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Topical review

A re-examination of pain–cognition interactions: Implications for neuroimaging

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1. Introduction

The interaction between pain and cognition has become a hot area of research; basic scientists are studying its underlying mechanisms, and clinicians are interested in applications for treating pain. The analgesic effects of distraction may result from a form of divided attention, whereby competition for attentional and emotional resources in the brain affects the pain experience. Indeed, several studies (see below) have shown that pain can be modulated when simultaneously performing a cognitive task and suggest that as cognitive load increases, so will its distracting effect on pain. Yet, while several studies have shown that cognitive engagement can reduce pain-related brain activity, especially in primary and secondary somatosensory, insula, and cingulate cortices (Bushnell et al., 1999; Peyron et al., 1999; Frankenstein et al., 2001; Bantick et al., 2002; Tracey et al., 2002; Petrovic et al., 2004; Seminowicz et al., 2004; Valet et al., 2004; Wiech et al., 2005), the relationship between pain and attention appears to be complex (see Seminowicz and Davis, 2006). Furthermore, there is evidence that pain can affect large cortical networks involved in allocating attentional resources (Seminowicz and Davis, 2007). Several factors that can influence the two-way pain–cognition interactions (i.e., the effect of pain on cognition and the effect of cognitive load on pain) must be considered when designing neuroimaging experiments.

2. Pain and divided attention: concepts and definitions

Divided attention pertains to the ability to attend to multiple stimuli at once. Conversely, focused attention allows for background information to be ignored. Therefore, when we focus attention on something in particular, we suppress attention to and sometimes awareness of other information. During focused attention, stimulus-evoked activity in some neurons is enhanced (Bushnell et al., 1985; Hsiao et al., 1993) and the background activity in other, non-specific neurons is reduced (Chelazzi et al., 1993). The term “selective attention” implies that the focus of attention is chosen. The degree to which one can selectively attend to something is partly dependent on the salience or biological importance of the stimulus (Crick and Koch, 2006).

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For example, pain is highly salient and draws attention for extended periods (Downar et al., 2003).

Selective attention is rarely so restrictive as to completely exclude all else from entering our consciousness. Rather, attention is usually divided to a certain degree. Therefore, pain distraction studies more closely reflect "divided attention" because pain demands attention and is probably never completely unattended (c.f. Loose et al., 2003).

We consider divided attention within the context of the hypothesis of limited cognitive resources, in which attention to pain and a cognitive task competes for a finite amount of brain resources (Norman and Bobrow, 1975; Friedman and Polson, 1981; Cioffi, 1991; Eccleston and Crombez, 1999). The model of limited capacity predicts poorer performance when attention is divided between two tasks. When one task "out competes" the other, the other task suffers and these effects may be reflected by behavioural measures such as reaction times (Norman and Bobrow, 1975).

3. Effects of pain on cognitive performance

There is substantial evidence that chronic pain can impair cognitive abilities (Kewman et al., 1991; Eccleston, 1995a; Eccleston et al., 1997; Grossi et al., 2001; Park et al., 2001; Dick et al., 2002; Harman and Ruyak, 2005). One possible mechanism for this effect is based on cortical plasticity and involves impairment of brain function. Another possible mechanism, not exclusive of the first, is based on the concept of limited processing capacity, whereby ongoing pain demands attention and limits the amount of resources available for task performance. Several studies have reported an association between chronic pain and hypervigilance (McDermid et al., 1996; Asmundson et al., 1997; Roelofs et al., 2002; Roelofs et al., 2003; Asmundson et al., 2005). Constant attention focused on threats to the state of the body would limit the amount of resources available to perform other cognitive functions.

