Dissociating Anticipation from Perception: Acute Pain Activates Default Mode Network

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Abstract: Few studies have explored the effect of acute pain on attentional networks and on the default mode network. Moreover, these studies convey conflicting results, seemingly caused by design. To reassess this issue, we studied 20 healthy subjects with functional magnetic resonance imaging while delivering painful electric shocks. The design was purposely constructed to separate rest, anticipation, and pain perception. We found that default mode network activity in response to pain was biphasic. It deactivated during anticipation when the dorsal attentional network was activated. During pain perception, the default mode network was activated, as were attentional networks. The left posterior fusiform gyrus showed the same dynamics as the default mode network, and its activity was negatively correlated to the subject's pain intensity rating. The associative pregenual anterior cingulate cortex seemed to play a key role in these coactivations. These results concur with data from the literature showing that enhanced pain perception results in greater default mode network activity and that the anticorrelation between the default mode network and the dorsal attentional network disappears in chronic pain patients. *Hum Brain Mapp* 34:2228–2243, 2013. © 2012 Wiley Periodicals, Inc.

Key words: brain; pain; attention; default mode; anterior cingulate cortex

INTRODUCTION

Acute pain anticipation is common in clinical situations, particularly in anaesthesiology. Indeed, during presurgical management, patients expect pain in response to venous or bladder catheterization, and sometimes to mobilisation.

In this context, it is recommended to administrate anxiolytic premedication drugs in advance [Franssen et al., 1993; Kanto et al., 1996; Sokolowski et al., 2010]. These drugs alter attention and are likely to interfere with the patient's ability to anticipate and perceive pain. Thus, understanding the response to pain, and especially the effect of anticipation, is a matter of interest for clinicians.

Using fMRI, Ploghaus et al. published pioneering work in humans exploring how the cortical areas were activated by painful stimuli. To do this, they used a sequence which allowed the dissociation of anticipation from pain perception [Ploghaus et al., 1999, 2000, 2001, 2003]. However, limited knowledge at that time precluded the identification of the main structures of neuronal network dynamics. These networks were only formally identified when it became possible to combine network activity triggered by specific tasks with the analysis of spontaneous fluctuations of brain-oxygen-labeled-dependent signals in the low frequency range. Indeed, functional connectivity analysis as

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well as data-driven analysis by independent component analysis have been used to highlight the relationship between the function and the topology of neuronal networks. This data processing has shown the similarity of networks implicated in specific tasks and networks spontaneously implicated in low frequency activities [Corbetta and Shulman, 2002; Fox et al., 2006; Fox et al., 2005; Raichle et al., 2001]. Subsequently, continuing progress allowed for the performance of increasingly complex sequences to explore the interaction between pain perception and neuronal network activity [Seminowicz and Davis, 2007].

At present, only a few studies have explored the dynamics of the default mode network (DMN) in response to acute pain perception [Kong et al., 2010; Seminowicz and Davis, 2007]. The DMN is a functional network known to be active when at rest and undisturbed by external stimuli [Ingvar, 1979; Raichle et al., 2001]. It has been shown to be systematically deactivated by attention-demanding tasks [Shulman et al., 1997]. Furthermore, resting state functional connectivity (RSFC) analysis has shown that spontaneous DMN activity in the low frequency range is anticorrelated to that of the spatial orienting dorsal attentional network (dATT) [Fox et al., 2005]. However, studies exploring the effect of acute pain on DMN dynamics have differed in design, which complicates a comparison of results. Moreover, in these studies, the authors disregarded the methodology proposed by Ploghaus et al. providing for a clear dissociation between anticipation and the perception of pain. Rather, these two components were merged, leading to potentially conflicting results.

Indeed, Seminowicz et al. [2007] found that the interaction between pain and a cognitive-demanding task both enhances dATT network activity and reduces DMN activity as the pain and cognitive loads increase. Conversely, Kong et al. [2010], when studying the effect of pain intensity on DMN activation, found an intriguing and counter-intuitive result: high-intensity pain decreased DMN activity to a lesser extent than did moderate-intensity pain. Therefore, Seminowicz and Kong observed opposite relationships between DMN activity and pain intensity. A recent functional connectivity analysis further contributed to this debate by showing that the activity of the pregenual anterior cingulate cortex (pACC), known to be a key region in pain control mechanisms [Peyron et al., 2007; Zubieta et al., 2005], was positively correlated to DMN activity in the resting state [Yu et al., 2011]. The aim of this study was to reconsider the issue of DMN activation in response to acute pain using the original methodology proposed by Ploghaus et al. This methodology was conceived to allow for dissociating pain anticipation from pain perception by inserting a cue before anticipation. We also allowed an anticipation period long enough to be discernible from the pain perception period. Thereby, we hoped to differentiate DMN behavior during pain anticipatory and pain perception periods as well as to solve the apparent discrepancies that are seen in the available literature.

MATERIAL AND METHODS

Subjects

Twenty neurologically intact right-handed healthy full-time physicians from our institution [5 females, 35 years, (26–56 years)] who volunteered to participate were included in this study. This study received approval from our local ethics committee and all participants provided written informed consent.

Neural Stimulus

The electric shock was delivered by a nerve stimulator (Tens Eco® Schwa Médico France™, Rouffach, France) via two carbon electrodes placed on the anterior face of the right forearm. Perception and pain thresholds were determined for each participant prior to scanning as follows. First, we evaluated the intensity allowing nonpainful perception of a 6 s, 2 Hz, 300- μ s repetitive electric shock (Shock_{Min}). The intensity of the shock was then increased in increments of 1 mA. At each intensity level, subjects were asked if they could tolerate a further increase of 1 mA in shock intensity until reaching maximal intensity tolerance (Shock_{Max}).

Task Design

The design of the task was adapted from the studies by Ploghaus et al. [Ploghaus et al., 1999, 2000, 2001, 2003].

The scanner room was kept dark during image acquisition. Subjects performed four consecutive mixed design sessions of 13 min 33 s each while lying in the scanner. Throughout the sessions, they looked through a prism at a screen displayed at their feet, facing them.

Four consecutive sessions were performed in each subject. Each session was built in the form of an m-sequence comprising three pseudorandom conditions to yield the same signal intensity whatever the condition studied [Buracas and Boynton, 2002]. The four sessions were built according to a shifted phase version of the m-sequence of reference. Each session consisted of a series of 27 sequences of 30 s each which started with a 3-s red fixation cross on a black screen. Each 30-s sequence consisted of five successive events (Fig. 1).

