Published in final edited form as:

J Pain. 2018 November ; 19(11): 1352–1365. doi:10.1016/j.jpain.2018.05.012.

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 non-harmful but forceful mobilization of the painful joint, thereby disrupting the relationship between 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 controls (HC) were scanned while observing and rating video clips depicting back-straining or neutral physical exercises, which they knew they would have to

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Study concept and design: VN, RRE, NK, MLL; acquisition of data: EP, IM, DME; analysis and interpretation of data: DME, VN, NK, MLL; drafting of the manuscript: DME; critical revision of the manuscript for important intellectual content: DME, VN, EP, IM, MHK, DS, DOS, RRE, NK, MLL; statistical analysis: DME; technical, or material support: MHK, DS, DOS; study supervision: NK, MLL.

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Disclosures: This work was supported by the NCMIC foundation (M.L.L.), Norwegian Research Council /Marie Skłodowska-Curie Actions (FRICON/COFUND-240553/F20 to D.M.E.), the National Center for Research Resources (P41RR14075; CRC 1 UL1 RR025758, Harvard Clinical and Translational Science Center); Martinos Computing facilities; NIH S10RR023401; S10RR019307; S10RR019254; S10RR023043. None of the authors have any conflicts of interest.

perform at the end of the visit. This task was repeated after a single session of spinal manipulation (SMT_{manip}; cLBP and HC) or mobilization (SMT_{mobil}; cLBP only), in separate visits.

Compared to HC, 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, demonstrated higher BOLD signal in brain circuitry that has previously been implicated in salience, social cognition and mentalizing, while observing backstraining, compared to neutral exercises. The engagement of this circuitry was reduced after SMT, and especially SMT_{manip}, 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.

Keywords

Pain anticipation; Expectation; Fear of movement; Fear-avoidance; Physical exercise; chronic Low Back Pain; Spinal Manipulative Therapy; Manual Therapy; functional Magnetic Resonance Imaging; fMRI

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 non-harmful but forceful mobilization of the painful joint, thereby disrupting the relationship between 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 controls (HC) 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 (SMT_{manip}; cLBP and HC) or mobilization (SMT_{mobil}; cLBP only), in separate visits.

Compared to HC, 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, demonstrated higher BOLD signal in brain circuitry that has previously been implicated in salience, pain anticipation, social cognition and mentalizing, while observing back-straining, compared to neutral exercises. The engagement of this circuitry was reduced after SMT, and especially SMT_{manip}, 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 chronic Low Back Pain (cLBP) patients investigated how Spinal Manipulative Therapy (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.

Introduction

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 recovery⁵⁰. Higher fear-avoidant behavior is associated with higher disability^{12, 29, 68, 69, 71}, and reduction in fear/anxiety can predict successful therapy⁷⁰. 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 avoidance⁴⁰. This cycle has been linked to Pavlovian and operant conditioning^{21, 67}, in which pain initially represents an unconditioned response (UR) to a nociceptive unconditioned stimulus, (US), but may be elicited by a progressively wider range of non-harmful movements (CS)^{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, since 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 responses²⁵ and altered brain processing in circuitry consistent with social cognition, salience and mentalizing, such as 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 CS or CR consistently occurs without leading to UR – e.g. a perceived harmful motion is not followed by pain or harm. There is evidence that exposing patients to (feared) non-harmful physical activity, in order 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 processing²².

