Open-label Placebo Injection for Chronic Back Pain: A Randomized Trial with Functional Neuroimaging

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Key Points

Question: Can open-label (honestly prescribed) placebo treatments effectively treat chronic back pain, and if so, what are the brain mechanisms?

Findings: In this randomized trial of 101 adults with chronic back pain, an open-label subcutaneous placebo (saline) injection led to significant improvements in pain intensity, mood, and sleep relative to usual care. The placebo treatment relative to usual care also led to reduced somatomotor activity and increased medial prefrontal activity during evoked back pain, and to increased medial prefrontal-brainstem functional connectivity during spontaneous pain.

Meaning: Open-label placebo treatments can confer meaningful clinical benefits to patients with chronic back pain by engaging prefrontal-brainstem pathways linked to pain regulation and opioidergic function.

Request social media post (257 characters):

Open-label (non-deceptive) placebo injection for chronic back pain improves pain, mood, and sleep – with gains observed at 1 year post-treatment – along with reduced somatomotor activity and increased mPFC activity and mPFC-brainstem connectivity @yoniashar @torwager

Abstract

Importance: Chronic back pain (CBP) is a leading cause of disability. Placebo responses in CBP are large, often providing as much pain relief as *bona fide* treatments like steroid injections. Open-label (honestly prescribed) placebos (OLP) can provide relief from CBP without deception. OLP mechanisms remain poorly understood.

Objectives: To investigate the long-term efficacy and neurobiological mechanisms of OLP for CBP.

Design: A randomized controlled trial of CBP with longitudinal functional MRI comparing OLP vs. Usual Care, with 1-year follow-up.

Setting: University research setting and a community orthopedic clinic.

Participants: Adults aged 21–70 with CBP.

Interventions: Participants randomized to OLP received a one-time subcutaneous lumbar saline injection presented as placebo accompanied by information about the power of placebo to relieve pain, alongside their ongoing care. Usual Care participants continued their ongoing care.

Main Outcomes and Measures: The primary outcome was pain intensity (0–10) at 1-month post-treatment. Secondary outcomes included pain interference, depression, anxiety, anger, and sleep quality. Functional MRI was collected pre- and post-treatment during evoked and spontaneous back pain.

Results: We enrolled 101 adults (51.4% female, 87.1% White, M age=40.3 years) with moderate-severity CBP (M=4.10/10 intensity, duration M=9.7 years). Compared with Usual Care, OLP reduced CBP intensity post-treatment (relative reduction of 0.6 on a 0-10 pain scale; Hedges' g=0.45, $p<0.05$). At 1-year, pain relief did not persist, though significant benefits were observed in all secondary outcomes—pain interference, depression, anger, anxiety, and sleep (g=0.3–0.6, all $p<0.05$). Brain responses to evoked back pain for OLP vs. Usual Care increased in rostral anterior cingulate and

ventromedial prefrontal cortex and decreased in somatomotor cortex and thalamus. During spontaneous pain, functional connectivity analyses identified OLP vs. Usual Care increases in vmPFC connectivity to the rostral ventral medulla, a pain-modulatory brainstem nucleus.

Conclusions: In this randomized controlled trial of OLP vs. usual care, placebos without deception, in the form of a single injection, reduced CBP intensity for 1-month post-treatment and provided benefits lasting for at least 1-year post-treatment. Brain mechanisms of OLP in a clinical population overlap with those of deceptive placebos in healthy volunteers, including engagement of prefrontal-brainstem pain modulatory pathways.

Trial Registration: NCT03294148

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Placebo or sham treatments for chronic pain are powerful: in many cases, they provide as much or nearly as much pain relief as *bona fide* pills, injections, and surgeries.[1–4] Traditionally, the efficacy of placebo treatment was thought to hinge on deception of the patient, creating the illusion of an active treatment being administered. Yet, recent research has upended this belief by investigating "open-label placebo" treatments, which are disclosed to both patients and providers as placebo.[5]

Open-label placebo (OLP) treatments have demonstrated benefits for several conditions, including migraine, cancer-related fatigue, irritable bowel syndrome, and chronic back pain.[6–9] Chronic back pain (CBP) is a leading cause of disability globally and the top contributor to medical expenditures in the US.[10–12] In most cases, peripheral pathology (e.g., disc bulge) cannot explain CBP, and plasticity in central nervous system processes is the predominant cause of ongoing pain.[13–15] OLP treatments, which primarily engage brain and behavioral processes, may thus target core mechanisms of CBP. Two prior trials have demonstrated that OLP treatments can reduce chronic back pain intensity,[16,17] but it remains unknown how OLP treatments engage putative brain mechanisms to relieve CBP.

Prior neuroimaging studies have focused on traditional (deceptive) placebo treatments in healthy volunteers in experimental pain paradigms (typically, heat pain applied to the forearm). Broadly, these studies have identified three major findings induced by placebo manipulations: decreased activity in brain regions related to somatosensory and nociceptive processing (e.g., thalamus, somatomotor cortex), increased activity in prefrontal pain-regulatory regions (e.g., rostral anterior cingulate, rACC; ventromedial prefrontal cortex, vmPFC; dorsolateral prefrontal cortex, dlPFC), and the engagement of multiple brainstem nuclei modulating afferent input and exerting descending control, especially the periaqueductal gray (PAG) and rostral ventral medulla (RVM).[18–25] Yet, how the brain mechanisms identified in laboratory paradigms testing healthy volunteers relate to those of patients receiving clinical treatments remains poorly understood.[26,27] In particular, the brain mechanisms of an OLP treatment in a patient population has never been investigated.

Here, we sought to evaluate the effects of a novel OLP treatment—a one-time subcutaneous injection of saline into the back. We measured multiple patient-reported outcomes over a 1-year follow-up period, as prior studies have provided conflicting evidence on the durability of OLP effects in CBP.[28,29] We conducted longitudinal functional MRI (fMRI) to assess the effects of OLP on back pain-related brain activity

and on functional connectivity during spontaneous pain. We hypothesized that the neurobiological effects of OLP in CBP would resemble the neuroimaging findings from laboratory pain paradigms.

Method

The trial was pre-registered (NCT #03294148) and conducted from 2017-2018, with 1-year follow-up completed by November 2019. The trial was designed to facilitate two comparisons of interest: a test of a psychotherapy intervention with OLP serving as a control condition (presented in a previous manuscript[30]), and the comparison of OLP vs. usual care on mechanistic and clinical outcomes—the focus of this manuscript. The OLP vs. Usual Care comparison on clinical and neuroimaging outcomes and longitudinal follow-up has not been published previously. The trial and this analytic plan were preregistered on ClinicalTrials.gov (NCT03294148). Participants provided written informed consent as approved by the University of Colorado Institutional Review Board. Our report follows CONSORT reporting guidelines.

