**STUDY BRIEF TITLE: Virtual Reality Treatment for Adults With Chronic Back Pain**

**NCT: NCT04468074**

**DOCUMENT TITLE: STUDY PROTOCOL**

University of Colorado Boulder

**TITLE: Study on the Use of Virtual Reality Neuropsychological Therapy Technology (VRNT) for Chronic Back Pain**

**PROTOCOL VERSION DATE:** August 29, 2020
**VERSION:** 4

## PRINCIPAL INVESTIGATOR (PI):

Name: Marta Ceko

## KEY PERSONNEL

**Name**: Tassilo Baeuerle
**Role in project**: Co-Investigator (CognifiSense, Inc.)

**Name**: Lynn Webster, MD
**Role in project**: Co-Investigator (CognifiSense, Inc.)

## GENERAL RESEARCH STAFF

Two undergraduate/graduate research assistants will assist with this protocol at a time. The PI will ensure appropriate CITI and protocol specific training is maintained. General Research Staff responsibilities will include distributing flyers, administering survey instruments, assisting with fMRI scanning, and data entry.

## I. OBJECTIVES

The purpose of this study is to determine the clinical feasibility of a new virtual reality therapy, called **Virtual Reality Neuropsychological Therapy** (**VRNT**), in achieving lasting pain reduction in moderate to severe chronic back (CBP) patients, and to collect user feedback to help further refine the current product prototype.

- Primary objective of the study is to test the efficacy of VRNT in CBP patients. Specifically, we will determine to what extent VRNT: (1) Has a cumulative effect in decreasing pain and increasing function over an 8-week period; and (2) Once discontinued, has any lasting effects (2 weeks).

- Secondary objective of the study is to establish brain mechanisms associated with treatment response: (1) Establish neurobiological correlates of improvement in pain and disability, (2) Establish brain mechanisms for treatment response at the brain systems level.

## II. BACKGROUND AND SIGNIFICANCE

Chronic pain affects 100 million Americans, ~45 million of whom are considered to have “high impact chronic pain” (Van Korff et al. 2016), characterized by added psychological burden and perceived lack of control over pain. Traditional pharmacological treatments carry serious potential side-effects, and some carry a risk of addiction. Opioids commonly prescribed for chronic pain only have a ~30% responder rate (Santos et al. 2015). Some non-pharmacological approaches, such as Cognitive Behavioral Therapy (CBT), seek to address psychological factors contributing to pain, but are expensive, often inaccessible to rural patients, and rely heavily on provider training / quality; i.e., they show a broad range of efficacy and are thus difficult to scale. CognifiSense, Inc. has developed a full working prototype of a patented, new virtual reality therapy called Virtual Reality Neuropsychological Therapy (VRNT) aimed at providing a lasting reduction in chronic pain. Unlike centrally acting analgesics, which mainly affect patients’ immediate pain experience and comfort, VRNT is designed to address the underlying maladaptive neuroplastic changes associated with chronic pain to create a lasting reduction in pain.

During the transition from acute to chronic pain the experience of pain shifts from a largely proportionate response to a nociceptive pain stimulus to a complex set of learned emotional-motivational factors driving the pain experience. The brain is, thus, in a state of continuous learning, in which persistent, inextinguishable pain leads the brain to continuously make aversive emotional associations; e.g., the brain may catastrophize, hyper-sensitize, or even “expand”/”move” pain, and it may do this long after the nociceptive source has healed. The inability to extinguish the pain helps to sustain this maladaptive cycle of learning (Mansour et al. 2014). The response to nociceptive stimulation is affected by the degree to which pain is perceived to be controllable, and self-efficacy can modulate pain tolerance and the ability to cope with intractable pain. Fear and avoidance are important contributors to the maladaptive learning cycle in chronic pain, as they lead to pain catastrophizing, hypervigilance, disuse, depression and

disability; all of these, in turn, drive the pain experience (Vlaeyen et al. 2012). Thus, for any lasting change in chronic pain, therapies must address these maladaptive learning processes; they must incorporate relearning (Flor et al. 2012) self-efficacy and extinguishing fear of pain. VRNT is a non-pharmacological, software-based pain therapy which aims to do exactly this.

## III. PRELIMINARY STUDIES

Research on therapies focusing on pain control, pain extinction and self-efficacy indicates that visual perception of body and pain have an important relationship with pain perception, and that manipulating imagery associated with pain and body can reduce pain in chronic pain patients (Moseley et al. 2008, Ramachandran et al. 2009, Foell et al. 2013).

VRNT provides the brain with a new set of signals intended to interrupt chronic pain's maladaptive learning cycles and replace it with positive learning cycles. VRNT provides the brain with new signals.

Through repeated use of the complete set of modules, VRNT is intended to condition the brain to reflexively use new pain perceptions and new protocols for pain control or response. It is, thus, intended to provide the brain with tools to interrupt the constant maladaptive associations. VRNT also seeks to interrupt the maladaptive fear-avoidance cycle. Finally, VRNT provides patients with reassessment modules during which patients learn to reassess the meaning of different pain sensations and emotions.

## IV. RESEARCH STUDY DESIGN

This study has 4 phases and will take ~6 months to complete. During the study participants will be randomized into two groups: Therapy Group and Waitlist Group. The Therapy Group will complete 5 surveys. The Waitlist Group will complete 8 surveys; each survey consists of multiple questionnaires, which will be administered on-line via Qualtrics. The study also includes 2 MRI scans. There will be 3 in-person sessions: MRI Scan #1 and #2, and one in-person VRNT Practice Session [all but the MRI scans were moved to a video call format as a result of the University's updated COVID-19 protocols]. There will also be two video-call sessions: one educational session and one Therapy Personalization session. In addition, participants will be scheduled for 8 weekly calls (~30 minutes) during the Therapy Period. Note: Participants who are assigned to the Waitlist will be asked to schedule one more very short visit to CINC to drop off the virtual reality equipment. Figures 1 and 2 provide an overview of the study.

