Data supplement for Wielgosz et al., Neural Signatures of Pain Modulation in Short-Term and Long-Term Mindfulness Training: A Randomized Active-Control Trial. Am J Psychiatry (doi: 10.1176/appi.ajp.21020145)

SUPPLEMENTAL METHODS

Sample Recruitment

Meditation-naïve participants (MNP) were recruited for a study on health and well-being through advertisements in Madison, WI, area newspapers, e-mails, and through postings and discussions with meditation teachers and groups. Long-term meditators (LTM) were recruited in the United States at meditation centers and through related mailing lists, in addition to flyers and advertisements in newspapers. MNP participants were scheduled into three cohorts. In each cohort, they were randomized into the three study groups (mindfulness-based stress reduction (MBSR), health enhancement program (HEP), or waiting list (WL) by a logistical staff member through a random-number generator. For complete details, see CONSORT chart, Figure S1.

Recruitment materials advertised for individuals with no history of seizure, brain damage, or psychiatric disorders. During screening, participants were excluded for any history of psychiatric medication, any active psychiatric diagnosis within the past 5 years, or a history of multiple depressive episodes. Participants were not excluded for single depressive episodes or anxiety disorders so long as remission occurred more than 5 years prior to the study.

Inclusion in the LTM group required at least 3 years of formal experience with mindfulness-related meditation practice; ongoing daily practice of 30 minutes or more; and completion of at

least 3 intensive meditation retreats of five days or longer. Additional details of LTM recruitment and practice history are available in a previous publication (1).

Neural Signatures of Pain

Validated neural measures of pain response are highly desirable for research and clinical use but historically, no such measures have been available. Functional neuroimaging data have provided a promising new potential source for such a measure. However, initial approaches to analysis, relying on simple averaging of activation across either anatomically or functionally defined brain regions, have proven inadequate for this purpose, demonstrating neither sufficient specificity or sensitivity to predict presence or intensity of pain (2–4). To address this problem, Wager and colleagues used a machine learning approach to develop multivariate neural signatures for pain. (5–8). These signatures consist of voxel-by-voxel regression weights, capturing of a brain-wide pattern of pain-relevant activation. Weight for a given voxel can be positive, representing activation to pain, or negative, representing deactivation to pain. The pattern is constructed such that applying these weights to a functional brain image, and summing across the relevant regions, provides a single numerical activation value, corresponding in a validated way to a pain-related neurocognitive process. Signatures are created using training and testing steps that optimize the measure's performance in predicting the presence and intensity of a particular aspect of physical pain. First, dimensional reduction techniques are applied to eliminate shared variance in the data. Next, classification algorithms are applied to generate a weighted map of brain voxels which optimally predicts pain ratings across participants in a relevant set of training examples. Cross-validation techniques are then applied to improve the stability and generalizability of the classifier, preventing overfitting or excessive influence of outlier values in the training data. Finally, the resulting signature is validated against reserved testing dataset to confirm its

performance outside the training sample. This process has been applied to generate two related neural pain signatures with distinct properties relevant to investigating the effects of mindfulness training.

Neurologic Pain Signature (NPS)

The Neurologic Pain Signature (NPS) was the first signature produced by the method described above (6), and is designed to represent pain processing directly linked to afferent peripheral nociceptive inputs. For the NPS, therefore, the training procedure was constrained to regions of the brain which reliably activate to painful stimuli across multiple experiments as indexed by the NeuroSynth repository (9). Training (model-fitting) steps were optimized for explaining maximum variance in stimulus intensity and pain report. The resulting pattern incorporated predictive regions widely distributed across the brain (see Figure S3), including loci in ventromedial prefrontal cortex, supplementary motor area, secondary somatosensory cortex, inferior frontal junction, fusiform gyrus, superior parietal lobule, supramarginal gyrus, middle temporal gyrus, occipital gyrus, dorsal ACC, posterior cingulate cortex, insula, thalamus, hypothalamus, PAG, and cerebellum.