Some studies have attempted to delineate the effects of acute pain on cognitive performance in healthy subjects. We and others have found that pain minimally affects cognitive ability in experimental settings in healthy individuals (Fig. 1) (Petrovic et al., 2000; Babiloni et al., 2004; Seminowicz et al., 2004; Buffington et al., 2005; Pud and Sapir, 2006; Seminowicz and Davis, 2006; Veldhuijzen et al., 2006). These negative findings could be related to the intensity or duration of the experimental pain stimulus. It is impossible to ascertain the proportions of attention directed to the task and to the pain. These tasks allow short breaks between responses, during which time subjects could switch attention between the task and pain, which might explain the minimal amount of interference of pain on task performance. Several studies have indicated that in order for pain to affect cognitive performance or cognitive-related brain activity, the task must be sufficiently difficult (Eccleston, 1995a; Dick et al., 2003; Legrain et al., 2003). Previous studies suggest that there is competition for attentional resources, reflected in attenuated task performance when a task is very demanding and pain is high (Eccleston, 1995a). However, this effect may be specific to patients with chronic pain or may depend on the degree to which the pain is threatening.

Pain catastrophizing and fear of pain are two additional factors that can influence how pain affects cognitive performance (Eccleston et al., 1997; Crombez et al., 1998; Crombez et al., 1999; Vancleef and Peters, 2006). Both variables are associated with heightened vigilance/awareness of the pain, and thus make it more attention-demanding. A full discussion of this topic is beyond the scope of this review.

4. Effects of cognitive engagement on pain ratings

The assumption that distraction disrupts pain is a contentious issue. Some studies found support for the concept that distraction attenuates pain in humans (McCaul and Haugtvedt, 1982; Bushnell et al., 1985; Miron et al., 1989; Lautenbacher et al., 1998; Petrovic et al., 2000; de Wied and Verbaten, 2001; Dowman, 2004; Terkelsen et al., 2004; Veldhuijzen et al., 2006). Electrophysiological and behavioural studies in animals have also shown that attentional state can modulate nociception (Dubner et al., 1981; Casey and Morrow, 1983; Bushnell et al., 1984). These studies also suggest that the pain modulatory effect is enhanced with increasing levels of distraction. In contrast, other studies reported that increasing cognitive demand did not affect pain ratings, tolerance, physiological, or behavioural responses to pain (Hodes et al., 1990; McCaul et al., 1992), and in one study, the effects of distraction disappeared when the pain became too strong to ignore (McCaul and Haugtvedt, 1982).

More recent studies have questioned the capacity of cognitive engagement to significantly affect both acute and chronic pain. For example, some studies reported that pain ratings are not affected when subjects are distracted from pain compared to focusing on the pain stimulus (Duker et al., 1999; Huber et al., 2006). Other studies reported a significant distraction effect on acute pain only in males (Keogh et al., 2000) or only in patients with chronic pain (Nouwen et al., 2006).

It is nearly impossible to quantify the unique effect of cognitive distraction on pain because of a paradox inherent in studies of divided attention: one cannot simultaneously attend to pain in order to give a rating while being distracted (see Roelofs et al., 2003). Any effect of distraction is lost the moment the subject is

