Amygdalar Function Reflects Common Individual Differences in Emotion and Pain Regulation Success

Regina C. Lapate[1], Hyejeen Lee[1], Tim V. Salomons[1,2], Carien M. van Reekum[1,3], Lawrence L. Greischar[1], and Richard J. Davidson[1]

Abstract

■ Although the co-occurrence of negative affect and pain is well recognized, the mechanism underlying their association is unclear. To examine whether a common self-regulatory ability impacts the experience of both emotion and pain, we integrated neuroimaging, behavioral, and physiological measures obtained from three assessments separated by substantial temporal intervals. Our results demonstrated that individual differences in emotion regulation ability, as indexed by an objective measure of emotional state, corrugator electromyography, predicted self-reported success while regulating pain. In both emotion and pain paradigms, the amygdala reflected regulatory success. Notably, we found that greater emotion regulation success was associated with greater change of amygdalar activity following pain regulation. Furthermore, individual differences in degree of amygdalar change following emotion regulation were a strong predictor of pain regulation success, as well as of the degree of amygdalar engagement following pain regulation. These findings suggest that common individual differences in emotion and pain regulatory success are reflected in a neural structure known to contribute to appraisal processes. ■

INTRODUCTION

Individual differences in affective functioning fundamentally color the processing of pain. In one extreme of the continuum between health and psychopathology, the comorbidity of mood disorders and pain syndromes is known to be high (Wiech & Tracey, 2009). Among chronic pain patients and healthy individuals, heightened experience of negative affect is associated with poorer pain outcomes (Strigo, Simmons, Matthews, Craig, & Paulus, 2008b; Price, 2000). Specifically, chronic pain sufferers high in emotional reactivity rate experimental pain as more unpleasant and report greater distress regarding the impact of pain for their future well-being (Price, 2000). Among pain-free individuals, increased levels of depression are associated with a larger ratio of unpleasantness-to-intensity ratings of experimental pain (Strigo et al., 2008b). Similarly, healthy individuals rate pain as more unpleasant following the induction of depressed mood (Berna et al., 2010). Given the overlap between the incidence of exacerbated emotionality and pain, one possibility is that individual differences in a general self-regulatory ability impact the experience of both emotion and pain. Moreover, as we review below, evidence concerning the neural correlates of volitional regulation of emotion, emotional modulation of pain, and trait-like variation in affective functioning suggest the amygdala as a site where individual differences in affective regulation may also impact pain processing.

The ability to regulate emotion in accordance with one's goals is paramount in promoting well-being and resilience. Although this skill is highly heterogeneous across individuals (Davidson, 2003), it is temporally stable within individuals (Lee, Shackman, Jackson, & Davidson, 2009). In a recent report, the ability to flexibly upregulate and downregulate emotion according to a situational goal predicted better adjustment to a novel stressful situation 1 year later (Bonanno, Papa, Lalande, Westphal, & Coifman, 2004). Numerous studies have shown that the volitional regulation of picture-induced negative affect recruits PFC circuitry, including the ventrolateral and dorsomedial regions (e.g., Eippert et al., 2007; van Reekum et al., 2007; Phan et al., 2005; Ochsner et al., 2004). Most of these studies have found amygdalar activity to covary with regulatory goal, suggesting that this region is a critical downstream target of regulatory efforts. Specifically, BOLD signal in the amygdala increases when negative emotion is upregulated and decreases when it is downregulated (Eippert et al., 2007; van Reekum et al., 2007; Urry et al., 2006; Ochsner et al., 2004). Furthermore, the degree of amygdalar signal change has been shown to be associated with self-reported success in regulation of negative affect (e.g., Eippert et al., 2007; Ochsner et al., 2004).

Electrophysiological and fMRI data suggest the amygdala may be an important site of integration of pain and affective motivational information. The amygdala responds with

[1]University of Wisconsin—Madison, [2]Toronto Western Research Institute, [3]University of Reading

greater activation to nociceptive stimuli of different modalities (Dube et al., 2009; Peyron et al., 2007; Bornhovd et al., 2002; but see also Petrovic, Carlsson, Petersson, Hansson, & Ingvar, 2004), where the degree of activation is associated with subjective pain ratings (Peyron et al., 2007; Bornhovd et al., 2002). Regarding its function, poor spatial coding of nociceptive stimuli suggests that the amygdala does not subserve sensory discrimination (Neugebauer, Li, Bird, & Han, 2004; Bernard, Huang, & Besson, 1992). Rather, the amygdala has been shown to mediate the emotional modulation of spinal nociceptive responses to painful electrical stimuli (Roy, Piche, Chen, Peretz, & Rainville, 2009). Furthermore, amygdalar responses to pain are augmented among depressed individuals (Strigo, Simmons, Matthews, Craig, & Paulus, 2008a) and in individuals who report increases in pain unpleasantness following a depressed mood induction (Berna et al., 2010). Together, these studies point to the amygdala as a site where individual differences in affective disposition may also influence pain processing.

A large corpus of data indicates that individual differences in vulnerability to mood and anxiety disorders are associated with dysregulated amygdalar responding during emotion-inducing paradigms (Drabant, McRae, Manuck, Hariri, & Gross, 2009; Etkin et al., 2004). We have demonstrated that the magnitude of BOLD response in the amygdala to a fearful stimulus is stable over time (Johnstone et al., 2005), suggesting that individual differences in amygdalar reactivity are trait-like. In addition, the extent of negative affect experienced over a month correlates with the degree of amygdalar activation to subliminally presented emotional stimuli a year later (Barrett, Bliss-Moreau, Duncan, Rauch, & Wright, 2007). Trait anxiety and habitual usage of reappraisal also closely predict amygdalar responses to fearful faces (Drabant et al., 2009; Etkin et al., 2004). Collectively, these data suggest functioning of the amygdala, a key target of regulatory attempts during emotion regulation paradigms, reliably reflects trait-like individual differences in affective disposition.

