Title of research study: Study on the Use of the Virtual Reality Neuropsychological Therapy Technology (VRNT) for Chronic Back Pain

IRB Protocol Number: 19-0526

Investigators: Marta Čeko, Tassilo Baeuerle, and Lynn Webster

Purpose of the Study

The purpose of this study is to see if a new virtual reality therapy (called Virtual Reality Neuropsychological Therapy or VRNT) can reduce chronic back pain long-term. The study will also test if the VRNT therapy leads to any changes in the brain. We will also ask you for your feedback that will help us refine the current VRNT product.

VRNT is a medical device that has not yet been approved by the FDA (Food and Drug Administration).

We expect that you will be in this research study for about 3 - 5 ½ months.

We expect about 60 participants will be in this research study.

Explanation of Procedures

This study is a collaboration between the University of Colorado, (CU) Boulder and CognifiSense, Inc., a company developing virtual reality (VR) technology for pain management.

You will have a total of three study visits to our facility at the University of Colorado - Center for Innovation and Creativity (CINC) at 1777 Exposition Drive, Boulder, CO 80302. Two of these visits are for MRI scan sessions and will last about 1 1/2 hours each. The other visit is for a (1 ½ hours) Practice Session in the use of the VR hardware and software. There will also be two video-calls using, for example, Zoom: one Educational Session (~1 ½ hours) and one Treatment Personalization Session (1 ½ hours). In addition, you will also be asked to complete several online surveys (see details below). If you are assigned to the Waitlist, you will be asked to schedule one more very short visit to CINC to drop off the virtual reality equipment (curb-side).

During the study you will be randomly assigned to one of two groups: A Therapy Group or a Waitlist Group. The group you are assigned to will be chosen by chance, like flipping a coin. Neither you nor the study personnel will choose what group you get. You will have an equal chance of being in the Therapy Group and Waitlist Group.

Both the Therapy Group and the Waitlist Group will receive the VRNT therapy; however, the Waitlist Group will "wait" and receive the therapy after the Therapy Group has completed the therapy. Participants in the Therapy Group complete the study in about 3 months. Participants in the Waitlist Group complete the study in about 5 ½ months.

Your Other Pain Therapies & Medications: No matter which Group you are assigned to, you may continue your normal medication and other (pain) treatments during the study. The study requires that your medication and other treatments are relatively stable; so, you will have to agree not to change / add / remove any current medication or treatments, unless your physician (or other healthcare professional you work with) asks you to. If you do make changes, please let the research team know as soon as possible. You will also be asked not to make large lifestyle changes (e.g., diet or exercise program) during the study. Keeping stable medications / treatments and lifestyle is important, because it helps us get a purer measure of what changes might come from VRNT therapy vs. some other change.

The following is an overview of the study, from the perspective of either the Therapy Group or the Waitlist Group. Please Note: You will be assigned to your Group after the first MRI scan; i.e., after Online Survey 2 and MRI Scan 1. This means that you will not know if you are in the Therapy Group or the Waitlist Group for the first three steps in the study (~2 weeks).

ALL PARTICIPANTS will have the following initial steps:

Online Survey 1 (1 hour): You will be asked to complete an online survey with some general information questions, and some specific questions about your lifestyle, your pain, and your thoughts and feelings. This first survey will take about 1 hour. For more information on the types of questions included in surveys, please see page 4.

Baseline Period – 2 weeks: During these two weeks you will be asked to fill a Daily online survey (Daily Pain Survey), requiring about 5 minutes each day. You will be asked to continue this Daily Pain Survey throughout the study.

Online Survey 2 (~1 hour and 20 minutes): You will complete an online survey. The survey has several different questionnaires.

MRI Scan 1 (~1 ½ hours): You will be asked to come to CINC for the MRI. You will complete a short survey on the computer. We will then get ready for the MRI scan (this will take about 30 mins) During the MRI scanning we will take several MRI images of your brain. This will take about 1 hour.

Random Assignment to a Group: After you complete the MRI scan you will be randomly assigned (like flipping a coin) to the Therapy Group or the Waitlist Group.

