Article

fMRI Reveals How Pain Modulates Visual Object Processing in the Ventral Visual Stream

Ulrike Bingel,[1,*] Michael Rose,[2] Jan Gläscher,[2] and Christian Büchel[2]
[1] NeuroImage Nord, Department of Neurology
[2] NeuroImage Nord, Department of Systems Neuroscience
University Medical Center Hamburg-Eppendorf, Germany
*Correspondence: bingel@uke.uni-hamburg.de
DOI 10.1016/j.neuron.2007.05.032

SUMMARY

It is well known that pain attracts attention and interferes with cognition. Given that the mechanisms behind this phenomenon are largely unknown, we used functional magnetic resonance imaging and presented visual objects with or without concomitant pain stimuli. To test for the specificity of pain, we compared this modulatory effect with a previously established modulatory effect of working memory on visual object processing. Our data showed a comparable behavioral effect of both types of modulation and identified the lateral occipital complex (LOC) as the site of modulation in the ventral visual stream, for both pain and working memory. However, the sources of these modulatory effects differed for the two processes. Whereas the source of modulation for working memory could be attributed to the parietal cortex, the modulatory effect of pain was observed in the rostral anterior cingulate cortex (rACC), an area ideally suited to link pain perception and attentional control.

INTRODUCTION

The processing of acute pain is essential for the reaction to potentially life-threatening situations. Therefore, painful stimuli must achieve salience in naturally complex sensory environments with several competing stimuli, each demanding attention and consequently interfering with ongoing processes. This phenomenon, referred to as the "interruptive function of pain" (Eccleston and Crombez, 1999), is evident in everyday experience as well as in the clinical setting. It applies to both acute (e.g., headache, experimental pain) and chronic pain states (e.g., chronic lower back pain), as has been shown by using a variety of cognitive tasks such as numerical interference tasks, memory tasks, or simple discrimination tasks (Crombez et al., 1994, 1998; Eccleston, 1994; Kuhajda et al., 2002; Morton, 1969).

In past years, neuroimaging has been used to characterize the neuronal basis of pain processing and percep-

tion and, more recently, to explore the mechanisms of "disengagement" from pain under distinct emotional (Rainville et al., 1997) or attentive states (Bantick et al., 2002; Petrovic et al., 2000). However, the reverse mechanisms (i.e., how pain gains attentional resources by interfering with ongoing cognitive processes) has only been characterised on the behavioral side (Eccleston and Crombez, 1999), and there is hardly any neurobiological data on the central mechanisms that allow pain to capture and maintain the attentional focus over competing perceptual influences.

Thus, the aim of the current study was to investigate whether and how pain modulates the processing of other stimuli in a complex sensory environment. We chose to test for the influence of pain processing on the visual system, where modulations by both bottom-up and top-down cognitive factors (e.g., attention, cognitive or perceptual load) have already been studied in great detail (Buchel and Friston, 1997; Buchel et al., 1998; Kastner and Unger-leider, 2000; Rees et al., 1997; Schwartz et al., 2005).

In a recent study, we were able to show that working memory load attenuated the processing of visual background information in the ventral visual cortex (Rose et al., 2005). In this study, the perceptual content of irrelevant visual background information was varied by presenting images at different visibility levels. The load of the relevant foreground task was modulated by working memory task difficulty.

To investigate how pain interferes with visual processing, we used a similar design but added the factor *Pain*, resulting in a 3 × 2 × 2 factorial design with factors (pain-intensity [*Pain*]: no/low/high; background image visibility [*Visibility*]: high/low; and working memory load [*WM load*]: high/low) (Figure 1). Using this design, we were able to compare the modulatory influence of pain with a previously characterized mechanism—working memory load (Rose et al., 2005)—and also to formulate a priori hypotheses about the site of modulation. Based on the evolutionary importance of pain, which inevitably signals a potential threat to the individual, we hypothesized that nociceptive information would take priority over less relevant information from other modalities and thus impair processing and perception of these stimuli. Given that we specifically probed the processing of visual-object-related information, we expected modulation to take place
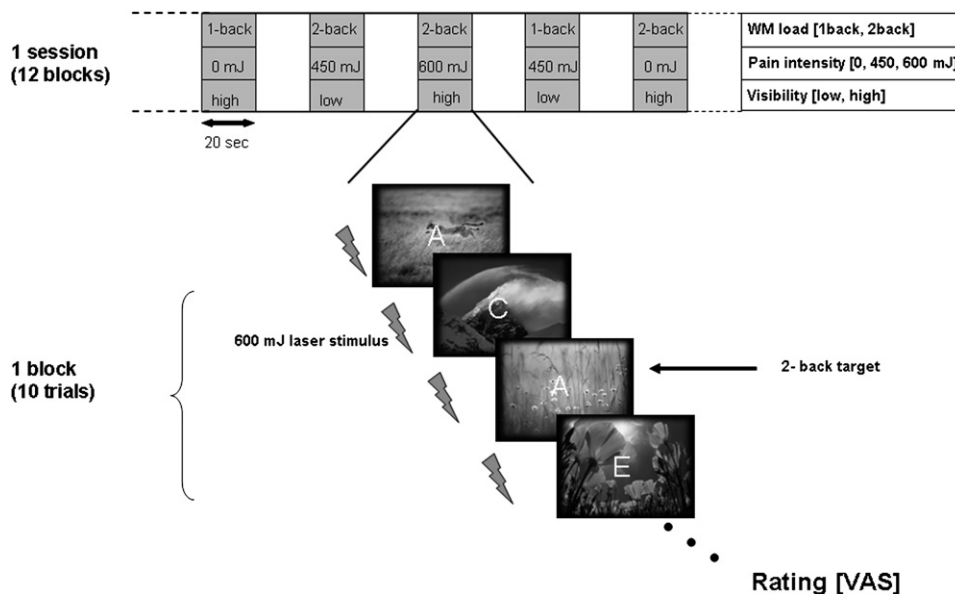
Figure 1. Experimental Design and Task

Each of the ten consecutive trials comprising one block consisted of letters overlaid on the irrelevant background image, which was presented for 1 s, and a concomitant laser stimulus applied to the subjects' dorsum of the left hand. The interstimulus interval (ISI) was 1 s, in which subjects had to maintain fixation on the letters. In parallel, participants performed the n-back working memory task on centrally presented letters overlaid on the task-irrelevant background images. At the end of each block, the average perceived pain intensity over the 20 s block was rated on the VAS. In the subsequent resting period, the cue, indicating the working memory task ("1" or "2," for one- or two-back) for the next block was presented. The pain intensity, visibility, and WM load levels were presented in a 3 × 2 × 2 factorial design (three pain levels × two WM load levels × two visibility levels), resulting in a total of 12 blocks of different conditions presented once per session in randomized order.

in the ventral visual pathway, in particular in the lateral occipital complex (LOC; Grill-Spector et al., 2001; Malach et al., 1995). Given that in our previous study (Rose et al., 2005) activity in LOC increased with object visibility and this increase was attenuated by high working memory load, we hypothesized a comparable modulation of LOC by pain. However, with respect to the source of these modulations, we expected different regions, the parietal or frontal cortex for the mediation of the working-memory-related modulation and the ACC as the source of the pain-related modulation of LOC. To assess the behavioral relevance of the suspected modulation, the degree of processing of the irrelevant background images was tested with a postexperiment surprise recognition task.

