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Vestibular prepulse inhibition of the human blink reflex

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HIGHLIGHTS

- This is the first report of a vestibular prepulse inhibition of the blink reflex.
- A vestibular prepulse inhibits the R2 and R2c area in healthy subjects but not in patients with bilateral peripheral vestibular failure.
- Vestibular PPI is a potential neurophysiological marker of vestibulo-motor integration at the brainstem level.

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ABSTRACT

Objective: Auditory and somatosensory prepulses are commonly used to assess prepulse inhibition (PPI). The effect of a vestibular prepulse upon blink reflex excitability has not been hitherto assessed.
Methods: Twenty-two healthy subjects and two patients with bilateral peripheral vestibular failure took part in the study. Whole body yaw rotation in the dark provided a vestibular inertial prepulse. Blink reflex was electrically evoked after the end of the rotation. The amplitude of R1 and the area-under-the-curve (area) of the blink reflex R2 and R2c responses were recorded and analysed.
Results: A vestibular prepulse inhibited the R2 ($p < 0.001$) and R2c area ($p < 0.05$). Increasing the angular acceleration did not increase the R2 and R2c inhibition ($p > 0.05$). Voluntary suppression of the vestibulo-ocular reflex did not affect the magnitude of inhibition ($p > 0.05$). Patients with peripheral vestibular failure did not show any inhibition.
Conclusions: Our data support a vestibular gating mechanism in humans.
Significance: The main brainstem nucleus mediating PPI – the pedunculopontine nucleus (PPN) – is heavily vestibular responsive, which is consistent with our findings of a vestibular-mediated PPI. Our technique may be used to interrogate the fidelity of brain circuits mediating vestibular-related PPN functions. Given the PPN's importance in human postural control, our technique may also provide a neurophysiological biomarker of balance.
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1. Introduction

Sensory gating is an essential physiological mechanism which allows the organism to focus on relevant stimuli and prevent overload or hyperresponsiveness to innocuous sensory inputs (Garcia-Rill et al., 2019, Kofler et al., 2023). This process can be probed through prepulse inhibition (PPI), a neurophysiological paradigm that involves the modulation of a reflex response. Although both sensory gating and PPI pertain to the control of sensory inputs, only PPI specifically requires a reflex response, and therefore it can be seen as a specialised instance of sensory gating (Kofler et al., 2024).

Disruption of PPI has been described in neurodegenerative disease, such as Parkinson's disease (Millian-Morell et al., 2018), multiple system atrophy (Zoetmulder et al., 2014), and Huntington's disease (Valls-Sole et al., 2004), and functional movement disorders (Hanzlikova et al., 2019).

PPI is a multimodal and cross-modal phenomenon in which the application of a weak sensory stimulus results in inhibition of a subsequent test response (Gomez-Nieto et al., 2020). The auditory startle reflex and the trigemino-facial blink reflex are the two commonest used test responses (Garcia-Rill et al., 2019, Kofler et al., 2024). Theoretically, all sensory modalities can be used as prepulses and may evoke an inhibition. Auditory and somatosensory

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prepulses are commonly used in PPI studies, although a few have used visual and laser prepulse stimuli (Garcia-Rill et al., 2019). Whatever the sensory modality, the degree of inhibition depends upon both the intensity of the prepulse (higher intensities eliciting more inhibition) (Csomor et al., 2005), and timing of the prepulse, with optimal interstimulus intervals ranging from a minimum of 60 ms for acoustic to 800 ms for vibrotactile stimuli (Blumenthal, 2015). Gender and hormonal status also contribute to modulating PPI (Kumari et al., 2010, Naysmith et al., 2022).

PPI is mediated by an extensive network, with components including the basal ganglia, the cerebellum, limbic cortical inputs and the pedunculopontine nucleus (PPN), which appears to be a critical hub in mediating PPI since PPN lesions in animal studies abolish PPI (Garcia-Rill et al., 2019). Interestingly, in animal models (including primates), the PPN receives significant innervation from the vestibular nuclei (Aravamuthan and Angelaki, 2012, Horowitz et al., 2005, Woolf and Butcher, 1989). Human neuroimaging and neurophysiological studies also support the notion that the PPN is part of the central vestibular network (Kirsch et al., 2016, Yousif et al., 2016).

Given the role of PPN in vestibular processing and its involvement in PPI, we hypothesized that vestibular stimuli are also filtered through such a gating mechanism via PPN and hence predicts the existence of a vestibular PPI (vPPI), i.e. a weak activation of the vestibular system (i.e. a vestibular prepulse) would reduce the magnitude of a subsequent test response. A neurophysiological interrogation of vestibular-linked PPN activity has potential clinical utility given that imbalance and falls in Parkinson's disease patients is linked to the loss of PPN cholinergic neurons (Karachi et al., 2010), and conversely PPN DBS modulates postural control in Parkinson's Disease patients (Yousif et al., 2016).

To test our prediction of a vPPI in healthy subjects, we combined blink reflex testing (via electrical stimulus to the supraorbital nerve) with a preceding vestibular stimulus provided via whole-body, constant yaw-plane accelerations in the dark. If the vestibular pre-pulse inertial stimulus behaves congruently with standard PPI responses as seen with non-vestibular modalities (e.g. somatosensory), we predict a prepulse-associated suppression of the R2 response, and a facilitation of the R1 response. To support the vestibular origin of our observations, we also assessed responses in two patients with bilateral peripheral vestibular dysfunction. Vestibular failure patients, who lack a vestibular prepulse input to the brainstem circuitry responsible for PPI, would be predicted to show no vPPI.

As for auditory and somatosensory PPI (sPPI), we similarly hypothesised an intensity-dependent inhibition of the prepulse on the blink reflex R2 response (Blumenthal, 2015). Therefore, we predicted that the magnitude of suppression of the blink response will increase by increasing the intensity of the vestibular prepulse as defined by the inertial angular acceleration. To support our hypothesis, we tested four different prepulse angular accelerations.

2. Methods

2.1. Participants

We designed three separate experiments. Fifteen subjects (6 women; aged 21–40) participated in Experiment 1, while 19 subjects (7 women; aged 21–40) participated in Experiment 2. Nine subjects participated in both experiments. Two patients clinically diagnosed with a bilateral vestibular failure participated in Experiment 3. Experiments were approved by the local Research Ethics Committee and were performed in accordance with the Declaration of Helsinki.