To test whether individual differences in emotion regulation success predict pain regulation success, we tested the same individuals three times over an approximately 3-year period (see Figure 1). Individuals came to the laboratory twice to participate in voluntary emotion regulation tasks, one in which peripheral physiological data were collected (Session 1) and one wherein neuroimaging data were collected (Session 2). Individuals returned a third time to the laboratory to participate in a voluntary pain regulation task when neuroimaging, peripheral physiological, and behavioral data were collected (Session 3). We hypothesized that individuals with greater ability to regulate negative emotion would also be more successful when regulating their responses to painful stimuli. Given that affect regulation and the emotional modulation of pain both target the amygdala, we further hypothesized that changes in amygdalar activity following regulation

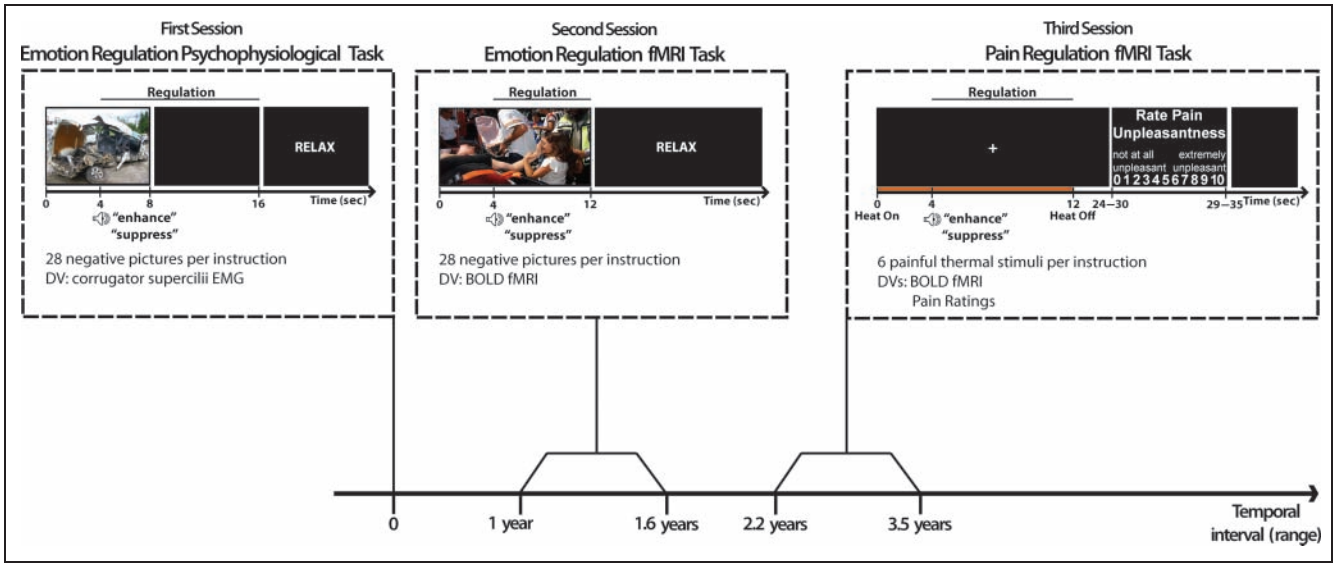

Figure 1. The time line and design of the emotion and pain regulation sessions. Participants initially came to the laboratory for two emotion reappraisal sessions, run on average 1.3 years apart, where they were instructed to either decrease or increase their emotional responses to negative pictures by imagining a better or worse outcome associated with them. The regulation instruction was presented 4 sec after picture onset, and participants were instructed to continue to regulate their emotional responses until they received an instruction to relax. Corrugator EMG was recorded continuously throughout Session 1, and BOLD fMRI was recorded during Session 2. Approximately 2.9 years after Session 1 of emotion regulation, participants returned to the laboratory for a similar paradigm where they were asked to regulate their responses to painful stimuli. After 4 sec of uninstructed pain, participants were asked to either increase or decrease their responses to the pain by imagining it represented either a negative or a more positive outcome in terms of their health or well-being. Pain unpleasantness ratings were acquired after each trial, whereas BOLD fMRI and heart rate were recorded continuously. Representative negative images were retrieved from commons.wikimedia.org/wiki/File:Kiuruvesi_railway_accident.jpg and commons.wikimedia.org/wiki/File:Mother_consoles_daughter_after_rocket_attack.jpg on July 22, 2011.

would reflect individual differences in regulatory success in both emotion and pain domains.

As individual differences in emotion regulation have been shown to be stable over time (Lee et al., 2009), in this longitudinal study, we conducted the psychophysiological (first) and the neuroimaging (second) emotion regulation sessions on average 1.3 years apart, whereas the pain regulation session (third) took place 2.9 years following the psychophysiological emotion regulation session. Participants used cognitive reappraisal as the strategy to modify their responses to negative visual stimuli in both emotion regulation sessions and to nociceptive thermal stimuli in the pain regulation session (Figure 1). Cognitive reappraisal involves voluntarily changing the meaning of an emotion-eliciting event according to a regulatory goal (Gross, 1998) and has been widely demonstrated to alter the experience of emotion, manifested by changes in subjective ratings, facial expression (Gross, 1998), and peripheral physiological output (Jackson, Malmstadt, Larson, & Davidson, 2000). In all three sessions, participants were instructed to either decrease ("suppress") or increase ("enhance") their emotional responses to the aversive stimuli by imagining a better or worse outcome associated with them.

To maximize our ability to detect amygdalar changes following regulation, regulatory success was computed as the difference score between responses in the enhance and suppress conditions. A larger score, therefore, indicates a greater ability to volitionally regulate responses to the aversive stimuli (Bonanno et al., 2004). The adoption of this difference score approach between two active conditions also allows us to control for effort expended during regulation, which has often been confounded in studies that included a passive control condition only (cf. Urry et al., 2006). Corrugator supercilii facial EMG, a well-validated index of emotional state (Lang, Greenwald, Bradley, & Hamm, 1993) that also provides a highly reliable estimate of individual differences in emotion regulation (Lee et al., 2009), was collected during the first emotion regulation session, whereas BOLD fMRI was collected during the second emotion regulation session. During the pain regulation session, we collected BOLD fMRI and pain unpleasantness ratings. Heart rate data were also available for a subset of participants, which were used to further validate the unpleasantness ratings as an index of regulatory success of the pain experience (Rainville, Bao, & Chretien, 2005).

First, we tested the hypothesis that greater emotion regulation success predicted greater pain regulation success by examining whether changes in corrugator EMG collected during the psychophysiological emotion regulation session predicted changes in self-reported pain unpleasantness during the pain regulation session. Second, we tested whether both emotion regulation and pain regulation success were associated with change in amygdalar activity and whether the neural correlates of regulatory success in the amygdala were consistent across modalities. Third, we investigated the commonality of skill across pain and emotion regulation paradigms at the neural level using an individual differences approach; specifically, we tested whether emotion regulation success measured by corrugator EMG predicted degree of amygdalar change during pain regulation. Finally, we tested whether individual differences in the degree of amygdalar change following emotion regulation predicted the degree of amygdalar change following the volitional regulation of pain as well as pain regulation success.