The following are the steps you can expect if you end up in the Therapy Group:

Therapy Period – 8 weeks: You will participate in two video calls: 1) an educational session (~1 hour 30 minutes) and 2) a VRNT Personalization session (~1 hour 30 minutes). In the educational session you will receive basic education on chronic pain and the role of VRNT.

At the end of the educational session you will receive a Self-Evaluation Exercise (15-30 mins). This exercise will allow you to explore some of the things you learned in the educational session. In the VRNT Personalization session, you will work with a member of the research team to create a 3-dimensional representation (like a 3-D drawing) of your pain in virtual reality. During this setup session we will ask you to describe your pain; for example, where do you feel your pain? What does it feel like? . The educational sessions will be open to up to 5 participants; however, the VRNT Personalization session will only be you with a team member(s). You will also attend one in-person VR Practice Session (1 ½ hours), where you will receive training in the use of the VR hardware and software and will get to practice using the software.

You will be provided with a VR headset, which you will use at home during the 8-week Therapy Period. You will be asked to complete exercise sessions once a day for 5 days each week. Each session lasts between 15 – 30 minutes. There may be a few days where the session may take longer, based in part on your interest. You will also get a workbook which explains specific exercises for each day. You will be asked to return the VR equipment at the end of that 8-week period; the workbook will be yours to keep. You will be asked to continue to fill out the Daily Pain Survey (5 minutes). You will also be scheduled for a 30 minute weekly call where we will check on your progress, answer any questions, and discuss upcoming exercises.

Next, a research team member will guide you through at least two of the first week's VRNT sessions as a practice.

Online Survey 3 (~30 minutes): 4 weeks into the Therapy Period you will be asked to complete an online survey.

Online Survey 4 (~1 hour and 25 minutes): At the end of the Therapy Period you will be asked to complete an online survey.

MRI Scan 2 (~1 ½ hours): Next, you will be asked to come to CINC to do another MRI session. Just like during the first session, you will complete a short survey on the computer (15 minutes to complete). We will then get ready for the MRI scan (this will take about 15 mins). We will again take several MRI images of your brain (1 hour; details below). The virtual reality equipment will be collected at this time.

Follow-Up Period: During the following two weeks you will be asked to continue to complete the online Daily Pain Survey (5 minutes).

Online Survey 5 (~1 hour and 25 minutes) and Debrief Call (45 minutes): At the end of the Follow-Up Period you will be asked to complete an online Survey. You will also be scheduled for a 45-minute debrief call. For more information on the Debrief Call, please see page 5.

Optional Focus Group: You will be invited to an optional 2-hour focus group to share your feedback on the study and VRNT along with other study participants. This focus group will take online.

That completes the study for the Therapy Group.

WAITLIST GROUP will have the following procedures

The following are the steps you can expect if you end up in the Waitlist Group.

Waiting Period – 8 weeks: You will be asked to continue to fill out the online Daily Pain Survey (5 minutes).

Online Survey 3 (~30 minutes): 4 weeks into the Waiting Period you will be asked to complete an online survey.

Online Survey 4 (~1 hours and 10 minutes): At the end of the Waiting Period you will be asked to complete an online survey.

MRI Scan 2 (~1 1/2 hours): Next, you will be asked to come to CINC to do another MRI session. Just like during the first session, you will complete a short survey on the computer (about 15 minutes), get ready for the MRI scan, and we will again take several MRI images of your brain (about 1 hour; details below). Why are you doing an MRI scan after the Waiting Period? This second MRI scan taken after Waiting (for Waitlist Group) and after Therapy (for Treatment Group) will allow us to compare effects on the brain of Therapy vs. Waitlist.

2nd Baseline Period: During the following two weeks you will be asked to simply continue to complete the online Daily Pain Survey (5 minutes).

Online Survey 5 (~1 hour and 20 mins): At the end of the 2nd Baseline Period you will be asked to complete an online survey.

Therapy Period – 8 weeks: You will be offered to receive the exact same treatment as explained above for Therapy Group

Online Survey 6 (~30 minutes): 4 weeks into the Therapy Period you will be asked to complete an online survey.

Online Survey 7 (~1 hour and 25 minutes): At the end of the Therapy Period you will be asked to complete an online survey.