2.2. Experimental set-up

We activated the vestibular system by using a passive, yaw-axis, whole-body rotation in dark (Seemungal et al., 2004). Participants sat on a computer-controlled, motorised and vibration-free rotating chair in total darkness and were instructed to keep looking ahead, keeping their head still against the headrest, relax their face, and minimise any spontaneous blinking response.

We used a symmetric triangular angular velocity waveform, with constant accelerations of 5, 10, 20, or 30°/second^2 for one second and a deceleration of identical magnitude and duration but in the opposite direction. Thus, the triangular angular velocity profile lasted a total of 2 s (Fig. 1).

The optimal interstimulus interval (ISI) for PPI varies across sensory modalities. Research suggests intervals between 60–240 ms for acoustic stimuli and 100–800 ms for vibrotactile stimuli (Blumenthal, 2015). Shorter interstimulus intervals tend to facilitate the electromyographic (EMG) response, as demonstrated in studies involving acoustic and visual stimuli (Blumenthal, 2015). While it's conceivable that a vestibular prepulse could induce inhibition at very brief interstimulus intervals due to rapid integration of vestibular input in the brainstem, we selected a conservative interstimulus interval of 300 ms to mitigate any potential EMG response facilitation.

The blink-reflex eliciting supraorbital nerve stimulus was delivered 300 ms after the end of the rotation, to avoid any confounding effect caused by the concomitant activation of vestibular and blink reflex circuits. The blink reflex was recorded via EMG of the orbicularis oculi muscles. An active recording electrode was positioned on the lower eyelid, halfway between the inner and outer edges of the orbit, while the reference electrode was placed on the ipsilateral temple. Surface electrodes were used to deliver supraorbital nerve stimuli, with the cathode placed over the supraorbital notch and the anode positioned 3 cm away along the course of the nerve on the ipsilateral forehead. One percutaneous stimulus lasting 0.2 ms was applied at irregular intervals of 25–30 s to minimise any habituation in the blink reflex. The stimulus intensity was set at three times the R2 motor threshold. R2 threshold was defined as the minimum stimulus intensity able to elicit a 50 uV baseline-to-peak amplitude in at least 4 out of 8 consecutive EMG responses. Amplification of the responses was performed using a Digitimer D360R-4 device (Digitimer, Welwyn Garden City, UK). The signal was filtered using a frequency range of 50 Hz–3 kHz. Data acquisition was carried out using Signal software, version 7.02 (Cambridge Electronic Devices, Cambridge, UK), and recorded on a laptop computer. For analysis, EMG traces were rectified, and all traces contaminated by EMG artifacts were discarded (Fig. 1). Latency and amplitude of R1, and lateny and area-under-the-curve (area) of ipsilateral R2 (R2), and contralateral R2 (R2c) responses were analysed.

2.3. Procedures

2.3.1. Experiment 1: Assessing the effect of a vestibular prepulse on the blink reflex

Based on available data on vestibular perceptual and nystagmic thresholds (Seemungal et al., 2004), we chose four acceleration values above the perceptual threshold (5, 10, 20, or 30°/second^2 respectively), ensuring an activation of the vestibular system in all subjects. Experiment 1 consisted of three different conditions: condition 1, measured the unconditioned blink reflex; condition 2, measured the vestibular-conditioned blink reflex; condition 3, rotating the chair with no supraorbital nerve stimulation, to control for the possibility of any blink reflex being elicited by the rotation of the chair itself. Four trials were collected for condition 1 and 3, whereas in condition 2, eight trials for each angular acceleration

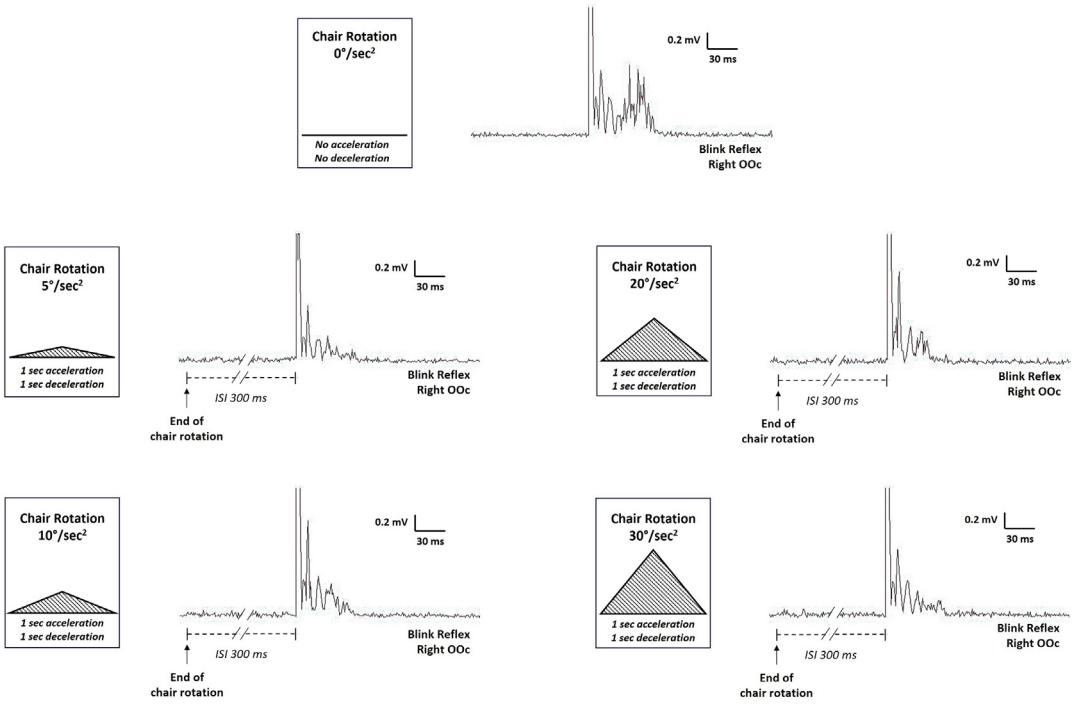


Fig. 1. Experimental set-up and prepulse modulation of the electrically induced R2 response of the blink reflex in one representative subject. The four different angular accelerations are reported, together with the rectified averaged EMG trace from the right orbicularis oculi for each condition. An inhibition of the R2 response and a facilitation of the R1 response are present in this subject.

were collected, four for right-to-left rotations and four for left-to-right rotations respectively. A total of 40 trials were collected.