METHODS

Participants

We recruited 24 right-handed men (mean age = 22 years, *SD* = 2.1 years, range = 21–28 years) from a larger longitudinal study ($n = 56$) of the neural correlates of successful emotion regulation (Lee, Heller, van Reekum, Nelson, & Davidson, 2010) for a pain regulation session to verify whether the stability of emotion regulation skill would also extend to the domain of pain processing. We excluded data of two participants because of image artifact caused by excessive field inhomogeneity in the scanner (both in the pain regulation session) and one participant because of excessive noise in his corrugator data (in the psychophysiological emotion regulation session). As we were interested in the relationship between emotion regulation and pain regulation, we only analyzed data of participants who showed evidence of regulation in both emotion and pain paradigms, defined as a non-negative value in the (enhance–suppress) subtractions in both corrugator EMG and pain unpleasantness ratings, respectively. Seventeen participants met this criterion, hence constituted the final sample retained for the current investigation. The University of Wisconsin-Madison Social and Behavioral Health Sciences Institutional Review Board approved all three studies. All participants provided informed consent and were paid for participation.

Stimuli

Emotion Regulation Sessions 1 and 2

Two sets of 84 negative and 42 neutral pictures were selected from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1999) based on the normative ratings of valence and arousal (see Supplementary Data for additional details). The assignment of Sets 1 and 2 to the psychophysiological and neuroimaging emotion regulation sessions was counterbalanced across participants.

Pain Regulation Session

Painful heat was delivered to the nondominant left forearm using a thermal stimulator (TSA-II; Medoc Advanced

Medical Systems, Haifa, Israel) and a 30 × 30 mm MRI-compatible Peltier device. A level of pain rated as "8 out of 10" was chosen for each subject (see Supplementary Data). The maximum temperature used could not exceed 49°C, and participants were excluded if their nociceptive thermal stimulus was less than 46°C. Participant-tailored temperatures were not correlated with either emotion or pain regulation success (see Supplementary Data).

Procedure

Emotion Regulation Sessions

During the suppress condition, participants decreased their emotional response to a negative picture by reappraising it as less negative (e.g., imagining that a picture of a car accident was a movie where nobody was hurt). In the enhance condition, participants increased their emotional response by reappraising the image as more negative (e.g., imagining the car accident resulted in casualties). Note that the imagined outcomes adopted during reappraisal in emotion and pain regulation paradigms were experimenter-cued but participant-chosen, such that participants could reappraise the meaning of the experimental stimuli by using the outcome they found most effective, as long as it was stimulus-based. Participants maintained their initial response on some trials (data used in a control analysis to disentangle the contributions of enhance vs. suppress in the commonality of regulatory success investigated here; see Supplementary Data).

Emotion regulation session 1. Following a 1-sec fixation cross, pictures were presented for 8 sec, with an intertrial interval (ITI) of 12 sec (Figure 1). Four seconds after the onset of negative pictures, participants were asked to regulate their emotional response. Participants regulated until receiving a cue to relax, at Second 16. Corrugator EMG was continuously acquired according to published guidelines (Tassinary, Cacioppo, & Geen, 1989).

Emotion regulation session 2. Following a 1-sec fixation cross, pictures were presented for 12 sec, with an average ITI of 7.41 sec (5.1–9.9 sec; see Figure 1). Regulation instruction was delivered 4 sec after the onset of negative pictures. Participants regulated for 8 sec.

Pain Regulation Session

Participants were familiarized with the thermal stimulation in the fMRI environment by undergoing a simulation session in a mock scanner. During this session (usually 1 day before the scanning session), we established the temperature used for testing. Next, participants practiced suppressing and enhancing their responses to pain. In the suppress condition, participants imagined the heat represented a good outcome (e.g., the pain from a hot tub). In the enhance condition, they imagined the heat represented a threat to their life and well-being (e.g., the pain resulting from a fire). On certain trials, they were asked to respond to the pain as they normally would (data used in a control analysis to disentangle the contributions of enhance vs. suppress in the commonality of regulatory success investigated here; see Supplementary Data).

On the day of the MRI session, a photoplethysmograph transducer was attached to the third finger of the nondominant hand to acquire pulse oxymetry throughout the experiment (for heart rate data acquisition and processing, see Supplementary Data). Pupil diameter was monitored to verify equivalent levels of engagement across the two active regulatory conditions (e.g., Urry et al., 2006; see Supplementary Data). During the task, eighteen 12-sec thermal stimulations were delivered (see Figure 1). Four seconds after stimulus onset, participants were asked to enhance, maintain, or suppress their response using the reappraisal strategies they had previously practiced. Nine seconds (±3 sec) after stimulus offset, participants rated pain intensity and unpleasantness on 11-point Likert scales (0 represented *not at all intense/unpleasant* and 10 represented *most intense pain imaginable/extremely unpleasant*). Rating screens were on for 5 sec and were separated by a 1-sec interval. As intensity ratings were not significantly affected by regulatory instruction, they are not discussed further. A 30-sec ITI (±3 sec) followed.

Data Processing and Analysis

Emotion Regulation Session 1

Corrugator EMG. Corrugator EMG data were continuously acquired with a gain of 10,000 using SAI Bioelectric amplifiers, which were calibrated before the start of each session. These data were high-pass filtered at 1 Hz and low-pass filtered at 400 Hz. An Fast Fourier Transform in 0.5-sec Hamming windowed chunks yielded power density values (μV^2/Hz for the 45- to 200-Hz EMG band) from artifact-free data. Values were log-transformed to correct for skewness and baseline-corrected by subtracting the averaged corrugator power from 1 sec preceding the onset of each trial. Corrugator power was averaged 4–16 sec after picture onset (i.e., following regulation instruction), as we have found corrugator EMG responses to be long-lasting following instruction to regulate (Supplementary Figure 1). Emotion regulation success was computed by subtracting corrugator responses in the suppress condition from responses in the enhance condition.

Pain Regulation Session

Pain unpleasantness ratings. Pain unpleasantness ratings across the 18 trials were inspected, and extreme values (i.e., data points higher or lower than three times the interquartile range) were identified as outliers and removed on a subject-by-subject basis, resulting in the discarding of 2.28% of trials. Pain regulation success was

operationalized as the ratings difference between the enhance and suppress conditions.

Emotion Regulation Session 2 and Pain Regulation Session

Imaging acquisition and statistical analyses. Functional and anatomical data were acquired with a 3.0-T GE scanner (GE Medical Systems, Waukesha, WI) using a quadrature head coil. High-resolution T1-weighted images were acquired for anatomical localization of functional activity (three-dimensional T1-weighted inversion recovery fast gradient-echo, matrix = 256 × 256, field of view = 240 × 240 mm, 124 axial slices, slice thickness = 1.1 mm). After the anatomical images were collected, functional images were acquired sagittally using whole-brain EPI, with 30 slices of 4 mm of thickness (1-mm interslice gap, echo time = 30 msec, repetition time = 2 sec, flip angle = 90°, field of view = 240 × 240, matrix = 64 × 64).