The first event consisted of a 3-s colored cue predictive of the intensity of the electric shock (Shock_{Min} or Shock_{Max}). For each session, a pair of colors was randomly presented to the subject who had to find and report at the end of each session the color of the cue associated with Shock_{Max}. The second event consisted of an anticipation period during which a red fixation cross appeared in the center of a black screen. This anticipation period lasted from 3 to 12 s, randomly. The third event consisted of a 6-s period of either Shock_{Max}, Shock_{Min} or no shock. The latter nil event (no shock) was evenly distributed between cue conditions: nil Shock_{Min} and nil Shock_{Max}. These nil

Figure 1.
Design of the study. See text for details

events were introduced to sustain attention throughout the session.

The fourth event consisted of a 6 s auto-evaluation of pain using a visual analogue scale (VAS) ranging from 0 to 10. Subjects were instructed (and trained before scanning) to rate perceived pain by pressing a joystick button placed in their left hand.

The fifth event consisted of a 3–12 s recovery period, complementary to the duration of the anticipatory period (for each session, the sum of anticipation and recuperation amounted to 15 s) during which the fixation cross appeared again on the black screen.

The total duration of the study was 54 min. Such a duration was justified by the need to optimize the signal-to-noise ratio, considering that we used a low magnetic field MRI scan, and also because of the scarcity of the painful events used to sustain the subject's attention. We also considered the possible bias resulting from patients learning the composition of the sequence schemes within each session. To minimize this effect, we used encrypted sessions (m-sequences).

The task was programmed using E-Prime 2.0TM software (Psychology SoftwareTools[®], Pittsburgh, PA), implemented for Windows XPTM and displayed on the screen via a personal computer and a video projector.

fMRI Acquisition

All datasets were acquired on a 1.5 T MR scanner (Magnetom Avanto[®], Siemens Medical SystemsTM, Erlangen,

Germany) equipped with a circular polarized head coil. An echo planar imaging sequence was used to acquire functional series in each participant (repetition time 3000 ms, echo time 50 ms, flip angle 90°, 32 axial slices interleaved, 5.0 mm thick, 0 mm gap, in a 64 × 64 plane matrix, yielding a voxel size of 3 × 3 × 5 mm³, field of view 240 mm), covering the whole brain including the cerebellum. We acquired four runs of 272 functional volumes per session. A T1-weighted anatomical three-dimensional data set covering the whole brain was also obtained (176 contiguous axial slices, 256 × 256 in-plane matrix, yielding a voxel size of 1 × 1 × 1 mm³) to coregister and normalize echo planar images.

Image Preprocessing

fMRI data were analyzed using SPM5TM (Wellcome Department of Imaging Neuroscience, University College, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>) running under MatlabTM (The MathWorks[®], Natick, MA). The three first acquisition volumes of each functional series were discarded to allow for stabilization of longitudinal magnetization.

Preprocessing was conducted as follows. First, each volunteer's native space images were corrected for the time delay between different slices. Then, they were realigned to the first volume and unwrapped to correct for head movements and susceptibility distortions. The anatomical dataset was segmented using VBM 5.0 toolbox for SPM[®]. Coregistration of images from different modalities was

achieved using gray matter segmentation as reference images and mean echo planar of slice-timed and motion-corrected unwrapped images as source images. Normalisation of echo-planar images to the standard template provided by the Montréal Neurological Institute (MNI template) was then based on the co-registered grey matter segments. Functional images were written out to a final resolution of $3 \times 3 \times 3 \text{ mm}^3$ before being smoothed by an isotropic Gaussian kernel of 8 mm full-width at half-maximum.

fMRI Analysis

A general linear model approach was used. For each individual, a time series of preprocessed data sets was analyzed by voxel-wise multiple regression. Data from the four sessions performed in each subject were entered in a single first-level analysis. Regressors corresponding to each of the 10 conditions were convolved with a model of canonical haemodynamic response incorporated in the SPM package. Low frequency noise was removed by high-pass filtering with a 128 s cut-off. No global signal normalization was applied. The conditions were the five successive epochs of a trial for the two modalities of shock (Shock_{Max} and Shock_{Min}): Cue, Anticipation, Shock, Rating, and Rest.

To obtain an overview of activation more specifically related to pain, elementary contrasts were individually determined using *t*-tests between the two modalities Shock_{Max} and Shock_{Min} for Cue, Anticipation and Shock (contrasts: Cue_{ShockMax} > Cue_{ShockMin}, Anticipation_{ShockMax} > Anticipation_{ShockMin}, Shock_{Max} > Shock_{Min}).

The dynamics of DMN activity in the Shock_{Max} trials were obtained by computing the contrast between Rest, Cue, Anticipation, and Shock_{Max} (contrasts: Rest > Anticipation_{ShockMax}, Anticipation_{ShockMax} > Cue_{ShockMax}, Rest > Shock_{Max} and also Shock_{Max} > Anticipation_{ShockMax}).

The 20 individual contrast images resulting from the first-level analysis were included in a second-level random effect analysis comparing within group activation with a one-sample *t*-test. Second-level analysis also included multiple regressions of the contrast Shock_{Max} > Shock_{Min}, using the means of the 36 VAS ratings obtained in each subject as the explicative covariates.

All tests were FDR-corrected for multiple comparisons with a minimum cluster extent of five contiguous voxels. Considering robust activation, contrasts between Shock_{Max} and Shock_{Min} trials were restrictively corrected with a voxel-wise threshold of $P < 0.001$. All other tests were corrected with a voxel-wise threshold of $P < 0.05$.

Identification of activated areas and cluster extent were processed using the ANATOMY toolbox v1.5 for SPM. Within the cingulate cortex, the pACC and anterior mid-cingulate cortex (aMCC) were identified using the criteria of Yu et al. [2011]. Subcortical areas not matching any probability map were manually identified using the MRI-

croN template and coordinates available in the literature [Fairhurst et al., 2007]. In the case of multiple local maxima in the same anatomical area within a cluster, only coordinates of peak activity are reported in the tables. The same toolbox allowed us to extract the time course of percent signal change in selected regions of interest. A one-way ANOVA of percent signal change between periods of interest was performed using Prism4® (GraphPad™).

RESULTS

Shock_{Min} was obtained at 1 mA except in two subjects who perceived Shock_{Min} at 2 mA. The mean maximal Shock_{Max} was $24 \pm 9 \text{ mA}$ (13–45 mA).

The mean Shock_{Max} VAS rating was 5.1 ± 1.3 (3.1–7.9). Shock_{Min} was rated 0 except in two subjects who occasionally rated 1. No correlation was found between the Shock_{Max} rating and stimulation intensity ($r = 0.12$, $P = 0.61$).