Here, we investigated the brain-based underpinnings anticipated pain and fear of physical exercises, and the effect of two 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 (e.g. the anterior cingulate cortex, insulae, and amygdalae), in addition to visual and fronto-parietal 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 chronic Low Back Pain (cLBP, 8 female, mean age $\pm$ SD = 37.7 $\pm$ 9.7) and 16 individually age- and sex-matched healthy controls (HC, 8 female, age 38.2 $\pm$ 10.4) were enrolled. One HC was excluded from final paired analyses as we were not able to recruit an age- and sex-matched cLBP for this individual. All subjects provided written informed consent prior to 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 and 65, nonspecific low back pain, diagnosed >6 months prior to enrollment, and ongoing pain that averaged at least 4 on a 0-10 scale of pain during the week prior to enrollment. Exclusion criteria included radicular pain (i.e., 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 Magnetic Resonance Imaging (fMRI), current or past history of major medical, neurological, or psychiatric illness other than chronic pain, peripheral nerve injury, diabetes, pregnancy, breastfeeding, less than 6 months post-partum, 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 healthy controls 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 (i.e., grade III of the Maitland Joint Mobilization Grading Scale²⁸, and an MRI visit with SMT manipulation (i.e., grade V of the Maitland Joint Mobilization Grading Scale). The order of the MRI visits was counterbalanced across subjects (interval between MRI visits was 24.7 $\pm$ 22.9, mean $\pm$ SD). The HC group completed 2 study visits - an initial behavioral visit and an MRI visit with grade V SMT. Since we did not anticipate SMT-induced changes in clinical outcomes for HC, 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), in order 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 (e.g., sit-ups, thrusts, leg lifts and pelvic tilts) and non-back-straining (e.g., 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 (see below).

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 min each, 2 before and 2 after SMT), participants were shown 4 videos (20 s each) – 2 depicting ‘high back-straining exercises’ (BSE) and 2 depicting ‘low back-straining exercises’ (Neutral) – in a pseudorandomized order (Figure 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, the BSE videos depicted an actor (sex-matched to the participant) performing the two back-straining exercises which 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. In order 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 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 (v. 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 preSMT fMRI and the postSMT 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 Kinesiophobia⁴⁵ (TSK), Pain Catastrophizing Scale⁵⁹ (PCS), Beck's Depression Inventory⁶ (BDI), Brief Pain Inventory⁶⁰ (BPI), and treatment credibility (1 = 'Definitely', 5 = 'Definitely not', Likert scale, modified from Sherman et al.⁵⁷). Additionally, they rated bothersomeness of low-back pain (0 = 'Not at all bothersome', 100 = 'Extremely bothersome', VAS), expected relief from SMT (0 = 'Does not work at all', 10 = 'Complete relief, VAS), 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 ANOVA with the factors GROUP (cLBP, HC) and VIDEO EXERCISE (BSE, Neutral), using baseline (preSMT) 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 (preSMT, postSMT). 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 two 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 (preSMT, postSMT). 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 (postSMT - preSMT) vs. 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 vs. SMT-induced changes in clinical pain, expected pain, and fearfulness. Behavioral data were analyzed using JASP (Version 0.8.1.5).

MRI data acquisition and preprocessing

BOLD fMRI data were collected using a whole brain, simultaneous multislice, T2*-weighted gradient echo BOLD EPI pulse sequence (TR = 1250 ms, TE = 33ms, flip angle = 65°, voxel size = 2mm isotropic, number of slices = 75, SMS factor = 5). A high resolution structural volume (multi-echo MPRAGE) was collected for the purposes of anatomical localization and spatial normalization (TR = 2530 ms, TE = 1.69 ms, flip angle = 7°, voxel size = 1mm 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 MCFLIRT³², fieldmap-based EPI unwarping using PRELUDE and FUGUE^{30, 31}, non-brain removal using BET⁵⁸, spatial smoothing (FWHM = 4mm), temporal high-pass filter (0.011 hz as computed by FSL's cutoffcaic), grand-mean intensity normalization by a single multiplicative factor. All 4 runs were realigned (6 dof) to a common space (the seventh volume of the first fMRI run) before first-level GLM analyses. The transformation matrix for the registration from functional to the high resolution anatomical image was computed using Boundary Based Registration (FreeSurfer's bbrregister tool²⁶). For structural-to-standard space registration, we used the FSL's Linear registration tool (FLIRT, 12 DOF)^{32, 33} followed by FSL's Non-linear registration tool (FNIRT)¹. All single-subject analyses were performed in functional space, and registration to standard space (MNI152) was applied before group analyses.

fMRI data analysis

Single-subject GLM analyses were carried out using FILM with local autocorrelation correction. For each run (two preSMT, and two postSMT), we modeled the epochs corresponding to the video presentation (BSE, Neutral) as regressors in a General Linear Model. 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 preSMT runs and across both postSMT runs separately, resulting in two sets of contrasts of parameter estimates for each contrast (preSMT and postSMT).

