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David A. Seminowicz[1,3] and Karen D. Davis[1,2,3]

[1]*Institute of Medical Science and* [2]*Department of Surgery, University of Toronto; and* [3]*Toronto Western Research Institute, Division of Brain, Imaging and Behaviour-Systems Neuroscience, University Health Network, Toronto, Canada*

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Seminowicz DA, Davis KD. Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. *J Neurophysiol* 97: 3651–3659, 2007. First published February 21, 2007; doi:10.1152/jn.01210.2006. Experimental and clinical evidence indicates that pain can affect cognitive processes, but the cortical networks involved in pain-cognition interactions are unclear. In this study, we determined the effect of pain on the activity of cortical areas involved in cognition acting as a whole (i.e., a network). Subjects underwent functional magnetic resonance imaging (fMRI) while engaged in an attention-demanding cognitive task (multisource interference task) of varying difficulty and simultaneously receiving painful stimuli at varying intensities. The control (baseline) condition was simple finger tapping that had minimal cognitive demands and without pain. Functional connectivity analysis revealed a cortical network consisting of two anti-correlated parts: a task-negative part (precuneus/posterior cingulate cortex, medial frontal and inferior parietal/temporal) the activity of which correlated negatively with the cognitive task and positively with the control baseline, and a task-positive part (inferior frontal, superior parietal, premotor, and anterior insula cortices) the activity of which correlated positively with the cognitive task and negatively with the baseline. Independent components analysis revealed these opposing networks were operating at a low frequency (0.03–0.08 Hz). The functional connectivity of the task-positive network was increased by cognitive demand and by pain. We suggest this attention-specific network balances the needs of general self-referential and environmental awareness versus focused attention to salient information. We postulate that pain affects cognitive ability by its reliance on this common attention-specific network. These data provide evidence that pain can modulate a network presumed to be involved in focused attention, suggesting a mechanism for the interference of pain on cognitive ability by the consumption of attentional resources.

INTRODUCTION

Pain is inherently salient and as such demands attention (Eccleston and Crombez 1999). However, the brain networks supporting the cognitive component of pain are not clear. In some situations, experimental pain can disrupt cognitive performance and task-related activity in specific cortical regions (Crombez et al. 1997; Houlihan et al. 2004; Lorenz and Bromm 1997). Accordingly, some people who suffer from chronic pain also show cognitive impairment (Dick et al. 2002, 2003; Eccleston 1995; Harman and Ruyak 2005; Kewman et al. 1991; Lorenz et al. 1997; Park et al. 2001; Veldhuijzen et al. 2006). The mechanism underlying the interaction between pain and attention/cognitive function is not understood but likely involves some common cortical elements because pain involves similar attentional resources as other cognitive processes.

It is well established that complex sensory experiences, like pain and cognition, evoke neural activity distributed among widespread regions of the brain. There have been several studies of how pain and cognitive tasks individually or interactively engage specific brain areas independently of other brain regions (Bantick et al. 2002; Buffington et al. 2005; Frankenstein et al. 2001; Nakamura et al. 2002; Petrovic et al. 2000; Remy et al. 2003; Seminowicz et al. 2004; Tracey et al. 2002; Valet et al. 2004; Villemure et al. 2003; Wiech et al. 2005), but it is not known how pain modulates brain networks that operate together as a functional unit. One candidate network that has been identified is activated by multiple types of cognitive tasks and is active during a basal (no instruction) state (Fox et al. 2005), the so-called "intrinsic" task-positive network.

We recently reported that a cognitive task of various levels of difficulty could be performed during concomitant experimental pain (Seminowicz and Davis 2006). Using a region of interest analysis approach, we showed that individual regions activated by performance of this specific task (i.e., cognitive-related areas) were not significantly modulated by pain. In that study, we used univariate analyses, which, although very useful for determining how individual brain regions are related to the experimental conditions, do not determine how the regions are cooperating as a network but rather how each individual region is related to an experimenter-specified design. Here we expand these findings by using functional connectivity analysis, which is based on the temporal correlations between activity in spatially distinct brain areas (Friston 1994). Network analysis considers the role of sets of brain regions working in unison (Friston and Price 2001; McIntosh 2004). Because the brain consists of efficient neuronal networks (Laughlin and Sejnowski 2003), network analysis is ideal for interrogating patterned brain activity. Network analysis has the potential to show not only how individual regions are modulated by a task or pain but also how whole networks—consisting of potentially many distributed nodes of activity—can be modulated. In fact, behavioral correlates might be better represented in patterns of connectivity than regional activity (Friston and Price 2001). Similarly, activity in a particular brain region could differentially affect associated brain regions so the activation of that region alone might not correlate with

Address for reprint requests and other correspondence: K. D. Davis, Toronto Western Research Institute, Toronto Western Hospital, University Health Network, Room MP14-306, 399 Bathurst St., Toronto, Ontario M5T 2S8, Canada (E-mail: kdavis@uhnres.utoronto.ca).

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a behavioral measure, whereas the way in which it is connected with other regions might (McIntosh 2004).