Emotion regulation and pain regulation neuroimaging data were preprocessed and analyzed using FEAT (Woolrich, 2008; FMRIB Software Library, www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Preprocessing steps included high-pass filtering at 100 sec, FILM correction for autocorrelation in the BOLD signal, motion correction using MCFLIRT, and creation of a confound matrix of points of outlier intensity changes left uncorrected by MCFLIRT to be used as regressors of noninterest in the analyses, thus removing movement-confounded activation. Data were smoothed at 5 mm using a Gaussian blur. Functional and structural data were registered to standardized space (Montreal Neurological Institute [MNI]) using FNIRT. In both neuroimaging paradigms, regressors for the 8 sec of the enhance and suppress conditions were derived by convolving each event with a canonical hemodynamic response function (γ) at the single-subject general linear model. As discussed in Introduction, to maximize our ability to detect amygdalar changes following regulation as well as to control for effort during regulation, the primary contrast of interest consisted of the difference in BOLD signal between the two active emotion regulation conditions (enhance–suppress).

To determine whether changes in the amygdala reflected regulation success in each stimulus modality, we ran a whole-brain voxelwise regression of the regulatory success on individual subjects' contrast maps for each regulation paradigm. Specifically, we regressed (1) (enhance–suppress) corrugator EMG changes on individual subjects' (enhance–suppress) contrast maps during emotion regulation and (2) (enhance–suppress) changes in pain unpleasantness ratings on individual subjects' (enhance–suppress) contrast maps during pain regulation.

All regressions were run using a mixed-effects model (FLAME). Automatic outlier deweighting was run on a voxelwise basis (Woolrich, 2008). Correction for multiple comparisons for the whole-brain voxelwise regressions was performed by using Gaussian random field theory at the cluster level, at $z > 1.65$, $p < .01$. We extracted parameter estimates from the neural correlates of pain regulation success within the amygdala as defined by the Jüelich probabilistic atlas at 50% threshold (Amunts et al., 2005). To determine whether there was spatial overlap of amygdalar clusters obtained following the voxelwise regression of regulatory success in emotion and pain paradigms, we took a logical "and" conjunction approach by taking the minimum z value of the cluster-corrected z maps associated with regulatory success in each paradigm (Nichols, Brett, Andersson, Wager, & Poline, 2005). All coordinates are reported in MNI space.

Paired sample t tests, correlations, and regression models were run using SPSS version 16.0 (SPSS, Inc., Chicago, IL). The alpha level for all of the analyses was set to $p < .05$.

RESULTS

Emotion Regulation Session: Corrugator EMG

We determined that corrugator EMG activity was significantly higher in trials wherein participants enhanced their responses to negative pictures ($M = 0.60$, $SEM = 0.10$) than in trials where they suppressed their responses ($M = 0.13$, $SEM = 0.03$), $t(16) = 5.42$, $p < .001$ (Supplementary Figure 2A).

Pain Regulation Session: Pain Unpleasantness Ratings

Participants reported more pain unpleasantness when asked to enhance their responses to the heat ($M = 7.56$, $SEM = 0.30$) than when asked to suppress them ($M = 6.17$, $SEM = 0.37$), $t(16) = 8.51$, $p < .001$ (Supplementary Figure 2B).

For a subset of participants for whom we had heart rate available, we verified that heart rate was higher when participants enhanced their responses to thermal pain ($M = 71.52$, $SEM = 2.85$) than when they suppressed them ($M = 69.91$, $SEM = 2.80$), $t(13) = 2.96$, $p < .01$ (Supplementary Figure 2C). Given the possibility that pain unpleasantness ratings were influenced by demand characteristics, a significant correlation between changes in an autonomic nervous system index and pain unpleasantness ratings, (enhance–suppress), $r(12) = .60$, $p = .023$ (Supplementary Figure 3A), further validates self-reported unpleasantness as an index of pain regulation success.

The Contribution of Emotion Regulation Success to Pain Regulation Success

As hypothesized, regulation success in response to negative pictures predicted regulation success in response to pain over 2 years later, such that greater change scores in corrugator EMG activity (enhance–suppress) during the emotion regulation task were associated with greater change scores

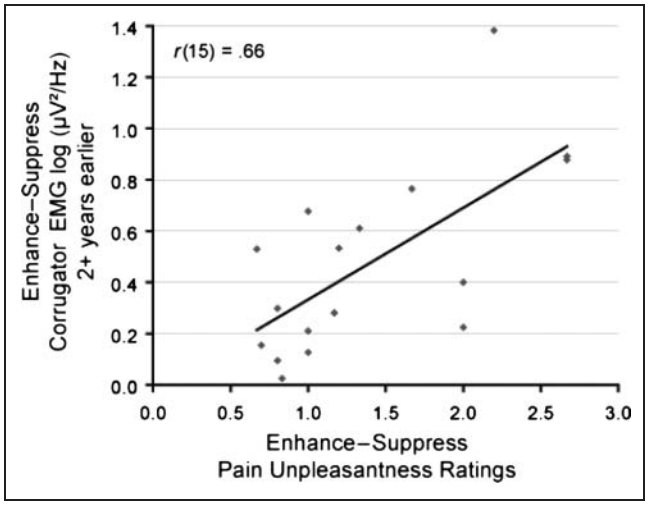

Figure 2. Emotion regulation success predicts pain regulation success over 2 years later. Correlation of participants' emotion regulation skill as indexed by the (enhance–suppress) change in corrugator EMG with their pain regulation skill measured over two years later as indexed by the (enhance–suppress) change in pain unpleasantness ratings. Correlation remains significant after removing the bivariate outlier, $r(14) = .64$, $p < .007$.

of pain unpleasantness ratings (enhance–suppress) during the pain regulation task, $r(15) = .66$, $p = .003$ (Figure 2). This finding suggests that self-regulatory ability in emotion generalizes to the domain of pain processing.

Amygdalar Activity as a Neural Correlate of Emotion and Pain Regulation Success

The results of a whole-brain voxelwise correlation between change in corrugator EMG activity (enhance–suppress) and BOLD signal for the corresponding contrast during the emotion regulation task replicated the previously demonstrated role of the amygdala: BOLD signal changes in left amygdala were significantly correlated with changes in emotion regulatory success as indexed by corrugator EMG (activation in other regions was also correlated with changes in emotion regulation success; for a complete listing, see Table 1).

Similarly, the voxelwise correlation between change in pain unpleasantness ratings (enhance–suppress) and BOLD signal for the enhance–suppress contrast during the pain regulation task across the whole brain confirmed the hypothesized role of the amygdala in pain regulation: BOLD signal changes in bilateral amygdala were significantly correlated with changes in regulatory success (for a complete listing of all regions whose activation correlated with changes in pain regulation success, see Table 2). In addition, we obtained further evidence that this bilateral amygdalar cluster was an important target of pain regulation efforts from the subset of participants for which we had heart rate data available: We observed a positive correlation between activity in this pain regulation amygdalar cluster and changes in heart rate following regulation (enhance–suppress), $r(12) = .70$, $p = .005$ (Supplementary Figure 3B).