2.3.2. Experiment 2: Assessing the effect of the vestibulo-ocular reflex suppression on PPI

To control for the possibility that any inhibition noted in Experiment 1 was linked secondarily to activation of the oculomotor system, we performed the vestibular pre-pulse task whilst subjects suppressed the vestibulo-ocular reflex by fixating on a visual cue. Experiment 2 consisted of two sub-experiments, each with two conditions: in 2A, we recorded an unconditioned blink reflex and a vestibular-conditioned blink reflex; in 2B, we record an unconditioned blink reflex and a vestibular conditioned blink reflex, but for the entire duration of the experiment subjects were instructed to keep their eyes open while staring at a chair-mounted head referenced red laser light in the dark (Jacobson et al., 2012), which was projected on a curtain surrounding the rotating chair. In both Experiment 2A and 2B, there were four trials, and the chair was rotated in the dark (except for point light source where indicated) with an angular acceleration of 10°/second^2.

2.3.3. Experiment 3: Assessing vPPI and sPPI in patients with bilateral vestibular dysfunction

To corroborate our findings from previous experiments, we performed the vestibular PPI task in two patients clinically diagnosed with a bilateral peripheral vestibular failure. One patient experienced bilateral vestibular failure following a traumatic brain injury, while the second patient developed bilateral vestibular failure as a result of Cogan's syndrome. These patients' peripheral vestibular failure was confirmed via video head impulse testing, bithermal caloric irrigation as well as by perceptual and nystagmic thresholds testing. Then, these patients underwent the same procedures outlined in Experiment 2a. In addition, to prove that other sensory modalities were still able to evoke PPI in these patients, we recorded the blink reflex response with and without a preceding somatosensory stimulation of the median nerve at the wrist. The intensity of the pre-pulse was set at two times the individual somatosensory threshold, and two interstimulus intervals (ie. 120 ms and 300 ms) were tested. We used an interval of 120 ms to confirm that patients exhibit a preserved sPPI, as this ISI is known to produce robust inhibition. Conversely, we employed an interval of 300 ms to match the ISI of the vPPI.

In all experiments, conditions were randomised, and an inter-trial interval of at least 25 s was used to avoid any possible habituation. Subjects were constantly monitored in dark through an infrared camera for safety reasons and to ensure that they remain alert for the duration of entire experiment. After each rotation, the lights were turned on to avoid any sleepiness and/or dump any residual post-rotational vestibular signal.

2.3.4. Data analysis and statistics

For the main experiment (experiment 1), an a-priori power analysis was conducted using G*Power version 3.1.9.6 (Faul et al., 2007) to determine the minimum sample size required to test the study hypothesis. We based our power analysis on the amount of inhibition observed in the literature by using other sensory modalities. Results indicated the required sample size to achieve 80% power for detecting a medium effect, at a significance criterion of $\alpha = 0.05$, was $N = 15$ for fixed effects one-way analysis of variance (ANOVA) test. Thus, the obtained sample size of $N = 15$ is adequate to test the study hypothesis. This number is also in line with previous sample sizes used in this research field. The experiment was not powered to account for differences in laterality given that we did not predict any differences between rightward or leftward rotations. Data comparing rightward vs. leftward rotations are reported. Homogeneity of variances was confirmed via Levene's test for equality of variances.

In Experiment 1, we measured latency of the R1, R2, and R2c responses, amplitude of R1, and area of the R2 and R2c components of the blink reflex in each single rectified trace in control and test

trials. We then averaged raw data per subject and per condition. We compared the effect of rotations at different accelerations on the latency of the R1, R2, and R2c responses, on the amplitude of R1, and on the area of the R2 and R2c responses by using a one-way ANOVA. Multiple-comparison correction for three one-way ANOVAs was performed and $p < 0.0167$ was considered statistically significant. Effect size was calculated by using Cohen's f (0.10 = small effect size; 0.25 = medium effect size; 0.40 or higher = large effect size) (Cohen, 2013). In case of a statistically significant main effect, Bonferroni corrected post-hoc tests were performed to assess the effect of each angular acceleration on the R1 amplitude, and on the R2, and R2c area.

For Experiment 2, we normalised the amount of inhibition for each subject, and we averaged the result per subject and per condition. PPI is expressed as $\frac{\text{R2conditioned area}}{\text{R2unconditioned area}} - 1$. Similarly, modulation of R1 is expressed as $\frac{\text{R1conditioned amplitude}}{\text{R1unconditioned amplitude}} - 1$. By using these formulas, values <0 reflect an inhibition, whereas values >0 reflect a facilitation of the response. We also report the percentage of facilitation/inhibition by multiplying this value for 100. We then compared the effects of the VOR suppression on PPI by using a paired sample *t*-test. Because of multiple t-tests, we applied Bonferroni's correction resulting in a significant *P*-value of 0.05/3 = 0.0167. Effect size was calculated by using Cohen's d (0.20 = small effect size; 0.5 = medium effect size; 0.8 or higher = large effect size) (Cohen, 2013).

All statistical analyses were performed in SPSS version 26.

3. Results

All participants completed the experiment without reporting any adverse effect. In all experiments, the blink reflex was never evoked by an isolated chair rotation.

3.1. Experiment 1

Data from Experiment 1 are reported in Tables 1 and 2, and in Figs. 2 and 4. A one-way ANOVA failed to reveal any differences in the latencies of R1, R2, and R2c responses of the blink reflex among conditions (for R1: $F(4, 70) = 0.071$, $p = 0.991$, Cohen's $f = 0.004$; for R2: $F(4,70) = 0.091$, $p = 0.985$, Cohen's $f = 0.005$; for R2c: $F(4,70) = 0.027$, $p = 0.999$, Cohen's $f = 0.002$) (see Table 1).

Fig. 2 shows that there was no difference in the R1 amplitude among conditions ($F(4, 70) = 0.824$, $p = 0.514$; Cohen's $f = 0.04$), although a trend towards a facilitation was observed (Table 2).

Fig. 3 shows that the R2 area was different among conditions ($F(4, 130) = 12.470$, $p < 0.0001$; Cohen's $f = 0.29$). The mean R2 area

Table 1
Effect of a vestibular prepulse on the latency of the blink reflexes responses. Average, confidence interval and standard error for latencies (ms) of R1, R2, and R2c response are reported for each condition.