To investigate brain responses to observing back-straining and neutral exercises, we carried out whole-brain voxelwise group GLMs separately for cLBP and HC from the baseline (preSMT) 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 / 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 voxel-wise threshold of $Z > 2.3$, and a (corrected) cluster significance threshold of $P < 0.05$.

We then conducted whole-brain voxel-wise GLMs to investigate SMT-induced change in BOLD responses ($\text{postSMT}_{\text{BSE-Neutral}} - \text{preSMT}_{\text{BSE-Neutral}}$) in $\text{cLBP}_{\text{manip}}$ relative to $\text{cLBP}_{\text{mobil}}$, and $\text{cLBP}_{\text{manip}}$ relative to HC.

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 ($\text{postSMT}_{\text{BSE-Neutral}} - \text{preSMT}_{\text{BSE-Neutral}}$) with SMT-induced changes in expected pain and fearfulness ratings ($\text{postSMT}_{\text{BSE-Neutral}} - \text{preSMT}_{\text{BSE-Neutral}}$) as regressors of interest. These regression analyses were performed separately for $\text{SMT}_{\text{manip}}$ and $\text{SMT}_{\text{mobil}}$, and for cLBP participants only since the HC group, as anticipated, did not show enough dynamic range in ratings of expected pain (12 out 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^{10, 65} (<http://www.nitrc.org/projects/caret/>).

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 to HC. For one LBP 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, expected more pain from, and were more fearful of, performing back-straining exercises

A mixed-design ANOVA confirmed that cLBP, relative to HC, anticipated the exercises depicted in the videos, when performed in first-person at the end of the visit, to be more painful (main effect of GROUP: $F(1, 13)=31.54$, $P<0.001$, partial eta squared: $\eta^2_p=0.71$). Furthermore, a main effect of VIDEO EXERCISE confirmed higher expected pain from BSE relative to Neutral ($F(1, 13)=35.87$, $P<0.001$, $\eta^2_p=0.73$). Most importantly, there was a GROUP*VIDEO EXERCISE interaction ($F(1, 13)=32.38$, $P<0.001$, $\eta^2_p=0.71$). A paired t-test between cLBP and HC revealed that the difference in expected pain between BSE and Neutral was significantly greater ($t(14)=5.82$, $P<0.001$, $d=1.50$) for cLBP (23.84 ± 15.32) compared to HC (1.25 ± 2.60). The mean and SD 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 relative to HC (main effect of GROUP: $F(1, 13)=6.88$, $P=0.021$, $\eta^2_p=0.35$). A main effect of VIDEO EXERCISE confirmed higher fearfulness of BSE relative to Neutral exercises ($F(1, 13)=20.79$, $P<0.001$, $\eta^2_p=0.62$). Importantly there was a GROUP*VIDEO EXERCISE interaction ($F(1, 13)=12.35$, $P=0.004$, $\eta^2_p=0.49$). This

difference was significantly greater ($t(14)=3.77$, $P=0.002$, $d=0.97$) for cLBP (6.75 ± 6.01) compared to HC (0.25 ± 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 to rest, are shown in Suppl. Figure 1. When observing BSE, compared to Neutral exercises, cLBP patients showed higher BOLD signal in multiple regions including Visual areas 1, 4, and 5, Supramarginal Gyrus (SMG), Angular Gyrus (AngGJ), 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 (PCC), anterior Mid-Cingulate Cortex (aMCC), ventrolateral (vlPFC), dorsomedial (dmPFC), and dorsolateral (dlPFC) Prefrontal Cortices, thalamus, caudate, putamen, cerebellum (Figure 3A).