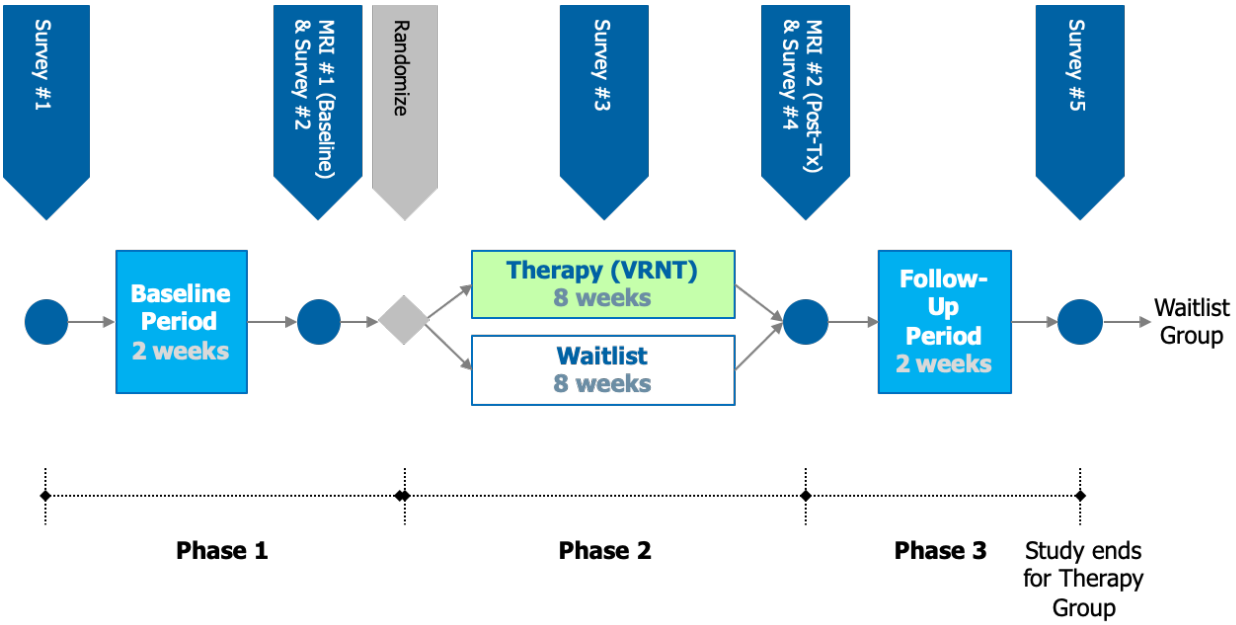


**Figure 1.** Study Design. Phases 1-3 (All participants participate in these phases).

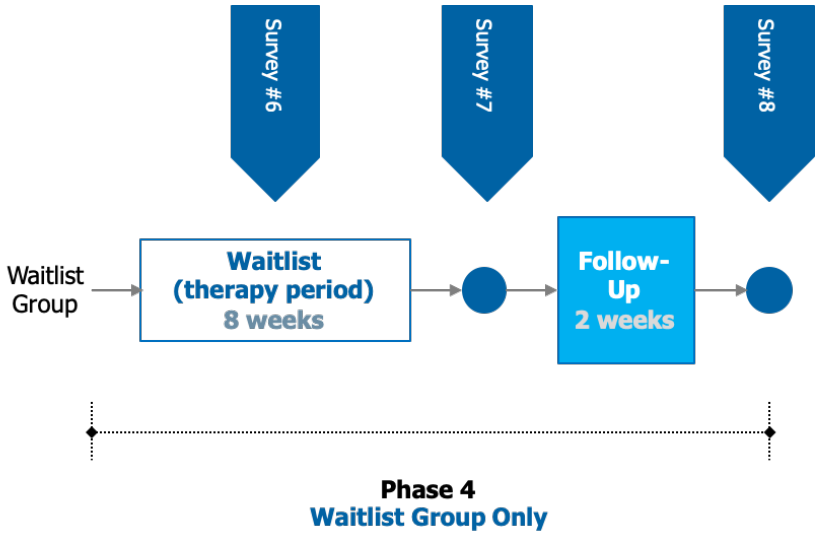


**Figure 2**. Study Design. Phase 4 (Waitlist Group participants only).

## Phases:

**Phase 1:** Collect (pre-therapy) baseline data on all outcome measures from all participants. A 2-week Baseline Period is used to average out day-to-day fluctuations in participant pain experiences. Data on certain outcome measures are collected before and after the Baseline Period to allow us to determine if there are any change due to simply participating in the Baseline. The first MRI session will be after the Baseline Period. Participants are randomized into a Therapy Group and a Waitlist Group at the end of Phase 1.

**Phase 2:** 8-week Therapy Period in which the Therapy Group receives VRNT; The Waitlist Group will receive the Therapy in Phase 4. The same data is collected from both groups. Exception: at the end of Phase 2 (in Survey #4), the Therapy Group completes additional questionnaires about their experience with VRNT (e.g., usability). This phase also includes the second MRI session. Finally, this phase includes 8 weekly calls (~30 minutes)) to track adherence / compliance / problems, answer participant questions, and to provide participants with more explanation of upcoming modules.

**Phase 3:** 2-week Follow-Up Period to determine if there is a lasting VRNT effect in the Therapy Group. The same data is collected from both groups. The study ends for the Therapy Group at the completion of Phase 3.

**Phase 4:** The purpose of this Phase is to allow the Waitlist Group to receive VRNT. Phase 4 includes both the 8-week Therapy Period and the 2-Week Follow-Up period. Data will be collected to evaluate any change in outcome measures (e.g. pain reduction); however, there is no direct control group in this Phase, therefore this data will be considered exploratory (longitudinal within-group changes not controlling for non-specific effects and natural history). Phase 4 does not include another MRI scan (post-Therapy) for the Waitlist Group, because a) there is no direct comparison group (e.g., we are not investigating the potential effects of being in the Waitlist Group, but differences in Treatment between the Therapy Group and Waitlist Group), and b) limited funding under the grant.

## **Data Collected** (by Aim)

**Aim 1:** Data will be collected on each participant's pain intensity and the impact of CBP on the participant's life to determine changes between Baseline, end of Therapy Period and end of Follow-Up Period:

1. Primary Outcome Measure: The impact of VRNT on pain intensity will be measured using:
    a. Brief Pain Inventory – Short Form (BPI-SF), which is a commonly used standardized pain assessment tool.
    b. Pain Intensity questions based on the BPI-SF; (worst, least, and average pain) will be administered daily ("Daily Pain Survey"). [Participants are also asked to note significant changes in medication, mood, activity, sleep or stress and report any such changes via email or phone to the study team. This is used to assess if there are factors which might impact the pain intensity]
2. Secondary Outcome Measure:
    a. back pain-related quality of life, measured using standard Quality of Life (HRQoL SF-12) questionnaire
    b. disability, measured using standard Oswestry Low Back Pain Disability questionnaire, and

c. pain bothersomeness (a measure of pain affect or emotional impact), measured using a self-reported back pain bothersomeness scale (0-10 scale: 0: not at all bothersome; 10: extremely bothersome) (Cherkin et al.2016).

AIM 1 - Additional Outcome Measures: To provide context for the primary and secondary outcome measures, several additional data measures will be collected:

3. Detailed assessment of current medications and therapies
4. Pain Catastrophizing Scale (PCS): Standardized assessment tool for propensity to catastrophize pain. This data will help us determine if there is a relationship between propensity to catastrophize and the efficacy of the therapy.
5. Fear of Pain Questionnaire: Standardized assessment tool for fear of pain. This data will help us determine if the therapy affects this fear (the fear-avoidance cycle is believed an important driver of pain catastrophizing).
6. Tampa Scale for Kinesiophobia (TSK, Fear of Movement): Standardized assessment tool for fear of movement. Fear of movement due to pain is considered an important driver of pain catastrophizing (fear-avoidance model). Certain modules in VRNT are designed to address this fear of movement; thus, this data will provide important context to the how the therapy, and these modules in particular, are impacting participants.
7. PROMIS-SF 43 (anger, sleep, depression, fatigue, sleep,): Standardized assessment tool for assessing the impact of pain on life. This is important additional data on how VRNT might impact participant's life.
8. Survey of Pain Attitudes SF, Emotion subscale (SOPA-Emo): Standardized assessment tool of emotional makeup. This will provide data on the relationship between VRNT and emotional makeup; e.g., does VRNT change these emotional states.
9. General Self-Efficacy Scale (GES): Standardized assessment of participant's perceived level of self-efficacy. This data will allow us to determine if VRNT improves the sense of self-efficacy, which is one of the intended effects.
10. Expectations of Treatment Success (pain relief, improvement in function, improvement in QoL): Standardized assessment tool. This data will be used to determine if there is a relationship between expectations and actual treatment outcomes.
11. Patient Global Impression of Change (PGIC): Standardized tool to assess participant's overall impression of treatment success.
12. Design Survey: Usability, Effort, Usefulness (10-pt scale): This survey will provide important data on the usability of the product. It may also provide insight onto whether there is a correlation between individual perception of usability and treatment outcome.
13. Life Orientation Test (LOT-R) is a scale that assesses optimism. Optimism has recently been shown to be a robust predictor of treatment success in chronic pain patients.
14. -16. The following questionnaires will be administered to assess pain regulation and relationship with pain, including emotional regulation strategies (Emotion

Regulation Questionnaire (ERQ)), mindfulness (Mindful Attention Awareness Scale (MAAS)), and pain coping styles (Coping Strategies Questionnaire (CPQ). These scales have been used in mind-body treatment studies of pain and they will provide data on the effect of VRNT on pain regulation capacity.

