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Brain Mechanisms of Anticipated Painful Movements and Their Modulation by Manual Therapy in Chronic Low Back Pain

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Abstract: **Heightened anticipation and fear of movement-related pain has been linked to detrimental fear-avoidance behavior in chronic low back pain (cLBP). Spinal manipulative therapy (SMT) has been proposed to work partly by exposing patients to nonharmful but forceful mobilization of the painful joint, thereby disrupting the relationship among pain anticipation, fear, and movement. Here, we investigated the brain processes underpinning pain anticipation and fear of movement in cLBP, and their modulation by SMT, using functional magnetic resonance imaging. Fifteen cLBP patients and 16 healthy control (HC) subjects were scanned while observing and rating video clips depicting back-straining or neutral physical exercises, which they knew they would have to perform at the end of the visit. This task was repeated after a single session of spinal manipulation (cLBP and HC group) or mobilization (cLBP group only), in separate visits. Compared with HC subjects, cLBP patients reported higher expected pain and fear of performing the observed exercises. These ratings, along with clinical pain, were reduced by SMT. Moreover, cLBP, relative to HC subjects, demonstrated higher blood oxygen level–dependent signal in brain circuitry that has previously been implicated in salience, social cognition, and mentalizing, while observing back straining compared with neutral exercises. The engagement of this circuitry was reduced after SMT, and especially the spinal manipulation session, proportionally to the magnitude of SMT-induced reduction in anticipated pain and fear. This study sheds light on the brain processing of anticipated pain and fear of back-straining movement in cLBP, and suggests that SMT may reduce cognitive and affective-motivational aspects of fear-avoidance behavior, along with corresponding brain processes.**

Perspective: ***This study of cLBP patients investigated how SMT affects clinical pain, expected pain, and fear of physical exercises. The results indicate that one of the mechanisms of SMT may be to reduce pain expectancy, fear of movement, and associated brain responses.***

Key words: *Pain anticipation, Expectation, Fear-avoidance, Physical exercise, chronic Low Back Pain, Spinal Manipulative Therapy, functional Magnetic Resonance Imaging.*

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Elevated anticipation of motion-related pain is common in chronic low back pain (cLBP),[69] and is associated with fear of movement and excessive avoidance behavior, which can be detrimental to health and quality of life, and prevent recovery.[50] Higher fear-avoidant behavior is associated with higher disability,[12,29,68,69,71] and reduction in fear/anxiety can predict successful therapy.[70] The fear-avoidance model of chronic pain posits that chronification of pain is often characterized by a vicious cycle whereby catastrophizing about pain leads to fear of movement and hypervigilance, which in turn can incite hypersensitization and exacerbation of pain, leading to yet more avoidance.[40] This cycle has been linked to Pavlovian and operant conditioning,[21,67] in which pain initially represents an unconditioned response to a nociceptive unconditioned stimulus, but may be elicited by a progressively wider range of nonharmful movements (conditioned stimulus).[27,46] While a large literature implicates psychological mechanisms of fear-avoidance behavior in pain, less is known about the brain mechanisms involved in the anticipation and fear of movement-evoked pain. Understanding these mechanisms is critically important, as they influence behavioral decisions to approach or avoid situations where a perceived harmful physical movement may occur.

Initial neuroimaging studies of cLBP patients observing back-straining maneuvers have found increased sympathetic responses[25] and altered brain processing in circuitry consistent with social cognition, salience, and mentalizing, such as the ventrolateral (vlPFC) and dorsomedial (dmPFC) prefrontal cortex, mid-anterior insula (m/aINS), middle temporal gyrus (MTG), superior temporal sulcus (STS), and amygdala. Notably, in these studies, participants passively viewed static pictures[4,5,61] or videos[43,44] depicting people in back-straining positions, without any actual prospect of executing physical activity by the participants themselves. Thus, the behavioral relevance of the context—and in turn fear—may have been limited.

Conditioned responses—such as fear of potentially harmful maneuvers—can be "unlearned" when the conditioned stimulus or conditioned response consistently occurs without leading to unconditioned response (eg, a perceived harmful motion is not followed by pain or harm). There is evidence that exposing patients to (feared) nonharmful physical activity, to extinguish fear responses, can reduce avoidance behavior in chronic musculoskeletal pain.[20,67,70] Interestingly, one proposed effect of spinal manipulative therapy (SMT), which involves salient sensory and proprioceptive feedback through passive mobilization of spine joints, is that it might help disrupt the association between fear, back-motion, and pain.[9,74] However, it has not yet been investigated whether SMT affects motivational aspects relevant to avoidance—such as anticipated pain and fear of movement. Moreover, very little is known about how SMT affects brain processing.[22]

Here, we investigated the brain-based underpinnings anticipated pain and fear of physical exercises, and the effect of 2 SMT techniques (grade 3 mobilization and grade 5 manipulation) on these outcomes. We hypothesized that, in cLBP, observation of back-straining, relative to neutral, exercises would elicit brain responses in circuitry involved in social cognition, fear, salience, and pain processing (eg, the anterior cingulate cortex, insulae, and amygdalae), in addition to visual and frontoparietal attention regions. Further, we hypothesized that SMT would reduce clinical pain, as well as fear, expected pain of back-straining exercises, and corresponding brain responses to observation of such exercises. Finally, we hypothesized that these effects would be stronger for SMT manipulation relative to mobilization, reflecting a dose response.

Methods

Subjects

Fifteen patients with cLBP (8 women, mean age 37.7 ± 9.7 years) and 16 individually age- and sex-matched healthy control (HC) subjects (8 women, mean age 38.2 ± 10.4 years) were enrolled. One HC subject was excluded from final paired analyses, as we were not able to recruit an age- and sex-matched cLBP patient for this individual. All subjects provided written informed consent before participation. The study was approved by the Human Research Committee of Massachusetts General Hospital and was conducted in accordance with the Declaration of Helsinki.

Inclusion criteria for cLBP patients included age ≥21 years and ≤65 years, nonspecific low back pain, diagnosed >6 months before enrollment, and ongoing pain that averaged at least 4 on a 0 to 10 scale of pain during the week before enrollment. Exclusion criteria included radicular pain (ie, pain radiating down below the knee); neural deficit in the lower extremity; positive dural tension signs; surgery within the past year related to back pain; pain management procedures during the study period; contraindications to functional MRI (fMRI); current or past history of major medical, neurological, or psychiatric illness other than chronic pain; peripheral nerve injury; diabetes; pregnancy; breast feeding; <6 months postpartum; history of head trauma; high blood pressure; use of opioid medications; use of recreational drugs; history of substance abuse; and back pain due to cancer, fracture, or infection. Exclusion criteria for HC subjects were, in addition to those for cLBP, chronic or acute low back pain.

Experimental Protocol

The study involved 3 study visits for cLBP patients—an initial behavioral visit, an MRI visit with SMT mobilization (ie, grade III of the Maitland Joint Mobilization Grading Scale),[28] and an MRI visit with SMT manipulation (ie, grade V of the Maitland Joint Mobilization Grading Scale). The order of the MRI visits was counterbalanced across subjects (mean interval between MRI visits was 24.7 ± 22.9 days). The HC group completed 2 study visits—an initial behavioral visit and an MRI visit with grade V SMT.

As we did not anticipate SMT-induced changes in clinical outcomes for HC subjects, we did not include an SMT mobilization visit for this group, as the comparison between SMT manipulation and SMT mobilization was aimed at investigating differences in clinical outcomes and associated brain responses. Therefore, our study had a mixed design, with both a within-subject (grade III vs grade V in cLBP patients) as well as a between-subject (Grade V in cLBP vs healthy participants) component. All visits took place at the MRI facilities at Martinos Center for Biomedical Imaging, Massachusetts General Hospital, between September 2014 and November 2016.

Behavioral Visit

Following informed consent, a licensed chiropractor performed a clinical evaluation (including history and physical examination) to further characterize the nature of the pain symptoms (or, in the case of healthy volunteers, to exclude the presence of back pain) and to determine the suitability and safety of manual therapy. All participants were also asked to perform a series of back-straining (eg, sit-ups, thrusts, leg lifts, pelvic tilts) and non–back-straining (eg, arm lifts, flexion-extension of the arms) physical exercises repeated 3 times each, rating the intensity (0 = no pain, 100 = the most intense pain tolerable) and unpleasantness (0 = neutral, 100 =extremely unpleasant) of their back pain after each repetition. The patients' responses to these exercises were used to guide the selection of subject-specific videos that most reliably exacerbated the patients' pain for use in the subsequent MRI visits.

