

# Social rejection shares somatosensory representations with physical pain

Ethan Kross<sup>a,1</sup>, Marc G. Berman<sup>a</sup>, Walter Mischel<sup>b</sup>, Edward E. Smith<sup>b,c,1</sup>, and Tor D. Wager<sup>d</sup>

<sup>a</sup>Department of Psychology, University of Michigan, Ann Arbor, MI 48109; <sup>b</sup>Department of Psychology, Columbia University, New York, NY 10027; <sup>c</sup>New York State Psychiatric Institute, New York, NY 10032; and <sup>d</sup>Department of Psychology, University of Colorado, Boulder, CO 80309-0345

Contributed by Edward E. Smith, February 22, 2011 (sent for review October 05, 2010)

**How similar are the experiences of social rejection and physical pain? Extant research suggests that a network of brain regions that support the affective but not the sensory components of physical pain underlie both experiences. Here we demonstrate that when rejection is powerfully elicited—by having people who recently experienced an unwanted break-up view a photograph of their ex-partner as they think about being rejected—areas that support the sensory components of physical pain (secondary somatosensory cortex; dorsal posterior insula) become active. We demonstrate the overlap between social rejection and physical pain in these areas by comparing both conditions in the same individuals using functional MRI. We further demonstrate the specificity of the secondary somatosensory cortex and dorsal posterior insula activity to physical pain by comparing activated locations in our study with a database of over 500 published studies. Activation in these regions was highly diagnostic of physical pain, with positive predictive values up to 88%. These results give new meaning to the idea that rejection “hurts.” They demonstrate that rejection and physical pain are similar not only in that they are both distressing—they share a common somatosensory representation as well.**

emotion | social pain | affective neuroscience | neuroimaging | psychological distress

Consider two scenarios. In the first, you spill a hot cup of coffee on your forearm and experience intense pain. In the second, you look at pictures of your former romantic partner, a person with whom you recently experienced an unwanted break-up; as you view each photo you feel rejected and experience another kind of “pain.” On the surface, these two events seem quite distinct. Whereas the former involves a noxious bodily stimulus, the latter involves the termination of a social relationship. However, cultures around the world use the same language—words like “hurt” and “pain”—to describe both experiences (1), raising the question: How similar are social rejection and physical pain?

Several recent studies have attempted to address this issue by examining the neural overlap between physical pain and social rejection. The consensus that has emerged is that a network of brain regions that support the aversive quality of physical pain (the “affective” component), principally the dorsal anterior cingulate (dACC) and anterior insula (AI), also underlie the feeling of social rejection. In contrast, the brain regions that support the somatic representation of physical pain, and are most closely aligned with the “sensory-discriminative” component—including the operculo-insular region [i.e., secondary somatosensory cortex (S2) and dorsal posterior insula (dpINS)]—are not activated by social rejection and do not factor into current theorizing about the neural overlap between social rejection and physical pain (1, 2).

At first glance, these findings seem intuitive. Both social rejection and physical pain are distressing, and both the dACC and AI respond broadly to stimuli that elicit negative affect (3). However, being rejected, however distressing, seems different from physical pain; it does not result from the presence of a noxious bodily stimulus. Thus, failure to observe activations in

brain regions that support the somatic representation of physical pain in response to rejection is not surprising.

As plausible as this rationale is, here we suggest an alternative: that the neural overlap between social rejection and physical pain is more extensive than current findings suggest. Specifically, we propose that experiences of social rejection, when elicited powerfully enough, recruit brain regions involved in both the affective and sensory components of physical pain.