The HC group also demonstrated higher BOLD signal during BSE relative to Neutral videos, however in a smaller number of regions (V5, SMG, TPJ, lateral PFC, aMCC, thalamus, putamen, and caudate; Figure 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 dorsomedial PFC, (Figure 3C, top). As illustrated by extracted mean Z-scores in these regions (Figure 3C, bottom), cLBP demonstrated significant activations during observation of back-straining exercises, compared to no activation (or, in some cases, deactivation) when observing the neutral exercises. The controls, 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 $cLBP_{BSE-Neutral}-HC_{BSE-Neutral}$ contrast was used for the subsequent ROI-based investigation of the effects of SMT on the brain responses to observing exercises.

SMT reduced clinical pain, and expected pain and fear of performing physical exercises

Clinical pain.—A significant ANOVA main effect of TIME ($F(1, 13)=13.34$, $P=0.003$, $\eta^2_p=0.51$) indicated that clinical pain was reduced after SMT (31.12 ± 16.83) relative to the preSMT baseline (41.69 ± 18.11). There was no main effect of SMT TECHNIQUE ($F(1,13)=0.25$, $P=0.63$, $\eta^2_p=0.02$) and no TIME*SMT TECHNIQUE interaction ($F(1,13)=0.22$, $P=0.65$, $\eta^2_p=0.02$). Thus, the data did not support the hypothesis that the effect of SMT on clinical pain is different between manipulation and mobilization (Figure 4A).

Expected pain.—A significant ANOVA main effect of TIME ($F(1, 13)=8.99$, $P=0.01$, $\eta^2_p=0.41$) 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 ($F(1,13)=29.85$, $P<0.001$, $\eta^2_p=0.70$), with BSE (34.95 ± 13.86) rated higher than Neutral (10.86 ± 13.15). There was a significant TIME*VIDEO EXERCISE interaction ($F(1,13)=6.28$, $P=0.026$, $\eta^2_p=0.33$). In line with our hypothesis, a direct t-test indicated that the SMT-induced reduction was stronger for BSE

([postSMT-preSMT]: -5.66 ± 7.6) than for Neutral ([postSMT-preSMT]: -2.21 ± 2.27) videos ($t(14)=1.99$, $p=0.034$, Figure 4B). There was a significant SMT TECHNIQUE*SCAN ORDER interaction ($F(1,13)=4.92$, $p=0.045$, $\eta^2_p=0.27$). There were no significant interactions between TIME*SMT TECHNIQUE ($F(1,13)=0.25$, $p=0.62$, $\eta^2_p=0.02$) or between TIME*VIDEO EXERCISE*SMT TECHNIQUE ($F(1,13)=1.35$, $p=0.27$, $\eta^2_p=0.09$). Thus, the data did not suggest 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 ($F(1,13)=4.89$, $p=0.046$, $\eta^2_p=0.27$) indicated fearfulness was reduced after SMT (7.13 ± 10.47) relative to before (7.91 ± 11.35 , Figure 4C). As expected, there was also a main effect of VIDEO EXERCISE ($F(1,13)=25.37$, $p>0.001$, $\eta^2_p=0.66$), 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 $P>0.06$). 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 vs. expected pain and fearfulness.—cLBP patients' change in clinical pain (postSMT – preSMT) correlated significantly with change in expected pain (postSMT_{BSE-Neutral} – preSMT_{BSE-Neutral}, $r=0.58$, $P=0.02$), 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 (Figure 4D). We did not find a statistically significant correlation between change in fearfulness and change in clinical pain ($r=0.17$, $P=0.55$).

