mechanistically, then operant techniques are simply a better way to study the same 'wrong' thing.

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Cognitive modulation of pain-related brain responses. Comments on Seminowicz et al. (Pain 2004;112:48–58)

The study presented by Seminowicz et al. (2004) aimed to investigate interactions between nociceptive and cognitive processing in the human brain using functionnal MRI. It is widely accepted that nociceptive processing can be modulated by concomitant processing of non-nociceptive information: directing attention away from nociceptive stimulation decreases reaction and perception of pain (Bushnell et al., 1985; Miron et al., 1989; Spence et al., 2002). On the other hand, it has been proposed that painful stimuli—because of their biological salience—have a higher capacity than non-nociceptive stimuli to involuntarily attract attention (Eccleston and Crombez, 1999), hence the processing of non-nociceptive information should be negatively affected by concomitant pain (Crombez et al., 1996; Van Damme et al., 2004). Seminowicz et al. (2004) attempted to study this bilateral interaction between top-down (or goal-directed) and bottom-up (or stimulus-driven) attentional influences on nociception. In comparison to previous brain-metabolic studies of pain, this objective is original and was tested with an appropriate paradigm that was already used by Bantick et al. (2002). However, in our opinion, the results reported by Seminowicz et al. (2004) are not compelling enough to fully support their interpretation of this double interaction.

(a) '*Bottom-up*' *influence of pain on cognitive processing*. Behavioral studies have shown distracting effects of pain on concomitant tasks (Arntz and Hopmans, 1998; Crombez et al., 1996; Lorenz and Bromm, 1997). Unlike these previous results, Seminowicz et al. (2004) failed to observe decreased performance (longer reaction times) in a very demanding task (counting Stroop) during concomitant distracting painful stimulation. A posteriori, authors identified two subgroups of subjects, one group with faster reaction times during pain (A group) and another group with slower reaction times (P group) (however, reaction times during non-painful tingle stimulation were not taken into account). Authors suggested that the two subgroups differed by the cognitive strategies to cope with interference between nociceptive and non-nociceptive processing. They proposed that subjects of the A group were more able to inhibit interference from painful stimuli in order to preserve behavioral performance in the counting Stroop task (top-down hypothesis), while subjects in the P group were more distracted by pain. In accordance with that, only the A group showed decreased activation in SI, SII and anterior insula in response to painful stimulation during the counting Stroop task. However, the two groups did not differ according to attention-related brain activity (bottom-up hypothesis). First, activation in the mid-part of the anterior cingulate cortex (mid-ACC), supposed to be involved in attentional orienting to pain (García-Larrea et al., 2003; Legrain et al., 2003; Peyron et al., 1999) but also in interference resolution (Bush et al., 2000), was not modulated by the concomitant visual task, neither in the A group nor in the P group. Second, as performance in the Stroop task was signicantly affected by concomitant pain in the P group, it is supposed that activity in Stroop-related attentional brain areas (i.e. prefrontal and parietal areas) would be also modified during painful stimulations. However, no significant modulation was shown in these areas, and more important, there was no difference between the two sub-groups of subjects. Because of this dissociation between behavioral and metabolic results, it may not be concluded that nociceptive processing *does not interfere* with cognitively demanding visual processing. So, it is unwarranted in our view to associate behavioral performances to different attentional strategies and related brain processes, and it is difficult to gain access to some understanding of the attentional mechanisms operating in the two sub-groups of subjects.

(b) '*Top-down*' *influence of cognitive distraction on pain processing*. Seminowicz et al. (2004) showed decreased brain metabolic responses in SI, SII and anterior insula by distraction, but only in some subjects (A group). Like previous neuro-imaging studies (Bushnell et al., 1999; Frankenstein et al., 2001; Peyron et al., 1999; Petrovic et al., 2000), they compared situations devoid of any explicit task with situations that needed sustained cognitive processing to non-nociceptive information. However, the "cognitive load influence" was actually not tested. Cognitive load can be defined as the "amount" of attentional resources that must

be allocated to a cognitive operation in order to be adequately processed (Kahneman, 1973; Shiffrin and Schneider, 1977). In the field of pain research, it is assumed that the more important is the cognitive load of a distractive task, the more it reduces the capacity to process pain (McCaul and Malott, 1984). And this is an important question for the development of effective attention-based coping strategies in order to improve pain control in chronic pain patients (Eccleston, 1995). So, the more difficult is a concomitant task, the more it reduces the attentional resources that can be allocated to nociceptive processing (McCaul and Malott, 1984). To test that hypothesis, authors should have compared conditions with the same kind of stimulations (visual and painful) but differing according to difficulty and attentional resources-demanding aspects of the visual task. In other words, neutral and counting Stroop conditions should have been contrasted during painful stimulation. This contrast was presented in the study of Bantick et al. (2002) that clearly showed decreased activation by cognitive load in mid-ACC and in the anterior insula and also increased activation in orbitofrontal and perigenual cingulate areas (see Valet et al., 2004). Unfortunately, although the paradigm used in both studies is very similar, Seminowicz et al. (2004) did not discuss the data of Bantick et al. (2002). In the same way, authors did not discuss the diverging results of Peyron et al. (1999) who showed attentional modulation in ACC without any modification in SI and opercular areas (SII/posterior insula), while Bushnell et al. (1999) and Petrovic et al. (2000) showed SI and SII modulation respectively without mid-ACC modulation.