15. The Big-5 SF, a commonly used scale for assessing personality traits, will be administered to test whether variable response to treatment across the study sample is related to some common personality traits previously shown to be associated with pain chronification and pain treatment outcomes.

***Data Collection Tools:*** Items 1-16 will be collected via online Qualtrics surveys. Except Items 1b and 2c (the Daily Pain Survey), the data will be collected during the Surveys (Figure 1-2); however, not all questionnaires are completed in each Survey; see Procedures for details regarding which questionnaires are administered during each Survey session. Items 1b and 2c (Daily Pain Survey) are collected online via Qualtrics throughout the study, starting after Survey #1 and ending with Survey #5 for the Therapy Group (Survey #8 for Waitlist Group). Research personnel will monitor whether participants are completing the Daily Pain Survey through Qualtrics and reach out to participants who are not completing it.

**Aim 2:** MRI data will be collected on each participant twice. The first scan will be before randomization of participants, and thus before the Therapy Group starts therapy. The second scan is 8 weeks later; for the Therapy Group this is after they complete the Therapy Period. Participants in the Waitlist Group will also be scanned a second time to provide comparative data. MRIs will be conducted according to the policies and procedures of Intermountain Neuroimaging Consortium (INC) at the Center for Innovation and Creativity in Boulder Colorado. Data collected shall be:
Pre-MRI Survey: This survey will be used to assess day-of-scanning sleep, medication intake, alcohol consumption, coffee consumption, and demographics.

MRI and physiological data: Three types of data are collected, and is needed to do the analyses of AIM 2:

a. MRI scan data (1) structural, (2) resting-state, (3) DTI. These measures brain morphometry (1) and functional (2) and structural (3) connectivity between brain regions.
b. Physiological data: Measures of autonomic response (heart rate, SCR, breathing) of participants while in the MRI scanner.

**OTHER DATA**
In addition to the outcome measures and safety data outlined above, we will be obtaining personal medical information from participants about their pain experience. Finally, we will collect qualitative information from participants during the Weekly Calls and a Final Debrief Interview. This data will be used to provide context to the study findings and to provide input for product improvements.

**Table 1** – Data Collection (Outcome Measures)

The listed items are data that will be collected during the study.

| Name of procedure/instrument/tool | Purpose (i.e., what data is being collected?) |
|---|---|
| **PRIMARY & SECONDARY OUTCOME MEASURES** | |
| **Brief Pain Inventory (BPI-SF)** | Measures current degree of pain (incl. intensity) and symptoms |
| **Daily Pain Survey** | Measures min, max and average daily pain intensities throughout study, and pain bothersomeness (pain affect / emotional impact of pain) |
| **Quality of Life (HRQoL SF-12)** | Measures quality of life |
| **Oswestry Low Back Pain Disability** | Measure of disability, social interaction, and interference of pain with daily activities in back pain patients |
| **ADDITIONAL OUTCOME MEASURES** | |
| **Detailed assessment of current medications** | Assesses current medications and therapies |
| **Pain Catastrophizing Scale (PCS)** | Measures maladaptive coping with pain |
| **Fear of Pain Questionnaire** | Measures fear of different types of pain |
| **Tampa Scale for Kinesiophobia (TSK, Fear of Movement)** | Measures fear of potentially pain-causing movements |
| **PROMIS-SF 43** | Assesses sleep, anger, depressive symptoms, fatigue, |
| **Survey of Pain Attitudes SF, Emotion subscale (SOPA-Emo)** | Measures patient's attitudes and beliefs about pain |
| **General Self-Efficacy Scale (GES)** | Measures perceived control in daily activities |
| **Expectations of Treatment Success** | Measures expectations of pain relief, improvement in function and improvement in quality of life due to treatment |
| **Patient Global Impression of Change (PGIC)** | Measures patient's perception about treatment success |

| | |
|---|---|
| **Design Survey** | Measures usability, effort needed, and usefulness of VRNT |
| **Life Orientation Test (LOTR)** | Measures dispositional optimism |
| **Emotion Regulation Questionnaire (ERQ)** | Measures emotion regulation styles |
| **Mindful Attention Awareness Scale (MAAS)** | Measures mindful traits (acting with awareness, present focus, responsiveness, social awareness) |
| **Coping Strategies Questionnaire (CPQ)** | Measures pain coping styles |
| **Big-5 short form (Big-5 SF)** | Measures personality traits |
| **MRI AND PHYSIOLOGICAL DATA** | |
| Pre-MRI Survey | Assess day-of-scanning sleep, medication intake, alcohol consumption, coffee consumption, and demographics |
| MRI scan data (1) structural, (2) resting-state, (3) DTI | Measures brain morphometry (1) and functional (2) and structural (3) connectivity between brain regions |
| Physiological data | Measures autonomic response (heart rate, SCR, breathing) of participants while in the MRI scanner |
| **OTHER DATA** | |
| Weekly Calls | Questions about adherence / compliance. Open-ended questions about any problems with VR and with therapy (incl. technical problems and adverse effects) |
| Final Debrief Interview | Open-ended questions about participants' experience with VR and with therapy |
| | |
| | |

**Sample Size.** We target a sample of N = 60 subjects completing the final surveys,30 per group. Since we estimate a ~20% attrition rate, we aim to enroll N = 76 patients into the study (N = 38 per group). Pre-screening of participants will take place on Qualtrics via an eligibility survey.

**Randomization Procedures.**
After the initial baseline information from Phase 1 (Survey #1, Baseline Period, Survey #2 and the MRI screen #1) is collected, participants will be randomized into a Therapy Group and a Waitlist Group, using a computer-generated random sequence.

**Control Group Rationale.**
A Waitlist Group will serve as control group. The Waitlist Group will not receive a sham treatment. It will provide the same outcome data as the Therapy Group, and it will provide two MRI scans pre-/post-waiting period as a comparable to the Therapy Group. Both the Therapy Group and the Waitlist Group will be allowed to continue their normal pain treatment (pharmacological and other), the Waitlist Group can serve as a control; that is, the VRNT is an adjunct therapy. Thus, the Waitlist Group serves as a reasonable control to the Therapy Group.

**Power Analysis.** The effect size for VRNT is still unknown. Effect sizes for mirror therapy for phantom limb pain have a Cohen's d = 0.52 (1.64 in subjects without telescoping) to 0.97 [1] whereas (mindfulness) mediation-based treatments for chronic pain have a Cohen's d = 0.27 to 0.45 (Maglione et al. 2018) For a two-group between person test with ~30 subjects per group, this design will allow us to detect a minimum clinically meaningful effect size of d = 0.75 with 80% power at two-tailed α = .05.

