The effect of non-invasive auricular vagus nerve stimulation paired with rehabilitation on gait and balance impairments in chronic stroke: A randomised controlled feasibility trial.

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Background

Stroke is a leading cause of disability in Australia, costing the economy $6.2 billion of direct cost and $26 billion of indirect cost from lost wellbeing and mortality in 2020 [1]. Recovery from stroke mainly occurs in the subacute stage, driven by a period of enhanced neuroplasticity [2]. However, a large proportion of stroke survivors endure long-term impairments including limb weakness, impaired mobility and balance [1]. Hence, there is an imminent need for novel treatments to enhance stroke recovery. Recently, promising studies have demonstrated that pairing invasive vagus nerve stimulation (iVNS) with rehabilitation can enhance motor function post-stroke. For example, a multicentred, triple-blind, randomized controlled trial that included 106 stroke survivors with upper limb weakness has shown that iVNS paired with repetitive task training (for 6 weeks, 3 x 1 hour weekly) led to greater upper limb recovery compared to sham treatment [3]. Interestingly, the improvement in the active group was two to three times higher than the sham group, and more importantly, this effect was preserved for 90 days after treatment. Following this study, iVNS received approval from the Food and Drug Administration (FDA) as adjuvant therapy for chronic stroke rehabilitation [4]. However, iVNS is costly and requires a surgical procedure, limiting accessibility and imposing potential safety risks including symptomatic bradycardia, localised infection, and transient vocal cord palsy [3, 5, 6].

Transauricular vagus nerves stimulation (taVNS) has been used successfully as a non-invasive, and potentially, safer alternative to iVNS as an adjuvant therapy for drug-resistant epilepsy and major depression [7, 8]. Recently, taVNS paired with rehabilitation was found to be a feasible and safe approach to improve upper-limb weakness in subacute [9] and chronic [6, 10] stroke. The first-in-human pilot study investigating taVNS to enhance upper-limb recovery in 14 adults with chronic stroke was conducted in 2017, showing that taVNS paired with robot-assisted rehabilitation was safe and feasible with effects in favour of the active compared to the sham group [6]. Similar results were observed in subacute stage of ischaemic stroke where taVNS paired with conventional rehabilitation improved upper-limb weakness in 21 people who received 30 minutes of taVNS followed by 30 minutes of conventional therapy for 15 consecutive days [9]. More importantly, the effect of taVNS was preserved 10 weeks from the end of the intervention. Although these early taVNS studies in stroke shared some key limitations, including small sample size, the use of different stimulation parameters, and different sham protocols, their promising results, along with the good quality evidence for iVNS in stroke recovery, warrants further exploration of taVNS role in enhancing stroke recovery.

Altered gait and balance dysfunction are two common stroke-related deficits. Gait dysfunction occurs in more than 80% of people with stroke [11]. This leads to difficulty with mobility and performing activities of daily living [12]. Impaired balance is also common after stroke with 70% of people reporting a fall within 1 year of their stroke [11]. The positive effect of taVNS on upper-limb motor function, likely driven by enhanced neuroplasticity [13, 14], suggests that pairing taVNS with other therapies might prove beneficial. However, the effect of taVNS combined with gait/balance training to enhance recovery of the lower limb has not been studied. This research aims to assess the feasibility, safety, and preliminary efficacy of taVNS

paired with rehabilitation for enhancing gait and balance impairments in people with chronic stroke (> 6 months).

Method:

Aim: The primary aim is to assess the feasibility and safety of taVNS to enhance gait and balance impairments in people with chronic stroke. The secondary aim is to gain preliminary data about the efficacy of taVNS in this population.

Study Design: This will be a randomised double-blinded sham-control trial. Participants will be assessed at baseline, immediately post, and at ≥ 30 days after completing the intervention.

Participants:

Participants will be recruited from the UniSA Health and Medical Clinic as well as advertising at Stroke SA, Stroke Foundation and via social media. All assessments and treatments will be conducted within the UniSA Health and Medical Clinic at the City West.

Power and sample size: A power calculation is not necessary for a feasibility study; further no studies have investigated the use of taVNS for enhancing gait and balance. However, to provide some insight, we have performed a power calculation based on effect sizes obtained from a previous upper limb taVNS study [10]. It was determined that 18 participants will be required (in each group) to detect a moderate effect size of 0.70, given an alpha level of 0.05 and power of 80 % [15].

Inclusion criteria: Aged 18 years or older; first-ever haemorrhagic or ischaemic stroke at least 6 months earlier; can walk 10 meters with or without a gait aid and with or without assistance (assessed using 10-meter walk test [16]), no history of other neurological conditions; gait and/or balance impairment; ability to give informed consent and to understand instruction.

