Research Paper

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The effects of virtual reality neuroscience-based therapy on clinical and neuroimaging outcomes in patients with chronic back pain: a randomized clinical trial

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Abstract

Chronic pain remains poorly managed. The integration of immersive technologies (ie, virtual reality [VR]) with neuroscience-based principles may provide effective pain treatment by targeting cognitive and affective neural processes that maintain pain and therefore potentially changing neurobiological circuits associated with pain chronification and amplification. We tested the effectiveness of a novel VR neuroscience-based therapy (VRNT) to improve pain-related outcomes in n = 31 participants with chronic back pain, evaluated against usual care (waitlist control; n = 30) in a 2-arm randomized clinical trial (NCT04468074). We also conducted pre-treatment and post-treatment MRI to test whether VRNT affects brain networks previously linked to chronic pain and treatment effects. Compared with the control condition, VRNT led to significantly reduced pain intensity (g = 0.63) and pain interference (g = 0.84) at post-treatment vs pre-treatment, with effects persisting at 2-week follow-up. These improvements were partially mediated by reduced kinesiophobia and pain catastrophizing. Several secondary clinical outcomes were also improved by VRNT, including disability, quality of life, sleep, and fatigue. In addition, VRNT was associated with increases in dorsomedial prefrontal functional connectivity with the superior somatomotor, anterior prefrontal and visual cortices, and decreased white matter fractional anisotropy in the corpus callosum adjacent to the anterior cingulate, relative to the control condition. Thus, VRNT showed preliminary efficacy in significantly reducing pain and improving overall functioning, possibly through changes in somatosensory and prefrontal brain networks.

Keywords: Chronic pain, Virtual reality, VR, Back pain, MRI

1. Introduction

Chronic musculoskeletal pain remains poorly managed, with leading behavioral interventions having generally small benefits in controlled trials.[27,30,65,95] The limited efficacy of behavioral approaches may stem from the fact that they are not guided by a conceptual model that places the brain as the centerpiece of the chronic pain experience, do not emphasize the possibility of substantially reducing pain by changing cognitive and affective processes that drive pain, and may lack powerful experiential exercises to change those thoughts and feelings.[50]

The integration of innovative immersive technologies with recent neuroscience-based behavioral approaches may provide a more effective pain treatment with potentially broader reach.[4,34,51,89,97] For example, virtual reality (VR) therapy can reduce pain during medical procedures and hospitalization, presumably by providing immersive distraction from pain.[28,34,72,75] More recently, VR-based interventions have shown preliminary efficacy as adjunctive[63] or stand-alone treatments for chronic or persistent pain.[22,23,55] Crucially, and in contrast to acute pain reduction afforded by distraction-based VR implementations, VR used for chronic pain has the potential for long-lasting pain relief,[29,89] likely reducing fearful beliefs about the bodily danger of pain and enhancing attributions of brain-based control of pain. Such cognitive and affective changes might be reflected in changes in neurobiological circuits associated with pain chronification and amplification.[5,9,62,65]

We created a VR self-management program for chronic back pain (CBP), "VR neuroscience-based therapy" (VRNT) to test the effect on clinical pain and brain outcomes. Virtual reality neuroscience-based therapy integrates contemporary pain and affect neuroscience by focusing on the brain as the key determinant of chronic pain experience through predictive processing by integrating nociceptive input with cognitive, emotional, and social factors.[5,26,42,62] In addition to a pain neuroscience education component, VRNT includes cognitive, behavioral, and affective exercises and experiences in the immersive virtual environment to increase real-time awareness of how the brain processes pain and decrease learned

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maladaptive cognitions and emotions, including catastrophizing and fear-related avoidance.

Chronic musculoskeletal pain has been associated with brain changes that reflect sensitization and neuroplasticity in distributed neural circuits,[2,6,8,9,10,16,29,37,38,41,42,44,48,49,61,62,73,86,94] including somatomotor and dorsolateral frontal cortices, mediofrontal-striatal circuitry, and default mode and cingulo-opercular networks, involved in somatomotor processes and sensory discrimination, reappraisal, self-reference, motivation, and attention allocation to salient stimuli. Limited evidence suggests that these brain changes could be partially reversed with successful behavioral treatments,[4,32,47,70,84,85] supporting the notion that pain-related maladaptive plasticity within these distributed large-scale neural networks could be normalized if pain is improved.[67]

The primary objective of this study was to assess the effectiveness of the VRNT program to reduce pain and improve functioning in patients with CBP. We hypothesized that VRNT would reduce pain intensity and interference compared with the waitlist control condition, with reductions in pain catastrophizing and kinesiophobia mediating the effects. We also conducted pre-treatment and post-treatment MRI and hypothesized that VRNT would affect structural and functional connectivity in the abovementioned brain networks associated with chronic pain and treatment effects.

2. Methods

2.1. Participants

Adults with CBP were recruited and enrolled through online advertising (Facebook) from the Boulder/Denver Colorado metro area. Inclusion criteria were aged 21 to 70 years, experiencing back pain on at least half the days of the past 6 months, and the average pain intensity over the last week of at least 4 of 10 at study entry. We excluded people with leg pain worse than back pain (to exclude those with neuropathic pain); other chronic pain besides CBP; major medical and neurological disorders; mental health disorders not controlled with medication; a history of substance abuse; pain-related compensation or litigation in the past year; a history of vertigo, dizziness, susceptibility to motion sickness, head injury within 6 months, (digital) eye strain, or computer vision syndrome; and standard MRI contraindications as determined by an MRI safety screen.

The institutional review board of the University of Colorado Boulder approved the study, and all participants provided written consent (through DocuSign). The study was preregistered on ClinicalTrials.gov (Identifier: NCT04468074). Study enrollment began in June 2020; randomization began in July 2020, and last follow-up was completed in June 2021. The study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines for social and psychological intervention (**Fig. 1**).[56]

2.2. Procedure

The study consisted of an 8-week VRNT program (or a waitlist control condition), with outcome measures (self-report measures, MRI) assessed at multiple timepoints. The consent process informed participants that they would be randomized into either the treatment condition ("VRNT") or waitlist condition ("control"), and that participants randomized to the waitlist condition would have the option to receive treatment after the main study was completed.

2.2.1. Study flow

Self-report measures were completed at home online (through Qualtrics), at study entry (week −2) and again at week 0 (with scores averaged across week −2 and 0 to create the pre-treatment timepoint), at post-treatment (week 8), and at 2-week follow-up (week 10). Several self-report measures were also collected at week 4 (midway through VRNT/control). MRI scans were collected at week 0 (pre-treatment MRI) and week 8 (post-treatment MRI). The study flow is depicted in **Figure 2A**.

2.2.2. Randomization

After the pre-treatment MRI, participants were randomized by a research assistant (using *random* in Python 3.7) to 1 of the 2 conditions (VRNT or control) in a 1:1 ratio, stratified by sex and age. Participants assigned to VRNT began the intervention immediately, whereas those assigned to the control condition were offered VRNT after the follow-up assessment.

2.2.3. Blinding

Research staff administering the MRI and analyzing data were blinded to condition assignment; participants were instructed not to discuss their assignment during these sessions. Research staff involved in recruitment, enrollment, and randomization were not involved in data analysis.

2.2.4. Standard care

All participants were encouraged to continue their standard care (eg, other medications and therapies, see **Table 1** for details), and standard care utilization was assessed at pre-treatment and post-treatment.