Contrasts Between Shock_{Max} and Shock_{Min} Trials

Cue

Cuing Shock_{Max} compared with cuing Shock_{Min} showed an increased fMRI signal in a set of regions including the left somatomotor cortex, right supplementary motor area (SMA), bilateral insulo-opercular regions (FIC), thalamus and junction of the midcingulate/anterior cingulate cortex, which we refer to as the anterior midcingulate (aMCC). The FIC, thalamus and aMCC are known to belong to a cingulo-opercular network also referred to as the salience network [Dosenbach et al., 2007; Dosenbach et al., 2008; Seeley et al., 2007; Sridharan et al., 2008] (Fig. 2 and Supporting Information Table I).

Anticipation

Shock_{Max} anticipation induced a large fMRI signal increase in somatomotor areas and, compared with the previous contrast, a further increase in areas of the salience network including the aMCC in association with subcortical structures (Fig. 3A and Supporting Information Table II).

Shock perception

Shock_{Max} produced an increase in the fMRI signal in the somatomotor network including the bilateral SMA and primary motor cortex and right, but not left, primary sensory cortex. The signal was increased in the FIC, with a marked right lateralization, and in subcortical networks. The signal was also increased in key elements of the dATT including the bilateral frontal eye fields (FEF) and the bilateral superior parietal gyrus/intraparietal sulcus [Corbetta et al., 2002; Paus, 1996]. In the vision-associated network, a bilateral increase was observed in the extrastriate occipital cortex. The dorsolateral prefrontal cortex

Figure 2.

Contrasting $\text{Cue}_{\text{ShockMax}} > \text{Cue}_{\text{ShockMin}}$. Enhanced activity for cuing $\text{Shock}_{\text{Max}}$ as compared with cuing $\text{Shock}_{\text{Min}}$ is shown in hot. aMCC, anterior midcingulate cortex; FIC, fronto-insular cortex; THAL, thalamus. The left sides of the axial and coronal images correspond to the left side of the brain. Whole brain group analysis. Significant activation projected onto a template brain slice in MNI stereotactic space. Regions of interest are circled in blue. Color bar indicates T values. Activations shown at the voxel level $P_{\text{FDRcorr}} < 0.001$, cluster size threshold five voxels.

(DLPFC), ventral frontal cortex (VFC) and inferior parietal cortex at the temporoparietal junction (supramarginal gyrus) were activated with a right lateralization. Such an activation pattern has been reported to be characteristic of the ventral attention system (vATT) [Fox et al., 2006] or “stimulus-driven attentional system” [Asplund et al., 2010]. A large increase in signal was observed bilaterally in the cerebellum. Finally, the signal increased in the pregenual anterior cingulate cortex (pACC) (Fig. 4 and Supporting Information Table III).

Rest, $\text{Cue}_{\text{ShockMax}}$, $\text{Anticipation}_{\text{ShockMax}}$, and $\text{Shock}_{\text{Max}}$

$\text{Anticipation}_{\text{ShockMax}} > \text{Cue}_{\text{ShockMax}}$ resulted in an increased signal in key elements of the dATT including the bilateral frontal eye fields (FEF) and bilateral superior parietal gyrus/intraparietal sulcus (Fig. 3B) as well as in a set of areas described in Supporting Information Table IV.

$\text{Rest} > \text{Anticipation}_{\text{ShockMax}}$ resulted in an increased signal in the posterior cingulate, frontal medial-orbital cortex, hippocampus, parahippocampus and angular gyri, which are areas that are known to be elements of the DMN, and also in the visual striate/extrastriate cortex, including the lingual and fusiform gyri [Margulies et al., 2009] (Fig. 5A, Table I).

$\text{Rest} > \text{Shock}_{\text{Max}}$ resulted in no area demonstrating an increase in the fMRI signal. This suggests a signal increase

within the DMN in the $\text{Shock}_{\text{Max}}$ condition in comparison with the preceding condition ($\text{Anticipation}_{\text{ShockMax}}$).

To see how the regions of the DMN which were deactivated during pain anticipation were reactivated during pain reception, we inclusively masked the contrast $\text{Shock}_{\text{Max}} > \text{Anticipation}_{\text{ShockMax}}$ with the binary mask of the contrast $\text{Rest} > \text{Anticipation}_{\text{ShockMax}}$. The $\text{Rest} > \text{Anticipation}_{\text{ShockMax}}$ contrast revealed the DMN. Using the binary mask issued from the $\text{Rest} > \text{Anticipation}_{\text{ShockMax}}$ contrast on $\text{Shock}_{\text{Max}} > \text{Anticipation}_{\text{ShockMax}}$ should only reveal the DMN zones with increased signal during $\text{Shock}_{\text{Max}}$ by comparison to $\text{Anticipation}_{\text{ShockMax}}$.

Most regions deactivated during $\text{Anticipation}_{\text{ShockMax}}$ relative to Rest were reactivated during pain perception, but to a lesser spatial extent in the ventromedial prefrontal cortex (Fig. 5B, Table II).

VAS and Regression Analysis

Regression analysis of the $\text{Shock}_{\text{Max}} > \text{Shock}_{\text{Min}}$ contrast by mean individual VAS disclosed a negative correlation in a set of clusters distributed over the whole brain (Fig. 6, Table III). Among these clusters, the posterior ones comprised the left posterior fusiform gyrus, left lingual gyrus, posterior precuneus, and hippocampal formation. The anterior ones comprised the bilateral ventral tegmental area/locus niger (VTA/LN), bilateral caudate, pACC and medio-dorsal thalamus. All these clusters are known to be parts of dopaminergic pathways [O’Doherty, 2004; Haber and Knutson, 2010; Schultz, 2000].

The strongest negative correlation was found in the posterior part of the left fusiform gyrus ($r = -0.9$, $P < 0.0001$). Figures 5A,B and 6D show that the posterior part of the left fusiform gyrus demonstrated the same pattern of deactivation/reactivation as the DMN during pain anticipation and pain perception, respectively.

Time Course of the fMRI Signal

The time course of fMRI signal change in key elements of the DMN across conditions is shown in Figure 7A,B. It confirms a decrease in the fMRI signal during $\text{Anticipation}_{\text{ShockMax}}$ compared with Rest and an increase in the fMRI signal produced during $\text{Shock}_{\text{Max}}$ compared with $\text{Anticipation}_{\text{ShockMax}}$ in the main regions of interest of the DMN. During $\text{Shock}_{\text{Max}}$, the signal in the posterior cingulate, ventromedial prefrontal cortex, and left angular gyrus returned to a level not different to that of the Rest condition, indicating the return to baseline activity in these regions. In all other regions of the DMN, during $\text{Shock}_{\text{Max}}$, the fMRI signal was of greater magnitude than in the Rest condition, thus indicating overactivation of these regions.

DISCUSSION

Our main finding was that a number of cerebral regions, including the bilateral precuneus, posterior cingulate,

Figure 3.