Exclusion criteria: Previous vagus nerve surgery; cognitive impairment and/or language impairment that might impact the person's ability to consent or understand instructions (MOCA score of less than 18); severe pain in any joints of the affected limb; advanced cardiac, pulmonary, kidney or liver condition; pregnancy; use of neuroactive medication [6]; active implants; cerebral shunts; open skin at the point of stimulation.

Intervention: The physical rehabilitation therapy component of the intervention will be tailored to participants' impairments and goals. It will consist of 15 sessions conducted over 6 weeks (2-3 x 1-hour sessions per week). Concurrently with the physical rehabilitation, participants will receive one of taVNS conditions (active or sham, allocation will be randomised).

taVNS stimulation parameters:
The stimulation will be provided using the tVNS® R device (tVNS Technologies GmbH, Reichenschwand, Germany). Stimulation intensity will be individually adjusted to a level that is above the individual's sensory threshold and below pain threshold (tolerable stimulus). A pulse width of 0.3 ms, a frequency of 25 Hz, and a pulse pause ratio of 30 sec on: 30 sec off will be used. The electrode will be placed at left ear, specifically at cymba concha. Participants will not be aware of the stimulation condition they are receiving for the duration of the treatment.

Randomisation, blinding, and concealment:

Participants will be assigned a number from 1 to 40 and allocation to intervention (active or sham taVNS) will be randomised (1: 1 ratio). Randomisation will be completed using the web application available at https://www.randomizer.org/. Subjects will be enrolled in consecutive order.

All participants will not be aware of the stimulation condition they are receiving for the duration of treatment. The sensory and pain threshold for taVNS stimulation will be measured for all participants in the first assessment session (baseline measures) and participants will be familiarised with the taVNS device. Prior to randomisation, all participants will be told that" In this study, we will use different stimulation parameters for different groups of participants. Depending on the parameters used in the group that you will be assigned to, you may feel the stimulus, normally a tingling/prickling/stinging/warmth/vibration sensation at the stimulation site, or feel nothing at all".

The physiotherapist who will provide the intervention will receive a sealed randomisation envelope imprinted with participants' numbers and will provide the appropriate intervention as indicated. The outcome assessor will be blinded.

Outcome Measures: A variety of outcome measures will be used throughout this study as follows:

1. **Feasibility:** This will be determined by measuring compliance to intervention, adverse events, patient satisfaction, and effectiveness of blinding using criteria described in table 1.

Table 1: Feasibility and Acceptability Criteria

	Proceed	Proceed with Protocol Amendments	Significant Amendments Required
Criteria	50% of eligible participants consent to participate	40% of eligible participants consent to participate	25% of eligible participants consent to participate
	60% of participants complete all the sessions of the intervention protocol	40% of participants complete the intervention protocol	25% of participants complete the intervention protocol
	50% found intervention useful (Likert ≥ 4/5) [17]	25% found intervention useful (Likert ≥ 4/5)	< 25% found intervention useful (Likert ≥ 4/5)
	50% found intervention helpful (Likert ≥ 4/5)	25% found intervention helpful (Likert ≥ 4/5)	< 25% found intervention helpful (Likert ≥ 4/5)
	50% found intervention delivery acceptable (Likert ≥ 4/5)	25% found intervention delivery acceptable (Likert ≥ 4/5)	< 25% found intervention delivery acceptable (Likert ≥ 4/5)
	Blinding ≥ 90% (Assessed using a blinding questionnaire that we developed, see appendix 1)	Blinding ≥ 50%	Blinding < 50%
	Moderate to severe adverse events occur in < 20 % of participants	Moderate to severe adverse events occur in ≥ 20% of participants.	Moderate to severe adverse events occur in ≥ 50 of participants.

1. **Safety:** We developed a safety questionnaire and it will be used to assess adverse events at the end of each week (see appendix 1). Participants will also be asked to report any AEs that occurs during any of the session immediately to the physiotherapist delivering the intervention. The AEs questionnaire was developed based on findings from a scoping review that our team has conducted recently (data has been synthesised but has not been published yet) and guided by a systematic review reporting on safety of non-invasive taVNS [10].

2. **Efficacy:** Preliminary efficacy will be assessed using outcome measures described in table 2. These outcome measures were chosen following recommendations in current stroke literature regarding standardised sensorimotor measurements in stroke recovery trials [16]. Measurements will be conducted at 3-time points (baseline, post-treatment, and 30 days follow-up)

Table 2: Proposed outcome measures

Efficacy outcomes	**Outcome measure**
Walking 1. Speed 2. Endurance 3. Gaitrite Balance Global Disability Self-efficacy	 10-meter walk test (10MWT) 6-minutes walk test (6MWT) Spatial and temporal parameters of gait Brief BESTest [18] Modified Rankin Score (mRS) [19] Stroke Self-Efficacy Scale (SSES) [20].

