS	**2.6 ± 0.9***	35.9 ± 16.8
Right-anodal GVS	**2.5 ± 1.1***	**28.3 ± 15.7***
OKS	2.7 ± 1.2	**30.0 ± 14.2***
Left-anodal GVS + OKS	**2.4 ± 1.0***	**28.9 ± 10.2***
Distraction	2.7 ± 1.0	32.5 ± 19.7
Baseline-f	3.0 ± 1.1	35.4 ± 14.4

*Corrected $P < 0.05$ with respect to Baseline-i. See Tables S3 and S4 for statistical values.

Pain rating (verbal numerical scale)

Subjective pain ratings in the two initial (Baseline-i-S1, Baseline-i-S2) and the two final (Baseline-f-S1, Baseline-f-S2) baselines were virtually identical (no significant difference by paired *t*-test) (see Table S2). Accordingly, the baseline values of each pair were averaged, thus yielding one single initial baseline ('Baseline-i') and one single final baseline ('Baseline-f') conditions for statistical purposes.

Analysis of variance (ANOVA) across all recording conditions revealed a significant main effect of condition (F (7, 98) = 4.377, $P = 0.0003$). In post-hoc comparisons (Fig. 2, Table 1; see also Table S3 for corrected P values), both the right-anodal and left-anodal GVS conditions yielded significantly reduced pain ratings with respect to the initial baseline (i.e., Baseline-i), and the former also showed a trend relative to the final baseline (i.e., Baseline-f). Also, the combination of left-anodal GVS and OKS yielded significantly lower pain ratings compared to both Baseline-i and Baseline-f. Conversely, the sham-GVS, the OKS alone and the distraction condition showed no significant differences relative to the baselines.

Of note, pain reductions during the right-anodal GVS and the combination of left-anodal GVS and OKS attained −30% from the initial baseline in 9 and 8 participants, respectively (i.e., responder rates being 60% and 53%, respectively), whereas those during the sham GVS did not attain −30% in any of participants (see Supplementary figure).

Cortical indices of nociception (LEPs)

No significant amplitude differences were observed between the initial baselines of the first and second series of recordings (i.e., Baseline-i-S1 and Baseline-i-S2) (no significant difference by paired *t*-test), nor for the two final baselines (i.e., Baseline-f-S1 and Baseline-f-S2) (see Table S2). The results were therefore averaged across the two series for statistical comparisons (i.e., yielding Baseline-i and Baseline-f, similarly to the analysis of subjective pain ratings).

Comparison across all conditions showed a significant main effect of condition (F (7, 98) = 4.799, $P < 0.0001$). Post-hoc comparisons (Fig. 2, Table 1; see also Table S4 for corrected P values) showed significantly lower LEP amplitudes during the right-anodal GVS with respect to both Baseline-i and sham-GVS. Left-anodal GVS failed to reduce significantly the LEP amplitudes relative to Baseline-i or sham-GVS, although it decreased pain ratings. However, the combination of left-anodal GVS and OKS reduced significantly the amplitudes with respect to both Baseline-i and sham-GVS. The OKS alone also induced smaller LEPs compared to Baseline-i, and an almost significant amplitude reduction relative to the sham-GVS. Neither the sham-GVS nor the distraction condition showed significant differences relative to the baseline.

Regarding latency results, there were no significant differences for any of comparisons with respect to the initial baseline (see Table S1 for details).

To summarize, all three conditions involving active GVS (i.e., both the left-anodal and right-anodal GVS and the combination of left-anodal GVS and OKS) were able to reduce significantly the subjective pain ratings with respect to the initial baseline. The latter two significantly reduced the brain potentials (LEPs) as well. Neither the sham GVS nor the distractive procedures attained such effects.

Discussion

Vestibular ascending volleys induced by trans-mastoidal direct-current stimulation (GVS) produced anti-nociceptive effects, as