Pain anticipation-related activity. **A:** Contrasting Anticipation- $\text{Shock}_{\text{Max}} > \text{Anticipation}_{\text{Shock}_{\text{Min}}}$; enhanced activity for anticipating $\text{SHOCK}_{\text{Max}}$ as compared with anticipating $\text{SHOCK}_{\text{Min}}$ is shown in hot. aMCC, anterior midcingulate cortex; FIC, fronto-insular cortex; medTHAL, medial thalamus; postCG, post-central gyrus; roLOP, rolandic operculum; VTA, ventral tegmental area; RVMM, rostro-ventral medial medulla. Activations shown at the voxel level $P_{\text{FDRcorr}} < 0.001$, cluster size threshold five voxels. **B:** Contrasting Anticipation- $\text{Shock}_{\text{Max}} > \text{Cue}_{\text{Shock}_{\text{Max}}}$; enhanced activity

for anticipating $\text{Shock}_{\text{Max}}$ as compared with cuing $\text{Shock}_{\text{Max}}$ is shown as hot. FEF: frontal eye fields, SIPS: superior intraparietal sulcus. Arrows: central sulcus (in yellow) and superior frontal sulcus (in white). Activations shown at the voxel level $P_{\text{FDRcorr}} < 0.05$, cluster size threshold five voxels. Whole brain group analysis. Significant activation projected onto template brain slices in MNI stereotactic space. Regions of interest are circled in blue. Color bar indicates T values. The left sides of the axial and coronal images correspond to the left side of the brain.

hippocampal formation, bilateral angular gyri, and ventromedial prefrontal cortex, are deactivated during pain anticipation and then reactivated during pain perception. All these regions belong to the DMN [Fox et al., 2005; Raichle et al., 2001]. The DMN is known to be active when subjects are awake and resting undisturbed. In this state, subjects are left to their internal mentation. When this state is interrupted by a salient external stimulus, the dATT is activated and the DMN is deactivated [Corbetta et al., 2002a; Fox et al., 2005; Raichle et al., 2001]. It is worth noting that dATT is known to be activated during a voluntary outward redirection of subjects' attention [Astafiev et al., 2003; Corbetta et al., 2000, 2005; Shulman et al., 1999, 2003]. The first observation of the deactivation of a key element of the DMN during anxious anticipation was made by Simpson et al. [2001]. These authors showed that an anxious anticipation of pain reduced the activity of the medial prefrontal cortex. This decrease in activity was inversely correlated to the clinically assessed level of anxiety. The decrease in activity of the ventromedial prefrontal component of the DMN, during the pain anticipation we

observed in our study, matches the findings of Simpson et al. However, we did not score anxiety in our subjects and thus cannot further compare our results to those of Simpson et al.

We observed activation of the salience network after cuing. This activation arose during the anticipation phase. Within the salience matrix, the anterior insula transforms information about the nature of salience into perceptual decisions about pain [Wiech et al., 2010]. Moreover, the salience matrix is known to be a crucial inhibitor of the DMN [Menon and Uddin, 2010; Sridharan et al., 2008]. In our study, pain anticipation and pain perception were both salient stimuli from the external world. Accordingly, DMN deactivation is expected during anticipation. However, reactivation of the DMN (to a superior or equal level for some regions compared with DMN activity at rest) observed during pain perception has not been described.

Before discussing our results further, one could ask whether the clusters which were deactivated during anticipation are core components of the DMN. Indeed, it has been shown that the DMN can be subdivided into distinct

Figure 4.

Contrasting $\text{Shock}_{\text{Max}} > \text{Shock}_{\text{Min}}$. **A:** Axial and coronal views; the left sides of the images correspond to the left side of the brain. Arrows: central sulcus (in yellow) and superior frontal sulcus (in white). **B:** Right and left sagittal view showing right lateralisation of insular and frontal activity. pACC, posterior anterior cingulate cortex; DLPFC, dorso-lateral prefrontal cortex; FEF, frontal eye fields; FIC, fronto-insular cortex; SIPS, superior intra-

parietal sulcus; SMG, supra-marginal gyrus. Whole brain group analysis. Significant activation projected onto template brain slices in MNI stereotactic space. Regions of interest are circled in blue. Color bar indicates T values. Enhanced activity for $\text{Shock}_{\text{Max}}$ as compared with $\text{Shock}_{\text{Min}}$ is shown in hot. Activations shown at the voxel level $P_{\text{FDRcorr}} < 0.001$, cluster size threshold five voxels.

subsystems: functional connectivity analysis using different seed ROI of the DMN results in partially overlapping maps [Buckner et al., 2008]. Cyto-architectural studies of the precuneus have revealed that this structure is composed of distinct areas with considerable variations in their position relative to macroanatomical landmarks [Scheperjans et al., 2008a,b]. However, a recent high-resolution connectivity analysis across the precuneus and posterior cingulate also revealed distinct connectivity patterns. Interestingly, the posterior cingulate ROI is the only area to demonstrate functional connectivity with the limbic system and ventromedial prefrontal cortex, typical of DMN structures. This suggests that the precuneus is not a core component of this network [Margulies et al., 2009].

If we apply these more stringent criteria in defining the DMN, we observe that key elements of the DMN (posterior cingulate, frontal medial-orbital cortex, hippocampus, parahippocampus, and angular gyri) effectively undergo anticipatory deactivation. The same set of areas appears to be reactivated during pain reception, however to a lesser extent in the frontal orbito-medial cortex. From this, we can note that the observation of DMN reactivation in response to painful stimuli was made possible by the

design purposely chosen for our study. Indeed, this design included two salient stimuli. The first one consisted of a priming cue (announcing a painful stimulus) followed by a waiting period (anticipation) of random duration. The second salient stimulus was the painful stimulus itself. The priming cue is important as it allows the separation of the resting period which follows a shock from the period corresponding to the expectation and anticipation of the next shock.

Using this design, we observed the expected increase in dATT activity during anticipation and a deactivation of the DMN. When pain perception occurred, the DMN was, surprisingly, reactivated, whereas the dATT remained activated. DMN activity during pain perception appeared to be of the same magnitude as during the Rest condition in the posterior cingulate, ventromedial prefrontal cortex, and left angular gyrus and of greater magnitude in the remaining regions of interest constituting the DMN (Fig. 7A,B).

These facts differ from those reported in the literature, probably as the result of different study designs. Semiovitz and Davis showed that the delivery of a painful stimulus when subjects performed a cognitive task led to an

Figure 5.