Relationship between expected relief of SMT vs. SMT outcomes.—cLBP patients' expected relief of SMT correlated significantly with change in clinical pain ($r=0.67$, $P=0.006$) and expected pain from performing exercise (postSMT_{BSE-Neutral} – preSMT_{BSE-Neutral}, $r=-0.64$, $P=0.01$). There was no significant correlation between expected relief from SMT and change in fearfulness ($r=-0.22$, $P=0.44$).

SMT reduced brain responses in circuitry involved in processing observed back-straining exercises

A whole-brain voxel-wise within-group interaction in the cLBP group (cLBP_{manip}[postSMT_{BSE-Neutral} – preSMT_{BSE-Neutral}] – cLBP_{mobil}[postSMT_{BSE-Neutral} – preSMT_{BSE-Neutral}]) showed a statistically significant difference in the effect of technique (manipulation vs mobilization) in left STS, right aINS, right SI, right Superior Temporal Gyrus (STG), bilateral dIPFC, vIPFC, vmPFC, pINS, paracingulate, medial occipital cortex, and cerebellum (Figure 5A). Furthermore, a between-group interaction (cLBP_{manip}[postSMT_{BSE-Neutral} – preSMT_{BSE-Neutral}] – HC [postSMT_{BSE-Neutral} – preSMT_{BSE-Neutral}]) indicated the presence of a statistically significant difference in the effect of manipulation across groups (cLBP vs HC; Figure 5A) in left TPJ and bilateral aINS, vIPFC, dIPFC, STS / MTG, medial occipital cortex, and right cerebellum (Figure 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 observing back-straining exercises (BSE-Neutral) for cLBP, compared to an increase for HC (Figure 5C). Exploratory

contrasts showing the contrast [postsMT_{BSE-Neutral} – preSMT_{BSE-Neutral}] separately for cLBP_{manip} and cLBP_{mobil} are shown in Suppl. 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 voxel-wise 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 (Figure 6A, left). To illustrate this relationship, we extracted mean Z-scores from two ROIs (aINS and STS) identified by the intersection of the correlation map and with the activation map from the baseline [cLBP_{BSE-Neutral} - HC_{BSE-Neutral}] contrast (Figure 3C), and plotted these values against SMT-induced expected pain (BSE-Neutral) (Figure 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 Grey matter (Figure 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 (Figure 6C).

Discussion

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 spinal manipulative therapy (SMT). cLBP, relative to age- and sex-matched healthy controls (HC), 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. While 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. 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, showed greater BOLD responses in vIPFC, 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 network⁷, 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, vIPFC, 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, one recent study found that cLBP relative to HC showed increased activation of vIPFC, aINS, STG/STS, and dmPFC/ACC in response to observing images of back-straining relative to neutral activities⁶¹. Another study also found increased vIPFC and amygdala activation for videos showing back-straining versus back-neutral activities, albeit no BOLD contrast difference between cLBP and HC⁴⁴. Another study found increased hippocampal activation for high-fear cLBP patients compared to HC⁵, while an earlier study found no patient versus HC contrast in fMRI response to still images of back-straining maneuvers⁴. These discrepancies may be due to protocol differences. Our study differs from earlier reports in two important ways. First, while most previous studies (except ref.⁶¹) used a pre-selected 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 amygdala, aMCC, and sgACC. One reason may be that, despite significantly higher cLBP fear ratings for back-straining compared to neutral videos, and compared to HC, 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/sgACC play important roles for chronic pain-related kinesiophobia in real-life situations involving stronger fear⁵⁴. 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 PAG^{62, 64} and the superior colliculus⁴¹.

Notably, we observed higher ratings of expected pain compared to 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 avoid⁷². Interestingly, we found that initial expectations of treatment relief correlated with reduction in expected pain from back-straining exercises (Figure 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 made³⁵.