MRI Visits

Participants were placed in a supine position in a 3T Siemens Skyra whole-body MRI scanner (Siemens Medical Systems, Erlangen, Germany). In each of 4 separate fMRI runs (~4.5 minutes each, 2 before and 2 after SMT), participants were shown 4 videos (20 seconds each)—2 depicting high back-straining exercises (BSE) and 2 depicting low back-straining exercises (Neutral)—in a pseudorandomized order (Fig 1, for illustrations of all the video material, see Supplemental Digital Content 1). For each cLBP patient, as well as his/her age- and sex-matched control subject, the BSE videos depicted an actor (sex-matched to the participant) performing the 2 back-straining exercises that most reliably elicited pain in the cLBP patient during the behavioral visit; in the control videos, the same actor performed non–back-straining exercises (identical in all participants). We decided to use videos rather than still images, as they are able to show the full dynamic of physical exercises, which likely increases their salience. To maximize the emotional impact of observing back-straining exercises, at the beginning of the imaging visit the participants were informed that at the end of the imaging visit they would be asked to perform the exercises they observed in the videos. Eight seconds after each video, the subjects were prompted to rate how much pain they expected from performing the exercise they saw on the previous video

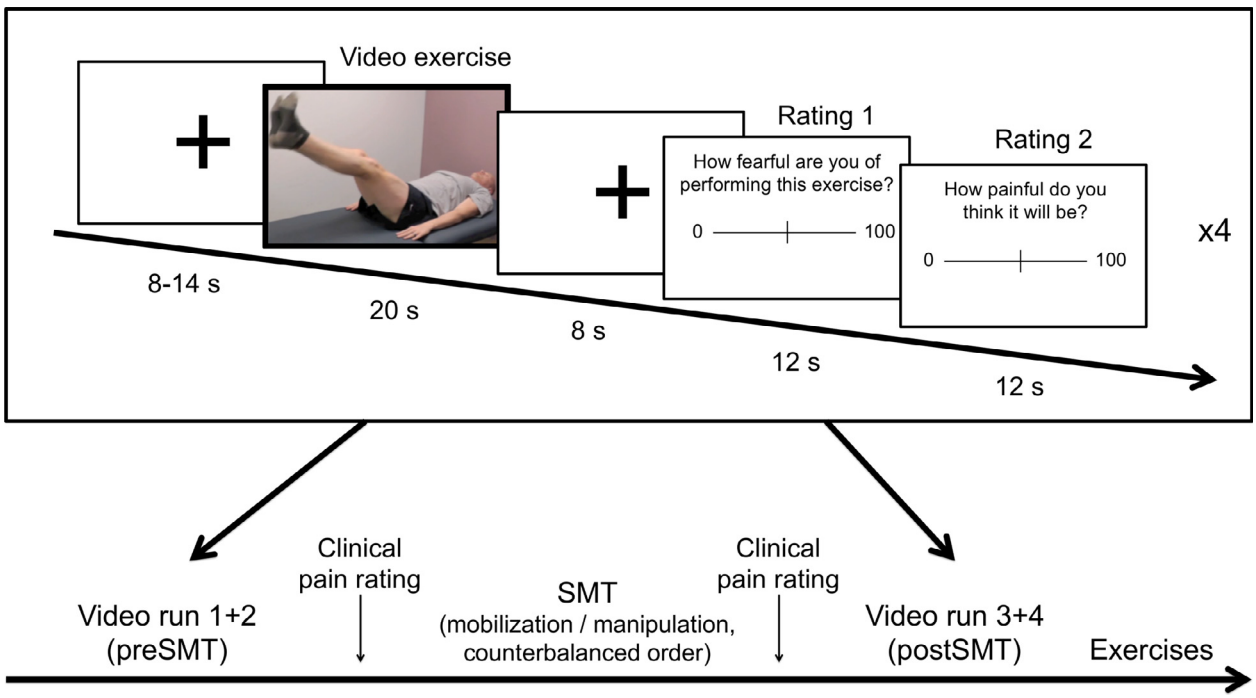

Figure 1. Experimental design. Participants viewed 20-second videos showing back-straining or neutral (non–back-straining) exercises in a pseudorandomized order. After each video, they rated fearfulness and expected pain from performing the exercise on visual analog scales. There were 8 videos (spread over 2 scan runs) before, and 8 videos after spinal manipulative therapy. At the end of each scan session, the participants were asked to perform the observed back-straining exercises, which had been established to be painful at the initial training visit for all chronic low back pain patients.

clip and how fearful they were of performing that exercise. After the first 2 fMRI runs, participants rated their clinical pain and were temporarily removed from the MRI bore, received SMT (either manipulation or mobilization) while on the scanner bed, rated their clinical pain again, and then were placed back into the MRI bore and completed the 2 final fMRI runs. At the end of the first visit, participants performed 5 repetitions of each of the back-straining and neutral exercises corresponding to the videos they had seen, in keeping with the instructions. The main purpose of this procedure was to ensure that the experimental induction of anticipation of clinical pain exacerbation would be still credible during the subsequent visit.

Psychophysical Measures

During the scanning procedures subjects used a button box for ratings, using scales displayed with E-Prime software version 1.1 (Psychology Software Tools, Sharpsburg, PA). Numerical rating scales (0–100) were used for low back pain (0 = no pain, 100 = the most intense pain tolerable) before and after the pre-SMT fMRI and the post-SMT fMRI runs. The same button box was used for ratings of expected pain from exercise (How painful do you think it will be?; 0 = no pain, 100 = the most intense pain tolerable) and fearfulness (How fearful are you of performing this exercise?; 0 = not at all fearful, 100 = extremely fearful).

At the training visit, participants filled out the following validated questionnaires for facilitating clinical characterization of the sample groups: Tampa Scale of Kinesiophobia (TSK),[45] Pain Catastrophizing Scale (PCS),[59] Beck Depression Inventory (BDI),[6] Brief Pain Inventory (BPI),[60] and a 5-point Likert-type treatment credibility scale modified from Sherman et al[57] (1 = definitely, 5 = definitely not). Additionally, they rated bothersomeness of low back pain on a visual analog scale (VAS) (0 = not at all bothersome, 100 = extremely bothersome), expected relief from SMT on a VAS (0 = does not work at all, 10 = complete relief), and desire for relief (0 = no desire for pain relief, 10 = the most intense desire for relief imaginable).

Psychophysics Data Analysis

To compare cLBP and HC groups on basic demographic, trait, and clinical characteristics, we performed paired t tests of age, TSK, PCS, BDI, and BPI scores; credibility of SMT; clinical pain at baseline; anxiety at baseline; low back bothersomeness; expected relief from SMT; and desire for relief.

To confirm that cLBP expected more pain from, and were more fearful of, performing back-straining relative to neutral exercises, we performed a mixed-design analysis of variance (ANOVA) with the factors group (cLBP, HC) and video exercise (BSE, Neutral), using baseline (pre-SMT) ratings from the first visit.

To investigate whether SMT affected cLBP patients' clinical pain, we performed an ANOVA with the factors SMT technique (manipulation, mobilization), and time (pre-SMT, post-SMT). Scan order (manipulation first, mobilization first) was included as a categorical covariate of no interest.

To investigate whether SMT affected cLBP patients' expected pain and fear of performing exercises, we used 2 separate repeated measures ANOVAs using each patient's mean expected pain and fearfulness (averaged across BSE and Neutral videos, separately), with the factors SMT technique (manipulation, mobilization), video exercise (BSE, Neutral), and time (pre-SMT, post-SMT). Scan order (manipulation first, mobilization first) was included as a categorical covariate of no interest.

We calculated Pearson correlation coefficients to investigate the relationship between SMT-induced change in clinical pain (post-SMT – pre-SMT) versus change in expected pain and change in fearfulness. To investigate the impact of positive expectation, we calculated Pearson correlation coefficients between expected relief from SMT versus SMT-induced changes in clinical pain, expected pain, and fearfulness. Behavioral data were analyzed using JASP (version 0.8.1.5 JASP Team, Amsterdam, Netherlands).

MRI Data Acquisition and Preprocessing

Blood oxygen level–dependent (BOLD) fMRI data were collected using a whole brain, simultaneous multislice, T2*-weighted gradient echo BOLD echo-planar imaging pulse sequence (repetition time = 1,250 ms, echo time = 33 ms, flip angle = 65°, voxel size = 2 mm isotropic, number of slices = 75, Simultaneous Multi-Slice (SMS) factor = 5). A high-resolution structural volume (multiecho MPRAGE) was collected for the purposes of anatomical localization and spatial normalization (repetition time = 2,530 ms, echo time = 1.69 ms, flip angle = 7°, voxel size = 1 mm isotropic).

fMRI data processing and analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.0, part of FSL (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl). The following preprocessing was applied: slice-timing correction, motion correction using MCFLIRT,[32] field map–based echo-planar imaging unwarping using PRELUDE and FUGUE,[30,31] nonbrain removal using BET,[58] spatial smoothing (full width at half maximum = 4mm), temporal high-pass filter (.011 Hz as computed by FSL's cutoffcalc), and grand-mean intensity normalization by a single multiplicative factor. All 4 runs were realigned (6 degrees of freedom) to a common space (the seventh volume of the first fMRI run) before first-level general linear model (GLM) analyses. The transformation matrix for the registration from functional to the high-resolution anatomical image was computed using Boundary Based Registration (FreeSurfer's bbregister tool).[26] For structural-to-standard space registration, we used the FSL's Linear registration tool (FLIRT, 12 degrees of freedom)[32,33] followed by FSL's nonlinear registration tool (FNIRT).[1] All single-subject analyses were performed in functional space, and registration to

Table 1. Subject Characteristics

	Group						95% Confidence Interval	
	cLBP	HC	t	df	P	Cohen's d	Lower	Upper
Age	37.7 ± 9.7	38.5 ± 10.1	.580	14	.571	.150	−1.258	2.191
Tampa Scale of Kinesiophobia	33.3 ± 5.7	33.1 ± 7.5	.854	14	.407	.221	−2.569	5.969
Pain Catastrophizing Scale	13.6 ± 10.2	6.2 ± 6.8	2.492	14	.026	.644	.972	12.962
Beck Depression Inventory	1.9 ± 2.7	4.1 ± 4.2	1.427	13	.177	.382	−1.082	5.296
Perceived credibility of SMT	1.8 ± .6	2.1 ± .8	−.942	13	.363	−.252	−.753	.295
Clinical pain (baseline, 0−100)	44.2 ± 18.6	.3 ± 1.2	8.484	13	<.001	2.268	32.889	55.361
Anxiety (baseline, 0−100)	12.2 ± 12.3	.8 ± 1.4	3.606	13	.003	.964	4.896	19.532
Brief Pain Inventory (severity, 0−10)	4.5 ± 1.4	.3 ± .4	1.768	14	<.001	2.780	3.358	5.029
Brief Pain Inventory (interference, 0−10)	3.2 ± 2.1	.1 ± .2	5.757	14	<.001	1.486	1.948	4.261
Low back bothersomeness (0−10)	5.0 ± 1.7	.5 ± 1.3	9.049	14	<.001	2.336	3.403	5.517
Expected relief (0−10)	5.3 ± 2.8	3.6 ± 3.3	1.363	14	.194	.352	−.962	4.315
Desire for relief (0−10)	9.0 ± 1.0	1.8 ± 3.4	7.150	14	<.001	1.846	5.101	9.472