Participants

Participants were recruited from the community using electronic and print announcements, social media, and referrals in 2017-2018. Recruitment materials described a “mind-body treatment” for CBP, explained to be an honest placebo during informed consent.

Participants aged 21 – 70 with back pain for at least half the days of the last 6 months and 1-week-average pain intensity $\geq$ 4/10 at screening were recruited from the Boulder, Colorado area. We targeted primary CBP, excluding patients with leg pain worse than back pain and self-reported diagnoses of inflammatory disorders or metastasizing cancers. We excluded people self-reporting psychosis, personality disorders, pain-related compensation or litigation in the past year, or inability to undergo MRI (details provided in eMethods p. 2). Power analysis targeted 80% power (α = .05) to detect a medium effect (d = .62) on pain intensity at the primary endpoint (eMethods p. 2-3). Participants self-reported race and ethnicity.

Participants completed an eligibility/consent session and a baseline assessment session with fMRI. They were subsequently randomized using an imbalance-minimization algorithm[31] to OLP or Usual Care, balancing on age, sex, baseline pain,

and opioid use (eMethods p. 3). Participants were unblinded due to the nature of the intervention. All research staff collecting data were blinded to group assignment.

The primary endpoint (post-treatment fMRI session) occurred 1 month after the baseline fMRI session. Participants completed online follow-up assessments at 1, 2, 3, 6, and 12 months after the post-treatment session (Figure 1). Adverse events were recorded when participants spontaneously reported them to study personnel.

Half the participants in the Usual Care arm were from a parallel, simultaneous clinical trial testing a psychotherapeutic intervention vs. Usual Care. To increase statistical power, we designed these two trials to support combining the two Usual Care arms: both trials recruited from an identical population using identical recruitment methods, collected identical assessment measures, and had the same instructions for the Usual Care arm.

Interventions, Materials and Procedures

Open-label placebo. OLP included an integrated cognitive, social, and physical (injection) intervention. Participants presented to a private orthopedic medical center in Golden, Colorado. They watched two videos (available for reuse upon request) and had a structured conversation with the treating physician (author KK) in the context of an empathic, validating clinical encounter. The videos and conversation aimed to convey that: 1) they were receiving a placebo—an inert treatment with no “active ingredients”, 2) placebos can have powerful effects, 3) placebos produce endogenous opioid release, establishing a rationale for pain relief, 4) placebos can work even when known to be inert by engaging automatic/non-conscious pathways, (e.g. “automatically triggering the body’s natural healing response”), 5) a positive attitude may be helpful but is not necessary, encouraging instead an open-minded attitude.[32] Participants changed into a medical gown, and a subcutaneous injection described as saline with no active medication was administered at the site of greatest back pain. Participants also continued any ongoing Usual Care for their back pain and agreed not to begin new treatments.

Usual Care. These participants were given no additional treatment by the study staff. They agreed to continue their ongoing care as usual and not start new treatments.

Clinical measures

Clinical outcomes. The primary outcome was average pain over the last week on a 0 – 10 Numerical Rating Scale (NRS), as assessed with the Brief Pain Inventory-Short Form (BPI-SF).[33] We adopted this as the primary outcome owing to its enhanced interpretability, high correlations ($r > .90$) with the fully BPI Severity scale scores, and recommendations from an NIH task force and the scale developers.[34–36] Secondary outcomes included: pain interference (BPI-SF), PROMIS short forms for depression, anxiety, anger, and sleep quality,[37,38] Patient Global Impression of Change (PGIC), and the Treatment Satisfaction Questionnaire[39] (see eMethods p. 3 for measure details). Outcomes were collected at pre-randomization and at all follow-up time points, except the PGIC and Treatment Satisfaction Questionnaire which cannot be measured at pre-randomization. Baseline values for primary and secondary outcomes were computed as the average score from two pre-randomization assessments (eligibility session and pre-treatment fMRI session). Additional measures of psychological functioning were measured at baseline for testing as potential moderators of OLP response (eMethods p. 7-8).

Neuroimaging Measures

We acquired both structural (T1 MPRAGE) and functional images (multiband gradient-echo EPI). Sequence parameters and a complete description of neuroimaging methods is provided in eMethods p. 3-4.

Evoked back pain. During fMRI, participants completed an evoked back pain task with a series of randomly ordered trials distending the back to one of four intensity levels. The evoked back pain task utilized a novel device providing experimental control over back pain during fMRI. Participants lay on a pneumatically-controlled cylindrical balloon, with increasing inflation causing increasingly painful back distention, and rated pain after each trial on a visual analog scale (VAS; 0 = no pain, 100 = worst pain imaginable).

Spontaneous pain (resting state). An 8-minute scan was collected for each participant at pre- and post-treatment. Participants were asked to keep their eyes open and fixate on a visual crosshair; once per minute, participants rated their spontaneous back pain intensity on a VAS.

Statistical Analysis

Clinical Outcomes

Intent-to-treat analyses including all randomized patients were performed. Primary and secondary outcome scores were modelled at post-treatment (the primary endpoint) with a mixed-effects model (*fitlme*, MATLAB 2023a) at a $p < 0.05$ significance level. Regressors included dummy-coded treatment group (OLP vs. Usual Care) and timepoint (Post vs. Pre) variables, a group by time interaction (OLP vs. Usual Care *x* Post vs. Pre), covariates for age and sex, and a random intercept and slope per participant. Treatment response rates were computed as the percentage of randomized participants reporting ≥30% and ≥50% pain reduction at post-treatment.

Effects of OLP on primary and secondary outcomes at 1, 2, 3, 6, and 12 months post-treatment were examined in three ways. First, we tested for OLP effects throughout the entire follow-up period in models including data from all follow-up timepoints. Regressors included a dummy-coded treatment group variable, a timepoint variable indicating months post-treatment and mean-centered at 6 months (the midpoint of the 12 month follow-up period), a group by time interaction, covariates for age and sex, and a random intercept and slope per participant. Time was centered at 6 months post-treatment to maximize power for detecting group effects throughout the entire follow-up period. Estimated effects of group can be interpreted as group differences at 6 months post-treatment, with the group*time interaction testing for changes in OLP vs. Usual Care effects across the 12-month follow-up period. Second, we estimated OLP vs. Usual Care effect sizes (Hedges' *g*) at each follow-up timepoint for each outcome, adjusting for baseline values of the outcome (eMethods p. 7). And third, we tested whether these OLP vs. Usual Care effect sizes were significant at 12-months post-treatment—our longest follow-up timepoint.

