



The effect of galvanic vestibular stimulation on postural balance in Parkinson's disease: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:

Postural control
Balance
Parkinson's disease
Sway
Falls
Non-invasive
Galvanic vestibular stimulation
Neurology

ABSTRACT

People with Parkinson's disease (PD) develop postural imbalance and falls. Galvanic Vestibular Stimulation (GVS) may potentially improve postural balance in humans and hence reduce falls in PD. This systematic review and meta-analysis investigate the effects of GVS on postural balance in PD.

Six separate databases and research registers were searched for cross-over design trials that evaluated the effects of GVS on postural balance in PD. We used standardized mean difference (Hedges' g) as a measure of effect size in all studies.

We screened 223 studies, evaluated 14, of which five qualified for the meta-analysis. Among $n = 40$ patients in five studies (range $n = 5$ to 13), using a fixed effects model we found an effect size estimate of $g = 0.43$ ($p < 0.001$, 95% CI [0.29, 0.57]). However, the test for residual heterogeneity was significant ($p < 0.001$), thus we used a random effects model and found a pooled effect size estimate of 0.62 ($p > 0.05$, 95% CI [-0.17, 1.41], $I^2 = 96.21\%$). Egger's test was not significant and thus trim and funnel plot indicated no bias. To reduce heterogeneity, we performed sensitivity analysis and by removing one outlier study ($n = 7$ patients), we found an effect size estimate of 0.16 ($p < 0.05$, 95% CI [0.01, 0.31], $I^2 = 0\%$).

Our meta-analysis found GVS has a favourable effect on postural balance in PD patients, but due to limited literature and inconsistent methodologies, this favourable effect must be interpreted with caution.

1. Background

Parkinson's disease (PD) is the second commonest neurodegenerative disease, and its prevalence is predicted to double in the next two decades [49]. Falls are a significant predictor in determining the quality of life of PD patients and are one of the main causes of hospitalisation in these patients [35]. Dopaminergic therapy, the mainstay of PD treatment, is effective in improving the cardinal PD features of tremor, rigidity and hypokinesia, but its effects upon imbalance in PD is inconsistent [1,13]. Despite the relative lack of effect of dopaminergic therapy upon falls in PD, Dopamine appears facilitatory upon other interventions for imbalance [52], explaining the rationale for testing balance interventions in PD patients who are on stable dopaminergic replacement in the 'ON' state.

The notion that postural instability and gait dysfunction – including

freezing of gait (FOG) – are components of a single deficit in PD (so-called 'PIGD': postural instability and gait disorder) [2,31] [16], is inaccurate, since much data support that notion that postural instability and gait are distinct both mechanistically as well as in clinical impact [7,11,14,24,38,57,60]. It follows that gait or postural imbalance outcomes should be considered separately in response to therapeutic interventions.

The interest in using non-invasive brain stimulation techniques for modulating behaviour has included the use of transcranial direct-current stimulation (tDCS) in PD to improve balance [4,32,42,48]. Such studies however have reported mixed findings, and a recent meta-analysis showing inconclusive evidence for the impact of tDCS on postural and dynamic balance in PD [32]. Moreover, the underlying mechanism of action of tDCS for modulating the postural balance remains unclear.

Galvanic vestibular stimulation (GVS) is another form of non-

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invasive brain stimulation, in which an electrical current is delivered to the vestibular afferents through the electrodes placed over the mastoids. GVS can be used in supra-threshold manner, in which the stimulation level is higher than the cutaneous perceptual threshold, i.e., subjects can perceive being stimulated through non-vestibular sensory afferents [48,56]. Supra-perceptual (usually with direct current) GVS if also suprathreshold for vestibular activation cause a standing subject to sway in different directions depending on the polarity of electrodes [48]. More recently, GVS has been used in a sub-threshold manner, in which stimulation is imperceptible to subjects, i.e., lower than the cutaneous threshold and is typically not linked to sway modulation [47]; [58]. The specific type of GVS depends on the stimulation parameters such as types of waveform (e.g. Direct current (DC), sinusoid (AC), random noise), frequency band of the stimulation waveform (e.g. narrow band (0–30 Hz), broadband (white-noise)), or the electrode configuration (e.g. monopolar or bipolar) [32].

Despite its lack of effect upon healthy subjects' sway, sub-threshold GVS has been counterintuitively used as a potential treatment to enhance postural balance during steady standing in young [21] and elderly healthy volunteers [20], in patients with bilateral vestibular failure [59] and also in PD, with most studies using random noise GVS.

GVS modulates the vestibular afferents [17,55], which connect to thalamus and basal ganglia [10,51]. A key vestibular node is the pedunculopontine nucleus (PPN) [10,54] a nucleus that has long been linked to balance and locomotion in animals, which provides the largest single cholinergic input to the thalamus. Importantly, cholinergic modulation is linked to imbalance and gait dysfunction although imbalance is linked to cholinergic PPN [6]; [8,22,38] whereas gait dysfunction is linked to cholinergic deficits in the basal forebrain nuclei [38]. Further, the PPN is highly vestibular responsive [3,60] and PPN cholinergic deficits are more linked to falls than basal forebrain cholinergic deficits, which, taken together, indicates a key role for the PPN in mediating vestibular-dependent mechanisms of postural balance and PD-related falls. That A previous study showed that GVS can modulate PPN connectivity in PD [10] suggests that GVS effects upon balance in PD may be mediated through activation of vestibular afferents that subsequently activates PPN-thalamic connections.