RESULTS

Behavioral Results

A three-factor repeated-measures ANOVA with factors *Pain*, *WM load*, and *Visibility* was used to analyze the influence of each experimental condition and their interactions on the following behavioral measures: pain rating, reaction time, and recognition performance.

Pain Rating

The different intensities of nociceptive laser stimulation resulted in significantly different VAS pain ratings—with higher ratings for the higher-intensity stimuli [ANOVA over all three intensities; $F_{(2,30)} = 108.9$, $p < 0.05$; Figure 2A]. Post hoc tests reveal that "low pain" evoked significantly stronger sensation compared to "no pain" and that "high pain" evoked significantly stronger pain than "low pain" (both $p < 0.05$). Interestingly, the no-pain condition was also rated significantly different from zero: [mean ± SEM: 12.9 ± 1.5, $t(15) = 11.8$, $p < 0.05$], which might be explained by the anticipatory state of the subjects (Ploghaus et al., 1999; Porro et al., 2002; Sawamoto et al., 2000), who were not aware of whether or at what intensity pain would be applied in the current block.

Influence of WM Load on Pain Rating. Ratings to the pain stimuli were attenuated with increasing task difficulty in the WM task [$F_{(1,15)} = 9.1$, $p < 0.05$]. The interaction analysis of *WM load* × *Pain* did not reach significance.

Influence of Visibility on Pain Rating. There was no main effect for *Visibility* on pain perception. We noted a positive interaction for the factors *Visibility* and *Pain* with higher pain ratings for the high-pain condition when pictures were presented with high visibility [$F_{(30,2)} = 6.8$, $p < 0.05$].

Reaction Times

The reaction times (RTs) for working memory responses showed an increase for the high WM load conditions [$F_{(1,15)} = 42.1$, $p < 0.05$] as well as for increasing levels of painful stimulation [$F_{(2,30)} = 3.9$, $p < 0.05$] and with increasing visibility of the background images [$F_{(1,15)} = 7.0$, $p < 0.05$]. RTs also showed an interaction effect for the factors *Pain* and *WM load* [$F_{(2,30)} = 8.0$, $p < 0.05$], with the slowest responses occurring when
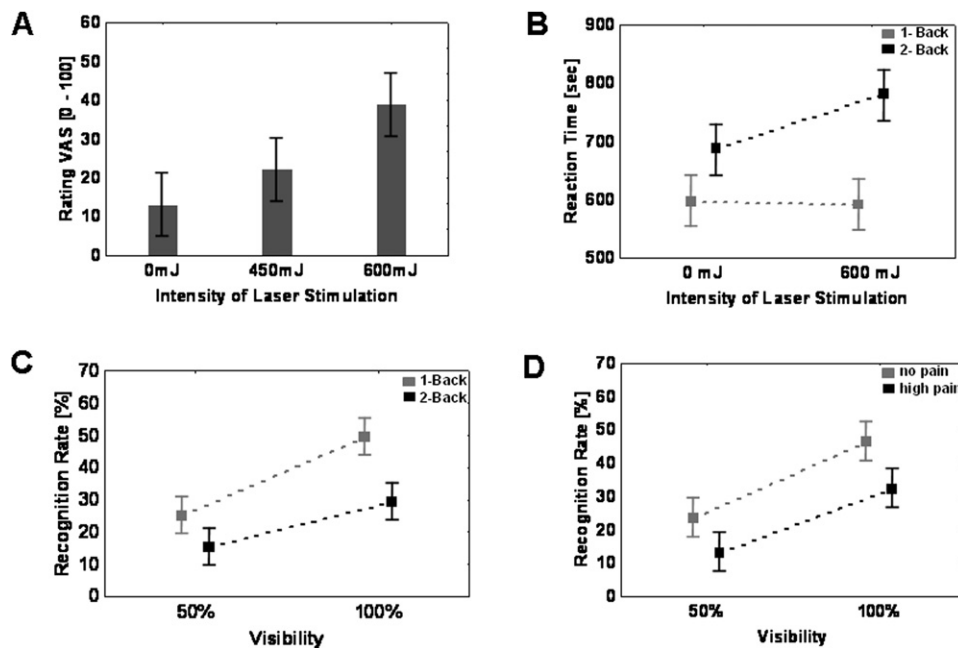
Figure 2. Behavioral Results

(A) Ratings to increasing painful stimulation. Rating of the perceived laser intensities (VAS [0–100]) related to the three different intensities of nociceptive stimulation (no, low, high) resulted in significantly different perceptions of pain.

(B) Reaction times. Reaction times (RTs) in the n-back working memory task increased with increasing workload and with increasing levels of painful stimulation. RTs also displayed an interaction effect for the factors Pain and WM load, with slowest responses when high pain and high WM load occurred together. The positions of values on the x axis are slightly shifted so as to not obliterate the error bars.

(C and D) Recognition performance for the background images. The degree of object encoding of the irrelevant background images was estimated in a surprise recognition task. Increasing visibility resulted in increasing memory of related objects, but later memory was impaired when images were seen under either high WM load (Figure 2C) or increasing degrees of painful stimulation (Figure 2D). The positions of values on the x axis are slightly shifted so as to not obliterate the error bars.

Error bars representing confidence intervals of condition effects in the within-subject design (according to Loftus and Masson, 1994) are shown.

both high pain and high WM load were present (see Figure 2B).

Recognition Task

In the behavioral experiment, we examined the consequences of increasing nociceptive stimulation on the processing of the irrelevant object images using a surprise recognition task after the study phase. We observed a main effect of *Visibility* [$F(1,15) = 138.0$, $p < 0.05$] (i.e., pictures that were presented with 100% visibility were recognized better than those presented with a visibility of 50%). In addition, we observed an effect of *WM load* (one-back or two-back) on memory performance [$F(1,15) = 90.8$, $p < 0.05$; Figure 2C], showing that pictures seen during one-back were better recognized than those seen during two-back. Both factors also showed a multiplicative effect on recognition performance, as indicated by a significant *WM load × Visibility* interaction [$F(1,15) = 9.7$, $p < 0.05$]. Most importantly, recognition accuracy also decreased with increasing intensity of concomitant nociceptive stimulation [$F(2,30) = 12.9$, $p < 0.05$, Figure 2D]. The interaction of *Pain × Visibility* failed to reach significance. Both *Pain* and high *WM load* decreased the recognition rate (pooled over both degrees of visibility) to a compara-

ble degree, from 35% to 23% for *Pain* and from 37% to 22% for *WM load* (data not shown).

Neuroimaging Results
Pain-Related Activity

Painful laser stimulation of the left hand [Pain (pooled over both pain intensities) > No Pain] led to statistically significant activation in contralateral secondary somatosensory cortices, the inferior parietal and the cingulate cortices (including midcingulate regions and the rostral anterior cingulate cortex), the dorsolateral-prefrontal cortex, and the insula. Subcortical responses were seen in the lateral thalamus and the putamen (Table 1A). The higher pain intensity [High Pain > Low Pain] led to stronger activation in the thalamus, anterior and posterior aspects of the insula, and secondary somatosensory cortex (SII).