In conclusion, although the experimental paradigm was well designed, the only striking result of this study is that subjects who could achieve a very attention-demanding visual task and could avoid interference from concomitant painful stimulation showed decreased pain-related activation in somatosensory and insular areas (top-down effect), as compared to subjects who were more distracted by painful stimulation (as revealed by reaction time data). However, unlike what is suggested by the title of this article, results were not sufficient to conclude, neither that this difference was due to different attentional strategies, nor to relate behavioral performance to specific attention-related brain mechanisms. Different sources of attentional modulation of nociceptive processing have been recently dissociated in electro- and magneto-encephalographic studies (Legrain et al., 2002; Lorenz and García-Larrea, 2003), but none of these complementary studies were discussed.

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Response to Legrain et al.

Legrain et al. suggest that in Seminowicz et al. (2004) we used a paradigm "already tested by Bantick et al (2002)". This statement is not accurate. We intentionally altered the paradigm used in Bantick et al. (2002) in several major ways to address different aspects of pain–attention interactions. First, we used a block design rather than an event-related design. Block designs generally produce more robust responses than event-related designs (Friston et al., 1999). Furthermore, the long blocks of painful stimuli more closely model sustained pain and cognition effects and may better reflect everyday experiences whereby pain and cognitive events develop/appear over longer time frames. This difference in protocol alone distinguishes our study from Bantick et al. (2002). Second, we purposely did not impose any pain assessment by the subjects since we wished to evaluate how one divides attentional resources between experiencing pain and performing a task, without an evaluation (rating) confound. Had we asked subjects to provide ratings during the fMRI session, they would have had to pay attention to their pain, evaluate its intensity and hold that evaluation in memory for later recall. We are quite aware that this precludes us knowing exactly how much pain the subjects are experiencing during fMRI acquisition. However, similar data has been reported by others and we ourselves collected some data to speak to this issue (manuscript in preparation). Third, our approach to the fMRI statistical analysis was quite different from the Bantick study. For example, we examined all areas related to pain for effects of modulation by attention, and all areas related to attention for modulation effects by pain.

Legrain et al. also questioned the lack of modulation in the anterior cingulate cortex (ACC) given its role in attentional orienting to pain and interference resolution. While it is certainly true that the ACC is implicated in these and many other cognition/attention functions (e.g. orienting, awareness, salience, etc.), it is in fact this complexity that must be considered when interpreting ACC activations (or lack thereof) in studies that use both pain and cognitive tasks. For instance, although it has been previously shown (Davis et al., 1997) that pain and attention tasks activate somewhat distinct regions of the ACC in individual subjects, these activations may spatially merge after the data preprocessing (e.g. group averaging and spatial smoothing) commonly used in modern fMRI studies. Also, we now know that pain-responsive neurons and attention-responsive neurons (Davis et al., 2000; Hutchison et al., 1999) coexist in the same region of the caudal ACC. Therefore, it is likely that modulating pain-related neuronal activity with a cognitive task that activates both pain- and attention-responsive neurons may not produce a net gain or loss of detectable fMRI activity in the ACC. These issues have been recently reviewed (Davis, 2003).

Legrain et al. also stated "…it may not be concluded that nociceptive processing does not interfere with cognitively demanding visual processing. So, it is unwarranted in our view to associate behavioral performance to different attentional strategies and related brain processes." Although we certainly agree with the first part of this statement, we do not consider the term 'visual processing' to accurately describe our task. To clarify, we were only stating (on page 53 of our paper) the lack of effect of pain on the cognitively evoked activity in our experimental paradigm and we speculated that such an effect might in fact occur for a more taxing task (see page 55 of our paper). Finally, our reaction time data support our claim concerning the interaction between pain and cognitive performance.

Continuing on this theme, Legrain et al. raise the issue of 'cognitive load' and further experiments that we should have done to test this. In fact, we did present data pertaining to cognitive load in Table 2, showing activity during both counting and neutral Stroop compared to fixation. We agree that the next logical step is to examine the dependence of load on pain–cognition interactions, and have in fact already completed such a study (Seminowicz and Davis, 2005).

The last criticism of Legrain et al. concerns a perceived lack of discussion of certain previous studies. We cited many studies (including Bantick et al., 2002; Petrovic et al., 2000; Peyron et al., 1999) but focused our discussion on issues we felt to be most relevant to the key aspects of our findings.