3. Participants experience with taVNS

Qualitative data will be obtained using a structured interview which will be conducted for each participant after 5 days of the final treatment session provided, using attached interview guide (see Appendix 2).

Statistical analysis: The feasibility will be reported against the criteria in table 1. For efficacy outcomes, a linear mixed model analysis will be used to compare two groups (active and sham) and 3-time points (baseline, post-intervention, and follow-up). Safety outcomes will be summarised descriptively. Qualitative interviews will be analysed and reported using thematic analysis. The effectiveness of the sham method in blinding participants will be assessed using a blinding questionnaire which was developed based on the work of Bang et al. (2010) [21] (see Appendix 3) that we developed, and results will be summarised descriptively.

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Appendix 1. **Symptoms and Adverse Events Following Non-invasive Auricular Vagus Nerve Stimulation**

Participant ID: _____ **Date: _____**

Symptom/Adverse Event	**Severity** Tick one box per symptom				**Persistence** Tick if symptom persisted after stimulation ceased (please detail duration of symptoms)	**Relatedness** Tick if you believe that symptom is related to stimulation	**Additional Comments**
	Nil	Mild	Moderate	Severe			
Redness/erythema	☐	☐	☐	☐	☐	☐	_____
Pain	☐	☐	☐	☐	☐	☐	_____
Irritation	☐	☐	☐	☐	☐	☐	_____
Ulcer	☐	☐	☐	☐	☐	☐	_____
Itching	☐	☐	☐	☐	☐	☐	_____
Dizziness	☐	☐	☐	☐	☐	☐	_____
Headache	☐	☐	☐	☐	☐	☐	_____
Fatigue	☐	☐	☐	☐	☐	☐	_____
Increased tinnitus	☐	☐	☐	☐	☐	☐	_____
Nausea	☐	☐	☐	☐	☐	☐	_____
Other events (please describe)							
_____	☐	☐	☐	☐	☐	☐	_____
_____	☐	☐	☐	☐	☐	☐	_____

Appendix 2. Interview guide

The effect of non-invasive auricular vagus nerve stimulation paired with physiotherapy on gait and balance impairments in chronic stroke: Phase 2-randomised controlled feasibility trial

Interview Guide

Please note that this interview is being recorded and will be transcribed for analysis. Do you consent to this?

Qu 1: How did you find your experience with using the non invasive auricular vagus nerve stimulation?

Qu 2: What things did you like about using non invasive auricular vagus nerve stimulation?

What things didn't you like about using non invasive auricular vagus nerve stimulation?

Qu 3: For the therapy sessions you were not able to complete, what would you say was the major factor preventing you from doing so?

Qu 4: Do you think your balance and mobility has changed since your stroke? In what way has it changed and do you think it was because of the non invasive auricular vagus nerve stimulation?

Qu 5: Has your participation in activities changed since your stroke? What is your opinion about the role of non invasive auricular vagus nerve stimulation in these changes?

Qu 6: If you were given the opportunity would you continue to use taVNS after this treatment finished?

Qu 7: How would you rate the comfort/ability to tolerate the device/stimulation?

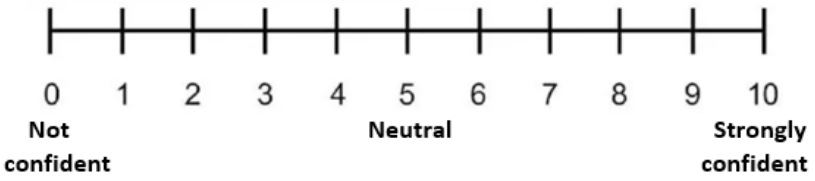
Qu 8: Do you think using equipment such as non invasive auricular vagus nerve stimulator in the future in clinics or at home would be worthwhile?

Qu 9: Are there any other comments you would like to make about your participation and experience in the trial?

Appendix 3. Blinding Assessment Questionnaire

BLINDING ASSESSMENT QUESTIONNAIRE- FOR RESEARCH PARTICIPANTS

This section is to be filled out by Research Team	
Recipient ID:	
Date:	
Protocol ID:	

QUESTION	**RESPONSE**
Which intervention do you believe you received?	Please circle: ACTIVE / SHAM / DON'T KNOW
If you answered 'don't know', please provide your best guess of the intervention you received.	Please circle: ACTIVE / SHAM
What made you believe you received this type of intervention?	_____ _____ _____ **On a scale of 1 to 10, please mark how confident you are in your answer:** 

Do you have other comments?

_____

_____

_____

_____