We extracted parameter estimates of individual subjects' contrasts from the amygdalar clusters associated with regulatory success in each emotion and pain neuroimaging paradigm separately (Figure 3A–C). The results of a conjunction analysis of the amygdalar neural correlates of emotion and pain regulation success (corrected for multiple comparisons) revealed that those were two separate amygdalar clusters across the two modalities of regulation. However, consistent with our individual differences finding of common skill across these two domains, emotion regulation success assessed with corrugator EMG changes

Table 1. MNI Coordinates of the Areas in the Enhance–Suppress Contrast during Emotion Regulation that Are Significantly Correlated with Successful Emotion Regulation as Indexed by (Enhance–Suppress) Corrugator EMG, Whole-brain Cluster-level Corrected for Multiple Comparisons at $z > 1.65$, $p < .01$

		Coordinates at Z Peak			
Brain Region	*Size (mm^3)*	*x*	*y*	*z*	*Z Peak*
L amygdala	168	−24	−2	−32	2.77
L hippocampus	1232	−20	2	−30	3.37
L middle frontal gyrus (BA 6)	1968	−46	8	52	3.30
L frontal pole (BA 10)	5944	−24	52	20	2.90
L temporal pole	1600	−34	20	−38	2.90
Frontal orbital cortex (BA 25)	1304	−12	16	−24	2.80
L precentral gyrus	1280	−62	2	26	2.77
L inferior frontal gyrus (BA 44) *(pars opercularis)*	1408	−52	18	10	2.74
L inferior frontal gyrus (BA 45) *(pars triangularis)*	280	−56	26	12	2.68

L = left; R = right.

Table 2. MNI Coordinates of the Areas in the Enhance–Suppress Contrast during Pain Regulation that Are Significantly Correlated with Successful Pain Regulation as Indexed by (Enhance–Suppress) Pain Unpleasantness Ratings, Whole-brain Cluster-level Corrected for Multiple Comparisons at $z > 1.65$, $p < .01$

Brain Region	Size (mm^3)	Coordinates at Z Peak			Z Peak
		x	*y*	*z*	
R amygdala	344	24	−10	−8	3.20
L amygdala	64	−18	−8	−20	1.97
R cerebellum	4776	24	−38	−26	3.63
L cerebellum	4552	−12	−48	−18	3.14
R hippocampus	912	24	−12	−12	3.05
L hippocampus	664	−30	−18	−20	2.47
R occipital cortex	864	14	−46	−8	2.12
L occipital cortex	7240	−4	−88	18	3.05
Brainstem	2400	6	−30	−24	3.02
Parahippocampal gyrus	296	20	−24	−22	2.91
Thalamus	96	−2	−16	4	2.80
Pallidum	512	20	−10	−6	2.79

L = left; R = right.

was robustly associated with the degree of change in BOLD response in the amygdalar cluster associated with pain regulation success, $r(15) = .56$, $p = .017$ (Figure 3D). Differently put, the greater a participant's ability to regulate negative emotion based on changes in an objective index of emotional state, the greater the resulting amygdalar change observed as a function of pain regulatory goal, more than 2 years later.

Consistently, we also found that participants who showed the greatest change in the BOLD response of the amygdalar cluster associated with emotion regulation success were the ones who experienced the greatest difference in pain unpleasantness as a function of pain regulatory instruction, $r(15) = .65$, $p = .004$ (Figure 3E). In other words, a participant's magnitude of change in amygdalar activity in response to voluntarily regulating picture-induced negative emotion was tightly linked with their reported success in volitionally regulating pain 1 year later. This was further corroborated by the significant correlation between the degree of change of amygdalar activity following emotion regulation (enhance–suppress) and changes of heart rate following pain regulation instruction for the corresponding (enhance–suppress) contrast over a year later, $r(12) = .61$, $p = .01$ (Supplementary Figure 3C). (For a full description of cross-paradigm associations between markers of regulatory success in emotion and pain regulation paradigms and brain activity, please see Supplementary Data and Supplementary Tables SI and SII).

Lastly, we found that individual differences in the degree of engagement of the amygdalar cluster associated with regulatory success in a picture-induced emotion regulation paradigm were a strong predictor of the degree of engagement of the amygdalar cluster associated with pain regulation success, $r(15) = .67$, $p = .003$ (Figure 3F). This means that the greater the change in amygdalar activity following volitional change of emotional responding to negative pictures, the greater the observed change in amygdalar activity following volitional regulation of thermal pain.

The contrast we adopted in our analyses, which consisted of a difference score between two active regulatory conditions (enhance–suppress), allowed us to appropriately measure amygdalar changes during reappraisal while successfully controlling for effort expended during regulation, which was indeed empirically validated by our analysis of the pupillometry data collected during pain regulation (see Supplementary Data). However, given the concern that the shared regulatory skill in emotion and pain paradigms could have been driven exclusively by the ability to either enhance or suppress negative affect, we took advantage of the passive (maintain) condition to assess the relative contributions of the enhance and suppress conditions in underlying this association. Although there were a greater number of significant relationships using (maintain–suppress) than when using (enhance–maintain) as a predictor of cross-paradigm relations, we found that the majority of such predictions were not significantly different from one another. This fact implies that both upregulation and downregulation skills contribute to the effects described here and both appear to contribute to a general self-regulatory ability (for a full description of this control analysis and the results, see Supplementary Data and Supplementary Table SIII).

DISCUSSION

By integrating neuroimaging, behavioral, and physiological methods in three independent assessments, we show that emotion regulation and pain regulation skills are a shared ability that is reflected in functioning of the amygdala. Specifically, greater success in voluntarily reappraising picture-induced negative emotion, as indexed by corrugator EMG, predicted greater success in reappraising heat-induced pain, as evidenced by changes in subjective ratings of pain unpleasantness and in the modulation of the activity of a bilateral amygdalar cluster during pain regulation associated with pain regulation success. Similarly, the ability to modulate the activity of the left amygdala during emotion regulation was also predictive of self-reported pain regulation success. Although these emotion and pain regulation amygdalar clusters did not spatially overlap, individual differences in the degree of modulation within these clusters were correlated across regulation paradigms. These associations were evident despite significant temporal gaps (1–3 years and more) between our assessments, which substantiate previous findings regarding the stability