2.3. Intervention: virtual reality neuroscience-based therapy

The VRNT program was initiated by a 34-minute educational video (presented through Zoom), which introduced the neuroscience of acute and chronic pain, drivers of chronic pain (eg, catastrophizing, stress, and fear/fear-avoidance cycle), pain triggers, and the scientific principles behind VRNT. The study coordinator then worked with each VRNT participant to personalize the VRNT application by selecting a 3-dimensional avatar (from 9 different avatar options of male/female/neutral gender and body shapes/sizes) and creating a 3D-animated, audiovisual representation of the participant's own pain experiences (shape, color, sound, and animation) in the translucent avatar; see Supplementary Figure 1, http://links.lww.com/PAIN/C15 for an example. This final customized representation was loaded into a mobile VR device and provided to the participant to use at home for the 8 weeks. The mobile VR device was a Samsung GearVR (2017), which included a head-mounted display, a hand controller, and a Samsung Galaxy S-9 phone. Participants were asked to complete 2 VRNT modules per day, 5 days per week, for a total of 40 days of module completion. A calendar prescribed the sequence of modules to be completed but allowed the participant to choose some of the sessions. An accompanying workbook provided background on each module. In addition, weekly calls served to answer participants' questions, obtain feedback on VRNT modules, and assess and encourage program adherence.

The content of the VRNT program was organized into 17 different exercises or "modules" of varying duration (daily time for 2 modules: 7-27 minutes; average 20 minutes). Each module had a prerecorded voiceover, providing education and/or guiding the participant through the exercise while

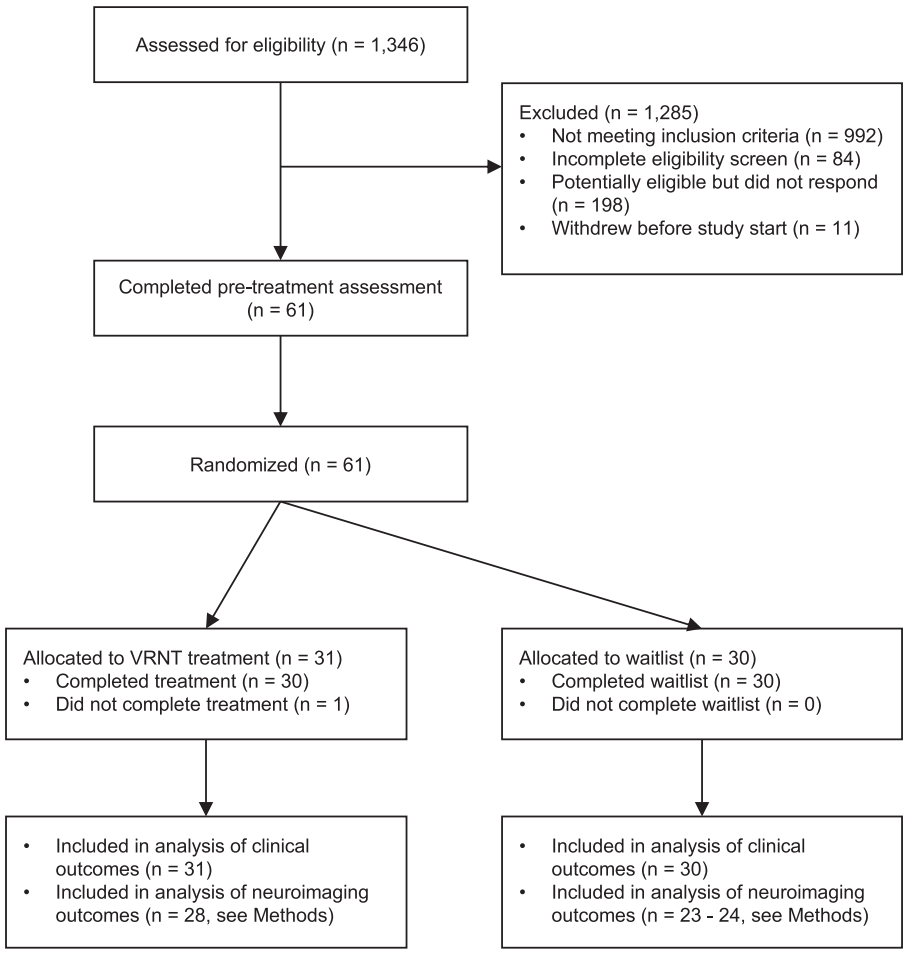

Figure 1. CONSORT participant flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

wearing the headset. Overall, the modules covered 8 categories, each with various techniques or exercises: (1) pain education (pain neuroscience and skills); (2) relaxation and mindfulness training (mindful scanning of the body and mindful detachment from thoughts and sensations); (3) interoception (identifying and labeling internal, usually somatic experiences); (4) mindful escapes, passive distraction, and shifting focus (distracting from pain and shifting focus toward or away from pain to improve attention control in real-world situations); (5) thought appraisal (tracking and evaluating automatic thoughts about pain); (6) diaphragmatic breathing (immersive breath training to support self-regulation and relaxation); (7) graded exposure therapy (hierarchical exposure of patients to their own pain, to pain triggers such as cold temperature, and to animated movements that commonly cause pain); and (8) emotion triggers (improving awareness and self-regulation of emotions). VRNT incorporates some techniques from traditional cognitive-behavioral pain management as well as newer approaches, such as pain reprocessing therapy (PRT) and emotional awareness and expression therapy (EAET), which have been shown to yield substantial pain reductions in several trials.[4,51,97] Consistent with these newer models, VRNT explicitly teaches participants about the reversibility of the central neuroplastic changes associated with pain chronification. VRNT also augments classic cognitive (neuroscience and skills) education with experiential learning by guiding the participant through self-discovery of how their own brain processes pain (eg, sensations, thoughts, and emotions); to this, VRNT leverages interoceptive modeling techniques in which the participant's own animated VR pain representation changes during the modules.

2.4. Measures

Following the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials[18] and National Institutes of Health Pain Consortium's Report on Research Standards for Chronic Low Back Pain,[17] we assessed multiple domains of self-report outcome measures. We had 2 primary outcomes (pain intensity and interference) and numerous secondary outcomes. All the outcomes and potential mediators listed below (except pain bothersomeness) were assessed twice at pre-treatment (weeks −2 and 0), and we averaged the 2 assessments to make a more reliable pre-treatment value of each measure.

2.5. Primary outcomes

2.5.1. Pain intensity

We used the single item ("average pain intensity over the past week"), rated 0 to 10, from the Short-Form Brief Pain Inventory (BPI-SF).[15] In addition to analyzing the condition means on this item, we also determined a clinically meaningful improvement as a reduction in pain intensity of at least 30% from pre-

