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Exercise responses with transcutaneous spinal cord stimulation (using electrodes placed on the skin surface) following spinal cord injury

Submission date
06/02/2024

Recruitment status
Recruiting

Registration date
08/02/2024

Overall study status
Ongoing

Last Edited
24/01/2025

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study is investigating the effects of a non-invasive form of spinal cord stimulation (called transcutaneous, meaning across the skin surface) on cardiovascular control, upper-body exercise performance, fitness and other health outcomes in individuals with a spinal cord injury (SCI). During exercise, individuals with higher levels of SCI (i.e., above the sixth thoracic segment) typically have lower peak heart rates and blood pressure that ultimately limit exercise performance and overall physical capacity. Overtime, this can significantly increase the risk of cardiovascular disease (e.g., stroke or heart attack) to a greater extent than the general population. Epidural spinal cord stimulation (involving an implanted electrical stimulator) has recently resolved low blood pressure and improved exercise performance in an individual with tetraplegia in North America, yet this requires an invasive and expensive surgical procedure that is not routinely offered in the UK. The first aim of this study to determine whether non-invasive TSCS can improve upper-body exercise performance during a single exercise session. The second aim of this study is to explore whether 8 weeks of upper-body exercise with TSCS will improve overall fitness, cardiovascular disease risk factors, cognition, motor function and quality of life in individuals with SCI.

Who can participate?
Individuals who have been living with a SCI for more than one year, which must be motor-complete (as determined by an AIS Grade A or B) between the C5 to T6 spinal segments. This study will also be recruiting healthy, non-injured participants that are the same age and sex as the SCI participants.

What does the study involve?
This study is formed of two parts (Aim 1 & Aim 2). For Aim 1, participants will perform three upper-body exercise sessions at a range of exercise intensities for between 20 to 40 minutes. Two of these sessions will be performed with TSCS. All exercise sessions will be conducted on separate days. This part of the study lasts 3 weeks with 5 assessment visits lasting around 2-3 hours each. Non-injured individuals who match the age and sex of the SCI participants already enrolled will be recruited for Aim 1 only to complete similar exercise trials without any form of

TSCS. For Aim 2, participants will complete an 8-week exercise intervention, consisting of high-intensity upper-body exercise two times per week whilst receiving TSCS. Participants will be randomly assigned to one of two study groups: one will receive TSCS that has been optimised to improve cardiovascular control and the other will receive a control TSCS that does not improve cardiovascular control. This part of the study lasts 9 weeks plus a 6 week follow-up period. There will be 6 assessment visits and 16 exercise intervention sessions with a total time commitment of approximately 34 hours.

Throughout Aim 1 and Aim 2, participants will undergo a number of assessments on their heart rate and blood pressure responses, physical fitness, cardiovascular health, cognitive function and balance. Participants will also be asked whether they would like to fill in questionnaires on their quality of life.

What are the possible benefits and risks of participating?
The costs of all tests, examinations and interventions as part of this study will be provided at no cost to participants. Compensation will be provided to participants to cover travel and study-related costs. Participating in this study will help improve knowledge on the effectiveness of using TSCS in the SCI community, both during exercise and at times when cardiovascular dysfunction may impact other activities of daily living. It is currently unknown whether being randomly assigned to the exercise intervention with cardiovascular-optimised TSCS will provide a personal therapeutic benefit to participants. However, others may benefit from the overall conclusions to be drawn from the results of this study. Upon request, participants will be able to obtain personalised feedback on how their health has changed over the course of the study and how their body has responded to exercise.

All assessments will take place in a controlled clinical/research environment. Every effort will be made to ensure safety, privacy, and comfort. All procedures will be conducted by experienced and trained members of the research team. These procedures offer minimal risks, however, the following risks/discomforts that could be associated with these procedures are outlined below:

1. There are risks associated with using spinal cord stimulation, yet adverse events are unexpected as this study will only be using parameters and electrodes (stickers) similar to individuals using a transcutaneous electrical nerve stimulation (TENS) machine. There may be a slight risk of skin irritation but we will monitor skin temperature. We will also confirm allergies before using any electrodes, gels and/or plasters.
2. The adhesive electrodes (stickers) used throughout may cause mild discomfort when removed. However, care will be taken to ensure comfort with placement and removal of these. If any skin irritation is experienced, we will advise for alternate sites to place the stickers or provide a fabric chest strap to support the attachment of specific equipment, given some are worn for a prolonged period of time.
3. The blood samples may cause a bruise and there is a potential risk of infection. These risks will be minimised by following good clinical practice. Some light-headedness or headaches may be experienced as a result of the overnight fast for the blood samples. This is equivalent to missing breakfast and is the minimal standardisation procedure for collecting fasting blood samples. Participants will be able to eat immediately once the blood sample procedure has been completed.
4. The ultrasound procedures are non-invasive and offer minimal risk. Participants may experience some discomfort due to the cold gel or because the assessments require lying on a procedure bed for an extended period of time. There is a very small risk that participants could fall off of the bed (e.g., due to strong, involuntary spasms), though steps will be taken to ensure this does not occur (e.g., using guard rails where appropriate).
5. Participants may experience some discomfort with the cuff inflation around the upper-arm