Self-reported pain during the evoked back pain task (average pain across trials) was also submitted to a mixed-effects model, as described above, testing for a group by time interaction effect. We further conducted exploratory analyses testing baseline measures of psychological functioning as predictors of response to OLP (eMethods p. 7-8).

Neuroimaging analyses

*Preprocessing and denoising***.** Standard fMRI preprocessing procedures were used, implemented in *fMRIprep* 1.2.4[40] which is based on Nipype 1.1.6.[41] This included coregistration, normalization of anatomical images to a template image (ICBM 152

Nonlinear Asymmetrical template version 2009c), susceptibility artifact distortion correction, and smoothing with a 6mm kernel.

Evoked pain task. A first-level model was estimated for each participant to identify brain activity associated with evoked back pain intensity. We constructed a continuous within-person estimate of evoked pain intensity based on post-trial pain ratings. This modelled pain experience throughout the evoked back pain task and provided a contrast image for each subject estimating how strongly each voxel was related to evoked pain (eMethods p. 3-5). Multiple covariates in the 1st level model controlled for head motion effects (eMethods p. 5-6).

Second-level models tested for OLP vs. Usual Care effects on evoked back pain-related brain activity. We conducted a voxelwise robust regression using SPM12 and the CanlabCore toolbox (https://github.com/canlab/CanlabCore) to estimate the OLP vs. Usual Care effect at post-treatment, controlling for age, sex, and pre-treatment values at the given voxel.[42,43]

Statistical thresholding was conducted using a non-parametric combination testing framework correcting both within and across regions of interest (ROIs).[44] We defined six ROIs reliably associated with placebo analgesia in prior meta-analyses,[18,20] including two areas showing placebo-induced increases (vmPFC/rACC, dlPFC) and four areas showing placebo-induced decreases (insula, midcingulate, medial somatomotor cortex, thalamus) (eMethods 7, eFigure 1). A permutation test conducted within each ROI was thresholded at $p<0.05$ familywise error rate (FWER) corrected across voxels, along with a permutation-based correction across ROIs (FWER $p<0.05$ across the set of ROIs) (eMethods p. 7).[44] Whole-brain uncorrected results are reported in the supplementary materials for archival purposes (eMethods p. 8, 10, eTable 2).

Connectivity analyses. Two vmPFC regions identified in evoked pain analyses above were submitted as seed regions to test for placebo-induced increases in spontaneous (resting) connectivity with the PAG and RVM, as shown in prior placebo analgesia studies,[24,25,45] with non-parametric combination testing to correct for multiple comparisons (eMethods 7-8). The spontaneous pain (resting state) task was preprocessed as above, along with global signal regression and bandpass filtering [.1 – .01 Hz] (eMethods p. 4-5). PAG and RVM were defined anatomically using a high-resolution brainstem atlas.[46]

Results

A total of *N*=101 participants were randomized. The sample included 52 (51.4%) females, aged *M* (*SD*)=40.4 (15.4) years old, and with all participants reporting at least some college education (Table 1). Of the 101 participants, 1 (1.0%) was American Indian or Alaskan Native, 2 (2.0%) were Asian/Pacific Islander, 3 (3.0%) were Black, 88 (87.1%) were White, and 7 (7.0%) were Other or Unknown (Table 1), with 4 (4.0%) participants of Hispanic ethnicity (Table 1). The sample had moderate pain intensity (*M*=4.10, *SD*=1.25) at pre-treatment, with CBP duration of *M*=9.7 (8.5) years. *N*=91 (90.1%) completed the post-treatment assessment session (Figure 1). Of 51 participants randomized to OLP, 4 (7.8%) were lost to follow-up and 3 (5.8%) withdrew from treatment (Figure 1). Of 50 participants randomized to usual care, 3 (6.0%) did not complete post-treatment assessment (Figure 1).

Patient-Reported Outcomes

OLP led to significant reductions in reported chronic back pain intensity at post-treatment relative to Usual Care, β=0.61 points on the 11-point pain scale, *t*(90.09)=2.29, *p*=.02, with Hedges' *g*=0.45 (Figure 2A). Of 44 patients randomized to OLP followed at post-treatment, 20 (45.4%) reported 30% pain reduction and 11 (24.4%) reported 50% pain reduction. Of 47 patients randomized to usual care followed at post-treatment, 18 (38.3%) reported 30% pain reduction and 7(14.9%) had a 50% pain reduction.

Among secondary outcomes at post-treatment, OLP vs. Usual Care led to improvements in pain interference, β=0.67, *t*(90.58)=2.65, *p*=0.01, and marginal improvements in anxiety, β=1.38, *t*(91.17)=1.80, *p*=0.08). No significant effects were found at post-treatment for other secondary outcomes, *p*s > .10.

At 1-year follow-up, there were no significant effects of OLP vs. Usual Care on pain intensity, indicating an attenuation of the improvements observed at post-treatment. Surprisingly, benefits of OLP vs. Usual Care were observed at long-term follow-up for all secondary outcomes, including pain interference, depression, anger, anxiety, sleep, global impression of change, and treatment satisfaction (all outcomes significant at $p < .05$, except pain interference was marginally significant, *p*=.06; Table 2). Effect sizes at the measured timepoints during the 1-year follow-up were generally medium sized, ranging mainly between 0.3 – 0.7 (Figure 2, eTable 1). There were no significant interactions between treatment assignment and time for any outcome, *p*s > .05, suggesting relatively stable effects of treatment throughout the one-year follow-up period; this was supported by visual inspection of effect size trajectories over time

(Figure 2). No adverse effects of treatment were reported by participants at any point. Greater levels of pain catastrophizing at baseline predicted enhanced response to OLP, whereas baseline treatment expectations, trait optimism, anxiety, and depression did not (eMethods p. 8).

fMRI Results

Evoked back pain analyses. OLP vs. Usual Care led to reduced pain ratings in the back pain evocation task with marginal significance, β=-6.97 on a 0-100 pain scale, $t(78)=-1.84$, $p=.07$. We observed OLP vs. Usual Care increases in evoked back pain-related activity in the vmPFC and rACC, and decreases in medial motor cortex (Area 4) and thalamus, all FWE-corrected $p < .05$ within ROIs. In addition, the overall combined test showed significant joint effects corrected across all ROIs tested ($p < 0.05$ FWER-corrected) (Figure 3). No effects were observed in the midcingulate, insula, or dlPFC. The thalamic clusters were labeled as ventral anterior and ventral lateral thalamus, with a predominantly prefrontal connectivity profile in the Oxford Thalamic Connectivity Atlas.[47,48]

Functional connectivity during spontaneous pain. Of the two vmPFC/rACC regions with increased OLP vs. Usual Care activity during evoked pain, the more anterior vmPFC region had significantly increased connectivity during spontaneous pain (resting state) with the RVM, $p < .05$ FWE-corrected (Figure 3), along with a trend towards connectivity increases with the PAG ($p < .1$ corrected).