This prediction is motivated by research indicating that the brain regions that support the sensory components of physical pain are more likely to become active in response to intensely painful stimuli (4–6, cf 7). This finding is noteworthy because extant fMRI research has induced feelings of rejection that may not be particularly intense. (One exception is ref. 8, which we mention in the *Discussion*.) For example, such studies have excluded participants from a computerized ball-tossing game called “Cyberball” (e.g., refs. 9–11), exposed them to rejection-themed paintings (12), or provided them with anonymous feedback that a stranger does not like them (13). Although these manipulations elicit distress, few would attribute to them the same level of intensity as the pain surrounding an unwanted romantic relationship breakup (14–16). Thus, it is possible that social rejection activates brain regions specific for somatic processes, but only when the stimulus is sufficiently intense (i.e., a rejection stimulus rated as intense as a physically painful stimulus on a comparable scale).

We tested this hypothesis by recruiting 40 individuals who felt intensely rejected as a result of recently experiencing an unwanted romantic relationship break-up (see *Methods*). Participants performed two counterbalanced tasks during functional MRI (fMRI) scanning: a Social Rejection task and a Physical Pain task (for design, see Fig. 1). Briefly, the Social Rejection task compared Ex-partner trials, in which participants viewed a headshot of their former partner and thought about their specific rejection experience, and Friend trials, in which participants viewed a headshot of a friend who was the same sex as their ex-partner and thought about a recent positive experience they shared with that person. The Physical Pain task also consisted of two types of trials: Hot trials, in which participants experienced noxious thermal stimulation on their left forearm, and Warm trials, in which participants experienced non-noxious thermal stimulation in the same area. Participants rated how they felt after each task trial using a five-point scale, with lower numbers reflecting more distress.

Author contributions: E.K., W.M., E.E.S., and T.D.W. designed research; E.K. performed research; E.K., M.G.B., and T.D.W. analyzed data; and E.K., M.G.B., W.M., E.E.S., and T.D.W. wrote the paper.

The authors declare no conflict of interest.

Freely available online through the PNAS open access option.

<sup>1</sup>To whom correspondence may be addressed. E-mail: eesmith@psych.columbia.edu or ekross@umich.edu.

This article contains supporting information online at [www.pnas.org/lookup/suppl/doi:10.1073/pnas.1102693108/-DCSupplemental](http://www.pnas.org/lookup/suppl/doi:10.1073/pnas.1102693108/-DCSupplemental).



the operculo-insular region, thalamus, dACC, and AI. Fig. 2B shows the conjunction of areas activated in the independent localizer and the physical pain and social rejection contrasts. The results again show that each of the pain intensity-encoding regions was activated in response to social rejection ( $P < 0.05$  FWER-corrected) (Table 2).

Prior research has identified two regions in the operculo-insular region that are specifically involved in pain-related somatosensory processing: OP1, the most caudal area of the parietal operculum, and dpINS (19–23). To identify whether social rejection and physical pain coactivated these areas, we performed a priori ROI analyses on these regions (see *Methods* for details regarding ROI definition). As Fig. 3 illustrates, the overlap between social rejection and physical pain fell within both of these regions bilaterally ( $P < 0.05$  FWER-corrected for each ROI) (see Fig. 3A and B for statistics).

To rule out the possibility that the activations observed in these sensory pain ROIs were a result of testing participants on both the Physical Pain and Social Rejection tasks in a within-subjects design, we reran these ROI analyses on the subset of participants who engaged in the Social Rejection task before the Physical Pain task ( $n = 19$ ). Consistent with our covariate analyses, which indicated that controlling for task order did not

**Table 1. Activations associated with whole-brain conjunction analysis examining the overlap between social rejection (Ex-partner > Friend) and physical pain (Hot > Warm) at  $P < 0.05$ , FWER-corrected**