when measuring blood pressure. There are no known risks associated with this short-lived restriction of blood flow to the arm. It is possible that there may be brief numbness and/or tingling in the hand, and a “pins and needles” sensation upon cuff deflation, but these sensations should only last a few minutes.
6. Performing any form of vigorous-intensity exercise carries a minor risk. Risks include sensations of fatigue, physical exhaustion and fainting. The sensation of fatigue is short-lived and will subside in a few minutes upon stopping exercise. The risk of a cardiovascular event (such as a heart attack) is extremely low, approximately a 0.01% chance. Participants will warm up before each exercise bout and will be closely monitored throughout for known indications for stopping exercise [including sustained maximum heart rate, pain in the chest (angina), confusion etc.]. Researchers are first aid trained (including cardiopulmonary resuscitation training) and will be present during all exercise testing sessions. The School of Sport, Exercise and Rehabilitation Sciences is equipped with an automated defibrillator in close proximity to the space where testing will take place. There is also a risk of mild muscle soreness after the arm cycling exercise. Participants are free to stop and rest at any point during the exercise sessions and are also free to stop the exercise intervention should they feel discomfort and wish to stop/withdraw from the study.
7. If participants have a higher-level spinal cord injury (above the sixth thoracic segment) then there is an increased risk of experiencing both high and low blood pressure. High-blood pressure is due to a condition called autonomic dysreflexia, which is triggered by a stimulus below the level of injury (e.g., full bladder). Participants will be asked to empty their bladder prior to any assessments. Some faintness or nauseous feelings may be experienced after exercise or upon moving from lying flat to a seated position. Blood pressure will be measured before and after exercise and the supervising member of staff will be trained to identify signs and symptoms of blood pressure instability, along with appropriate mitigation strategies if necessary.
8. There is also an opportunity to take part in an assessment using brain stimulation, which is non-invasive and harmless. It may cause mild discomfort but this is unlikely. The assessment will start at a lower intensity and only increase gradually if participants feel as though they can tolerate it. The procedure can be stopped at any point if it is too uncomfortable.
9. Participants may experience some negative emotions when researchers ask for personal information or when completing questionnaires that relate to current mood or ability to perform activities of daily living. Participants may find certain questions within the survey uncomfortable to answer, but these do not have to be answered (participants can say "prefer not to say" rather than answering the question). Responses will not be judged and will remain confidential. If participants are worried about any aspect of their physical or mental health, then they will be advised to discuss this with a member of their clinical care team or relevant healthcare practitioner. In addition, should participants feel any distress during the study they will be able to speak with the primary study contact who is trained in mental health first aid and can be a first-point of call should they wish to discuss anything either during a study visit or at home. Contact information for UK organisations that provide emotional support for people experiencing distress will also be provided to participants.

Where is the study run from?
The School of Sport, Exercise and Rehabilitation Sciences at the University of Birmingham (UK).

When is the study starting and how long is it expected to run for?
January 2023 to June 2026

Who is funding the study?
The International Spinal Research Trust (UK) and The Academy of Medical Sciences

Who is the main contact?
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For participants interested in taking part, please email stimex-sci@contacts.bham.ac.uk

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
333496

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 333496, RG_22-157

Study information

Scientific Title
Impact of transcutaneous spinal cord stimulation on autonomic cardiovascular control and upper-body exercise performance in individuals with a spinal cord injury (STIMEX-SCI): An exploratory study

Acronym
STIMEX-SCI

Study objectives
Current study hypothesis as of 01/11/2024:

Transcutaneous spinal cord stimulation that is optimised to modulate cardiovascular responses (i.e., CV-TSCS) will result in a longer time to exhaustion during an aerobic arm-crank exercise trial, in comparison to exercise performed with sham TSCS. We also expect that individuals who perform 8-weeks of vigorous-intensity exercise combined with CV-TSCS will exhibit greater changes in cardiorespiratory fitness and other therapeutic outcomes relative to individuals who perform exercise with sham TSCS.

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Previous study hypothesis:

Transcutaneous spinal cord stimulation that is optimised to modulate cardiovascular responses (i.e., CV-TSCS) will result in a longer time to fatigue during an aerobic arm-crank exercise trial, in comparison to exercise performed with sham TSCS. We also expect that individuals who perform 8-weeks of vigorous-intensity exercise combined with CV-TSCS will exhibit greater changes in cardiorespiratory fitness and other therapeutic outcomes relative to individuals who perform exercise with sham TSCS.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 03/11/2023, Wales Research Ethics Committee 7 (Public Health Wales Meeting Room, Building 1, St. David’s Park, Carmarthen, SA31 3HB, United Kingdom; +44 2922 941107; Wales.REC7@wales.nhs.uk), ref: 23/WA/0284

Study design

Single-centre single-blind acute randomized crossover trial and longitudinal randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic (>1 year) motor-complete (AIS A-B) spinal cord injury between C5-T6

Interventions
Current interventions as of 01/11/2024:

The project is formed of acute (Aim 1) and longitudinal (Aim 2) components. Aim 1 lasts 3 weeks with a total time commitment of approx. 11.5 hours, split across 5 assessment visits. Aim 2 lasts 9 weeks plus a 6-week follow-up period with a total time commitment of approx. 34 hours. This consists of 16 exercise sessions (2 sessions per week for 8 weeks) and 6 assessment visits.