Pain has a cognitive component: to evaluate the intensity and other qualities of the pain, attention needs be turned to the pain, and because of the biological importance of nociceptive pain, pain demands attention. Attention can be viewed broadly as the focusing of resources on a specific stimulus. Different attention-demanding tasks engage a common group of brain regions, including the posterior parietal, prefrontal, and anterior cingulate cortices (Cabeza and Nyberg 2000; Naghavi and Nyberg 2005). More recently, studies examining functional connectivity in the resting state have reported that these regions involved in focused attention are "connected" based on their common temporal activity patterns during rest (Fox et al. 2005; Fransson 2005; Laufs et al. 2003). This so-called task-positive network works in tandem with another functional network—the task-negative network. The activity in each network alternates at low frequencies (<0.1 Hz). The task-negative network is remarkably similar to the so-called "default mode" (Greicius and Menon 2004; Greicius et al. 2003; Raichle et al. 2001) resting state network and includes the precuneus/posterior cingulate cortex (precun/PCC), medial frontal cortex (MF), and inferior parietal cortex (iPar). The task-positive network consists of a set of regions commonly activated by cognitive tasks, including working memory and attention tasks, such as the frontal eye fields (FEFs), lateral parietal (LP), and the visual area MT+. The anti-correlated task-positive and -negative networks are thought to be intrinsically active and are functionally connected in several resting (task-free) scenarios (Fox et al. 2005; Fransson 2005). Furthermore, it appears that these functionally connected networks are stable over different tasks (Raichle and Gusnard 2005).

Whether pain affects cognitive-related functional networks is not known. Therefore in this study, we tested the hypothesis that pain increases activity in networks associated with focused attention. Because of the apparent involvement of these networks in a general attention framework, we hypothesized that both pain and cognitive task performance would activate the task-positive network and suppress the task-negative one, thus providing a common platform for pain-cognition interactions (Raichle et al. 2001).

METHODS

Twenty-three subjects [11 male, 12 female, age: 25.6 ± 4.1 (SD)] participated in a whole brain fMRI study of pain-cognition interactions. Subjects were healthy, medication free, and pain free and did not suffer from psychiatric illness. Subjects gave informed, written consent, and the study was approved by the University Health Network research ethics board.

The attention-demanding cognitive task was a variation of the multi-source interference task (MSIT) (Bush et al. 2003). Although the MSIT was originally designed to robustly activate cingulate cortex, it also activates other frontal and parietal areas considered part of a common executive network (Fan et al. 2005; Naghavi and Nyberg 2005). We exploited the complexity of the task to create different levels of cognitive demand based on reaction times and accuracy. The task involved detecting and responding to one of three characters visually presented that was different from the other two. For example, when 3 2 2 is presented, the correct response was "3." Subjects used their right hands to depress a button on a MRI-compatible button box to register their responses. In the tapping (T0) condition, the subject responded to the position of an asterisk, which simply moved from left to right (i.e., appeared in the 1st, 2nd, or 3rd position) sequentially on subsequent trials and thus involved no cognitive conflict. The other task levels (easy, moderate, difficult) manipulated positional and size characteristics of the target to obtain three additional levels (T1, T2, T3) of difficulty. In the easy task, T1, a number appeared in its correct corresponding position and the other positions contained an "x. " In T2 and T3, each of the three positions contained a number that may or may not correspond to its position. In the moderate task, T2, all the numbers were the same size, but in the difficult task, T3, one of the nontarget numbers was larger than the target number.

Pain was evoked by electrical left median nerve stimulation. The study was a block design consisting of three pain conditions [no stimulation (P0); mild intensity pain (P1), rated ~20 on numerical rating scale of 0 (no pain) to 100 (extremely intense pain); moderate intensity pain (P2, ~60/100)] and four task conditions (T0, T1, T2, and T3), combined for a total of 12 conditions. The condition P0T0 (no pain, tapping task) was the control (baseline) condition for this experiment and is assumed to have very low attentional demands. Subjects were instructed to perform the task as fast as possible without making mistakes. Experimental blocks were presented for 14 s in random order and were preceded by the control condition (P0T0) for 12 s. Each subject underwent three functional imaging runs (except for 3 subjects, for whom only 2 runs were analyzed: 1 subject because of a technical problem with the response box and the other 2 because of scanner problems) of 9 min 50 s, and each condition was repeated a total of six times.

Data were acquired on a 1.5-T Echospeed MRI (GE Medical Systems, Milwaukee, WI). Parameters for functional (T2*-weighted) scans were as follows: 25 4-mm axial slices; single shot spiral; TR = 2,000 ms; TE = 40 ms; FOV = 20 cm; 64 × 64 matrix; in-plane resolution 3.125 × 3.125 mm. The parameters for the structural (T1-weighted) scans were: 124 1.5-mm sagittal slices; TE = 5 ms; TR = 25 ms; flip = 45°; FOV = 24 cm; 256 × 256 matrix; in-plane resolution 0.9375 × 0.9375 mm. The first three frames of each run were discarded for signal equilibration, leaving a total of 292 frames per run.

Three different analyses were carried out [partial least squares (PLS) analysis is described in the following text]. *1*) *Task PLS of cognitive load*. This analysis was used to determine the spatial brain activity pattern associated with the increasing cognitive load (i.e., task difficulty). The resulting network would be attention-specific if its activity was graded with increasing task difficulty. *2*) *Task PLS using a mask*. The results for these analyses were limited to the spatial pattern identified in the first task PLS (i.e., tasks alone without pain). This was done by creating a mask, which included only the brain areas in the networks identified in step 1. The purpose of the mask was to ensure that the results reflect modulation of the attention-specific network rather than the involvement of other areas not identified as part of the task-related networks. Two analyses were performed. The first analysis was performed to show the effect of pain alone on the network and included only the pain conditions during the control task (P0T0, P1T0, P2T0). The second analysis was performed to show how the interaction between pain and cognitive load affected the network and included every condition. *3*) *Independent component analysis (ICA)*. This analysis was used to determine whether the spatial pattern identified in step 1 was robust across all conditions and to show the low-frequency, anti-correlated nature of the task-positive and negative parts of the attention-specific network.