Discussion

Placebo treatments for chronic pain often provide as much or nearly as much pain relief as *bona fide* pills, injections, and surgeries.[1–4] Recent research demonstrating the efficacy of non-deceptive open-label placebos (OLP) has upended the belief that placebos require deception, creating a novel path forward for ethical, feasible placebo treatment.[5,8] Yet, critical open questions remain regarding the efficacy, long-term benefits, and mechanisms of OLP treatments. In particular, the brain mechanisms of an OLP treatment in a clinical population have not been investigated. Here, in the context of a randomized trial comparing an OLP injection vs. usual care, we found: i) reduced pain intensity at 1 month post-treatment, ii) benefits of OLP on multiple secondary outcomes (but not pain intensity) at 1 year, and iii) altered brain responses to evoked back pain

and altered functional connectivity during spontaneous pain, consistent with engagement of descending modulatory pain pathways.

The magnitude of pain reductions we observed at 1 month post-treatment are nearly identical with a prior trial of OLP for chronic back pain (CBP).[17] Effects on pain were not large (pain reduction of 0.61 of 10, *d*=0.45) but can be considered clinically significant: many standard CBP treatments (e.g., NSAIDs, epidural steroid injections) yield comparable effects sizes but with more adverse events.[2,3] Another prior study of OLP for CBP reported larger pain reductions, suggesting that OLP effects may be magnified in certain contexts.[16]

OLP vs. Usual Care pain reductions were not significant through 1 year follow-up. This is consistent with a prior study including 3-year follow-up following OLP for CBP,[28] and parallels the effects of epidural steroid injections, whose benefits also typically fade with time. Patients thus often return for repeat steroid injections, though these must be limited due to safety concerns. As there are no safety concerns with repeated OLP injections, future studies could investigate repeated OLP injections as a maintenance treatment aiming to provide sustained pain reductions, with randomized withdrawal studies to estimate the effects of OLP discontinuation.

Sustained benefits of OLP vs. Usual Care through 1-year follow-up were observed on pain interference, depression, anxiety, sleep, and anger. These effects were not significant at 1-month post-treatment but emerged later in time. The delayed emergence of these effects could potentially be explained by mutually reinforcing improvements across these multiple processes (pain interference, sleep, mood) creating positive feedback loops providing increasing benefits over time, following an initial "incubation period".[49] As a prior trial found limited benefits of OLP vs. usual care on depression, stress, and disability at 3 years, these benefits may fade between years 1 and 3 post-treatment.[28]

During evoked back pain, we found OLP vs. Usual Care increases in two prefrontal regions, the vmPFC and rACC, as well as decreases in primary motor cortex and thalamus. These results are broadly consistent with investigations of placebo effects on experimental pain in healthy volunteers which have found activations in prefrontal pain-regulatory regions and reductions in somatomotor and nociception-related regions (with substantial variation in specific findings from study to study).[18–25] During spontaneous pain, we observed increased connectivity between the vmPFC and the RVM, a brainstem nucleus involved in pain modulation.[23,50,51] Increased vmPFC connectivity to

the PAG and RVM has been reported in multiple prior studies of placebo analgesia in healthy volunteers.[25,45] It suggests engagement of descending opioidergic projections from the prefrontal cortex to these brainstem nuclei and down to the dorsal horn of the spinal cord, inhibiting afferent nociceptive signals before they reach the brain.[24,50] Prior experimental work has demonstrated that OLP effects in a laboratory context are partially blocked by naloxone, an opioid antagonist, consistent with the notion that OLP engages opioidergic mechanisms.[52] As the RVM also includes ascending nociceptive pathways and encode aversive prediction errors, other interpretations of the increased connectivity are possible as well.[53] As we observed this increased vmPFC-brainstem coupling during the resting state (spontaneous pain), this raises the possibility that OLP relieves back pain by increasing tonic opioid release in daily life. Overall, these findings suggest that OLP for chronic pain may engage similar brain mechanisms as deceptive placebo for experimental pain, including engagement of prefrontal pain-regulatory regions with projections to brainstem nuclei and reduced activity in nociceptive target regions. To our knowledge, only two prior studies have examined OLP effects on brain function, both examining emotional distress induced by aversive images in healthy volunteers; one study reporting increased PAG activity, aligned with our findings.[54,55]

OLP Intervention effects were not driven by the inert injection *per se*, but by the psychosocial context surrounding the injection. The psychological components of the OLP intervention (e.g., specific patient education) are likely central to its therapeutic effects.[56,57]

Limitations

Limitations include a limited sample size, a sample low in racial and ethnic diversity, baseline group differences in exercise levels and pain duration of small-moderate size, and more missing data in the Usual Care arm at 12-month follow-up. As brainstem imaging is methodologically challenging, dedicated MRI sequences would improve signal strength and localization.[23] Recruitment materials describing a “mind-body intervention” may have biased the sample towards people open to accepting a placebo intervention; future research would be needed to test whether openness towards an OLP intervention influences its efficacy.

Conclusions

In this randomized controlled trial, a placebo injection without deception reduced CBP intensity for 1-month post-treatment and provided benefits lasting for at least 1-year post-treatment. Brain mechanisms of OLP in a clinical population overlapped with those

of deceptive placebos in healthy volunteers, including engagement of prefrontal-brainstem pain modulatory pathways.