Aim 1 (the acute component) adopts a single-blind randomised-crossover trial design. Following the provision of informed consent, participants will undergo a transcutaneous spinal cord stimulation (TSCS) mapping session to identify the specific stimulation parameters that robustly modulate cardiovascular outcomes (called CV-TSCS). A sham stimulation that does not modulate cardiovascular outcomes will be used as a control (called SHAM-TSCS). Essentially, TSCS will involve electrical stimulation delivered to the spinal cord through the skin and tissue using cathode electrodes to deliver the stimulation and anode electrodes to ground the circuit. Possible adjustable parameters include waveform (biphasic or monophasic), amplitude and location of cathodes along the spinal column (T8 - L2). Across two assessment visits, participants will partake in a series of tests designed to challenge the autonomic nervous system (ANS). Throughout the mapping session and during the ANS test battery, beat-to-beat heart rate, blood pressure and cerebrovascular blood velocity will be monitored, along with skin temperature near the electrodes. Following this, participants will perform a graded cardiopulmonary exercise test (CPET) on an arm-crank ergometer to volitional exhaustion to identify their peak oxygen uptake (VO2peak). On separate days they will then perform three submaximal exercise trials on an arm-crank ergometer at a range of exercise intensities (light, moderate and vigorous) corresponding to a percentage of their VO2peak. One will be a familiarisation trial without TSCS and two will be trials performed with the application of CV-TSCS or SHAM-TSCS in a randomised order. Time to exhaustion (primary outcome measure) will be measured as the duration of exercise performed. During these exercise trials, gas exchange variables will be recorded via a face mask connected to a metabolic cart. Heart rate will be recorded via a chest strap and cerebrovascular blood velocity will be assessed via Transcranial Doppler ultrasound. Skeletal muscle tissue haemodynamics and oxygenation will be measured using near-infrared spectroscopy. Ratings of perceived exertion, enjoyment and affective valence will be measured throughout and post-exercise. Venous blood samples will be taken from a forearm vein by a trained phlebotomist immediately before, immediately after and 90 minutes following exercise.

Healthy, non-injured participants will also be recruited to take part in Aim 1 that are age and sex-matched to the SCI cohort. These participants will not complete Aim 2. Enrolment will last 2 weeks with a total time commitment of approx. 10.5 hours, split across 4 assessment visits.

Participants will perform the same CPET and ANS test battery as the SCI participants. They will also perform a familiarisation exercise trial, an exercise trial with workloads corresponding to their own VO2peak, and an exercise trial at the same absolute workloads as the SCI participants. All tests and exercise trials will be conducted without any form of TSCS.

Aim 2 (the longitudinal component) adopts a single-blind randomised-controlled trial (RCT) design whereby participants will be randomised into two study groups: (1) CV-TSCS + aerobic arm-crank exercise (experimental group) or (2) SHAM-TSCS + aerobic arm-crank exercise (control group). Prior to the intervention, a trained phlebotomist will take a fasting (>10 hours) blood sample from a forearm vein. Central arterial stiffness will be determined, along with ultrasound assessments performed by a trained sonographer to determine cardiac function. Cognitive function will be assessed using a shortened neuropsychological test battery. A motor function assessment will be conducted to determine seated balance. Participants will be asked to complete four health-related quality of life questionnaires and wear a device to capture blood pressure instability over a 24-hour period. A physical activity monitor will also be worn for 4 days. An assessment of corticospinal drive to respiratory muscles utilising transcranial magnetic stimulation will be conducted before and after the first exercise intervention session. A CPET to volitional exhaustion and a sit-up test with beat-to-beat heart rate, blood pressure and cerebrovascular velocity will be performed at the midpoint of the intervention.

All participants will perform 2 x 48 minutes per week of vigorous-intensity aerobic arm-crank exercise, in keeping with SCI-specific exercise guidelines to improve cardiometabolic health. During each session, participants will perform 10 x 3-min of vigorous-intensity arm-crank exercise, interspersed by 2-min active-rest periods. Participants will be permitted longer rest periods if necessary. Exercise intensity will be prescribed at a power output corresponding to population-specific guidelines for individuals with paraplegia (~73%VO2peak) and tetraplegia (~79%VO2peak), determined from their baseline graded CPET. These values are believed to closely correspond to vigorous-intensity exercise classifications, in comparison to using non-disabled guidelines. Exercise intensity will be regulated during the 8-week intervention by capturing participants ratings of perceived exertion (RPE) at the end of each 3-min bout within an exercise session as well as an overall RPE at the end of each session. RPE's of 14-17 on a 6-20 Borg Scale will be classed as vigorous-intensity exercise. The actual targets for duration, intensity and frequency may be adjusted by an accredited clinical exercise physiologist based on the participants' tolerance to the training parameters. Where participants miss sessions due to illness or other circumstances, they will be provided with the opportunity to perform "make-up" sessions during an additional week. A 5-min light-intensity warm-up (corresponding to 31% and 37% of each participant's VO2peak for individuals with paraplegia and tetraplegia, respectively) will be performed before each exercise session. Participants will also be permitted to perform a 5-min cool down at a self-selected exercise intensity at the end of each session. Brachial blood pressure will be recorded pre-, mid- and post-exercise as a safety measure and to ensure the effects of stimulation have neither subsided (i.e., a drop in BP for CV-TSCS) or considerably modulated BP (i.e., increase in BP for SHAM-TSCS).