**Data Analysis.**
AIM 1. Test the efficacy of VRNT in moderate to severe Chronic Back Pain patients. The Primary outcome measure is pain (BPI–SF). Secondary Outcome measures are A) Disability (Oswestry Low Back Pain Disability), B) Quality of Life (SF-12), and C) Pain Bothersomeness. Daily pain scores (e.g. least, worst, average) and pain bothersomeness scores will be plotted and assessed for stability and distributional assumptions (normality, homoscedasticity, potential outliers), and transformed as appropriate to ensure validity of statistical tests. Average pain intensity and bothersomeness baseline and intervention phases will be calculated and the primary analysis (Aim 1) will use a General Linear Model (GLM) to estimate group differences (VRNT vs. control) in [baseline – post-intervention] change scores, controlling for baseline pain, age, and gender, with alpha = 0.05 two-tailed. The same test will be applied to other outcomes (Table 1). Secondary analyses will use the GLM to estimate within-person improvements in the VRNT group, to establish that between-group differences are driven by therapeutic improvement from baseline in the treatment group, and test whether treatment effects are moderated by age, gender, and prior medication use (e.g. opioids, NSAIDS).

AIM 2. Establish brain mechanisms associated with treatment response. Tasks. MRI imaging will consist of three types of images: (1) Structural T1 image suitable for localization of functional signals, voxel-based morphometry, and cortical

thickness/volumetric analyses; (2) Resting-state functional MRI collected during eyes-open fixation, widely acquired during large-scale studies, suitable for analysis of functional connectivity between brain regions (3) DTI scan suitable for the analysis of structural white matter connectivity between brain regions Preprocessing. We will employ standard, state-of-the art image preprocessing techniques (SPM12; Wellcome Department of Cognitive Neurology, UCL), using procedures detailed in our (i.e. Wager Lab) published work (Wager et al. 2011, Woo et al. 2017, Roy et al. 2014), with improvements described below. Structural images: inhomogeneity correction, co-registration to the mean realigned functional image, enhanced generative nonlinear normalization using SPM12. Functional images: distortion correction: we use two distortion correction images to adjust for nonlinear EPI distortion and field inhomogeneities (Calhoun et al. 2017) realignment/motion correction; application of normalization parameters, high-pass filtering with an optimized cutoff. Head movement**:** Tolerance for within-run movement is 1 mm displacement/1.5° rotation, achievable in ~95% of participants. Movement estimates and higher-order transformations (Lund et al. 2005) will be modeled as nuisance covariates in 1$^{st}$-level analyses. Gradient artifacts are minimized using a multivariate outlier detection method, with outliers (typically < 1% of images) modeled as nuisance regressors (Wager et al. 2013). Quality control plots and image loss rates are reviewed by study personnel on an ongoing basis and compared with quality metrics from other studies. Analysis. Primary analyses will focus on fMRI and white matter connectivity related to chronic back pain. Secondary, exploratory analyses will identify group differences in post- vs. pre-treatment fMRI and white-matter connectivity across the brain using standard GLM analyses. As we will develop exploratory brain maps, the following power analysis will apply to the brain mapping: 80% power to detect effects of d = 1.22 or larger at P < 0.001 (which often satisfies whole-brain False Discovery Rate q < 0.05 where large signals exist). We will focus on frontostriatal connectivity between ventromedial prefrontal (coordinates [2 52 -2], 8 mm sphere) and accumbens (coordinates [10, 12, -8]) areas identified by Baliki et al. 2012. as predicting the transition to chronic back pain and shown to mediate effects of cognitive regulation on pain (Woo et al. 2017). We will also examine other a priori brain measures as they become available.

## V. FUNDING

An NIH Small Business Innovation Research (SBIR) grant.

## VI. ABOUT THE SUBJECTS

We anticipate enrolling ~76 participants in order to reach our goal of N = 60 given estimated attrition rate of 20% based on previous studies). Interested applicants will receive an email requesting them to complete the online eligibility survey.

To maximize potential enrollment, no specific pharmacological therapies were excluded. Participants will provide therapy and dosage data (see Table 1) and must notify the team

of any changes in medication/treatments. They must agree not to change/add/remove any current treatments (unless indicated by their physician) or make large lifestyle changes (e.g., diet or exercise) during the study. All subjects who meet eligibility criteria for a research study, regardless of race or gender, will be screened for inclusion. The inclusion of women and minorities is not expected to affect any of the dependent measures of this study, but will, in fact, bolster the generalizability of data obtained. Children will not be studied at this time, due to differences in treatment methods. Moreover, the study's length would make obtaining guardian consent challenging.

**Inclusion criteria:**
Self-reported:

1. Participants aged 21 to 70 with Chronic Back Pain.
2. Chronic Back Pain will be defined according to criteria established by recent NIH task force. Pain duration must be ≥ 3 months, with back pain being an ongoing problem for at least half the days of last 6 months; i.e., either pain every day for past 3 months, or half or more of the days for past 6+ months.
3. Subjects must rate pain intensity at ≥ 4/10 on Brief Pain Inventory (average pain over the last week).
4. Participants must also be comfortable and able to communicate via email, text message, or phone in English. Participants must also be comfortable using a video-conferencing service such as Zoom to complete the on-line sessions

**Exclusion criteria:**
Self-reported:

1. Applicants, who are pregnant, planning pregnancy, or breastfeeding
2. Back pain associated with compensation / litigation within 1 year.
3. Leg pain greater than back pain (suggests neuropathic pain; may be less responsive to psychological therapy).
4. Chronic pain other than chronic back pain
5. Diagnoses of schizophrenia, multiple personality dissociative identity disorder.
6. History of major depressive disorder not controlled with medication or other conditions that produce significant cognitive or emotional disability.
7. History of substance abuse.
8. Inability to undergo MRI (determined at screening; see XVI: Risks to Participants).
9. Any clinically significant unstable medical abnormality or acute or chronic disease of cardiovascular, gastrointestinal, respiratory (e.g., chronic obstructive pulmonary disease), hepatic, or renal systems; including: history of cardiovascular disease or issues (e.g., recent heart attack), stroke; brain surgery, or brain tumor; Diabetes; cancer (last 12 months); diagnosis of a specific inflammatory disorder: rheumatoid arthritis, polymyalgia rheumatica, scleroderma, Lupus; polymyositis; or Cauda Equina syndrome.
10. History of seizure disorder, epilepsy, convulsions, or increased intracranial pressure anytime except pediatric febrile seizures
11. History of vertigo, dizziness, susceptibility to motion sickness
12. History of head injury within 6 months,
13. Unexplained, unintended weight loss of ≥ 20 lbs in past year.

14. Self-reported history of (digital) eye strain or computer vision syndrome.
15. Unable or unwilling to meet study attendance requirements.
16. MRI contraindications as determined by MRI safety screen (e.g., pregnancy, metal in body, claustrophobia, using the standard screen conducted by the MRI imaging facility).

| Subject Population(s) | Number to be enrolled in each group |
|---|---|
| **Chronic back pain community sample** | Therapy (VRNT) Group: 38<br>Waitlist Group: 38 |

## VII. VULNERABLE POPULATIONS

None

## VIII. RECRUITMENT METHODS

Patients will be recruited through two channels:

a. Members of the research team will contact previous back pain study participants from the CANLab, who have consented to being re-contacted for future studies. Participants who were enrolled in a previous back pain study run through the Cognitive and Affective Neuroscience lab and have expressed written consent to be contacted for future studies by the lab may also be notified by the study team. The CANLab has a recruitment database of back pain patients that the lab's PI has access to. These are patients from a previous study who have consented to being re-contacted for future studies.
b. Advertisement via flyers, electronic bulletin boards, and social media (e.g., Facebook).

| Recruitment methods/materials |
|---|
| 1. **Re-contact previous back pain study participants** |
| 2. **Physical flyer** |
| 3. **Online advertisement** |

## IX. COMPENSATION

Participants will be paid $200 in cash or check at the conclusion of the study. In the event that a participant withdraws partway through the study, they 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 |

## X. INFORMED CONSENT

Following completion of the screening form and passing the screening requirements, informed consent will be obtained as follows: (1) participants will be sent an email link to an online DocuSign consent form, (2) study staff will schedule a time to call the potential participant to conduct consent interview, (3) participant will sign consent (via DocuSign ) after the consent interview has occurred. Participants will also be asked to note whether the study personnel have permission to re-contact them regarding future studies. Coercion and undue influence will be minimized by reminding participants that their participation is voluntary, and that the VRNT treatment is not appropriate for everyone.