Data were analyzed using multivariate techniques, including ICA implemented in BrainVoyager QX 1.6.1 (Brain Innovation, Maastricht, The Netherlands), and PLS (McIntosh et al. 1996) to assess functional connectivity. Data were preprocessed in BrainVoyager QX 1.1.6 and SPM99 (Friston et al. 1996). Data to be used in PLS analyses (see following text) were preprocessed in SPM99 using the following parameters: scan slice timing correction; motion correction; normalization to MNI (Montreal Neurological Institute) template; spatial smoothing of 6 mm FWHM (full width, half maximum) no temporal

filtering. Data analyzed with BrainVoyager QX was preprocessed in BVQX1.1.6 with the following parameters: scan slice timing correction; motion correction; spatial smoothing of 6 mm FWHM; transformation to Talairach space.

PLS (McIntosh et al. 1996) was performed to ascertain functional connectivity. (For a review of PLS mathematics and applications to neuroimaging, see McIntosh and Lobaugh 2004.) We used connectivity analysis, task PLS, which produces a whole brain functional map that covaries with the experimental conditions. PLS is similar to principal components analysis with the major difference that the resultant covariance pattern is constrained to the conditions of the experiment. The task data are optimally fit to the functional map, and new variables, or "latent variables" (LVs, akin to PCA components) are created and ordered by the amount of variance they explain. The output of a PLS analysis is a covariance map that is related to the design structure in a given way. Thus this analysis can be considered data-driven because no design structure is specifically given as would be done in a general linear model (GLM). The "design scores" indicate how strongly and in which direction a given condition covaries with the functional map. Design scores can be positively or negatively related to the spatial covariance map. In the task PLS analysis, design scores resemble experimenter-designated contrast weights in a GLM. The major difference between preset contrast weights and design scores is that the latter are optimally fit to account for as much variance as possible between the task conditions and the fMRI data. The grand mean deviation PLS analysis method was used. Data were averaged within and across blocks of the same condition within each subject (i.e., for each subject, 1 data point for each condition was used in the analyses).

Two statistical tests are performed in PLS: the first assesses significance by performing 500 permutation tests per LV in which conditions are reassigned and the resultant structure is compared back to the calculations for the original design. This yields a P value for each LV. The significance level was set to $P < 0.05$ and, because permutations assess significance of the overall spatial pattern rather than on a voxel-wise basis, correction for multiple comparisons is not required. The second test determines reliability by determining standard errors of the saliences for each voxel using 100 bootstrap samples. The bootstrapping method uses resampling with replacement, and the PLS is rerun for each new set of samples. A reliable effect does not vary depending on the samples included. This method yields confidence intervals for the LVs and also provides a bootstrap ratio (BSR) for each voxel and for the overall LV. BSRs are approximately equal to a z score, where 1.96 is $P = 0.05$. BSR images were thresholded at 1.96, although individual peak voxels had much higher BSRs as seen in Table 1. Reported coordinates are in Talairach space and were converted from MNI space using a nonlinear transformation (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

ICA was carried out using BrainVoyager QX 1.6.1 (Brain Innovation B.V.). A cortex-based mask was created for each subject using

TABLE 1. *Peak voxels from task PLS covariance map with task conditions without stimulation*

	Region Name	BA	R/L	x	y	z	BSR
Task-positive regions							
Frontal	Inferior frontal	44	R	51	10	15	6.67
	Inferior frontal	44	L	−44	5	20	9.95
	Middle frontal	9	L	−48	40	23	6.44
	Middle frontal	9	L	−40	50	23	6.4
	Middle frontal	46	R	48	40	15	7.48
	Premotor/motor	6/4	L	−26	−4	46	11.54
	Premotor	6	R	28	4	45	10.07
Cingulate	Anterior cingulate	32	R	6	19	36	7.39
Parietal	Inferior parietal	40	L	−34	−47	33	10.9
	Inferior parietal	40	R	42	−46	48	10.71
	Dorsal precuneus	7	R	2	−65	57	5.94
Insula	Anterior insula		R	38	19	1	7.36
	Anterior insula		L	−36	19	−1	7.25
Occipital	Occipital	18/19	L	−28	−75	19	6.75
Task-negative regions							
Medial Prefrontal	Dorsal medial frontal	8	L	−20	27	36	−13.76
	Dorsal medial frontal	8	L	−10	32	47	−5.95
	Dorsal medial frontal	9	R	22	42	28	−6.5
	Medial frontal	10	L	−16	50	19	−6.73
	Medial frontal	10	R	18	50	−4	−6.16
Posterior Cingulate/Precuneus	Posterior cingulate	31	L	−4	−57	16	−10.79
	Posterior cingulate	31	L	−8	−31	39	−7.41
	Precuneus	31	R	14	−45	33	−7.04
	Precuneus	7/31	R	10	−31	44	−6.74
Cingulate	Pregenual cingulate	32	L	−12	44	−7	−9.41
Temporal	Superior temporal	22	L	−51	−61	22	−9.04
	Superior temporal	22	R	59	−63	13	−8.79
	Middle temporal inferior	21	R	53	−1	−22	−8.17
	Middle temporal inferior	21	L	−55	−12	−16	−6.03
	Middle temporal inferior	21	R	51	−18	−8	−7.17
	Middle temporal	21	R	65	−60	3	−6.75
	Parahippocampal		R	42	−4	−12	−6.26
	Parahippocampal		L	−32	−6	−10	−7.04
Parietal	Secondary somatosensory	40	R	50	−26	18	−5.7
Insula	Posterior insula	13	L	−38	−11	11	−7.89
	Posterior insula	13	R	40	−14	1	−7.44
Subcortical	Putamen		L	−32	−23	3	−6.91