References

1. Louw A, Diener I, Fernández-de-Las-Peñas C, Puentedura EJ. Sham Surgery in Orthopedics: A Systematic Review of the Literature. *Pain Med*. 2017;18(4):736-750. doi:10.1093/pm/pnw164
2. Enthoven WTM, Roelofs PD, Koes BW. NSAIDs for Chronic Low Back Pain. *JAMA*. 2017;317(22):2327. doi:10.1001/jama.2017.4571
3. Bicket MC, Gupta A, Brown CH th, Cohen SP. Epidural Injections for Spinal Pain: A Systematic Review and Meta-analysis Evaluating the "Control" Injections in Randomized Controlled Trials. *Anesthesiology*. 2013;119(4):907-931. doi:10.1097/ALN.0b013e31829c2ddd
4. Kallmes DF, Comstock BA, Heagerty PJ, et al. A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures. *New England Journal of Medicine*. 2009;361(6):569-579. doi:10.1056/nejmoa0900563
5. Kaptchuk TJ. Open-label placebo reflections on a research agenda. *Perspect Biol Med*. 2018;61(3):311-334. doi:10.1353/pbm.2018.0045
6. Lembo A, Kelley JM, Nee J, et al. Open-label placebo vs double-blind placebo for irritable bowel syndrome. *Pain*. 2021;Publish Ah(00). doi:10.1097/j.pain.0000000000002234
7. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-Label Placebo Treatment for Cancer-Related Fatigue: A Randomized-Controlled Clinical Trial. *Sci Rep*. 2018;8(1):2784. doi:10.1038/s41598-018-20993-y
8. von Wernsdorff M, Loef M, Tuschen-Caffier B, Schmidt S. Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):1-14. doi:10.1038/s41598-021-83148-6
9. Kam-Hansen S, Jakubowski M, Kelley JM, et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci Transl Med*. 2014;6:218ra5. doi:10.1126/scitranslmed.3006175
10. Murray CJL. The State of US Health, 1990-2010. *JAMA*. 2013;310(6):591. doi:10.1001/jama.2013.13805
11. Dieleman JL, Cao J, Chapin A, et al. US Health Care Spending by Payer and Health Condition, 1996-2016. *JAMA - Journal of the American Medical Association*. 2020;323(9):863-884. doi:10.1001/jama.2020.0734
12. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*. 2012;380(9859):2163-2196. doi:10.1016/S0140-6736(12)61729-2
13. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. *The Lancet*. 2021;397(10289):2098-2110. doi:10.1016/S0140-6736(21)00392-5
14. Nijs J, George SZ, Clauw DJ, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *Lancet*. 2021;9913(21):1-10. doi:10.1016/S2665-9913(21)00032-1
15. Baliki MN, Apkarian AV. Nociception, Pain, Negative Moods, and Behavior Selection. *Neuron*. 2015;87(3):474-491. doi:10.1016/j.neuron.2015.06.005

16. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment in chronic low back pain. *Pain*. 2016;0(0):1. doi:10.1097/j.pain.0000000000000700
17. Kleine-Borgmann J, Schmidt K, Hellmann A, Bingel U. Effects of open-label placebo on pain, functional disability, and spine mobility in patients with chronic back pain: A randomized controlled trial. *Pain*. 2019;160(12):2891-2897. doi:10.1097/j.pain.0000000000001683
18. Ashar YK, Chang LJ, Wager TD. Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account. *Annu Rev Clin Psychol*. 2017;13(1):73-98. doi:10.1146/annurev-clinpsy-021815-093015
19. Wager TD, Rilling JK, Smith EE, et al. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science*. 2004;303(2004):1162-1167. doi:10.1126/science.1093065
20. Zunhammer M, Spisák T, Wager TD, et al. Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. *Nat Commun*. 2021;12(1):1-11. doi:10.1038/s41467-021-21179-3
21. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia--imaging a shared neuronal network. *Science*. 2002;295(5560):1737-1740. doi:10.1126/science.1067176
22. Amanzio M, Benedetti F, Porro CA, Palermo S, Cauda F. Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Hum Brain Mapp*. 2013;34(3):738-752. doi:10.1002/hbm.21471
23. Napadow V, Sclocco R, Henderson LA. Brainstem neuroimaging of nociception and pain circuitries. *Pain Rep*. 2019;4(4). doi:10.1097/PR9.0000000000000745
24. Tinnermann A, Geuter S, Sprenger C, Finsterbusch J, Büchel C. Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science (1979)*. 2017;358(6359):105-108. doi:10.1126/science.aan1221
25. Bingel U, Lorenz J, Schoell E, Weiller C, Büchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. *Pain*. 2006;120(1-2):8-15. doi:10.1016/j.pain.2005.08.027
26. Benedetti F, Colloca L, Torre E, et al. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nat Neurosci*. 2004;7(6):587-588. doi:10.1038/nn1250
27. de la Fuente-Fernández R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl a J. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science*. 2001;293(5532):1164-1166. doi:10.1126/science.1060937
28. Kleine-Borgmann J, Dietz T niklas, Schmidt K, Bingel U. placebo treatment for chronic low back pain: a 3-year follow-up of a randomized controlled trial. *Pain*. 2022;00(00).
29. Carvalho C, Pais M, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo for chronic low back pain: a 5-year follow-up. *Pain*. 2020;Publish Ah(00):1-7. doi:10.1097/j.pain.0000000000002162
30. Ashar YK, Gordon A, Schubiner H, et al. Effects of Pain Reprocessing Therapy vs Placebo and Usual Care for Patients with Chronic Back Pain: A Randomized

Clinical Trial. *JAMA Psychiatry*. 2022;79:13-23. doi:10.1001/jamapsychiatry.2021.2669

31. Xiao L, Yank V, Ma J. Algorithm for balancing both continuous and categorical covariates in randomized controlled trials. *Comput Methods Programs Biomed*. 2012;108(3):1185-1190. doi:10.1016/j.cmpb.2012.06.001
32. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One*. 2010;5(12):e15591. doi:10.1371/journal.pone.0015591
33. Cleeland C. Brief pain inventory (short form). *Pain Research Group [viitattu*. Published online 1991:9-10. http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Brief+Pain+Inventory+(+Short+Form+)#7
34. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1-2):9-19. doi:10.1016/j.pain.2004.09.012
35. Ramasamy A, Martin ML, Blum SI, et al. Assessment of Patient-Reported Outcome Instruments to Assess Chronic Low Back Pain. *Pain Medicine*. Published online 2017:1-13. doi:10.1093/pm/pnw357
36. Cleeland C, Ryan K. *The Brief Pain Inventory*. Pain Research Group; 1991.
37. Stone AA, Broderick JE, Junghaenel DU, Schneider S, Schwartz JE. PROMIS fatigue, pain intensity, pain interference, pain behavior, physical function, depression, anxiety, and anger scales demonstrate ecological validity. *J Clin Epidemiol*. Published online November 25, 2015. doi:10.1016/j.jclinepi.2015.08.029
38. Licciardone J, Worzer WE, Hartzell MM, Kishino N, Gatchel RJ. An Overview of the Patient-Reported Outcomes Measurement Information System (PROMIS) for Assessing Chronic Low Back Pain Patients. *J Appl Biobehav Res*. Published online 2017:1-22. doi:10.1111/jabr.12057
39. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes*. 2004;2(1):12. doi:10.1186/1477-7525-2-12
40. Esteban O, Markiewicz CJ, Blair RW, et al. fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nat Methods*. 2019;16(1):111-116. doi:10.1038/s41592-018-0235-4
41. Gorgolewski K, Burns CD, Madison C, et al. Nipype: A Flexible, Lightweight and Extensible Neuroimaging Data Processing Framework in Python. *Front Neuroinform*. 2011;5:13. doi:10.3389/fninf.2011.00013
42. Judd CM, Mcclelland G, Ryan C. *Data Analysis: A Model Comparison Approach*. Routledge; 2009.
43. O Connell NS, Dai L, Jiang Y, et al. Methods for Analysis of Pre-Post Data in Clinical Research: A Comparison of Five Common Methods. *J Biom Biostat*. 2017;08(01):1-8. doi:10.4172/2155-6180.1000334
44. Winkler AM, Webster MA, Brooks JC, Tracey I, Smith SM, Nichols TE. Non-parametric combination and related permutation tests for neuroimaging. *Hum Brain Mapp*. 2016;37(4):1486-1511. doi:10.1002/hbm.23115