Re-consent procedure (June 9 amendment): Some participants will need to be re-consented for the modified procedures with the new consent form (IRB amendment to protocol submitted June 9, 2020). Immediately upon approval of the requested changes to the protocol, these participants will be sent an email summarizing the changes to the protocol and a link to the new online DocuSign consent form.
Re-consent procedure (June 16 amendment): Some participants will need to be re-consented for the modified procedures with the new consent form (IRB amendment to protocol submitted June 16, 2020). Immediately upon approval of the requested changes to the protocol, these participants will be sent an email summarizing the changes to the protocol and a link to the new online DocuSign consent form.

In accordance to 21 CFR 50.27(a), participants will have a signed copy of the consent form in DocuSign.

## XI. PROCEDURES

The study Procedures, as experienced by each participant group (Therapy vs. Waitlist), are as follows. Note: the participant will not actually be assigned to a participant group until after Survey #3 & MRI #1.

# THERAPY GROUP PROCEDURES

### Phase 1

After the Consent Form is completed, study personnel will contact participants via their preferred contact method (e.g. email / phone; asked in the Eligibility form) to schedule their MRI #1 ~2 weeks later. The MRI's will be conducted at the Intermountain Neuroimaging Consortium (INC) facility, located within Center for Innovation and Creativity (CINC). Participants will also receive an email with instructions for completing Survey #1, an explanation of how they are to complete the "Daily Pain Survey", and an overview of upcoming steps in the study.

Survey #1 (~ 1 hour). On-line Qualtrics survey. Participants will be sent a link via email. Survey #1 includes the following questionnaires

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Detailed assessment of current medications
5. Pain Catastrophizing Scale (PCS)
6. Fear of Pain Questionnaire (FOP)
7. Tampa Scale for Kinesiophobia (TSK)
8. PROMIS-SF 43 (anger, sleep, depression, fatigue, sleep)
9. Survey of Pain Attitudes SF, Emotion subscale (SOPA-Emo)
10. General Self-Efficacy Scale (GES)

Baseline Period (2 weeks). During these two weeks all participants will be asked to complete the Daily Pain Survey online via Qualtrics once a day, which takes about 5 minutes to complete (last thing in evening. The Daily Pain Survey includes pain intensity questions (based on BPI-SF), including worst, least, and average pain and current pain (each on a 11-point NRS), and pain bothersomeness scale (a 11-point NRS). Participants are also asked to note significant changes in medication, mood, activity, sleep or stress and report any such changes via email or phone to the study team.

Survey #2 (~1 hour and 20 mins). At the end of the Baseline Period, all participants will complete Survey #2 online via Qualtrics. Survey #2 includes the following questionnaires:

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Detailed assessment of current medications
5. Pain Catastrophizing Scale (PCS)
6. Fear of Pain Questionnaire (FOP)
7. Tampa Scale for Kinesiophobia (TSK)
8. PROMIS-SF 43
9. Survey of Pain Attitudes SF, Emotion subscale (SOPA-Emo)
10. General Self-Efficacy Scale (GES)

11. Expectations of Treatment Success (pain relief, improvement in function, improvement in QoL)
12. Life Orientation Test (LOT-R)
13. Emotion Regulation Questionnaire (ERQ)
14. Mindful Attention Awareness Scale (MAAS)
15. Coping Strategies Questionnaire (CPQ)

MRI #1 (~1hour and 30 mins): Participants will have an in-person session at CINC for MRI #1. Prior to the MRI, participants will fill out a short survey ('Pre-MRI Survey') on a computer at CINC and change into scrubs for the scan (30 mins). The MRI scanning will last ~1 hour.

MRI session details The participant will undergo 3 MRI scans: (1) a 7-minute structural MRI scan, during which the participant can have their eyes open or closed, (2) ~10-minute resting-state functional MRI (fMRI) scan, during which the participant is asked to have their eyes open and fixated on a plus-sign displayed on the screen in front of them, and a (3) ~6-minute Diffusion Tensor Imaging (DTI) scan, during which the participant can have their eyes open or closed. While participants are in the MRI scanner, we will also monitor their physiological responses (e.g., heart rate, skin conductance, respiration). We will collect these measures by using non-invasive sensors, which are not associated with any uncomfortable, harmful or painful sensations.
MRIs will be conducted according to the policies and procedures of Intermountain Neuroimaging Consortium at the Center for Innovation and Creativity in Boulder Colorado. INC MRI technologists are not trained to read the scans for abnormalities; however, should an anomaly be observed, these images will be flagged and read by a neurologist or licensed radiologist at the Mind Research Network. Subjects will be notified by the INC staff of the results of the radiology report, regardless of the outcome. Subjects will also receive a letter from the Mind Research Network that includes the radiology report.

All participants will be scheduled for an MRI #2 approximately 8 weeks later (after the Therapy Period is completed, see below for details).

Randomization. After MRI #1, participants will be randomized (50/50) to the Therapy and Waitlist groups, using a computer-generated random sequence. Randomization is after the MRI #1 to avoid potential bias. This is the point at which participants find out that they are in the Therapy Group.

## Phase 2

Therapy Period (8 weeks). Participants assigned to the Therapy Group will begin the VRNT protocol. NOTE: Therapy Group participants will be asked to maintain their other pain treatments (e.g. pharmacological or other therapies), unless otherwise directed by a physician; participants will be asked to report major changes. Participants will be asked to continue to maintain their "Daily Pain Survey" (Qualtrics online) throughout the Therapy Period.

VRNT has four components: 1) Education, 2) Treatment Personalization, 3) VRNT Practice Session, and 3) "Therapy" Modules. The Education and Treatment Personalization sessions are completed together with a research team member at CINC. Participants will be scheduled for one or two (depending on participant availability) in-person meetings at CINC [Due to changes in the University's COVID-19 protocols, all one-on-one sessions were moved to video conferencing over the course of the study]. Participants will be given the option to complete the Education session with other participants; Treatment Personalization sessions will be done only in private sessions. The Therapy Modules are done by the participants at home.

1) Education (~1 hour and 30 mins; via video-conferencing): Completed via video-call service (e.g. Zoom), this session will include a (PowerPoint-based + short Video) education of each participant in the science behind chronic pain. To help reinforce some key points and help participants to engage in self-evaluation based on the learnings from this session, a voluntary Self-Evaluation will be sent out via Qualtrics at the end of the session.

2) Treatment Personalization (~ 1 hour and 30 mins; via video-conferencing): In this session, certain aspects of the VR therapy are personalized for each participant. After the session, the personalization files will be ported as an "app" onto a smartphone, which the participant will later use, together with a mobile VR headset, at home; the mobile VR "app" provides the Therapy Modules.