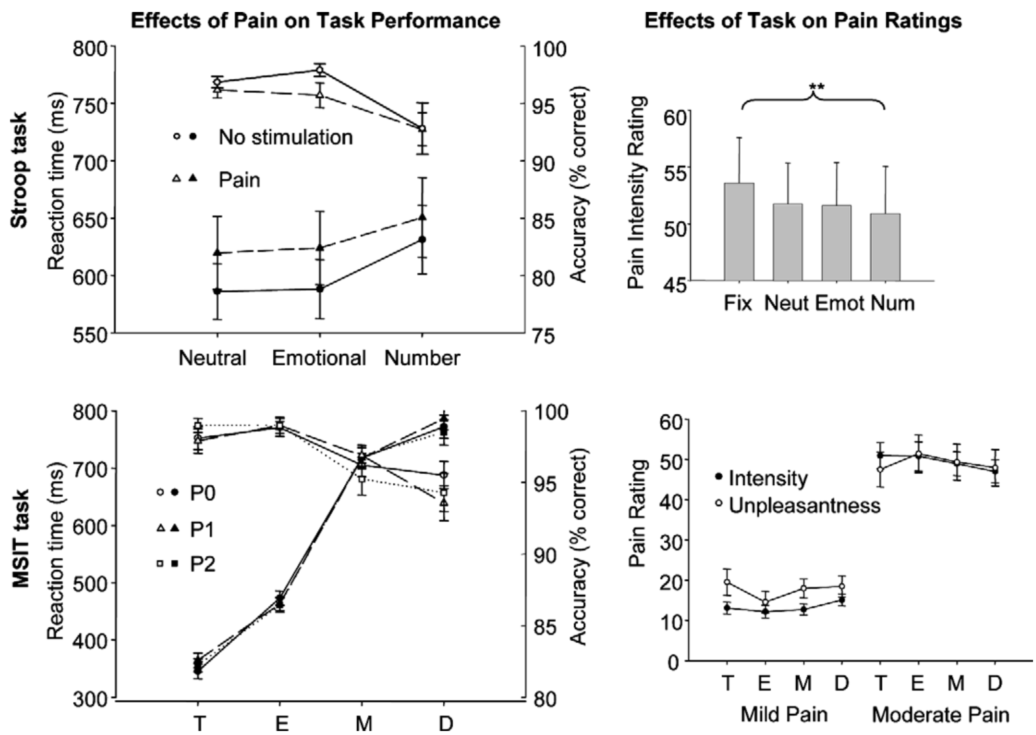

Fig. 1. Do pain and cognitive task performance interact in a meaningful way? Data from our experiments indicate that when subjects are asked to rate the pain immediately after a short block of pain with various cognitive task demands, pain ratings are only minimally affected. In only one case was there a significant reduction of pain by cognitive task, and this average drop of 3/100 is unlikely to be clinically meaningful. Furthermore, the presence of pain while performing a cognitive task did not significantly affect performance measures accuracy or reaction time. The Stroop experiment (top row) involved performing a Stroop task or fixation task while receiving no stimulation or moderate pain. The multi-source interference task (MSIT) experiment (bottom row) involved performing a task that has four distinct difficulty levels, while receiving no stimulation, mild pain, or moderate pain. Therefore, while several previous imaging studies have acquired ratings at the end of the experimental session and shown significant changes, it is uncertain whether pain ratings were actually changed during the experiment, or if any of several other factors mentioned in the text were responsible for these post-session ratings. Pain was evoked with electrical median nerve stimulation. The graphs in the left column show data for the ''no stimulation'' condition (circles) and ''pain'' condition (triangles, squares), with the open symbols representing the accuracy data and the closed symbols representing the reaction time data. $^{**}p < .01$, repeated measures ANOVA with post hoc (Bonferroni) test for Fixation + pain versus Number (high conflict) + pain. Fix, fixation, P0, no stimulation, P1, mild pain, P2, moderate pain, T, tapping (motor-visual control), E, M, D, easy, moderate, difficult tasks, respectively. The bottom, right panel was reproduced from Seminowicz and Davis (2006).

asked to rate the pain. We should therefore distinguish between pain *evaluation* and pain *perception*. Once a subject begins to describe the perception, he/she has begun to evaluate it, which may in turn affect the perception (i.e. the Heisenberg uncertainty principle). This problem complicates the interpretation of neuroimaging studies that reported decreased pain ratings during cognitive task performance (Bantick et al., 2002; Remy et al., 2003; Valet et al., 2004; Wiech et al., 2005). An alternate approach that limits this complication is to assess pain immediately after the cognitive (distraction) task, since such ratings are consistent with those given in real-time (Koyama et al., 2004). We have used this approach in our recent studies of pain–cognition interactions. We instructed subjects to perform cognitive tasks as quickly as possible, without making erroneous responses, during concurrent painful stimuli. We did not assess pain perception during acquisition of imaging data, but did so in an additional (non-imaging) session (Seminowicz et al., 2004; Seminowicz and Davis, 2006). Ratings of pain intensity and unpleasantness were minimally affected by the simultaneous performance of a cognitive task (Fig. 1).