A: Contrasting Rest > Anticipation_{ShockMax}: decreased activity for Anticipation_{ShockMax} as compared with Rest is shown in blue. Deactivations are shown at the voxel level $P_{FDRcorr} < 0.05$, cluster size threshold five voxels. **B:** Contrasting Shock_{Max} > Anticipation_{ShockMax} (calculated at the voxel level $P_{FDRcorr} < 0.05$, cluster size threshold five voxels) masked inclusively by contrasting to Anticipation_{ShockMax} < Rest. Enhanced activity for Shock_{Max} as compared with Anticipation_{ShockMax} in areas showing decreased activity for Anticipation_{ShockMax} relative to Rest

are shown in hot. Whole brain group analysis. Significant deactivation and activation projected onto template brain slices in MNI stereotactic space. Regions of interest are circled in red for deactivation and blue for activation. Color bar in blue indicates T-values for deactivation, color bar in hot indicates T-values for activation. The left sides of the axial and coronal images correspond to the left side of the brain. PHP, para-hippocampal gyrus; ANG, angular gyrus; PCC, posterior cingulate cortex; FMO, frontal medio-orbital gyrus.

interaction between these two phenomena: DMN activity decreased in parallel with an increase in pain stimulus intensity and of cognitive task difficulty. The design of this study, in contrast to ours, did not allow for the separation of the resting state, anticipation and pain perception. Moreover, the tapping task at rest and the interaction between pain and the performance of a demanding cognitive task could have diverted the subject's attention from the painful stimulus. It could also change the dynamics of the activation/deactivation status of the dATT/DMN.

Kong et al. [2010] explored DMN activation using two levels of painful stimuli. They found that pain was associated with deactivation in regions corresponding to the core of the DMN. They reported an unexpected finding: the DMN was more profoundly deactivated by a mid-level intensity painful stimulus than a high-intensity one. However, the design included a priming cue presented at the beginning of each painful stimulation. In such a design, anticipation induced by a visual cue and pain cannot be separated and are thus merged.

The results of the study of Kong et al. seem to be explained by the opposite effects of pain anticipation and

pain perception: anticipation deactivates the DMN whereas pain activates it proportionally to pain intensity. Hence, only a design allowing separate and successive steps from anticipation to pain perception allows for assessing the transitory states of the DMN and dATT.

This finding is supported by two more recent studies. Berna et al. [2010] explored a paradigm using induced acute depression in conjunction with a painful stimulus. Such an acute depression resulted in more intense perceived pain, which in turn reduced the level of DMN deactivation. The second study, by Baliki et al. [2008], addressed the case of patients suffering from chronic pain. This state sharpened the correlation between the DMN and dATT.

Overall, these studies lead to the conclusion that when the context enhances pain perception (high-intensity electric shock in Kong et al. and potentialization of pain perception by a depressed mood in Berna et al.), the DMN is more intensively activated. Moreover, acute and chronic pain seem to share a common condition, i.e., the disappearance of the classic anticorrelation between DMN and dATT. The fact that a salient external stimulus such as a

TABLE I. Significant activation peaks of contrast rest > anticipation_{ShockMax}

Region	T^{19}	Cluster size	x	y	z
Left cuneus	8.9	3410	3	-93	21
Right superior occipital gyrus	7.12		24	-96	12
Left angular gyrus	6.63		-42	-72	42
Left fusiform gyrus	6.6		-30	-39	-18
Right precuneus	6.42		3	-60	33
Right cuneus	6.18		9	-84	39
Left inferior occipital gyrus	6.11		-36	-75	-9
Right calcarine gyrus	5.69		21	-93	3
Left parahippocampal gyrus	5.65		-30	-24	-18
Right middle occipital gyrus	5.44		33	-81	33
Right fusiform gyrus	5.38		33	-36	-15
Left superior parietal lobule	5.24		-27	-78	48
Right angular gyrus	5.06		54	-66	27
Right hippocampus	4.99		27	-33	0
Right inferior occipital gyrus	4.71		39	-72	-9
Right lingual gyrus	4.64		15	-84	-9
Left hippocampus	4.57		-24	-36	-3
Left lingual gyrus	4.54		-9	-48	3
Left calcarine gyrus	4.43		-12	-51	6
Left caudate	4.33		-12	24	-9
Left precuneus	4.26		-3	-75	51
Left superior occipital gyrus	4.05		-15	-90	33
Left middle/posterior cingulate cortex	3.35	302	0	-42	36
Right rectal/medial orbito frontal gyrus	8.59		3	45	-15
Left rectal/medial orbito frontal gyrus	7.78		-12	45	-15
Left caudate	4.33		-12	24	-9
Right superior medial frontal gyrus	3.8	158	9	54	3
Right olfactory cortex	3.21		6	24	-6
Left middle frontal gyrus	5.58		-24	27	54
Left superior frontal gyrus	4.12		-21	39	45
Left middle frontal gyrus	3.53		-21	30	39
Right superior frontal gyrus	5.93		18	42	45
Right hippocampus	4.89		33	-15	-21
Right middle temporal gyrus	4.33		60	-9	-24
Right inferior temporal gyrus	3.84		54	-12	-27
Left superior medial frontal gyrus	3.95		-12	60	18
Left inferior temporal gyrus	3.85	5	-51	-3	-30

Voxel level $P < 0.05$ FDR corrected, cluster-size threshold 5 voxels; T^{19} value = T value for 19° of freedom; in case of multiple peaks in the same anatomic area of a cluster, only maximal peak is reported for this anatomic area; x,y,z = the original SPM coordinates in millimeters of the MNI space.

painful stimulus activates the DMN may seem surprising. We suggest that the duration of the painful stimulation may not only represent a salient phenomenon, but induces the search for an alternative strategy to escape pain. Thereby, attention is probably redirected towards the volunteer's self, resulting in an increase in DMN activity. This corresponds to the interpretation made by Kong et al. regarding the proportional relationship between DMN activity and the magnitude of pain intensity. The anterior cingulate cortex seems to be the structure involved in the coordination between the attentional networks responding to external inputs and the DMN. Indeed, the anterior cingulate cortex presents an anatomical and functional organisation [Bush et al., 2000; Devinsky et al., 1995]; its caudal parts comprise a "cognitive" division (aMCC) involved in

the attentional processes common to attention and pain [Davis et al., 1997; Kwan et al., 2000] and its rostral part (pACC) comprises an "emotional" division which is also known to be a key region involved in pain perception and control [Peyron et al., 2007; Vogt 2005; Zubieta et al., 2005]. Furthermore, within the ACC, a mutual balance of activity is observed between the pACC and aMCC [Ban-tick et al., 2002; Petrovic et al., 2008; Whalen et al., 1998]. We observed activation of the aMCC during anticipation and an elective activation of the pACC during pain perception. This was accompanied by deactivation of the DMN followed by reactivation. The study of functional connectivity has shown that pACC activity is correlated to that of the DMN, whereas aMCC activity is anticorrelated to it [Yu et al., 2011]. It is noteworthy that the pACC is the