		95% Confidence Interval Mean			
		Mean	Upper	Lower	Std. Error
R1	Baseline	9.873	10.509	9.237	0.296
	5°/sec^2	10.036	10.742	9.331	0.329
	10°/sec^2	10.103	10.841	9.364	0.344
	20°/sec^2	9.953	10.651	9.255	0.325
	30°/sec^2	10.000	10.709	9.290	0.3307
R2	Baseline	28.413	30.101	26.72	0.787
	5°/sec^2	28.763	29.970	27.555	0.562
	10°/sec^2	28.764	30.197	27.329	0.668
	20°/sec^2	28.890	30.284	27.495	0.650
	30°/sec^2	28.926	30.366	27.487	0.671
R2c	Baseline	31.673	33.410	29.935	0.810
	5°/sec^2	31.440	32.693	30.186	0.584
	10°/sec^2	31.490	32.976	30.003	0.693
	20°/sec^2	31.633	32.777	30.062	0.632
	30°/sec^2	31.531	33.211	30.055	0.735

Table 2
Effect of a vestibular prepulse on blink reflexes responses. Average, confidence interval and standard error for amplitude (mV) of R1 and area (mV*ms) of R2 and R2c responses are reported for each condition. Blink Reflex modulation is reported as a percentage, with facilitation represented by positive values and inhibition by negative values. *P*-values after Bonferroni correction are reported. BR: blink reflex.

		95% Confidence Interval Mean					
		Mean	Upper	Lower	Std. Error	BR modulation	*p*-value
R1	Baseline	0.810	1.093	0.528	0.132	–	–
	5°/sec^2	0.977	1.265	0.687	0.134	+20.4%	n.s.
	10°/sec^2	1.079	1.412	0.747	0.155	+33.2%	n.s.
	20°/sec^2	1.075	1.394	0.756	0.149	+32.6%	n.s.
	30°/sec^2	1.146	1.465	0.829	0.149	+41.4%	n.s.
R2	Baseline	26.136	27.691	24.581	0.794	–	–
	5°/sec^2	19.408	21.447	17.369	0.856	−25.7%	$P < 0.001$
	10°/sec^2	17.681	18.975	16.386	0.594	−32.3%	$P < 0.001$
	20°/sec^2	17.887	19.883	15.892	0.733	−31.5%	$P < 0.001$
	30°/sec^2	19.584	21.793	17.375	0.861	−25.1%	$P < 0.001$
R2c	Baseline	21.944	24.857	19.030	1.487	–	–
	5°/sec^2	16.464	18.513	14.414	0.954	−24.9%	$P < 0.05$
	10°/sec^2	15.216	17.283	13.148	0.814	−31.7%	$P < 0.001$
	20°/sec^2	15.209	16.889	13.528	0.654	−31.7%	$P < 0.001$
	30°/sec^2	17.711	20.114	15.308	1.089	−19.3%	n.s.

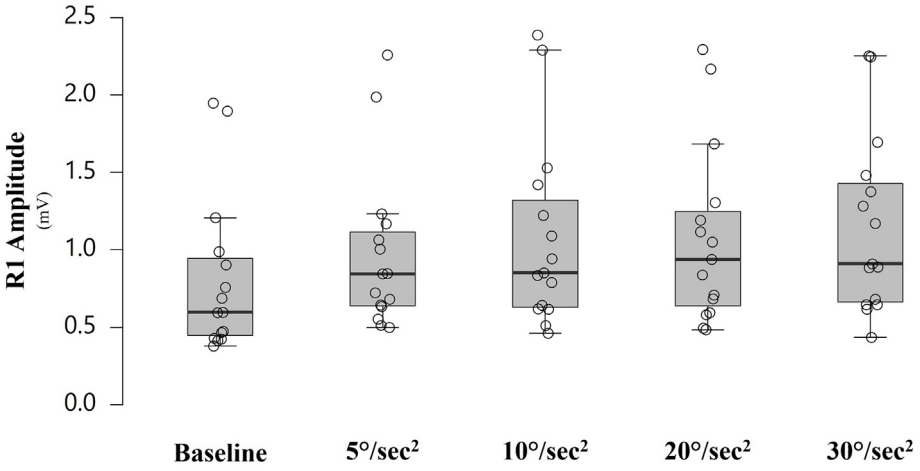


Fig. 2. Modulation of R1 amplitude according to the magnitude of vestibular prepulse. R1 amplitude (mV) is presented for each condition. No statistically significant difference was observed, although a trend towards an increase in the amplitude was noted.

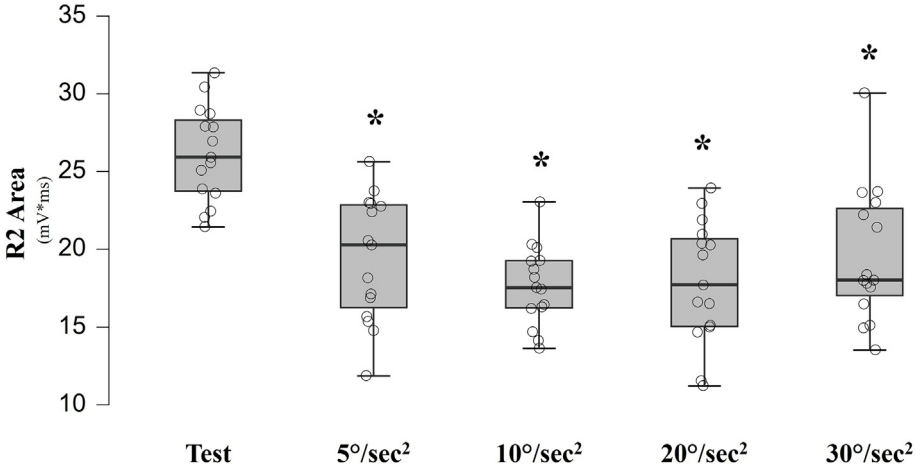


Fig. 3. Modulation of R2 area according to the magnitude of vestibular prepulse. R2 area (mV*ms) is presented for each condition. All vestibular prepulses reduced the R2 area of a subsequent test response. *<0.05.

Table 3
Effect of the vestibulo-ocular reflex suppression on vPPI. Average, confidence interval and standard error for amplitude (mV) of R1 and area (mV*ms) of R2 and R2c are reported for each condition. vPPI is reported as a percentage, with facilitation represented by positive values and inhibition by negative values. VOR: vestibulo-ocular reflex; PPI: prepulse inhibition.