The lower pain ratings under the WM task were paralleled by decreased pain-related activity under the high WM load condition in classical pain-related areas such as the anterior insula extending into the SII region bilaterally (36, -18, 15, $Z = 3.9$, $p < 0.05$ corrected; -36, -18, 18, $Z = 3.2$, $p < 0.001$), midcingulate area extending into the SMA (0, -18, 51, $Z = 4.2$, $p < 0.05$ corrected), the contralateral

Table 1. Neuroimaging Results (Group Analysis)

Region	Coordinate (X, Y, Z in mm)		Voxel Level (Z)
	R	L	R/L
A) Main Effect of Pain (Pooled over Both Pain Intensities)			
DLPFC	36, 54, 9	−27, 51, 6	5.2*/5.6*
SII	39, −15, 18		5.7*/
Insula	36, 9, 9	−30, 18, 6	6.0*/5.4*
Midcingulate	15, −12, 54		3.2+/
rACC	9, 36, 9	−12, 36, 9	5.3*/4.6*
Thalamus	21, −9, 12		2.7*/
Putamen	27, 12, 6	−27, 15, 6	3.5+/3.3+
(B) Main Effect of Visibility			
Dorsal occipital	42, −87, 6	−48, −84, 0	5.5*/5.3*
LOC	42, −84, 0	−48, −78, −6	6.4*/6.0*
Fusiform gyrus	42, −60, −15	−36, −57, −12	5.0*/5.6*
(C) Interaction Analysis: Working Memory Load × Visibility			
LOC	54, −66, −9	−48, −75, −6	3.3*/3.5*
(D) Interaction Analysis: Pain × Visibility			
LOC	48, −57, −15	−51, −63, −12	3.0+/4.4*
Occipital pole	12, −99, −12	−3, −99, 3	3.3+/3.3+
Fusiform gyrus		−27, −72, −15	/3.3+
Lingual gyrus		−18, −54, −12	/4.2+

*p < 0.05 corrected, + p < 0.001 uncorrected. SII, secondary somatosensory cortex; DLPFC, dorsolateral prefrontal cortex; rACC, rostral anterior cingulate cortex; LOC, lateral occipital complex.

SI/MI region (30, −21, 51, Z = 3.7, p < 0.05 corrected), and the rostral anterior cingulate cortex (rACC) [−6, 39, 0, Z = 3.3, p < 0.001) as well as the ventromedial prefrontal cortex (3, 54, −6, Z = 4.9, p < 0.05 corrected) (see Figure S1 in the Supplemental Data available with this article online).

There was no effect of *Visibility* on pain-related activity in the pain matrix.

Working Memory Load Related Activity

To evaluate the main effect of the working memory manipulation, we identified cortical areas in which the BOLD signal increased with WM load. In several areas, which have previously been associated with working memory performance (Rose et al., 2005), activity was greater during the high-load task (two-back) than during the low-load task (one-back). These areas included predominantly bilateral frontal eye fields (FEF), the inferior parietal cortex reaching into the superior parietal area, and prefrontal cortex. Subcortical responses were observed in the thalamus and cerebellum bilaterally (data not shown). There was no significant effect of pain on working-memory-related activity.

Activity in Visual Areas

Main Effect of Visibility. To identify cortical areas involved in the processing of the background images, we looked for a correlation of the BOLD signal and image visibility. Such an effect of increasing image visibility was observed in dorsal occipital areas, the lateral occipital complex (LOC), and ventral extrastriate visual areas (Table 1B).

Interaction of Working Memory Load and Visibility. The interaction contrast of [*WM load* × *Visibility*] was used to identify areas in which the activation due to the processing of background images was modulated by working memory load. Such WM load-dependent attenuation of the BOLD signal with increasing image visibility was observed in LOC bilaterally (Figure 3A and Table 1C).

Interaction of Pain and Visibility. In a similar manner, the interaction of [*Pain* × *Visibility*] was investigated. This contrast revealed areas in which the BOLD increase as a function of object visibility was attenuated by painful stimulation. In analogy to the effect of WM load, a negative modulation by pain was observed in LOC (Figure 3B), the occipital poles, the left lingual gyrus, and the fusiform gyrus (Table 1D).

Restricting the Analysis to a Functionally Defined ROI. In a second step, each analysis (*WM load* × *Visibility* and *Pain* × *Visibility*) was restricted to the main effect of object visibility (testing for stronger BOLD responses with increasing image visibility, thresholded at p < 0.001). This approach allows us to state that that modulation takes place in areas involved in object processing. Applying this ROI, we observed the same peak coordinates for
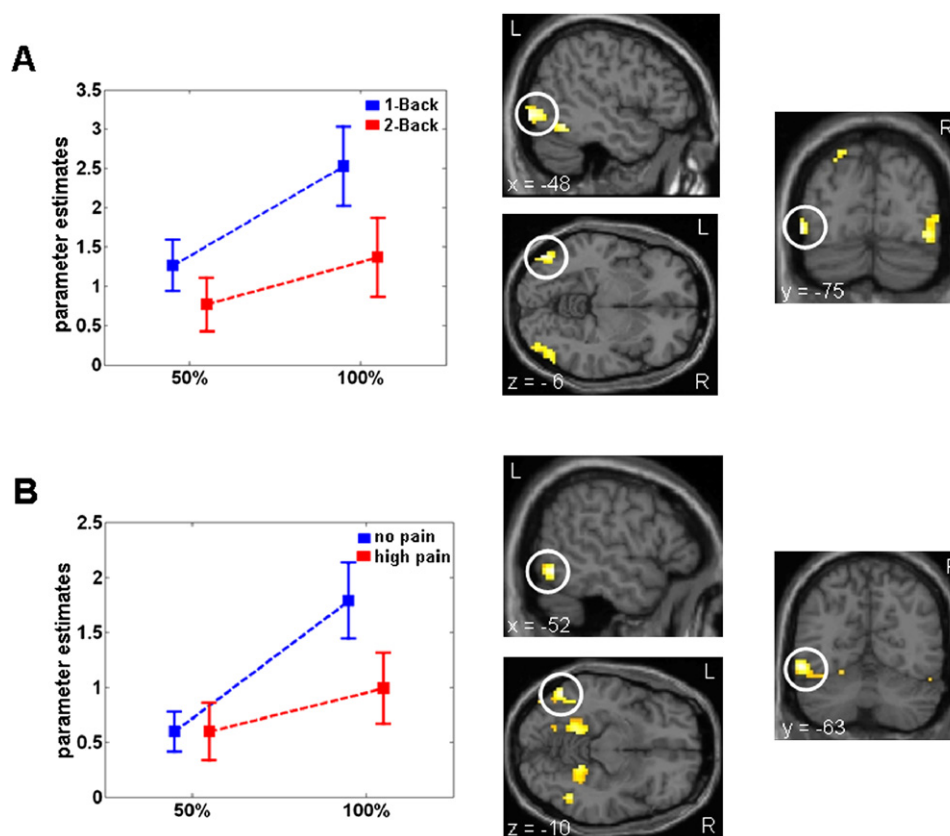
Figure 3. Modulation of Object Representation in the Ventral Visual Stream by Working Memory and Pain
(A) Activation (thresholded at p < 0.05) related to the interaction *WM load × Visibility*, restricted to the main effect of object *Visibility*, thresholded at p < 0.001, overlaid on axial, sagittal, and transversal slices of a T_1-weighted template image. fMRI effects of the interaction of background visibility with WM load were observed in bilateral LOC, reflecting a phasic modulation of LOC activity. Related parameter estimates (representing the parameters β in the GLM) for the conditions low visibility (50%) and high visibility (100%) with low and high WM load (one-back, two-back).
(B) Corresponding activation (thresholded at p < 0.05) and parameter estimates related to the interaction of *Pain × Visibility*.
The positions of values on the x axis are slightly shifted so as to not obliterate the error bars.

both interaction effects as in the interaction analyses without applying this functional ROI (Table 1C and 1D).