Several forms of validation were performed for the NPS using independent participant samples from the training data. The NPS was shown to discriminate between the experience of physical pain and a variety of related phenomena, including non-painful physical sensation, social pain, pain recall and pain anticipation. Further, the NPS was shown to predict pain report values with considerable accuracy, with a correlation of r=0.74 and an average error of less than 1 point on a 9-point rating scale. Finally, while the NPS was highly responsive to pain induced by nociceptive stimuli, its activation was independent of changes in pain experience due to several forms of

non-nociceptive psychological manipulation, including both expectancy manipulations and placebo induction (6).

Stimulus Intensity Independent Pain Signature (SIIPS1)

The Stimulus Intensity Independent Pain Signature (SIIPS1) is a second pain signature that is designed to complement the NPS, by accounting for non-nociceptive influences on pain (7). The SIIPS1 was trained using a similar procedure to the NPS; however, before training the signature, variance related to both the NPS and to stimulus intensity were removed from the training datasets. Thus, SIIPS1 was trained to fit residual variance in pain reports not accounted for by NPS activity or by objective stimulus intensity (i.e., stimulus temperature for the thermal pain induction method used in the training data) (7). In addition, to incorporate broader cognitive processes, training of SIIPS1 incorporated activity from the entire brain and not only neural regions directly associated with nociceptive stimulation as was done for the NPS (7).

Heavily weighted regions in the SIIPS1 activation map fall into three categories (see Figure S4). The first category includes regions which are established targets for afferent nociceptive activity, particularly insula, thalamus, and cingulate cortex. Regions in this category have positive weights, indicating that activation predicts greater pain even after accounting for NPS activation and stimulus intensity. While they overlap with NPS, patterns of weighting are not correlated with those for the NPS. The second category includes regions which are also positively weighted but are extra-nociceptive, meaning they are not associated with direct input from spinal nociception pathways. This category includes regions associated with evaluative, motivational, and self-referential processing, such as dorsomedial prefrontal cortex, medial temporal gyrus, caudate, and ventrolateral prefrontal cortex. In the third category are extra-nociceptive regions

with negative weights, meaning activation predicts reduced pain. Regions in this category include VMPFC, nucleus accumbens, parahippocampal cortex and posterior DLPFC. SIIPS1 also captures fine structure in these regions, with, for example, opposing weights in sub-regions corresponding to the core and shell of the nucleus accumbens, the superficial/central and basolateral nuclei of the amygdala, anterior and posterior caudate, and hippocampal nuclei versus parahippocampal gyrus. (7)

The properties of the SIIPS1 were validated both independently and in combination with the NPS. Testing was performed using both cross-validation on four original training datasets and independent testing on two novel datasets (7). In the test dataset, SIIPS1 and NPS were found to each predict unique variance in pain experience. SIIPS1 also surpassed the predictive accuracy of a brain-wide activation map derived from conventional voxelwise univariate analysis. Finally, SIIPS1 activation captured mediating variance in pain for two distinct forms of experimental psychological modulation – expectancy and perceived control – that NPS activation did not (7).

Availability of signatures and code

Analysis scripts used to generate neural signature activations are open source and publicly available (https://github.com/canlab/). The NPS is available for non-commercial research use with a signed Material Transfer Agreement from Dr. Wager (tor@dartmouth.edu). The SIIPS1 signature is freely available for download from https://github.com/canlab/Neuroimaging_Pattern_Masks. The signatures are weights that can be applied to brain images that have been normalized to the same template – the Montreal Neurologic Institute avg152t1 template – to yield a "pattern response" value for the test image.

Software to apply patterns can be found in the CANlab Core toolbox at canlab.github.io (i.e., apply_mask.m), or other neuroimaging packages can be used.

Interventions

The active intervention, Mindfulness-based Stress Reduction (MBSR), and the active control intervention, the Health Enhancement Program (HEP), were structured equivalently. Both interventions used a group format to introduce a series of practices targeting stress management, meeting once a week for 2.5 hours (3 hours for first and last sessions) for 8 weeks with an ‘‘all day’’ component (9 a.m. to 4 p.m.) after week 6. Furthermore, all participants were asked by their instructors to complete 45 minutes of practice at home for 6 of 7 days each week.