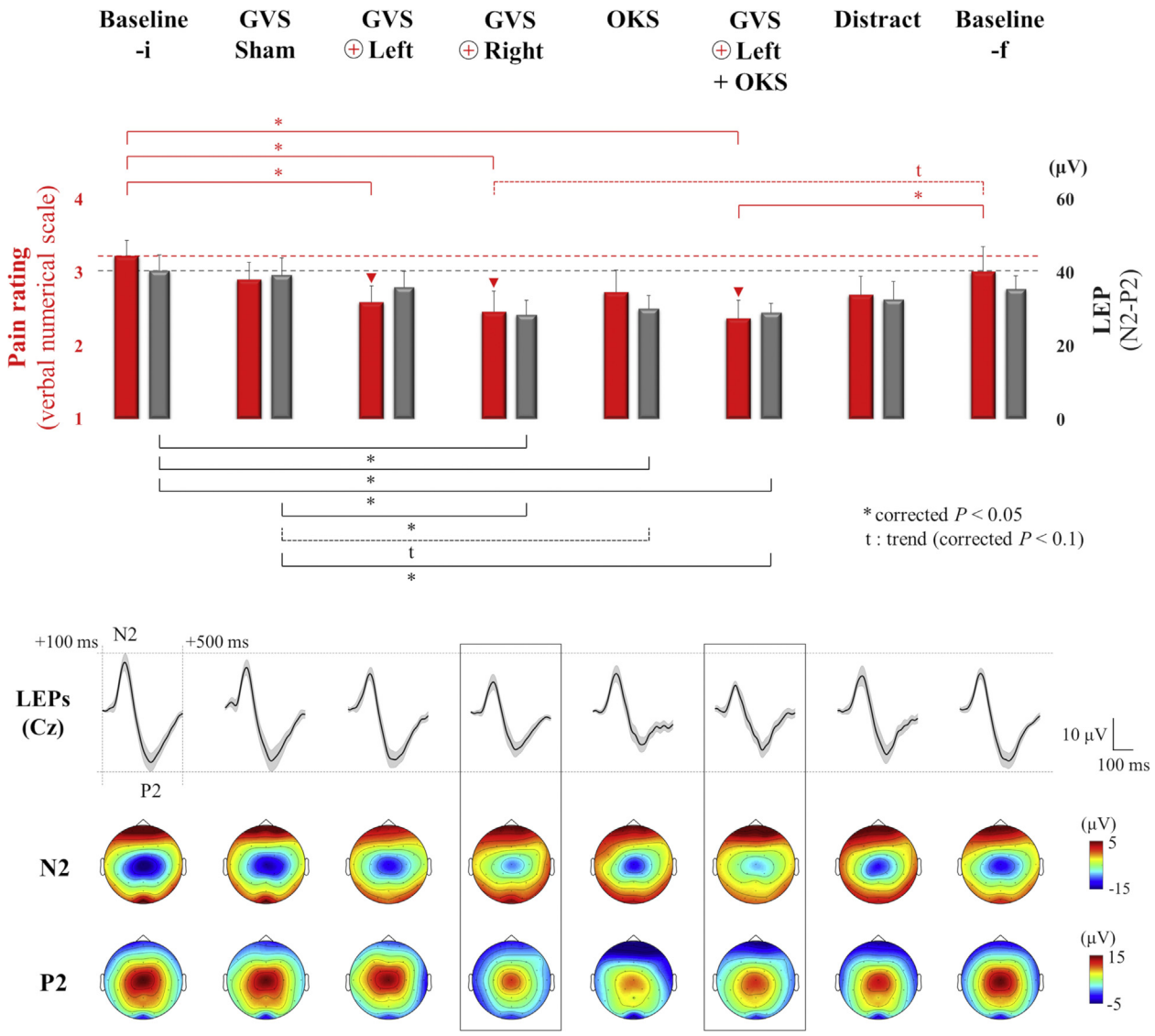

Fig. 2. Reductions of pain ratings and LEPs. (*Upper figure*) Histograms showing mean values of pain ratings (verbal numerical scales) (red histograms) and LEP (N2–P2) amplitudes (gray histograms). Error bars denote standard errors of mean. The dotted horizontal lines on the histograms indicate mean values of Baesline-i for pain ratings (red) and LEPs (gray), respectively. Note that only the three conditions with active GVS (i.e., left- and right-anodal GVS, the combination of left-anodal GVS and OKS) were able to reduce significantly the pain ratings with respect to Baseline-i. See Table 1 for a summary of pain ratings (verbal numerical scales) and LEP amplitudes. (*Middle figures*) Grand-average LEPs of each recording condition. Shaded areas represent standard errors of mean. (*Lower figures*) Grand-average scalp topographies at N2 and P2 peaks. Note that only the right-anodal GVS and the combination of left-anodal GVS and OKS were able to reduce both pain ratings and LEPs with respect to the initial baseline (highlighted with rectangles).

reflected both in subjective pain ratings and objective evoked brain responses. We interpret these results as the reflect of an action of GVS on the multisensory posterior insula, where convergent processing of nociceptive and vestibular information takes place.