Three-Way Interaction. The three-way interaction [*Pain × Visibility × WM load*] revealed that concomitant painful stimulation even amplifies the modulatory effect of *WM load* on visual processing in LOC (51, −75, −12, Z = 2.8, p < 0.01) and vice versa.

Post Hoc Analyses Concerning the Interaction Effects of Pain and WM Load and Visibility
After having identified the interaction effects of *Pain* and *WM load* on *Visibility* in the lateral occipital complex at the group level, the question arises about the precise location and potential overlap of these effects within this area. To address this issue, we performed additional analyses at the group and the single-subject levels.

Conjunction Analysis. To not only restrict the interaction analysis to object-related areas (see functional ROI procedure) but to test for the combination of all three effects (i.e., main effect of *Visibility*, modulatory influence of *WM load*, and *Pain* in the same voxels within the object-related area), we performed a conjunction analysis of all three

independent comparisons (i.e., main effect of *Visibility*, *WM load × Visibility* and *Pain × Visibility*). A conjunction analysis reveals the minimum conjoint t map of these three independent analyses and thus assigns each voxel the smallest t value of all three comparisons. The conjunction analysis revealed an overlap of the two modulatory mechanisms in the lateral occipital complex bilaterally (48, −57, −12, Z = 2.3 and −48, −51, −15, Z = 2.3, both p = 0.01; Figure S2).

Single-Subject Analysis. To statistically test for potential differences between the locations of both interaction effects, the interaction analyses were also performed at the single-subject level. Therefore, for each individual subject, LOC was identified as the set of voxels in the ventral occipito-temporal cortex that were activated more strongly (p < 0.001) by intact than by scrambled images (i.e., main effect of *Visibility*). The peak voxels for the interaction effect of *WM load × Visibility* and *Pain × Visibility* in the ventral-occipito-temporal cortex were then identified within these predefined ROIs. Five volunteers did not show a main effect of *Visibility* at the required

threshold of p < 0.001 and were therefore not included in this analysis. There was no statistical difference for the average location across subjects or consistent spatial difference in each individual for the *Pain × Visibility* and *WM load × Visibility* effect obtained from individual subject analyses (comparison of the x, y, z coordinates of peak voxels for both effects by a two-sample and paired t test revealed no significant effect at p < 0.05; Table S1 and Figure S3). To account for the fact that potential overlap of areas modulated by pain and by working memory might be related to smoothing, the single-subject analysis was performed with data that were minimally smoothed with a 4 mm FWHM kernel.

Psychophysiological Interaction—Motivation and Hypothesis

To investigate the underlying mechanisms of modulation of visual processing, a psychophysiological interaction (PPI) (Friston et al., 1997) analysis was performed. A PPI analysis can reveal context-dependent functional connectivity between areas. This analysis is based on activation patterns that stem from the standard analyses and an anatomical model (see below). This analysis is an attempt to explain the underlying mechanism of the observed modulations (i.e., interactions) by regional activity. In our case, this analysis tests whether the effect of a stimulus feature (image visibility being the psychological factor) on a brain region is significantly altered by the activity of another modulatory brain region (physiological factor). In relation to our experiment, we specifically hypothesized that the mechanism of pain-dependent modulation of LOC involves a pain- and attention-related region. Among all pain-responsive regions, the rostral anterior cingulate cortex (rACC) has been suggested not only to be involved in primary pain processing, such as pain-intensity coding, but also in mechanisms of cognitive modulation of pain, such as attention, anticipation, and placebo analgesia (Bantick et al., 2002; Petrovic et al., 2002; Ploghaus et al., 1999; Porro et al., 2003; Rainville et al., 1997). In addition, the rACC is closely anatomically linked to the ACC, which plays an important role in attentional control (Crottaz-Herbette and Menon, 2006; Fan et al., 2005), response selection (Turken and Swick, 1999), and conflict monitoring (Botvinick et al., 1999). Basically, all of these mechanisms of cognitive control are thought to resolve conflicts through the attentional biasing of perceptual processing, emphasizing task-relevant stimulus information (Egner and Hirsch, 2005). It thus appears to be a possible structure to serve as the modulatory source of the *Pain × Visibility* interaction found in LOC.

Similarly, a working-memory-related brain region should be responsible for the working-memory-dependent modulation of LOC. Working memory consists of different cognitive components, and thus the main effect of working memory revealed a number of brain regions, most prominently, the bilateral frontal and bilateral parietal regions (Rose et al., 2005). However, given that we were specifically interested in the attentional consequences of an ongoing working memory task, we hypothesized that

the inferior parietal region would act as the source of LOC modulation in the context of *WM load*. This area has an essential role in the storage and retrieval of verbal working memory processes (Jonides et al., 1998; Smith and Jonides, 1998) and seems to play a major role in mediating top-down attentional control on the visual cortex (Corbetta et al., 1993; Kastner and Ungerleider, 2000; Nobre et al., 1997). We therefore performed a connectivity analysis that tested whether LOC is also modulated by the right inferior parietal area dependent on the working memory load. Please see Experimental Procedures for a detailed description of the PPI analysis.

Psychophysiological Interaction Analysis

The psychophysiological interaction analysis—which tested for brain areas that show activation patterns covarying with rACC activity (indirectly reflecting pain intensity), depending on whether the background images are applied at low or high visibility—revealed an interaction in LOC bilaterally (−42, −81, −9, Z = 3.1, p < 0.05 corrected; 48, −78, 3, Z = 2.5, p < 0.01; Figure 4A). The second psychophysiological interaction analysis using the inferior parietal cortex as the source of modulation also revealed an interaction in LOC (−39, −81, 0, Z = 3.2, p < 0.05 corrected; 36, −78, −12, Z = 2.9, p < 0.01, Figure 4B). Please note that a PPI analysis only tests for a single predefined anatomical model and thus cannot rule out the possibility that regions other than the rACC or the inferior parietal region can exert a modulatory influence.

DISCUSSION

We observed that pain interfered with visual object processing in the ventral visual system, in particular LOC, as reflected by the reduced increase of activity with object visibility under the high-pain conditions. This modulation of visual processing by pain was behaviorally relevant, as it was paralleled by impaired recognition accuracy for background pictures seen at the same time. The task-specific source of this modulatory influence of pain is located in the rACC, an area that is ideally suited to link pain perception and pain-related influences on attentional control.

These findings are in line with the notion that pain imposes a high and overriding priority on an action-oriented attentional system because it is evolutionarily important to signal harm and the urge to escape. Our data substantiate previous psychophysiological studies demonstrating that pain interferes with ongoing processes (Crombez et al., 1994, 1998; Eccleston, 1994; Kuhajda et al., 2002; Morton, 1969) but most importantly elucidate the neural correlates of the modulatory influence of acute pain.