			95% Confidence Interval Mean					
	VOR		Mean	Upper	Lower	Std. Error	PPI	*p*-value
R1	Present	Baseline	0.766	1.013	0.519	0.117	–	–
R1	10°/sec²	0.933	1.208	0.658	0.131	+21.8%	–	
R1	Suppressed	Baseline	0.698	0.939	0.458	0.115	–	–
R1	10°/sec²	0.902	1.184	0.621	0.133	+29.2%	0.355	
R2	Present	Baseline	22.891	24.896	20.886	1.023	–	–
R2	10°/sec²	17.359	19.024	15.694	0.849	−24.2%	–	
R2	Suppressed	Baseline	20.798	22.588	19.007	0.914	–	–
R2	10°/sec²	15.607	17.461	13.752	0.946	−25%	0.732	
R2c	Present	Baseline	20.888	22.953	18.824	1.053	–	–
R2c	10°/sec²	16.239	17.748	14.731	0.769	−22.3%	–	
R2c	Suppressed	Baseline	18.753	20.463	17.042	0.873	–	–
R2c	10°/sec²	14.836	16.727	12.944	0.965	−21.9%	0.930	

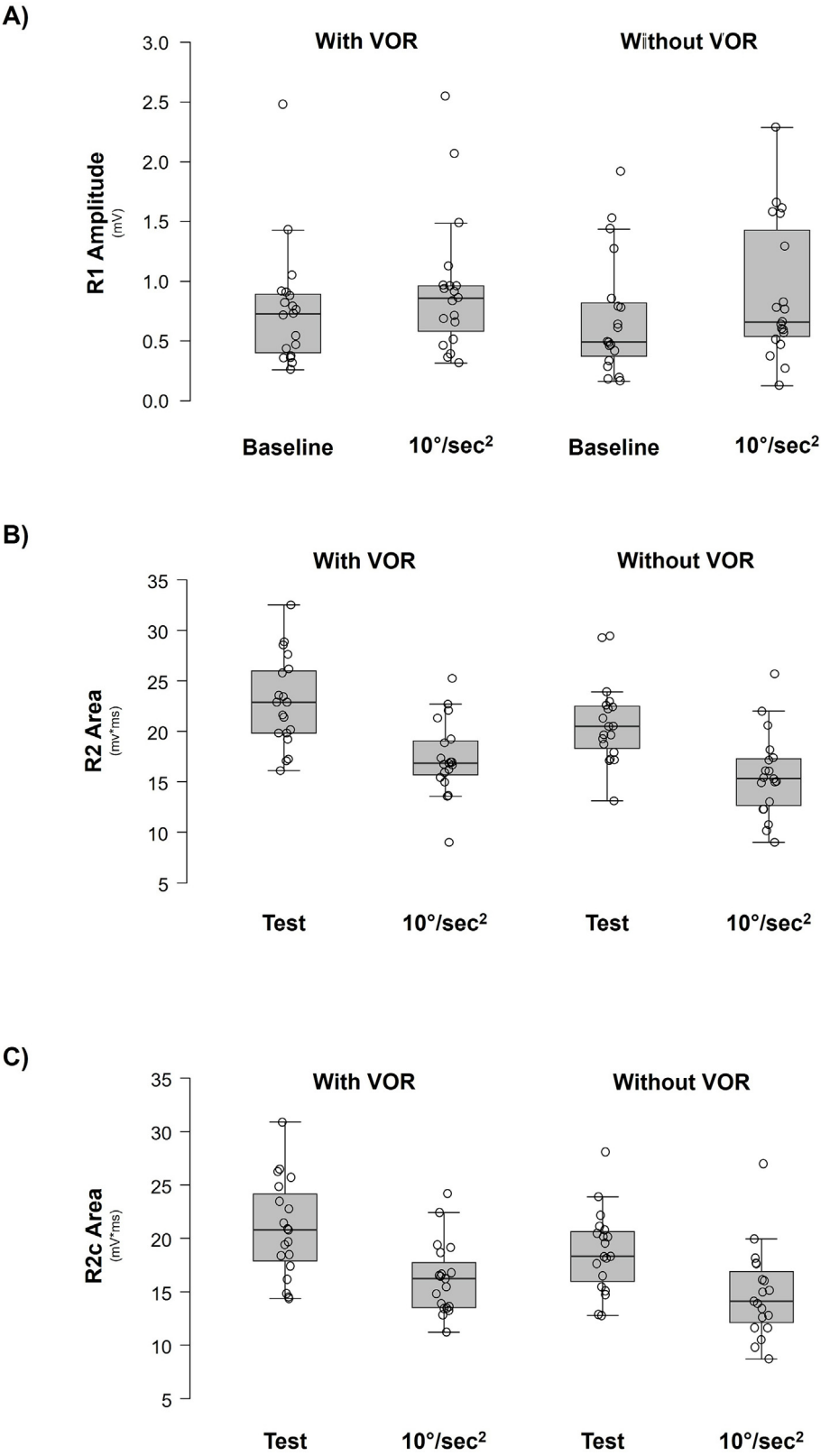


Fig. 4. Modulation of R1 amplitude (A), and R2 (B) and R2c area (C) with and without suppression of the vestibulo-ocular reflex. Grand average and standard error for trials with and without vestibulo-ocular reflex are presented for R1 amplitude (mV), and R2 and R2c area (mV*ms). Vestibulo-ocular reflex suppression did not change the magnitude of PPI. VOR: vestibulo-ocular reflex.

Table 4
Effect of gender on vPPI. Magnitude of inhibition and standard error of R1, R2, and R2c responses are reported for each group. Facilitation is represented by positive values and inhibition by negative values. T scores, *p*-values, and Cohen's d are reported.

		Mean	Std. Error	*t*-score	*p*-value	Cohen's *d*
R1	Males	0.441	0.14	–	–	–
	Females	0.246	0.11	1.045	0.309	0.453
R2	Males	−0.272	0.03	–	–	–
	Females	−0.218	0.04	−1.100	0.284	0.467
R2c	Males	−0.253	0.03	–	–	–
	Females	−0.17	0.05	−1.526	0.143	0.638

was different between the test and all the post-rotational responses (Table 2).

Similar results ($F(4, 130) = 5.885$, $p < 0.0001$; Cohen's $f = 0.15$) were observed in the R2c response at $5°/s^2$, $10°/s^2$, and $20°/s^2$, while no difference was observed at $30°/s^2$ (Table 2).

No difference between right and left rotations was observed for R1 ($F(2, 119) = 0.082$, $p > 0.05$, Cohen's $f = 0.0063$), R2 ($F(2,130) = 22.330$, $p > 0.05$, Cohen's $f = 0.261$), and R2c ($F(2,130) = 12.201$, $p > 0.05$, Cohen's $f = 0.157$).

3.2. Experiment 2

Data from Experiment 2A and 2B are reported in Table 3 and Fig. 4.