Innocuous GVS exerts anti-nociceptive effects

The current study showed that GVS can effectively reduce experimental pain and nociceptive-related brain potentials. GVS attained these analgesic effects without any undesirable side-effects. Therefore, it extends the applicability of vestibular-mediated analgesia and, in case of significant clinical effect, may allow long-term maintenance use in patients. Further to the enhanced feasibility, our results indicate that anti-nociceptive GVS effects are specific, rather than deriving from distraction or other non-specific factors.

To date, the primary motor cortex has been the standard target for non-invasive cortical stimulation therapies of neuropathic pain. Repetitive trans-cranial magnetic (rTMS) and trans-cranial direct-current (tDCS) stimulations targeting this cortex have shown significant analgesic efficacy in neuropathic pain patients, whilst being effective only in a proportion (roughly 50%) of them [56–59]. Several studies, motivated by anti-depressive effects of stimulation to the dorsolateral prefrontal cortex, have investigated possible analgesic impact of this region, with mixed results so far [56,60,61]. A few studies have also attempted somatosensory cortex stimulation, but the evidence is scarce and far from encouraging so far [a review in Ref. [62]]: an rTMS study in neuropathic pain patients have shown negative results for the primary somatosensory cortex [63], and rTMS over the secondary somatosensory cortex has shown efficacy only in limited conditions such as visceral pain and orofacial neuropathic pain [64,65]. Accumulating evidence now allow to hypothesize that analgesic effects could be achieved by

stimulating the major spinothalamic-receiving region, namely the posterior insular cortex [66,67]. Indeed, anatomical studies in primates showed that 70% of ascending spinothalamic input reached the posterior insula and adjacent parietal operculum [66]. In accordance with this, direct-intracortical recordings in human insula have consistently shown that this region is the earliest to be activated in response to nociceptive input [43,68–70]. Of note, direct intra-cortical high-frequency stimulation of the human insula was shown to decrease thermal nociception [71], and a recent study using a rodent model of neuropathic pain gave credence to the anti-nociceptive effects of insular stimulation [72].

The insular cortex is deeply-situated and entirely covered by the opercular regions. Thus, it is hardly accessible to the conventional transcranial approaches (rTMS, tDCS), which unavoidably activate surface regions and tend to be spread and attenuated before reaching the insula. Employing rTMS to stimulate the posterior insula may entail a high risk of epileptic seizure events [73], possibly due to concomitant vast activation of the anterior insula [74]. By contrast, GVS activates the posterior insula by inducing physiological vestibular input [33–36], and may therefore trigger anti-nociceptive effects via physiological action on the insular nociceptive networks. As noted by Ramachandran et al. [19], close proximity between nociceptive and vestibular areas of the brain makes evolutionary sense, as it would allow “gating” of otherwise disabling pain, when the organism makes a sudden movement —hence vestibular activation to avoid a predator. Together with the above mechanisms, descending interoceptive modulation from the insula on brainstem ‘homeostatic’ sites such as the periaqueductal gray matter (PAG) [75,76] has been postulated to reduce pain [21]. Indeed, insular stimulation-induced anti-nociceptive effects in a rodent model of painful neuropathy were associated with modulation of opioid and cannabinoid systems in the PAG [72].

OKS, a potential adjunct to vestibular-mediated analgesia by GVS

The OKS is another classical way to activate the PIVC [for primate studies, [13,77,78]; for human fMRI studies [8,79]]. Neuronal recording studies in non-human primates demonstrated polymodal PIVC neurons which respond to both vestibular and optokinetic stimuli [13,77,78,80], and neuroimaging studies in humans also showed consistent involvement of the posterior insula and retroinsular region in visual-vestibular processing [8,79,81–85]. It has been suggested that the visual-vestibular convergence within the posterior insula subserves integration of self-motion (allocentric) and visual-motion (egocentric) information so that self-referenced information can be transformed into external environment-referenced mode [11,12,80]. In the current study, the OKS employed alone showed significant reductions of LEPs, whereas the mere visual-attentional distraction did not. In line with our results, a recent study showed significant reductions of evoked potentials to contact heat-pain stimulation during OKS, while non-optokinetic visual stimuli did not show similar effects [32]. Therefore, although subjective pain reductions did not attain significance, OKS appeared to exert visual-vestibular-specific effects on LEPs, which in turn might be used to augment the effects of GVS. Indeed, while the left-anodal GVS alone was not able to attain significant LEP reductions, the combined condition with OKS reduced not only pain ratings but also LEPs to a significant degree. Therefore, we suggest that the OKS is a potentially useful means to enhance the anti-nociceptive effects of GVS.