Common Site of Modulation for Pain and WM Load

Given that we probed the processing of irrelevant background images with different degrees of visibility, we expected the modulation to primarily take place in the ventral visual pathway, which is an important system for visual object processing (Gimenez-Amaya, 2000; Ishai et al., 1999). In humans, a central stage in this pathway is the
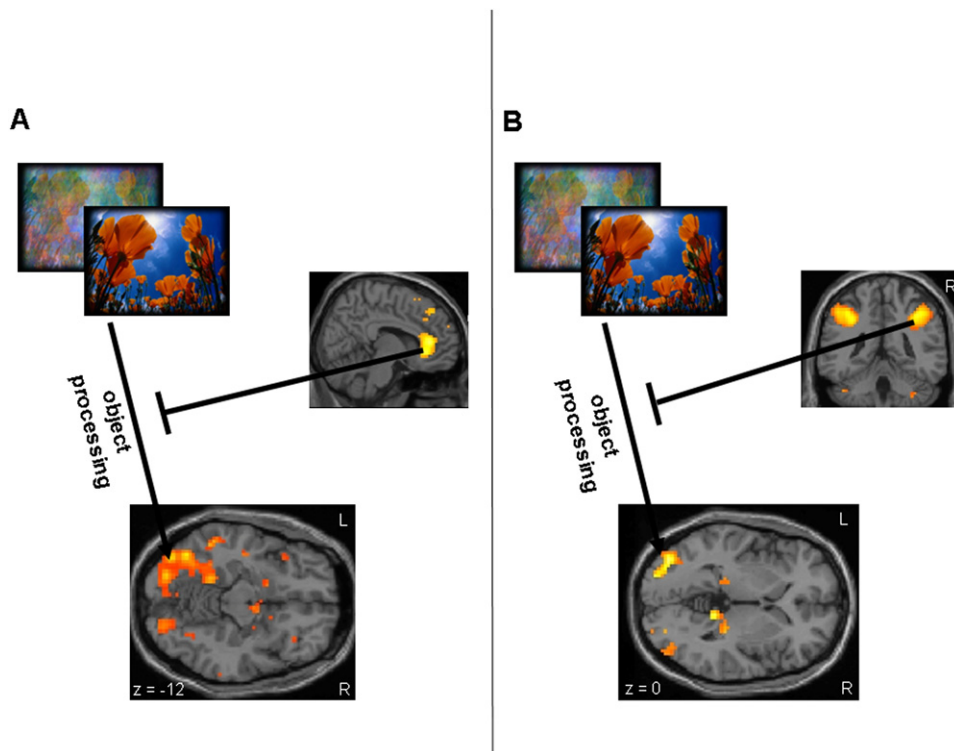
Figure 4. Connectivity Analyses Revealing Different Sources but Identical Sites of Modulation of Visual Processing by Pain and Working Memory

(A) The source of modulatory control of pain over LOC is the pain-related rACC. A psychophysiological interaction analysis (PPI) revealed a modulation of visibility on LOC influences by rACC activity, suggesting the rACC to be the modulatory source by which pain exerts control over visual areas. The results of the PPI are thresholded at $p < 0.05$; the pain-related activity in the rACC is thresholded at $p < 0.001$.

(B) The source of modulatory control of WM load is the inferior parietal cortex. The second PPI revealed a modulation of visibility on LOC influences by right inferior parietal activity, suggesting the inferior parietal region to be the modulatory source by which working memory load exerts control over visual areas. The results of the PPI are thresholded at $p < 0.05$; the inferior parietal activity related to the working memory task is thresholded at $p < 0.001$.

LOC, which is preferentially activated by visual objects compared to scrambled images or textures (Grill-Spector et al., 2001; Malach et al., 1995). As in our previous study (Rose et al., 2005), working memory load led to a modulation of the processing of irrelevant background images in exactly this region. The replication of our previous results demonstrates the robustness of our tasks for probing visual processing by taking away attentional resources depending on the load of the cognitive task in a parametrical matter.

Most interestingly, we found the same site of modulation when investigating the effect of pain on visual processing. Our data demonstrate that modulation of visual information processing in LOC represents a common site for different types of modulatory influences. The conjunction analysis and the single-subject analysis demonstrate that (1) both types of modulation impair object processing in object-related areas in the lateral occipito-temporal region and (2) that there was no statistical difference of the location where pain and working memory load dependent modulation in this region occurs. Interestingly, this spatial commonality of modulation was mirrored by a comparable effect on the behavioral level: high pain

intensities and high working memory demands reduced the recognition rate to a comparable degree.

In the group analysis, a trend of pain-related attenuation of visual processing was also observed in visual areas outside the LOC, such as the occipital pole, the left-sided fusiform, and lingual gyrus. However, no such effect was seen in the single-subject analyses or for the effect of working memory load.

Different Source of Modulation

To better understand the mechanism of the observed modulation, we employed a PPI analysis testing for the possibility that regional activity can explain the modulation observed in LOC. In particular we found that parietal activity could explain the modulation of LOC activity by WM load and conversely that rACC activity could account for the modulation of LOC by pain. In agreement with this observation, attentional modulation of ventral visual stream areas has been previously demonstrated using fMRI (Kastner et al., 1999). More importantly, this study suggests that this effect can be mediated by parietal and/or frontal areas. In all of these studies, the modulatory

effect leads to attention-dependent activation in ventral visual areas. Several other studies have substantiated the view that the parietal region plays a major role in mediating top-down attentional control on the visual cortex (Corbetta et al., 1993; Kastner and Ungerleider, 2000; Nobre et al., 1997). Our observation that high WM load resulted in a reduced increase of BOLD signal with image visibility and the PPI analysis demonstrating that the source of this modulatory influence of WM load on LOC can be attributed to the right inferior parietal region ties in with the common assumption that, by occupying parietal areas with a working memory task, as in our experiment, the ability of these structures to exert this positive modulatory influence on ventral visual areas decreases.

However, given that the main effect of pain does not predominantly involve these regions, the occupation of a fronto-parietal attentional network would not sufficiently explain the effect of pain on visual processing. The key regions of pain processing include a somatosensory network and the ACC. Given its involvement in pain processing (Peyron et al., 2000) and its intensive link to various mechanisms of cognitive control (Benedict et al., 2002; Devinsky et al., 1995; Isomura et al., 2003; Swick and Jovanovic, 2002), the rostral part of the ACC (rACC) especially represents a well-suited structure among other pain-related areas to serve as the modulatory source for the pain-related modulatory effect found in LOC. In accord with this hypothesis, we identified a modulation of LOC by rACC activity, suggesting a role of the rACC as a modulatory source, by which pain can modulate visual processing. The notion of a functional connection between the cingulate cortex and visual areas is also supported by anatomical data from nonhuman primates; the cingulate cortex holds extensive connections into occipito-temporal regions (Vogt and Pandya, 1987). In addition, a recent study has also described a functional connection between area 24 (rACC) and the ventral visual pathway through the ventral posterior cingulate cortex (vPCC) (Vogt et al., 2006).

Previous studies have documented the role of the rACC in the cognitive modulation of pain. These mechanisms could broadly be categorized under "disengagement" from pain. Interestingly, the rACC has also been linked to the initiation of antinociceptive mechanisms (as in placebo analgesia) (Bingel et al., 2006; Petrovic et al., 2002), which might contain a "disengaging attention from pain" component. Importantly, our data suggest that the rACC is also involved in the reverse mechanism, namely shifting and engaging attention to pain. Taken together, these connectivity analyses demonstrate a common site (LOC) but different sources of task-related modulations on visual processing—namely, rACC for pain and right inferior parietal cortex for working memory-related modulation of visual input into LOC.