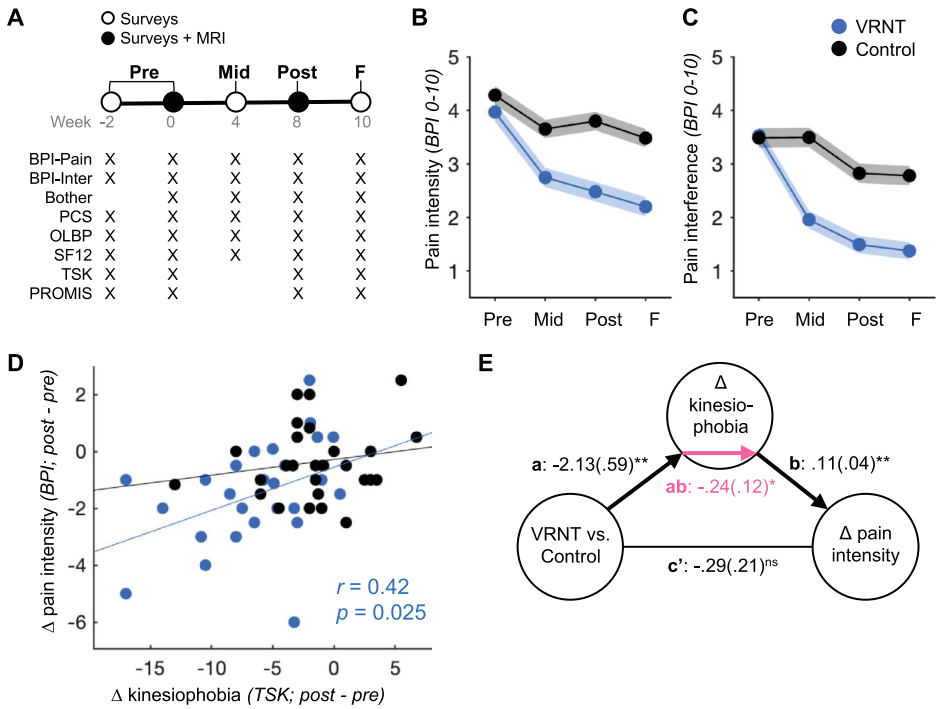

Figure 2. Treatment effects on behavioral outcomes. (A) The study design consisted of 5 assessments, including online questionnaires administered at week −2 and 0 (averaged as pre-treatment timepoint scores), at week 4 (mid-treatment timepoint), at week 8 (post-treatment timepoint), and at week 10 (follow-up timepoint) and 2 MRI sessions (at weeks 0 and 8). (B) Plot shows pain intensity levels per timepoint; shading indicates SE. (C) Plot shows pain interference levels per timepoint; shading indicates SE. (D) Scatter plot shows the relationship between the pain intensity post–pre difference score and the kinesiophobia post–pre difference score for each individual. (E) Mediation analysis testing whether the kinesiophobia post–pre difference score mediates the relationship between condition assignment (VRNT, control) and the pain intensity post–pre difference score. Mediation coefficients tested for significance using 10,000 bootstrap samples. $^{**}P < 0.01$; 2-sided tests. Bother, bothersomeness; BPI, brief pain inventory; BPI-Inter, pain interference; BPI-Pain, pain intensity; F, follow-up; Mid, mid-treatment; OLBP, Oswestry Low Back Pain Questionnaire; PCS, Pain Catastrophizing Scale; Post, post-treatment; Pre, pre-treatment; PROMIS, Patient-Reported Outcomes Measurement Information System; SF12, Short-Form Quality of Life Questionnaire; TSK, Tampa Scale of Kinesiophobia; VRNT, virtual reality neuroscience-based therapy.

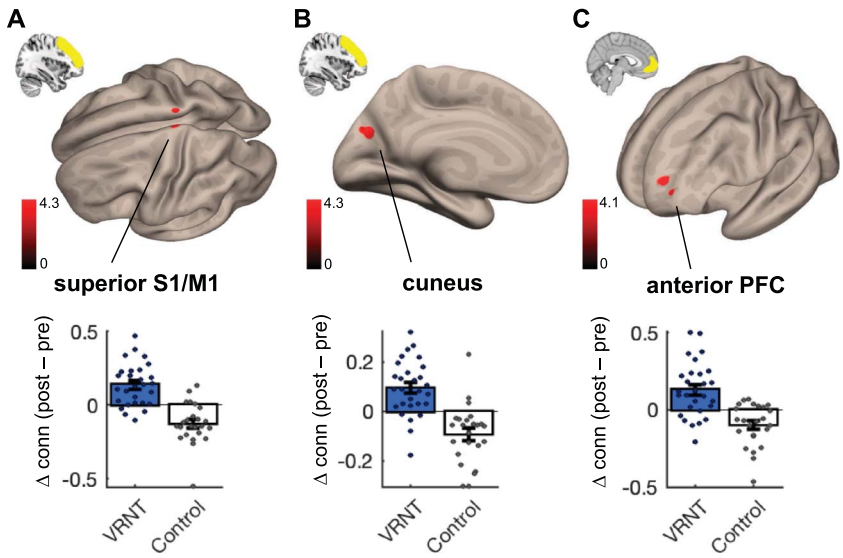

Figure 3. Treatment effects on functional connectivity. (A–C) Brain maps show clusters of significant condition by time interaction, controlled for age and sex, of brain-wide correlation coefficient ("functional connectivity") maps for each ROI (left dLPFC, right dLPFC, MPFC; shown in yellow); cluster-forming threshold $P < 0.001$, $P < 0.05$ FWE-corrected; 2 × 2 ANOVA with 2 conditions (VRNT, control) and 2 timepoints (pre, post); computed with CONN toolbox (20.b; SPM 12, MATLAB 2018b). Bar plots show connectivity post–pre difference scores between ROI and selected regions; dots are individual scores; bars are mean and SE; blue, VRNT; white, control. S1/M1, primary somatomotor cortex; PFC, prefrontal cortex.

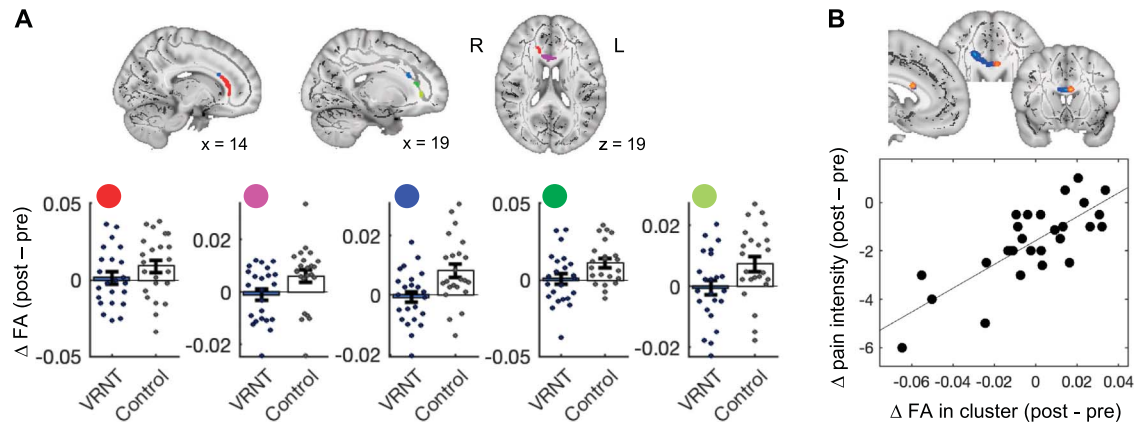

Figure 4. Treatment effects on white matter fractional anisotropy (FA). (A) Brain maps show clusters of significant condition by time interaction, controlled for age and sex, of white matter FA tested across the entire white matter skeleton; $P < 0.05$ TBSE-corrected; 2-sided t test of difference maps (VRNT (post-pre), control (post-pre)) computed with TBSS in FSL. Bar plots show FA post–pre difference scores; dots are individual scores; bars are mean and SE; blue, VRNT; white, control. (B) Scatter plot shows for each individual participant the relationship between the pain intensity post–pre difference score and FA post–pre difference scores in the area of significant condition by time interaction, controlled for age and sex. L, left; R, right.

Table 1

Sample characteristics at study entry.