MBSR

MBSR was originally developed as a means of addressing debilitating stress in ambulatory medical patients, often those with chronic pain (10). Since that time, it has been applied to numerous additional therapeutic contexts (11). The focus of the intervention is on cultivation of mindful awareness through both structured formal practices and informal practice during everyday activities. Formal practices taught include sitting and walking meditation; mindful movement, based on hatha yoga; and body scan meditation, which involves directing awareness sequentially towards individual regions of the body. Meditation training begins by emphasizing focused attention, directing present-centered awareness toward a specific object, such as breath or walking, and progresses to incorporate open awareness, a monitoring of experience without restricting the aperture of attention to a single focus. MBSR also includes further instruction on maintaining mindful awareness in everyday activities and in stressful situations. Additional

details on the design and content of MBSR are available in our recent review (11) as well as in published standards of practice and curriculum for the intervention (12, 13).

HEP

HEP was developed specifically to match MBSR as precisely as possible on non-specific factors. To do so, it includes four components which each correspond to a major element of MBSR: (1) physical activity (e.g., walking); (2) balance, agility, and core strength; (3) nutritional education; and (4) music therapy. Each component includes a valid therapeutic basis but does not incorporate training of mindful awareness in either the rationale or the practice itself. For example, the purpose of walking meditation in MBSR is to cultivate awareness in movement, whereas the purpose of walking in HEP is the cardiovascular benefits of the physical activity for cardiovascular training, following recommendations from the Centers for Disease Control regarding intensity and frequency of physical activity. Additional details on the design and content of HEP and its validation as an active control for MBSR are available in our previous publication on its development (14).

Task Design

Four thermal stimuli were delivered during each of five scanner runs, for a total of 20 thermal stimulation trials (see Figure S2). Each thermal stimulus was preceded by a distractor task and cue period and followed by a recovery period and subjective ratings. Timing of the trial periods was: distractor task (16 seconds); fixation (5 seconds); cued anticipation (6/8/10/12 seconds, jittered); thermal stimulation (12 seconds, including ramp up/down; 8 seconds at target temperature); recovery period (18 seconds); rating cue (2 seconds); intensity rating (5 seconds); unpleasantness rating (5 seconds).

Thermal Stimulation

Thermal stimuli were provided by a TSA-2001 thermal stimulator (Medoc Advanced Medical Systems, Haifa, Israel) with a 30 mm × 30 mm flat thermode, which was applied to the inside of the left wrist. Thermal stimuli were delivered at one of two temperature levels. The distractor task was followed by brief fixation display, and then an anticipation period during which participants were shown a cue indicating the trial type: "Hot" or "Warm". This was followed by a 12-second thermal stimulation period, consisting of a 2 second rise time window, 8 seconds at plateau, and 2 seconds for offset and return to 32ºC baseline temperature. During Hot trials, the plateau temperature was set as described below. On Warm trials, the temperature was set to provide a detectable but not painful stimulation, either the Hot temperature minus 6ºC or a fixed temperature of 36ºC. An equal number of Hot and Warm trials were delivered with order counterbalanced across the five scanner runs. The offset window was followed by an 18 second recovery period during which a fixation cross was displayed followed by a 2-second rating cue ("Get ready"). Participants then rated the intensity and unpleasantness of the thermal stimulus, each on a 0 to 20 scale.

Calibration Procedure

Prior to the main data collection sessions, each participant's thermal pain tolerance was assessed using a stepped calibration procedure. Seven thermal stimuli were applied to the participant's inside left wrist, with temperatures ranging from 42°C up to a maximum of 49°C in one-degree increments. The target temperature was sustained for 8 seconds. Participants rated the intensity of each stimulus on a pain scale of 0-20, with 0 being completely painless and 20 being unbearable (15). As ratings were collected, they were used to a fit a linear regression of intensity against temperature. This model was used to identify a target temperature for scanner sessions

corresponding to the participant's rating of 14 out of 20. Before each scanner session, a single test stimulus was delivered at the target temperature, and the participant was asked if they were comfortable with receiving further stimuli at that temperature. If not, the target temperature was reduced by increments of one degree and the procedure repeated until the participant was comfortable continuing.