3) In-Person VRNT Practice Session (~ 1 hour and 30 mins; in-person; moved to video-conferencing): This session will be in-person at CINC / Zoom call. Sessions will involve only one participant at a time. A team member will explain how to use the hardware and software. The participant will then get to practice at least three modules, including one of the modules from the first week and two more challenging modules.

4) "Therapy" Modules (3-15 mins each): All the Modules are in the VRNT app on the mobile VR equipment. Based on a prescribed schedule (detailed in an accompanying Workbook), the participant will select from several therapy modules.

Participants will be given a Workbook which specifies the modules they should complete each day; it also provides some additional exercises to be completed in the real world. While the Workbook contains instructions on how to use VRNT, participants will also be provided with short video tutorials, covering basic navigation of the app and how to navigate the more intricate modules. Participants are asked to use VRNT a minimum of once a day for 5 days per week. Each session lasts between 15 – 30 minutes. There may be days where the session may take longer, based in part on participant interest. The VRNT program will encourage participants to explore movement, exercise and activities (of increasing challenge) in their regular life that they previously felt they could not do. In this way, the program seeks to incorporate the experiential learnings from VRNT into the participant's life. However, participants will NOT be asked to perform any

special physical exercise program; they are merely encouraged to apply their learnings from VRNT in the real world.

Weekly Calls (~30 mins each). Participants will be scheduled for a weekly call. A team member will use specific and open-ended questions to check on adherence / compliance, and technical problems or side effects. Participants will be given the option of doing these sessions via telephone or video call (e.g. Zoom, Skype).

Survey #3 (~30 mins). On-line Qualtrics survey. Participants will be sent an email link 4 weeks into the Therapy Period (mid-way point). Survey #3 includes the following questionnaires:

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Pain Catastrophizing Scale (PCS)
5. General Self-Efficacy Scale (GES)

Survey #4 (~ 1 hour and 25 mins). At the end of the Therapy Period, participants will complete Survey #4 online via Qualtrics. Survey #4 includes the following questionnaires:

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Detailed assessment of current medications
5. Pain Catastrophizing Scale (PCS)
6. Fear of Pain Questionnaire
7. Tampa Scale for Kinesiophobia (TSK, Fear of Movement)
8. PROMIS-SF 43
9. Survey of Pain Attitudes SF, Emotion subscale (SOPA-Emo)
10. General Self-Efficacy Scale (GES)
11. Patient Global Impression of Change (PGIC)
12. Design Survey: Usability, Effort, Usefulness
13. Life Orientation Test (LOT-R)
14. Emotion Regulation Questionnaire (ERQ)
15. Mindful Attention Awareness Scale (MAAS)
16. Coping Strategies Questionnaire (CPQ)

MRI #2 (~1 hour and 30 mins). At the end of the Therapy Period, participants will have an in-person session at CINC for MRI #2. Prior to the MRI, participants will fill out a short survey. The MRI procedures are the same as for MRI #1. Prior to scanning, participants will complete the short Pre-MRI Survey (minus the demographic questions) and MRI Screening Form and change into scrubs for the scan (~ 30 mins).

Debrief call (~45 minutes). A debrief call will be scheduled for the week following the MRI #2 session. In the Debrief call participants will be asked open-ended questions about their experience with VRNT.

**Phase 3**

Follow-Up Period (2 weeks). Participants will be asked to continue the "Daily Pain Survey" in Qualtrics.

Survey #5. (~ 1 hour and 25 mins) On-line Qualtrics survey. At the end of the Follow-Up Period participants will be sent an email link. Survey #5 includes the following questionnaires:

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Detailed assessment of current medications
5. Pain Catastrophizing Scale (PCS)
6. Fear of Pain Questionnaire
7. Tampa Scale for Kinesiophobia (TSK, Fear of Movement)
8. PROMIS-SF 43 (anger, sleep, depression, fatigue, sleep, social interaction, pain interference)
9. Survey of Pain Attitudes SF, Emotion subscale (SOPA-Emo)
10. General Self-Efficacy Scale (GES)
11. Patient Global Impression of Change (PGIC)
12. Life Orientation Test (LOT-R)
13. Emotion Regulation Questionnaire (ERQ)
14. Mindful Attention Awareness Scale (MAAS)
15. Coping Strategies Questionnaire (CPQ)
16. Big-5 Short Form (Big5-SF)

Focus group session (~2 hours, optional). An optional "focus group" session for Therapy Group participants will be scheduled in the 2 weeks after the Follow-Up period. Structured and open-ended questions will be used to obtain feedback on the product and therapy, the perception of how VRNT worked, problems and recommendations. In addition, questions will seek context for the quantitative measures, including those related to the mechanisms behind VRNT. Based on state and university guidelines at the time, this session may be offered in-person (following appropriate – e.g., social distancing – guidelines) or via a video call (e.g. Zoom).

## WAITLIST GROUP PROCEDURES

**Phase 1.** Procedures are identical to the Therapy Group.

## Phase 2

Waiting Period (8 weeks). Waitlist Group (control) participants will be asked to maintain their current pain management protocols, unless otherwise directed by a physician; participants will be asked to report major changes. The control is needed to isolate treatment effects from the effects of time and any effects associated with simply enrolling in a study. No additional therapy or VR app will be provided during the waiting period to maintain Waitlist "illusion", limit workload, and to limit confounding effects.

Survey #3 (~ 30 mins). On-line Qualtrics surveys. Participants will be sent an email link 4 weeks into the Waiting Period (mid-way point). Survey #3 includes the following questionnaires

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Pain Catastrophizing Scale (PCS)
5. General Self-Efficacy Scale (GES)

Survey #4 (~1 hour and 10 mins). Same procedures as for the Treatment Group, except that the Waitlist Group participants do not complete the PGIC and Design Survey questionnaires, as they have not completed the therapy (therefore Survey #4 is 15 mins shorter than for the Treatment Group)

MRI #2 (~1 hour and 30 mins): Same procedures as for the Treatment Group.

## PHASE 3

Follow-Up Period (2 weeks). Participants will be asked to continue the "Daily Pain Survey" in Qualtrics. For the Waitlist Group this period actually serves as a pre-therapy baseline period.

Survey #5 (~1 hour and 20 mins). On-line Qualtrics survey. At the end of the Follow-Up Period the Waitlist Group will be sent an email link. Survey #5 includes the same questionnaires as Survey #5 for Treatment Group above, except that Waitlist Group participants do not complete the PGIC, as they have not completed the therapy (therefore Survey#5 is 5 mins shorter than for Therapy Group).

## PHASE 4

Waitlist Therapy Treatment. After completing Survey #5, Waitlist participants are scheduled to receive the Educational, Treatment Personalization and VRNT Practice session(s), Waitlist participants will then complete the 8-week Therapy Period, all with the same protocol as the Therapy Group. They will maintain their "Daily Pain Surveys" on Qualtrics throughout the period and will be scheduled for the 8 Weekly calls.