Vestibular-specific effects on LEPs

It is noteworthy that the analgesic effects of vestibular stimulations were consistently accompanied by reductions of LEPs (CVS in Ref. [29]; GVS and OKS in the present study). We analyzed the vertex component (N2–P2), a commonly-measured waveform in clinical practice to explore specifically the spinothalamic-mediated nociceptive transmission system [51,86,87]. The vertex N2–P2 complex to laser stimuli reflects cortical potentials derived from insulo-opercular, cingulate and prefrontal cortices [88,89], and its modulation by conventional modes of neurostimulation (i.e., those targeting at the motor cortex) has been inconsistent so far [90,91]. This is likely because the analgesic efficacy of conventional techniques is principally mediated via its modulatory effects within high-order networks including those involved in affective-motivational aspects of pain, rather than within the spinothalamo-cortical networks [91]. By contrast, vestibular stimulation preferentially acts on the sensory networks involving the posterior insula, which may explain their frank effects on the LEPs. Therefore, the vestibular-mediated analgesic strategy might have the potentiality to be used either as an alternative or a complementary therapeutic option in patients not responding to conventional neuromodulation strategies.

Limitations and perspectives

Despite significantly reduced pain ratings to both right-anodal and left-anodal stimulations, only the former attained statistically significant LEP reductions. Such laterality of effects on LEPs was unexpected given the bilateral cortical representation of vestibular processing [a review in Ref. [11]] and indeed the successful pain relief during both GVS conditions. Prior fMRI and PET studies in human subjects have suggested relative predominance of right PIVC activation [11,35,49,50,92], and an fMRI study showed that right-anodal GVS activated PIVC bilaterally, whereas its left-anodal counterpart activated the right PIVC exclusively [35]. Although such lateralization has not yet been consistently established [12,14], future studies should address whether laterality of pain or the possible hemispheric predominance for vestibular processing can influence the anti-nociceptive effects of GVS.

Although we carefully displaced the stimulus site after each stimulus in order to minimize pain habituation (see Supplementary data for dynamics of pain ratings, which shows virtually no habituation during each condition), this may not exclude the long-term habituation. However, while the distraction and OKS conditions were temporally randomized, only OKS showed significantly reduced LEPs. These results cannot be explained by mere habituation. Furthermore, the differential effects of the two GVS conditions (i.e., right-anodal vs. left-anodal GVS) on LEPs also argues against non-specific effects due to habituation.

CVS has been shown to activate anterior cingulate cortex (ACC) [14], while such activation has rarely been reported following GVS [34]. ACC activation to caloric stimuli was principally located in caudal, rather than rostral part of the ACC, and is therefore likely to reflect attentional orienting and motor control responses [14]. Such caudal ACC activation can hardly explain the anti-nociceptive properties of vestibular stimulations (either CVS or GVS).

Anti-nociceptive properties of a given procedure in healthy subjects cannot be easily transposed to its efficacy in chronic pain patients, hence we cannot anticipate whether it will eventually become of clinical use. For instance, high-frequency rTMS, albeit useful for neuropathic pain, did not show much effect on experimental pain in healthy subjects [91]. Nevertheless, vestibular activation using CVS has already been shown to be effective in a variety of chronic pain conditions [19–25], which supports the use of the procedure described here in future clinical trials involving chronic pain patients. Once applied clinically, whether GVS could be equipotent to CVS for alleviating chronic pain also needs to be addressed. Lastly, we do not exclude the use of CVS, which has its

advantages such as no machinery investments, no skin burn/irritation risks and already existing evidence as noted above. GVS would be a useful option when CVS is not tolerated/contraindicated or when giving weight to the enhanced feasibility of sham/placebo conditions.

Conclusions

GVS showed the potentiality to be a well-tolerated alternative to CVS for vestibular-mediated pain relief. Other modes of vestibular activation (e.g., OKS) can be synergistic to the anti-nociceptive effects of GVS. We propose GVS as a practical tool for pain relief, easy to apply, and with potentialities to be used for non-invasive cortical stimulation therapies in neuropathic pain patients.

Declaration of competing interest

None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.10.009.

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