Upon completion of the exercise intervention, participants will undergo the same assessments as pre-intervention with the addition of the same ANS test battery conducted in Aim 1, with and without CV-TSCS, and a CPET to volitional exhaustion. Participants will also be asked to complete a usability and satisfaction questionnaire at the end of the intervention period. Six weeks following the intervention, participants will be asked to complete the heath-related quality of life questionnaires for a final time.

Previous interventions:

The project is formed of acute (Aim 1) and longitudinal (Aim 2) components. Aim 1 lasts 3 weeks with a total time commitment of approx. 11.5 hours, split across 5 assessment visits. Aim 2 lasts 9 weeks plus a 6-week follow-up period with a total time commitment of approx. 34 hours. This consists of 16 exercise sessions (2 sessions per week for 8 weeks) and 6 assessment visits.

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Healthy, non-injured participants will also be recruited to take part in Aim 1 that are age and sex-matched to the SCI cohort. These participants will not complete Aim 2. Enrolment will last 2 weeks with a total time commitment of approx. 10.5 hours, split across 4 assessment visits. Participants will perform the same CPET and ANS test battery as the SCI participants. They will also perform a familiarisation exercise trial, an exercise trial with workloads corresponding to their own VO2peak, and an exercise trial at the same absolute workloads as their matched SCI counterpart. All tests and exercise trials will be conducted without any form of TSCS.

Aim 2 (the longitudinal component) adopts a single-blind randomised-controlled trial (RCT) design whereby participants will be randomised into two study groups: (1) CV-TSCS + aerobic arm-crank exercise (experimental group) or (2) SHAM-TSCS + aerobic arm-crank exercise (control group). Prior to the intervention, a trained phlebotomist will take a fasting (>10 hours) blood sample from a forearm vein. Central arterial stiffness will be determined, along with ultrasound assessments performed by a trained sonographer to determine cardiac structure and function. Cognitive function will be assessed using a shortened neuropsychological test battery. A motor function assessment will be conducted to determine seated balance, along with an assessment of corticospinal excitability utilising transcranial magnetic stimulation. Participants will be asked

to complete four health-related quality of life questionnaires and wear a device to capture blood pressure instability over a 24-hour period. A physical activity monitor will also be worn for 4 days. A CPET to volitional exhaustion and a sit-up test with beat-to-beat heart rate, blood pressure and cerebrovascular velocity will be performed at the midpoint of the intervention.

All participants will perform 2 x 48 minutes per week of vigorous-intensity aerobic arm-crank exercise, in keeping with SCI-specific exercise guidelines to improve cardiometabolic health. During each session, participants will perform 10 x 3-min of vigorous-intensity arm-crank exercise, interspersed by 2-min active-rest periods. Participants will be permitted longer rest periods if necessary. Exercise intensity will be prescribed at a power output corresponding to population-specific guidelines for individuals with paraplegia (~73%VO2peak) and tetraplegia (~79%VO2peak), determined from their baseline graded CPET. These values are believed to closely correspond to vigorous-intensity exercise classifications, in comparison to using non-disabled guidelines. Exercise intensity will be regulated during the 8-week intervention by capturing participants ratings of perceived exertion (RPE) at the end of each 3-min bout within an exercise session as well as an overall RPE at the end of each session. RPE's of 14-17 on a 6-20 Borg Scale will be classed as vigorous-intensity exercise. The actual targets for duration, intensity and frequency may be adjusted by an accredited clinical exercise physiologist based on the participants' tolerance to the training parameters. Where participants miss sessions due to illness or other circumstances, they will be provided with the opportunity to perform "make-up" sessions during an additional week. A 5-min light-intensity warm-up (corresponding to 31% and 37% of each participant's VO2peak for individuals with paraplegia and tetraplegia, respectively) will be performed before each exercise session. Participants will also be permitted to perform a 5-min cool down at a self-selected exercise intensity at the end of each session. Brachial blood pressure will be recorded pre-, mid- and post-exercise as a safety measure and to ensure the effects of stimulation have neither subsided (i.e., a drop in BP for CV-TSCS) or considerably modulated BP (i.e., increase in BP for SHAM-TSCS).