Region of activation	Brodmann's area	t	Tal coordinates			Voxels
			x	y	z	
Cluster 1		6.00	12	14	3	319
Anterior cingulate	32	4.37	9	26	24	33
Caudate		6.00	12	14	3	82
Caudate		4.86	-15	3	23	35
Caudate		4.05	12	-3	18	18
Caudate		3.91	15	20	14	10
Putamen		4.83	21	9	17	16
Thalamus		5.46	6	-4	7	124
Cluster 2		5.20	-21	-63	-14	170
Cerebellum		5.20	-21	-63	-14	164
Cerebellum		3.87	-9	-62	-6	6
Cluster 3		4.68	-30	11	14	105
Insula/claustrium		4.68	-30	11	14	53
Insula/claustrium		4.28	-30	3	12	11
Insula/inferior frontal gyrus	13	4.60	-36	23	8	32
Putamen		4.18	-18	2	9	9
Cluster 4	40	4.39	62	-28	36	74
Inferior parietal lobule	40	4.39	62	-28	36	64
Inferior parietal lobule	40	4.30	59	-29	24	10
Cluster 5	32	4.32	15	35	16	34
Anterior cingulate	32	4.32	15	35	16	29
Caudate		4.02	18	28	5	5
Cluster 6		3.95	-9	11	3	15
Caudate		3.95	-9	11	3	15
Cluster 7		3.75	9	-1	62	11
Superior frontal gyrus	6	3.75	9	-1	62	11

The coordinates listed next to each "cluster" represent the cluster's peak coordinate and are identical to the coordinates associated with the largest local maxima within each cluster. Local maxima associated with each cluster are indented and ordered alphabetically. The voxel count associated with each "cluster" represents the number of contiguous voxels observed in the entire region of activation; the voxel count associated with each local maxima represents the number of voxels attributed to each peak within the larger activation cluster.

**Table 2. Activations associated with an ROI analysis examining the overlap between social rejection (Ex-partner > Friend) and physical pain (Hot > Warm) in pain-processing network regions defined by an independent localizer for physical pain at  $P < 0.05$ , FWER-corrected**

Region of activation	Brodmann's area	t	Tal coordinates			Voxels
			x	y	z	
Cluster 1		5.46	6	-4	7	124
Caudate		4.05	12	-3	18	13
Thalamus		5.46	6	-4	7	111
Cluster 2		5.20	-21	-63	-14	73
Cerebellum		5.20	-21	-63	-14	73
Cluster 3		4.60	-36	23	8	41
Inferior frontal gyrus	13	4.60	-36	23	8	33
Insula	13	4.53	-33	11	14	8
Cluster 4		4.31	6	26	24	16
Anterior cingulate	24	4.31	6	26	24	16
Cluster 5		4.15	59	-26	24	23
Inferior parietal lobule	40	4.15	59	-26	24	23
Cluster 6		3.72	36	28	5	6
Inferior frontal gyrus	45	3.72	36	28	5	6

The coordinates listed next to each "cluster" represent the cluster's peak coordinate and are identical to the coordinates associated with the largest local maxima within each cluster. Local maxima associated with each cluster are indented and ordered alphabetically. The voxel count associated with each "cluster" represents the number of contiguous voxels observed in the entire region of activation; the voxel count associated with each local maxima represents the number of voxels attributed to each peak within the larger activation cluster.

substantively alter the pattern of whole-brain results, these analyses revealed activity in both sensory pain ROIs (right OP1: 88 voxels; right dpINS: 54 voxels).\*

**Pain-Specificity Analyses.** To further test the specificity of these activations to pain-related somatic processing, we used a meta-analytic database of 524 studies to compare the frequency with which published studies of physical pain (24) led to activations within 10 mm of the peak coordinates in right and left OP1 and dpINS (see Fig. 3C for coordinates), in comparison with published studies on a range of tasks that do not involve physical pain or intense social rejection; the latter included studies of positive and negative emotion (25), cognitive-interference resolution (26), long-term memory encoding and retrieval (27), attention switching (28), and working-memory (29). Consistent with prior research, activations in OP1 [right hemisphere:  $\chi^2(5) = 92.32$ ,  $P < 0.001$ ; left hemisphere:  $\chi^2(5) = 37.21$ ,  $P < 0.005$ ] and dpINS [right hemisphere:  $\chi^2(5) = 91.83$ ,  $P < 0.001$ ; left hemisphere:  $\chi^2(5) = 32.19$ ,  $P < 0.01$ ] were selective for physical pain. As Fig. 3C illustrates, out of the 524 studies we examined, the positive predictive value for physical pain (i.e., the probability that a study involved physical pain given activation) was 0.88 in the right OP1, 0.74 in the left OP1, 0.87 in the right dpINS, and 0.75 in the left dpINS. In short, intense social rejection activated somatosensory regions that are strongly associated with physical pain, which are virtually never associated with emotion as typically studied.