Boot strap ratio (BSR) (approximately equal to a z score) for the overall map was set to 5 to reduce cluster size and isolate more peak voxels. PLS, portial least squares; BA, Brodmann area.

his/her anatomical scan (Formisano et al. 2004). ICA, using a fastICA algorithm, was run over a whole functional run and a component having an activation pattern similar to that of the intrinsic task-negative (or default mode) pattern (as in Fig. 1*A*, particularly medial frontal and posterior cingulate cortices active) was identified by sight from the first 30 components for each run. This component is easily identified even when a task is being performed (see Esposito et al. 2006), based on its spatial pattern and the low frequency (<0.1 Hz) (Cordes et al. 2001) of its time course. An example of this pattern is shown for one subject in Fig. 2*C*. The frequency of the independent component was estimated using spectral analysis of the time-course, performed in SPSS for Windows (version 12.0.1, SPSS, Chicago, IL). An example spectral analysis for one run of one subject is shown in Fig. 2B. Time-course data from the IC of interest (i.e., the task-negative component from each subject) were input into a random effects GLM (performed in BrainVoyager QX) with transformation to percent signal change across the datasets of each individual, and data were corrected for multiple comparisons using false discovery rate.

We present and discuss the results of the PLS and ICA analyses in terms of network "activations" rather than considering the role of individual regions. Thus the term "activated" in terms of networks means that regions are positively correlated with the condition (task and/or pain) and are also functionally connected. "Increased activation" refers to both the increased activity in individual regions of the network as well as the connectivity between regions. When activity in a network is "deactivated," it is negatively correlated with the condition.