We found that SMT reduced not only patients' clinical back pain, but also the aversiveness of the observed back-straining exercises, i.e., 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 SII (SMT_{manip}) and for reduction in fear and BOLD responses in STS/MTG, pINS, PCC, 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 US/UR (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 exercises⁶⁷. 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 analgesia¹³. Future studies should systematically compare these motivational aspects during pain relief from treatments involving exteroceptive/proprioceptive stimuli of the painful limb (such as SMT for cLBP) versus treatment that does not (e.g. pharmacotherapy). According to the fear-avoidance model, fear learning is a key component of chronification of pain (and emerging avoidance behavior), and 'unlearning' – e.g. 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 pain³, 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 (CBT), may have the advantage of targeting this learning aspect of chronic pain, along with other putative mechanisms such as counter-irritation 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 relative to HC showed widespread reductions in BOLD responses to back-straining videos after SMT_{manip}, notably in circuitry identified in the baseline contrast, such as dlPFC, aINS, vlPFC, TPJ, and STS/MTG. Direct comparison indicated that, for cLBP, SMT_{manip} induced stronger BOLD contrast reductions in 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 to 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 kinesiophobia⁴⁵. Importantly however, cLBP showed significantly higher fear and expected pain from observed back-straining exercises compared to 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 HC⁴⁴, 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 (e.g., 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 compared to HC, 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 two 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 aversiveness (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 Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Patients with cLBP show higher BOLD signal when observing physical exercises
- SMT reduces clinical pain, expected pain, and fear of movement in cLBP
- SMT manipulation and mobilization equally improves clinical outcomes
- SMT reduces brain responses to observing back-straining exercises in cLBP

Figure 1: Experimental design.

Participants viewed 20 s 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 Analogue Scales. There were 8 videos (spread over 2 scan runs) before, and 8 videos after SMT. 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.

Figure 2: Ratings of videos showing back straining and neutral exercises.

Patients with chronic Low Back Pain (cLBP) expected back straining exercises to be more painful than neutral exercises (A), and were more fearful of performing these exercises (B). 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 to Healthy Controls. **p<0.01; ***p<0.005.

Figure 3: BOLD responses to observing back straining relative to neutral exercises.

Activation maps show cluster-corrected BOLD responses (voxel-based Z-scores, prior to Spinal Manipulative Therapy) to viewing videos of back straining (BSE) relative to neutral exercises in chronic Low-Back Pain patients (cLBP, A) and age / sex matched healthy controls (HC, B), and in cLBP relative to HC (C). There were no significant voxels in the opposite contrast (HC – cLBP). Bar plots show mean Z-scores within Regions of Interest (ROIs) drawn from the $[cLBP_{BSE-Neutral} - HC_{BSE-Neutral}]$ contrast, indicating the interaction was driven by increased BOLD responses to BSE videos for cLBP. Error bars represent Standard Error of the Mean. aINS = anterior Insula; vlPFC = ventrolateral Prefrontal Cortex; dlPFC = dorsolateral Prefrontal Cortex; STS = Superior Frontal Sulcus; MTG = Middle Temporal Gyrus; TPJ = Temporoparietal Junction.

SMT effects on clinical pain, expected pain, and fear of movement

SMT change in expected pain vs. clinical pain / expected relief

Figure 4: SMT-induced change in clinical pain and expected pain from, and fear of, performing physical exercises.

A) SMT significantly reduced clinical pain ($p=0.003$), but this pain change did not differ between SMT_{manip} and SMT_{mobil} ($p=0.65$). B) SMT reduced expected pain from performing exercises in cLBP ($p=0.01$). This reduction was significantly stronger for back straining relative to neutral exercises ($p=0.03$). C) SMT reduced overall fear of performing exercises in cLBP ($p=0.046$). D) SMT-induced change in clinical pain (postSMT – preSMT) 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).
cLBP = chronic Low-Back Pain; HC = Healthy Control; SMT = Spinal Manipulative
Therapy. * $p < 0.05$

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Figure 5: Manual therapy reduced BOLD responses to videos showing back straining relative to neutral exercises in cLBP patients.