TABLE II. Significant activation peaks of contrast Shock_{Max} > Anticipation_{ShockMax} masked inclusively with contrast Rest > Anticipation_{ShockMax}

Region	T^{19}	Cluster size	x	y	z
Right calcarine gyrus	25.38	2567	24	-93	0
Left middle occipital gyrus	23.29		-27	-87	6
Right middle occipital gyrus	21.5		33	-81	3
Left inferior occipital gyrus	21.5		-30	-87	-3
Right lingual gyrus	19.61		21	-87	-9
Left fusiform gyrus	15.73		-33	-66	-12
Right inferior temporal gyrus	14.43		45	-72	-6
Right inferior occipital gyrus	13.34		36	-78	-9
Left superior parietal lobule	12.24		-21	-75	48
Right fusiform gyrus	11.15		30	-72	-15
Right superior parietal lobule	9.86	113	18	-66	60
Right superior occipital gyrus	8.86		30	-75	42
Right hippocampus	7.96		24	-32	0
Right angular gyrus	7.76		39	-63	24
Right middle temporal gyrus	7.67		45	-57	21
Right precuneus	6.87		12	-75	51
Left calcarine gyrus	6.67		3	-84	9
Left precuneus	5.77		-12	-72	57
Left cuneus	5.38		-6	-66	24
Left angular gyrus	5.18		-48	-60	30
Right cuneus	4.88	94	15	-81	45
Right middle / posterior cingulate cortex	4.78		3	-42	36
Left middle temporal gyrus	3.88		-42	-60	21
Left lingual gyrus	3.68		-18	-69	-3
Left middle / posterior cingulate cortex	3.48		-9	-45	33
Right parahippocampal gyrus	2.59		30	-27	-18
Left fusiform gyrus	8.76	63	-30	-45	-18
Left hippocampus	7.57		-15	-36	0
Left middle frontal gyrus	5.08		-39	18	45
Left superior frontal gyrus	3.38		-18	27	42
Right superior medial gyrus	5.97		12	42	42
Right superior frontal gyrus	5.38		27	24	51
Left lingual gyrus	3.88	54	-9	-45	3
Right inferior temporal gyrus	5.28		51	-15	-24
Left rectus / medial orbito frontal gyrus	4.28		-12	45	-18
Left mid orbital gyrus	2.29		-9	48	-12
Left superior parietal lobule	6.27		-33	-66	57
Right hippocampus	3.68		30	-9	-24

Voxel level $P < 0.05$ FDR corrected, cluster-size threshold 5 voxels; T^{19} value = T value for 19° of freedom; in case of multiple peaks in the same anatomic area of a cluster, only maximal peak is reported for this anatomic area; x,y,z = the original SPM coordinates in millimeters of the MNI space.

only cingulate region which is functionally connected with all other cingulate subregions, thus allowing the exchange of information between the emotional, cognitive and sensorimotor networks and the DMN [Yu et al., 2011]. This associative pattern of the pACC may explain why, in our study, the pACC was coactivated with attentional, sensorimotor, and default mode networks in response to pain. These findings are compatible with a more general model of cerebral functioning. Friston has proposed such a general model of neural response which is structured as a hierarchical inference machine able to optimize its own representations [Carhart et al, 2010; Friston, 2005] This optimization has been transposed mathematically in terms

of hierarchical dissipation of the free energy bound to sensory inputs [Friston, 2009]. Such a hierarchical structure has recently been validated for the whole brain using graph theory and Granger causality analysis. These analyses have identified the directionality of information flow across main neuronal networks. Accordingly, it has been shown that “the driving hubs are predominantly located in the components of the attentional network and driven hubs are predominantly located in the components of the DMN” [Yan and He, 2011]. This supports the fact that there is cooperation between the attentional network and the DMN and seems to imply that the DMN is located on top of the structures performing hierarchical integration.

Figure 6.

A, B: Multiple regression group analysis of contrasting $\text{Shock}_{\text{Max}} > \text{Shock}_{\text{Min}}$ over the entire brain. Negative correlations between the fMRI signal across subjects and the means of individual values of pain rating on the visual analogue scale (VAS) are shown in hot. **A:** Peak negative correlation was found in the posterior part of the left fusiform gyrus at the coordinates $[-33, -75, -12]$. The left sides of the axial and coronal images correspond to the left side of the brain. **B:** Sagittal view of the significant

correlations found in the posterior part of the precuneus around the coordinates $[+12, -66, +48]$ (circled in blue). Dashed green line: occipito-parietal sulcus. The left side of the sagittal image corresponds to the posterior part of the brain. Significant correlations projected onto template brain slices in MNI stereotactic space. Color bar indicates T values. Correlations are shown at the voxel level $P_{\text{FDRcorr}} < 0.05$, cluster size threshold five voxels.

Considering the Friston approach on free energy dissipation, an unpredictable painful stimulus should cross all levels of hierarchical integration upwards. Our observation of activation of the DMN by acute pain seems to support the Friston hypothesis.

Our second main result is that during the $\text{Shock}_{\text{Max}}$ trials, a set of areas (including the left posterior fusiform gyrus, hippocampus, primary, and associative visual cortex extending to cuneus and precuneus as well as a more anterior network all belonging to dopaminergic pathways) presented activity which was negatively correlated to pain rating (Fig. 6 and Table 9). The strongest correlation was found in the left posterior fusiform gyrus. Many functions have been attributed to this structure, namely the retrieval of concepts for tools [Tranel et al., 1997], processing of pictures showing complex social situations [Geday et al., 2003] and reading [Cohen et al., 2002]. It is also robustly activated by tasks that do not engage word processing at all [Price and Devlin, 2003]. The fusiform gyrus, as suggested by Damasio [Damasio and Damasio, 2011] could be a convergence zone with more integrating than segregat-

ing properties. As a consequence, the functions of the fusiform gyrus may critically depend on the regions which interact with it. This is exemplified by the data in Table III, showing that the areas associated with the fusiform gyrus which are negatively correlated to the VAS are distributed along the antero-posterior axis. Considering this antero-posterior distribution, there is a cluster located in the posterior part of the right precuneus along the parieto-occipital fissure (the “visual precuneus” or Brodman area 7 m) [Vogt and Laureys, 2005]. This area has been shown to share specific RSFC patterns with the visual prestriate regions and fusiform gyrus [Margulies et al., 2009].