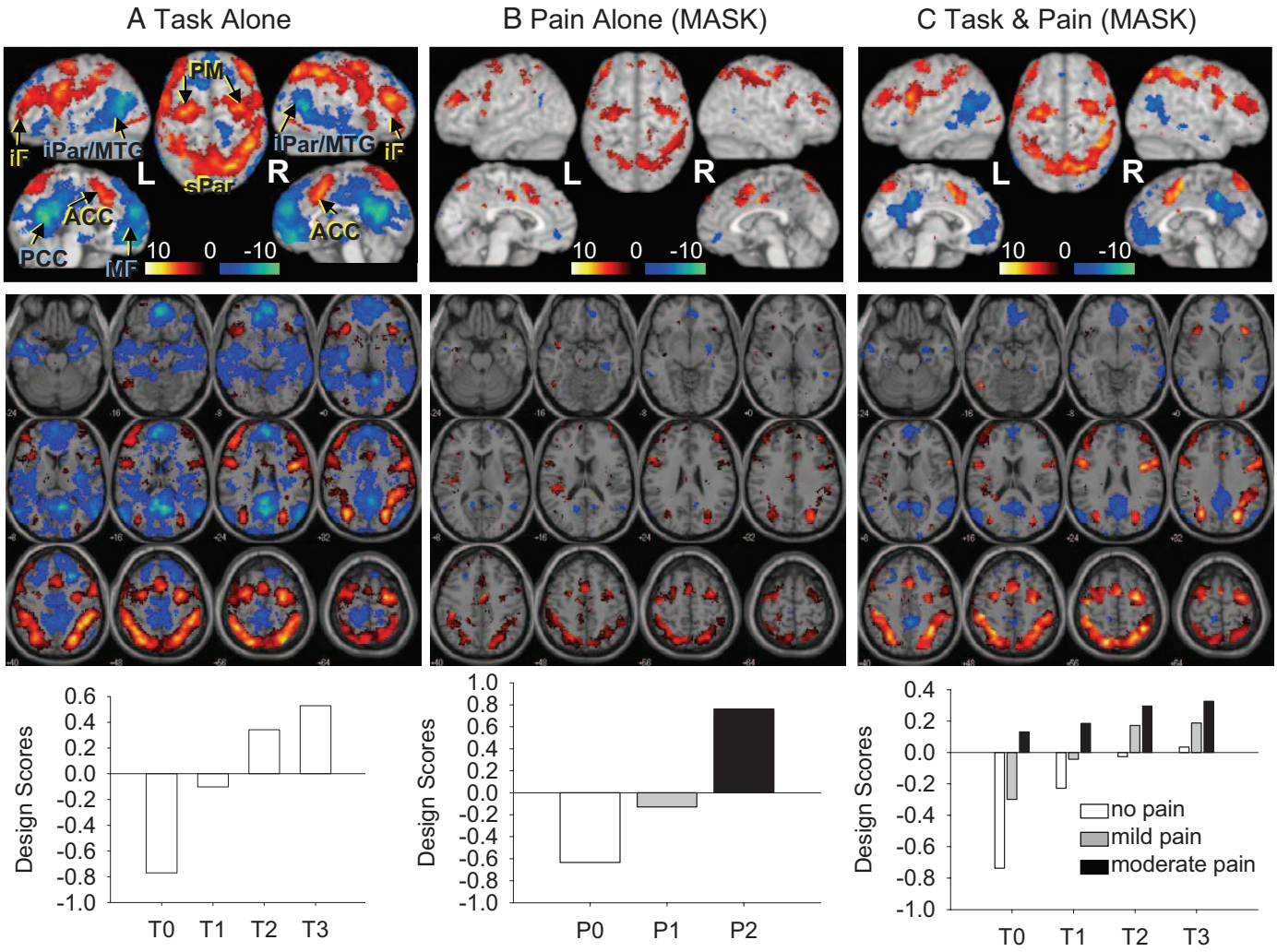

FIG. 1. Pain and cognitive load activate an intrinsic task-negative/task-positive network. An attention-specific network was identified in a partial least squares analysis with 4 levels of cognitive demand in a pain-free state and displayed as a covariance map (bootstrap threshold = 1.96, color scale shows bootstrap ratio (approximately equal to z-score)). *A*: design scores (*bottom*) indicate how the covariance pattern was represented by each condition. For example, for T0, the design score value was negative, so blue areas co-vary positively with this task and red areas co-vary negatively with the task and with the blue areas; T3 covaried most strongly with the task-positive network (red) and negatively with the task-negative network (blue). From this spatial pattern of activity, a mask was created, including only those voxels that were significantly associated with the design. *B*: conditions with no, mild, and moderate pain during the control task (lowest cognitive load) were included in the analysis in which the mask was applied to limit the areas to the task-positive and -negative networks. The design scores (*bottom*) indicate that as pain increases, activity in the task-positive network also increases (with 1 difference: bilateral S2/posterior insula are included in the task-positive here, whereas those regions were part of the task-negative network identified using only task conditions). Thus pain alone activates the task-positive network. *C*: all pain and task conditions. The results indicate that task difficulty is associated with increased activity of the task-positive network and reduced activity in the task-negative network, and pain further activates the task-positive network, and suppresses the task-negative network. iF, middle/inferior frontal, iPar/MTG, inferior parietal/middle temporal gyrus, ACC, anterior cingulate cortex, PM, premotor cortex, MF, medial frontal, PCC, precuneus/posterior cingulate cortex, sPar, superior parietal.

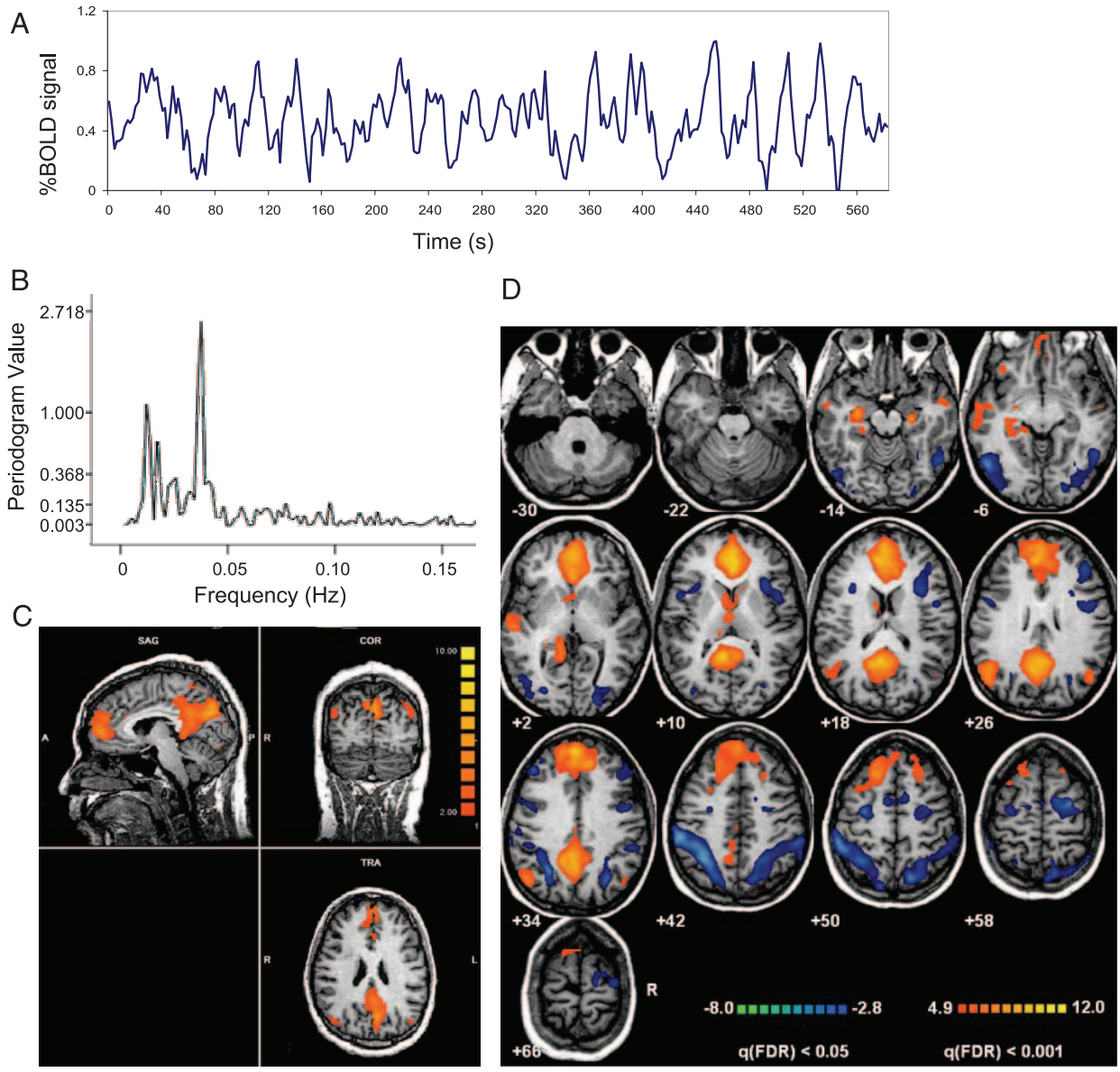

FIG. 2. Independent component analysis (ICA) results. One independent component of interest (default mode or task-negative network; single run from one subject), showing the time course (*A*) and its spectral analysis (*B*) and the spatial map (*C*) (*z* values shown in color bar). The periodogram in *B* shows the relative amount of variance each frequency contributes to the signal. *D*: resultant map from general linear model (GLM} of the task-negative network independent component time course. The analysis is based on all 23 subjects (63 runs), and each individual's time course is used. This figure shows an intrinsic network with anti-correlated task-positive (blue) and task-negative (red) parts. Numbers below each slice refer to the Talairach *z* coordinate. Color bars show *t*-scores.