To investigate SMT effects on BOLD responses to observing back straining exercises (BSE), we compared whole-brain contrast parameters [$\text{postSMT}_{\text{BSE-Neutral}} - \text{preSMT}_{\text{BSE-Neutral}}$] for cLBP_{manip}, relative to cLBP_{mobil} and HC. cLBP_{manip} showed a widespread reduction of BOLD contrast relative to cLBP_{mobil} (A) and HC (B). C) To illustrate directionality, mean Z values were extracted from ROIs where the cLBP-HC contrast overlapped with voxels that showed a stronger BOLD signal in response to BSE for cLBP relative to HC at baseline (the [$\text{cLBP}_{\text{BSE-Neutral}} - \text{HC}_{\text{BSE-Neutral}}$] contrast; see Figure 3C). Error bars represent Standard error of the mean. aINS = anterior Insula; vlPFC = ventrolateral Prefrontal Cortex; dlPFC = dorsolateral Prefrontal Cortex; STS = Superior Frontal Sulcus; MTG = Middle Temporal Gyrus; TPJ = Temporoparietal Junction; cLBP = Low Back Pain; HC=Healthy Control; Manip = Grade 5 manipulation; Mobil = Grade 3 mobilization.

Fig. 6: Correlation between SMT-induced change in 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 BOLD responses (postSMT – preSMT) correlated with expected pain (postSMT – preSMT). To illustrate directionality, scatterplots show ROI-extracted mean Z-scores from two regions (left aINS and left STS, marked green) identified by the intersection of the correlation map and the [cLBP_{BSE-Neutral}–HC_{BSE-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 SMT_{manip} (B) and SMT_{mobil} (C). To illustrate directionality, ROI-extracted mean Z-scores are shown from Left STS, a region that showed an overlap with the baseline [cLBP_{BSE-Neutral} – HC_{BSE-Neutral}] activation map. aINS

= anterior Insula; STS = Superior Temporal Sulcus, MTG = Middle Temporal Gyrus; SMT = Spinal Manipulative Therapy, BSE = Back straining Exercise videos.

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Table 1:

Subject characteristics

	Mean±SD (cLBP)	Mean±SD (HC)	t	df	p	Cohen's <i>d</i>	95% Confidence Interval	
							Lower	Upper
Age	37.7±9.7	38.5±10.1	0.580	14	0.571	0.150	-1.258	2.191
Tampa Scale of Kinesiophobia	33.3±5.7	33.1±7.5	0.854	14	0.407	0.221	-2.569	5.969
Pain Catastrophizing Scale	13.6±10.2	6.2±6.8	2.492	14	0.026	0.644	0.972	12.962
Beck's Depression Inventory	1.9±2.7	4.1±4.2	1.427	13	0.177	0.382	-1.082	5.296
Perceived credibility of SMT	1.8±0.6	2.1±0.8	-0.942	13	0.363	-0.252	-0.753	0.295
Clinical pain (Baseline, 0-100)	44.2±18.6	0.3±1.2	8.484	13	<0.001	2.268	32.889	55.361
Anxiety (Baseline, 0-100)	12.2±12.3	0.8±1.4	3.606	13	0.003	0.964	4.896	19.532
Brief Pain Inventory (Severity, 0-10)	4.5±1.4	0.3±0.4	10.768	14	<0.001	2.780	3.358	5.029
Brief Pain Inventory (Interference, 0-10)	3.2±2.1	0.1 ±0.2	5.757	14	<0.001	1.486	1.948	4.261
Low back bothersomeness (0-10)	5.0±1.7	0.5±1.3	9.049	14	<0.001	2.336	3.403	5.517
Expected relief (0-10)	5.3±2.8	3.6±3.3	1.363	14	0.194	0.352	-0.962	4.315
Desire for relief (0-10)	9.0±1.0	1.8±3.4	7.150	14	<0.001	1.846	5.101	9.472

Abbreviations: cLBP = chronic Low Back Pain; HC = Healthy Control; SMT = Spinal Manipulative Therapy