Distractor Probe

The distractor probe consisted of a 2-second cue followed by 8 repetitions of an affective pain-related dot-probe task (16), with each repetition lasting 2 seconds. For the purposes of this present study, this task provided a brief induction of cognitive load intended to "reset" participants' attentional and cognitive processes to a consistent state in between thermal stimulation trials. Secondarily, the content of the task provided a supplementary behavioral measure of pain-related cognition. Specifically, the form of dot-probe used here provides an affective bias index towards pain-related negative words relative to non-pain-related negative words. Four categories of word were presented in the dot-probes: positive, neutral, negative, and pain-related, selected randomly for each trial. To allow contrast of dot-probe responses following Hot and Warm trials, an additional 16-second distractor task was delivered following the final thermal stimulation of each scanner run. Analyses of behavioral responses in the dot-probe task revealed no differences across trial conditions or relationships with mindfulness training and were not analyzed further.

Data Acquisition

Anatomical scans consisted of a high-resolution 3D T1-weighted inversion recovery fast gradient echo image (inversion time = 450 ms, 256 x 256 in-plane resolution, 256 mm FOV, 124 x 1.0

mm axial slices, voxel size 1 x 1 x 1 mm). Five functional scan runs were acquired using a gradient echo EPI sequence (64 x 64 in-plane resolution, 240 mm FOV, TR/TE/Flip = 2000 ms/25 ms/60º, 40 x 4 mm interleaved sagittal slices and 175 3D volumes per run, voxel size 4 x 3.75 x 3.75 mm).

Image Processing

FMRI data processing was conducted using FEAT 6.00, part of FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl). Image registration was conducted using FLIRT / FNIRT; BOLD images were first registered to an anatomical scan, then to MNI-152 standard space. Motion correction was performed using MCFLIRT, with non-brain removal using BET. Additional steps prior to statistical modeling included spatial smoothing with a Gaussian kernel with full width-half maximum of 5mm, grand-mean intensity normalization, high-pass temporal filtering, and pre-whitening using FILM.

Image Analysis

Statistical modeling for BOLD data was performed in FEAT using a General Linear Model (GLM). A first level model was constructed for each run using boxcar regressors for each epoch of the task, convolved with a double-gamma hemodynamic response function (HRF). The first-level model included 12 nuisance regressors for head motion, as well as first derivatives of all regressors. Second level models were used to model within-subject variance for the 5 runs in each session and the 2 pre-/post-intervention sessions. Unless specified otherwise, all signature activations reported are computed against the Hot - Warm contrast for the Pain epoch of the task.

Neural signature activations were calculated from second-level model outputs in Matlab r2017b using publicly available analysis scripts (https://github.com/canlab/). For each image and each

signature, a scalar activation value was generated using a dot-product metric, which constituted the pain-related brain measure.

SUPPLEMENTAL RESULTS

Sample

The study included 5 participants with non-exclusionary history of psychiatric diagnosis. All 5 participants were in the MNP sample. The only condition reported was depression, single episode, with remission ≥ 5 years prior to enrollment. Of these 5 participants, 2 were randomized to MBSR, 1 to HEP, and 2 to waitlist. No participants with history of any psychiatric diagnosis were enrolled in the LTM group.

Validation of Neural Signatures

Both signatures showed good performance in discriminating pain vs. anticipation (SIIPS1: AUC = 0.86, accuracy = 0.78; NPS: AUC = 0.88, accuracy = 0.79) and recovery (SIIPS1: AUC = 0.87, accuracy = 0.79; NPS: AUC_{NPS} = 0.84, accuracy = 0.76) epochs. Both signatures were highly accurate in discriminating pain stimulus versus retrospective rating (SIIPS1: AUC = 1.00, accuracy = 0.97; NPS: AUC_{NPS} = 0.98, accuracy = 0.96). Both signatures were positively associated with thermode temperature, SIIPS1: $r = 0.18$, 95% CI [0.02, 0.35], $t(142) = 2.21$, $p = .028$, Cohen's d = 0.37; NPS: $r = 0.36$, 95% CI [0.20, 0.51], $t(142) = 4.56$, $p < .001$, d = 0.77. SIIPS1 response furthermore showed positive associations with both mean intensity ratings, $r = 0.19$, 95% CI [0.02, 0.35], $t(142) = 2.25$, $p = .026$, d = 0.38, and mean unpleasantness ratings, $r = 0.18$, 95% CI [0.02, 0.35], $t(142) = 2.24$, $p = .027$, d = 0.38. Correlation between the signatures was moderate, $r = 0.43$, 95% CI [0.28, 0.58], $t(143) = 5.72$, $p < .001$, d = 0.96. NPS response was independently associated with thermode temperature after controlling for SIIPS1 response, $r = 0.34$, 95% CI [0.17, 0.51], $t(141) = 3.93$, $p < .001$, d = 0.66.