Abbreviations: cLBP = chronic low back pain; HC = healthy control; SMT = spinal manipulative therapy.
NOTE. Values are mean ± SD unless otherwise indicated.

standard space (Montreal Neurological Institute 152) was applied before group analyses.

fMRI Data Analysis

Single-subject GLM analyses were carried out using FILM with local autocorrelation correction. For each run (2 pre-SMT and 2 post-SMT), we modeled the epochs corresponding to the video presentation (BSE, Neutral) as regressors in a GLM. In the same design matrix we also modeled rating periods, the first temporal derivative of each time course, and the 6 motion parameters as regressors of no interest. From this first-level analyses we computed a total of 6 contrasts: BSE—rest, Neutral—rest, BSE—Neutral, and their opposites. In a second-level fixed-effect analysis, we averaged the contrast maps across both pre-SMT runs and across both post-SMT runs separately, resulting in 2 sets of contrasts of parameter estimates for each contrast (pre-SMT and post-SMT).

To investigate brain responses to observing back-straining and neutral exercises, we carried out whole-brain voxelwise group GLMs separately for cLBP and HC subjects from the baseline (pre-SMT) scans at the first visit, for each of the 6 contrasts. Because the patient and control groups were recruited in a matching-pairs design (with each patient matched for age and sex to a control subject), the group contrasts were evaluated using paired t tests comparing age- and sex-matched cLBP and HC groups. Group inference was performed using FLAME (FMRIB's Local Analysis of Mixed Effects) 1 + 2, and the resulting statistical maps were cluster corrected for multiple comparisons using a cluster-forming voxelwise threshold of $Z > 2.3$, and a (corrected) cluster significance threshold of $P < .05$.

We then conducted whole-brain voxelwise GLMs to investigate SMT-induced change in BOLD responses (post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$) in $cLBP_{manip}$ relative to $cLBP_{mobil}$, and $cLBP_{manip}$ relative to HC subjects.

To investigate whether SMT-induced changes in expected pain and fear of movement were associated with changes in brain responses to these videos, we carried out whole-brain voxelwise regression analyses (post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$) with SMT-induced changes in expected pain and fearfulness ratings (post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$) as regressors of interest. These regression analyses were performed separately for SMT_{manip} and SMT_{mobil}, and for cLBP participants only since the HC group, as anticipated, did not show enough dynamic range in ratings of expected pain (12 of 15 rated expected pain as 0 both before and after SMT).

Visualization of brain imaging data was produced using FSL's FSLView for data displayed on volumes (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslView), FreeSurfer's Freeview for brain surfaces (https://surfer.nmr.mgh.harvard.edu), and Caret for cerebellar surfaces (http://www.nitrc.org/projects/caret/).[10,65]

Results

Demographic, Trait, and Clinical Characteristics

CLBP and HC groups did not significantly differ in age, TSK or BDI scores, perceived credibility of SMT, and expected relief from SMT (Table 1). We found significantly higher PCS scores, clinical pain (baseline VAS, BPI, and low back bothersomeness), baseline anxiety, and desire for relief for cLBP compared with HC subjects. For 1 cLBP patient, we did not obtain BDI, credibility, clinical pain, and anxiety. However, all participants were retained for data collection of all other data for both imaging visits.

cLBP Patients, Relative to HC Subjects, Expected More Pain From, and Were More Fearful of, Performing Back-Straining Exercises

A mixed-design ANOVA confirmed that cLBP patients, relative to HC subjects, anticipated the exercises depicted in the videos, when performed in first-person

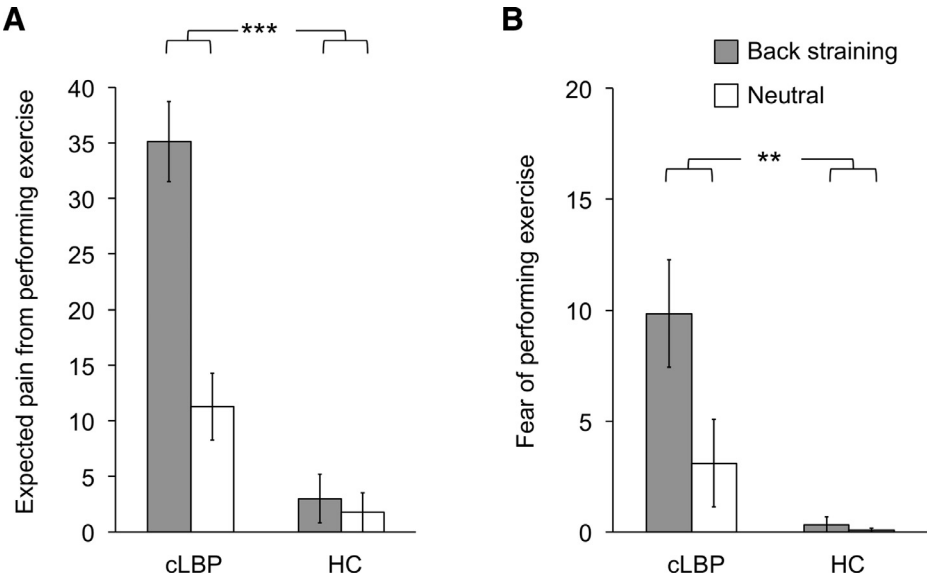

Figure 2. Ratings of videos showing back-straining and neutral exercises. Patients with chronic low back pain (cLBP) **(A)** expected back straining exercises to be more painful than neutral exercises, and **(B)** were more fearful of performing these exercises. There was a significant interaction, confirming that the difference in ratings between videos of back-straining and neutral exercises was significantly larger for cLBP compared with healthy control (HC) subjects. $^{**}P < .01$; $^{***}P < .005$.

at the end of the visit, to be more painful (main effect of group: $F_{1,13} = 31.54$, $P < .001$, $\eta^2_p = .71$). Furthermore, a main effect of video exercise confirmed higher expected pain from BSE relative to Neutral ($F_{1,13} = 35.87$, $P < .001$, $\eta^2_p = .73$). Most importantly, there was a group × video exercise interaction ($F_{1,13} = 32.38$, $P < .001$, $\eta^2_p = .71$). A paired t test between cLBP patients and HC subjects revealed that the difference in expected pain between BSE and Neutral conditions was significantly greater ($t_{14} = 5.82$, $P < .001$, $d = 1.50$) for cLBP patients (23.84 ± 15.32) compared with HC subjects (1.25 ± 2.60). The mean and SD data of the video ratings are presented in Figure 2.

A repeated-measures ANOVA confirmed higher fear of performing the exercises depicted in the videos for cLBP patients relative to HC subjects (main effect of group: $F_{1,13} = 6.88$, $P = .021$, $\eta^2_p = .35$). A main effect of video exercise confirmed higher fearfulness of BSE relative to Neutral exercises ($F_{1,13} = 2.79$, $P < .001$, $\eta^2_p = .62$). Importantly, there was a group × video exercise interaction ($F_{1,13} = 12.35$, $P = .004$, $\eta^2_p = .49$). This difference was significantly greater ($t_{14} = 3.77$, $P = .002$, $d = .97$) for cLBP patients (6.75 ± 6.01) compared with HC subjects (.25 ± 1.36).

Brain Responses to the Observation of Back Straining Relative to Neutral Physical Exercises

Baseline group brain responses to BSE and Neutral videos, compared with rest, are shown in Supplementary Figure 1. When observing BSE, compared with Neutral exercises, cLBP patients showed higher BOLD signal in multiple regions including visual areas (V) 1, 4, and 5; supramarginal gyrus; angular gyrus; temporoparietal junction (TPJ); a cluster in the superior parietal sulcus (STS)/middle temporal gyrus (MTG) compatible with the extrastriate body area; anterior insula (aINS); posterior cingulate cortex; anterior mid-cingulate cortex (aMCC); ventrolateral (vlPFC), dorsomedial (dmPFC), and dorsolateral (dlPFC) prefrontal cortices; thalamus; caudate; putamen; and cerebellum (Fig 3A).

The HC group also demonstrated higher BOLD signal during BSE relative to Neutral videos, but in a smaller number of regions (V5, supramarginal gyrus, TPJ, lateral PFC, aMCC, thalamus, putamen, and caudate) (Fig 3B).

A direct group comparison (cLBP vs HC) of the BSE−Neutral contrast revealed statistically significant clusters in bilateral dlPFC, left vlPFC/aINS, left STS/MTG, left TPJ, and dmPFC (Fig 3C, top). As illustrated by extracted mean Z scores in these regions (Fig 3C, bottom), cLBP patients demonstrated significant activations during observation of back-straining exercises, compared with no activation (or, in some cases, deactivation) when observing the neutral exercises. The HC subjects, on the other hand, showed no significant activation in response to either of the videos, and little or no difference across video type. A binarized mask created from regions significant in the $cLBP_{BSE\text{-}Neutral}$-$HC_{BSE\text{-}Neutral}$ contrast was used for the subsequent region of interest (ROI)−based investigation of the effects of SMT on the brain responses to observing exercises.