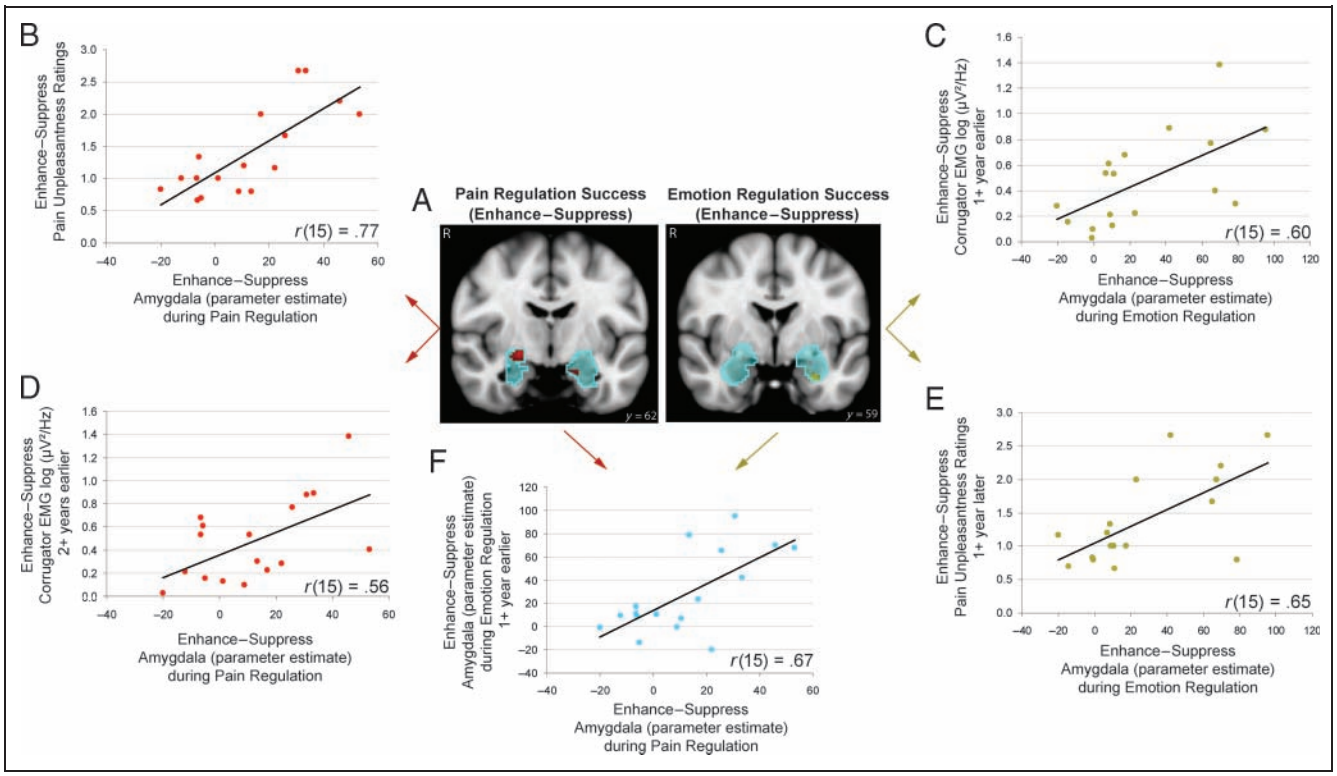

Figure 3. Amygdala reflects regulatory success in both emotion and pain regulation paradigms. (A) In red, amygdalar cluster identified by correlating changes in pain unpleasantness ratings (enhance–suppress) across individuals with the parameter estimates of the corresponding (enhance–suppress) contrast during pain regulation (whole-brain cluster-level corrected for multiple comparisons at $z > 1.65$, $p < .01$). In yellow, amygdalar cluster identified by correlating changes in corrugator EMG (enhance–suppress) across individuals with the parameter estimates of the corresponding (enhance–suppress) contrast during emotion regulation (whole-brain cluster-level corrected for multiple comparisons at $z > 1.65$, $p < .01$). The outline in blue demarks the area with at least 50% probability of belonging to the amygdala (Amunts et al., 2005). (B) The scatterplot of the pain regulation statistical map shown in A, collapsed across right and left amygdalae. (C) The scatterplot of the emotion regulation statistical map shown in A, for the left amygdala. (D) Corrugator EMG during emotion regulation as a function of amygdalar activation during pain regulation, over 2 years later. (E) Changes in pain unpleasantness during pain regulation as a function of degree of change in the amygdala during emotion regulation, measured over a year earlier. (F) Amygdalar changes following emotion regulation as a function of amygdalar changes following pain regulation, measured over a year later.

of individual differences in emotion regulation (Davidson, 2003; Lee et al., 2009).

Our results point to a previously unreported commonality between emotion regulatory and pain regulatory success. Prior evidence stemming from various fields has highlighted the frequent co-occurrence of pain and negative affect (Wiech & Tracey, 2009; Neugebauer et al., 2004; Price, 2000). Negative affect deeply permeates both psychopathological and pain states (Rainville et al., 2005; Price, 2000), as illustrated, for example, by the fact that the anxiolytic effects of benzodiazepines provide pain relief despite their lack of analgesic properties (Dellemijn & Fields, 1994). Thus, skill at volitionally regulating emotions may generalize to pain. We tested this hypothesis using three experimental paradigms that together examined individual ability to reappraise negative emotion and pain. We found that regulatory ability in response to negative pictures predicted success while regulating responses to pain, which suggests that common skills underlie the regulation of both emotion and pain.

Our study further extends previous findings showing that changing the meaning of a negative event impacts functioning of the amygdala. This subcortical region is considered part of the brain's early appraisal system (LeDoux, 2000), and recent evidence suggests that it tracks a combination of valence and arousal dimensions of one's subjective experience in response to an emotional stimulus (Winston, Gottfried, Kilner, & Dolan, 2005). Following this rapid tracking, the amygdala recruits behavioral, endocrine, and autonomic responses via its efferent projections to brainstem nuclei (Winston et al., 2005; LeDoux, 2000). Relatedly, direct amygdalar stimulation increases activity of the corrugator muscle (Lanteaume et al., 2007), which is well known to be associated with valence judgments (Lang et al., 1993). Accordingly, amygdalar activity has been known to be sensitive to regulatory goals of increasing and decreasing negative affect as revealed by cognitive reappraisal paradigms (van Reekum et al., 2007; Urry et al., 2006; Phan et al., 2005; Ochsner et al., 2004), wherein the extent of change in amygdalar activation during regulation correlates with self-reported changes in arousal and negative affect (e.g., Ochsner et al., 2004). Here, we extended this finding using an objective metric of emotional state, wherein our participants' emotion regulatory

abilities, as measured by corrugator EMG activity, were predictive of the degree of change in activity of a left amygdalar cluster following emotion regulation instruction (Lee et al., 2010).