We compared the amount of inhibition obtained with and without vestibulo-ocular reflex suppression. A paired sample *t*-test did not show any difference in the R1 ($t = -0.793$; $p > 0.05$; Cohen's $d = 0.226$), R2 ($t = 0.348$; $p > 0.05$; Cohen's $d = 0.075$), and R2c ($t = -0.089$; $p > 0.05$; Cohen's $d = 0.034$) responses among conditions.

To explore a possible gender-related modulation of PPI, we compared the magnitude of PPI between males ($n = 12$) and females ($n = 10$). No statistically significant difference was noted in the R1 amplitude, and R2 and R2c area (see Table 4), although a slightly higher inhibition was observed in males.

3.3. Experiment 3

Results from experiment 3 are reported in Figs. 5 and 6, and Table 5. Briefly, both patients did not show any inhibition when the vestibular pre-pulse was delivered. PPI was conserved for the somatosensory modality at both interstimulus intervals.

4. Discussion

The present data demonstrate how the activation of the vestibular system can inhibit the R2 response of a subsequent blink reflex. Our data are the first that support the notion for a vestibular-evoked gating mechanism, and this can be quantified using a standard measure – the PPI - as previously demonstrated for other prepulse modalities. Our data did not show any modulation for increasing vestibular angular accelerations, however the range we used was clustered toward the lower end of head accelerations found in physiological movements. The lack of effect by vestibulo-ocular reflex suppression and the lack of inhibition in patients with bilateral vestibular failure indicate that vPPI is likely linked to vestibular activation specifically (and not an indirect effect of eye movements and the associated motor circuits or a direct effect of a proprioceptive modulation).

4.1. Characteristics of vPPI

The finding that vestibular system activation modulates the blink reflex supports the hypothesis that a vestibular pulse can activate the PPI network. The vestibular activation was carefully controlled by the use of 2 s long, symmetric triangular stimuli, so as to avoid any post-rotational vestibular activation linked to prolonged displacement of the cupola (Guedry, 1974), thereby minimising any residual activity in the peripheral vestibular system while evoking the blink reflex. In addition, visual and auditory inputs were controlled for by testing in a silent and dark room with continuous background noise of 30 dB arising primarily from electrical hum of the laboratory equipment, whereas somatosensory inputs were minimised using a vibrationless computer-controlled rotating chair. This suggests that, in concert with the preliminary results from the vestibular failure patients, the inhibition of the blink reflex solely depends on pre-activation of the vestibular system, as seen in classic prepulse inhibition paradigms (Valls-Sole et al., 1999).

vPPI was observed even with a conservative ISI of 300 ms. Physiologically, vestibular stimuli rapidly reach the vestibular nuclei in the brainstem, allowing integration within the vestibular network (Guedry, 1974). As PPI commences as soon as the prepulse stimulus reaches the brainstem (Correa et al., 2019), it is possible that vPPI might occur even at shorter ISIs. However, the vestibular network is widely distributed throughout the brain, involving several cortical and subcortical structures (Kirsch et al., 2016). Notably, some of these structures are also activated during sensory gating experiments (Naysmith et al., 2021). Nonetheless, since the PPI network consists of a modulation and a mediation network (Schmajuk and Larrauri, 2005), using an ISI of 300 ms likely infers top-down modulation of PPI by structures shared between the cortical vestibular network and the PPI modulation network (Li et al., 2009). Further research is required to determine the range of ISIs at which vPPI can be observed and to ascertain whether different ISIs within this range reflect the activity of structures within the mediation or modulation PPI networks.

Our results are consistent with some observations about PPI. Firstly, we can support the observation that if the intensity of the prepulse stimulus is enough to generate a response (i.e. the vestibulo-ocular reflex in our experiment), such response does not interfere with inhibition of the R2 response (Kofler et al., 2023). Secondly, we observed a tendency to facilitation of the R1 response, although it did not reach statistically significant levels. We expected a facilitation in the R1 response, as R1 reflects the facilitatory effects induced in facial motoneurons by vestibular prepulse inputs. Vestibular inputs from the vestibular nucleus are integrated in the ventrolateral tegmental nucleus of the pons, which sends strong projections to the facial nuclei as part of the startle reflex circuit (Yeomans and Frankland, 1995). It is possible that the conservative ISI we used in this experiment has abated the amount of R1 facilitation, as R1 modulation varies according to the ISI (Inui et al., 2023, Valls-Sole et al., 1999). More detailed