Upon completion of the exercise intervention, participants will undergo the same assessments as pre-intervention with the addition of the same ANS test battery conducted in Aim 1, with and without CV-TSCS, and a CPET to volitional exhaustion. Participants will also be asked to complete a usability and satisfaction questionnaire at the end of the intervention period. Six weeks following the intervention, participants will be asked to complete the heath-related quality of life questionnaires for a final time.

Intervention Type
Behavioural

Primary outcome(s)
Current primary outcome measure as of 01/11/2024:

Aim 1:
Time to exhaustion assessed as the duration of exercise performed during an aerobic arm-crank exercise trial at a range of workloads corresponding to light, moderate and vigorous-intensity exercise, both with and without CV-TSCS.

Aim 2:
Cardiorespiratory fitness assessed as the peak oxygen uptake (VO2peak) achieved during a graded cardiopulmonary exercise test performed on an arm-crank ergometer until volitional

exhaustion. Expired gases will be collected using a calibrated, metabolic cart (Vyntus CPX, Jaeger, Germany). Cardiorespiratory fitness will be assessed pre-intervention, mid-intervention (Week 4) and post-intervention (Week 8).

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Previous primary outcome measure:

Aim 1:
Time to fatigue assessed as the duration of exercise performed during an aerobic arm-crank exercise trial at a range of workloads corresponding to light, moderate and vigorous-intensity exercise, both with and without CV-TSCS.

Aim 2:
Cardiorespiratory fitness assessed as the peak oxygen uptake (VO2peak) achieved during a graded cardiopulmonary exercise test performed on an arm-crank ergometer until volitional exhaustion. Expired gases will be collected using a calibrated, metabolic cart (Vyntus CPX, Jaeger, Germany). Cardiorespiratory fitness will be assessed pre-intervention, mid-intervention (Week 4) and post-intervention (Week 8).

Key secondary outcome(s))

Current secondary outcome measures as of 01/11/2024:

Aim 1:
1. Blood pressure instability (self-report). Measured via the Autonomic Dysfunction Following SCI Questionnaire. Assessed at baseline.
2. Beat-to-beat heart rate, blood pressure and cerebrovascular blood velocity responses to a battery of autonomic nervous system stress tests. Measured via electrocardiogram, non-invasive finger plethysmography and Transcranial Doppler ultrasound, respectively. Assessed with and without CV-TSCS at baseline.
3. Respiratory function. Functional vital capacity, forced expiratory volume in 1 second, ratio (FEV1/FVC), and peak expiratory flow will be measured via standard spirometry testing procedures in accordance with the American Thoracic Society and European Respiratory Society. Assessed with and without CV-TSCS at baseline.
4. Gas exchange variables (oxygen uptake, respiratory exchange ratio, end tidal CO2). Measured via a calibrated, metabolic cart (Vyntus CPX, Jaeger, Germany). Assessed during the cardiopulmonary exercise test at baseline, familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
5. Oxygen pulse. Measured using heart rate (Polar Electro, Kempele, Finland) and oxygen uptake (Vyntus CPX, Jaeger, Germany) and used as a reasonable surrogate for stroke volume. Assessed during the cardiopulmonary exercise test at baseline, familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
6. Beat-to-beat cerebrovascular blood velocity in the left and right middle cerebral artery. Measured via Transcranial Doppler ultrasound. Assessed during the familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
7. Haemodynamics and oxygenation of lower extremity skeletal muscle tissue. Measured using near-infrared spectroscopy (NIRS-500, Hamamatsu Photonics, Japan). Assessed during the familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
8. Ratings of perceived exertion, exercise enjoyment and affective valence. Measured via the Borg scale (6 to 20), the Stanley, Williams & Cumming scale (1 to 7), and the Hardy & Rejeski scale (-5 to +5). Assessed during the familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.

9. Blood biomarkers including metabolic (e.g., lactate), cytokines (e.g., interleukin-6), catecholamines (e.g., adrenaline, noradrenaline) and brain-derived neurotrophic factor. Blood samples taken immediately before and after the exercise trials with CV-TSCS and SHAM-TSCS.
10. Immune cell dynamics. Measured via automated haematology followed by phenotyping using flow cytometry. Blood samples taken immediately before, immediately after, and 90 minutes following the exercise trials with CV-TSCS and SHAM-TSCS.
11. Adverse events. Recorded throughout.