	VRNT (n = 31)	Control (n = 30)	*P*
Age (y), mean (SD)	34.8 (9.9)	33.5 (9.2)	0.60
Sex (M, F)	16 (53%), 15 (47%)	15 (50%), 15 (50%)	0.99
Pain duration (y), mean (SD)	8.7 (6.1)	8.4 (8.1)	0.90
Race			
White	28	27	0.97
Black	1	2	
Native Hawaiian or Pacific Islander	0	1	
American Indian or Alaska Native	2	0	
Asian	0	0	
BMI	27.1 (5.1)	27.0 (5.3)	0.94
Education			
High school and some college	15	15	0.68
College	8	10	
More than college	8	5	
Employment status (full-time, other)			
Full-time	21	20	0.93
Other	10	10	
Annual income ($ K per year), mean (SD)	84.1 (94.8)	71.6 (56.4)	
Current medication (past 4 wk)*			
Over-the-counter pain relievers	24	16	0.71
Anxiety medication	1	3	
Antidepressants	1	1	
Anticonvulsants	2	1	
Cannabinoids	13	8	
Current therapies (past 4 wk)*			
Therapeutic exercise (eg, PT, OT, and prescribed home exercise)	13	14	0.97
Hands-on treatment (eg, massage, chiropractic adjustment, and acupuncture)	12	10	
Modality treatment (eg, TENS, ice or hot pack, and menthol crème product)	14	15	
Behavioral/mental health treatment (eg, from a psychologist, licensed social worker, mental health counselor, and therapist)	0	1	

P-values are derived from a 2-sample t test or from a χ^2 test (across subcategories).
* Response missing in some participants.

Table 2

Primary and secondary clinical self-report outcomes.

	VRNT (n = 31) M (SD)	Control (n = 30) M (SD)	Condition by time	
			Effect size*	*P*
Primary outcomes				
Pain intensity (BPI-SF, range 0-10)				
Pre-treatment	4.0 (1.2)	4.3 (1.4)		
Mid-treatment	2.7 (1.5)	3.6 (1.7)	0.41	0.106
Post-treatment	2.5 (1.6)	3.8 (1.8)	0.63	0.014
Follow-up	2.2 (1.7)	3.5 (1.7)	0.74	0.006
Pain interference (BPI-SF, range 0-10)				
Pre-treatment	3.5 (1.4)	3.5 (1.6)		
Mid-treatment	2.0 (1.5)	3.5 (1.8)	1.07	<0.001
Post-treatment	1.5 (1.4)	2.8 (2.0)	0.84	0.002
Follow-up	1.4 (1.4)	2.8 (2.2)	0.92	<0.001
Secondary outcomes				
Pain bothersomeness (Bother, range 0-10)†				
Pre-treatment	3.3 (1.7)	3.9 (1.7)		
Mid-treatment	2.3 (1.7)	3.1 (3.2)	0.05	0.767
Post-treatment	1.9 (1.6)	3.3 (2.5)	0.39	0.105
Follow-up	1.5 (1.7)	3.1 (2.2)	0.43	0.067
Quality of life (SF-12, range 0-100)‡				
Pre-treatment	45.7 (5.1)	45.2 (5.4)		
Mid-treatment	47.8 (6.0)	43.9 (5.6)	0.97	<0.001
Post-treatment	49.3 (4.9)	46.1 (6.0)	0.63	0.016
Follow-up	49.6 (4.9)	46.0 (6.4)	0.70	0.007
Disability (OLBPQ, range 0-50)				
Pre-treatment	11.4 (5.2)	10.5 (4.2)		
Mid-treatment	7.7 (4.1)	12.2 (5.9)	1.33	<0.001
Post-treatment	7.2 (3.9)	10.1 (6.4)	0.75	0.007
Follow-up	6.3 (3.6)	10.3 (7.2)	0.90	<0.001
Anxiety (PROMIS, range 8-40)				
Pre-treatment	19.5 (6.7)	20.7 (5.1)		
Post-treatment	17.3 (6.7)	19.8 (6.0)	0.29	0.271
Follow-up	17.0 (6.7)	19.2 (5.8)	0.09	0.617
Depression (PROMIS, range 8-40)				
Pre-treatment	15.8 (6.8)	16.7 (6.2)		
Post-treatment	14.4 (6.4)	16.3 (6.0)	0.13	0.548
Follow-up	14.3 (6.5)	17.5 (7.2)	0.31	0.177
Anger (PROMIS, range 5-25)				
Pre-treatment	12.3 (3.3)	12.7 (4.2)		
Post-treatment	11.4 (3.5)	12.3 (4.1)	0.14	0.572
Follow-up	10.7 (3.2)	13.0 (3.7)	0.46	0.087
Sleep problems (PROMIS, range 8-40)				
Pre-treatment	24.1 (6.6)	24.6 (7.8)		
Post-treatment	20.5 (6.8)	24.7 (8.4)	0.71	0.008
Follow-up	20.0 (6.4)	23.9 (7.4)	0.63	0.015
Fatigue (PROMIS, range 8-40)				
Pre-treatment	22.8 (6.7)	23.1 (8.1)		
Post-treatment	19.8 (7.0)	23.0 (7.8)	0.61	0.022
Follow-up	19.5 (6.2)	23.4 (8.7)	0.50	0.037

* Effect sizes show the group difference in change from pre-treatment (condition by time interaction). Effect size (Hedges' g) estimated with bootstrapping procedure (10,000 samples).
† Score based on pre-treatment 2 assessment (no data available from pre-treatment 1 assessment).
‡ Higher score indicates better physical and mental health functioning.
BPI-SF, Brief Pain Inventory, short form; M, mean; PROMIS, Patient-Reported Outcomes Measurement Information System; SF-12, Health Survey, short form.

treatment (post-treatment minus pre-treatment) and substantial pain reduction as at least 50% from pre-treatment.[87,98]

2.5.2. Pain interference

We averaged the ratings (0-10) of the 7 items from the BPI-SF pain interference subscale to assess the degree to which participants' pain interfered with daily life activities over the past week. Again, we analyzed both the condition means and the frequency of clinically meaningful (at least 30%) and substantial (at least 50%) reductions in interference pre-treatment.

2.6. Secondary outcomes

2.6.1. Pain bothersomeness

Back pain bothersomeness over the past week was assessed using a 0 to 10 rating, as used previously.[12]

2.6.2. Pain-related disability

The 10 items of the Oswestry Low Back Pain Disability Questionnaire (OLBPQ)[20] were summed.

Table 3

Potential mediators of treatment.

	VRNT (n = 31) M (SD)	Control (n = 30) M (SD)	Effect size*	P
Pain catastrophizing (PCS-13, range 0-52)				
Pre-treatment	20.3 (9.8)	20.9 (9.5)		
Post-treatment	9.8 (7.5)	17.5 (11.4)	0.86	0.0019
Follow-up	9.4 (9.2)	21.9 (14.1)	1.09	<0.001
Fear of movement (TSK-11, range 11-44)				
Pre-treatment	27.0 (4.9)	27.3 (4.9)		
Post-treatment	21.3 (5.0)	25.6 (6.0)	0.94	0.007
Follow-up	21.1 (5.2)	25.0 (5.9)	0.63	0.0169

* Effect sizes show the condition difference in change from pre-treatment (condition by time interaction). Effect size (Hedges' g) estimated with bootstrapping procedure (10,000 samples).

2.6.3. Psychological distress

Short-form measures from the Patient-Reported Outcomes Measurement Information System (PROMIS)[46,76]; assessed depressive symptoms (form 8a), anxiety (form 8a), and anger (form 5a) over the past week; and sums of item ratings for each separate scale were analyzed.

2.6.4. Sleep

The PROMIS measure (form 8a) assessed sleep quality over the past week; the sum of items was analyzed.

2.6.5. Fatigue

The PROMIS measure (form 8a) assessed fatigue over the past week; the sum of items was analyzed.

2.6.6. Quality of life

The Short-Form Health Survey (SF-12)[93] assessed the impact of health on everyday life. The final score was averaged across 2 subscale scores (mental health and physical health).

2.7. Potential treatment mediators

Two variables were examined as potential mediators of treatment effects on the primary outcomes.

2.7.1. Kinesiophobia

The 11-item Tampa Scale of Kinesiophobia (TSK[86]) assessed fear of movement and beliefs that pain indicates injury. Item ratings were summed.