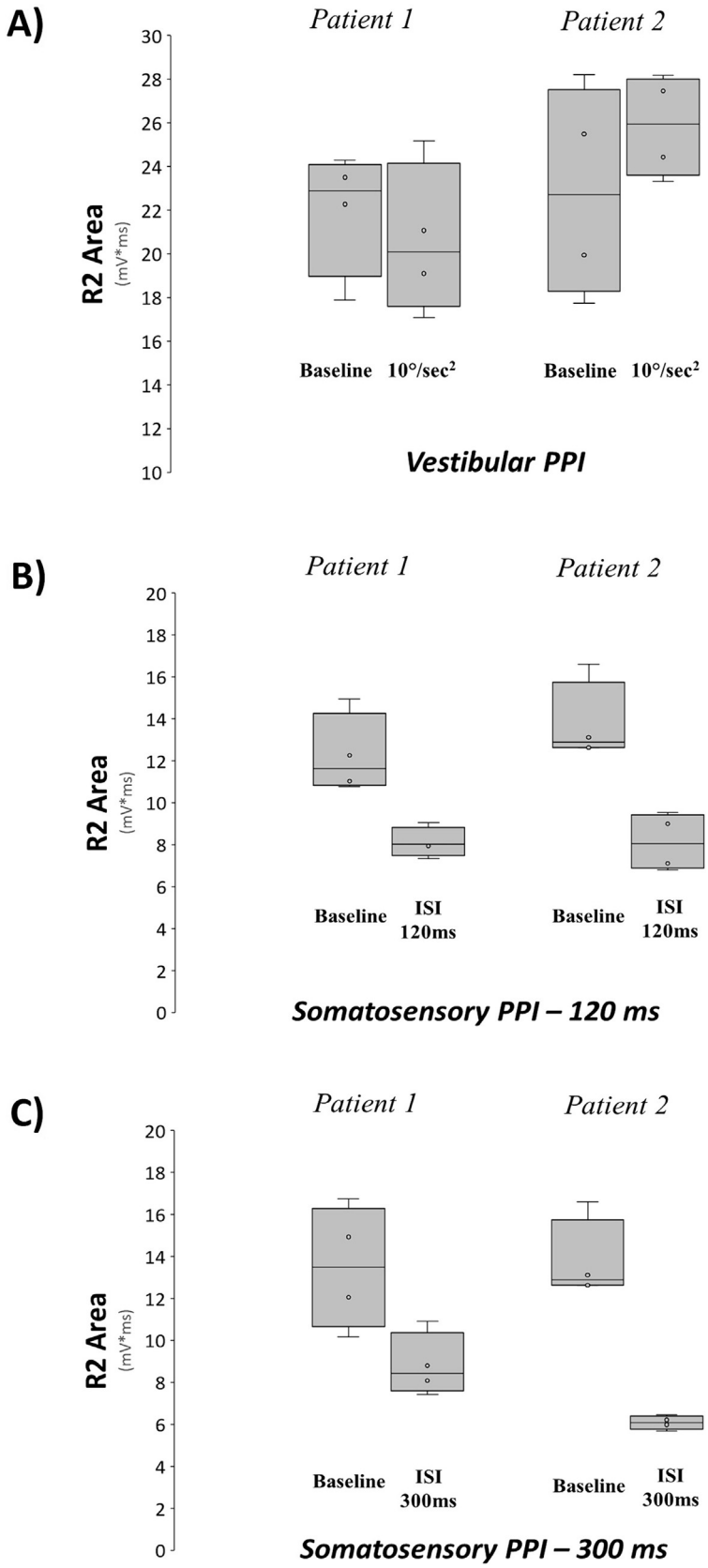


Fig. 5. Modulation of the R2 component of the blink reflex in patients with bilateral vestibular failure. In A, average and standard deviation of the R2 response area for trials unconditioned (“baseline”) and conditioned by a vestibular prepulse (“10°/sec²”) for patient 1 (left) and patient 2 (right). No inhibition is present. Similarly, in B, average and standard deviation of the R2 response area for trials unconditioned (“baseline”) and conditioned by a somatosensory prepulse delivered 120 ms before the blink reflex (“ISI 120 ms”) for patient 1 (left) and patient 2 (right). Finally, in C, the unconditioned R2 response (“baseline”) and the R2 response conditioned by a somatosensory prepulse delivered 300 ms before the blink reflex (“ISI 300 ms”) for patient 1 (left) and patient 2 (right). Somatosensory PPI is preserved for both ISIs. Area: mV*ms. OOc: orbiculary oculi muscle. ISI: interstimuls interval. mV: millivolts.

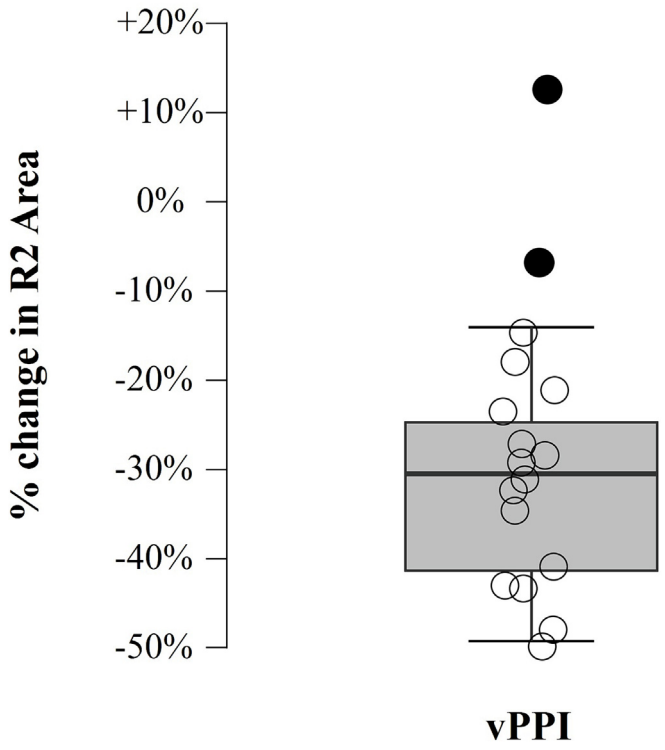


Fig. 6. Comparison of vPPI between patients with bilateral vestibular failure and healthy subjects. This scatter plot illustrates the relative changes (%) in the R2 area. Unfilled circles denote % changes in the R2 response area for subjects in Experiment 1, while filled circles represent % changes for patients with bilateral vestibular failure. Mean and standard deviation from experiment 1 raw values were used to calculate z-scores for the responses for patients 1 and 2. Specifically, vPPI for patients 1 and 2 was significantly reduced (i.e. $P < 0.025$ corrected for 2 comparisons), given z-scores for their responses were 2.356 (or $P = 0.018$; for a two-tailed comparison) and 4.157 ($P < 0.0001$), respectively.

neurophysiological studies should take into account the precise timing of the vestibular prepulse stimulus to elucidate the effects on the R1 modulation.

Similar to other sensory modalities, we were expecting for vPPI to be reactive to prepulse intensity and participant's gender. Interestingly, inhibition was present at all tested angular acceleration, without clear modulation related to angular acceleration. This contrasts with auditory and somatosensory PPI findings (Blumenthal, 2015), where increasing the prepulse amplitude resulted in greater inhibition. Although we selected four pulses of angular acceleration which were 5–30 times larger than the perceptual threshold in healthy subjects and 10–60 times larger than the vestibulo-ocular reflex threshold (Seemungal et al., 2004), these values are much lower than typical peak head angular accelerations during normal movements (Carriot et al., 2014). Unexpectedly, we observed a slight reduction in the inhibition of the R2 and R2c at $30°/s^2$ compared to other angular accelerations. Given the vestibular system's vital role in gaze stabilization, balance control, and perception of spatial orientation and motion, it is possible that increasing the angular acceleration could progressively decreases vPPI to allow the brain to encode the vestibular signal properly. The lack of modulation at $5°/s^2$, $10°/s^2$, and $20°/s^2$ might relate to using stimuli at the lower end of vestibular apparatus's physiological dynamic range. Further studies are needed to confirm intensity-dependent vPPI modulation over a wider range of angular accelerations (Carriot et al., 2014).

Regarding gender, we noticed a trend towards a higher magnitude of inhibition in men. This is in line with previous literature, which reports a difference of approximately 20–40% in the magnitude of PPI between healthy young men and women (Aasen et al., 2005, Kofler et al., 2013, Swerdlow et al., 1993). This difference may be more pronounced when considering the menstrual cycle status, with more inhibition in the early follicular phase compared to the luteal phase (Kumari et al., 2010). In our study, we did not record data on participants' menstrual cycle, therefore future studies should address this potential biological difference.