The mechanism through which random noise GVS is thought to act is via stochastic resonance in which adding noise to a non-linear system enhances the detection of weak signals – in this case vestibular signals of head motion – and improves the fidelity of the vestibular signal used for postural control [36]. The random noise has an optimal range of postural balance improvement, reducing or adding further noise can degrade detectability of the weak stimulus producing an inverted-U response of balance performance, typical of a stochastic resonance phenomenon. Translating this to human studies using random noise GVS the stochastic resonance phenomenon could be the optimisation of the head movement transduction process via the vestibular organs and nerves. If so, this would assume that it is the enhanced head motion detectability that is thought to improve postural balance. Clinical studies using random noise GVS have used similar approach, where random noise stimulation intensity is increased in a graded manner to identify an optimal range to improve balance performance in patients [26,47] as well as healthy volunteers [20,21,37]; [58].

The potential promise of GVS as a treatment for reducing falls risk in PD through modulating postural balance is still unproven. Recent studies however show that GVS may promise as a possible clinically applicable non-invasive neuro-modulatory treatment for PD. Thus, the aim of this meta-analysis was to assess the current evidence for the effect of GVS upon postural balance in patients with PD.

2. Methods

2.1. Eligibility

2.1.1. Inclusion criteria

2.1.1.1. Types of studies. We included only cross-over trials that evaluated the effects of GVS on postural balance in patients with PD. We excluded any conference proceedings or incomplete trials.

2.1.1.2. Types of participants. We included trials that specified patients with PD as diagnosed by the UK Parkinson's Disease Bank or an equivalent clinical diagnosis regardless of time since diagnosis, medication status, age, or Hoehn and Yahr (H&Y) stage. We excluded trials that did not specifically focus on PD.

2.1.1.3. Types of intervention. We included trials if they used GVS in patients with PD. The 'placebo' group is defined as a sham GVS group tested pre and post sham. GVS was included regardless of type of stimulation characteristics (direct current, alternating current, random noise, frequency bandwidth, intensity, electrode arrangement/size and correlation.)

2.1.2. Exclusion criteria

Review articles, case reports, study protocols, trials assessing conditions other than postural balance, or interventions other than GVS. We furthermore excluded studies that did not use GVS but alternative methods of non-invasive brain stimulation such tDCS, transcranial alternate current stimulation (tACS), or transcranial magnetic stimulation (TMS).

2.2. Outcome measures

The primary outcomes were any form of postural balance assessments while standing. We included the following postural balance measures: 1.root mean square (RMS) sway 2. Sway path 3. sway area, 4. sway velocity 5. Mean of centre of pressure (COP) 6. postural angles. In scenarios when postural balance was assessed on either hard or soft surfaces with eyes open or closed, we only used the eyes closed soft surface condition. Postural balance assessment during eyes closed over soft surface has for long been shown to be the most sensitive of these conditions for identifying poor balance in patients [5,14,27].

2.3. Electronic search

We performed our systematic review and meta-analysis based on criteria given by the PRISMA statement (See Appendix). Our search strategy searched the following databases: MEDLINE (from 1993 to 20 July 2020), Web of Science Core Collection, AMED (from 1993 to 1 Jan 2020), Cochrane Central Register of Controlled Trials, Google Scholar (from 2004 to 10 April 2020), The Physiotherapy Evidence Database and Rehabdata. We conducted a comprehensive search strategy to focus on peer-reviewed articles that reported an effect of GVS on a postural balance in PD patients. We adapted our search strategy according to the database (see Appendix). We identified and searched the following ongoing trial and research registers: current controlled trials, clinicaltrials.gov, European Union Clinical Trials Register, World Health Organization International Clinical Trials Registry Platform.

2.4. Data collection and analysis

2.4.1. Selection of studies

Two review authors (MM and MP) read through the titles and abstracts identified in the electronic search. Studies were then selected according to the inclusion criteria, detailed above. Two review authors

(MM and MP) then individually read through the full papers and selected those studies that were relevant according to our exclusion criteria.

2.4.2. Data extraction

From the selected studies, three authors (MM, ZH, MP) independently extracted the relevant data from the same studies. A standardized data extraction table was designed and included information about the following:

Study parameters: descriptive data, blinding, study-design, control condition.

Participant characteristics: numbers, PD staging (H&Y, disease duration), UPDRS motor assessment and whether the study was conducted during 'on' or 'off' Levodopa medication.

GVS parameters: type of noise, intensity, frequency bandwidth, duration, correlation, electrode (location, size and arrangement).

Results: sample size, mean and variances pre- and post-GVS, mean difference.

2.4.3. Assessment of risk of bias and trial quality

We used the Risk of Bias 2 (RoB) for crossover trials using the Cochrane Collaboration Tool [50]. For each study, MM, ZH rated the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. These were rated from low, high or uncertain based on the guidance provided by Cochrane.

2.4.4. Dealing with missing information

In the case of any missing information, we contacted the authors of

the relevant studies with the details of the data required. If we were unable to receive a response or to receive the missing data that was required for analysis, we excluded this study.

2.4.5. Meta-analytic techniques and statistical analyses

We used standardized mean difference (Hedges' g) as a measure of effect size in all studies. Effect size calculations were performed using the method for within-subject study designs [9]. A positive effect size denotes improvement in measured parameters in response to stimulation and vice versa for a negative effect size. A Pearson's correlation coefficient (r), required for the effect size calculations of paired group (pre-post comparisons) designs, was calculated where raw data was available. If neither correlation coefficient was reported nor raw data was available, then correlation coefficient was imputed based on raw data available from the other studies included in the analysis.

The meta-analysis was performed in JASP software [34]. Pooled effect-size was first estimated using a fixed-effects model. The heterogeneity between each group was tested using the I^2 test in JASP. $>50\%$ and significant residual heterogeneity ($p < 0.05$) was considered high heterogeneity. A random-effects model was applied if high heterogeneity was observed. Sensitivity analysis was performed if there was still considerable heterogeneity, and to control for any imputed values.