Follow-Up Period: During the following two weeks you will be asked to continue to complete the Daily Pain Survey (5 minutes).

Online Survey 8 (~1 hour 25 minutes) and Debrief Call (~45 minutes): At the end of the Follow-Up Period you will be asked to complete an online survey. You will also be scheduled for a 45-minute debrief call. For more information on the Debrief Call, see page 5. We will also arrange for you to return the virtual reality equipment.

That completes the study for the Waitlist Group.

Information About the Surveys
The surveys include a variety of questions about your pain and its impact on your life, about your health, any medications you are taking, as well as questions about your thoughts and feelings, particularly as they pertain to your pain. Not all surveys will be the same; some questions may only be asked at certain points in the study.

Information about Daily Pain Survey
The Daily Pain Survey will ask questions about your level of pain and how much your pain bothers you.

Information About the Debrief Call
During the debrief call we will ask you various questions which allow you more freedom to explain what you experienced during the study; for example, we will ask you about your overall experience with using VRNT, if and how the therapy impacted your pain, what you thought about the product, and any suggestions you have for changing the VRNT therapy.

Information about MRI scanning
As part of this study, you will have two magnetic resonance imaging scans (or MRI's). This is a non-invasive scan of the brain. During the MRI session you will receive several different MRI scans for a duration of around 1 hour.

The magnetic field of a magnetic resonance (MR) environment has the potential to cause burns or bodily injury if ferrous (contains iron) metal objects are implanted in the body or if personal articles containing ferrous material are brought into the scanner environment. Therefore, before going into the MRI scanner, our team member and an MRI technologist on duty will ask you to change into scrubs and to remove all jewelry and metal objects from your pockets. You will also be asked to complete a screening form to ensure it is safe for you to go into the MR environment.

Because the effect of MRI on fetuses (an unborn child) has not been determined, women who are pregnant or planning pregnancy cannot participate in this study. There are pregnancy tests available for women who wish to take a pregnancy test before going into the scanner.

When you go into the scanner, you will lie down on a padded table and will be placed into a long donut-shaped tube that is only slightly larger than your body. Your head and waist will be enclosed in the tube. If you are uncomfortable being in small or cramped places, please tell the research team.

While you are in the MRI scanner, we will monitor your heart rate, breathing and the skin conductance response. We will do so by placing little sensors on your hand or foot and torso in order to record your body's responses throughout the experiment. These sensors don't cause any uncomfortable, harmful or painful sensations.

A specially designed coil will be placed around your head to provide better images (as is done with standard clinical examinations). The scanning will begin with a 7-minute structural image of your brain. Then you will receive a 10-minute resting state scan, where you will be asked to keep your eyes open and focused on a cross presented to you on a screen. Finally, there will be a 6-minute Diffusion Tensor Imaging (DTI) scan, in which there is nothing for you to do except remain still.

As the MRI scans are performed, you will hear loud rapping and knocking noises that are normal for MRI scanning. We will give you headphones to block out some of the noise. You will still be able to hear the researchers and the MRI technician through an intercom and will be able to squeeze a ball to get their attention and stop the scan at any point.

VR Equipment
The VRNT software runs on standard consumer VR equipment. We will give you a Samsung smartphone and a GearVR headset to use during the Therapy Period. You will need to return this equipment at the end of the Therapy Period. You will be given training on how to use this equipment.

VRNT Therapy
VRNT is an experimental therapy, which incorporates principles from various psychological therapies used to treat pain. VRNT is considered a medical device by the FDA. It has not yet been approved by the FDA, and so is not commercially available.

Data Collected
During the study we will collect various types of data:

1) Responses to survey questions
2) Daily Pain Survey data
3) Usage data: the VRNT app tracks how often the user uses the app and which modules the user selects
4) Your answers to questions during the Debrief Call
5) The 3-D pain "drawing" of your pain

All these data will be anonymized by assigning a random participant ID to it. This means your name and any other information that might link the data to you will be removed from the data so that all your data is safe (anonymous).

Voluntary Participation and Withdrawal

Whether or not you take part in this research is **your** choice. You can leave the research at any time and it will not be held against you. You have the right to refuse to answer any question(s) or refuse to participate in any procedure or part of the study for any reason. Refusing to participate in this study will not result in any penalty or loss of benefits to which you are otherwise entitled; see the section on Payment for Participation below for impact of early withdrawal on compensation.