Aim 2:
1. Beat-to-beat heart rate, blood pressure and cerebrovascular blood velocity responses to a battery of autonomic nervous system stress tests. Measured via electrocardiogram, non-invasive finger plethysmography and Transcranial Doppler ultrasound, respectively. Assessed with and without CV-TSCS at baseline (as part of Aim 1) and post-intervention.
2. Blood pressure instability over a 24-hour period. Measured via periodic (day time: every 15 minutes; night-time: every 60 minutes) brachial blood pressure measurements using an ambulatory blood pressure monitor (IEM Mobil-O-Graph). Assessed pre-intervention and post-intervention.
3. Heart rate variability (HRV). The non-stationary balance between sympathetic and parasympathetic branches of the cardiac autonomic nervous system will be measured using ECG in accordance with best practice recommendations. Assessed pre-intervention and post-intervention.
4. Central arterial stiffness. Arterial pulse waveforms will be acquired at two locations (carotid and femoral arteries) simultaneously to determine pulse transit time and carotid-to-femoral pulse wave velocity (cfPWV); measured using the Vicorder (Smart Medical, UK) system with standard vascular cuffs. Assessed pre-intervention and post-intervention.
5. Cardiac function. Transthoracic echocardiography (TTE) will be performed using a Vivid iq ultrasound system (General Electric Medical, Norway) in accordance with recommendations of the American Society for Echocardiography. Assessed pre-intervention and post-intervention.
6. Cardiovascular disease risk and growth factor blood biomarkers including: triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, insulin, C-reactive protein, HbA1c/Hb, apolipoprotein B, and nerve growth factor. Assessed pre-intervention and post-intervention.
7. Characterising daily energy expenditure. Participants will wear an individually calibrated multisensor device for 4 days. The ActiheartTM, which incorporates tri-axial accelerometry and physiological signals, will be used to predict physical activity energy expenditure and minutes per week of activity within certain intensity thresholds (sedentary, light, moderate, and vigorous). Assessed pre-intervention and post-intervention.
8. Cognitive function. A shortened neuropsychological test battery will be utilised that includes the Digit Span and Symbol Digit Modality Test (SDMT) to give a global indication of cognitive function. Assessed pre-intervention and post-intervention.
9. Seated balance. Measured via the Function in Sitting Test in SCI (FIST-SCI). Assessed pre-intervention and post-intervention.
10. Corticospinal excitability of the respiratory muscles. Assessed using surface electromyography and transcranial magnetic stimulation. Assessed before and after the first exercise intervention session to explore the acute (single-session) effects of receiving CV-TSCS or SHAM-TSCS during exercise. It will then be assessed again post-intervention but at rest only, with the data from baseline used as a comparison to investigate longitudinal changes.
11. Respiratory function. Functional vital capacity, forced expiratory volume in 1 second, ratio (FEV1/FVC), and peak expiratory flow will be measured via standard spirometry testing procedures in accordance with the American Thoracic Society and European Respiratory Society. Assessed with and without CV-TSCS pre-intervention (as part of AIM 1) and post-intervention without CV-TSCS only.

12. Health-related quality of life. Physical and emotional quality of life will be measured via the SF-36 walk/wheel questionnaire. Bowel function will be measured via the Neurogenic Bowel Dysfunction Score. Bladder function will be measured via the Neurogenic Bladder Symptom Score. Sexual function will be measured by the International Index of Erectile Function or the Female Sexual Function Index for males and females, respectively. Assessed pre-intervention, post-intervention and six weeks post-intervention.
13. Blood pressure instability (self-report). Measured via the Autonomic Dysfunction Following SCI Questionnaire. Assessed at baseline (as part of Aim 1), post-intervention and six weeks post-intervention.
14. Adverse events. Recorded throughout.

Feasibility outcomes (Aim 2):
1. Participant recruitment rate: the proportion of eligible participants who express interest and agree to participate in the research study.
2. Retention and adherence: the proportion of participants who complete the study and the proportion of exercise intervention sessions completed.
3. Acceptability of the intervention and study design. Measured via the Participant Evaluation of Feasibility and Acceptability Questionnaire which will obtain information on the usability and satisfaction of adopting TSCS during an exercise intervention, along with the biggest facilitators for exercise; the biggest challenges/barriers to exercise; benefits received from participating in the TSCS + exercise intervention; and suggestions for other individuals with SCI to engage in such exercise interventions.
4. Completion rates for each outcome measure evaluated to determine if an outcome measure should be removed.

Previous secondary outcome measures:

Aim 1:
1. Blood pressure instability (self-report). Measured via the Autonomic Dysfunction Following SCI Questionnaire. Assessed at baseline.
2. Beat-to-beat heart rate, blood pressure and cerebrovascular blood velocity responses to a battery of autonomic nervous system stress tests. Measured via electrocardiogram, non-invasive finger plethysmography and Transcranial Doppler ultrasound, respectively. Assessed with and without CV-TSCS at baseline.
3. Gas exchange variables (oxygen uptake, respiratory exchange ratio, end tidal CO_2). Measured via a calibrated, metabolic cart (Vyntus CPX, Jaeger, Germany). Assessed during the cardiopulmonary exercise test at baseline, familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
4. Oxygen pulse. Measured using heart rate (Polar Electro, Kempele, Finland) and oxygen uptake (Vyntus CPX, Jaeger, Germany) and used as a reasonable surrogate for stroke volume. Assessed during the cardiopulmonary exercise test at baseline, familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
5. Beat-to-beat cerebrovascular blood velocity in the left and right middle cerebral artery. Measured via Transcranial Doppler ultrasound. Assessed during the familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
6. Haemodynamics and oxygenation of lower extremity skeletal muscle tissue. Measured using near-infrared spectroscopy (NIRS-500, Hamamatsu Photonics, Japan). Assessed during the familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
7. Ratings of perceived exertion, exercise enjoyment and affective valence. Measured via the Borg scale (6 to 20), the Stanley, Williams & Cumming scale (1 to 7), and the Hardy & Rejeski scale