2.7.2. Pain catastrophizing

The 13-item Pain Catastrophizing Scale[77] assessed rumination, magnification, and helplessness related to pain. Item ratings were summed.

Other potential mediators included fear of pain, pain attitudes, self-efficacy, optimism, meaning and purpose in life, mindfulness, and emotion regulation capacity. Results of analyses of these variables are reported in Supplementary Table 1, http://links.lww.com/PAIN/C15.

2.8. Secondary neuroimaging outcomes

We collected several neuroimaging outcomes as secondary outcomes to establish preliminary brain mechanisms associated with treatment response. Neuroimaging outcomes comprised 2 types of images: resting-state MRI suitable for analysis of functional connectivity between brain regions and diffusion-weighted images (DWI) suitable for the analysis of white matter fractional anisotropy (FA), indicative of structural white matter integrity between brain regions.

Table 4

Resting-state functional connectivity, significant condition by time interaction results.

Results per seed	L/R	MNI (x, y, z)	Size (voxels)	P* (P < 0.05 FWE-corr.)
Increased connectivity				
dLPFC L				
S1/M1	L	2, −26, 76	15	0.026345
dLPFC R				
Cuneus	L	−10, −78, 28	20	0.003744
MPFC (anterior DMN)				
aPFC	L	−28, 60, 6	16	0.024830
aMCC, aINS L, aINS R (cingulo-opercular network)				
No significant clusters				
Decreased connectivity				
NAc L				
MOG	L	−50, −74, 10	28	0.000277
NAc R				
No significant clusters				

Increased connectivity indicates VRNT > control, post > pre; decreased connectivity indicates VRNT < control, post > pre.

* Derived from a 2 × 2 ANOVA GLM, controlling for age and sex; cluster-forming threshold $P < 0.001$ (t (48) > 3.27) across the brain.

aINS, anterior insula; aMCC, anterior midcingulate cortex; aPFC, anterior prefrontal cortex; dLPFC, dorsolateral prefrontal cortex; DMN, default mode network; L, left; MOG, middle occipital gyrus; MPFC, medial prefrontal cortex; NAc, nucleus accumbens; R, right; S1/M1, primary somatomotor cortex.

Table 5

White matter results.

Region	L/R	MNI (x, y, z)	Size (voxels)	Peak t-value*	P† (TFCE-corr.)
Condition by time interaction					
Corpus callosum	R	14, 30, 13	86	−2.29	<0.05
	R	4, 19, 17	48	−2.73	<0.05
	R	17, 25, 22	32	−3.06	<0.05
	R	19, 34,14	14	−2.58	<0.05
	R	19, 40, 1	13	−2.88	<0.05
Correlation with pain reduction in the VRNT condition‡					
Corpus callosum	L	−4, 16, 20	3	6.03	<0.05

* Value derived from unpaired *t* test of difference maps (VRNT condition (post-pre) − control condition (post-pre)).
† Two-sided test.
‡ Examined for regions showing significant condition by time interaction.

2.9. MRI acquisition

Neuroimaging outcomes were collected at pre-treatment session 2 and at post-treatment. Whole-brain fMRI data were acquired on a 3T Siemens MAGNETOM Prisma MRI scanner at the Intermountain Neuroimaging Consortium facility at the University of Colorado, Boulder. Structural images were acquired using high-resolution T1 spoiled gradient recall images (SPGR) and were used for anatomical localization and warping to standard MNI space only. Functional images were acquired with a multiband echo-planar imaging (EPI) sequence (TR = 460 ms, TE = 27.2 ms, field of view = 220 mm, multiband acceleration factor = 8, flip angle = 44°, 64 × 64 matrix, 2.7 × 2.7 × 2.7-mm voxels, 56 interleaved ascending slices, and phase encoding posterior >> anterior). One resting-state functional scan of 6-minute duration was acquired. Participants were instructed to keep their eyes open, focus on the crosshair in the middle of the screen, and remain as still as possible during the scan. Diffusion-weighted images were acquired with a single-shot, multiband, multishell protocol (TR = 4000 ms, TE = 77.0 ms, multiband acceleration factor = 3, field of view = 224 mm, 52 × 52 matrix, 2.0 × 2.0 × 2.0-mm voxels, interleaved 72 slices, and total duration ~ 12 minutes) with 4 diffusion-weighted shells at b = 2400 s/mm^2 with varying diffusion directions (44, 47, 42, and 40).

2.10. MRI data preprocessing

MRI data were preprocessed using standardized pipelines with default settings, with steps summarized in Supplementary Methods, http://links.lww.com/PAIN/C15. Anatomical and resting-state data were preprocessed using *fmriprep* 21.0.0,[19] which is based on *nipype* 1.6.1.[24] Diffusion-weighted image (white matter) data were preprocessed using QSIPrep,[13] and FA maps were derived using DTIFIT in FSL by fitting a diffusion tensor model in each voxel of the preprocessed DWI data and calculating voxelwise FA values.

2.11. Statistical analyses

2.11.1. Sample size estimation

Power analysis using G*power[21] targeted 80% power ($\alpha = 0.05$) to detect a large effect (f = 0.40) on pain intensity at post-treatment. The large effect size estimate was based on studies of several non-VR therapies that share VRNT's conceptual framework of the importance of experiential learning to change brain processes that generate or amplify pain: movement representation techniques such as mirror therapy,[83] pain reprocessing therapy,[4] and emotional awareness and expression therapy.[97] A total sample of 52 was needed, and we overrecruited slightly, expecting some attrition.

2.11.2. Treatment effects on primary and secondary self-report outcomes

Intent-to-treat analyses (including all randomized patients) were performed for primary and secondary outcomes using a mixed-effects model (fitlme, MATLAB 2020b), including a condition by time interaction (VRNT vs control x post-treatment vs pre-treatment), covariates for age and sex, and a random intercept per participant. For further analyses, change scores were post-treatment minus pre-treatment for participants with available pre-treatment and post-treatment data (N = 30 per condition). Treatment effect sizes were calculated as the VRNT vs control difference in change scores divided by the pooled SD of change scores, with the Hedge's *g* correction and bootstrapped (n = 10,000) confidence intervals (mes toolbox,[26] MATLAB 2020b). Conditions were compared on frequency of at least 30% and 50% improvement from pre-treatment to post-treatment) on the 2 primary outcomes through chi-square tests (https://www.socscistatistics.com/tests/chisquare/).

2.11.3. Potential mediators of treatment

To examine potential mechanisms of VRNT treatment, we first compared the VRNT and control conditions on change in potential mediators using the same approach as for outcomes (condition by time interaction analyses, controlled for age and sex). Next, we computed Pearson correlations between mediator change and primary outcome change scores for the entire sample, and significant correlations were examined further with a formal mediation analysis, which tested whether a change in the mediator accounted for treatment condition effects on change in each primary outcome (ie, VRNT vs control → Δ potential mediator → Δ primary treatment outcome). Mediation analyses were computed using the Canlab Mediation Toolbox (MATLAB 2020b).[92] Statistical significance of mediation was derived with 10,000 bootstrapped iterations.

2.11.4. Functional connectivity analysis of resting-state fMRI data

Resting-state data were "denoised" and analyzed using CONN 20.b (SPM12, MATLAB 2018b). Denoising included band-pass filtering (0.008-0.09 Hz), and motion correction[14,60,64] by regressing out

signals from the white matter (5 components) and CSF (5 components) to remove physiological noise, and low-frequency signal as well as "despiking" to remove the influence of any remaining motion spikes from the data.