If you stop being in the research study, already collected data may not be removed from the study database.

If you are a CU Boulder student or employee, taking part in this research is not part of your class work or duties. You can refuse to enroll, or withdraw after enrolling at any time, with no effect on your class standing, grades, or job at CU Boulder. You will not be offered or receive any special consideration if you take part in this research.

Incidental Findings

The MRI scans for this study are for research purposes only; however, should we observe an abnormality, the scans will be read by a licensed radiologist or neurologist at the Mind Research Network. You will be notified by the MRI staff of the results of the radiology report. You will also receive a letter from the Mind Research Network that includes the radiology report. If incidental findings from study result in the need for further evaluation / treatment, then you or your insurance will be responsible for additional clinical evaluation / treatment that may be needed.

Risks and Discomforts

There are some potential risks if you take part in this study. These may include:

VR Technology

Virtual reality (VR) applications may cause motion sickness or temporary headaches. You will be instructed to only use the VR software while seated or lying down. Therefore, we do not anticipate risks associated with movement, standing, walking, or falling injury while in the VR environment. You will also be asked not to operate a vehicle or heavy machinery for at least 15 minutes after the use of the VR application.

VR applications may cause headaches in people with (digital) eye strain or computer vision syndrome; please inform the study personnel if this concern applies to you.

MRI Scanning - Physical Risks and Discomforts

MRI studies are among the safest of all non-invasive medical procedures, but certain hazards exist. To minimize these hazards, only trained technicians are in the immediate area and all participants are screened prior to entering the MR scanner. However:

Your participation in this research study is voluntary. Please think about the information below carefully. Feel free to ask questions before making your decision whether or not to participate. If you decide to participate, you will be asked to sign this form and will receive a copy of the form.

You may experience nervousness and/or feelings of claustrophobia during the MRI scan. Should this occur, you will be able to communicate with the MRI technician and can stop the MRI at any time. Before the scan begins, you will be given a squeeze ball. Should you wish to stop the scan for any reason, you can do so by squeezing the ball.

It is important that you tell the Investigators, **Marta Čeko** or **Tassilo Baeuerle** if you think you have been injured as a result of taking part in this study. You can reach them at ***marta.ceko@colorado.edu*** *or* ***tassilo@cognifisense.com****.*

Payment for Research Related Injury

If you need medical care because of taking part in this research study, seek medical attention immediately (if it is a medical emergency, first call 911). Generally, this care will be billed to you, your insurance, or other third party. The University of Colorado, Boulder has no program to pay for medical care for research-related injury. Please contact the investigator as soon as possible to report the event.

Potential Benefits

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include reduction of chronic pain.

Alternatives

Instead of being in the research, your choices include:

- Over-the-counter or prescription medication
- Medical devices (e.g. transcutaneous electrical nerve stimulation, back braces, muscle stimulators, spinal cord stimulators)
- Surgery and various medical procedures (e.g. nerve blocks)
- Physical therapy, exercise, massage, yoga
- Psychological therapies, such as Cognitive Behavioral Therapy, Acceptance and Commitment Therapy, and Mindfulness Meditation
- Other alternative therapies, such as acupuncture

- Other procedures or courses of treatment recommended to you by your health care provider
- No treatment

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. Research information that identifies you may be shared with the University of Colorado Boulder Institutional Review Board (IRB), study personnel at CognifiSense, Inc. and the University of Colorado, and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of the Office for Human Research Protections. The information from this research may be published for scientific purposes; however, your identity will not be given out.

As with other data for similar research studies, data will be stored on restricted access servers and/or in locked filing cabinets in a locked room, to which only members of the research team have access. These procedures will minimize the risk of personal information being divulged to non-members of the research team. No identifying information will be linked to the data from the study, except by a master list accessible only to the principal investigators and the research assistants.

Strict standards of confidentiality are maintained. MRI data will be electronically stored and referenced using ID codes. If the data are published, you will remain anonymous in all publications. Data will be stored indefinitely and will not be shared with other researchers without explicit permission from the CU Boulder's Institutional Review Board (a committee responsible for ethics oversight of research).