3. Results and discussion

3.1. Study classification

Fig. 1 shows the number of studies screened, included, and excluded.

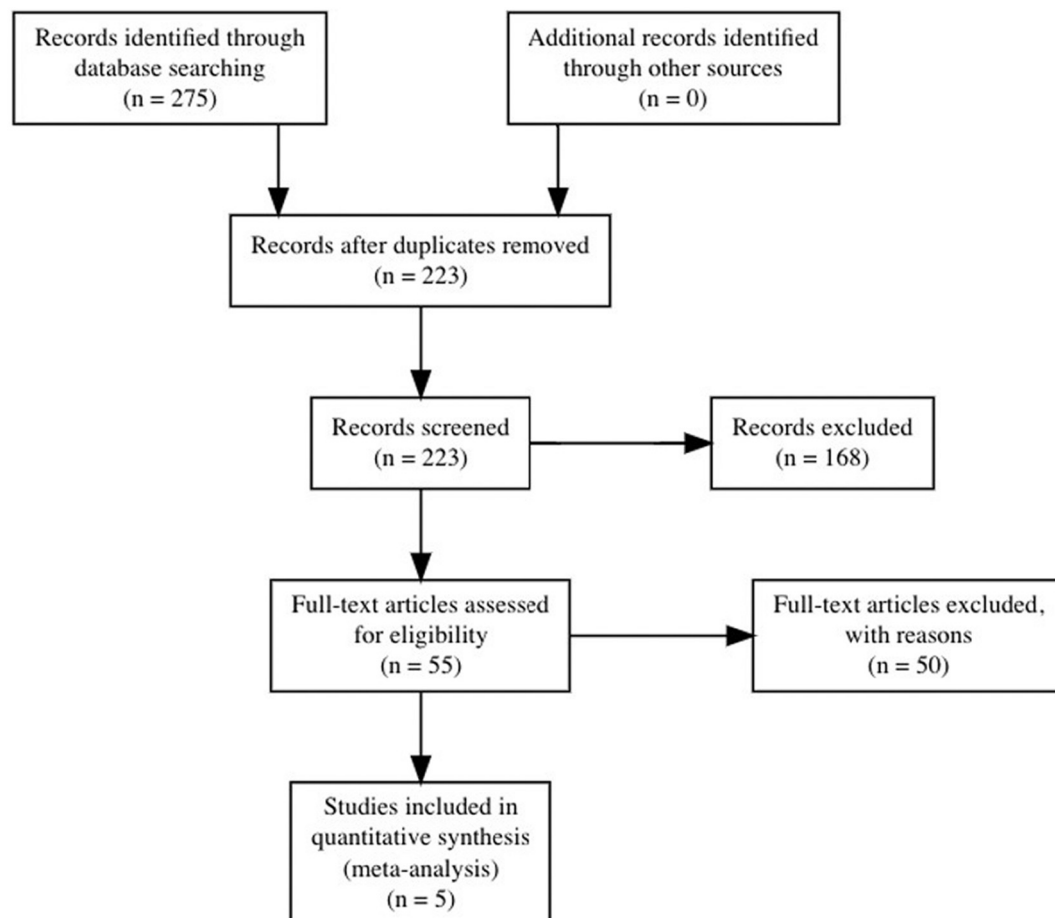


Fig. 1. PRISMA flow diagram – from a total of 275 identified research article using the appropriate screening and inclusion criteria the synthesis included five studies in total.

Our search resulted in 275 hits and after removal of duplicates, 223 were screened. 55 full-length articles were assessed and after excluding any conference proceedings, irrelevant study designs/interventions/patients, we were left with 14 articles. Of these, five were eligible and included in the meta-analysis [28,41,43,45,53].

3.2. Study design and participant characteristics (Tables 1 and 2)

3.2.1. Stimulation characteristics

A total of $n = 40$ subjects were included in the analysis from five studies (Table 3) [28,41,43,45,53]. One [43] of the five studies used pre-fixed stimulus intensities of 0 mA, 0.1 mA, 0.3 mA, and 0.5 mA. Two of five studies [28,41] had similar protocols in which GVS stimulation was ramped up slowly to 0.7 mA and then stimulation was applied for 20 min. The remaining two studies used stimulation intensities based on a subject's individual cutaneous perceptual thresholds [45,53].

All studies involve electrode placement over the mastoid processes, however, one study used two cathodes over mastoids with anode over the C7 vertebrae [43] and two studies also stimulated trapezius muscles in addition to mastoids [28]. Two of the studies [41,53] used monopolar stimulation, two used bipolar [28,45], and one [43] used bicathodal stimulation over the mastoids. The duration of the stimulation was 26 s [43], 60 s [53], 20 min [28,41], and up to 3 h [45].

One [43] of the five included studies did not specify the frequency band of the random noise in noisy GVS. Two studies [28,41] did not mention the choice of frequency band, possibly due to the use of Direct Current GVS, however, it was not explicitly mentioned. One study used white noise in 0.4–30 Hz band [53] and one other used 1/f noise in 0–30 Hz band [45].

All five studies used PD patients who were assessed during the ON medication condition, while the OFF condition was also present in some studies. However, for the sake of homogeneity, only the results for the ON condition are included.

Table 1

Study design, stimulation dosage and outcome measures used in the included studies.