\*Although we did not observe bilateral activation in dpINS and OP1 in this subset of participants, we found no evidence of lateralization when we compared the  $\beta$ -values extracted from right and left OP1, and right and left dpINS (all,  $F_s < 0.318$ , ns). We suspect that failure to observe bilateral activations among this subset of participants in these ROIs may be an issue of power, as we observed bilateral activation in the full sample, which was double the size.



stimulus. Research on empathy for pain indicates, for example, that under some circumstances the S2 becomes activated when individuals observe other people in physical pain (see refs. 40 and 41 for reviews). The current results differ from these findings by demonstrating that the S2 (as well as the dpINS) also respond to distress related to social-rejection when it is elicited intensely. An important question for future research is whether observing someone else experiencing intense social (rather than physical) pain (i.e., a parent witnessing their child's rejection) also recruits sensory-pain processing regions.

Before concluding, it is important to acknowledge that all of the participants in this study were trained on the Social Rejection and Physical Pain task before scanning and knew that they would be engaging in both tasks during the fMRI scan. Thus, it is possible that participants were primed to think about receiving physical pain on Social Rejection trials, which may have in turn played some role in accounting for the social rejection-related somatosensory activations that we observed. Three aspects of our design argue against this interpretation. First, participants were explicitly told that the Social Rejection and Physical Pain tasks would be administered separately, and they were informed during the scan when each task was about to begin and when each task was over. Second, the thermode was not placed on participants' forearms during the Social Rejection task, so they knew it was impossible for them to receive thermal stimulation on Social Rejection trials. Finally, participants were trained to relive their rejection experience on Social Rejection trials to powerfully manipulate social rejection and minimize the influence of task-irrelevant thoughts. Participants' ratings and postscan interviews suggested that they complied with these instructions. These caveats notwithstanding, research is needed to determine whether powerfully manipulating social rejection in the absence of any physical pain manipulations likewise recruits somatosensory activations. As research on this topic continues, it will likewise be important to examine whether having the expectation that one will be rejected in the future is capable of activating sensory pain regions, as physical pain expectancies have been shown to do (e.g., refs. 42 and 43).

## Methods

**Sample.** Forty individuals (21 females) gave informed consent. All participants experienced an unwanted romantic relationship break-up within the past 6 months ( $M = 2.74$  mo;  $SD = 1.70$  mo), and indicated that thinking about their break-up experience led them to feel rejected; all participants scored above the midpoint on a 1 (not at all rejected) to 7 (very rejected) scale that asked them to rate how rejected they felt when they thought about their rejection experience ( $M = 5.60$ ,  $SD = 1.06$ ). Columbia University's Institutional Review Board approved the study.

Participants were recruited via flyers posted around Manhattan and advertisements posted on Facebook and Craig's List. The sample consisted of 60% Caucasian, 20% Asians, 10% African Americans, and 10% other. The mean age was 20.78 ( $SD = 2.59$ ). All participants were right-handed native English language speakers and received \$175 for their participation. Participants were screened to ensure that they did not suffer from any neurological or psychiatric illness, experience chronic pain, take psychoactive medications, antihistamine or steroids, have metal in their bodies, or have a history of substance use or abuse.