RESULTS

Mean reaction times for each of the tasks without pain were 422, 531, 823, and 856 ms for tapping, easy, moderate, and difficult tasks, respectively, and pain did not significantly affect task performance (see Seminowicz and Davis 2006).

In the first step of our PLS analyses, we identified a network (LV 1, $P < 0.001$) using only the task conditions (T0, T1, T2, T3) without pain (Fig. 1*A*). This analysis extracted a network remarkably similar to the so-called intrinsic network reported recently (Fox et al. 2005; Fransson 2005) and consisted of task-negative and -positive parts. The task-negative part correlated negatively with task and positively with the control condition and included precun/PCC, MF, and inferior parietal/temporal area. The task-positive part correlated positively with task and negatively with the control condition and included middle/inferior frontal (iF), superior parietal (sPar), premotor (PM), and bilateral anterior insula (aIC) cortices. This network is henceforth referred to as the attention-specific network, consisting of task-negative and -positive parts.

We next wished to test how pain affected the attention-specific network. To restrict our analyses to only that network and exclude the contribution of potentially pain-related activations per se, we used a mask from the preceding results. We then ran a task PLS analysis including only the pain conditions during the control task (Fig. 1*B*). The task-positive network was activated by increasing pain intensity, and the task-negative was slightly reduced. This indicates that pain alone has similar effects on a task-related network as does performing a

cognitive task. One area that differed was bilateral secondary somatosensory cortex/posterior insula (S2/pIC), which was part of the task-negative network with task conditions and had decreased with increasing task difficulty, while increased pain intensity led to increased activity in this area.

To investigate how pain and cognitive task performance interact in terms of affecting activity in these networks, we performed a PLS analysis including all 12 task and pain conditions, again using the mask described preceding text to include only the areas identified as part of the task-positive and -negative networks. The results indicate that pain further activated the task-positive network (Fig. 1*C*). In other words, activity in this network increases with increased task difficulty and further with increasing pain intensity.

Finally, to show that the attention-specific network we identified could also be identified in a model-free analysis and consisted of two anti-correlated parts, we used an entirely data-driven method, ICA, to interrogate brain activity for a resting state-like pattern. Unlike PLS, which uses the data averaged within blocks, ICA isolates spatial patterns based on regional activity throughout the entire functional run. In 63 of 66 runs, we found a highly reliable pattern similar to the task-negative network, including MF, precun/PCC, and bilateral iPar. Figure 2, *A–C*, shows, for one run of one subject, the time course of the IC of interest as well as the spectral analysis and the component spatial pattern. These component time courses were then entered in a random effects GLM analysis, which revealed the same attention-specific network as preceding text with task-negative and -positive parts (Fig. 2*D;* Table 2), occurring at low frequencies (~0.03–0.08 Hz) not directly related to the task conditions. This shows that an intrinsic "resting state" anti-correlated network operates across multiple conditions. To demonstrate the anti-correlated nature of the network, Fig. 3 presents the extracted blood-oxygenation-level-dependent (BOLD) signals for two regions over a whole run with one region belonging to the task-negative network (PCC/precun, blue line) and the other to the task-positive network (pPar, red line). These data from a single subject demonstrate the anti-correlated activity of these two regions.

DISCUSSION

This study has identified an attention-specific network that has task-positive and -negative parts and showed that the network is modulated by cognitive load and pain. The network was identified using two different multivariate techniques, each of which revealed specific characteristics. The task PLS results indicate that with increasing cognitive demand, the task-positive network activity is increased and the task-negative network deactivated. Pain alone has a similar effect on this attention-specific network, and, most importantly, the interaction of pain and cognitive load further activates this network. ICA analysis confirmed that the network could be identified in a model-free analysis, using whole time-course data. The frequency of the two anti-correlated networks identified is consistent with previous reports (~0.03–0.08 Hz) (Fox et al. 2005; Fransson 2005). These data provide the first evidence that pain can modulate a network presumed to be involved in focused (task-positive) or general self-environmental attention (task-negative).

These findings provide a new view to understand the brain mechanisms underlying pain-cognition interactions. It appears that in the context of this network, the effect of pain is similar to the effect of an additional load. According to Eccleston and Crombez (1999), pain should affect cognitive ability because it is an attention-demanding process that utilizes resources shared with cognition. However, our previous fMRI study showed that pain does not significantly attenuate cognitive-related activations (Seminowicz and Davis 2006; Seminowicz et al. 2004), although other studies using event related potentials have