Study	Study design	Dosage		Outcomes
		Trials of verum condition	Time between trials	
Pal et al. [43]	Single-blinded Non-randomised Sham-controlled	6 trials of each intensity and condition (24 total)	No data	Mean centre of pressure (Anterior-Posterior & Medial-lateral direction)
Kataoka et al. [28]	Double-blinded Randomised Crossover Sham-controlled	1 trial	1 week between verum and sham	Anterior trunk bending angle
Samoudi et al. [45]	Double-blinded Randomised Crossover Sham-controlled	1 trial	Crossover performed on separate days, time	Sway (sway-path)
Okada et al. [41]	Single-blinded Randomised Sham-controlled	1 trial	1 week between crossovers	Anterior bending angles
Tran et al. [53]	Single-blinded Randomised Sham-controlled	4 trials	60 s rest between trials	Mean centre of pressure (Anterior-Posterior & Medial-lateral direction)

3.2.2. Methodological quality

RoB for crossover studies was used to assess the quality of RCTs and assess methodological areas for concern. Four of the five included studies were randomised, however no study mentioned the method of randomisation. There were no concerns identified by RoB due to carry over effects in four studies and some concern in one study (Fig. 2. DS). Two studies had some concern due to deviation from intended intervention while three studies were low risk (Fig. 2. D2). None of the studies had missing outcome data and thus all were considered low risk (Fig. 2. D3). Four studies had low concern for outcome measurement whereas one study had some concern (Fig. 2. D4). Two of the studies were considered high risk whereas three considered low risk for reporting correct results and pre-specifying the analysis performed (Fig. 2. D5).

3.2.3. Overall effect of GVS on postural balance

Using a fixed-effects model, we found an effect size estimate of $g = 0.43$ ($p < 0.001$, 95% CI [0.29,0.57]) (Fig. 3), with test for residual heterogeneity indicating significant heterogeneity between studies ($p < 0.001$). We thus used a random effects model and found the pooled effect size estimate to be 0.62 ($p > 0.05$, 95% CI [−0.17, 1.41], $I^2 = 96.21\%$) (Fig. 4). The Egger's test was not significant and thus a funnel plot (Fig. 5) indicated no bias, however, heterogeneity was considerably high ($I^2 = 96.21\%$). The high heterogeneity was not unexpected considering the presence of a study with a large effect size (Hedge's $g = 2.19$) and small sample [41] in the pooled effect size estimate. To reduce heterogeneity, we performed sensitivity analysis and, by removing the outlier study [41] with $n = 7$, we found the effect size estimate to be 0.16 ($p < 0.05$, 95% CI [0.01, 0.31], $I^2 = 0\%$), shown in Fig. 6. Note that the Egger's test was still not significant, suggesting the funnel plot indicated no publication bias after removal of the outlier (Fig. 7).

After removing the outlier study to reduce heterogeneity, there was one study [45] for which the correlation coefficient (r) was imputed ($r = 0.8$). However, sensitivity analysis by imputing different ' r ' values ($r = 0.6$ & $r = 0.7$) showed no change in pooled effect size estimate or its statistical significance. One study [43] used fixed stimulus intensities of 0 mA, 0.1 mA, 0.3 mA, and 0.5 mA. We selected 0.5 mA intensity for pooling effect sizes as it was closest to the other studies optimal intensities [28,41,45,53]. However, to minimise bias, we performed a sensitivity analysis and found that there was little change in effect size estimate for both 0.1 mA (SMD = 0.12, $p > 0.05$, 95% CI [−0.08, 0.32], $I^2 = 20.95\%$) and 0.3 mA (SMD = 0.15, $p > 0.05$, 95% CI [−0.05, 0.36], $I^2 = 0\%$) and that both were not statistically significant (Fig. 8 and Fig. 9 respectively).

4. Discussion

Our meta-analysis investigated the effects of GVS on postural balance outcomes in PD patients. We found that GVS has a favourable effect on the postural balance of PD patients, however, we advise caution in interpreting our findings as this meta-analysis is limited by the small number of studies, with small sample sizes, and high heterogeneity of stimulation protocols. None of the five studies included in the meta-analysis met the correct standards of a randomised controlled trial and only two of five studies were double-blinded.

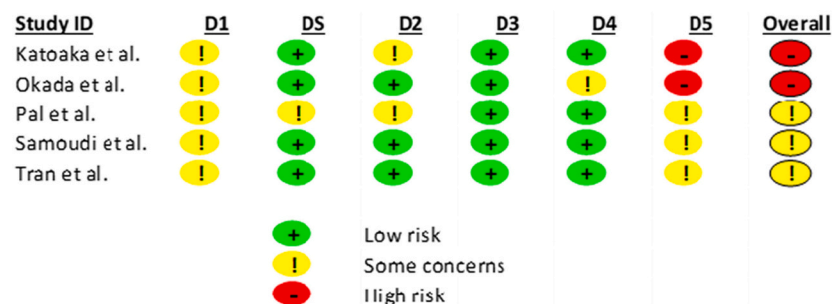
GVS protocols used between studies were inconsistent, thus decreasing the confidence in the evidence and increased heterogeneity. One [43] of the five studies used pre-fixed stimulus intensities of 0 mA, 0.1 mA, 0.3 mA, and 0.5 mA. Two of five studies [28,41] had similar protocol in which the GVS stimulation was ramped up slowly to 0.7 mA and then the stimulation was applied for 20 min. Whereas, the remaining two of the five studies used stimulation intensities based upon subjects individual cutaneous perceptual thresholds [45,53]. Previous studies have shown that a subject-specific noisy GVS can improve the postural and dynamic balance in both patients [26,47] and healthy volunteers [20,21,37];[58]. Similar findings have also been reported in

Table 2
Study and participant characteristics.

Study	Participants		Hoehn and Yahr stage	Disease duration (years)	UPDRS	Medication (On or Off)
	Healthy	Parkinsons disease				
Pal et al. [43]	Number: 20 Mean age: 36.9 y Sex (M:F): 9:11	Number: 5 Mean age: 70 Y Sex (M:F): 3:2	Median: 2 Range: 1–2.5	5.0 ($\pm$ 2.3)	Not available	On
Kataoka et al. [28]	N/A	Number: 5 Mean age: 69 Y Sex (M:F): 1:4	Mean $\pm$ SD: 3.33 $\pm$ 0.52 Median: 3 Range: 3–4	11.2 ($\pm$ 6.09)	UPDR-3 only Mean: 25.4 Range: 13–34	On
Samoudi et al. [45]	N/A	Number: 10 Mean age: 61 Y Sex (M:F): 6:4	Mean $\pm$ SD: 2.4 $\pm$ 0.39 Median: 2.5 Range: 2–3	7.1 ($\pm$ 3.23)	UPDR-3 only Mean: 31.2 Range: 16–49	On and Off
Okada et al. [41]	N/A	Number: 7 Mean age: 71 Y Sex (M:F): 3:4	Mean $\pm$ SD: 3.23 $\pm$ 0.49 Median: 3 Range: 3–4	11.3 ($\pm$ 4.35)	UPDR-3 only Mean: 21 Range: 6–32	On
Tran et al. [53]	Number: 12 Mean age: 67 Y Sex (M:F): 5:7	Number: 13 Mean age: 67 years Sex (M:F): 7:6	Mean: 1.54 SD: 0.78 Median: Not available Range: Not available	4.23 ($\pm$ 2.62)	UPDR-3 only Mean: 17.9 Range: 4–32	On

Table 3
Stimulation characteristics.

Study	Noise	Intensity (mA)	Frequency Bandwidth	Duration	DC Offset	Location	Electrode Configuration and Size
Pal et al. [43]	1/f	0, 0.1, 0.3, 0.5	Not stated	26 s	Not stated	Mastoid and C7 vertebrae	Bicathodal (two cathodal at mastoid and one anodal at C7) 15
Kataoka et al. [28]	Not stated	Ramped to 0.7	Not stated	20 min	Not stated	Mastoid and trapezius muscle OR ipsilateral-contralateral sides of trunk flexion	binaural monopolar 10.2
Samoudi et al. [45]	1/f	Optimal Intensity (range: 0.1–0.9 mA)	0–30 Hz	<3 h	zero	Mastoid	Bipolar binaural 24
Okada et al. [41]	Not stated	Ramped to 0.7 (patient exception of A, B (0.2 mA, 0.5 mA))	Not stated	20 min	N/A	Mastoid and trapezius	Binaural monopolar 10.2
Tran et al. [53]	White noise	70% of cutaneous sensory threshold	0.4–30 Hz	60s	zero	Mastoid (monopolar trials also had anodes on ipsilateral acromion)	Bipolar and Monopolar Size: not stated

**Fig. 2.** The Cochrane's risk of bias summary; review authors' judgements about each risk of bias item for each included study. This suggests overall concerns or high risk for all studies. D1 – Randomisation process, D5 Bias arising from period and carryover effects, D2 Deviations from intended interventions, D3 Missing outcome data, D4 Measurement of the outcome, D5 Selection of the reported result.

studies using fixed stimulation intensities for all subjects [25,48,56]. It is unclear which of fixed intensity GVS or subject-specific noisy GVS is the more effective in modulating posture, either in healthy or any patient groups since both types of GVS have reported improvement in postural balance measures. From the studies included in this meta-analysis, ([45,53] used nGVS with subject specific (optimal) intensities but only [45] found improved postural balance in PD. Moreover, [43] using fixed intensity stimuli also found improved postural balance. Thus, more studies that compare stimulation types are required for better understanding.

During our sensitivity analysis, we found no impact of imputing different correlation values on the effect size estimate or its significance suggesting there was unlikely to be a bias because of imputed correlation value. One study [43] had multiple stimulation intensities, however, we selected 0.5 mA intensity for pooling effect sizes as it was closest to the other studies included in the meta-analysis [28,41,45,53]. A sensitivity analysis was performed to minimise bias and we found that only 0.5 mA had resulted in overall statistically significant effect size estimate. The stimulus intensities of 0.1 mA and 0.3 mA resulted in an overall statistically insignificant effect size estimate; however, it is important to

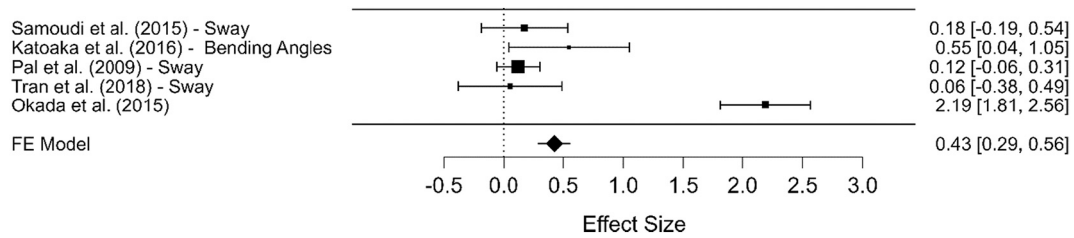


Fig. 3. Forest Plot for Fixed Effects Model. Pooled effect size estimate using fixed effects model was $g = 0.43$ ($p < 0.001$, 95% CI [0.29,0.57]).