(-5 to +5). Assessed during the familiarisation session and exercise trials with CV-TSCS and SHAM-TSCS.
8. Blood biomarkers including metabolic (e.g., glucose, lactate), cytokines (e.g., interleukin-6), catecholamines (e.g., adrenaline, noradrenaline) and brain-derived neurotrophic factor. Blood samples taken immediately before and after the exercise trials with CV-TSCS and SHAM-TSCS.
9. Immune cell dynamics. Measured via automated haematology followed by phenotyping using flow cytometry. Blood samples taken immediately before, immediately after, and 90 minutes following the exercise trials with CV-TSCS and SHAM-TSCS.
10. Adverse events. Recorded throughout.

Aim 2:
1. Beat-to-beat heart rate, blood pressure and cerebrovascular blood velocity responses to a battery of autonomic nervous system stress tests. Measured via electrocardiogram, non-invasive finger plethysmography and Transcranial Doppler ultrasound, respectively. Assessed with and without CV-TSCS at baseline (as part of Aim 1) and post-intervention.
2. Blood pressure instability over a 24-hour period. Measured via periodic (day time: every 15 minutes; night-time: every 60 minutes) brachial blood pressure measurements using an ambulatory blood pressure monitor (IEM Mobil-O-Graph). Assessed pre-intervention and post-intervention.
3. Heart rate variability (HRV). The non-stationary balance between sympathetic and parasympathetic branches of the cardiac autonomic nervous system will be measured using ECG in accordance with best practice recommendations. Assessed pre-intervention and post-intervention.
4. Central arterial stiffness. Arterial pulse waveforms will be acquired at two locations (carotid and femoral arteries) simultaneously to determine pulse transit time and carotid-to-femoral pulse wave velocity (cfPWV); measured using the Vicorder (Smart Medical, UK) system with standard vascular cuffs. Assessed pre-intervention and post-intervention.
5. Cardiac structure and function. Transthoracic echocardiography (TTE) will be performed using a Vivid iq ultrasound system (General Electric Medical, Norway) in accordance with recommendations of the American Society for Echocardiography. Assessed pre-intervention and post-intervention.
6. Cardiovascular disease risk blood biomarkers including: triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, insulin and C-reactive protein. Assessed pre-intervention and post-intervention.
7. Characterising daily energy expenditure. Participants will wear an individually calibrated multisensor device for 4 days. The ActiheartTM, which incorporates tri-axial accelerometry and physiological signals, will be used to predict physical activity energy expenditure and minutes per week of activity within certain intensity thresholds (sedentary, light, moderate, and vigorous). Assessed pre-intervention and post-intervention.
8. Cognitive function. A shortened neuropsychological test battery will be utilised that includes the Digit Span and Symbol Digit Modality Test (SDMT) to give a global indication of cognitive function. Assessed pre-intervention and post-intervention.
9. Seated balance. Measured via the Function in Sitting Test in SCI (FIST-SCI). Assessed pre-intervention and post-intervention.
10. Corticospinal excitability of the respiratory muscles and muscles below the injury. Assessed using surface electromyography and transcranial magnetic stimulation. Assessed pre-intervention and post-intervention.
11. Respiratory function. Functional vital capacity, forced expiratory volume in 1 second, ratio (FEV1/FVC), and peak expiratory flow will be measured via standard spirometry testing procedures in accordance with the American Thoracic Society and European Respiratory Society. Assessed with and without CV-TSCS pre-intervention and post-intervention.
12. Health-related quality of life. Physical and emotional quality of life will be measured via the

SF-36 walk/wheel questionnaire. Bowel function will be measured via the Neurogenic Bowel Dysfunction Score. Bladder function will be measured via the Neurogenic Bladder Symptom Score. Sexual function will be measured by the International Index of Erectile Function or the Female Sexual Function Index for males and females, respectively. Assessed pre-intervention, post-intervention and six weeks post-intervention.
13. Blood pressure instability (self-report). Measured via the Autonomic Dysfunction Following SCI Questionnaire. Assessed at baseline (as part of Aim 1), post-intervention and six weeks post-intervention.
14. Adverse events. Recorded throughout.

Feasibility outcomes (Aim 2):
1. Participant recruitment rate: the proportion of eligible participants who express interest and agree to participate in the research study.
2. Retention and adherence: the proportion of participants who complete the study and the proportion of exercise intervention sessions completed.
3. Acceptability of the intervention and study design. Measured via the Participant Evaluation of Feasibility and Acceptability Questionnaire which will obtain information on the usability and satisfaction of adopting TSCS during an exercise intervention, along with the biggest facilitators for exercise; the biggest challenges/barriers to exercise; benefits received from participating in the TSCS + exercise intervention; and suggestions for other individuals with SCI to engage in such exercise interventions.
4. Completion rates for each outcome measure evaluated to determine if an outcome measure should be removed.