SMT Reduced Clinical Pain, Expected Pain, and Fear of Performing Physical Exercises

Clinical Pain

A significant ANOVA main effect of time ($F_{1,13} = 13.34$, $P = .003$, $\eta^2_p = .51$) indicated that clinical pain was reduced after SMT (31.12 ± 16.83) relative to the pre-SMT baseline (41.69 ± 18.11). There was no main effect

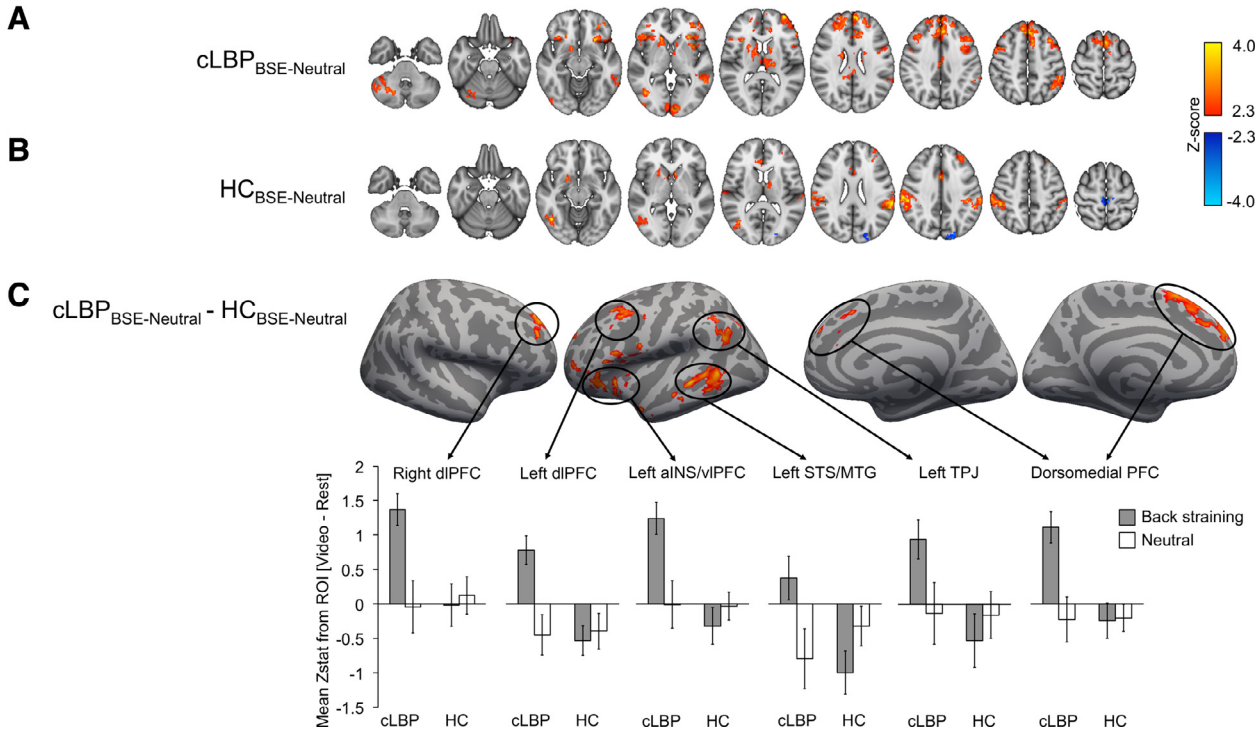

Figure 3. Blood oxygen level–dependent (BOLD) responses to observing back-straining exercises (BSE) relative to neutral exercises (Neutral). **(A)** Activation maps show cluster-corrected BOLD responses (voxel-based Z scores, before spinal manipulative therapy) to viewing BSE relative to Neutral videos in chronic low back pain (cLBP) patients, and **(B)** age- and sex-matched healthy control (HC) subjects, and **(C)** in cLBP patients relative to HC subjects. There were no significant voxels in the opposite contrast (HC subjects – cLBP patients). Bar plots show mean Z scores within regions of Interest (ROIs) drawn from the [$cLBP_{BSE\text{-}Neutral} - HC_{BSE\text{-}Neutral}$] contrast, indicating the interaction was driven by increased BOLD responses to BSE videos for cLBP patients. Error bars represent SEM. Abbreviations: dlPFC = dorsolateral prefrontal cortex; aINS = anterior insula; mPFC = medial prefrontal cortex; STS = superior temporal sulcus; MTG = middle temporal gyrus; TPJ = temporoparietal junction; PFC = prefrontal cortex.

of SMT technique ($F_{1,13} = .25$, $P = .63$, $\eta^2_p = .02$) and no time × SMT technique interaction ($F_{1,13} = .22$, $P = .65$, $\eta^2_p = .02$). Thus, the data did not support the hypothesis that the effect of SMT on clinical pain is different between manipulation and mobilization (Fig 4A).

Expected Pain

A significant ANOVA main effect of time ($F_{1,13} = 8.99$, $P = .01$, $\eta^2_p = .41$) indicated that expected pain from the exercises was reduced after SMT (20.94 ± 16.97) relative to before (24.87 ± 19.08). As hypothesized, there was a significant main effect of video exercise ($F_{1,13} = 29.85$, $P < .001$, $\eta^2_p = .70$), with BSE (34.95 ± 13.86) rated higher than Neutral (10.86 ± 13.15). There was a significant time × video exercise interaction ($F_{1,13} = 6.28$, $P = .026$, $\eta^2_p = .33$). In line with our hypothesis, a direct t test indicated that the SMT-induced reduction was stronger for BSE (Δ[post-SMT – pre-SMT]: −5.66 ± 7.6) than for Neutral (Δ[post-SMT – pre-SMT]: −2.21 ± 2.27) videos ($t_{14} = 1.99$, $P = .034$) (Fig 4B). There was a significant SMT technique × scan order interaction ($F_{1,13} = 4.92$, $P = .045$, $\eta^2_p = .27$). There were no significant interactions between time × SMT technique ($F_{1,13} = .25$, $P = .62$, $\eta^2_p = .02$) and time × video exercise × SMT technique ($F_{1,13} = 1.35$, $P = .27$, $\eta^2_p = .09$). Thus, the data did not suggest that that the effect of SMT on expected pain was different depending on the SMT technique used.

Fear of Movement

A significant main effect of time ($F_{1,13} = 4.89$, $P = .046$, $\eta^2_p = .27$) indicated fearfulness was reduced after SMT (7.13 ± 10.47) relative to before (7.91 ± 11.35) (Fig 4C). As expected, there was also a main effect of video exercise ($F_{1,13} = 25.37$, $P > .001$, $\eta^2_p = .66$), showing higher fearfulness ratings of BSE (11.80 ± 11.13) relative to Neutral videos (3.24 ± 8.82). There were no other significant main effects or interactions (all Ps > .06). Thus, the data did not suggest that an SMT-induced reduction in fearfulness was different across different video types or SMT techniques.

Relationship Between Clinical Pain Versus Expected Pain and Fearfulness cLBP patients' change in clinical pain (post-SMT – pre-SMT) correlated significantly with change in expected pain ($post\text{-}SMT_{BSE\text{-}Neutral} - pre\text{-}SMT_{BSE\text{-}Neutral}$) ($r = .58$, $P = .02$), indicating that patients with the greatest reduction in clinical pain following SMT also had the greatest reduction in expected pain from performing the observed back-straining exercises (Fig 4D). We did not find a statistically significant correlation between change in fearfulness and change in clinical pain ($r = .17$, $P = .55$).

Relationship Between Expected Relief of SMT Versus SMT Outcomes cLBP patients' expected relief of SMT correlated significantly with change in clinical pain ($r = .67$, $P = .006$) and expected pain from performing