Survey #6. On-line Qualtrics surveys. Participants will be sent an email link 4 weeks into the Therapy Period (mid-way point). This survey takes roughly 30 minutes to complete. Survey #6 Includes:

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Pain Catastrophizing Scale (PCS)
5. General Self-Efficacy Scale (GES)

Survey #7. At the end of the Therapy Period, participants complete the Survey #7 online via Qualtrics. Survey #7 includes the following questionnaires, and takes about 1 hour and 25 minutes to complete:

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Detailed assessment of current medications
5. Pain Catastrophizing Scale (PCS)
6. Fear of Pain Questionnaire
7. Tampa Scale for Kinesiophobia (TSK, Fear of Movement)
8. PROMIS-SF 43 (anger, sleep, depression, fatigue, sleep,)
9. Survey of Pain Attitudes SF, Emotion subscale (SOPA-Emo)
10. General Self-Efficacy Scale (GES)
11. Patient Global Impression of Change (PGIC)
12. Design Survey: Usability, Effort, Usefulness
13. Life Orientation Test (LOT-R)
14. Emotion Regulation Questionnaire (ERQ)
15. Mindful Attention Awareness Scale (MAAS)
16. Coping Strategies Questionnaire (CPQ)

Debrief call. During the MRI #2 session, participants will be asked to schedule a 45-minute debrief call. In the Debrief call participants will be asked open-ended questions about their experience with VRNT.

Equipment Drop-Off. Participants will be asked to schedule a short visit to CINC to return the VR equipment (curb-side).

Follow-Up Period (2 weeks). Participants will be asked to continue the "Daily Pain Survey" in Qualtrics.

Survey #8. On-line Qualtrics surveys. At the end of the Follow-Up Period will be sent an email link. This survey will take roughly 1 hour and 25 minutes to complete. Survey #8 Includes:

1. Brief Pain Inventory – Short Form (BPI-SF)
2. Quality of Life (HRQoL SF-12)
3. Oswestry Low Back Pain Disability
4. Detailed assessment of current medications
5. Pain Catastrophizing Scale (PCS)
6. Fear of Pain Questionnaire
7. Tampa Scale for Kinesiophobia (TSK, Fear of Movement)
8. PROMIS-SF 43 (anger, sleep, depression, fatigue, sleep, social interaction, pain interference)
9. Survey of Pain Attitudes SF, Emotion subscale (SOPA-Emo)
10. General Self-Efficacy Scale (GES)
11. Patient Global Impression of Change (PGIC)
12. Life Orientation Test (LOT-R)
13. Emotion Regulation Questionnaire (ERQ)
14. Mindful Attention Awareness Scale (MAAS)
15. Coping Strategies Questionnaire (CPQ)

**Procedures and time requirements**

| Visit # | Procedures/Tools | Location | How much time the visit will take |
|---|---|---|---|
| **THERAPY GROUP** | | | |
| | | | |
| Survey #1 (from Home) | Survey #1 Questionnaires - Qualtrics online | Online | 1 hour |
| Baseline Period - 2 weeks (from Home) | "Daily Pain Survey" - Qualtrics online | Online | 5 minutes |
| Survey #2 & MRI #1 | Survey #2 Questionnaires - Qualtrics online | Online | 1 hour 20 minutes |
| | Preparation for scanning (MRI Screening Form and Pre-MRI survey, change into scrubs, use restroom) | Center for Innovation and Creativity (CINC) | 30 minutes |

| | | | |
|---|---|---|---|
| | MRI scan | CINC | 1 hour |
| Therapy Period - 8 weeks | 1) Education | Video Call | 1 hour and 30 mins |
| | 2) Treatment Personalization | Video Call | 1 hour and 30 mins |
| | 3) VRNT Practice Session | CINC [Video Call] | 1 hour and 30 mins |
| | 4) Therapy Modules: min. once a day for 5 days / week | Online | 20-39 hours over an 8-week period (each day will require about 15-30 minutes of participation time) |
| | “Daily Pain Survey" - Qualtrics online | Online | 5 minutes |
| | Weekly Calls | Phone | 30 minutes |
| Survey #3 (from Home) | Survey #3 Questionnaires - Qualtrics online | Online | 30 minutes |
| Survey #4 & MRI #2 | Survey #4 Questionnaires - Qualtrics online | Online | 1 hour 25 minutes |
| | Preparation for scanning (MRI Screening Form and Pre-MRI survey, change into scrubs, use restroom) | CINC | 30 minutes |
| | MRI scan | CINC | 1 hour |
| Follow-Up Period - 2 weeks (from Home) | “Daily Pain Survey" - Qualtrics online | Online | 5 minutes |
| Survey #5 (from Home) | Survey #5 Questionnaires - Qualtrics online | Online | 1 hour 25 minutes |
| | Final Debrief Interview | Phone | 45 minutes |

| | | | |
|---|---|---|---|
| OPTIONAL Focus Group | Focus group questions | Online | 2 hours |
| | | | |
| **WAITLIST GROUP** | | | |
| | | | |
| Survey #1 (from Home) | Survey #1 Questionnaires - Qualtrics online | Online | 1 hour |
| Baseline Period - 2 weeks (from Home) | “Daily Pain Survey" - Qualtrics online | Online | 5 minutes |
| Survey #2 & MRI #1 | Survey #2 Questionnaires - Qualtrics online | Online | 1 hour 25 minutes |
| | Preparation for scanning (MRI Screening Form and Pre-MRI survey, change into scrubs, use restroom) | Center for Innovation and Creativity (CINC) | 30 minutes |
| | MRI scan | CINC | 1 hour |
| Waiting Period - 8 weeks | “Daily Pain Survey" - Qualtrics online | Online | 5 minutes |
| Survey #3 (from Home) | Survey #3 Questionnaires - Qualtrics online | Online | 30 minutes |
| Survey #4 & MRI #2 | Survey #4 Questionnaires - Qualtrics online | Online | 1 hour 10 minutes |
| | Preparation for scanning (MRI Screening Form and Pre-MRI survey, change into scrubs, use restroom) | Center for Innovation and Creativity (CINC) | 30 minutes |
| | MRI scan | CINC | 1 hour |
| Follow-Up Period (Waitlist's pre-treatment baseline) - 2 weeks (from Home) | “Daily Pain Survey” – Qualtrics online | Online | 5 minutes |

| | | | |
|---|---|---|---|
| Survey #5 (from Home) | Survey #5 Questionnaires – Qualtrics online | Online | 1 hour and 20 mins |
| Waitlist Group's Therapy Period - 8 weeks | 1) Education | Video Call | 1 hour and 30 mins |
| | 2) Treatment Personalization | Video Call | 1 hour and 30 mins |
| | 3) VRNT Practice Session | CINC [Video Call] | 1 hour and 30 mins |
| | 4) Therapy Modules: min. once a day for 5 days / week | Online | 20-39 hours over a 8-week period (each day will require about 15-45 minutes participation time) |
| | "Daily Pain Survey" - Qualtrics online | Online | 5 minutes |
| | Weekly Calls | Phone | 30 minutes |
| Equipment Drop Off | Return VR equipment | CINC (curb-side) | 10 minutes |
| Survey #6 (from Home) | Survey #6 Questionnaires - Qualtrics online | Online | 30 minutes |
| Survey #7 | Survey #7 Questionnaires - Qualtrics online | Online | 1 hour 25 minutes |
| Follow-Up Period - 2 weeks (from Home) | "Daily Pain Survey" - Qualtrics online | Online | 5 minutes |
| Survey #8 (from Home) | Survey #5 Questionnaires - Qualtrics online | Online | 1 hour 25 minutes |
| | Final Debrief Interview | Phone | 45 minutes |

## XII. SPECIMEN MANAGEMENT

N/A

## XIII. DATA MANAGEMENT

According to HRP-211, the security requirements for this study are Level 2.

Study data will be accessed through authenticated mediums on a need to know basis. The study team (key personnel and research staff) will have access to the data.

Strict standards of confidentiality will be maintained. Study data will be collected via pen-and-paper (Debriefing call, weekly calls, MRI screening form), Qualtrics (Survey questionnaires), MRI, and VRNT software.