Crossmodal Interaction
Our study clearly demonstrates that nociceptive information affects the processing of information in another sensory modality (vision). The issue of whether "load" in one modality interferes with the processing of information in another modality is of great interest in the attention literature (Rees et al., 2001). Our finding of crossmodal modulation of information processing supports a previous report of this phenomenon in a fear-conditioning study by Carter and colleagues (Carter et al., 2003). In contrast, a previous study specifically addressing the issue of whether auditory perceptual load interferes with visual processing failed to show such an effect (Rees et al., 2001). Our findings are not necessarily in contrast to this result, because of the exceptional role of pain related to its evolutionary importance. It appears conceivable that the attentional demand requested by painful stimuli is stronger than the attentional demand of, for example, simple auditory stimuli (Rees et al., 2001), as has been demonstrated in a number of behavioral studies (Crombez et al., 1997; Van Damme et al., 2004). In agreement with this notion, pain also interfered with the relevant task (i.e., working memory) as shown by the increased reaction times when high working memory load and pain occurred together. However, this effect was not reflected in the neuroimaging data, presumably because of the more complex system involved in working memory and multiple possible sites of interference.

Other Attentional Interactions Observed in the Experiment
Although the primary goal of the study was to elucidate the underlying mechanisms of how pain interferes with visual processing, we also observed a reciprocal interaction between *Pain* and *WM load*: pain interfered with the working memory task as shown by the increased reaction times when high working memory load and pain occurred together. This effect was not reflected in the neuroimaging data, presumably because of the more complex system involved in working memory to interfere with. On the other hand, pain ratings clearly attenuated under the high WM load condition. The impaired pain ratings under the high WM load were paralleled by decreased activity in classical pain-related areas such as the anterior insula and SII bilaterally and the contralateral SI/M1 region. These effects are in accord with previous studies on the impact of cognitive tasks on pain perception (Bantick et al., 2002; Petrovic et al., 2000). On the behavioral level, we also noted a positive interaction for the factors *Visibility* and *Pain*, with higher pain ratings when pictures were presented at high visibility.

Conclusion
Several important findings emerge from this study. (1) As hypothesized, pain interferes with the processing of other, less relevant stimuli to gather salience in a complex environment. (2) The modulation of visual processing by pain is behaviorally relevant, since it was paralleled by impaired recognition accuracy of respective pictures. (3) The fMRI connectivity analysis suggests that the source of this modulation is located in the rACC. (4) Comparing the

effect of pain on visual processing with the effect of working memory demonstrated that physiologically distinct mechanisms of modulation may act on the same site of modulation by different task-specific, spatially distributed sources of these modulatory mechanisms.

EXPERIMENTAL PROCEDURES

Subjects
Sixteen healthy male subjects (mean age 26 years, range 22–30 years) participated in this fMRI study. All subjects had normal pain thresholds at the site of laser pain application and no history of neurological or psychiatric disease, particularly no history of pain syndromes. All subjects were right handed and had normal or corrected-to-normal vision. The study was conducted in accord with the Declaration of Helsinki and approved by the local Ethics Committee. Subjects gave written informed consent to participate and were free to withdraw from the study at any time. Only those volunteers that had demonstrated competence at both levels of the working memory task in a behavioral training session before the actual fMRI study were enrolled in the actual experiment.

Subjects Preparation/Instruction
Prior to the experiment, subjects were familiarized with the laser stimuli and trained to rate their perceived pain intensity on a 0–100 visual analog scale (VAS), which was presented in the same fashion as during the fMRI experiment. Subjects were informed that the different pain intensities administered during the training session would be the same as those applied during the scanning session. The VAS was presented on a computer screen during the training session. It consisted of a bar that could be moved between the left and the right ends of a line indicating sensations from 0 (no sensation) to 100 (maximum pain used in the experiment). Even though it has been a major requirement for the subjects to perform properly on the n-back task in the behavioral selection session, all subjects also performed a 10 min session of the n-back task immediately prior to the fMRI experiment. The subjects were informed that the purpose of the study was to evaluate cognitive task performance in the presence of pain.

fMRI Experiment
The paradigm used in the present experiment was designed to specifically address the interaction of irrelevant visual background information and interfering factors (i.e., working memory and pain). In the current study, two manipulating factors were investigated at the same time: (1) the presence and intensity of concomitantly applied painful laser stimulus and (2) working memory load in the form of an n-back task. The factor working memory load was added to the design as an internal control condition, since the interference of cognitive load on visual processing was shown in a previous study done in our group with different volunteers (Rose et al., 2005). This results in a three-factorial design (including the factors pain intensity [*Pain*], visibility of irrelevant background images [*Visibility*], and working memory load [*WM load*].

Subjects were investigated in three consecutive scanning sessions, each lasting 6–8 min. The factors *Pain*, *Visibility*, and *WM load* were presented in a 3 × 2 × 2 factorial design (three pain levels × two visibility levels × two n-back levels), resulting in a total of 12 blocks of different conditions presented once per session in randomized order. Each block lasted for 20 s and consisted of ten trials with identical pain, visibility, and n-back level followed by the request to rate the average perception of laser stimulation on the VAS. Each of the ten consecutive trials of a single block consisted of the presentation of a letter (A, B, C, D, E, or G) overlaid on the irrelevant background image (presentation time 1 s) and a laser stimulus concomitantly applied to the subjects' dorsum of the left hand. The interstimulus interval (ISI) was 1 s, in which subjects had to maintain fixation on the letter. The n-back task was performed on the centrally presented letters overlaid

on the task-irrelevant background images. A cue ("1" or "2") proceeding the active block indicated whether a one-back or two-back task should be performed. Targets (three in each block) had to be indicated via button press on an MR-compatible device. At the end of each block, the average pain intensity perceived over the 20 s block was rated on the VAS. The experimental design is illustrated in Figure 1.

Stimuli
Laser Stimulation
A Tm-YAG-infrared laser (Neurolaser Wavelight, Starnberg, Germany) was used to apply computer-controlled brief pain stimuli. To avoid sensitization and tissue damage, the stimulus site was slightly changed after each stimulus. The choice of parameters for the painful stimuli applied to the hand was based on previous fMRI and psychophysical experiments. For the high-pain condition, a 600 mJ laser stimulus was chosen, which in previous studies evoked a very brief, but clearly "pin-prick-like" painful sensation without any warmth or tactile components (Buchel et al., 2002). For the low-pain condition, a 450 mJ stimulus was applied.
Visual Stimuli
Visual stimuli were presented using the software "Presentation" (http://www.neurobehavioralsystems.com) that ensured synchronization with the MR scanner. An LCD projector projected the stimuli on a screen behind the head coil, which was viewed by the subjects through a mirror (10° × 15° field of view). Each of the visual stimuli used in the experiment consisted of a background image with a superimposed letter, on which the one/two-back task was based. Background images contained defined degrees of visibility (50%/100%) and subtended 10° × 7.5° of visual angle. Visibility of images was modulated by scrambling them according to a method described previously (Rainer et al., 2001; Reinders et al., 2005; Rose et al., 2005). In short, different degrees of scrambling (i.e., noise) patterns were generated by manipulating a fraction of the image phase before transforming the amplitude and phase components back into image space. In this study, either 0% or 50% of the phase information was substituted by random phase information, resulting in "visibility levels" of 100% and 50%, respectively.