2.11.4.1. Condition by time interaction analysis

For each participant, the mean time series in each seed was correlated with the time series of each gray matter voxel. Correlation coefficient *(r)* maps were examined for condition by time interactions, controlling for age and sex, using the GLM framework with 2 conditions (VRNT and control) as "subject effects," 2 timepoints as "conditions") and the default canonical resting-state networks as "seeds/sources." The between-subject contrast for [VRNT control condition age sex] was set to [1 −1 0 0], and the between-condition contrast for [pre post] was set to [−1 1]. The resulting statistical maps were thresholded at a voxelwise cluster-forming threshold of $P < 0.001$ uncorr. ($t > 3.27$) familywise error (FWE)-corrected for multiple comparisons at $P < 0.05$ across the brain. Based on previous literature implicating functional brain circuitries in chronic pain (and effects of treatment), the functional connectivity analyses were performed using the following seeds of interest in CONN: "SM.Superior," "SM.Lateral Left," and "SM.Lateral Right" (somatomotor network (SM)); "MidFG L" and "MidFG R" (dorsolateral prefrontal cortex (dLPFC)); "DMN.mpfc" and "DMN.pcc" (default mode network (DMN), comprising medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC)); "Accumbens.L" and "Accumbens.R" (nucleus accumbens (NAc)); and "aMCC," "aINS Left," and "aINS Right" (cingulo-opercular network comprising anterior midcingulate (aMCC) and anterior insula (aINS)).

2.11.4.2. Relationship of treatment effects with pain reduction

The relationship between VRNT effects on pre-to-post resting-state connectivity and pain reduction was examined in networks showing a significant condition by time interaction, while controlling for age and sex. The between-subject contrast for [VRNT WL delta_pain_VRNT delta_pain_WL age sex] was set to [0 0 1 −1 0 0], and the between-condition contrast for [pre post] was set to [−1 1]. As above, a voxelwise cluster-forming threshold of $P < 0.001$ across the whole brain, FWE-corrected for multiple comparisons at $P < 0.05$, was used.

2.11.5. Fractional anisotropy analysis of white matter diffusion-weighted image data

2.11.5.1. Condition by time interaction analysis

Statistical analysis of the white matter FA was performed using Tract-Based Spatial Statistics (TBSS) [74] in FSL. First, pre–post FA difference maps were created for each participant by subtracting the pre from post maps. TBSS was performed using *randomise*, a permutation-based inference tool for nonparametric statistical thresholding, with the number of permutations set at 5000. For condition comparisons of pre–post FA difference maps, we used GLMs controlling for age and sex, with cluster correction for multiple comparisons across the whole brain set at $P < 0.05$ (2-sided) using threshold-free cluster enhancement (TFCE) with default parameters (H = 2, E = 0.5).

2.11.5.2. Regression with pain reduction

The relationship between pre–post FA and pre–post pain reduction was examined in the VRNT condition in the mask of regions showing a significant condition by time effect, controlling for age and sex and cluster-corrected across the mask at $P < 0.05$ (2-sided) using TFCE, as above.

3. Results

As shown in **Figure 1**, we randomized 61 participants (31 male, 30 female; age M = 34.3 years, SD = 9.6; pain duration M = 8.5 years, SD = 7.1) into VRNT vs control, which had comparable sociodemographic characteristics across the 2 conditions (**Table 1**). Of the 31 participants randomized to VRNT, 30 completed treatment and all online assessments (one participant dropped out mid-treatment because of time constraints), and all 30 control participants completed all online assessments. Both pre-MRI and post-MRI sessions were completed by 28 VRNT participants and 24 control participants (**Fig. 1**).

3.1. Treatment effects on primary and secondary self-report outcomes

The VRNT condition reported significantly reduced pain intensity at post-treatment vs pre-treatment, compared with the control condition (condition by time interaction controlled for age and sex, $g = 0.63$, medium-to-large effect size, $P = 0.014$; mean (SD) values at each timepoint are listed in **Table 2**). The VRNT condition averaged 35.9% ± (SD) 40.4 reduction in pain intensity vs 11.9% ± 38.6 in the control condition, **Fig. 2B**, **Table 2**). Clinically meaningful pain intensity reduction (ie, at least 30% from pre-treatment) was observed in 60% (18/30) of VRNT participants compared with 30% (9/30) of controls ($X^2 = 5.45$, $P = 0.019$), and substantial reduction (at least 50%) was observed in 47% (14/30) of VRNT participants compared with 13% (4/30) of controls ($X^2 = 7.94$, $P = 0.005$).

Similar to the findings with pain intensity, the VRNT condition had significantly greater reduction in pain interference at post-treatment vs pre-treatment, compared with the control condition (condition by time interaction controlled for age and sex $g = 0.84$, large effect size, $P = 0.002$; mean (SD) values at each timepoint are listed in **Table 2**). The VRNT condition averaged 56.3% ± 37.1 reduction in pain interference vs 10.6% ± 73.5 reduction in the control condition, **Fig. 2C**, **Table 2**). At least 30% reduction in pain interference was observed in 77% (23/30) of VRNT participants compared with 53% (16/30) of controls ($X^2 = 3.59$, $P = 0.058$), and an at least 50% reduction was observed in 60% (18/30) of VRNT participants compared with 30% (9/30) of controls ($X^2 = 5.45$, $P = 0.019$).

Improvements on primary outcomes were significantly correlated with each other ($r = 0.42$, $P = 0.025$; **Fig. 2D**). Treatment effects for both outcomes were already evident at mid-treatment (**Table 2**) and continued to improve at 2-week follow-up (slightly larger between-condition effect sizes on both primary outcomes than at post-treatment), indicating some lasting effects of VRNT and possibly continued improvement on pain outcomes (**Table 2**).

The VRNT condition also had significant improvements compared with the control condition on several secondary outcomes at post-treatment, with medium to large effect sizes (**Table 2**): reduced disability (condition x time interaction: $g = 0.75$, $P = 0.01$), improved quality of life ($g = 0.63$, $P = 0.016$), reduced sleep problems ($g = 0.71$, $P = 0.008$), and reduced fatigue ($g = 0.61$, $P = 0.022$). As observed above for primary outcomes, treatment effects were largely already evident at mid-treatment (if assessed) and persisted at follow-up. Pain bothersomeness showed a similar but weaker trend that was not

significant ($g = 0.39$, $P = 0.105$), and the treatment effects on measures of psychological distress were not significant for anxiety ($P = 0.271$), depressive symptoms ($P = 0.548$), or anger ($P = 0.572$).

3.2. Potential mediators of treatment

Compared with the control condition, the VRNT condition reported significant improvements at post-treatment in pain catastrophizing (condition by time interaction controlled for age and sex: $g = 0.86$, $P = 0.002$) and kinesiophobia ($g = 0.94$, $P = 0.007$; **Table 3**), with large effects. Although kinesiophobia and pain catastrophizing were significantly correlated (at baseline $r = 0.56$, $P < 0.001$; pre-treatment to post-treatment change scores $r = 0.52$, $P < 0.001$), suggesting they are partially overlapping constructs, their change scores were differentially related to changes on the primary outcomes (pain intensity and pain interference), regardless of condition. Across the full sample (VRNT and control conditions combined), the change in kinesiophobia correlated positively with the change in pain intensity ($r = 0.42$, $P = 0.001$) and in pain interference ($r = 0.54$, $P < 0.001$), whereas the change in pain catastrophizing correlated positively with the change in pain interference only ($r = 0.35$, $P = 0.008$; correlation with pain intensity $r = 0.15$, $P = 0.280$). For the significant correlations with primary outcomes in the full sample, we next tested whether changes in kinesophobia and pain catastrophizing mediated the effect of VRNT vs control on changes in the relevant primary outcomes. The mediation path VRNT vs control → Δ TSK → Δ pain intensity was significant; that is, the reduction in kinesiophobia fully mediated the reduction in pain intensity from VRNT ($\beta_{ab} = -0.24$, $P = 0.031$; β_c (direct effect) $= -0.53$, $P = 0.009$, $\beta_{c'}$ (controlling for mediator) $= -0.29$, $P = 0.178$ **Fig. 2E**). The reduction in kinesiophobia also fully mediated the reduction in pain interference from VRNT (VRNT vs control → Δ TSK → Δ pain interference: $\beta_{ab} = -0.35$, $P = 0.002$; β_c (direct effect) $= -0.69$, $P = 0.001$, $\beta_{c'}$ (controlling for mediator) $= -0.35$, $P = 0.127$). Finally, the reduction in pain catastrophizing partially mediated the reduction in pain interference from VRNT (VRNT vs control → Δ PCS → Δ pain interference: $\beta_{ab} = -0.16$, $P = 0.048$; β_c (direct effect) $= -0.69$, $P < 0.001$, $\beta_{c'}$ (controlling for mediator) $= -0.53$, $P = 0.029$).

