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

NCT: NCT04468074

DOCUMENT TITLE: STATISTICAL ANALYSIS PLAN

STATISTICAL ANALYSIS PLAN

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), and B) Quality of Life (SF-12). Daily pain scores (e.g. least, worst, average) were plotted and assessed for stability and distributional assumptions (normality, homoscedasticity, potential outliers). Average pain intensity baseline and intervention phases were calculated and the primary analysis (Aim 1) used a Linear Mixed Effects Model (LMEM) 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 was applied to other outcomes. Secondary analyses used the LMEM 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 and gender.

POWER: At the start of the study, the effect size for VRNT was still unknown. The power analysis was derived as follows: Effect sizes for mirror therapy for phantom limb pain have a Cohen's d = 0.52 (1.64in subjects without telescoping) to 0.97 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.

AIM 2. Establish brain mechanisms associated with treatment response. Tasks. MRI imaging consisted 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 employed 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) were modeled as nuisance covariates in 1st-level analyses. Gradient artifacts were 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 were reviewed by study personnel on an ongoing basis and compared with quality metrics from other studies.

Analysis. Primary analyses focused on fMRI and white matter connectivity related to chronic back pain. Secondary, exploratory analyses focused on identifying group differences in post- vs. pre- treatment fMRI and white-matter connectivity across the brain using standard GLM analyses.

POWER: As we developed 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 brain regions associated with chronic pain and treatment (Cauda et al. 2014; Seminowicz et al. 2011, 2013; Jensen et al. 2012; Ceko et al. 2015; Davis et al. 2017) and other a priori brain measures as they become available.