45. Eippert F, Bingel U, Schoell ED, et al. Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia. *Neuron*. 2009;63:533-543. doi:10.1016/j.neuron.2009.07.014
46. Singh K, García-Gomar MG, Bianciardi M. Probabilistic Atlas of the Mesencephalic Reticular Formation, Isthmic Reticular Formation, Microcellular Tegmental Nucleus, Ventral Tegmental Area Nucleus Complex, and Caudal-Rostral Linear Raphe Nucleus Complex in Living Humans from 7 Tesla Magnetic Reso. *Brain Connect*. 2021;11(8):613-623. doi:10.1089/brain.2020.0975
47. Iglesias JE, Insausti R, Lerma-Usabiaga G, et al. A probabilistic atlas of the human thalamic nuclei combining ex vivo MRI and histology. *Neuroimage*. 2018;183(June):314-326. doi:10.1016/j.neuroimage.2018.08.012
48. Behrens TEJ, Johansen-Berg H, Woolrich MW, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci*. 2003;6(7):750-757. doi:10.1038/nn1075
49. Walton GM. The New Science of Wise Psychological Interventions. *Curr Dir Psychol Sci*. 2014;23(1):73-82. doi:10.1177/0963721413512856
50. Wager TD, Fields HL. Placebo analgesia. In: McMahon S, Koltzenburg M, Tracey I, Turk DC, eds. *Wall & Melzack's Textbook of Pain*. 6th ed. Elsevier Health Sciences; 2013:362-373. doi:10.1017/CBO9781107415324.004
51. Mills EP, Di Pietro F, Alshelh Z, et al. Brainstem pain control circuitry connectivity in chronic neuropathic pain. *The Journal of Neuroscience*. 2017;7063:1647-17. doi:10.1523/JNEUROSCI.1647-17.2017
52. Benedetti F, Shaibani A, Arduino C, Thoen W. Open-label nondeceptive placebo analgesia is blocked by the opioid antagonist naloxone. *Pain*. 2022;Publish Ah(00):0-6. doi:10.1097/j.pain.0000000000002791
53. Roy M, Shohamy D, Daw N, Jepma M, Wimmer GE, Wager TD. Representation of aversive prediction errors in the human periaqueductal gray. *Nat Neurosci*. 2014;17(11):1607-1612. doi:10.1038/nn.3832
54. Guevarra DA, Moser JS, Wager TD, Kross E. Placebos without deception reduce self-report and neural measures of emotional distress. *Nat Commun*. 2020;11(1):1-8. doi:10.1038/s41467-020-17654-y
55. Schaefer M, Kühnel A, Schweitzer F, Enge S, Gärtner M. Neural underpinnings of open-label placebo effects in emotional distress. 2022;(July):1-7. doi:10.1038/s41386-022-01501-3
56. Locher C, Nascimento AF, Kirsch I, Kossowsky J, Meyer A, Gaab J. Is the rationale more important than deception? A randomized controlled trial of openlabel placebo analgesia. *Pain*. 2017;0(0):1. doi:10.1097/j.pain.0000000000001012
57. Buergler S, Sezer D, Bagge N, et al. Imaginary pills and open - label placebos can reduce test anxiety by means of placebo mechanisms. *Sci Rep*. Published online 2023:1-12. doi:10.1038/s41598-023-29624-7
58. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: Preliminary data in healthy white women. *Health Psychology*. 2000;19(6):586-592. doi:10.1037/0278-6133.19.6.586

Table 1

Participant Demographics

	OLP No. patients (%)	Usual Care No. patients (%)
Demographics		
Age, mean (SD), years	39.4 (14.9)	41.3 (15.9)
Sex n (%)		
Female	25 (49.0%)	27 (54.0%)
Male	26 (50.9%)	23 (46.0%)
Education n (%)		
High School or less	0 (0.0%)	0 (0.0%)
Some college	15 (29.4%)	15 (30%)
College graduate	36 (70.6%)	35 (70%)
Married n (%)	25 (49.0%)	30 (60%)
Race n (%)		
American Indian or Alaskan Native	0 (0%)	1 (2.0%)
Asian/Pacific Islander	2 (3.9%)	0 (0.0%)
Black (not of Hispanic origin)	2 (3.9%)	1 (2.0%)
White (not of Hispanic origin)	45 (88.2%)	43 (86.0%)
Other or Unknown	2 (3.9%)	5 (10.0%)
Hispanic ethnicity n (%)	2 (3.9%)	2 (4.0%)
Employment status n (%)		
Full time (30+ hrs/week)	26 (51.0%)	28 (56.0%)
Part time (5-30 hrs/week)	12 (23.5%)	13 (26.0%)
Unemployed/lightly employed (<5 hrs/week)	13 (25.5%)	9 (18.0%)
SSES mean (SD), 1-10	6.4 (2.0)	6.7 (1.6)
Exercise n (%)		
Almost none	1 (2.0%)	4 (8.0%)
1 hour/week	7 (13.7%)	9 (18.0%)
3 hours/week	23 (45.1%)	14 (28.0%)
7 hours/week	18 (35.3%)	21 (42.0%)
14+ hours/week	2 (3.9%)	2 (4.0%)
Pain-related characteristics		
Pain duration, mean (SD), years	8.9 (8.2)	10.5 (8.9)
Current opioid use, *n* (% yes)	2 (3.9%)	2 (4.0%)

Pain in body sites besides back, *n* (%)		
None	9 (17.6%)	4 (8.0%)
A little	24 (47.1%)	28 (56.0%)
A moderate amount	15 (29.4%)	16 (32.0%)
A lot	3 (5.9%)	2 (4.0%)

Abbreviations: SSES = subjective socioeconomic status, rated on a 1 – 10 ladder.[58]

Table 2

Effects of OLP vs. Usual Care through the 1-year follow-up period.