Two additional factors affect the outcome of pain–cognition interaction studies. One is the instruction set given to subjects (Eccleston, 1995b). For example, a subject's beliefs or expectations can be manipulated if the instructions intimate an expected direction of effect (e.g., that the pain will be less during task performance). The second factor is the delay between the effect of interest and the acquisition of pain ratings. A short delay between a pain stimulus and acquisition of a pain rating is likely not problematic (e.g. Koyama et al., 2004), but longer delays can introduce error. For instance, several imaging studies assessed pain at the end of an experiment, long after the stimulus was given (e.g. Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004). Memory for pain may not be accurate (e.g. Beese and Morley, 1993) long after the pain manipulation. Christenfeld (1997), for example, reported that pain ratings were not affected by cognitive task performance when obtained immediately following stimulation, but were significantly lower when subjects were asked to rate ten minutes following removal of the stimulus. Studies in which ratings are given long after removal of the stimulus could be measuring beliefs about pain. For instance, Bantick et al. (2002) instructed subjects to "pay attention to the task throughout but maintain an awareness of the rating they would give to the thermal stimuli" because at the end of the experiment, they would be asked to "compare pain intensity for the interference and neutral conditions" (p. 312). This instruction suggests to the subject that there should be a difference in pain perception in the two tasks, and likely contributed to the reported decrease in pain intensity for the interference condition.

Clearly, the findings on the effects of cognitive engagement on pain ratings are inconsistent and can differ for experimental versus clinical pains. While there is evidence that cognitive engagement can affect pain ratings, the interpretation of such findings should include whether the cognitive engagement is active (e.g. involving manipulation of subjects' beliefs) or passive (e.g. distraction, where subjects have no expectations), as well as the instructions given to subjects and their potential for influencing the type of engagement.

5. Clinically relevant pain attenuation

The experimental findings of cognitive manipulation of pain often do not translate into a clinically relevant effect. For instance, some studies report small but statistically significant reductions in pain intensity of the order of 5%, but the clinical importance of such a change is minimal (e.g. Todd, 1996; Turk, 2000). There is some general agreement that pain must be reduced by at least 30% for it to be meaningful to patients (Goldsmith et al., 1993; Farrar et al., 2000; Farrar et al., 2001; Cepeda et al., 2003; Farrar et al., 2003; Salaffi et al., 2004; Hanley et al., 2006). The absolute amount of pain reduction needed to achieve patient-reported improvement is highly variable, starting at as low as 9 on a 100-point visual analog scale (Kelly, 1998). However, it should be noted that as baseline pain severity increases, so does the minimum reduction of pain ratings to provide satisfactory improvement (Cepeda et al., 2003). Therefore, many studies of cognitive distraction in healthy individuals do not translate to a clinically meaningful decrease in pain.

6. Recommendations for neuroimaging studies

We offer the following specific recommendations for neuroimaging studies investigating pain–cognition interactions:

(1) Carefully consider the baseline condition to which the distraction condition is compared. Unattended pain is a difficult concept to grasp considering that pain inherently grabs attention, so the term "divided attention" is often more appropriate to describe these pain–cognition interactions.
(2) Test whether modulation of brain activity is specific to pain, since attentional manipulations can affect non-nociceptive systems in monkeys (Hsiao et al., 1993; Steinmetz et al., 2000; Meftah et al., 2002) and humans (Johansen-Berg et al., 2000; Hamalainen et al., 2002).
(3) Investigate the two-way interaction between pain and cognition as previously recommended (Eccleston, 1995b). The effects of pain on cognitive-related activity are often overlooked, but can be crucial to understanding the interaction (e.g. Seminowicz and Davis, 2007).
(4) Ensure that the instructions to subjects clearly match the intended type of modulation (passive or active).
(5) Consider whether the cognitive manipulation directly affects pain, and whether this result would be clinically relevant.