Association of Changes in Respiration Rate and Pain Response for MBSR Group

Change in mean respiration rate from pre- to post-intervention within the MBSR group did not correlate significantly with either neural response (NPS: r = .05, p = .81; SIIPS1: r = -.14, p = .53) or subjective pain report (intensity: r = .07, p = .84; unpleasantness: r = .37, p = .34).

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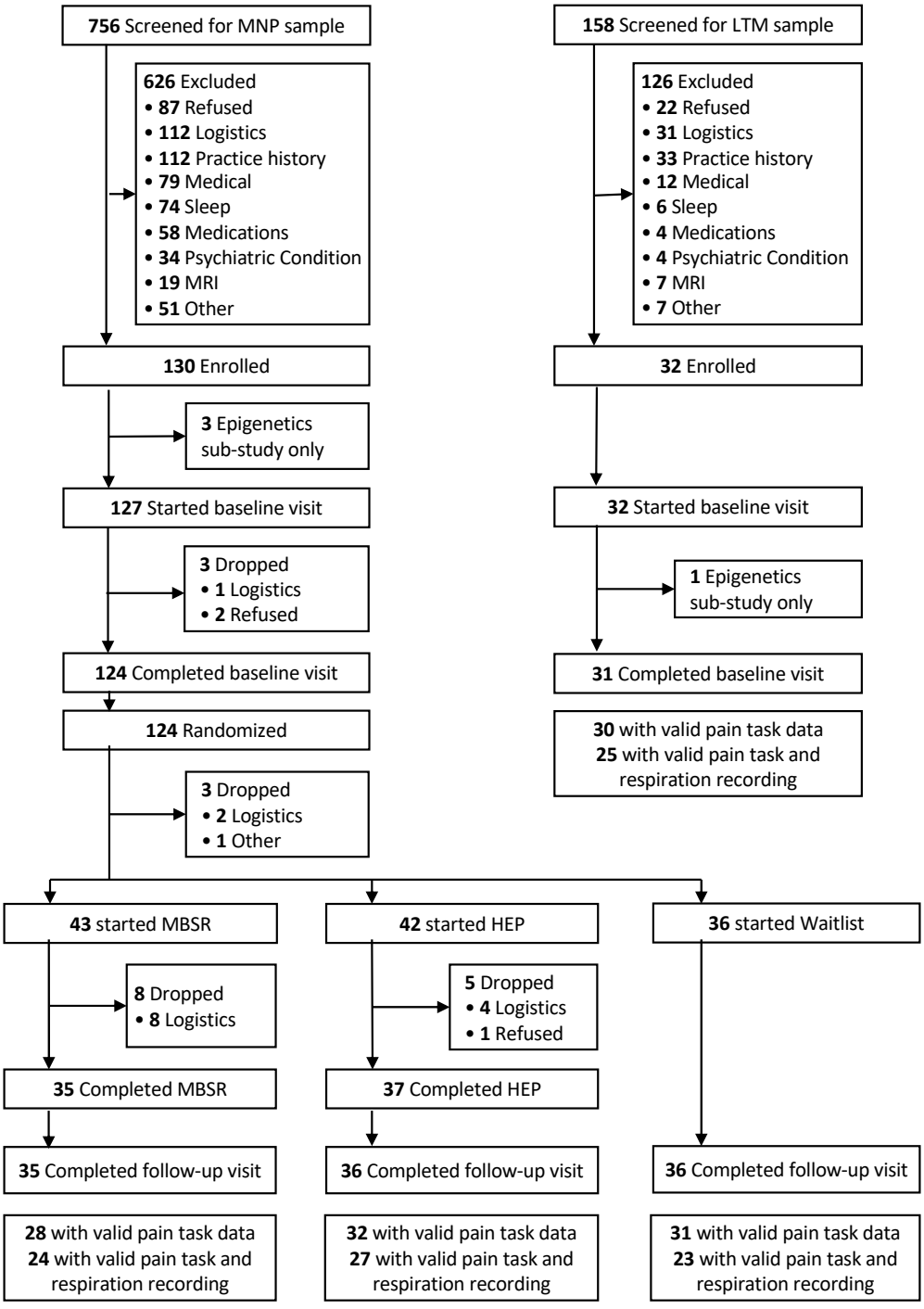
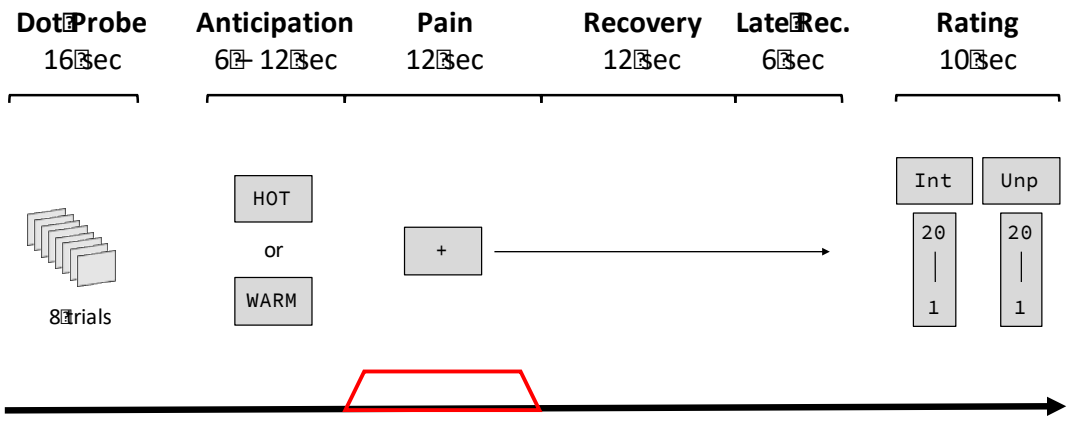
FIGURE S1. CONSORT diagram for intervention trial participants