TABLE 2. *Significantly activated clusters in the GLM ICA analysis*

	Region Name	BA	R/L	No. of Voxels	*x*	*y*	*z*
Task-positive regions							
Frontal	Superior/inferior frontal		R	11584	39	19	22
	Superior frontal	9	L	1052	−41	39	33
	Inferior frontal	9	L	1392	−47	4	30
	Supplementary motor	6	L	133	−11	−7	61
	Supplementary motor	6	R	8250	18	−4	56
	Premotor	6	L	2230	−28	−7	52
Parietal	Inferior parietal	40	L	21119	−38	−48	44
	Superior parietal	7	R	19012	30	−54	45
Insula	Anterior insula	13	L	1201	−37	15	13
Occipital	Middle occipital	18	L	372	−28	−79	1
	Inferior occipital	19	L	7475	−44	−71	−5
	Inferior occipital	19	R	7048	36	−72	−5
Task-negative regions							
Medial prefrontal	Medial frontal	9	L	56984	−3	42	26
Posterior cingulate/precuneus	Posterior cingulate	29	L	32180	−8	−47	19
Frontal	Inferior frontal	47	L	429	−36	24	−8
Temporal	Superior temporal	21	R	907	55	−6	−10
	Superior temporal	21	L	3638	−57	−16	−3
	Middle temporal	39	R	1246	44	−65	27
	Middle temporal	39	L	5626	−49	−61	27
	Hippocampus		R	538	25	−18	−12
Subcortical	Caudate		R	160	11	16	13
	Caudate		L	2979	−3	1	9

$P < 1\times10^{-8}$ for every cluster; GLM, general lineas model; ICA, independent component analysis. Number of voxels are 1 mm^3.

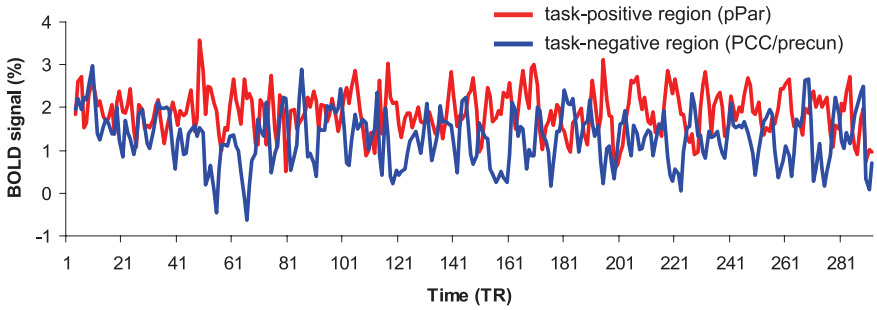

FIG. 3. Example time course blood-oxygen-level-dependent (BOLD) activity of 1 region from the task-negative network (PCC/precun, blue line) and another region from the task-positive network (pPar, red line), illustrating the anti-correlated activity between the 2 regions. The data are from a single run of 1 subject. TR = 2 s.

shown that pain modulates cognitive-related potentials (Houlihan et al. 2004; Lorenz and Bromm 1997). Furthermore, the behavioral results (reaction time, accuracy; see Seminowicz and Davis 2006) indicate that pain did not affect performance of the task. Thus it seems plausible to speculate that when pain occurs, one must engage this network to a stronger degree to maintain task performance. Further studies need to link associated intrinsic networks with a behavioral outcome, such as pain responsiveness and sensitivity. Our results clearly demonstrate the utility of using network modulation analysis to examine pain-cognition interactions.

Another possible interpretation of the task-positive network is that it is involved in arousal, rather than attention, specifically. That pain activates this network would be in keeping with its effects on arousal. The noradrenergic arousal system has widespread brain stem-cortical projections (see Robbins 1997), and neuroimaging studies have demonstrated brain stem, thalamic, cingulate, prefrontal, and parietal activations associated with various types of arousal (Tracy et al. 2000). Furthermore, manipulating arousal pharmacologically or otherwise can affect attention and task performance (see Coull 1998). The use of blocks of electrical stimuli to evoke pain likely reduces the impact of the initial alerting effect of pain onset that would be encountered in an event-related design. We could not, however, discount the possibility that the effects we report were due in part to an effect on arousal. Future studies that include measures of autonomic tone can provide some insight into this possibility.

Network analysis provides some information not accessible to univariate methods, such as those results we reported previously (Seminowicz and Davis 2006). An ROI analysis can determine how each individual region is affected by task and pain. For example, if each region is considered to be linked with a unique behavior, then affecting activity in that specific region would directly change the associated behavior. A different approach is used in a network analysis, which considers the role of sets of regions working in unison (Friston and Price 2001; McIntosh 2004). For example, the medial prefrontal cortex has been shown to be involved in self-referential (emotional) processes (Fossati et al. 2003; Lane et al. 1997). Thus in the context of pain, one might expect this region to be activated. However, when one considers this region's role as part of the network involved in nonspecific attention, it is apparent why this area was deactivated by task performance as well as by pain, when attention is focused. Figure 4 summarizes the findings in this study with a comparison to the findings presented in Seminowicz and Davis (2006). In the *top panel,* results from the general linear model (GLM) are shown in which the assumption is that during the baseline condition (P0T0), regions are relatively inactive. Performance of the difficult task in the absence of painful stimulation (i.e., P0T3) resulted in the activation (shown in red, including dorsolateral prefrontal cortex, aIC, PM, anterior cingulate cortex, and pPar) and deactivation (shown in blue, including MF, iPar/middle temporal gyrus, and PCC/precun) of several regions, which were called attention-related (de)activations. Subsequent ROI analyses revealed that only two of these regions were activated significantly by moderate pain alone, and the level of activation of these regions was low compared with task performance. In conditions where the task was performed simultaneously with pain, this method revealed no significant differences in the activation levels compared with task performance alone. The darkness of the color indicates the relative strength of the activation with darker indicating a more significant activation. In the *bottom panel,* the results from the PLS analyses are summarized. Here rather than interrogating each region independently, the view is of an attention-specific network with two parts, task positive and negative. During the baseline condition, the task-negative network is active and functionally connected, whereas the task-positive is mildly deactivated. With task performance, the task-positive network becomes active, and the task-negative is deactivated. Pain alone has a similar effect as task performance, although to a smaller extent. When the task is performed during pain, the task-positive network becomes more active, and the task-negative network is further deactivated. The degree of activation and the strength of the connections are based on the saliences of given areas with higher saliences indicating stronger connections to other regions as well as in relation to the task structure.