Interestingly, vPPI is independent from the presence of the vestibulo-ocular reflex. Previous studies have shown a differential integration and modulation of vestibular inputs subserving different functions, e.g. those circuits processing the vestibulo-ocular reflex versus vestibular perceptual signals of self-motion (Seemungal, 2015). Whether a vPPI is present for vestibular input subthreshold for motion perception is unclear, and further experiments will be needed, particularly to elucidate the relationship between vPPI and individual vestibular perceptual thresholds.

4.2. vPPI and functional neuroanatomy

The vestibular network shares structures with the PPI functional network, involving fibres that converge in the PPN area to regulate motor output via the nucleus reticularis pontis caudalis (Gomez-Nieto et al., 2020). The PPN is one of the midbrain structures where the circuits that mediate PPI overlap with the vestibular network (Kirsch et al., 2016). In humans, the PPN participates in controlling a broad set of functions, such as posture and locomotion (Breit et al., 2023, Joza et al., 2022, Lin et al., 2023), eye movements (Ewenczyk et al., 2017, Gallea et al., 2021), sleep (Gallea et al., 2017), and cognition (Mena-Segovia and Bolam, 2011, Petzold et al., 2015). Some of these functions rely on the integration of different sensory feedback loops, and PPI has been already advocated as a promising tool to measure how the brainstem integrates peripheral feedbacks (Kofler et al., 2023), also during tasks where the modulation of the PPN may have a pivotal role (Versace et al., 2019). As vestibular inputs are relevant for most of the activities mediated by the PPN (Cullen, 2023), we suggest that vPPI might be a useful tool to measure how the vestibular sig-

Table 5
Prepulse inhibition in patients with bilateral vestibular failure. Magnitude of inhibition/facilitation of R1, R2, and R2c responses are reported for each patient for each prepulse modality. Facilitation is represented by positive values and inhibition by negative values. vPPI: vestibular prepulse inhibition; sPPI 120 ms: somatosensory prepulse inhibition with an interstimulus interval of 120 ms. sPPI 300 ms: somatosensory prepulse inhibition with an interstimulus interval of 300 ms.

		vPPI %	sPPI 120 ms %	sPPI 300 ms %
R1	Patient 1	+15.3	+32.76	+297.5
	Patient 2	−1.53	+21.26	+70.66
R2	Patient 1	−6.25	−33.73	−34.69
	Patient 2	+13.16	−40.97	−55.75
R2c	Patient 1	−8.11	−57.12	−29.66
	Patient 2	+20.4	−40.89	−60.85

nal is integrated with respects to the abovementioned PPN-related activities.

Further research is required to determine if a direct connection between vestibular nuclei and PPN exists in humans or if indirect connections via the cerebellum or other cortical structures are involved. While PPI is primarily an automatic brainstem process (Lei et al., 2021), it can be influenced by higher-order cognitive processes, and various brain regions are activated during PPI in healthy groups (Naysmith et al., 2021, Rohleder et al., 2016, Santos-Carrasco and De la Casa, 2023). Integrating the vestibular network with the PPI functional network remains a topic for future research.

4.3. Clinical implications

The modulation of vestibular signalling by means of non-invasive brain stimulation techniques has gained increasing interest over the recent years as a treatment for some neurodegenerative conditions. Particularly, galvanic vestibular stimulation has been used to improve balance and vestibular outputs in patients with bilateral vestibulopathy (Schniepp et al., 2018), Parkinson's disease (Mahmud et al., 2022), multiple sclerosis (Lotfi et al., 2021), and dizziness (Woll et al., 2019).

Galvanic vestibular stimulation may modulate balance, potentially by modulating the PPN-thalamic connections, as shown in neuroimaging studies (Cai et al., 2018). However, a proper neurophysiological measure of the interaction between the vestibular system and PPN function is missing. To this extent, vPPI is a promising tool, as it offers the opportunity to investigate the integration of vestibular inputs in the PPN. Further studies will be needed to elucidate the neuroanatomy and neurophysiology of vPPI, as these are vital to ascertaining whether this novel technique has any potential as a marker of vestibulo-motor integration at the brainstem level and hence whether it can be used to interrogate the utility of treatments for improving PPN-mediated functions such as balance in human brain disease.

4.4. Limitations

Our study has some limitations which should be stated. First, the number of patients with bilateral vestibular failure is small, and therefore findings should be interpreted cautiously (although describing vPPI in bilateral vestibular failure patients was out of the scope of this paper). We recommend an appropriate sample size calculation for future studies addressing PPI in this group of patients.

Then there are two relevant considerations needed on the prepulse and the ISI we used for this experiment. Firstly, our prepulse lasts longer than the ones used in other PPI studies using different modalities. It is possible that by using a 2-second long prepulse we might have reduced the magnitude of the subsequent inhibition, as PPI is sensitive to variations in prepulse duration (Blumenthal, 2015). Secondly, we only investigated one ISI. We opted for a conservative interval of 300 ms for several reasons. This ISI falls within the range of intervals where PPI can be observed in other sensory modalities (Blumenthal, 2015), and it has been already shown to give a reliable inhibition in other PPI studies (Valls-Sole et al., 1999). In addition, shorter ISI can facilitate the EMG response (Aitken et al., 1999), and investigating a possible facilitation of the blink reflex was out of the scope of this research. However, it is possible for ISIs shorter than 300 ms to be more effective in inducing an inhibition in the blink reflex. As previously shown, the inhibitory effect of the prepulse begins when the afferent volley reaches the brainstem (Correa et al., 2019), therefore a vPPI might be expected at very short ISIs. Future studies might be focused on investigating other ISIs, mainly to explore at which ISI the strongest inhibition of the blink reflex can be observed.

5. Conclusion

Our findings support the existence of a vPPI in humans, which can be measured by means of the blink reflex. A vestibular prepulse should be added to the list, alongside the auditory and somatosensory prepulses, as capable of evoking an inhibition in the blink reflex response. vPPI might reflect the sensorimotor gating of vestibular inputs at the level of the brainstem as well as being a measure of how the PPN integrates vestibular information. Further studies will confirm the role of vPPI as a possible marker of vestibulo-motor integration at the brainstem level, particularly in relation to non-invasive brain stimulation techniques of the vestibular system.

Authorship statement

All co-authors have reviewed and approved the contents of the manuscript, and the submission is not under review at any other publication.

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