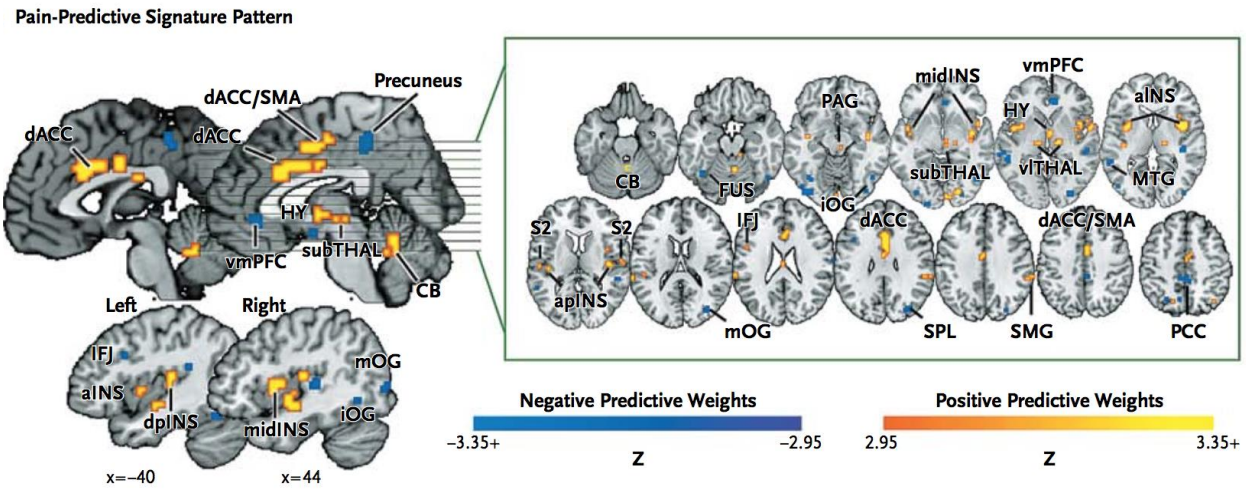
MNP: meditation-naïve participant; LTM: long-term mindfulness practitioner; MBSR: mindfulness-based stress reduction; HEP: health enhancement program.