**Design.** See Fig. 1 for the design of the study.<sup>†</sup>

<sup>†</sup>Following this study, half the participants ( $n = 20$ ) received a placebo manipulation and the other half did not ( $n = 20$ ). All participants then engaged in the social rejection and physical pain tasks again. The results of this placebo manipulation on subsequent social rejection and physical pain-related neural activity are the focus of a subsequent article, and thus are not reported here. The between-subjects placebo vs. control manipulation was independent of all of the within-subjects effects that are the focus of the present article, and controlling for placebo vs. control manipulation at the group level did not qualitatively alter any of the results.

**Social Pain Task Stimuli.** The Social Rejection task was modeled after (i) fMRI research that used photographs provided by participants to elicit powerful emotions, including maternal love, romantic love, and rejection (8, 44–46), and (ii) behavioral research indicating that cueing people to recall autobiographical rejection experiences is an effective way of reactivating social rejection-related distress (e.g., refs. 36, 47, and 48). The stimuli for this task consisted of: (i) a headshot photograph of each participant's ex-partner and a same-gendered friend with whom they shared a positive experience around the time of their break-up ( $M = 2.46$  mo;  $SD = 1.70$  mo), and (ii) cue phrases appearing beneath each photograph that directed participants to focus on a specific experience they shared with each person. For additional details, see *SI Methods*.

**Physical Pain Task Stimuli.** The stimuli for the Physical Pain task consisted of thermal stimulations delivered to participants left volar forearm that participants judged to be nonpainful (level 2 on a 10-point scale) vs. near the limit of pain tolerance (level 8 on a 10-point scale). Following prior research (49–51), we used calibrated painful and nonpainful temperatures on a participant-by-participant basis to ensure that the subjective intensity of the stimuli was constant across participants. The temperature of these painful (i.e., Hot) and nonpainful (i.e., Warm) stimulations was determined via a pain-calibration task that took place before the experiment on the day of scanning. For details on physical pain calibration, see *SI Methods*.

**Task Training.** Before scanning, the experimenter walked participants through each step of the Social Rejection task (referred to as the "photograph" task to participants) and the Physical Pain task (referred to as the "heat" task to participants). They were told that that during the "photograph" task they would see the photographs of their ex-partner and friend. The experimenter explained that beneath each photograph, the cue-phrases they generated earlier would appear. When they saw each photograph they were asked to look directly at it and think about how they felt during the specific experience associated with the cue-phrase. Thus, when participants viewed the photograph of their ex-partner they were directed to think about how they felt during their break-up experience with that person; when they viewed the photograph of their friend they were directed to think about how they felt during their positive experience with that person. During the Physical Pain task, participants were instructed to focus on the fixation cross that appeared on the screen during the trials and think about the sensations they experienced as the thermode on their arm heated up. They were then instructed how to rate their affect after each type of trial and how to perform the visuospatial control task (see Fig. 1 for a description of these tasks and events).

**Functional MRI Acquisition and Analysis.** Whole-brain functional data were acquired on a GE 1.5 T scanner in 24 axial slices ( $3.5 \times 3.5 \times 4.5$  mm voxels) parallel to the anterior commissure-posterior commissure (AC-PC) line with a T2\*-weighted spiral in-out sequence developed by Dr. Gary Glover [repetition time (TR) = 2,000 ms, echo time (TE) = 40 ms, flip angle = 84, field of view (FOV) = 22 cm]. Structural data were acquired with a T1-weighted spoiled gradient-recalled sequence ( $1 \times 1 \times 1$  mm; TR = 19 ms, TE = 5 ms, flip angle = 20).

Functional scans were preprocessed with SPM5, using slice-time correction, motion correction, spatial normalization to the MNI space, and spatial smoothing using a 6-mm full-width at half-maximum Gaussian kernel. Spatial normalization was performed by first coregistering the T1 spoiled gradient recalled (SPGR) to the mean functional image, normalizing the T1 to the SPM template using the "unified segmentation" algorithm applying the normalization parameters to the functional images, and sampling the resulting images at  $3 \times 3 \times 3$ -mm resolution.