3.3. Treatment effects on secondary brain outcomes

Of participants who had available pre-MRI and post-MRI data, all were included in the resting-state analysis, and one participant's data were excluded from the white matter analysis, for final included samples of resting-state analysis, 28 VRNT, 24 control; white matter analysis, 28 VRNT, 23 control.

3.3.1. Resting-state fMRI functional connectivity

We tested treatment effects on functional connectivity of brain circuitries implicated in chronic back pain and shown to be affected by treatment, comprising the somatomotor cortices, dLPFC, midline aspects of the DMN (PCC, MPFC), NAc, and the cingulo-opercular network (aMCC, aINS). We observed significant condition by time interaction (controlled for age and sex) in functional connectivity between lateral prefrontal cortices and somatomotor, medial prefrontal and visual cortices, with the VRNT condition showing in both networks increased resting-state connectivity after treatment vs control condition (**Table 4**). Specifically, in the VRNT condition, the left dLPFC had significantly increased connectivity with the bilateral superior somatomotor cortex (T (48) = 6.76) and the right dLPFC with the left cuneus (T (48) = 6.05; **Figs. 3A and B**; $P < 0.05$ FWE-corr., see **Table 4** for exact values). The MPFC (anterior DMN) had significantly increased connectivity after treatment vs control condition with the left anterior LPFC (T (48) = 5.23, $P <$ 0.05 FWE-corr.; **Fig. 3C**, **Table 4**). No significant condition by time interaction effects (controlled for age and sex) were observed for the connectivity of the cingulo-opercular network nor the somatomotor network at this threshold. When examined at a more liberal statistical threshold (cluster-forming threshold of $P < 0.005$ (instead of $P < 0.001$), $P < 0.05$ FWE-corr.; reported in Supplementary Table 2, http://links.lww.com/PAIN/C15), the findings overall also converge onto VRNT-related increases in prefrontal—somatomotor and medial—dorsal prefrontal connectivity, among other findings.

We also tested the connectivity of the NAc to examine any treatment effects on the mediofrontal-striatal (NAc-MPFC) circuitry implicated in chronic pain. No significant condition by time interaction effects (controlled for age and sex) were observed for the connectivity of either left or right NAc with MPFC. However, left NAc had significantly decreased connectivity after treatment vs control with the left middle occipital gyrus (T (48) $= -7.52$, $P <$ 0.05 FWE-corr., **Table 4**).

We observed no significant relationship between VRNT-related changes in functional connectivity and pain reduction in regions showing significant condition by time interactions listed in **Table 4**.

3.3.2. White matter fractional anisotropy

We observed several clusters showing significant condition by time interaction (controlled for age and sex) in FA in the white matter adjacent to the aMCC (largely in the right corpus callosum, **Table 5**), with the VRNT condition showing decreased FA with treatment as compared to the control condition (**Fig. 4A**). Within this region, we observed a cluster where the pre-to-post FA reduction in the VRNT condition was significantly positively correlated with the pre-to-post pain reduction (**Fig. 4B**).

3.4. Secondary analyses

3.4.1. Healthcare utilization

All participants—both VRNT and waitlist control—continued to receive their usual care, as is standard in behavioral trials. The usual care consisted of medications and various therapies, as listed in **Table 1**. At the 8-week post-treatment assessment, most participants reported no change in medication, except for one VRNT participant (discontinued several medications) and one control participant (added CBD cream). All participants in both arms (except one VRNT participant at post-treatment) reporting using at least one type of medication or therapy (see **Table 2** for the full list) at both pre-treatment and post-treatment. The average (SD) number of used types of medication or therapy was 3.33 (1.26) at pre-treatment, and this number remained largely unchanged at post-treatment (3.05 (1.63); paired $t = 0.16$; pre-treatment and post-treatment assessments available in n = 37 participants). We also assessed the frequency of healthcare utilization for each participant for each type of medication/therapy. Averaged across participants, 45% of health care was used at unchanged frequency at post-treatment vs pre-treatment. Of the remaining 55%, the pattern of frequency change was similar in both arms, with a similar number of participants in each arm reporting a mostly minor change in frequency across their medications or therapies (overall

decrease/overall increase/"switch," ie, decrease in some and increase in others: number of participants per category in VRNT 13/3/5, control 7/5/3; chi-square 1.8, 2-tailed $P = 0.4$).

3.4.2. Virtual reality neuroscience-based therapy effects in the waitlist control condition

After the conclusion of the main study, the control condition participants, who had been waitlisted during the primary study, were offered the VRNT treatment (In this poststudy period, the main-study 2-week follow-up served as the pre-treatment assessment, followed by a post-treatment assessment 8 weeks later and a 2-week follow-up). A total of 18 of the 30 control participants opted to complete VRNT. We found significant reductions in pain intensity (pre to post $t = 4.38$, $P < 0.001$, $g = 0.72$, pre to follow-up $t = 4.78$, $P < 0.001$, $g = 0.58$) and pain interference (pre to post $t = 2.76$, $P = 0.014$, $g = 0.70$, pre to follow-up $t = 2.49$, $P = 0.024$, $g = 0.56$; see Supplementary Table 3, http://links.lww.com/PAIN/C15 for data). These medium- to large-effect improvements are generally consistent with the within-condition changes in pain intensity and interferences observed for participants randomized to VRNT in the primary study: change in pain intensity pre to post $t = 4.63$, $P < 0.001$, $g = 0.98$, pre to follow-up $t = 6.33$, $P < 0.001$, $g = 0.98$; change in pain interference pre to post $t = 7.07$, $P < 0.001$, $g = 1.14$; pre to follow-up $t = 8.09$, $P < 0.001$, $g = 1.46$ (see data in **Table 2**).

4. Discussion

We tested the effects of a VR behavioral intervention (VRNT) on clinical and brain outcomes in patients with CBP. Compared with waitlisted controls, VRNT led to significantly reduced pain intensity and pain interference at post-treatment, which persisted at 2-week follow-up, and these effects were partially mediated by a reduction in kinesiophobia and pain catastrophizing. Several secondary outcomes were also improved including disability, quality of life, sleep, and fatigue. In addition, VRNT was associated with significant brain changes compared with the waitlist control condition.