FIGURE S2. Thermal stimulation task



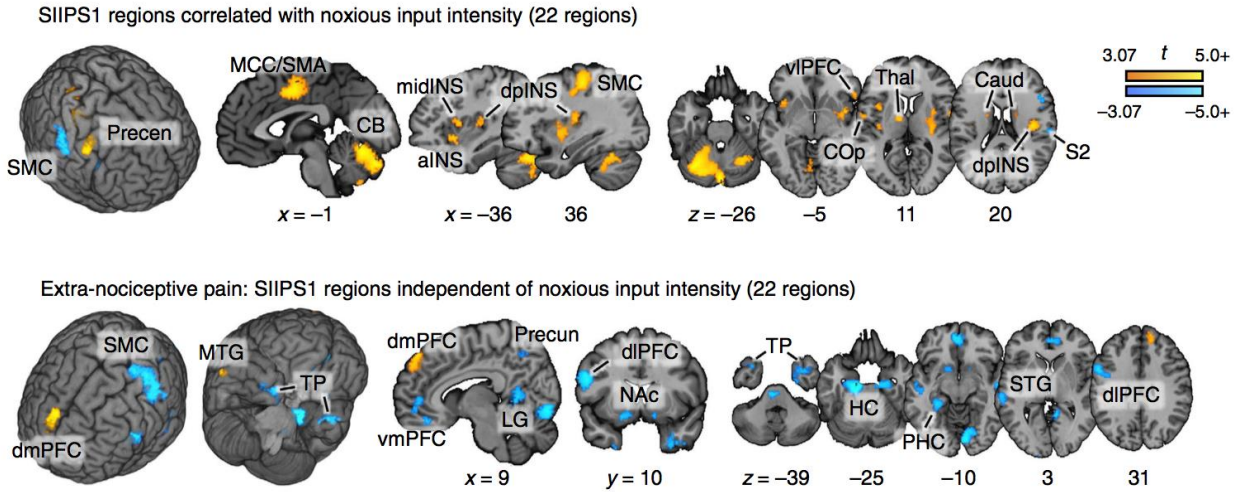
Int: intensity; Unp: unpleasantness; Late Rec.: late recovery.

FIGURE S3. Key regions in the neurologic pain signature



T-values indicate weights for voxels within each neural region. ACC = anterior cingulate cortex; CB = cerebellum; FUS = fusiform; HY = hypothalamus; IFJ = inferior frontal junction; INS = insula; MTG = middle temporal gyrus; OG = occipital gyrus; PAG = periaqueductal gray matter; PCC = posterior cingulate cortex; PFC = prefrontal cortex; S2 = secondary somatosensory cortex; SMA = supplementary motor area; SMG = supramarginal gyrus; SPL = superior parietal lobule; TG = temporal gyrus; THAL = thalamus. Direction is indicated with preceding lowercase letters as follows: a = anterior; d = dorsal; i = inferior; l = lateral; m = middle; mid = mid-insula; p = posterior; v = ventral. Reproduced with permission from Wager et al. (2013), Copyright Massachusetts Medical Society.

FIGURE S4. Key regions of the SIIPS1 signature



T-values indicate weights for voxels within each neural region. aINS = anterior insula; Caud = caudate; CB = cerebellum; dmPFC = dorsomedial PFC; dlPFC = dorso-lateral PFC; dpINS = dorsal posterior insula; HC = hippocampal area; LG = lingual gyrus; MCC = middle cingulate cortex; midINS = middle insula; MTG = middle temporal gyrus; NAc = nucleus accumbens; PHC = parahippocampal area; Precen = precentral cortex; Precun = precuneus; S2 = secondary somatosensory cortex; SMA = supplementary motor area; SMC = sensory motor cortex; STG = superior temporal gyrus; Thal = thalamus; TP = temporal pole; vlPFC = ventrolateral PFC; vmPFC = ventro-medial PFC. Reproduced with permission from Woo et al., (2017) under a Creative Commons Attribution 4.0 International License.