Statistical analyses were conducted using the general linear model framework implemented in Brain Voyager. Boxcar regressors, convolved with the canonical hemodynamic response function, modeled periods for the 15-s photo/heat period, 5-s affect rating, and 18-s visuospatial control task. The fixation-cross epoch was used as an implicit baseline. Voxelwise statistical parametric maps summarizing differences between trial types were calculated for each participant and then entered into random-effects group analyses, with statistical maps thresholded at  $P < 0.05$  FWER-corrected for multiple comparisons across gray and white matter. This correction entailed a primary threshold of  $P < 0.001$ , with an extent threshold of 11 voxels, which was determined using a Monte Carlo simulation method, which was calculated using NeuroElf's (<http://neuroelf.net/>) instantiation of AlphaSim (52). This technique controls for the FWER by simulating null datasets with the same spatial autocorrelation found in the residual images and creates a frequency distribution of different cluster sizes. Clusters larger than the minimum size corresponding to the a priori chosen FWER are then retained for additional analysis. This cluster-based method of thresholding is often

more sensitive to activation when one can reasonably expect multiple contiguous activated voxels (52, 53), and is widely used in fMRI research.

**Physical pain-processing localizer analysis.** We localized pain-processing regions in a separate group of individual ( $n = 75$ ) drawn from three separate thermal pain studies that contrasted high (level 8) vs. low (level 2) stimulation (Fig. S1). For additional details, see *SI Methods*.

**Operculo-insular ROIs.** We used the SPM Anatomy Toolbox (V1.6) to create ROIs bilaterally around the OP1 based on cytoarchitectonic mapping of the lateral operculum (54). We performed an ROI analysis on the dpINS bilaterally by building a 10-mm sphere around: (i) the peak dpINS coordinate (34, -14, 19) that evoked painful stimulation restricted to the upper limb in a direct electrical stimulation study of the insula (19); and (ii) the mirror site on the left hemisphere (-34, -14, 19). Monte Carlo simulations, calculated by using

NeuroElf's instantiation of AlphaSim, indicated that a  $P < 0.05$ , 15-voxel minimum cluster size preserved an FWER  $\alpha = 0.05$  threshold for both the OP1 and dpINS ROIs. One-tailed tests were used for these analyses because we had a priori hypotheses about activity increases with physical pain and social rejection.

**ACKNOWLEDGMENTS.** We thank P. Clasen, D. Abraham, and P. Enock for their assistance, and O. Ybarra, O. Ayduk, and J. Jonides for critical discussion and reading of the manuscript. This research was supported by National Institutes of Health National Institute of Mental Health Grant R01MH076136, National Institute on Drug Abuse Grant RC1DA028608 (to T.D.W.), and National Institutes of Health Grant P41 RR009784 (to Gary Glover), which supported the development of the spiral sequence used in this study.