Notably, we found that emotion regulation success measured by corrugator EMG and left amygdalar activation during emotion regulation were both predictors of the modulation of amygdalar activation that was associated with pain regulation success. As noted earlier, the amygdala has been found to reflect emotion-dependent modulation of spinal nociceptive responses (Roy et al., 2009) and pain unpleasantness (Berna et al., 2010) following negative mood inductions. Here, we found that the degree of change in amygdalar activity while upregulating versus downregulating pain was associated with corresponding changes in subjective pain unpleasantness and heart rate. Of note, we found separate amygdalar clusters associated with regulatory success in the negative picture-induced emotion and in the thermal pain paradigms. Although our whole-brain image acquisition is not ideally suited to support claims regarding the involvement of specific amygdalar nuclei during our tasks, it is possible that sensory modality-specific demands of our paradigms may have primarily engaged different areas of amygdalar reappraisal circuitry. For example, extracellular recordings of neurons located in the central nucleus of the amygdala of rats have demonstrated that the majority of them respond to thermal and mechanical, but not visual or auditory, stimuli (Neugebauer et al., 2004; Bernard et al., 1992). In contrast, projections from the visual cortex in the monkey have been shown to be primarily to basal and lateral nuclei (Iwai, Yukie, Suyama, & Shirakawa, 1987). Another related possibility is that reappraising noxious thermal stimulation, an intrinsically threatening stimulus, evoked marked arousal processing in the amygdala, which has been shown to be primarily reflected in dorsal nuclei activity (Davis, Johnstone, Mazzulla, Oler, & Whalen, 2010), consistent with the location of the peak in amygdalar BOLD signal associated with pain regulation success. In contrast, the reappraisal of negative images containing varying arousal levels and the reflection of reappraisal outcome in corrugator EMG, which is known to be particularly sensitive to the valence, rather than arousal, dimension of one's emotional responding (e.g., Lang et al., 1993), might have contributed to our finding a neural correlate of emotion regulatory success in a more ventral amygdalar region, previously shown to be implicated in valence processing (Davis et al., 2010). Despite our having found separate clusters reflecting amygdalar engagement across these two modalities of negative affect modulation, our finding that skills in reappraising negative emotion predicted the magnitude of change in the activation of the amygdala during pain regulation suggests that an important way in which affective style may influence the processing of pain is via an individual's ability to effectively modulate appraisal processes that are at least partially reflected in this brain area. The finding that individual differences in degree of modulation of the amygdala during an emotion regulation paradigm strongly predict individual differences in the degree of modulation of amygdalar activity during a pain regulation paradigm further corroborates this idea.

The unusual nature of this study, with independent assessments of regulatory skill following multiyear temporal intervals, provided us with an excellent opportunity to examine the stability of individual differences in affective responding. The fact that our predictions were confirmed despite significant intervals is a strong indicator of the stability of affective style (Davidson, 2003). The amygdala is one of a few regions for which the reliability of hemodynamic responses to emotional stimuli (i.e., fearful faces) has been verified (Johnstone et al., 2005). Our results not only reinforce these findings by providing further evidence of the temporal stability of individual skill in voluntary regulation of negatively valenced emotional experience (Lee et al., 2009) but also indicate that they may be extended to the emotional components involved in pain processing via the engagement of the amygdala.

In our current report of trait-like variability in emotion and pain regulation success, we adopted a contrast between two active regulatory conditions (enhance and suppress), which maximized our ability to identify individual differences in change in activity in a known primary neural target of regulation (i.e., the amygdala). Although the focus in our analysis was on the amygdala, future work should address common involvement of cortical circuitry in picture-induced emotion regulation and pain regulation, both across active regulation conditions (controlling for cognitive demand) and across the more commonly analyzed contrasts that include a passive control condition. Of note, the ventrolateral PFC has been shown to play a crucial role in the instantiation of top–down control of both emotion (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008) and pain processing (Salomons, Johnstone, Backonja, Shackman, & Davidson, 2007). Such analyses will shed light on whether circuitry involving the ventrolateral PFC is common across similar reappraisal processes of emotion-eliciting information from different modalities.

Two limitations of the current work warrant future research. First, the nociceptive neuronal population in the amygdala is known to be heterogeneous: Although the majority of neurons respond to pain in an excitatory manner, some are inhibitory (Neugebauer et al., 2004; Bernard et al., 1992), which may underlie the amygdalar participation in stress-induced analgesia (Fields, 2000; Fox & Sorenson, 1994). Thus, delineating which neuronal groups in the amygdala are recruited under differential psychological contexts, leading to analgesic or hyperalgesic outcomes, requires further study. Lastly, although the inclusion of only men is a limitation, we previously found no gender differences in the reliability of emotion regulation skills as indexed by corrugator, suggesting that the predictive value of individual differences in affective style may be similarly valid across men and women (Lee et al., 2009). Future work should, however, include both women and men.

In conclusion, our findings provide novel evidence that emotion regulation skills predict skill in regulating pain and that the amygdala reflects processes common to these two domains.

Acknowledgments

We thank A. S. Fox, A. S. Heller, K. N. Javaras, T. Johnstone, J. M. Ollinger, and A. N. DeClercq for helpful comments; L. Angelos, M. Anderle, A. M. Detloff, and R. Fisher for assistance in data acquisition; and D. M. Cole and I. Dolski at the Waisman Laboratory for Brain Imaging and Behavior for administrative support. This study was supported by National Institute of Mental Health grants R01-MH43454 and P50-MH069315 to R. J. D.

Reprint requests should be sent to Richard J. Davidson, Waisman Laboratory for Brain Imaging and Behavior, 1500 Highland Avenue, Madison, WI 53705-2280, or via e-mail: rjdavids@wisc.edu.

REFERENCES

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N. J., et al. (2005). Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. *Anatomy and Embryology, 210,* 343–352.

Barrett, L. F., Bliss-Moreau, E., Duncan, S. L., Rauch, S. L., & Wright, C. I. (2007). The amygdala and the experience of affect. *Social Cognitive and Affective Neuroscience, 2,* 73–83.

Berna, C., Leknes, S., Holmes, E. A., Edwards, R. R., Goodwin, G. M., & Tracey, I. (2010). Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. *Biological Psychiatry, 67,* 1083–1090.

Bernard, J. F., Huang, G. F., & Besson, J. M. (1992). Nucleus centralis of the amygdala and the globus pallidus ventralis: Electrophysiological evidence for an involvement in pain processes. *Journal of Neurophysiology, 68,* 551–569.

Bonanno, G. A., Papa, A., Lalande, K., Westphal, M., & Coifman, K. (2004). The importance of being flexible: The ability to both enhance and suppress emotional expression predicts long-term adjustment. *Psychological Science, 15,* 482–487.

Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., & Buchel, C. (2002). Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: A single-trial fMRI study. *Brain, 125,* 1326–1336.