Pen-and-paper data will be stored in a locked file cabinet in a locked room at CINC.

Qualtrics is a secure, widely used data collection tool managed by CU Boulder. Only CU Boulder team members (Dr. Ceko and study RA's) will have access to the Qualtrics data platform. Identifying information will be collected during the online screen, which asks for participants' names, phone numbers, and email addresses. After study completion, this information will be removed from the Qualtrics database, permanently de-identifying the Qualtrics data.

MRI data will be stored according to standard INC data management procedures. MRI images will be housed on a CU Boulder RCserver. Metadata (name and contact information) will be entered into the COINS database by study personnel. Each COINS entry will receive a unique research subject identifier. This code will be associated with the images. A copy of the MRI images will be sent to the Georgia State University for data sharing and storage. No identifying information is included in the images.

VRNT data on the Personalized Treatment will be synched periodically via a DropBox application with a file accessible only to the team. However, the data will only be encoded with the subject identifier number. Only the core team members will have access to a written matrix tracking participant name to participant identifier.

## XIV. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Data collection will only occur in private contexts, whether at CINC or the participant's home, in order to ensure privacy of all participants. Additionally, Participants will complete the Education session individually, unless they indicate that they would be willing to complete it in a group setting. The only other group session are the focus groups, which are voluntary.

Any information that identifies individual participants will only be accessible to study personnel. Furthermore, participants have the right to refuse to provide any identifying information.

## XV. WITHDRAWAL OF PARTICIPANTS

Participants may withdraw voluntarily from a study at any time. Participants may either withdraw from a particular session, or request that they be removed entirely from the participant pool. Withdrawn participants will have no further data collected from them, and there will be no follow up contact with them.

We may withdraw participants from the study if: we learn that they added, changed, or stopped any concurrent treatment for their pain (for example, undergoing back surgery mid-study); participants' back pain dramatically worsens and we judge they need more intensive treatment than that provided in this study.

Withdrawn subjects will have no further data collected from them, and there will be no follow up contact with them. They will be replaced with new participants.

## XVI. RISKS TO PARTICIPANTS

### VR

Virtual reality (VR) applications have been known to cause motion sickness or temporary headaches. Exclusion criteria are designed to exclude applicants with high susceptibility to motion sickness. Participants are 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. The program does encourage participants to gradually increase movement and activity in their lives. Participants will be asked to check with their physicians before engaging in any major new physical movement or activity. VR applications have also been known to cause headaches in people with (digital) eye strain of computer vision syndrome. The exclusion criteria are aimed at excluding such applicants.

### MRI Scans

Subjects may experience nervousness and/or claustrophobia during the MRI. While generally safe, it is not known whether an MRI would harm a fetus.

The risks of MRI are:

- The MRI may cause discomfort due to scanner noise.
- There may be some discomfort from lying still and in one position for a long time.
- Peripheral nerve stimulation (PNS/tingling). At sufficient exposure levels, peripheral nerve stimulation is perceptible as "tingling" or "tapping" sensations. PNS symptoms will usually subside shortly after the scan is completed.

MRI anomalies: While the images are taken for research purposes, participants will be notified should an anomaly of clinical importance be observed, as is standard practice for INC/MRN images.

### Risk of Suicide

Chronic pain populations can have a higher risk of suicide.

## XVII. MANAGEMENT OF RISKS

### VR

A member of the research team will email or text subjects 3 days after receiving treatment to enquire about any adverse events. Additionally, participants will be asked to report any side effects (e.g., nausea) to the PI immediately, who will evaluate and act as appropriate. During the pre-screening, we confirm with each subject that they are comfortable with phone, email or text message communication, which is needed for completion of the Daily Pain Surveys described above.

### fMRI Scans

The MRI-related risks will be managed in the following way. The MRI scan will be performed using an MR scanner employing pulse sequences and hardware that have been approved by the FDA for human clinical use. The field strength is 3 Tesla and all relevant operating characteristics (RF power deposition, rate of change of the field gradients, coil design) fall within the limits of FDA guidelines for NMR exposure. Participants will be carefully screened to exclude those who may have metal in or on their bodies that cannot be removed (e g., bullets, metal filings, body piercings, etc.). MR Facility rules strictly forbid staff from entering the magnet room carrying metal objects. Additionally,

- Discomfort from scanner noise will be minimized with high-quality noise-blocking earbuds.
- Discomfort from laying in the scanner will be minimized by making sure the subject is lying comfortably with head and neck supported.
- With regard to PNS, participants are given a squeeze ball to use in case of an emergency. They are informed that if they experience PNS related sensations or are otherwise uncomfortable, they can alert the MRI technologist via the squeeze ball and the technologist will stop the scan immediately.
- The risk of claustrophobia is minimized by screening subjects for self-reported claustrophobia and, providing a mirror to see out, a button to signal distress, and an intercom.
- Pregnant women are excluded to minimize risk to the fetus. In accordance with standard INC procedures, female participants unsure as to whether they are pregnant will be given the opportunity to complete a urine pregnancy test immediately before the scanning period, and those with a positive result will not be scanned. Alternatively, female participants may sign a waiver that they do not believe themselves to be pregnant.

### Risk of Suicide

If a participant relays thoughts of suicide during any part of the project, the participant will be followed up with a clinically trained psychologist, who will provide a list of psychological resources, both on the college campus and within the community. If the psychologist forms the impression in the conversation that the participant is experiencing elaborated thoughts of suicide (including suicidal plans), a licensed clinical psychologist will be contacted immediately. If he / she is unavailable, the Boulder Community Hospital

Suicide line will be called. Additional action will be taken to ensure the subject's personal safety as per recommendations made for that specific subject.

### ADVERSE EVENTS

In addition to the above risk mitigation procedures, Dr. Marta Čeko will monitor any reports of adverse events and be responsible for reporting adverse events to the IRB. Participants will be encouraged to report immediately any side-effects via phone/text/email.

## XVIII. POTENTIAL BENEFITS

Subjects may experience a reduction in back pain and / or an improvement in quality of life (e.g. coping) from using the VRNT system.

The benefits to society stem from advancing scientific understanding of chronic pain, which imposes a large societal burden. This study will assess a novel virtual reality intervention for treating chronic pain.

## XIX. PROVISIONS TO MONITOR THE DATA FOR THE SAFETY OF PARTICIPANTS

A team member will contact subjects periodically and subjects are encouraged to report any issues immediately via phone/text/email. Any information concerning safety shall be reported to the PI's immediately.

The research team will monitor the weekly reports in order to maintain that participants are using the device correctly and responding to surveys. The PI's will monitor these reports and be responsible for reporting adverse events.

## XX. MEDICAL CARE AND COMPENSATION FOR INJURY

N/A

## XXI. COST TO PARTICIPANTS

There will be no cost to participants. Parking at CINC is free.

## XXII. DRUG ADMINISTRATION

N/A

## XXIII. INVESTIGATIONAL DEVICES

VRNT software is a developmental stage Investigational Device subject to regulation by the FDA; it is, thus, not available for marketing.

During the study, VRNT will not be altered, except as follows:

- **Bug Fixes:** necessary software modifications to fix any software bugs interfering with the proper functioning of VRNT

## XXIV. COLLABORATIVE STUDIES

CognifiSense team members will be involved in recruitment, participant education and the creation of VR representations of pain ("drawing" pain), surveys, follow-ups and analysis.

## XXV. SHARING OF RESULTS WITH PARTICIPANTS

There are no plans to share research results with participants. Participants will be offered structural MRI images of their brain immediately after the first scan session.