- Macdonald G, Leary MR (2005) Why does social exclusion hurt? The relationship between social and physical pain. *Psychol Bull* 131:202–223.
- Eisenberger N (2008) Understanding the moderators of physical and emotional pain: A neural systems-based approach. *Psychol Inq* 19(3–4):189–195.
- Wager TD, et al. (2008) *The Neuroimaging of Emotion* (Oxford University Press, New York), 3rd Ed.
- Coghill RC, Sang CN, Maisog JM, Iadarola MJ (1999) Pain intensity processing within the human brain: A bilateral, distributed mechanism. *J Neurophysiol* 82:1934–1943.
- Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis. *Clin Neurophysiol* 30:263–288.
- Price DD (2000) Psychological and neural mechanisms of the affective dimension of pain. *Science* 288:1769–1772.
- Apkarian AV, Bushnell MC, Treede RD, Zubieta JK (2005) Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 9:463–484.
- Fisher HE, Brown LL, Aron A, Strong G, Mashek D (2010) Reward, addiction, and emotion regulation systems associated with rejection in love. *J Neurophysiol* 104(1): 51–60.
- Eisenberger NI, Lieberman MD, Williams KD (2003) Does rejection hurt? An fMRI study of social exclusion. *Science* 302:290–292.
- Eisenberger NI, Way BM, Taylor SE, Welch WT, Lieberman MD (2007) Understanding genetic risk for aggression: Clues from the brain's response to social exclusion. *Biol Psychiatry* 61:1100–1108.
- Krill A, Platek SM (2009) In-group and out-group membership mediates anterior cingulate activation to social exclusion. *Front Evol Neurosci* 1(1):1–7.
- Kross E, Egner T, Ochsner K, Hirsch J, Downey G (2007) Neural dynamics of rejection sensitivity. *J Cogn Neurosci* 19:945–956.
- Somerville LH, Heatherton TF, Kelley WM (2006) Anterior cingulate cortex responds differentially to expectancy violation and social rejection. *Nat Neurosci* 9:1007–1008.
- Davis D, Shaver PR, Vernon ML (2003) Physical, emotional, and behavioral reactions to breaking up: The roles of gender, age, emotional involvement, and attachment style. *Pers Soc Psychol Bull* 29:871–884.
- Cacioppo JT, Patrick W (2009) *Loneliness: Human Nature and the Need for Social Connection* (W. W. Norton, New York, London), pp xiv, 317 pp.
- Panksepp J (2003) Neuroscience. Feeling the pain of social loss. *Science* 302:237–239.
- Downey G, Feldman SI (1996) Implications of rejection sensitivity for intimate relationships. *J Pers Soc Psychol* 70:1327–1343.
- Rosenberg M (1965) *Society and the Adolescent Self Image*. (Princeton University Press, New Jersey).
- Brooks JC, Zambreanu L, Godinez A, Craig AD, Tracey I (2005) Somatotopic organization of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage* 27:201–209.
- Mazzola L, Isnard J, Peyron R, Guénot M, Mauguère F (2009) Somatotopic organization of pain responses to direct electrical stimulation of the human insular cortex. *Pain* 146(1–2):99–104.
- Eickhoff SB, Amunts K, Mohlberg H, Zilles K (2006) The human parietal operculum. II. Stereotaxic maps and correlation with functional imaging results. *Cereb Cortex* 16: 268–279.
- Baumgärtner U, Tiede W, Treede RD, Craig AD (2006) Laser-evoked potentials are graded and somatotopically organized anteroposteriorly in the operculoinsular cortex of anesthetized monkeys. *J Neurophysiol* 96:2802–2808.
- Baumgärtner U, et al. (2010) Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: A high-resolution fMRI study. *J Neurophysiol* 104:2863–2872.
- Wager TD, Barret LF (2004) From affect to control: Functional specialization of the insula in motivation and regulation. Available at <http://wagerlab.colorado.edu/papers/>. Accessed May 1, 2010.
- Kober H, et al. (2008) Functional grouping and cortical-subcortical interactions in emotion: A meta-analysis of neuroimaging studies. *Neuroimage* 42:998–1031.
- Nee DE, Wager TD, Jonides J (2007) Interference resolution: Insights from a meta-analysis of neuroimaging tasks. *Cogn Affect Behav Neurosci* 7(1):1–17.