TABLE S1. Relationships of baseline characteristics with neural and subjective pain response

Measure	Characteristic	df	*b*	95% CI	*t*	*p*		*d*
NPS	Age	143	-0.26	[-0.42, -0.10]	-3.24	.001	*	-0.54
	Gender	143	0.17	[-0.16, 0.51]	1.02	.309		0.17
SIIPS1	Age	143	-0.31	[-0.47, -0.16]	-3.97	<.001	*	-0.66
	Gender	143	0.00	[-0.34, 0.34]	0.01	.992		0.00
Int.	Age	143	0.00	[-0.04, 0.03]	-0.19	.846		-0.03
	Gender	143	-0.02	[-0.84, 0.79]	-0.06	.955		-0.01
Unp.	Age	143	-0.04	[-0.09, 0.01]	-1.67	.096		-0.28
	Gender	143	0.35	[-0.71, 1.40]	0.65	.519		0.11

NPS: neural pain signature; SIIPS1: stimulus intensity independent pain signature; Int: intensity; Unp: unpleasantness.
* $p < .05$.

TABLE S2. Relationships of mindfulness training to mean respiration rate and pain tolerance

Measure	Training	Comparison						
Resp.	Short-term	Group by time	df	*b*	95% CI	*t*	*p*	*d*
Rate		MBSR-HEP	70	-0.59	[-1.33, 0.14]	-1.61	.112	-0.38
		MBSR-WL	70	-0.34	[-1.10, 0.43]	-0.88	.384	-0.21
		HEP-WL	70	0.26	[-0.48, 1.00]	0.70	.489	0.17
		Within group	df	*b*	95% CI	*t*	*p*	*d*
		MBSR	23	-0.61	[-1.21, -0.01]	-2.10	.047 *	-0.44
		HEP	26	0.02	[-0.48, 0.51]	0.07	.944	0.01
		WL	22	-0.25	[-0.79, 0.29]	-0.96	.348	-0.20
	Long-term	Between groups	df	*b*	95% CI	*t*	*p*	*d*
		LTM-MNP	23	-0.63	[-2.02, 0.75]	-0.90	.369	-0.16
		Practice hours	df	*b*	95% CI	*t*	*p*	*d*
		Retreat	24	-0.27	[-0.66, 0.12]	-1.41	.171	-0.58
		Daily	24	-0.29	[-0.66, 0.09]	-1.59	.124	-0.65
		Total	24	-0.36	[-0.73, 0.00]	-2.04	.052	-0.83
Measure	Training	Comparison						
Calib.	Short-term	Group by time	df	*b*	95% CI	*t*	*p*	*d*
Temp.		MBSR-HEP	87	-0.22	[-0.52, 0.08]	-1.46	.149	-0.31
		MBSR-WL	87	-0.23	[-0.54, 0.07]	-1.53	.129	-0.33
		HEP-WL	87	-0.01	[-0.30, 0.28]	-0.10	.921	-0.02
		Within group	df	*b*	95% CI	*t*	*p*	*d*
		MBSR	27	-0.21	[-0.46, 0.03]	-1.80	.083	-0.35
		HEP	31	-0.03	[-0.18, 0.11]	-0.44	.662	-0.08
		WL	30	-0.03	[-0.29, 0.23]	-0.25	.801	-0.05
	Long-term	Between groups	df	*b*	95% CI	*t*	*p*	*d*
		LTM-MNP	143	0.15	[-0.36, 0.67]	0.59	.557	0.10
		Practice hours	df	*b*	95% CI	*t*	*p*	*d*
		Retreat	28	0.00	[-0.39, 0.38]	-0.01	.989	-0.01
		Daily	28	-0.21	[-0.59, 0.17]	-1.12	.272	-0.42
		Total	28	-0.09	[-0.48, 0.29]	-0.48	.634	-0.18

For short-term training, between groups effects represent relative change from pre- to post-intervention, adjusting for pre-intervention. Within group effects represent paired t-test of absolute change for post- vs. pre-intervention. For long-term practitioners, between groups effects represent

cross-sectional comparison of meditation-naïve practitioners (MNP) at pre-intervention with long-term meditators (LTM). Lifetime practice hours represents regression of signature response against cumulative lifetime practice hours in the LTM sample across categories of intensive retreat, daily practice, and combined total. Effects for pain signatures and practice hours are standardized; group comparisons for subjective reports are on the outcome scale of measurement. Resp. Rate: mean respiration rate during task; Calib. Temp: calibrated thermode temperature during task (i.e., pain tolerance).
* $p < .05$.