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References

Asmundson GJ, Kuperos JL, Norton GR. Do patients with chronic pain selectively attend to pain-related information?: preliminary evidence for the mediating role of fear. Pain 1997;72:27–32.

Asmundson GJ, Wright KD, Hadjistavropoulos HD. Hypervigilance and attentional fixedness in chronic musculoskeletal pain: consistency of findings across modified stroop and dot-probe tasks. J Pain 2005;6:497–506.

Babiloni C, Brancucci A, Arendt-Nielsen L, Babiloni F, Capotosto P, Carducci F, et al. Attentional processes and cognitive performance during expectancy of painful galvanic stimulations: a high-resolution EEG study. Behav Brain Res 2004;152:137–47.

Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain 2002;125:310–9.

Beese A, Morley S. Memory for acute pain experience is specifically inaccurate but generally reliable. Pain 1993;53:183–9.

Buffington AL, Hanlon CA, McKeown MJ. Acute and persistent pain modulation of attention-related anterior cingulate fMRI activations. Pain 2005;113:172–84.

Bushnell MC, Duncan GH, Dubner R, He LF. Activity of trigeminothalamic neurons in medullary dorsal horn of awake monkeys trained in a thermal discrimination task. J Neurophysiol 1984;52:170–87.

Bushnell MC, Duncan GH, Dubner R, Jones RL, Maixner W. Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. J Neurosci 1985;5:1103–10.

Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B. Pain perception: is there a role for primary somatosensory cortex? Proc Natl Acad Sci USA 1999;96:7705–9.

Casey KL, Morrow TJ. Nocifensive responses to cutaneous thermal stimuli in the cat: stimulus–response profiles, latencies, and afferent activity. J Neurophysiol 1983;50:1497–515.

Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? Pain 2003;105:151–7.

Chelazzi L, Miller EK, Duncan J, Desimone R. A neural basis for visual search in inferior temporal cortex. Nature 1993;363:345–7.

Christenfeld N. Memory for pain and the delayed effects of distraction. Health Psychol 1997;16:327–30.

Cioffi D. Beyond attentional strategies: cognitive-perceptual model of somatic interpretation. Psychol Bull 1991;109:25–41.

Crick FC, Koch C. What are the neuronal correlates of consciousness? In: Hemmen JL, Sejnowski TJ, editors. 23 problems in systems neuroscience. Oxford: Oxford University Press; 2006. p. 474–90.

Crombez G, Eccleston C, Baeyens F, Eelen P. When somatic information threatens, catastrophic thinking enhances attentional interference. Pain 1998;75:187–98.

Crombez G, Vlaeyen JWS, Heuts PHTG, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. Pain 1999;80:329–39.

de Wied M, Verbaten MN. Affective pictures processing, attention, and pain tolerance. Pain 2001;90:163–72.

Dick B, Eccleston C, Crombez G. Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients. Arthritis Rheum 2002;47:639–44.

Dick BD, Connolly JF, McGrath PJ, Finley GA, Stroink G, Houlihan ME, et al. The disruptive effect of chronic pain on mismatch negativity. Clin Neurophysiol 2003;114:1497–506.

Dowman R. Distraction produces an increase in pain-evoked anterior cingulate activity. Psychophysiology 2004;41:613–24.

Downar J, Mikulis DJ, Davis KD. Neural correlates of the prolonged salience of painful stimulation. Neuroimage 2003;20:1540–51.

Dubner R, Hoffman DS, Hayes RL. Neuronal activity in medullary dorsal horn of awake monkeys trained in a thermal discrimination task. III. Task-related responses and their functional role. J Neurophysiol 1981;46:444–64.

Duker PC, van den Bercken J, Foekens MA. Focusing versus distraction and the response to clinical electric shocks. J Behav Ther Exp Psychiatry 1999;30:199–204.