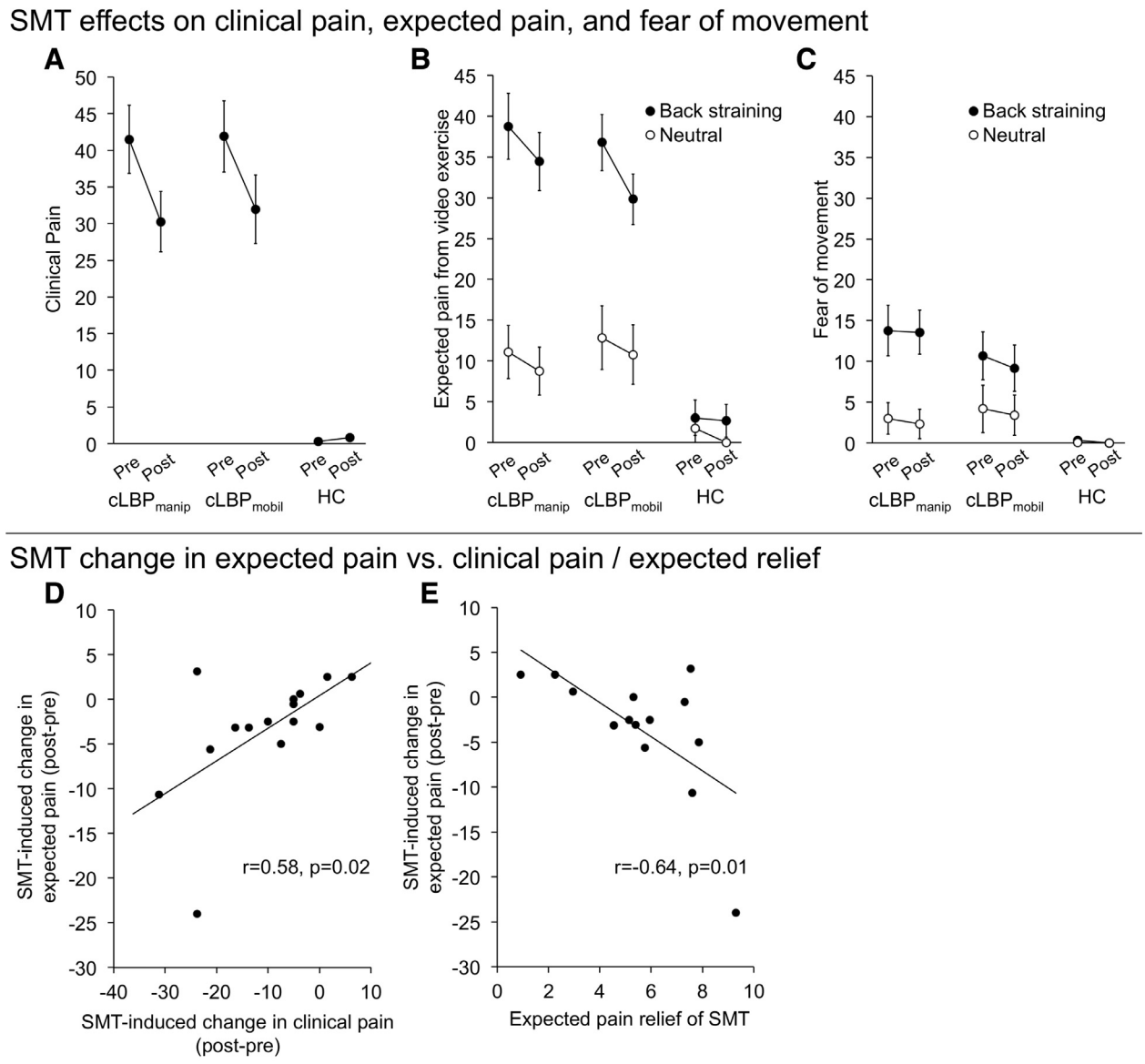

Figure 4. Spinal manipulative therapy (SMT)–induced change in clinical pain and expected pain from, and fear of, performing physical exercises. **(A)** SMT significantly reduced clinical pain ($P = .003$), but this pain change did not differ between SMT_{manip} and SMT_{mobil} ($P = .65$). **(B)** SMT reduced expected pain from performing exercises in chronic low back pain (cLBP) patients ($P = .01$). This reduction was significantly stronger for back-straining exercises relative to neutral exercises ($P = .03$). **(C)** SMT reduced overall fear of performing exercises in cLBP patients ($P = .046$). **(D)** SMT-induced change in clinical pain (post-SMT − pre-SMT) correlated with SMT-induced change in expected pain, such that those with the strongest pain reduction also had the strongest reduction in expected pain of performing back-stressing exercises. **(E)** In cLBP patients, expected pain relief of SMT correlated significantly with SMT-induced change in expected pain from performing exercise (back-straining − neutral). *$P < .05$. Abbreviation: HC = healthy control.

exercise (post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$) ($r = -.64$, $P = .01$). There was no significant correlation between expected relief from SMT and change in fearfulness ($r = -.22$, $P = .44$).

SMT Reduced Brain Responses in Circuitry Involved in Processing Observed Back-Straining Exercises

A whole-brain voxelwise within-group interaction in the cLBP group ($cLBP_{manip}$[post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$] − $cLBP_{mobil}$ [post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$]) showed a statistically significant difference in the effect of technique (manipulation vs mobilization) in left STS, right aINS, right S1, right superior temporal gyrus (STG), bilateral dlPFC, vlPFC, vmPFC, posterior insula, paracingulate, medial occipital cortex, and cerebellum (Fig 5A). Furthermore, a between-group interaction ($cLBP_{manip}$[post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$] − HC [post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$]) indicated the presence of a statistically significant difference in the effect of manipulation across groups (cLBP vs HC) (Fig 5A) in left TPJ and bilateral aINS, vlPFC, dlPFC, STS/MTG, medial occipital cortex, and right cerebellum (Fig 5B). The examination of Z-stat values from these regions suggested that the interaction was driven by a BOLD contrast reduction following SMT_{manip}, when

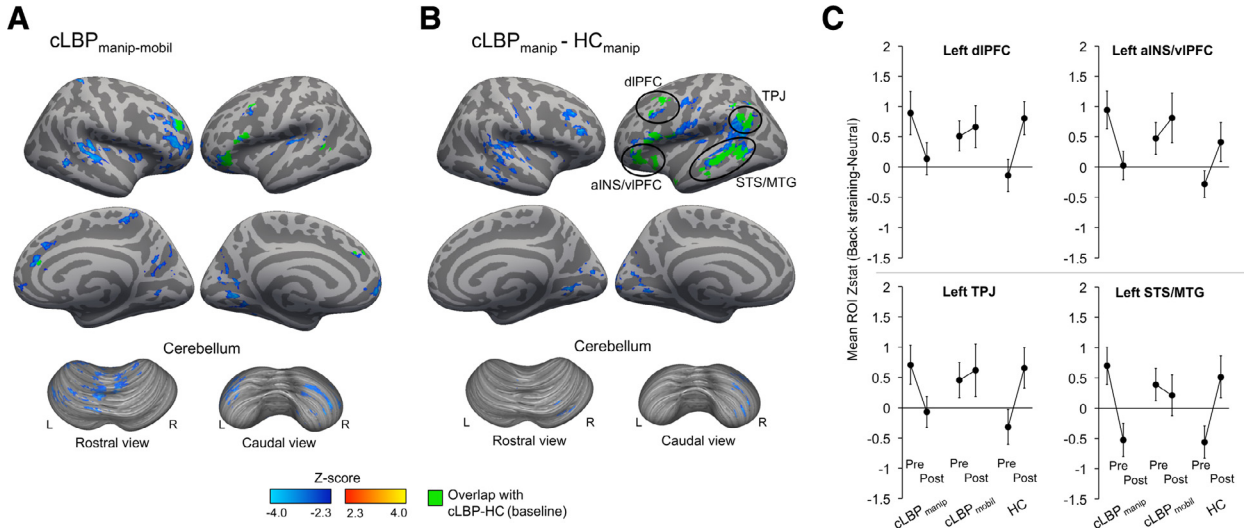

Figure 5. Manual therapy reduced blood oxygen level–dependent (BOLD) responses to videos showing back-straining exercises relative to neutral exercises in chronic low back pain (cLBP) patients. To investigate spinal manipulative therapy (SMT) effects on BOLD responses to observing back straining exercises (BSE), we compared whole-brain contrast parameters (post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$) for chronic low back pain (cLBP) patients receiving grade 5 manipulation ($cLBP_{manip}$) relative to those receiving grade 3 mobilization ($cLBP_{mobil}$) and healthy control (HC) subjects. $cLBP_{manip}$ showed a widespread reduction of BOLD contrast relative to **(A)** $cLBP_{mobil}$ and **(B)** HC. **(C)** To illustrate directionality, mean Z values were extracted from regions of interest (ROIs) where the cLBP patient/HC subject contrast overlapped with voxels that showed a stronger BOLD signal in response to BSE for cLBP patients relative to HC subjects at baseline (the [$cLBP_{BSE\text{-}Neutral}$ − $HC_{BSE\text{-}Neutral}$] contrast= (see Figure 3C). Error bars represent SEM. Abbreviations: dlPFC = dorsolateral prefrontal cortex; TPJ = temporoparietal junction; vlPFC = ventrolateral prefrontal cortex; aINS = anterior insula; mPFC = medial prefrontal cortex; STS = superior temporal sulcus; MTG = middle temporal gyrus.

observing back-straining exercises (BSE-Neutral) for cLBP patients, compared with an increase for HC subjects (Fig 5C). Exploratory contrasts showing the contrast (post-$SMT_{BSE\text{-}Neutral}$ − pre-$SMT_{BSE\text{-}Neutral}$) separately for $cLBP_{manip}$ and $cLBP_{mobil}$ are shown in Supplementary Figure 2.

SMT-Induced Change in Expected Pain Correlated With SMT-Induced Change in Brain Responses to Observation of Back-Straining Exercises

A whole-brain voxelwise regression analysis indicated that, for $cLBP_{manip}$, those patients with the largest SMT-induced reduction in expected pain from performing back-straining exercises also had the largest SMT-induced reduction in BOLD fMRI responses to videos in right TPJ, left STS/STG, left m/aINS, aMCC, and SMA (Fig 6A, left). To illustrate this relationship, we extracted mean Z scores from 2 ROIs (aINS and STS) identified by the intersection of the correlation map and with the activation map from the baseline ($cLBP_{BSE\text{-}Neutral}$ -$HC_{BSE\text{-}Neutral}$) contrast (Fig 3C), and plotted these values against SMT-induced Δexpected pain (BSE-Neutral) (Fig 6A, right). There was no significant correlation between SMT-induced change in expected pain and BOLD responses to videos for $cLBP_{mobil}$. For $cLBP_{manip}$, there was a significant correlation between SMT-induced change in fear of movement and BOLD responses to videos (BSE-Neutral) in right MTG, right lateral occipital cortex, medial thalamus, and the periaqueductal gray matter (Fig 6B). For $cLBP_{mobil}$, there was a significant correlation between SMT-induced change in fear of movement and BOLD responses to videos (BSE-Neutral) in left STS/MTG, left mid-posterior insula, posterior cingulate cortex, precuneus, medial occipital cortex, and cerebellum (Fig 6C).