Outcome, Scale range	**Estimate (SE)[a]**	***t*-statistic[a]**	***p*-value[a]**	**Effect size at 1 year, *g*[b]**
Pain intensity, 0 – 10	-0.41 (0.27)	-1.53	0.13	-0.33†
Secondary Outcomes				
Pain interference, 0 – 10	-0.53 (0.28)	-1.91	0.06	-0.30
Depression, 0 – 24	-1.68 (0.54)	-3.13	0.002	-0.50*
Anger, 0 – 20	-1.25 (0.50)	-2.53	0.01	-0.38*
Anxiety, 0 – 32	-1.77 (0.73)	-2.43	0.02	-0.40*
Sleep disruption, 0 – 32	-2.11 (0.78)	-2.70	0.01	-0.46*
Patient Global Impression of Change, 0 – 7	0.69 (0.31)	2.21	0.03	0.18
Treatment satisfaction, 0 – 100	10.73 (4.96)	2.16	0.03	0.44*

[a] Open-label placebo injection (OLP) vs. Usual Care led to improvements in multiple patient-reported outcomes during 1-year follow-up. Estimates from a model testing effects throughout the 1-year follow-up period are presented in the first three columns. Data were centered at 6 months, the midpoint of the follow-up time period. To aid interpretation, β estimates are presented in raw units, with the range of each measure provided after its name.

[b] We estimated the OLP vs. Usual Care effect size (Hedges' *g*) at 1 year, our longest follow-up time point. Values for each outcome at each timepoint are provided in eTable 1. Significance at $p < .1$ is indicated by † and at $p < .05$ by *.

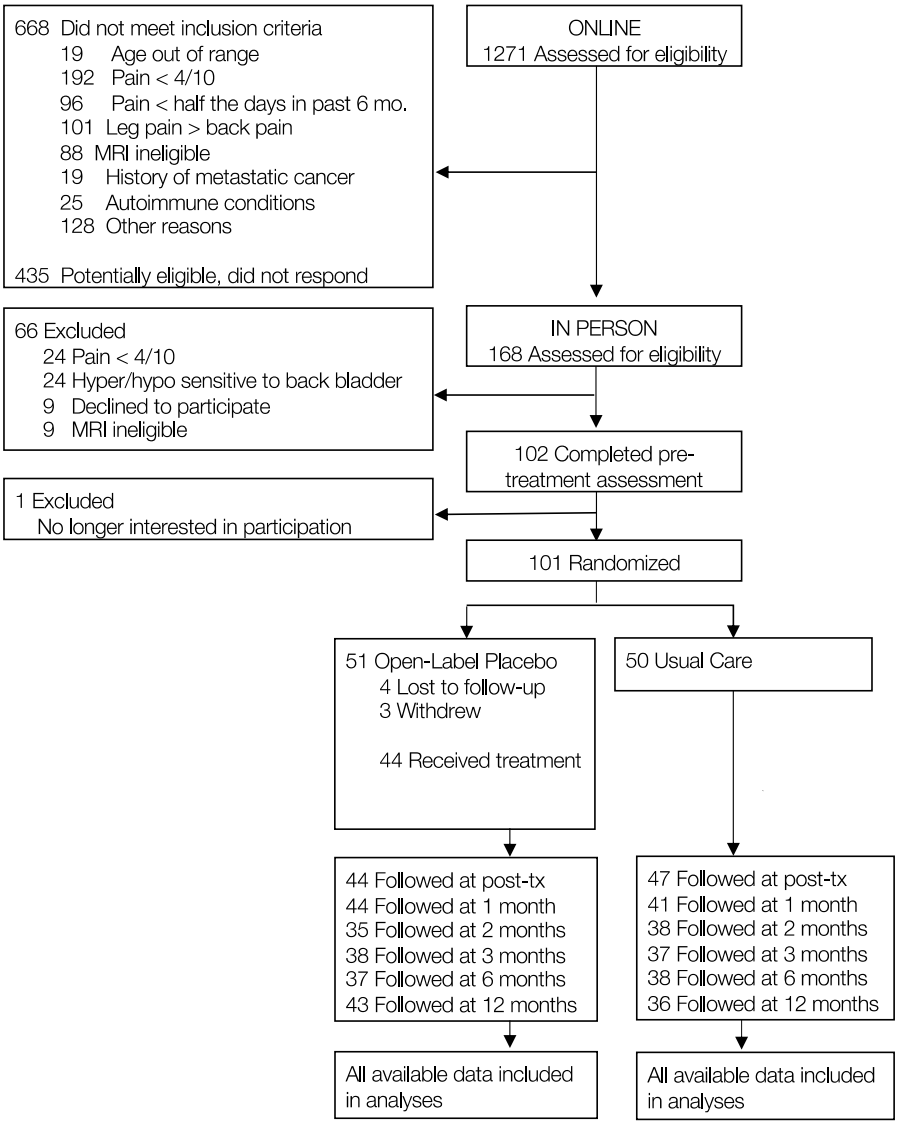


Figure 1. CONSORT diagram depicting participant flow through the trial.

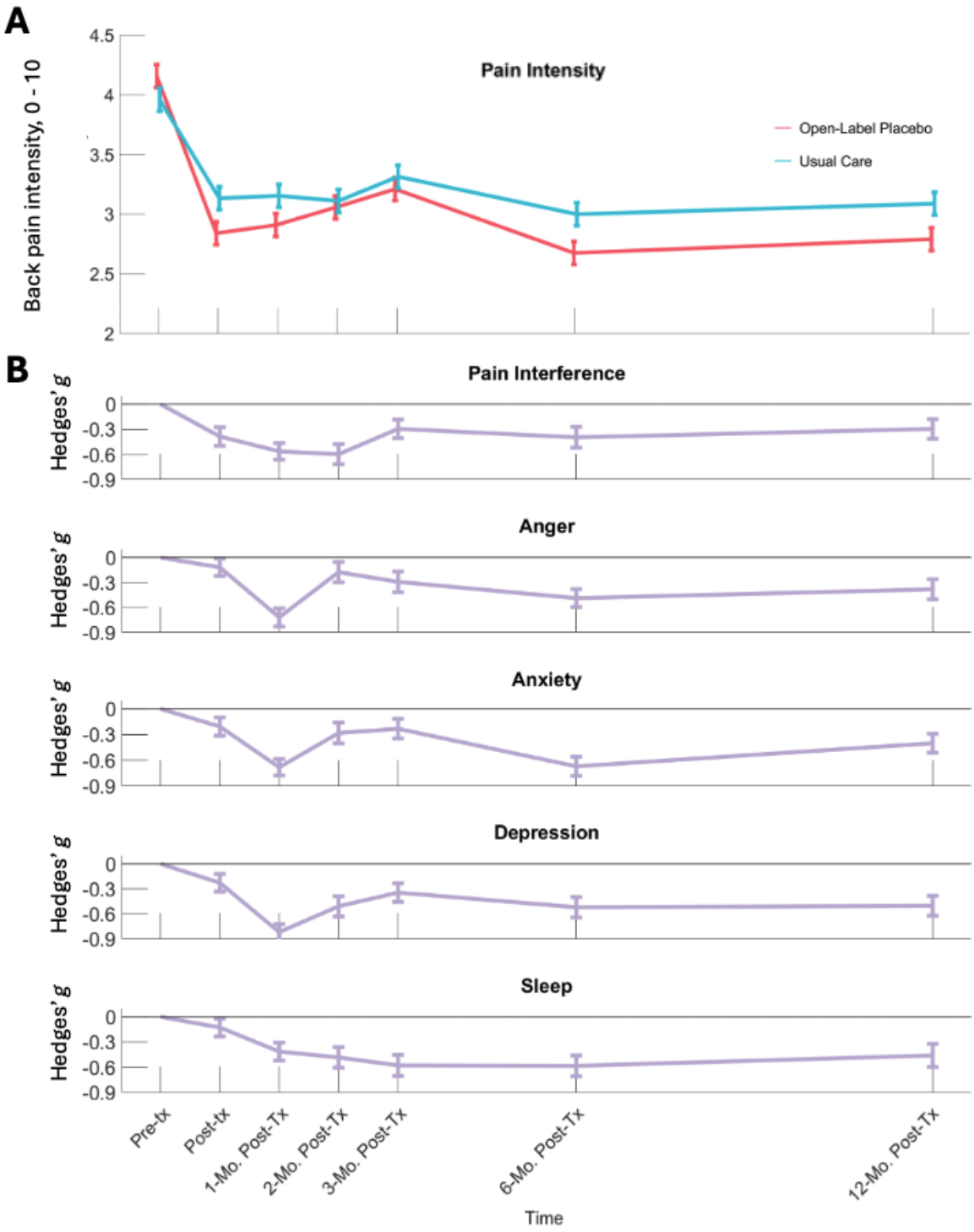
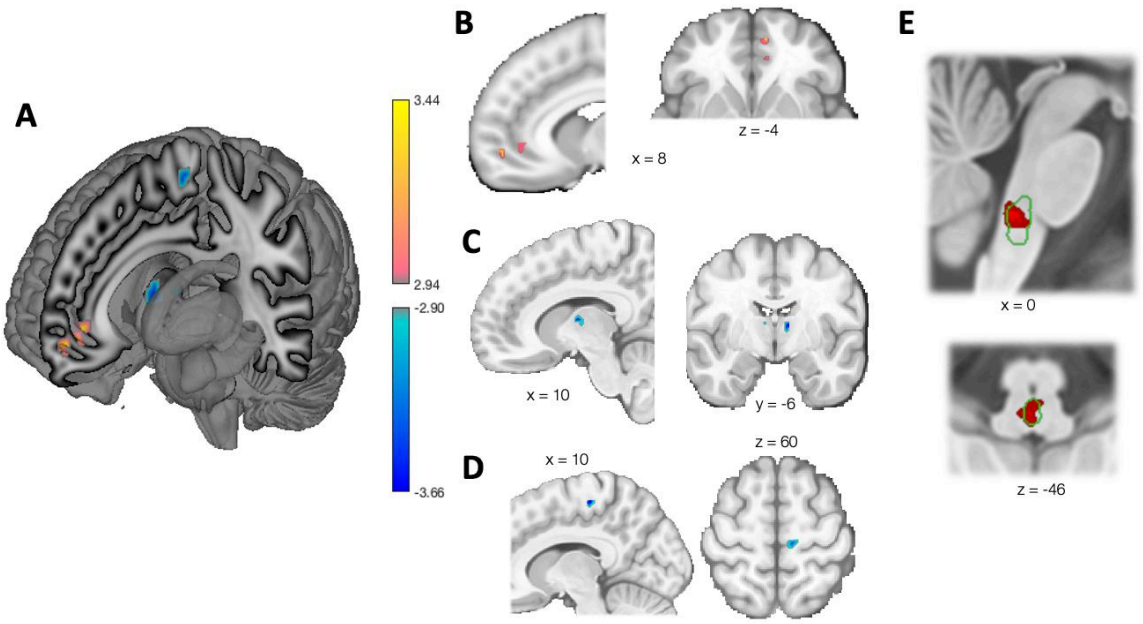


Figure 2. Effects of Open-label placebo (OLP) vs. Usual Care on patient-reported outcomes through 1-year follow-up. **A)** OLP vs. Usual Care led to reduced chronic back pain intensity (primary outcome, 0 – 10 scale) at post-treatment (primary endpoint), p = .03. OLP effects on pain intensity were not significant when testing throughout the entire follow-up period, though a marginally significant effect was observed at 1-year follow-up

(Table 2). Lines reflect sample means and error bars show within-subject SEM. **B)** OLP vs. Usual Care effect sizes on secondary patient-reported outcomes. Effect sizes were computed as group differences in change from baseline to the given timepoint (Hedges' g), with negative effects indicating greater improvement for OLP vs. Usual Care. Error bars depict standard error for the OLP vs. Usual Care effect size, adjusting for baseline scores.



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693 **Figure 3**. Effects of open-label placebo (OLP) vs. Usual Care on brain function in
694 chronic back pain. **A)** During evoked back pain, OLP vs. Usual Care led to increased
695 activity in the ventromedial prefrontal cortex (vmPFC, red) and decreased activity in
696 primary motor cortex and thalamus (blue), FWE $p < .05$ uncorrected. Insets show
697 findings for **B)** vmPFC, **C)** thalamus, and **D)** motor cortex. **E)** During spontaneous pain
698 (resting state), OLP vs. Usual Care led to increased functional connectivity between the
699 more anterior vmPFC region and the rostral ventral medulla (RVM), a brainstem nucleus
700 involved in pain processing and modulation; FWE $p < .05$. Green outlines show RVM
701 location with vmPFC connectivity increases shown in red.