Recognition Task
A surprise recognition task was performed immediately after the volunteers left the scanning room. In the recognition task, we presented all of the images that had been shown in the imaging experiment plus an identical number of new images that were not shown to the participant during scanning. To assess the degree of object processing independent of physical attributes, we used images with full visibility (0% scrambling) for the recognition task.

Image Acquisition
MR scanning was performed on a 3 T MRI system (Siemens Trio) with a standard headcoil. Fourty-two axial slices (slice thickness: 3 mm, no gap) were acquired using a gradient echo echo-planar (EPI) T2*-sensitive sequence (TR, 2.41 s; TE, 25 ms; flip angle, 80°; field of view, 192 × 192 mm; matrix size, 64 × 64 pixels).

Image Processing and Statistical Analysis
The statistical analysis was performed at both the group and single-subject levels. Image processing and statistical analysis were carried out using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). All volumes were realigned to the first volume, spatially normalized (Ashburner and Friston, 1999; Friston et al., 1995) to a standard EPI template (Evans et al., 1993), and finally smoothed using an 8 mm full-width at half-maximum isotropic Gaussian kernel. A reduced smoothing kernel of 4 mm FWHM was used for the single-subject analyses.

Data analysis was performed using the general linear model (GLM). Our model contained a total of 13 regressors per session: 12 regressors coded for the 12 different conditions and an additional regressor coded for the rating response. Each boxcar stimulus function was convolved with a canonical hemodynamic response function as implemented in SPM2. A high-pass filter with a cut-off period of

120 s was used. Specific effects were tested with appropriate linear contrasts of the parameter estimates for the regressors of all trial types, resulting in a t statistic for each voxel. Data were analyzed for each subject individually (first-level analysis) and for the group using a random-effects approach (Friston et al., 1999), treating inter-subject variability as a random factor. The threshold for statistical testing was set to $p < 0.05$, corrected for multiple comparisons. For regions in which we had an a priori hypothesis, a small volume correction (SVC) was performed. In the classical pain areas (for review see Peyron et al., 2000), including thalamus, insula, SII, SI, and the cingulate cortex, significance of activation was corrected for a volume of a 15 mm radius sphere, except for the thalamus, where an 8 mm radius sphere was applied. Since our paradigm was specifically designed to probe visual object processing, we expected modulation of irrelevant visual information to take place in ventral visual areas, as seen in a previous study, in particular LOC (Rose et al. 2005). In these areas, correction was based on a search volume of 4123 mm³, representing a 10 mm radius sphere.

Psychophysiological Interaction

To reveal the underlying connectivity of LOC modulation dependent on our different tasks (i.e., pain and working memory), we performed two PPI analyses.

To test whether the pain-related influence of LOC can be attributed to the rACC, we performed a PPI analysis with the activity in pain-inten-sity-related rACC (as identified by the contrast high > low pain [9, 36, 9 for x, y, and z]) representing the *physiological variable* and the visibility of background images representing the *psychological variable*. This PPI identifies areas that show activation patterns covarying with the visibility of the background images modulated by rACC activity.

Therefore, time series were extracted from a sphere (6 mm radius) centered on the rostral anterior cingulate maximum of the high > low pain contrast for each individual volunteer using the first eigen time se-ries (principal component) of this area. The PPI regressor was computed as the element-by-element product of the mean-corrected rACC activ-ity and a vector coding for the differential effect of visibility during the psychological conditions: low or high (-1 for low visibility, 1 for high visibility). Our analysis of connectivity was thus specific for context-dependent rACC influences that occurred over and above any task effects and context-independent rACC influences. Brain sites receiving contextual influences of the pain-intensity-related rACC depending on the visibility of background images were determined by a t test.

To test, whether the working-memory-related modulation of LOC can be attributed to the right inferior parietal region, we performed a similar PPI analysis, except that activity in the right inferior parietal region (as identified by the contrast high > low working memory load [39, -42, 45 for x, y, and z]) represented the *modulatory variable*. This PPI analysis identifies regions that show activation patterns cova-rying with the visibility of the background images modulated by activity in right inferior parietal cortex.

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/55/1/157/DC1/.

REFERENCES

Ashburner, J., and Friston, K.J. (1999). Nonlinear spatial normalization using basis functions. Hum. Brain Mapp. *7*, 254–266.

Bantick, S.J., Wise, R.G., Ploghaus, A., Clare, S., Smith, S.M., and Tracey, I. (2002). Imaging how attention modulates pain in humans using functional MRI. Brain *125*, 310–319.

Benedict, R.H., Shucard, D.W., Santa Maria, M.P., Shucard, J.L., Abara, J.P., Coad, M.L., Wack, D., Sawusch, J., and Lockwood, A. (2002). Covert auditory attention generates activation in the rostral/dorsal anterior cingulate cortex. J. Cogn. Neurosci. *14*, 637–645.

Bingel, U., Lorenz, J., Schoell, E., Weiller, C., and Buchel, C. (2006). Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain *120*, 8–15.

Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S., and Cohen, J.D. (1999). Conflict monitoring versus selection-for-action in anterior cin-gulate cortex. Nature *402*, 179–181.

Buchel, C., and Friston, K.J. (1997). Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. Cereb. Cortex *7*, 768–778.

Buchel, C., Josephs, O., Rees, G., Turner, R., Frith, C.D., and Friston, K.J. (1998). The functional anatomy of attention to visual motion. A functional MRI study. Brain *121*, 1281–1294.

Buchel, C., Bornhovd, K., Quante, M., Glauche, V., Bromm, B., and Weiller, C. (2002). Dissociable neural responses related to pain inten-sity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. J. Neurosci. *22*, 970–976.

Carter, R.M., Hofstotter, C., Tsuchiya, N., and Koch, C. (2003). Work-ing memory and fear conditioning. Proc. Natl. Acad. Sci. USA *100*, 1399–1404.

Corbetta, M., Miezin, F.M., Shulman, G.L., and Petersen, S.E. (1993). A PET study of visuospatial attention. J. Neurosci. *13*, 1202–1226.

Crombez, G., Baeyens, F., and Eelen, P. (1994). Sensory and temporal information about impending pain: the influence of predictability on pain. Behav. Res. Ther. *32*, 611–622.

Crombez, G., Eccleston, C., Baeyens, F., and Eelen, P. (1997). Habit-uation and the interference of pain with task performance. Pain *70*, 149–154.

Crombez, G., Eccleston, C., Baeyens, F., and Eelen, P. (1998). Atten-tional disruption is enhanced by the threat of pain. Behav. Res. Ther. *36*, 195–204.

Crottaz-Herbette, S., and Menon, V. (2006). Where and when the ante-rior cingulate cortex modulates attentional response: combined fMRI and ERP evidence. J. Cogn. Neurosci. *18*, 766–780.

Devinsky, O., Morrell, M.J., and Vogt, B.A. (1995). Contributions of anterior cingulate cortex to behavior. Brain *118*, 279–306.

Eccleston, C. (1994). Chronic pain and attention: a cognitive approach. Br. J. Clin. Psychol. *33*, 535–547.

Eccleston, C., and Crombez, G. (1999). Pain demands attention: a cog-nitive-affective model of the interruptive function of pain. Psychol. Bull. *125*, 356–366.

Egner, T., and Hirsch, J. (2005). Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nat. Neurosci. *8*, 1784–1790.