Conclusions

We used fMRI to investigate brain processes supporting fear of movement and anticipated pain of back-straining exercises in cLBP patients, and modulation of this brain circuitry by SMT. cLBP, relative to age- and sex-matched HC subjects, reported higher fear, and anticipated pain, of performing back-straining exercises depicted by observed videos, which was accompanied by increased BOLD fMRI responses in brain circuitry involved in social processing, emotion regulation, and salience. SMT reduced clinical pain, fear of movement, and expected pain from back-straining exercises. Furthermore, reductions in fear and expected pain correlated with reductions in BOLD responses to observing back-straining exercises. Although there were no differences between SMT techniques on self-report assessment, SMT_{manip} was associated with stronger reduction in BOLD responses, relative to SMT_{mobil} and HC subjects. These results shed light on 1) the brain processing underpinning aversive anticipation of back-straining movements in cLBP and 2) how SMT might affect these motivational processes.

We found that cLBP patients, relative to HC subjects, showed greater BOLD responses in the vlPFC,

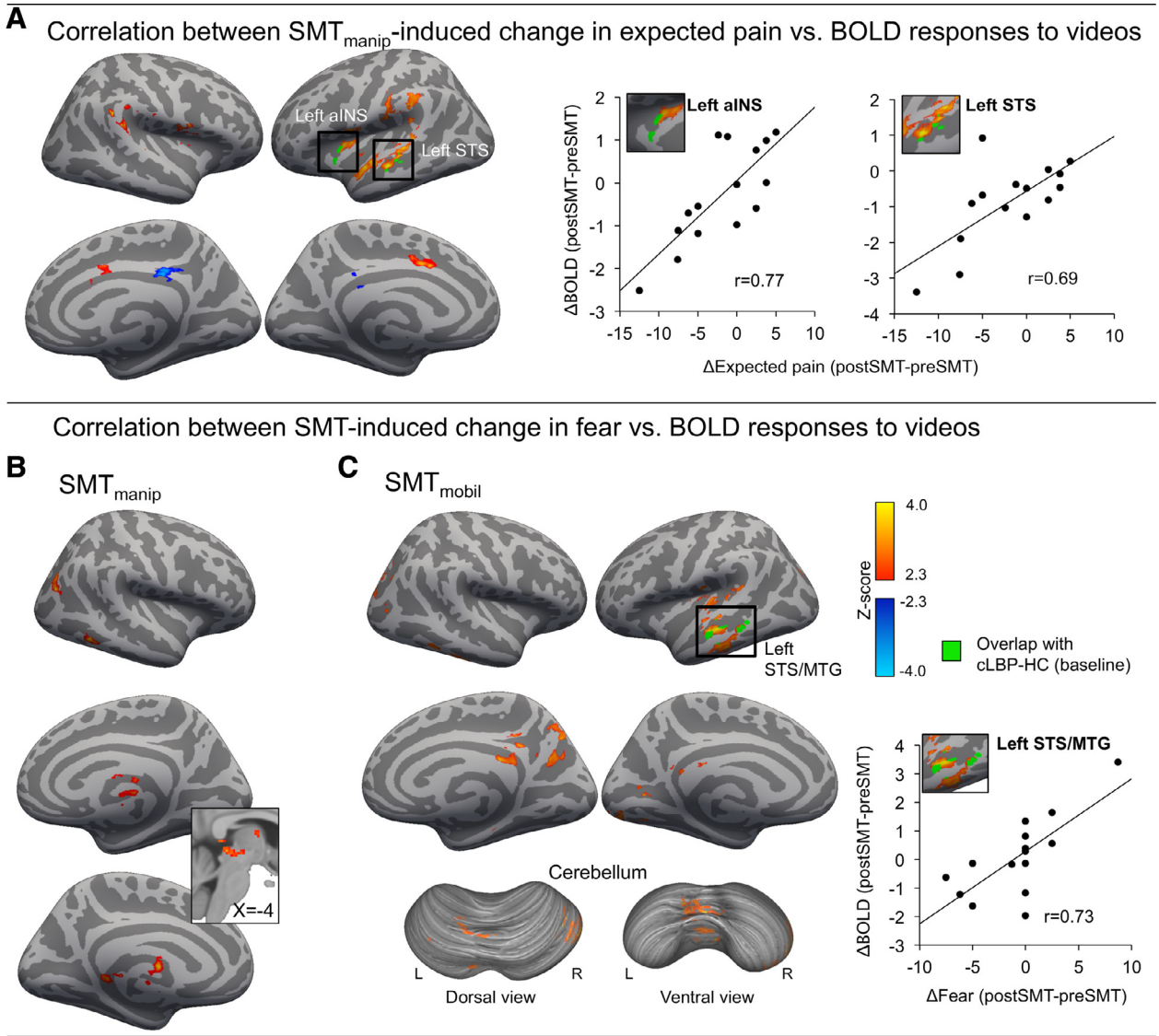

Figure 6. Correlation between spinal manipulative therapy (SMT)–induced change in blood oxygen level–dependent (BOLD) responses to videos and change in expected pain from, and fear of, performing back-straining exercises. **(A)** Activation maps (whole-brain cluster-corrected) show brain regions where SMT-induced ΔBOLD responses (post-SMT − pre-SMT) correlated with Δexpected pain (post-SMT − pre-SMT). To illustrate directionality, scatterplots show region of interest (ROI)–extracted mean Z-scores from 2 regions (left anterior insula [aINS] and left superior temporal sulcus [STS], marked green) identified by the intersection of the correlation map and the [$cLBP_{BSE\text{-}Neutral}$ − $HC_{BSE\text{-}Neutral}$] activation map at baseline (both cluster-corrected significance thresholded). There were no significant correlations with change in expected pain for SMT_{mobil}. Furthermore, SMT-induced change in fear of movement correlated with BOLD changes elicited by **(B)** SMT_{manip} and **(C)** SMT_{mobil}. To illustrate directionality, ROI-extracted mean Z scores are shown from left STS, a region that showed an overlap with the baseline [$cLBP_{BSE\text{-}Neutral}$ − $HC_{BSE\text{-}Neutral}$] activation map. Abbreviations: MTG = middle temporal gyrus; cLBP = chronic low back pain; HC = healthy control.

aINS, dmPFC, dlPFC, TPJ, and STS/MTG when observing videos of individuals performing back-straining relative to neutral exercises. Several of these regions (dmPFC, aINS, and dlPFC) are known nodes of the salience network,[7] and have been implicated in pain anticipation.[23,48] These regions have also been implicated in goal formation, prediction error processing, and top-down modulation of pain.[37,47,52,72] Furthermore, vlPFC, TPJ, and STS have been consistently implicated in mentalizing, theory of mind, and social cognition more generally.[18,55,56,66] Finally, the STS/MTG cluster is consistent with the extrastriate body area, which is implicated in processing observed bodies and body parts.[14,36]

Previous studies investigating fear of movement in cLBP have produced mixed results. Consistent with our findings, 1 recent study found that cLBP relative to HC showed increased activation of vlPFC, aINS, STG/STS, and dmPFC/ACC in response to observing images of back-straining relative to neutral activities.[61] Another study also found increased vlPFC and amygdala activation for videos showing back-straining versus back-neutral activities, albeit no BOLD contrast difference between cLBP and HC.[44] Another study found increased hippocampal activation for high-fear cLBP patients compared with HC subjects,[5] while an earlier study found no patient versus HC subject contrast in fMRI response to still images of back-straining maneuvers.[4] These

discrepancies may be due to protocol differences. Our study differs from earlier reports in 2 important ways. First, while most previous studies (except [61]) used a preselected pool of aversive stimuli, we used individually tailored back-straining videos for each patient based on which exercises were most painful, maximizing the contrast between back-straining and neutral stimuli. Second, our stimuli were likely more behaviorally relevant than in previous studies, as the participants knew they would be asked to perform the same exercises depicted in the videos. This may have improved our sensitivity in recording relevant brain processes.

We did not find increased BOLD responses in circuitry typically associated with fear, such as the amygdala, aMCC, and subgenual ACC. One reason may be that, despite significantly higher cLBP fear ratings for back-straining compared with neutral videos, and compared with HC subjects, the task did not appear to induce intense kinesiophobia, with relatively small magnitude of fear overall, and with several patients reporting no fear at all. Thus, it is still possible that amygdala/subgenual ACC play important roles for chronic pain-related kinesiophobia in real-life situations involving stronger fear.[54] Moreover, previous studies have also reported limited fear and perceived aversiveness of specifically designed "fear-evoking" visual stimuli,[4,5,44] some of which nevertheless reported increased BOLD responses in the amygdala.[42,44] Future studies may use brainstem-optimized acquisition to investigate the involvement of other key structures important for fear conditioning, such as the posterior and medial hypothalamic nuclei,[16,19,64,73] dorsal periaqueductal gray matter,[62,64] and the superior colliculus.[41]

Notably, we observed higher ratings of expected pain compared with fear, suggesting patients still found the observed exercises aversive, but perhaps on a more cognitive level, with limited affect. Expectations play a crucial role in pain. Expectations about whether pain will improve or worsen following an intervention can lead to hypo- or hyperalgesia, respectively.[2,17,34,51] Importantly, expectations and beliefs about the outcome of certain actions guide behavioral decisions on whether to approach or avoid.[72] Interestingly, we found that initial expectations of treatment relief correlated with reduction in expected pain from back-straining exercises (Fig 3E). Fear responses likely play a crucial role in the acquisition of avoidance behavior, and are elicited in situations where such feared movements are likely to occur. Nevertheless, explicit fear may potentially be limited during abstract cognitive evaluation of the outcomes of movement—such as in the context of our study—during which avoidance decisions are often made.[35]