For the MRI scan, basic identifying information will be collected from you (e.g., name, address, phone number) for scheduling visits, etc. as well as to mail a radiological review letter to you in the case of an incidental finding. The Mind Research Network (MRN) is comprised of a group of brain researchers within the Intermountain Neuroimaging Consortium (INC), the University of Colorado Boulder and the University of New Mexico in Albuquerque New Mexico. All researchers use a common website called COINS to register and store MRI data as well as basic identifying information. The COINS web service employs the highest security for registering participants and requires each researcher to gain permission from INC and MRN before being allowed access to COINS. The website stores identifying information separately from MRI data. You will be given an identifying number in COINS. Your identifying number will be linked with your identifying information so that your identifying information and MRI data are not directly linked. Outside of the individuals on the research team and the administrative team that coordinates the radiological reviews in case of incidental findings, no one will be able to connect your MRI data with your identifying information. All MRI data (identified by identifying number and not by your personal information) will be stored at MRN and at CU Boulder in highly secure computing systems. In addition, MRN will maintain information associated with the identifying number but not the scanning data (e.g., your name and contact information) in a highly secure cloud computing service such as Amazon Web Services.

We will also discard any personally identifying information we collect from you as soon as we are able to, ensuring that any data we retain cannot be linked back to you. Subsequently, your data will be retained indefinitely in a de-identified form using a randomly assigned identification number, and will be stored on password-protected computers accessible only to the research team. All paper forms will be kept in locked offices in locked filing cabinets. Electronic consent forms and completed questionnaires will be stored safely and only accessible to members of the research team.

In addition to the research team, anonymized data from this study may be shared with the Food & Drug Administration, the National Institute of Health / The Department of Health and Human Services and CognifiSense, Inc.

The sponsor, monitors, auditors, the IRB, and the US Food and Drug Administration will be granted direct access to your research records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

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.

This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. This certification means that the researchers cannot be forced to tell people who are not connected with the study, such as the court system, about your participation in this study. But, if you request that we do so, we will release information that is unique to you.

There are three exceptions to this promise of confidentiality:

1. If we see or are told information that makes us reasonably suspect that a child or at-risk adult is being or has been abused, mistreated, or neglected, we will immediately report that information to the county department of social services or a local law enforcement agency.
2. If we learn of a serious threat of imminent physical violence against a person, we will report that information to the appropriate legal authorities and make reasonable and timely efforts to notify the potential victim.
3. This promise of confidentiality does not include information we may learn about future criminal conduct.

Clinically relevant research results, including individual research results, will not be disclosed to you, as a participant.

After the study is completed, we will deidentify the data by removing the identifiers that link it to you. The deidentified data may be used for future research purposes by the Principal Investigators of this study. The deidentified data may also be shared with another investigator for future research.

Payment for Participation

If you agree to take part in this research study, at the conclusion of the study we will pay you $200 for your time and effort. Payments will be made in cash or by check. If you decide to withdraw before completion of the study, you will be paid a prorated rate, depending on the surveys completed as follows:

Survey #1	$25
Survey #2 & MRI #1	$70
Survey #3	$10
Survey #4 & MRI #2	$70
Survey #5	$25
Survey #6-8 (Waitlist)	No compensation

It is important to know that payment for participation is taxable income.

Contact for Future Studies

We would like to keep your contact information on file so we can notify you if we have future research studies we think you may be interested in. This information will be used by only the principal investigator of this study and only for this purpose.
Please initial your choice below:

___ Yes, you may contact me for future research studies. The best way to contact me is: (enter preferred telephone number and/or email address)

_____

___ No, you may not contact me for future research studies.

Questions

If you have questions, concerns, or complaints, or think the research has hurt you, please contact the research team at VRPainStudy@gmail.com, ***marta.ceko@colorado.edu (Phone: mobile 443-835-6587, office 303-735-510)*** *or* ***tassilo@cognifisense.com.***

This research has been reviewed and approved by an IRB. You may talk to them at (303) 735-3702 or irbadmin@colorado.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

Signatures

Your signature documents that you have reviewed the above information, have had a chance to ask questions, and agree to take part in this study.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	