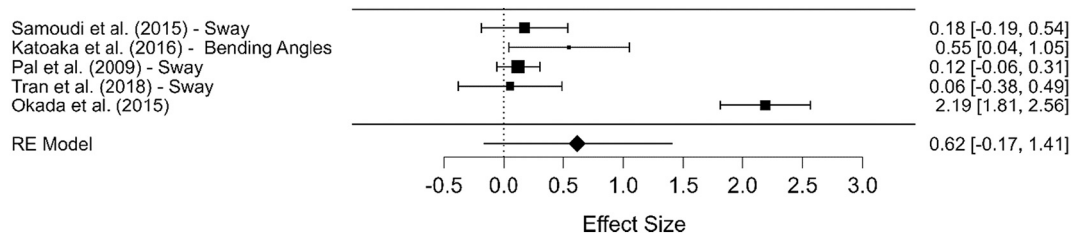


Fig. 4. Forest Plot for Fixed Effects Model. Pooled effect size estimate using fixed effects model was $g = 0.43$ ($p < 0.001$, 95% CI [0.29,0.57]).

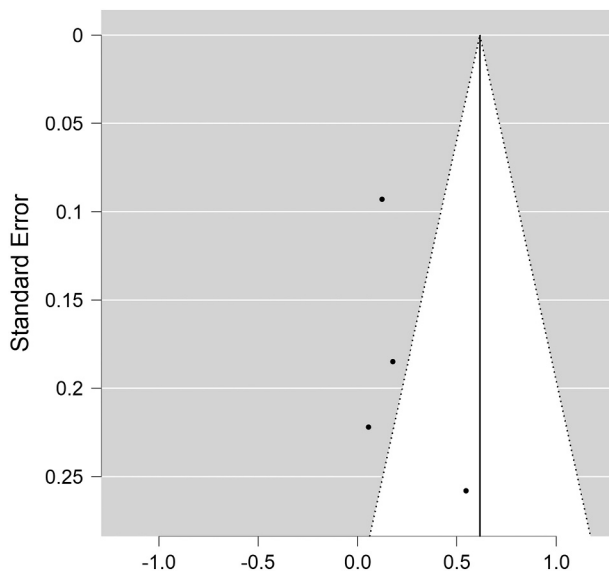


Fig. 5. Funnel plot. The Egger's test was not significant ($p < 0.05$), which indicates publication bias was not present (note that this does not indicate the absence of publication bias). However, one of the studies [41] had quite large effect size (Hedge's $g = 2.19$), thus adding a visually observable publication bias in the funnel plot.

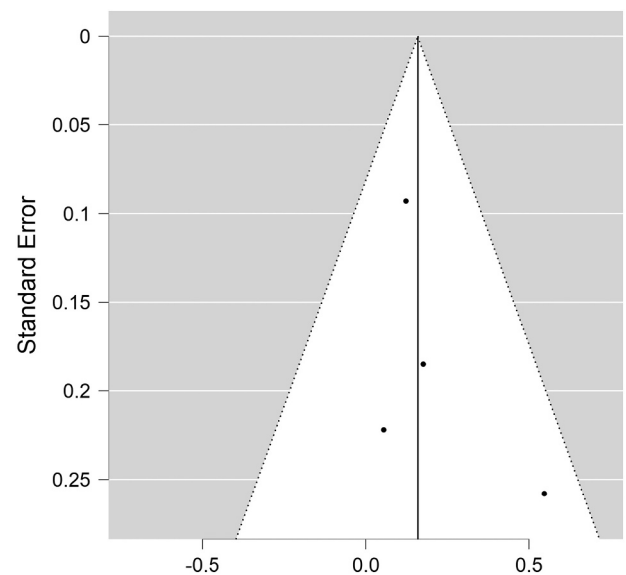


Fig. 7. Funnel Plot after Outlier Removal. Egger's test was not statistically significant and visual inspection of funnel plot also indicated publication bias was not present (note that this does not indicate the absence of publication bias).

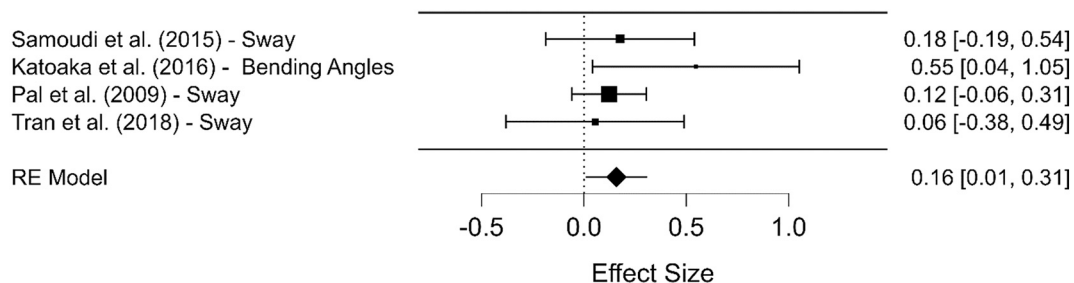


Fig. 6. Forest Plot after Outlier Removal. After removal of the outlier study [41], pooled effect size estimate using random effects model was 0.16 ($p < 0.05$, 95% CI [0.01, 0.31], $I^2 = 0\%$).