Completion date
30/06/2026

Eligibility

Key inclusion criteria
For individuals with spinal cord injury:
1. Male or female of at least 16 years of age.
2. Chronic SCI (non-progressive, with motor-complete paralysis) between the C5 – T6 spinal segments and ≥1-year post injury.
3. Documented presence of cardiovascular dysfunction including presence of persistent low resting BP and/or symptoms of autonomic dysreflexia and/or orthostatic hypotension. This will be assessed using the The Autonomic Dysfunction Following SCI questionnaire.
4. American Spinal Injury Association Impairment Scale A or B (motor-complete SCI).
5. Willing and able to comply with all clinic visits and study-related procedures.
6. Able to understand and complete study-related questionnaires (i.e., English language speaking only).
7. No painful musculoskeletal dysfunction, unhealed fracture, pressure sore, or active infection that may interfere with testing activities.
8. Can move their arms/hands voluntarily to operate the arm-crank ergometer.
9. Must provide informed consent.

For non-injured individuals:
1. Male or female of at least 16 years of age.
2. Willing and able to comply with all clinic visits and study-related procedures.
3. Able to understand and complete study-related questionnaires (i.e., English language speaking only).

4. No painful musculoskeletal dysfunction, unhealed fracture, or active infection that may interfere with testing activities.
5. Must provide informed consent.

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 01/11/2024:

For individuals with a spinal cord injury:
1. Presence of severe acute medical issues that in the investigator's judgement would adversely affect the participant's participation in the study. Examples include, but are not limited to, acute urinary tract infections; pressure sores; active heterotopic ossification; newly changed antidepressant medications (tricyclic antidepressants); or unstable diabetes.
2. Ventilator dependent
3. Use of any medication or treatment that in the opinion of the investigator indicates that it is not in the best interest of the participant to participate in this study.
4. Cardiovascular, cerebrovascular, respiratory, metabolic, musculoskeletal, bladder, or renal disease unrelated to SCI.
5. The individual is a member of the investigational team or his/her immediate family.
6. Any implanted metal in the trunk or spinal cord (between the anode and the cathode) that would prevent the use of TSCS.
7. Have previously suffered from brain trauma, a psychiatric disorder or epilepsy (including family history of epilepsy).
8. Are = currently taking neuromodulatory drugs.
9. Implanted with an epidural stimulator or other device that would contraindicate the use of electrical stimulation (e.g., stimulators, pacemakers, medication pumps etc.).
10. Females that are pregnant.
11. Does not speak English.

For non-injured individuals:
1. Individuals with any acquired SCI (i.e. traumatic, infection, cancer).
2. Any known history of cardiovascular, cerebrovascular, respiratory, metabolic, musculoskeletal, bladder, or renal disease, or individuals with diabetes mellitus. A General Health Questionnaire will be administered to screen potential participants.
3. Use of any medication or treatment that in the opinion of the investigator indicates that it is not in the best interest of the participant to participate in this study.
4. Have previously suffered from brain trauma, a psychiatric disorder or epilepsy (including

family history of epilepsy).
5. Females that are pregnant.
6. Does not speak English.

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Previous exclusion criteria:

For individuals with a spinal cord injury:
1. Presence of severe acute medical issues that in the investigator's judgement would adversely affect the participant's participation in the study. Examples include, but are not limited to, acute urinary tract infections; pressure sores; active heterotopic ossification; newly changed antidepressant medications (tricyclic antidepressants); or unstable diabetes.
2. Ventilator dependent
3. Use of any medication or treatment that in the opinion of the investigator indicates that it is not in the best interest of the participant to participate in this study.
4. Cardiovascular, cerebrovascular, respiratory, metabolic, musculoskeletal, bladder, or renal disease unrelated to SCI.
5. The individual is a member of the investigational team or his/her immediate family.
6. Any implanted metal in the trunk or spinal cord (between the anode and the cathode) that would prevent the use of TSCS.
7. Have not previously suffered from brain trauma, a psychiatric disorder or epilepsy (including family history of epilepsy).
8. Are not currently taking antidepressants or neuromodulatory drugs.
9. Implanted with an epidural stimulator.
10. Females that are pregnant.
11. Does not speak English.

For non-injured individuals:
1. Individuals with any acquired SCI (i.e. traumatic, infection, cancer).
2. Any known history of cardiovascular, cerebrovascular, respiratory, metabolic, musculoskeletal, bladder, or renal disease, or individuals with diabetes mellitus. A General Health Questionnaire will be administered to screen potential participants.
3. Use of any medication or treatment that in the opinion of the investigator indicates that it is not in the best interest of the participant to participate in this study.
4. Have not previously suffered from brain trauma, a psychiatric disorder or epilepsy (including family history of epilepsy).
5. Females that are pregnant.
6. Does not speak English.

Date of first enrolment
06/02/2024

Date of final enrolment
31/01/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Birmingham
School of Sport, Exercise and Rehabilitation Sciences (Building Y14)
College of Life and Environmental Sciences
University of Birmingham
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
International Spinal Research Trust

Alternative Name(s)
Spinal Research

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		15/01/2025	24/01/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes