Paired Associative Stimulation to Facilitate Plantarflexor Power Following Stroke

NCT04515407

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California Experimental Subject's Bill of Rights

The rights below are the rights of every person who is asked to be in a medical research study. As an experimental subject, you have the following rights:

1. To be told what the study is trying to determine.
2. To be told what will happen to you and whether any of the procedures, drugs, or devices is different from what would be used in standard practice.
3. To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to you for research purposes.
4. To be told if you can expect any benefit from participating and, if so, what the benefit might be.
5. To be told the other choices you have and how they may be better or worse than being in the study.
6. To be allowed to ask any questions concerning the study, both before agreeing to be involved and during the course of the study.
7. To be told what sort of medical treatment is available if any complications arise.
8. To refuse to participate or to change your mind about participating after the study is started. This decision will not affect your right to receive the care you would receive if you were not in the study.
9. To receive a copy of the signed and dated consent form.
10. To be free of pressure when considering whether you wish to agree to be in the study.

If you have other questions, please ask the researcher or research assistant.
You may also ask the VA Northern California Health Care System (VANCHCS) Human Research Protection Program (HRPP). The HRPP protects volunteers in research projects. You may call the HRPP at 916-366-5359 from 8:00 a.m. to 4:30 p.m. Monday through Friday. You may also write to the HRPP. The address is: VANCHCS HRPP (151), 10535 Hospital Way, Mather, CA 95655. You may also call VA Chief Counsel at 415-750-2288.

Purpose of the Study

This is a research study. Research studies only include individuals who choose to take part. You do not have to be in this research study. You should read the information that follows. Please ask questions about anything you do not understand before deciding if you want to be in this research study. Please take your time to make your decision.

You qualify to take part in this project because you are over the age of 18, you have had a stroke, and you still have weakness or difficulty walking. We hope to learn more about walking recovery for persons following stroke.

The purpose of this study is to investigate ways to enhance strength generated from the ankle during walking. We will do this with a procedure called Paired Associative Stimulation (PAS). Paired Associative Stimulation is a procedure that uses Transcranial Magnetic Stimulation (TMS) and Peripheral Nerve Stimulation (PNS) together to potentially induce changes in the nervous system called neuroplasticity. Neuroplasticity is the ability of your brain and nervous system to form new neural connections or change the strength of existing connections. For this study we are targeting the pathway that controls ankle movement. PAS, TMS, and PNS are explained in further detail under “Peripheral Nerve Stimulation (PNS)” and “Transcranial Magnetic Stimulation (TMS) and Paired Associative Stimulation (PAS)” in the Procedures section on pages 4 and 5 of this consent form.

There will be up to 24 subjects taking part in this study at VANCHCS.

Study Length (How long will I be in the study and how long will the study last?)

Total commitment to the study should last no more than one month and about 7-13 hours in total. More information follows in this document.

Researchers will conduct this study for approximately 2 years.

1. Researcher’s Financial Disclosure

The Department of Veterans Affairs, Rehabilitation Research & Development is paying for this study. When researchers complete the study, there may be money left over. Carolynn Patten, Ph.D., PT, the Principal Investigator, may use it for research or education.

Carolynn Patten, Ph.D., PT, is an inventor of a custom helmet for stabilizing the TMS coil that will be used in the study. If the helmet is sold commercially, she and the University of Florida could benefit financially.

2. Study Procedures

You will come to the research lab 3 times over the span of 3-4 weeks. Each visit will be 2-3.5 hours long. These 3 visits will occur one week apart from each other. Depending on your health and endurance, the time involved in each session could be longer.

Before beginning study procedures, researchers will ask you about any medical problems and medications you may be taking. Researchers will use this information to decide if it is alright for you to take part in the study, or to stay in the study.

At each visit, researchers may ask for any updates to your medical condition or medications. Researchers may also measure your blood pressure, pulse, temperature, and/or weight.

This study does not use experimental therapy or drugs.

PROCEDURES

Clinical and Functional Assessments

You will first be evaluated for functional impairments and physical performance using standardized clinical assessments. These will involve questionnaires regarding your activity level, the tasks you can and cannot do, and your quality of life. Next, you will be examined while you perform basic movements, activities of daily living, and tests of movement function – these tests are similar to ones done in a rehabilitation clinic. These tests will help us assess any problems you have with your mobility, your activity level, and your quality of life.

These tests will take approximately 1 hour and will only be done during the first visit.

Motion Capture

We will use motion capture technology to study your body movements during walking. This is the same technology used for animated movies or video games. To do this, we will place reflective markers over major landmarks on your body. The markers are small and lightweight and once in place you may not notice them.

Measurement of Muscle Activity

Your muscle activity will be measured using electromyography (EMG). EMG is a standard procedure that measures electrical activity produced by your muscles to determine how active they are at a given point in time. To collect EMG, we will place small sensors on your skin over the muscles being recorded on both legs. The sensors are small boxes or disks that are attached to your skin via adhesive material.

Peripheral Nerve Stimulation (PNS)

Peripheral nerves are the nerves that connect your muscles to your brain and spinal cord. Peripheral nerve stimulation involves placing a stimulation electrode on your leg. An electrical current is sent to the electrode to stimulate a nerve that controls leg muscles. We will use this electrical stimulation of peripheral nerves to produce and examine motor responses from your leg muscles. This will occur both at rest and during movement. At a minimum, stimulation from the electrode could feel like a small prick. At a maximum it could feel like being snapped with a stiff rubber band. Stimulation should not induce pain, though may feel uncomfortable at times.

Transcranial Magnetic Stimulation (TMS) and Paired Associative Stimulation (PAS)

Transcranial magnetic stimulation is a non-invasive procedure used to measure the communication between your brain and muscles. To deliver TMS, a coil is focused on a specific part of your head to generate a response in the specific part of your brain that controls leg movement. To generate a response in your brain the coil produces a weak magnetic field that produces an electrical signal in the specific part of your brain being targeted. At a minimum, you may not feel anything, at a maximum it may feel like you are getting flicked on the head. You may feel a twitch in the leg muscles as well.

We will use TMS while you are standing and performing basic movements to determine the lowest setting on the TMS unit that will make your muscles respond. This setting is deemed a “threshold” and recorded. Once this is determined, we will make a custom fit helmet using a bag filled with Styrofoam beads. The bag will be positioned on your head and will surround the TMS coil. We will use a vacuum to form the custom shape. This will stabilize the TMS coil during walking.

Paired associative stimulation, or PAS, is delivered using the TMS and PNS methods described above. In other words, PAS is a single term for using TMS and PNS together. Like in the TMS methods, a “threshold” for PNS will be determined. Using this threshold, and the TMS threshold,

stimulations will be administered together in each of the experimental conditions. Both TMS and PNS are non-invasive and safe for human research.

VISIT OUTLINE

Pre-Experimental Condition

You will be asked to walk on a Stepscan walkway that uses pressure sensors to record your footsteps and pattern of walking. We will use measurements from this walkway to determine your Self-Selected Walking Speed (SSWS) and Fastest Comfortable Walking Speed (FCWS).

We will then administer TMS during standing to determine the "threshold" as described above. You will then be asked to walk on a treadmill at both SSWS and FCWS, these speeds may be different on a treadmill than they are during walking over ground. For safety we will have you wear a mountain climbing harness attached to an overhead support that will prevent you from falling if you slip or trip. If needed, you may have a few minutes of practice on the treadmill to become comfortable. After determining your treadmill walking speed, the threshold setting will be used to deliver TMS while you walk. We will collect TMS stimulations from different phases of your walking. The data will be collected in increments of one-minute bouts. Therefore, you have the option to continue walking or take a short break after any of the one-minute collection periods. Approximately 100-120 stimulations will be collected over the duration of the walking portion, which may take 7-10 minutes in total.

Experimental Condition

You will undergo PAS in three experimental conditions: seated – at rest, seated – active, and during walking. You will perform only one of these conditions at each visit. The visits will be separated by about one week. It is preferable for the visits to take place on the same day and time each week. In each condition you will receive 200 pairs of stimulations separated into four blocks of 50 pairs each. There will be rest periods between each stimulation block.

During the seated – rest condition, you will be asked to remain still during PAS delivery. We will show you scenic images that change every 5th stimulation to keep you alert.

During the seated – active condition, you will produce a steady contraction of ~10% effort. To establish this level, you will be asked to produce a maximal voluntary contraction (MVC) at your ankle. We will then display a target zone shown on a screen and provide feedback of the force you produce to ensure you maintain the correct level of activity.

During the walking condition, you will be asked to walk on the treadmill at SSWS while PAS is being delivered during one specific phase of the gait cycle. As in the pre-post collections, data will be collected in one-minute bouts to allow you the option of continuing to walk or take a break, as needed. Regardless of your ability, a rest break will be provided after each block of 50 stimulations.

Post-Experimental Condition

This is done to determine how much the PAS changed your neural connections and whether it affected your walking ability. You may be asked to walk on the Stepscan walkway again to see if there are any changes in your walking pattern and/or walking speed. You will be asked to again stand and/or perform basic movements to determine your TMS threshold. This threshold will be used to deliver TMS while you walk on the treadmill. Stimulations will again be delivered at different phases of your gait. Approximately 100-120 stimulations will be delivered in one-minute bouts of walking. You have the option to continue walking or take a rest, as needed, after each one-minute bout.

Follow up Condition

One hour after PAS is finished, the post-experimental condition will be repeated using the procedure described above. This is done to determine how long the neural changes last and which of the 3 conditions has the biggest effect one hour after PAS. Stimulations will again be delivered at different phases of your gait. Approximately 100-120 stimulations will be delivered in one-minute bouts of walking. You have the option to continue walking or take a rest, as needed, after each one-minute bout.

Photographs, audiotaping, or videotaping

With your permission, by providing your signature below, the researchers may videotape or take photographs of your testing sessions. If the researchers record video or take pictures, any identifying information will be removed or blocked out to protect your privacy. Any picture or video will be used solely by the research team for presentations or examination of methodology. No media will be released to entities outside of the research lab.

The study team has also explained that you will not receive any royalty, fee, or other compensation for such use. If you refuse to grant consent, there will be no effect on any VA benefits to which you may be entitled. You may at any time exercise the right to cease being

filmed, photographed, or recorded, and may rescind your consent for any media to be used by the research team.

Signature: _____ Date: _____

3. Potential Risks and Discomforts

You may experience adverse events or discomforts while in this study. These may occur at the time of the research or later. You should discuss these with the researcher and/or your regular physician. Many side effects will go away shortly after the conclusion of each session.

Risks and side effects related to the study include:

Physical Risks

All physical risks are unlikely to occur.

- Abrasion and/or reaction to tape
- Fatigue and/or muscle soreness
- Headache/neck ache following TMS
- Electric shock from TMS machine misuse (very low likelihood of occurring)

Psychological Risks

- It is possible that completing the Center for Epidemiological Studies Depression Scale may be triggering of negative thoughts or depression. If this occurs, resources will be provided for support. If depression is such that it interferes with ability to complete the study safely, participation will be halted.
- The study may be boring to you

Privacy Risks

- Legal Risks:
  There is a real, but small, risk of breach of confidentiality regarding medical and personal information. This risk is minimized via VA data protection procedures.
- Employment or Economic Risks:
  If you are currently employed, the length of time required to participate in the study could result in lost time in normal employment. There will be compensation to mitigate this risk.
- Social Risks:
  None

For more information about risks and side effects, ask the researcher team or contact the Principle Investigator, Carolynn Patten, Ph.D., PT at 916-734-5029.

Unforeseeable Risk

The researcher does not know all the side effects that may happen. You may experience a side effect or risk that the researchers do not know about at this time.

New Information

The research team will contact you with any significant new knowledge or findings that would affect your willingness to continue in this research.

4. Expected Benefits to Subjects

You may not benefit from taking part in this research.

5. Expected Benefits to Others

We hope to learn more about recovery from stroke from your taking part in this study. The information we get from this study may help us to treat future patients with stroke better.

6. Other Options to Taking Part in this Study

Your alternative is not to take part in this study.

7. Right to Withdrawal from the Study

Your taking part in this research is voluntary. You can stop taking part at any time. If you choose not to take part in this study, you will not be penalized or lose any benefits to which you are entitled. Your decision will not affect your relationship with the researcher. Tell the researcher if you are thinking about stopping or decide to stop. The researcher will tell you how to stop safely. It is important to tell the study researcher if you are thinking about stopping.

If you withdraw from this study, your research information will no longer be collected. However, information that has already been collected will continue to be used to the extent that the researchers have used it in this research study.

Researchers may withdraw you from the study without your consent for the following reasons:

- You do not meet the study eligibility criteria
- Failure to follow instructions
- The investigator decides that continuation could be harmful to you
- You have a change in your health and physical functioning making it difficult for you to comply with the protocol
- You need treatment not allowed in the study
- The study is canceled
- Other reasons affecting administration of the research project

8. Confidentiality

We will do our best to keep your medical records and personal information private. However, we cannot guarantee absolute confidentiality. We will disclose your personal information if required by law. We will disclose your information to protect your rights or welfare. We will disclose your information if the researcher becomes aware that you may be a danger to yourself or to others. We will disclose your information if the researcher becomes aware that acts of child, elder, or dependent adult abuse or neglect may have occurred.

Researchers may publish or present the results of this study. They will not reveal your name or identity. We will code your research data without using your name. Only the Principle Investigator and authorized members of the research team will have the key to the code that links your identity to your research data. All data on paper will be kept in a locked cabinet in a secured office. Electronic data will be stored in a password protected database on a secure, password protected VA network. Non-sensitive data (containing no personal health information)

will be stored electronically on a secure, password protected computer network at University of California, Davis. Research data collected for this study will be retained in accord with VA Record Control Schedule.

The research sponsor, Department of Veterans Affairs, Rehabilitation Research & Development Service may also look at your research files and medical record. Organizations may inspect and/or copy your research records for quality assurance and data analysis. One of these is the Institutional Review Board (otherwise known as the Human Subjects Subcommittee) at VA Northern California Health Care System. The Institutional Review Board is a committee whose purpose is to review and monitor research studies that involve human subjects.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Participation in this study will not affect your VA healthcare including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

Health Information Portability and Accountability Act (HIPAA)

There are rules to protect your private health information. Federal and state laws and the federal medical law, known as the HIPAA Privacy Rule, also protect your privacy. By signing this form, you provide your permission, called your 'authorization', for the use and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records such as medical history and stroke diagnosis.

The research team may also need to disclose your health information and the information it collects to others as part of the study progress. Others may include the Institutional Review Board, Food and Drug Administration, Office (FDA), Office of Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), and the Government Accountability Office (GAO).

Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Principal Investigator for this study at the following address:

UC Davis – School of Medicine
Ellison Ambulatory Care Center
4860 Y Street, Suite 3850
Sacramento, CA 95817

If you revoke (take back) your permission, you will no longer be able to participate in this study but the benefits to which you are entitled will NOT be affected. If you revoke (take back) your permission, the research team may continue to use or disclose the information that it has already collected before you revoked (took back) your permission which the research team has relied upon for the research. Your written revocation is effective as soon as it is received by the study's Principal Investigator. The research team will not collect information about you after you revoke (take back) the authorization.

Treatment, payment, or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. Unless you revoke your permission, your authorization to allow us to use and/or disclose your information will expire at the end of this research study for the data use and collection.

9. Research Related Injury

If you are injured as a result of being in this study, treatment will be available. If you are eligible for veteran's benefits, the costs of such treatment will be covered by the Department of Veterans Affairs. If not, the costs of such treatment may be covered by the Department of Veterans Affairs, or the study sponsor depending on a number of factors. The Department of Veterans Affairs, and the study sponsor, do not normally provide any other form of compensation for injury. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form. For further information about this, you may call the VA Chief Counsel at 415-750-2288.

10. Costs to Study Subjects

As a research subject, you are not required to pay for treatment received for research purposes while participating in a VA research program.

You are not required to pay for care or services related to this research study. Some veterans are required to pay co-payments for medical care and services specifically related to their medical care provided by the VA. These co-payments will continue to apply to medical care and services provided by VA that are not part of this study.

11. Payment for Taking Part in the Study

In return for your time, effort, and travel expenses, you will be paid $50/session, up to $150 total, for taking part in this study. Additionally, you will be reimbursed for your transportation costs at the current Federal mileage rate (see www.irs.gov). You will receive study compensation and mileage reimbursement as an electronic transfer of money directly to your bank account. If you are already set up to receive VA benefit payments electronically, there is nothing that you need to do. If you are not already set up to receive VA benefit payments directly to your bank account, then you will be directed to fill out payment forms required by the VA for payment processing.

If you withdraw from the study before completion, you will be compensated for the time you participated in the study up to that point. All payment processing will begin at the conclusion of your participation in the study. Time to receive payment will depend on processing time at the VA.

12. Re-Contact

You may qualify for future studies at the VA. If we become aware of a research study that you would be eligible for, we would call you to ask you whether you would be interested in participating. Please initial here if you are willing to be contacted for future research that you may be eligible for. [_____]

***13.* Disclosure of Results**

On request, your results of the study can be shared with you. These results would be provided by study personnel and are typically graphical representations and interpretation of the data. Your individual results may not be indicative of results from the study as a whole.

14. Questions About this Study

If you have any questions, concerns, or complaints about this study, contact one of the researchers on this study:

Principle Investigator: Carolynn Patten, Ph.D., PT at 916-734-5029

15. Questions About Research Subject Rights

You may have questions about your research subject rights, or you may want to obtain information or offer input. You may also have questions that you feel cannot be discussed with the researcher. You may call the VANCHCS Human Research Protection Program. The phone number is 916-366-5359. You may also call the VA Chief Counsel. The phone number is 415-750-2288.

RESEARCH SUBJECTS' RIGHTS: I have read or have had read to me all of the above. The researchers have explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but my records will not be revealed unless required by law.

In case there are medical problems or questions, I have been told I can call Carolynn Patten, Ph.D., PT at 916-734-5029. If any medical problems occur in connection with this study, the VA will provide emergency care.

I understand my rights as a research subject, and I voluntarily consent to participate in this study and authorize the use and disclosure of my health information for this study. I understand what the study is about and how and why it is being done. I will receive a signed copy of this consent form.

_____	_____	_____
Participant's Name	Participant's Signature	Date

_____	_____	_____
Name of person obtaining consent	Signature of person obtaining consent	Date