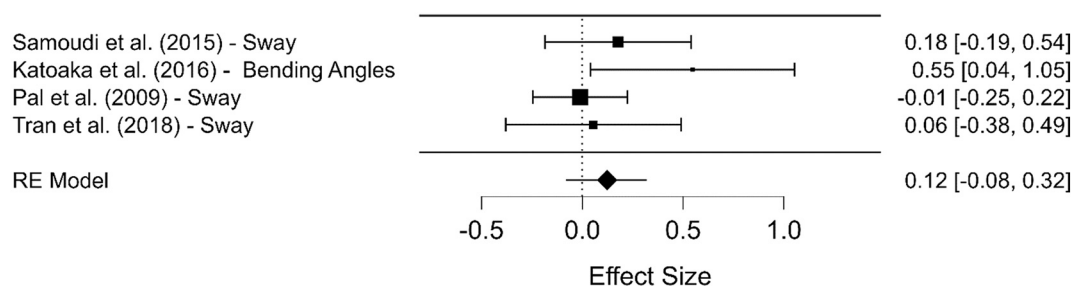


Fig. 8. Forest Plot for Sensitivity Analysis for [43]. For intensity of 0.1 mA, pooled effect size estimate using random effects model was 0.12 ($p > 0.05$, 95% CI [-0.08, 0.32], $I^2 = 20.95\%$).

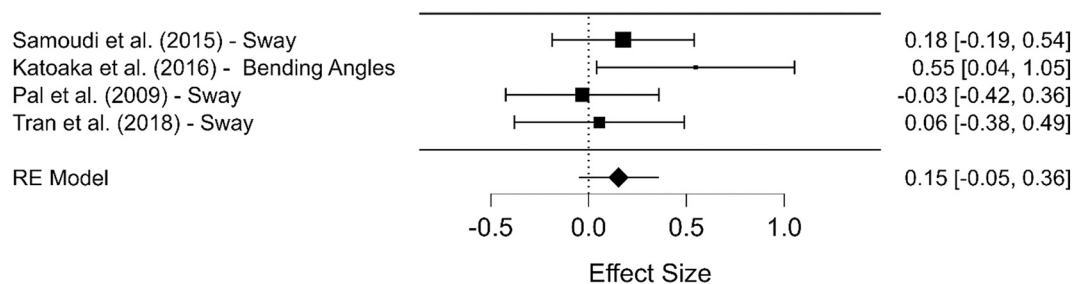


Fig. 9. Forest Plot for Sensitivity Analysis for [43]. For intensity of 0.3 mA, pooled effect size estimate using random effects model was 0.15 ($p > 0.05$, 95% CI [-0.05, 0.36], $I^2 = 0\%$).

notice that actual effect sizes do not vary much with 0.1 mA (Hedge's $g = 0.12$), 0.3 mA ($g = 0.15$), and 0.5 mA ($g = 0.16$).

All studies involve electrode placement over mastoid processes, however, one study used bicathodal stimulation over the mastoids with the anode placed on the C7 vertebra [43] and two studies also stimulated trapezius muscles in addition to mastoids [28]. It is unclear if differences in electrode positioning could have affected on the study outcomes considering all included studies stimulated mastoids. However, contrary to the traditional stimulation configuration of bipolar electrode placement used in noisy GVS studies, two studies [41,53] used monopolar stimulation and one [43] used bicathodal stimulation over the mastoids.

The duration of the stimulus also varied greatly. Some studies used durations as short as 26 s [43] or 60 s [53] whilst others used longer durations of 20 min [28,41] extending up to 3 h [45]. There is dispute in the literature over the duration for post-stimulation effects of short-duration galvanic vestibular stimulation. Some studies have noted a significant persisting effect post-stimulus lasting hours [19,20] while some studies have questioned the validity of these results due to unreliable protocols [29,40].

Three [28,41,43] of the five included studies did not specify the frequency band of the noisy GVS and only two studies reported the type of noise as well as frequency band with one using white noise in 0.4–30 Hz band [53] and other using 1/f noise in 0–30 Hz band [45]. The consensus is that this likely reflects a physiological basis with low-frequency range of 0–30 Hz is optimal for engaging the vestibular system [15]. However, studies have also reported the variable nature of outcome when using random noise stimulation without optimising for individual patients, since band-limited sinusoidal stimulus also showed varied outcomes in different frequency bands (< 30 Hz or > 30 Hz) [33].

From the five studies included in the meta-analysis, the pooled effect size was estimated from $n = 40$ samples from five studies, which was further reduced to $n = 33$ when an outlier study [41] was removed to reduce the heterogeneity. From the studies included in the meta-analysis, the maximum sample size of PD patients was 13 [53] with all other samples either 10 [45] or lower. In addition, none of the studies provided any justification of their selection of sample size or power

calculations. This highlights the need for properly designed studies that fulfil all requirements of a RCT.

Another important consideration was that only two studies used control groups (Table 2). It is a common practice to not compare the effect of pre-post GVS in patient cohorts with a pre-post healthy control group. Without a healthy control group comparison, however, the pre-post difference in patient groups may reflect only normal variance of data [39]. Only two studies [43,53] we assessed in this review compared controls and patient groups.

There are mechanisms that support a clinical impact for GVS to improve postural instability in PD and therefore falls risk. Firstly, postural mechanisms controlling steady standing are relatively more vestibular dependent than gait, which involves more feedforward motor control and relatively less sensory feedback [14]. Second, prior studies [7,14,38] support a key role for the Pedunculo pontine Nucleus (PPN), a major thalamic cholinergic input, in imbalance in PD. In contrast, the cholinergic basal forebrain nuclei (including the nucleus basalis of Meynert) mediate gait features such as its speed as well as being linked to freezing of gait (FoG) in PD. Importantly, PPN-linked cholinergic dysfunction and postural imbalance was more clearly linked to falls than gait impairment, including FoG. Taken together, these findings are consistent with the vestibular-dependent nature of postural deficits particularly since PPN neurones are heavily vestibular responsive [3] and PPN stimulation in humans modulates both postural control and higher order vestibular function [60]. Indeed, recent animal work confirms the important role of PPN pathways gating thalamocortical circuits [24] that enhance interhemispheric connectivity, with multiple studies showing intracortical pathways (e.g. the inferior longitudinal fasciculus) being linked to postural control in PD [57] and non-PD [11] brain disease patients. Taken together, these findings thus provide a logical basis for the use of vestibular stimulation techniques for improving postural control which may be mediated via PPN-linked thalamocortical pathways that may enhance vestibular signalling in cortical circuits involved in postural control. Conversely, the data provide less support for using GVS in gait.