In our previous study, we reported that pain did not significantly affect activity in cognitive-related brain areas (Seminowicz and Davis 2006). The coordinates of the peak activity in these areas were approximately the same as those in the task-positive and -negative networks reported here. But only network analysis revealed that this brain activity pattern was modulated by pain. This finding provides further support for the use of multivariate approaches in neuroimaging.

Our results provide additional information about the so-called intrinsically active, anti-correlated (task-negative/task-positive) brain network. We suggest that the task-negative part provides a network for general self-referential environmental awareness through which a person monitors his/her surroundings. The task-positive part, on the other hand, provides a mechanism for attentional focus. At rest, one might monitor the environment generally, and thus the task-negative network is active and the task positive deactivated. Conversely, when one focuses on a task or when a perception demands attention, the task-positive focusing network is activated, and the general

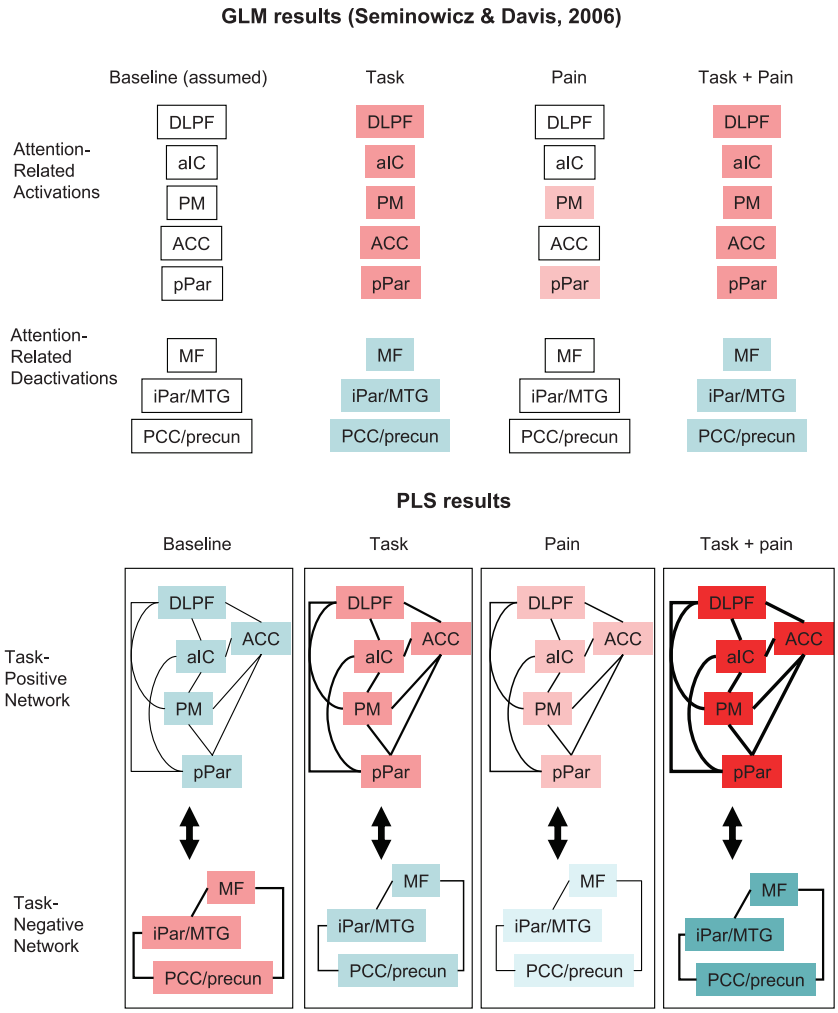

FIG. 4. Schematic comparison between the results presented in Seminowicz and Davis (2006) and the present study. The figure shows how a group of regions associated with MSIT performance behave in terms of detectable responses derived from the GLM (*top*) and in terms of network activity derived from a network analysis approach (PLS; *bottom*). Relative activity of each region is indicated by the darkness of the color (red for activation, blue for deactivation), whereas the line thickness between regions in the network analysis indicates the connectivity strength. See text for details. DLPF, dorsolateral prefrontal cortex; aIC, anterior insula cortex; pPar, posterior parietal cortex.

environmental monitoring network deactivated. This interpretation is supported by a recent imaging study of piano performance in which pianists playing a piece (focused attention) compared with playing scales (routine, unfocused) caused much greater deactivation of regions in the task-negative network, including precun/PCC and MF (Parsons et al. 2005). Although the cognitive processes involved in a complex task like piano playing are likely different from those required to perform the MSIT, the performance measures (RT, accuracy) on the MSIT conditions indicate distinct difficulty levels, which implies distinct levels of cognitive load (see Lavie et al. 2004). Our interpretation of attention-specific network function also has implications for conditions in which "resting state" attentional focus is altered, such as in patients with chronic pain in whom attention may already be focused on ongoing pain. We predict that in these patients, a more active task-positive network operates at "rest," because even in this state attentional focus is centered on pain. Because this network is already taxed, it could explain why in some chronic pain patients cognitive abilities are diminished (Dick et al. 2002).

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