- Van Snellenberg JX, Wager TD (2009) Cognitive and motivational functions of the human prefrontal cortex. *Luria's Legacy in the 21st Century*, eds Christensen A-L, Bougakov D, Goldberg E (Oxford University Press, New York).
- Wager TD, Jonides J, Reading S (2004) Neuroimaging studies of shifting attention: A meta-analysis. *Neuroimage* 22:1679–1693.
- Wager TD, Smith EE (2003) Neuroimaging studies of working memory: A meta-analysis. *Cogn Affect Behav Neurosci* 3:255–274.
- Barsalou LW (2008) Grounded cognition. *Annu Rev Psychol* 59:617–645.
- Niedenthal PM (2007) Embodying emotion. *Science* 316:1002–1005.
- Damasio AR, et al. (2000) Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat Neurosci* 3:1049–1056.
- Eisenberger NI, Inagaki TK, Rameson LT, Mashal NM, Irwin MR (2009) An fMRI study of cytokine-induced depressed mood and social pain: The role of sex differences. *Neuroimage* 47:881–890.
- Way BM, Taylor SE, Eisenberger NI (2009) Variation in the mu-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. *Proc Natl Acad Sci USA* 106:15079–15084.
- Leary M, Springer C (2001) Hurt feelings: The neglected emotion. *Behaving Badly: Aversive Behaviors in Interpersonal Relationships*, ed Kowalski RM (American Psychological Association, Washington, D.C.), pp 151–175.
- Leary M, Springer C, Negel L, Ansell E, Evans K (1998) The causes, phenomenology, and consequences of hurt feelings. *J Pers Soc Psychol* 74:1225–1237.
- Macdonald G (2007) Social pain and hurt feelings. *Cambridge Handbook of Personality Psychology*, eds Corr PJ, Matthews G (Cambridge University Press, New York), Vol 541–555.
- Phan KL, et al. (2004) Neural correlates of individual ratings of emotional salience: A trial-related fMRI study. *Neuroimage* 21:768–780.
- Waugh CE, Hamilton JP, Gotlib IH (2010) The neural temporal dynamics of the intensity of emotional experience. *Neuroimage* 49:1699–1707.
- Keysers C, Kaas JH, Gazzola V (2010) Somatosensation in social perception. *Nat Rev Neurosci* 11:417–428.
- Hein G, Singer T (2008) I feel how you feel but not always: The empathic brain and its modulation. *Curr Opin Neurobiol* 18(2):153–158.
- Ploughhaus A, et al. (1999) Dissociating pain from its anticipation in the human brain. *Science* 284:1979–1981.
- Porro CA, et al. (2002) Does anticipation of pain affect cortical nociceptive systems? *J Neurosci* 22:3206–3214.
- Aron A, et al. (2005) Reward, motivation, and emotion systems associated with early-stage intense romantic love. *J Neurophysiol* 94:327–337.
- Bartels A, Zeki S (2000) The neural basis of romantic love. *Neuroreport* 11:3829–3834.
- Bartels A, Zeki S (2004) The neural correlates of maternal and romantic love. *Neuroimage* 21:1155–1166.
- Ayduk O, Mischel W, Downey G (2002) Attentional mechanisms linking rejection to hostile reactivity: The role of “hot” versus “cool” focus. *Psychol Sci* 13:443–448.
- Pickett CL, Gardner WL, Knowles M (2004) Getting a cue: The need to belong and enhanced sensitivity to social cues. *Pers Soc Psychol Bull* 30:1095–1107.
- Buhle J, Wager TD (2010) Performance-dependent inhibition of pain by an executive working memory task. *Pain* 149(1):19–26.
- Wager TD, et al. (2004) Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 303:1162–1167.
- Wager TD, Scott DJ, Zubieta JK (2007) Placebo effects on human mu-opioid activity during pain. *Proc Natl Acad Sci USA* 104:11056–11061.
- Forman SD, et al. (1995) Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magn Reson Med* 33:636–647.
- Petersson KM, Nichols TE, Poline JB, Holmes AP (1999) Statistical limitations in functional neuroimaging. II. Signal detection and statistical inference. *Philos Trans R Soc Lond B Biol Sci* 354:1261–1281.
- Eickhoff SB, Schleicher A, Zilles K, Amunts K (2006) The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. *Cereb Cortex* 16:254–267.