We found that SMT reduced not only patients' clinical back pain, but also the aversiveness of the observed back-straining exercises (ie, both fear and expected pain). Moreover, this correlated with SMT-induced reduction in BOLD responses. Specifically, patients with stronger reduction in expected pain also had stronger reduction in BOLD responses in aINS, STS/STG, aMCC, and Secondary Somatosensory Area II (SII) (SMT_{manip}) and for reduction in fear and BOLD responses in STS/MTG, posterior insula, posterior cingulate cortex, and cerebellum (SMT_{mobil}). One possibility is that SMT may disrupt the association between low back movement, fear, and pain.[9,74] Within the fear-avoidance framework, SMT elicits salient sensory and proprioceptive input from the painful region (low back), presumably followed by not only an absence of a unconditioned stimulus/unconditioned response (nociception/pain), but also a reduction of pain. This might help disrupt the association between low back sensations and fear responses—somewhat reminiscent of exposure therapy—which may in turn reduce the aversiveness of back-straining exercises.[67] Alternatively, the reduction in fear and expected pain could be a direct consequence of reduced clinical pain, as people are more aversive to movements when in more pain.[15,63] If so, we would expect a similar reduction regardless of the location or mode of analgesia.[13] Future studies should systematically compare these motivational aspects during pain relief from treatments involving exteroceptive/proprioceptive stimuli of the painful limb (eg, SMT for cLBP) versus treatment that does not (eg, pharmacotherapy). According to the fear-avoidance model, fear learning is a key component of chronification of pain (and emerging avoidance behavior), and unlearning (eg, through exposure to motion) is suggested as a key mechanism to reduce avoidance behavior and disability.[20,67] Pharmacological treatment alone has limited prolonged efficacy for chronic pain,[3] potentially due to an inability to target the deeply engrained association between pain anticipation, fear, physical maneuvers, and pain.[21,24] SMT, either as monotherapy or potentially in combination with psychological therapy such as cognitive behavioral therapy, may have the advantage of targeting this learning aspect of chronic pain, along with other putative mechanisms such as counterirritation and improved local circulation due to reduced muscle tension.[8,38]

We did not find evidence that different techniques of SMT had a differential effect on clinical pain, fear of movement, or expected pain. Previous studies have similarly not found notable differences in efficacy between techniques.[11,22,39,49,53] However, we did find differences between techniques in brain responses to the observations of back-straining exercises. cLBP patients relative to HC subjects showed widespread reductions in BOLD responses to back-straining videos after SMT_{manip}, notably in circuitry identified in the baseline contrast, such as the dlPFC, aINS, vlPFC, TPJ, and STS/MTG. Direct comparison indicated that, for cLBP, SMT_{manip} induced stronger BOLD contrast reductions in the dlPFC, vlPFC, aINS, posterior STS/STG, and dmPFC, relative to SMT_{mobil}. Taken together, these results suggest that in cLBP patients, SMT_{manip} induced stronger reduction of BOLD responses in circuitry involved in processing observed back-straining relative to neutral exercises, compared with SMT_{mobil}. This is in line with our hypothesis that SMT_{manip}, which involves greater amplitude of manipulation directed to the spine joints, would elicit stronger effects on clinical outcomes. However, the lack of a difference in subjective reports warrants a more cautious interpretation.

There are several limitations in our study. First, we assessed outcomes from only a single session of SMT_{manip} and SMT_{mobil}. Longitudinal studies involving multiple

sessions may better parse SMT-induced changes in brain responses with clinically relevant outcomes. Second, we did not observe group differences (cLBP/HC) in trait kinesiophobia.[45] Importantly however, cLBP showed significantly higher fear and expected pain from observed back-straining exercises compared with neutral, which is more central for testing our hypotheses. Furthermore, we observed similar trait kinesiophobia scores as previous studies.[4,5,43,44] Notably, previous studies have also shown no differences in trait kinesiophobia between chronic pain samples and HC subjects,[44] highlighting the possibility that generalized trait kinesiophobia might not be as relevant for chronic pain as situational kinesiophobia that is being acquired through individualized history of movement, fear, and pain. Another limitation is that the sample size, while similar to those of many other fMRI studies, was relatively limited and may be susceptible to type II errors. As such, this study should be followed up by replication in larger samples. This would also allow more advanced (eg, mediation and moderation) analyses aimed at more directly evaluating the possible causal relationship between brain and behavioral changes induced by SMT.

In conclusion, we found that observation of back-straining exercises was associated with increased fear and expected pain of performance in cLBP patients compared with HC subjects, and elicited increased BOLD responses in vlPFC, aINS, dlPFC, dmPFC, TPJ, and STS/MTG. In cLBP patients, both SMT_{manip} and SMT_{mobil} reduced both clinical pain and aversiveness (fear and expected pain) of observed back-straining exercises. Although the 2 techniques did not differentially affect these clinical outcomes, SMT_{manip} relative to SMT_{mobil} elicited stronger overall reduction of brain circuitry involved in appraisal of observed back-straining exercises. Importantly, stronger reduction in averseness (fear and expected pain) was associated with stronger reduction in BOLD responses in this circuitry to observing back-straining exercises. Potentially, SMT might modulate the aversiveness of performing back-straining maneuvers through disruption of the association between these (exteroceptive and proprioceptive) sensations and fear/pain. Future studies should address the effect of therapies such as SMT on motivational aspects and avoidance behavior more directly, and include multiple sessions of therapy.

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.jpain.2018.05.012.

References

1. Andersson J, Jenkinson M, Smith S: Non-linear registration, aka spatial normalisation, FMRIB technical report TR07JA2, 2010.

2. Atlas LY, Bolger N, Lindquist MA, Wager TD: Brain mediators of predictive cue effects on perceived pain. J Neurosci 30:12964-12977, 2010

3. Ballantyne JC, Mao J: Opioid therapy for chronic pain. N Engl J Med 349:1943-1953, 2003

4. Barke A, Baudewig J, Schmidt-Samoa C, Dechent P, Kroner-Herwig B: Neural correlates of fear of movement in high and low fear-avoidant chronic low back pain patients: an event-related fMRI study. Pain 153:540-552, 2012

5. Barke A, Preis MA, Schmidt-Samoa C, Baudewig J, Kroner-Herwig B, Dechent P: Neural correlates differ in high and low fear-avoidant chronic low back pain patients when imagining back-straining movements. J Pain 17:930-943, 2016

6. Beck AT, Steer RA, Brown GK: Beck depression Depression inventoryInventory-II. (Corporation, P., Ed.), San Antonio, TX, Psychological Corporation, 1996.

7. Beckmann CF, DeLuca M, Devlin JT, Smith SM: Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360:1001-1013, 2005

8. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ: The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. Man Ther 14:531-538, 2009

9. Bishop MD, Torres-Cueco R, Gay CW, Lluch-Girbes E, Beneciuk JM, Bialosky JE: What effect can manual therapy have on a patient's pain experience. Pain Manag 5:455-464, 2015

10. Chou R, Shekelle P: Will this patient develop persistent disabling low back pain. JAMA 303:1295-1302, 2010

11. Cleland JA, Glynn P, Whitman JM, Eberhart SL, MacDonald C, Childs JD: Short-term effects of thrust versus nonthrust mobilization/manipulation directed at the thoracic spine in patients with neck pain: a randomized clinical trial. Phys Ther 87:431-440, 2007

12. Cook AJ, Brawer PA, Vowles KE: The fear-avoidance model of chronic pain: validation and age analysis using structural equation modeling. Pain 121:195-206, 2006

13. Coronado RA, Gay CW, Bialosky JE, Carnaby GD, Bishop MD, George SZ: Changes in pain sensitivity following spinal manipulation: a systematic review and meta-analysis. J Electromyogr Kinesiol 22:752-767, 2012

14. Costantini M, Urgesi C, Galati G, Romani GL, Aglioti SM: Haptic perception and body representation in lateral and medial occipito-temporal cortices. Neuropsychologia 49:821-829, 2011

15. Crombez G, Eccleston C, Van Damme S, Vlaeyen JW, Karoly P: Fear-avoidance model of chronic pain: the next generation. Clin J Pain 28:475-483, 2012

16. dos Anjos-Garcia T, Ullah F, Falconi-Sobrinho LL, Coimbra NC: CB1 cannabinoid receptor-mediated anandamide signalling reduces the defensive behaviour evoked through GABA(A) receptor blockade in the dorsomedial division of the ventromedial hypothalamus. Neuropharmacology 113:156-166, 2017

17. Ellingsen DM, Wessberg J, Eikemo M, Liljencrantz J, Endestad T, Olausson H, Leknes S: Placebo improves

pleasure and pain through opposite modulation of sensory processing. Proc Natl Acad Sci U S A 110:17993-17998, 2013

18. Etkin A, Buchel C, Gross JJ: The neural bases of emotion regulation. Nat Rev Neurosci 16:693-700, 2015

19. Falconi-Sobrinho LL, dos, Anjos-Garcia T, Elias DH, Coimbra NC: Unravelling cortico-hypothalamic pathways regulating unconditioned fear-induced antinociception and defensive behaviours. Neuropharmacology 113:367-385, 2017

20. Fordyce WE, Shelton JL, Dundore DE: The modification of avoidance learning pain behaviors. J Behav Med 5:405-414, 1982

21. Gatzounis R, Schrooten MG, Crombez G, Vlaeyen JW: Operant learning theory in pain and chronic pain rehabilitation. Curr Pain Headache Rep 16:117-126, 2012

22. Gay CW, Robinson ME, George SZ, Perlstein WM, Bishop MD: Immediate changes after manual therapy in resting-state functional connectivity as measured by functional magnetic resonance imaging in participants with induced low back pain. J Manipulative Physiol Ther 37:614-627, 2014

23. Geuter S, Koban L, Wager TD: The cognitive neuroscience of placebo effects: concepts, predictions, and physiology. Annu Rev Neurosci 40:167-188, 2017

24. Giles LG, Muller R: Chronic spinal pain: a randomized clinical trial comparing medication, acupuncture, and spinal manipulation. Spine 28:1490-1502, 2003.. discussion 1502-1503

25. Glombiewski JA, Riecke J, Holzapfel S, Rief W, Konig S, Lachnit H, Seifart U: Do patients with chronic pain show autonomic arousal when confronted with feared movements? An experimental investigation of the fear-avoidance model. Pain 156:547-554, 2015

26. Greve DN, Fischl B: Accurate and robust brain image alignment using boundary-based registration. Neuroimage 48:63-72, 2009

27. Harvie DS, Moseley GL, Hillier SL, Meulders A: Classical conditioning differences associated with chronic pain: a systematic review. J Pain 18:889-898, 2017

28. Hengeveld E, Banks K, eds. Maitland's Vertebral Manipulation: Management of Neuromusculoskeletal Disorders, London, Churchill-Livingstone-Elsevier, 2014

29. Houben RM, Leeuw M, Vlaeyen JW, Goubert L, Picavet HS: Fear of movement/injury in the general population: factor structure and psychometric properties of an adapted version of the Tampa Scale for Kinesiophobia. J Behav Med 28:415-424, 2005

30. Jenkinson M: Fast, automated, N-dimensional phase-unwrapping algorithm. Magn Reson Med 49:193-197, 2003

31. Jenkinson M: Improving the registration of B0-distorted EPI images using calculated cost function weights. In: Presented at the International Conference on Human Brain Mapping (HBM); June 13-17, 2004

32. Jenkinson M, Bannister P, Brady M, Smith S: Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825-841, 2002

33. Jenkinson M, Smith S: A global optimisation method for robust affine registration of brain images. Med Image Anal 5:143-156, 2001

34. Jensen KB, Kaptchuk TJ, Kirsch I, Raicek J, Lindstrom KM, Berna C, Gollub RL, Ingvar M, Kong J: Nonconscious activation of placebo and nocebo pain responses. Proc Natl Acad Sci U S A 109:15959-15964, 2012

35. Kirsch I, Lynn SJ, Vigorito M, Miller RR: The role of cognition in classical and operant conditioning. J Clin Psychol 60:369-392, 2004

36. Kitada R, Yoshihara K, Sasaki AT, Hashiguchi M, Kochiyama T, Sadato N: The brain network underlying the recognition of hand gestures in the blind: the supramodal role of the extrastriate body area. J Neurosci 34:10096-10108, 2014

37. Kucyi A, Davis KD: The dynamic pain connectome. Trends Neurosci 38:86-95, 2015

38. Lascurain-Aguirrebena I, Newham D, Critchley DJ: Mechanism of action of spinal mobilizations: a systematic review. Spine 41:159-172, 2016

39. Leaver AM, Maher CG, Herbert RD, Latimer J, McAuley JH, Jull G, Refshauge KM: A randomized controlled trial comparing manipulation with mobilization for recent onset neck pain. Arch Phys Med Rehabil 91:1313-1318, 2010

40. Lethem J, Slade PD, Troup JD, Bentley G: Outline of a fear-avoidance model of exaggerated pain perception—I. Behav Res Ther 21:401-408, 1983

41. Li L, Feng XL, Zhou Z, Zhang HQ, Shi QQ, Lei ZG, Shen PL, Yang QN, Zhao BH, Chen SR, Li L, Zhang YL, Wen PJ, Lu ZH, Li X, Xu FQ, Wang LP: Stress accelerates defensive responses to looming in mice and involves a locus coeruleus-superior colliculus projection. Curr Biol 28:859-871.e5, 2018

42. Meier ML, Stämpfli P, Humphreys BK, Vrana A, Seifritz E, Schweinhardt P: The impact of pain-related fear on neural pathways of pain modulation in chronic low back pain. Pain Rep 2:e601, 2017

43. Meier ML, Stampfli P, Vrana A, Humphreys BK, Seifritz E, Hotz-Boendermaker S: Fear avoidance beliefs in back pain-free subjects are reflected by amygdala-cingulate responses. Front Hum Neurosci 9:424, 2015

44. Meier ML, Stampfli P, Vrana A, Humphreys BK, Seifritz E, Hotz-Boendermaker S: Neural correlates of fear of movement in patients with chronic low back pain vs. pain-free individuals. Front Hum Neurosci 10:386, 2016

45. Miller RP, Kori SH, Todd DD: The Tampa Scale: A measure of kinisophobia. Clin J Pain 7:51, 1991

46. Moseley GL, Vlaeyen JW: Beyond nociception: the imprecision hypothesis of chronic pain. Pain 156:35-38, 2015

47. Onat S, Buchel C: The neuronal basis of fear generalization in humans. Nat Neurosci 18:1811-1818, 2015

48. Palermo S, Benedetti F, Costa T, Amanzio M: Pain anticipation: an activation likelihood estimation meta-analysis of brain imaging studies. Hum Brain Mapp 36:1648-1661, 2015

49. Penza CW, Horn ME, George SZ, Bishop MD: Comparison of two lumbar manual therapies on temporal summation of pain in healthy volunteers. J Pain 18:1397-1408, 2017

50. Rainville J, Smeets RJ, Bendix T, Tveito TH, Poiraudeau S, Indahl AJ: Fear-avoidance beliefs and pain avoidance in low back pain—translating research into clinical practice. Spine J 11:895-903, 2011

51. Reicherts P, Gerdes AB, Pauli P, Wieser MJ: Psychological placebo and nocebo effects on pain rely on expectation and previous experience. J Pain 17:203-214, 2016

52. Roy M, Shohamy D, Daw N, Jepma M, Wimmer GE, Wager TD: Representation of aversive prediction errors in the human periaqueductal gray. Nat Neurosci 17:1607–1612, 2014

53. Salom-Moreno J, Ortega-Santiago R, Cleland JA, Palacios-Cena M, Truyols-Dominguez S, Fernandez-de-las-Penas C: Immediate changes in neck pain intensity and widespread pressure pain sensitivity in patients with bilateral chronic mechanical neck pain: a randomized controlled trial of thoracic thrust manipulation vs non-thrust mobilization. J Manipulative Physiol Ther 37:312-319, 2014

54. Salomons TV, Davis KD: Fear avoidance and neuroimaging: falsification or just failure to confirm? Pain 153:511-512, 2012

55. Schurz M, Radua J, Aichhorn M, Richlan F, Perner J: Fractionating theory of mind: a meta-analysis of functional brain imaging studies. Neurosci Biobehav Rev 42:9-34, 2014

56. Schurz M, Tholen MG, Perner J, Mars RB, Sallet J: Specifying the brain anatomy underlying temporo-parietal junction activations for theory of mind: A review using probabilistic atlases from different imaging modalities. Hum Brain Mapp 38:4788–4805, 2017

57. Sherman KJ, Hogeboom CJ, Cherkin DC, Deyo RA: Description and validation of a noninvasive placebo acupuncture procedure. J Altern Complement Med 8:11-19, 2002

58. Smith SM: Fast robust automated brain extraction. Hum Brain Mapp 17:143-155, 2002

59. Sullivan MJL, Bishop SR, Pivik J: The Pain Catastrophizing Scale: development and validation. Psychol *Assess* 7:524-532, 1995

60. Tan G, Jensen MP, Thornby JI, Shanti BF: Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 5:133-137, 2004

61. Taylor AM, Harris AD, Varnava A, Phillips R, Taylor JO, Hughes O, Wilkes AR, Hall JE, Wise RG: A functional magnetic resonance imaging study to investigate the utility of a picture imagination task in investigating neural responses in patients with chronic musculoskeletal pain to daily physical activity photographs. PLoS One 10, 2015:e0141133

62. Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM: Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 22:2748-2752, 2002

63. Trost Z, France CR, Thomas JS: Exposure to movement in chronic back pain: evidence of successful generalization across a reaching task. Pain 137:26-33, 2008

64. Ullah F, dos Anjos-Garcia T, dos Santos IR, Biagioni AF, Coimbra NC: Relevance of dorsomedial hypothalamus, dorsomedial division of the ventromedial hypothalamus and the dorsal periaqueductal gray matter in the organization of freezing or oriented and non-oriented escape emotional behaviors. Behav Brain Res 293:143-152, 2015

65. Van Essen DC: Windows on the brain: the emerging role of atlases and databases in neuroscience. Curr Opin Neurobiol 12:574-579, 2002

66. Van Overwalle F: A dissociation between social mentalizing and general reasoning. Neuroimage 54:1589-1599, 2011

67. Vlaeyen JW: Learning to predict and control harmful events: chronic pain and conditioning. Pain 156(Suppl 1): S86-S93, 2015

68. Vlaeyen JW, Kole-Snijders AM, Boeren RG, van Eek H: Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. Pain 62:363-372, 1995

69. Vlaeyen JW, Kole-Snijders AM, Rotteveel AM, Ruesink R, Heuts PH: The role of fear of movement/(re)injury in pain disability. J Occup Rehabil 5:235-252, 1995

70. Vlaeyen JW, Morley S, Linton SJ, Boersma K, de Jong J: Pain-Related Fear: Exposure Based Treatment for Chronic Pain. Seattle, IASP Press, 2012

71. Wertli MM, Rasmussen-Barr E, Weiser S, Bachmann LM, Brunner F: The role of fear avoidance beliefs as a prognostic factor for outcome in patients with nonspecific low back pain: a systematic review. Spine J 14:816-836, 2014.. e4

72. Wiech K, Tracey I: Pain, decisions, and actions: a motivational perspective. Front Neurosci 7:46, 2013

73. Wilent WB, Oh MY, Buetefisch CM, Bailes JE, Cantella D, Angle C, Whiting DM: Induction of panic attack by stimulation of the ventromedial hypothalamus. J Neurosurg 112:1295-1298, 2010

74. Zusman M: Mechanisms of musculoskeletal physiotherapy. Phys Ther Rev 9:39-49, 2013