Eccleston C. Chronic pain and distraction: an experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain. Behav Res Ther 1995a;33:391–405.

Eccleston C. The attentional control of pain: methodological and theoretical concerns. Pain 1995b;63:3–10.

Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychol Bull 1999;125:356–66.

Eccleston C, Crombez G, Aldrich S, Stannard C. Attention and somatic awareness in chronic pain. Pain 1997;72:209–15.

Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. J Pain Symptom Manage 2003;25:406–11.

Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88:287–94.

Farrar JT, Young Jr JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–58.

Frankenstein UN, Richter W, McIntyre MC, Remy F. Distraction modulates anterior cingulate gyrus activations during the cold pressor test. Neuroimage 2001;14:827–36.

Friedman A, Polson MC. Hemispheres as independent resource systems: limited-capacity processing and cerebral specialization. J Exp Psychol Hum Percept Perform 1981;7:1031–58.

Goldsmith CH, Boers M, Bombardier C, Tugwell P. Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. OMERACT Committee. J Rheumatol 1993;20:561–5.

Grossi ML, Goldberg MB, Locker D, Tenenbaum HC. Reduced neuropsychologic measures as predictors of treatment outcome in patients with temporomandibular disorders. J Orofac Pain 2001;15:329–39.

Hamalainen H, Hiltunen J, Titievskaja I. Activation of somatosensory cortical areas varies with attentional state: an fMRI study. Behav Brain Res 2002;135:159–65.

Hanley MA, Jensen MP, Ehde DM, Robinson LR, Cardenas DD, Turner JA, et al. Clinically significant change in pain intensity ratings in persons with spinal cord injury or amputation. Clin J Pain 2006;22:25–31.

Harman K, Ruyak P. Working through the pain: a controlled study of the impact of persistent pain on performing a computer task. Clin J Pain 2005;21:216–22.

Hodes RL, Howland EW, Lightfoot N, Cleeland CS. The effects of distraction on responses to cold pressor pain. Pain 1990;41:109–14.

Hsiao SS, O'Shaughnessy DM, Johnson KO. Effects of selective attention on spatial form processing in monkey primary and secondary somatosensory cortex. J Neurophysiol 1993;70:444–7.

Huber MT, Bartling J, Pachur D, Woikowsky B, Lautenbacher S. EEG responses to tonic heat pain. Exp Brain Res 2006;V173:14–24.

Johansen-Berg H, Christensen V, Woolrich M, Matthews PM. Attention to touch modulates activity in both primary and secondary somatosensory areas. Neuroreport 2000;11:1237–41.

Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998;5:1086–90.

Keogh E, Hatton K, Ellery D. Avoidance versus focused attention and the perception of pain: differential effects for men and women. Pain 2000;85:225–30.

Kewman DG, Vaishampayan N, Zald D, Han B. Cognitive impairment in musculoskeletal pain patients. Int J Psychiatry Med 1991;21:253–62.

Koyama Y, Koyama T, Kroncke AP, Coghill RC. Effects of stimulus duration on heat induced pain: the relationship between real-time and post-stimulus pain ratings. Pain 2004;107:256–66.

Lautenbacher S, Pauli P, Zaudig M, Birbaumer N. Attentional control of pain perception: the role of hypochondriasis. J Psychosom Res 1998;44:251–9.

Legrain V, Guerit JM, Bruyer R, Plaghki L. Electrophysiological correlates of attentional orientation in humans to strong intensity deviant nociceptive stimuli, inside and outside the focus of spatial attention. Neurosci Lett 2003;339:107–10.

Loose R, Kaufmann C, Auer DP, Lange KW. Human prefrontal and sensory cortical activity during divided attention tasks. Hum Brain Mapp 2003;18:249–59.

McCaul KD, Haugtvedt C. Attention, distraction, and cold-pressor pain. J Pers Soc Psychol 1982;43:154–62.