The right 7 m area and left posterior fusiform gyrus have been attributed a role in successful episodic memory retrieval at coordinates similar to ours ($[12, -74, 54]$ and $[-40, -70, -14]$, respectively) [Cavanna and Trimble, 2006; Lundstrom et al., 2005]. It thus appears that the posterior network that we found to be correlated to the VAS is probably engaged in a mental imagery process related to the retrieval of shock perception. Interestingly, left posterior fusiform gyrus activity follows the same dynamic as

TABLE III. Significant negative correlation peaks of contrasts $\text{Shock}_{\text{Max}} > \text{Shock}_{\text{Min}}$ with mean individual pain rating on visual analogic scale

Region	T^{19}	Cluster size	x	y	z
Left fusiform gyrus	8.41	1282	-33	-75	-12
Left cerebellum (crus 1)	7.06		-9	-87	-18
Left middle occipital gyrus	6.13		-27	-87	15
Right superior occipital gyrus	6.1		24	-72	33
Left lingual gyrus	6.03		-15	-87	-9
Left cuneus	5.84		3	-81	36
Left superior occipital gyrus	5.64		-9	-81	42
Right middle occipital gyrus	5.28		33	-84	15
Left calcarine gyrus	4.91		-9	-81	6
Right calcarine gyrus	4.91		24	-96	0
Right precuneus	4.78		12	-66	48
Left inferior occipital gyrus	4.52		-24	-93	-3
Right cuneus	4.25		6	-96	15
Right posterior cingulate cortex	4.52	237	15	-42	12
Right lingual gyrus	3.92		9	-45	3
Cerebellar vermis (4/5)	3.63		6	-45	-3
Left caudate nucleus	5.84	206	-15	0	24
Left middle frontal gyrus	3.59		-24	12	54
Left hippocampus	7.15	140	-21	-30	-6
Left ventral tegmental area/locus niger	5.84		-12	-24	-18
Left parahippocampus	5.84		-21	-24	-18
Left hypothalamus	3.92		-18	-12	-9
Left fusiform gyrus	3.53		-18	-39	-12
Right caudate nucleus	4.88	111	15	-3	21
Left precuneus	4.38	39	-12	-42	63
Right caudate nucleus	4.52	23	18	30	6
Left superior occipital gyrus	5.24	20	-21	-66	33
Left lingual gyrus	4.45	19	-24	-51	-9
Right middle frontal gyrus	4.55	18	45	42	15
Right superior medial gyrus	2.48	15	15	45	0
Left anterior cingulate cortex	3.92	14	-9	42	9
Left superior medial gyrus	3.3		-15	51	9
Left middle temporal gyrus	3.63	12	-45	-75	18
Right cerebellum (9)	4.35	12	6	-42	-39
Right insula lobe	3.73	11	30	27	9
Right inferior frontal gyrus (p. triangularis)	3.59		36	30	9
Medial thalamus	3.89	11	0	-6	9
Right ventral tegmental area/locus niger	3.92	11	12	-18	-21
Right cerebellum (crus 1)	4.09	8	39	-81	-27
Right precuneus	3.43	6	15	-45	60
Left inferior parietal lobule	3.99	6	-60	-33	42
Left supramarginal gyrus	3.99		-60	-33	39
Right inferior frontal gyrus (p. orbitalis)	3.79	6	27	33	-15
Right middle occipital gyrus	3.63	5	36	-78	0
Left middle temporal gyrus	3.89	5	-48	-12	-24

Voxel level $P < 0.05$ FDR corrected, cluster-size threshold 5 voxels; T^{19} value = T value for 19° of freedom; in case of multiple peaks in the same anatomic area of a cluster, only maximal peak is reported for this anatomic area; x,y,z = the original SPM coordinates in millimeters of the MNI space.

those of the DMN during anticipation and pain perception; this appears to be consistent with the internal mentation process associated with DMN activity.

Along the antero-posterior axis mentioned above, a set of anterior clusters (VTA/locus niger, bilateral caudate and pACC), which are also correlated to the VAS, belong

to dopaminergic networks. These networks are known to be implicated in the hedonic and motor aspects of reward processing [Haber and Rauch, 2010b; O'Doherty, 2004; Schultz, 2000]. One may then question whether the activity of all these anterior regions participate in the down-regulation of pain, as the finding of a negative correlation

Figure 7.

A,B: Group mean percent fMRI signal changes across trial modalities (black: Shock_{Max}, white: Shock_{Min}) and conditions (cue, anticipation, shock, rating, and rest) in peak voxels of the precuneus and key elements of the DMN from Table II. Percent signal changes are expressed by reference to the mean value of the signal across all conditions. The nil event conditions have not been included in this model and do not appear in the figures. Hence, as the DMN is active during Rest, we considered it as the reference condition. Accordingly, statistical comparisons refer to Rest. In the posterior

cingulate, ventromedial prefrontal cortex and left angular gyrus, the signal change decreased compared with Rest during Anticipation-Shock_{Max}, but was not different from Rest during Shock_{Max}. In all the remaining regions of interest, the signal change decreased compared with Rest during Anticipation-Shock_{Max}, but it was superior to Rest during Shock_{Max}. Following one-way ANOVA, the *P*-value indicated a significant difference with Bonferroni's multiple comparison test, n.s., not significant. Multiple comparisons were restricted to the conditions Shock_{Max}, Anticipation-Shock_{Max}, and Rest.

between the activity of these areas and the VAS may suggest. The answer is probably positive and may rely on the fact that, as previously discussed, the pACC is implicated in the down-regulation of pain [Bantick et al., 2002; Ossipov et al., 2010; Petrovic et al., 2002; Peyron et al., 2007; Zubieta et al., 2005]. It also relies on the fact that dopaminergic and opioid pathways act jointly within the ACC for pain down-regulation and reward processing [Becerra et al., 2001; Borsook et al., 2010; Narita et al., 2010].

Some limits to our study should be discussed. First, we did not achieve the level of statistical power required to test contrasts at the more stringent Family Wise Error threshold. However, we introduced a correction for multiple statistical comparisons which makes a statistical bias unlikely. The paradigm we used may appear somewhat artificial. Indeed, its circular aspect cannot ascertain that a causal relationship between cortical response and pain rating exists. Moreover, the subjects were required not to move in response to pain. This condition is far from the natural condition in which movement is a reflex response aimed at escaping/avoiding pain. This limitation does not apply to anaesthesia, where a patient is commanded not to move, as during the insertion of a venous catheter.

We conclude that dissociating anticipation and pain perception makes the observation of DMN activation in response to pain possible. The pACC may play a key role in the coactivation of the DMN and somatomotor as well as attentional networks. The left posterior fusiform gyrus explains individual variability in pain rating. Some frontal clusters may also participate in the down-regulation of pain perception. The activation of the DMN by acute pain could reflect an internal mentation process associated with episodic memory retrieval. However, these hypotheses should be confirmed. This is the aim of an ongoing study exploring how the DMN and attentional networks are modulated by premedication drugs in volunteers.