Virtual reality neuroscience-based therapy demonstrated clinically substantial reductions in pain intensity and pain interference, with medium to large between-condition effect sizes. Nearly half of participants receiving VRNT obtained 50% or greater pain reduction (compared with 13% of waitlist controls), and VRNT doubled the frequency of obtaining 50% or greater reduction in pain interference (60% vs 30% in controls). These effects seem to exceed the effects of leading behavioral/psychological therapies—CBT and acceptance and mindfulness-based therapies.[27,30,61,88,95] The limited efficacy of these latter approaches may be due to the fact they are not guided by contemporary conceptual models of pain that place the brain as the centerpiece of a changeable—even potentially reversible—chronic pain experience, and their exercises/techniques may not be experientially powerful. Newer therapies based on this model—such as PRT and EAET—have yielded substantial pain reduction,[4,50] including superior outcomes to CBT on some pain-related variables in 2 trials.[51,97] This suggests that interventions targeting the brain's role in chronic pain, as in VRNT, by changing one's attributions for the etiology of the pain (from body to brain) and reducing pain-related and broader emotional and interpersonal fears—including fear of movement (kinesiophobia)—may lead to greater pain reduction compared with conventional behavioral therapies. There also is hope that VR interventions for chronic pain will yield better longer-term outcomes than the traditional approaches,[22,29,79,89] which often exhibit small follow-up effects.[95] Although our test of VRNT had only a 2-week follow-up—and future studies warrant a longer follow-up—our preliminary results suggest maintained or continued gains in pain-related outcomes.

Psychological therapies generally face limitations because of their reliance on the availability, training, and skills of therapists, as well as patient access and comfort with interpersonal, face-to-face treatments, and are limited in the types of experiential exercises they can provide. The use of VR-assisted approaches might overcome these limitations by offering first-person experiential learning. We speculate that in our study, the VRNT program's active learning experience with a personalized avatar and audiovisual representation of pain helped patients shift from fearful attributions of bodily causes of their pain to changeable central causes, Moreover, as in our study, VR approaches can be patient-led and used at home, making these types of therapies more accessible and overcoming feasibility barriers of in-person, therapist-led treatments. Notably, our study was conducted during the COVID pandemic, testing VRNT's accessibility in a real-world scenario, with all interactions with study personnel either conducted virtually (educational video, training session, and weekly calls) or heavily restricted and regulated (MRI scanning under strict COVID protocols). Despite these restrictions, participants were able to follow the study procedures, and participant retention was nearly perfect.

Virtual reality neuroscience-based therapy showed significant improvements in pain and functioning but did not lead to significant changes in psychological distress (depressive symptoms, anxiety, and anger), at least at 2 weeks after treatment. Similar outcomes have been observed with EAET[50] and a pain neuroscience-related intervention,[40] suggesting that achieving improvements in negative affect might be more challenging, delayed, or less reliable with these newer interventions. The strong focus on changing attributions and fears about pain's etiology, without specific techniques or components to improve mood, could explain the improved pain-related outcomes but lack of impact on negative affect. To achieve improved affect, we may need longer VRNT interventions, more specialized intervention components specifically targeting affect, a longer follow-up to see whether the improved pain is followed by improved affect.

To investigate purported neural mechanisms of action, we conducted pre-MRI and post-MRI, hypothesizing that VRNT would affect structural and functional connectivity in brain circuitries most consistently associated with chronic pain and treatment effects, including lateral prefrontal and somatomotor cortices, default mode network (DMN), cingulo-opercular network, and mediofrontal-striatal circuitry. We report VRNT-related pre-to-post treatment increases (vs. control) in functional connectivity between the left dLPFC and superior somatomotor cortex, right dLPFC and cuneus, and anterior DMN (MPFC) and left anterior LPFC, as well as decreases in white matter FA in corpus callosum adjacent to the anterior cingulate.

These findings partly align with limited evidence linking successful behavioral interventions for pain with increased prefrontal-somatosensory functional connectivity[4] and gray matter volume,[70] and increased pain reappraisal–related recruitment of prefrontal cortices.[32] Prefrontal and somatomotor cortices are commonly implicated in musculoskeletal chronic pain,[9,69] with dLPFC, MPFC, and primary somatomotor cortex being among the regions showing the most robust changes with prolonged pain and the most promising effects of

nonpharmacological pain interventions,[4,11,31,32,40,43,47,48,53,54,66,70,71,80,94] suggesting that these treatments might result in neurobiologically detectable improvements. In addition, some recent studies using noninvasive brain stimulation have successfully targeted left dLPFC and primary somatomotor cortices to alleviate musculoskeletal pain,[1,68] cf.,[3] lending further support to the key roles these areas play in chronic pain and recovery.[33] Together with earlier work, we speculate that our findings may reflect increased prefrontal recruitment in service of top-down pain control regulation through the dLPFC (possibly through cognitive reappraisal) as well as altered ("normalized") somatosensory processing of noxious (and non-noxious) input—away from the threatening words such as "pain" towards more benign terms such as "sensation." Such a shift in language to describe the patients' experience was noted anecdotally in some VRNT participants in the current study and was found in qualitative analyses of the reports of patients with back pain receiving PRT.[85] We did not observe any treatment effects in the MPFC-NAc connectivity, previously implicated in the transition to chronic pain[7,29] and cognitive regulation of evoked pain.[96] Recent studies have reported mixed findings and lack of treatment effects in this circuitry,[4,58,59] suggesting that MRI findings in this particular neural circuitry might not be a reliable marker of chronic pain in humans.

Treatment effects on white matter FA values were due to an increase in FA post-treatment vs pre-treatment in the waitlist control condition, which was not observed in the VRNT condition. The lack of FA increase in the VRNT condition was associated with pain reduction, so that VRNT participants experiencing the greatest pain relief had the most preserved FA values post-treatment relative to pre-treatment, suggesting that the preserved FA might be clinically relevant. Several other studies have also shown increased white matter FA, largely in the corpus callosum, anterior cingulum, and frontal white matter, in chronic musculoskeletal pain,[11,45,52,78] with one small study indicating that interventions for chronic pain might potentially normalize this FA increase.[11] However, because studies have also reported decreased white matter FA in participants with musculoskeletal pain compared with controls,[10,35,47,91] and with limited evidence of potential treatment-related reversals of either increases or decreased FA,[11,45] the neurobiological relevance of white matter findings and treatment effects in musculoskeletal pain remains unclear.

This study has several limitations. The sample size, although adequately powered to identify the medium-to-large effects that were observed, is still relatively small. Although the sample was balanced in gender, it was restricted in race to almost all White participants. Replication with a larger, more racially/ethnically diverse sample and with a longer follow-up time is needed. Second, like most behavioral interventions, VRNT has multiple components, and it is not clear which components contribute the most to the mediator changes and clinical outcomes. Trials that dismantle the intervention or that eliminate certain components could test which aspects of the intervention are most efficacious. Third, this trial had a waitlist control, which, although controlling some potential confounds (eg, history, regression to the mean, and assessment effects), does not rule out other factors such as expectation, engagement, and clinical contact. Although it is typical to conduct an initial trial to demonstrate a treatment effect against a relatively inert control (ie, waitlist) as we have performed here, subsequent trials should use an active placebo control (ie, sham or education), as has been performed with another successful VR approach for chronic pain,[23] to further specify VRNT's effects. Finally, our functional connectivity analyses were restricted to hypothesis-driven regions and networks of interest and therefore likely biased by previous positive research findings.

In conclusion, VRNT showed preliminary efficacy in significantly improving pain-related outcomes, and it may do so through changes in somatosensory and prefrontal brain networks as well as reducing kinesiophobia. Our results contribute to the literature on the value of VR for chronic pain and offer an approach based on newer principles of brain-based, reversible pain and novel VR experiential components—a personalized avatar and changeable pain representations. Dissemination and implementation of VRNT thus has the potential for substantial impact on the epidemic of chronic pain.

Conflict of interest statement

T.A.B is the CEO of CognifiSense. M.C. and M.L. are scientific advisors to CognifiSense. T.D.W. is on the Scientific Advisory Board of Curable Health. No conflicts of interest exist for L.W.

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Data availability statement: Behavioral outcomes, statistical brain maps, and code used to generate behavioral results are posted in a private Github repository (https://github.com/marta-ceko/Ceko_VRNT) (and accessible upon reasonable request from the corresponding author).

Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/C15.

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