Evans, A.C., Collins, D.L., Mills, D.R., Brown, E.D., Kelly, R.L., and Peters, T.M. (1993). 3D statistical neuroanatomical models from 305 MRI volumes. Proc IEEE-Nuclear Science Symposium and Medical Imaging *1–3*, 1813–1817.

Fan, J., McCandliss, B.D., Fossella, J., Flombaum, J.I., and Posner, M.I. (2005). The activation of attentional networks. Neuroimage *26*, 471–479.

Friston, K.J., Holmes, A.P., Worsley, K.P., Poline, J.-B., Frith, C.D., and Frackowiak, R.S.J. (1995). Statistical parametric maps in functional imaging: A general linear approach. Hum. Brain Mapp. *2*, 189–210.

Friston, K.J., Büchel, C., Fink, G.R., Morris, J., Rolls, E., and Dolan, R.J. (1997). Psychophysiological and modulatory interactions in neuroimaging. Neuroimage *6*, 218–229.

Friston, K.J., Holmes, A.P., and Worsley, K.J. (1999). How many subjects constitute a study? Neuroimage *10*, 1–5.

Gimenez-Amaya, J.M. (2000). Functional anatomy of the cerebral cortex implicated in visual processing. Rev. Neurol. *30*, 656–662.

Grill-Spector, K., Kourtzi, Z., and Kanwisher, N. (2001). The lateral occipital complex and its role in object recognition. Vision Res. *41*, 1409–1422.

Ishai, A., Ungerleider, L.G., Martin, A., Schouten, J.L., and Haxby, J.V. (1999). Distributed representation of objects in the human ventral visual pathway. Proc. Natl. Acad. Sci. USA *96*, 9379–9384.

Isomura, Y., Ito, Y., Akazawa, T., Nambu, A., and Takada, M. (2003). Neural coding of "attention for action" and "response selection" in primate anterior cingulate cortex. J. Neurosci. *23*, 8002–8012.

Jonides, J., Schumacher, E.H., Smith, E.E., Koeppe, R.A., Awh, E., Reuter-Lorenz, P.A., Marshuetz, C., and Willis, C.R. (1998). The role of parietal cortex in verbal working memory. J. Neurosci. *18*, 5026–5034.

Kastner, S., and Ungerleider, L.G. (2000). Mechanisms of visual attention in the human cortex. Annu. Rev. Neurosci. *23*, 315–341.

Kastner, S., Pinsk, M.A., De Weerd, P., Desimone, R., and Ungerleider, L.G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. Neuron *22*, 751–761.

Kuhajda, M.C., Thorn, B.E., Klinger, M.R., and Rubin, N.J. (2002). The effect of headache pain on attention (encoding) and memory (recognition). Pain *97*, 213–221.

Loftus, G.R., and Masson, M.E. (1994). Using confidence intervals in within-subject designs. Psychol. Bull. *I*, 476–490.

Malach, R., Reppas, J.B., Benson, R.R., Kwong, K.K., Jiang, H., Kennedy, W.A., Ledden, P.J., Brady, T.J., Rosen, B.R., and Tootell, R.B.H. (1995). Object-related activity revealed by functional magnetic-resonance- imaging in human occipital cortex. Proc. Natl. Acad. Sci. USA *92*, 8135–8139.

Morton, J. (1969). Categories of interference: verbal mediation and conflict in card sorting. Br. J. Psychol. *60*, 329–346.

Nobre, A.C., Sebestyen, G.N., Gitelman, D.R., Mesulam, M.M., Frackowiak, R.S., and Frith, C.D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. Brain *120*, 515–533.

Petrovic, P., Petersson, K.M., Ghatan, P.H., Stone-Elander, S., and Ingvar, M. (2000). Pain-related cerebral activation is altered by a distracting cognitive task. Pain *85*, 19–30.

Petrovic, P., Kalso, E., Petersson, K.M., and Ingvar, M. (2002). Placebo and opioid analgesia–imaging a shared neuronal network. Science *295*, 1737–1740.

Peyron, R., Laurent, B., and Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta- analysis (2000). Neurophysiol. Clin. *30*, 263–288.

Ploghaus, A., Tracey, I., Gati, J.S., Clare, S., Menon, R.S., Matthews, P.M., and Rawlins, J.N. (1999). Dissociating pain from its anticipation in the human brain. Science *284*, 1979–1981.

Porro, C.A., Baraldi, P., Pagnoni, G., Serafini, M., Facchin, P., Maieron, M., and Nichelli, P. (2002). Does anticipation of pain affect cortical nociceptive systems? J. Neurosci. *22*, 3206–3214.

Porro, C.A., Cettolo, V., Francescato, M.P., and Baraldi, P. (2003). Functional activity mapping of the mesial hemispheric wall during anticipation of pain. Neuroimage *19*, 1738–1747.

Rainer, G., Augath, M., Trinath, T., and Logothetis, N.K. (2001). Nonmonotonic noise tuning of BOLD fMRI signal to natural images in the visual cortex of the anesthetized monkey. Curr. Biol. *11*, 846–854.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., and Bushnell, M.C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science *277*, 968–971.

Rees, G., Frith, C.D., and Lavie, N. (1997). Modulating irrelevant motion perception by varying attentional load in an unrelated task. Science *278*, 1616–1619.

Rees, G., Frith, C., and Lavie, N. (2001). Processing of irrelevant visual motion during performance of an auditory attention task. Neuropsychologia *39*, 937–949.

Reinders, A.A., den Boer, J.A., and Buchel, C. (2005). The robustness of perception. Eur. J. Neurosci. *22*, 524–530.

Rose, M., Schmid, C., Winzen, A., Sommer, T., and Buchel, C. (2005). The functional and temporal characteristics of top-down modulation in visual selection. Cereb. Cortex *15*, 1290–1298. Published online December 22, 2005. 10.1093/cercor/bhi012.

Sawamoto, N., Honda, M., Okada, T., Hanakawa, T., Kanda, M., Fukuyama, H., Konishi, J., and Shibasaki, H. (2000). Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. J. Neurosci. *20*, 7438–7445.

Schwartz, S., Vuilleumier, P., Hutton, C., Maravita, A., Dolan, R.J., and Driver, J. (2005). Attentional load and sensory competition in human vision: modulation of fMRI responses by load at fixation during task-irrelevant stimulation in the peripheral visual field. Cereb. Cortex *15*, 770–786.

Smith, E.E., and Jonides, J. (1998). Neuroimaging analyses of human working memory. Proc. Natl. Acad. Sci. USA *95*, 12061–12068.

Swick, D., and Jovanovic, J. (2002). Anterior cingulate cortex and the Stroop task: neuropsychological evidence for topographic specificity. Neuropsychologia *40*, 1240–1253.

Turken, A.U., and Swick, D. (1999). Response selection in the human anterior cingulate cortex. Nat. Neurosci. *2*, 920–924.

Van Damme, S., Crombez, G., Eccleston, C., and Goubert, L. (2004). Impaired disengagement from threatening cues of impending pain in a crossmodal cueing paradigm. Eur. J. Pain *8*, 227–236.

Vogt, B.A., and Pandya, D.N. (1987). Cingulate cortex of the rhesus monkey: II. Cortical afferents. J. Comp. Neurol. *262*, 271–289.

Vogt, B.A., Vogt, L., and Laureys, S. (2006). Cytology and functionally correlated circuits of human posterior cingulate areas. Neuroimage *29*, 452–466.