McCaul KD, Monson N, Maki RH. Does distraction reduce pain-produced distress among college students? Health Psychol 1992;11:210–7.

McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification. Pain 1996;66:133–44.

Meftah E, Shenasa J, Chapman CE. Effects of a cross-modal manipulation of attention on somatosensory cortical neuronal responses to tactile stimuli in the monkey. J Neurophysiol 2002;88:3133–49.

Miron D, Duncan GH, Bushnell MC. Effects of attention on the intensity and unpleasantness of thermal pain. Pain 1989;39:345–52.

Norman DA, Bobrow DG. On data-limited and resource-limited processes. Cogn Psychol 1975;7:44–64.

Nouwen A, Cloutier C, Kappas A, Warbrick T, Sheffield D. Effects of focusing and distraction on cold pressor-induced pain in chronic back pain patients and control subjects. J Pain 2006;7:62–71.

Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. Arthritis Rheum 2001;44:2125–33.

Petrovic P, Petersson KM, Ghatan PH, Stone-Elander S, Ingvar M. Pain-related cerebral activation is altered by a distracting cognitive task. Pain 2000;85:19–30.

Petrovic P, Petersson KM, Hansson P, Ingvar M. Brainstem involvement in the initial response to pain. Neuroimage 2004;22:995–1005.

Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, et al. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 1999;122:1765–80.

Pud D, Sapir S. The effects of noxious heat, auditory stimulation, a cognitive task, and time on task on pain perception and performance accuracy in healthy volunteers: a new experimental model. Pain 2006;120:155–60.

Remy F, Frankenstein UN, Mincic A, Tomanek B, Stroman PW. Pain modulates cerebral activity during cognitive performance. Neuroimage 2003;19:655–64.

Roelofs J, Peters M, Zeegers M, Vlaeyen J. The modified Stroop paradigm as a measure of selective attention towards pain-related stimuli among chronic pain patients: a meta-analysis. Eur J Pain 2002;6:273.

Roelofs J, Peters ML, McCracken L, Vlaeyen JW. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. Pain 2003;101:299–306.

Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain 2004;8:283–91.

Seminowicz DA, Mikulis DJ, Davis KD. Cognitive modulation of pain-related brain responses depends on behavioral strategy. Pain 2004;112:48–58.

Seminowicz DA, Davis KD. Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. J Neurophysiol 2007. [jn.01210.2006].

Seminowicz DA, Davis KD. Interactions of pain intensity and cognitive load: the brain stays on task. Cereb Cortex 2006. [bhl052].

Steinmetz PN, Roy A, Fitzgerald PJ, Hsiao SS, Johnson KO, Niebur E. Attention modulates synchronized neuronal firing in primate somatosensory cortex. Nature 2000;404:187–90.

Terkelsen AJ, Andersen OK, Molgaard H, Hansen J, Jensen TS. Mental stress inhibits pain perception and heart rate variability but not a nociceptive withdrawal reflex. Acta Physiol Scand 2004;180:405–14.

Todd K. Clinical versus statistical significance in the assessment of pain relief. Ann Emerg Med 1996;27:439–41.

Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, et al. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 2002;22:2748–52.

Turk DC. Statistical significance and clinical significance are not synonyms! Clin J Pain 2000;16:185–7.

Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, et al. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain-an fMRI analysis. Pain 2004;109:399–408.

Vancleef LMG, Peters ML. Pain catastrophizing, but not injury/illness sensitivity or anxiety sensitivity, enhances attentional interference by pain. J Pain 2006;7:23–30.

Veldhuijzen DS, Kenemans JL, de Bruin CM, Olivier B, Volkerts ER. Pain and attention: attentional disruption or distraction? J Pain 2006;7:11–20.

Wiech K, Seymour B, Kalisch R, Enno SK, Koltzenburg M, Driver J, et al. Modulation of pain processing in hyperalgesia by cognitive demand. Neuroimage 2005;27:59–69.