This study was limited by the small sample and heterogeneity of participants that were included in this meta-analysis. The variability in

clinical status of the participants PD can be seen by the H&Y stage range and means (Table 2). But due to the limited numbers we cannot conclude in this present study the exact contributions of severity of PD based on clinical scoring on postural control. It should be noted however that although a patient may have a H&Y score indicating no clinical postural imbalance, this should not necessarily preclude the inclusion of such patients in GVS-balance studies since they may show a measurable improvement in postural control with GVS via laboratory-based posturography, as in so doing, provide a means for assessing the potential of the intervention for improving balance per se. Despite this between-study inconsistency, two studies [28,41] which demonstrated the largest effect sizes ($g = 0.55$ and $g = 2.15$ respectively) were also the two with the highest mean H&Y stages for PD patients at baseline (Fig. 3). Future studies should therefore try to compare how clinical characteristics of PD including H&Y could influence the effect of GVS. Finally, one must consider how postural balance measures in PD are interpreted. Early data initially suggested that patients with PD have increased sway [23] but it seems a majority of later studies find a decreased sway at baseline [12,30,46], and some studies suggesting this increased sway does indeed correlate with increased falls risk [18,44].

5. Conclusion

In conclusion, the use of GVS in patients with PD shows an overall positive impact on postural balance, however the evidence is inconclusive for the following reasons: 1) low statistical power, 2) heterogeneous stimulation parameters and methodologies, 3) lack of appropriate randomisation. This suggests that future research into this field would benefit from appropriately powered and randomised studies that assess appropriate outcome measures of postural control in Parkinson's disease.

Author contributions

MM - Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Roles/Writing - original draft; review & editing. ZH - Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing - review & editing. MP - Conceptualization; Data curation; Formal analysis; Visualization; Roles/Writing - original draft. MC - Methodology, Writing - review & editing. ARS, YP, GS - Writing - review & editing. BMS - Supervision; Funding; Writing - review & editing.

Funding

Funding received from Medical Research Council (MRC), The Jon Moulton Charity Trust, Department of Defense (DOD), Racing Foundation and Imperial Health Charity.

Data availability

Data and code for the meta-analysis can be found here:

Declaration of Competing Interest

None declared.

Acknowledgments

We would like to thank all authors who kindly responded to our data requests.

Appendix A. Appendix

A.1. Search strategy used for PubMed/MEDLINE and Google Scholar

("vestibular stimulation"[tw] OR "Galvanic Vestibular Stimulation"[tw] OR "GVS"[tw] OR stochastic[tw] OR "noisy vestibular stimulation"[tw] OR "stochastic galvanic vestibular stimulation"[tw] OR "stochastic vestibular stimulation"[tw]) AND (Parkinson[tw] OR "Parkinson's Disease"[tw] OR Parkinson's[tw] OR PD[tw] OR IPD[tw] OR "Lewy Body Parkinson's Disease"[tw] OR "Primary Parkinsonism"[tw] OR "Paralysis Agitans"[tw] OR Parkinson's) AND ("randomised controlled trials" OR "randomized controlled trials" OR "random allocation" OR "controlled clinical trials" OR control* OR double-blind* OR single-blind* OR placebo OR "placebo effect" OR "cross-over" OR "cross-over study" OR therapies, investigational OR research design OR evaluation study* OR "randomized controlled trial"[pt] OR controlled clinical trial [pt] OR random*[tw] OR controlled adj5 trial* OR clinical* trial*[tw] OR cross-over[tw] OR crossover [tw] OR "Cross over"[tw] OR placebo*[tw] OR Sham[tw] OR controls[tw] OR assign*[tw] OR alternate[tw] OR allocat*[tw] OR counterbalance*[tw] OR multiple baseline [tw] OR versus[tw] OR ((control OR treatment OR experiment* OR intervention) adj5 (group* OR subject* OR patient*)) [tw] OR (quasi-random* OR quasi random* OR pseudo-random* OR pseudorandom*) [tw] OR ((multicenter OR multicentre OR therapeutic) adj5 (trial* OR stud*)) [tw] OR ((control OR experiment* OR conservative) adj5 (treatment OR therapy OR procedure OR manage*)) [tw] OR ((singl* OR doubl* OR tripl* OR trebl*) adj5 (blind* OR mask*)) [tw])

Types of databases:

MEDLINE:

- Search strategy above
- 137 search results found
- 20 screened
- Found: Okada, katoaka, Samoudi,

Web of Science Core Collection

- "Vestibular stimulation, Parkinson's"
- 68 results found
- Duplicates: 21
- 22 screened
- Found: Tran, Pal

AMED:

- "Vestibular stimulation, Parkinson's"
- 34 search results found
- Duplicates: 20
- 5 screened

Cochrane Central Register of Controlled Trials

- "Vestibular stimulation, Parkinson's"
- 24 search results
- Duplicates: 5
- Screened: 5

Google Scholar

- Search strategy above
- 10 results
- 4 duplicates
- Screened: 3

The Physiotherapy Evidence Database

- “Vestibular stimulation, Parkinson’s”
- 1 result found
- Duplicates: 1
- 0 screened

Rehabdata

- “Vestibular stimulation, Parkinson’s”
- 1 result found
- Duplicates: 1
- 0 screened

CINAHL - No access.

Inspec - No access.

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