Davidson, R. J. (2003). Affective neuroscience and psychophysiology: Toward a synthesis. *Psychophysiology, 40,* 655–665.

Davis, F. C., Johnstone, T., Mazzulla, E. C., Oler, J. A., & Whalen, P. J. (2010). Regional response differences across the human amygdaloid complex during social conditioning. *Cerebral Cortex, 20,* 612–621.

Dellemijn, P. L., & Fields, H. L. (1994). Do benzodiazepines have a role in chronic pain management? *Pain, 57,* 137–152.

Drabant, E. M., McRae, K., Manuck, S. B., Hariri, A. R., & Gross, J. J. (2009). Individual differences in typical reappraisal use predict amygdala and prefrontal responses. *Biological Psychiatry, 65,* 367–373.

Dube, A. A., Duquette, M., Roy, M., Lepore, F., Duncan, G., & Rainville, P. (2009). Brain activity associated with the electrodermal reactivity to acute heat pain. *Neuroimage, 45,* 169–180.

Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., & Anders, S. (2007). Regulation of emotional responses elicited by threat-related stimuli. *Human Brain Mapping, 28,* 409–423.

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R., et al. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron, 44,* 1043–1055.

Fields, H. L. (2000). Pain modulation: Expectation, opioid analgesia and virtual pain. *Progress in Brain Research, 122,* 245–253.

Fox, R. J., & Sorenson, C. A. (1994). Bilateral lesions of the amygdala attenuate analgesia induced by diverse environmental challenges. *Brain Research, 648,* 215–221.

Gross, J. J. (1998). Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology, 74,* 224–237.

Iwai, E., Yukie, M., Suyama, H., & Shirakawa, S. (1987). Amygdalar connections with middle and inferior temporal gyri of the monkey. *Neuroscience Letters, 83,* 25–29.

Jackson, D. C., Malmstadt, J. R., Larson, C. L., & Davidson, R. J. (2000). Suppression and enhancement of emotional responses to unpleasant pictures. *Psychophysiology, 37,* 515–522.

Johnstone, T., Somerville, L. H., Alexander, A. L., Oakes, T. R., Davidson, R. J., Kalin, N. H., et al. (2005). Stability of amygdala BOLD response to fearful faces over multiple scan sessions. *Neuroimage, 25,* 1112–1123.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1999). *The International Affective Picture System (IAPS): Technical manual and affective ratings*. Gainsville, FL: University of Florida.

Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiology, 30,* 261–273.

Lanteaume, L., Khalfa, S., Regis, J., Marquis, P., Chauvel, P., & Bartolomei, F. (2007). Emotion induction after direct intracerebral stimulations of human amygdala. *Cerebral Cortex, 17,* 1307–1313.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23,* 155–184.

Lee, H., Heller, A., van Reekum, C. M., Nelson, B., & Davidson, R. J. (2010). *Successful down-regulation of negative affect is associated with amygdala–PFC decoupling*. Paper presented at the 16th Annual Meeting of the Organization for Brain Mapping, Barcelona, Spain.

Lee, H., Shackman, A. J., Jackson, D. C., & Davidson, R. J. (2009). Test–retest reliability of voluntary emotion regulation. *Psychophysiology, 46,* 874–879.

Neugebauer, V., Li, W., Bird, G. C., & Han, J. S. (2004). The amygdala and persistent pain. *The Neuroscientist, 10,* 221–234.

Nichols, T., Brett, M., Andersson, J., Wager, T., & Poline, J. B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage, 25,* 653–660.

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., et al. (2004). For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage, 23,* 483–499.

Petrovic, P., Carlsson, K., Petersson, K. M., Hansson, P., & Ingvar, M. (2004). Context-dependent deactivation of the amygdala during pain. *Journal of Cognitive Neuroscience, 16,* 1289–1301.

Peyron, R., Kupers, R., Jehl, J. L., Garcia-Larrea, L., Convers, P., Barral, F. G., et al. (2007). Central representation of the RIII flexion reflex associated with overt motor reaction: An fMRI study. *Clinical Neurophysiology, 37,* 249–259.

Phan, K. L., Fitzgerald, D. A., Nathan, P. J., Moore, G. J., Uhde, T. W., & Tancer, M. E. (2005). Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. *Biological Psychiatry, 57,* 210–219.

Price, D. D. (2000). Psychological and neural mechanisms of the affective dimension of pain. *Science, 288,* 1769–1772.

Rainville, P., Bao, Q. V., & Chretien, P. (2005). Pain-related emotions modulate experimental pain perception and autonomic responses. *Pain, 118,* 306–318.

Roy, M., Piche, M., Chen, J. I., Peretz, I., & Rainville, P. (2009). Cerebral and spinal modulation of pain by emotions. *Proceedings of the National Academy of Sciences, U.S.A., 106,* 20900–20905.

Salomons, T. V., Johnstone, T., Backonja, M. M., Shackman, A. J., & Davidson, R. J. (2007). Individual differences in the effects of perceived controllability on pain perception: Critical role of the prefrontal cortex. *Journal of Cognitive Neuroscience, 19,* 993–1003.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23(Suppl. 1),* S208–S219.

Strigo, I. A., Simmons, A. N., Matthews, S. C., Craig, A. D., & Paulus, M. P. (2008a). Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Archives of General Psychiatry, 65,* 1275–1284.

Strigo, I. A., Simmons, A. N., Matthews, S. C., Craig, A. D., & Paulus, M. P. (2008b). Increased affective bias revealed using experimental graded heat stimuli in young depressed adults: Evidence of "emotional allodynia." *Psychosomatic Medicine, 70,* 338–344.

Tassinary, L. G., Cacioppo, J. T., & Geen, T. R. (1989). A psychometric study of surface electrode placements for facial electromyographic recording: I. The brow and cheek muscle regions. *Psychophysiology, 26,* 1–16.

Urry, H. L., van Reekum, C. M., Johnstone, T., Kalin, N. H., Thurow, M. E., Schaefer, H. S., et al. (2006). Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *Journal of Neuroscience, 26,* 4415–4425.

van Reekum, C. M., Johnstone, T., Urry, H. L., Thurow, M. E., Schaefer, H. S., Alexander, A. L., et al. (2007). Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. *Neuroimage, 36,* 1041–1055.

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., & Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron, 59,* 1037–1050.

Wiech, K., & Tracey, I. (2009). The influence of negative emotions on pain: Behavioral effects and neural mechanisms. *Neuroimage, 47,* 987–994.

Winston, J. S., Gottfried, J. A., Kilner, J. M., & Dolan, R. J. (2005). Integrated neural representations of odor intensity and affective valence in human amygdala. *Journal of Neuroscience, 25,* 8903–8907.

Woolrich, M. (2008). Robust group analysis using outlier inference. *Neuroimage, 41,* 286–301.