REFERENCES

- Asplund CL, Todd JJ, Snyder AP, Marois R (2010): A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. *Nat Neurosci* 13:507–512.
- Astafiev SV, Shulman GL, Stanley CM, Snyder AZ, Van E, Corbetta M (2003): Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *J Neurosci* 23:4689–4699.
- Baliki MN, Geha PY, Apkarian AV, Chialvo DR (2008): Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci* 28:1398–1403.
- Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I (2002): Imaging how attention modulates pain in humans using functional MRI. *Brain* 125:310–319.
- Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D (2001): Reward circuitry activation by noxious thermal stimuli. *Neuron* 32:927–946.
- Berna C, Leknes S, Holmes EA, Edwards RR, Goodwin GM, Tracey I (2010): Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. *Biol Psychiatry* 67:1083–1090.
- Borsook D, Upadhyay J, Chudler EH, Becerra L (2010): A key role of the basal ganglia in pain and analgesia—Insights gained through human functional imaging. *Mol Pain* 6:27.
- Buckner RL, Andrews-Hanna JR, Schacter DL (2008): The brain's default network: Anatomy, function, and relevance to disease. *Ann NY Acad Sci* 1124:1–38.
- Buracas GT, Boynton GM (2002): Efficient design of event-related fMRI experiments using M-sequences. *NeuroImage* 16:801–813.
- Bush G, Luu P, Posner MI (2000): Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 4:215–222.
- Carhart-Harris RL, Friston KJ (2010): The default-mode, ego-functions and free energy: A neurobiological account of Freudian ideas. *Brain* 133:1265–1283.
- Cavanna AE, Trimble MR (2006): The precuneus: A review of its functional anatomy and behavioural correlates. *Brain* 129:564–583.
- Cohen L, Lehericy S, Chochon F, Lemer C, Rivaud S, Dehaene S (2002): Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. *Brain* 125:1054–1069.
- Corbetta M, Kincade JM, Ollinger JM, McAvooy MP, Shulman GL (2000): Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nat Neurosci* 3:292–297.
- Corbetta M, Kincade JM, Shulman GL (2002): Neural systems for visual orienting and their relationships to spatial working memory. *J Cogn Neurosci* 14:508–523.
- Corbetta M, Shulman GL (2002): Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 3:201–215.
- Corbetta M, Tansy AP, Stanley CM, Astafiev SV, Snyder AZ, Shulman GL (2005): A functional MRI study of preparatory signals for spatial location and objects. *Neuropsychologia* 43:2041–2056.
- Damasio AR, Damasio H (2011): Cortical systems for the retrieval of concrete knowledge: The convergence zone framework. In: Koch C, editor. *Large Scale Neuronal Theories of the Brain*. Cambridge MA: MIT Press. pp 61–74.
- Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ (1997): Functional MRI of pain- and attention-related activations in the human cingulate cortex. *J Neurophysiol* 77:3370–3380.
- Devinsky O, Morrell MJ, Vogt BA (1995): Contributions of anterior cingulate cortex to behaviour. *Brain* 118 (Part 1):279–306.
- Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, Fox MD, Snyder AZ, Vincent JL, Raichle ME, Schlaggar BL, Petersen SE (2007): Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci USA* 104:11073–11078.
- Dosenbach NUF, Fair DA, Cohen AL, Schlaggar BL, Petersen SE (2008): A dual-networks architecture of top-down control. *Trends Cogn Sci* 12:99.
- Fairhurst M, Wiech K, Dunckley P, Tracey I (2007): Anticipatory brainstem activity predicts neural processing of pain in humans. *Pain* 128:101–110.
- Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME (2006): Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci USA* 103:10046–10051.
- Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci USA* 102:9673–9678.

- Franssen C, Hans P, Brichant JF, Noirot D, Lamy M (1993): Comparison between alprazolam and hydroxyzine for oral premedication. *Can J Anaesth* 40:13–17.
- Friston K (2005): A theory of cortical responses. *Phil Trans R Soc B* 360:815–836.
- Friston K (2009): The free-energy principle: A rough guide to the brain? *Trends Cogn Sci* 13:293–301.
- Geday J, Gjedde A, Boldsen AS, Kupers R (2003): Emotional valence modulates activity in the posterior fusiform gyrus and inferior medial prefrontal cortex in social perception. *NeuroImage* 18:675–684.
- Haber SN, Knutson B (2010): The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology* 35:4–26.
- Haber SN, Rauch SL (2010): Neurocircuitry: A window into the networks underlying neuropsychiatric disease. *Neuropsychopharmacology* 35:1–3.
- Ingvar DH (1979): "Hyperfrontal" distribution of the cerebral grey matter flow in resting wakefulness: On the functional anatomy of the conscious state. *Acta Neurol Scand* 60:12–25.
- Kanto J, Watanabe H, Namiki A (1996): Pharmacological premedication for anaesthesia. *Acta Anaesthesiol Scand* 40:982–990.
- Kong J, Loggia ML, Zyloney C, Tu P, Laviolette P, Gollub RL (2010): Exploring the brain in pain: Activations, deactivations and their relation. *Pain* 148:257–267.
- Kwan CL, Crawley AP, Mikulis DJ, Davis KD (2000): An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious cutaneous heat and cold stimuli. *Pain* 85:359–374.
- Lundstrom BN, Ingvar M, Petersson KM (2005): The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *NeuroImage* 27:824–834.
- Margulies DS, Vincent JL, Kelly C, Lohmann G, Uddin LQ, Biswal BB, Villringer A, Castellanos FX, Milham MP, Petrides M (2009): Precuneus shares intrinsic functional architecture in humans and monkeys. *Proc Natl Acad Sci USA* 106:20069–20074.
- Menon V, Uddin LQ (2010): Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct* 214:655–667.
- Narita M, Matsushima Y, Niikura K, Narita M, Takagi S, Nakahara K, et al. (2010): Implication of dopaminergic projection from the ventral tegmental area to the anterior cingulate cortex in mu-opioid-induced place preference. *Addict Biol* 15:434–447.
- O'Doherty JP (2004): Reward representations and reward-related learning in the human brain: Insights from neuroimaging. *Curr Opin Neurobiol* 14:769–776.
- Ossipov MH, Dussor GO, Porreca F (2010): Central modulation of pain. *J Clin Invest* 120:3779–3787.
- Paus T (1996): Location and function of the human frontal eye-field: A selective review. *Neuropsychologia* 34:475–483.
- Petrovic P, Kalso E, Petersson KM, Ingvar M (2002): Placebo and opioid analgesia—Imaging a shared neuronal network. *Science* 295:1737–1740.
- Petrovic P, Pleger B, Seymour B, Kloppel S, De Martino B, Critchley H, et al. (2008): Blocking central opiate function modulates hedonic impact and anterior cingulate response to rewards and losses. *J Neurosci* 28:10509–10516.
- Peyron R, Failliot I, Mertens P, Laurent B, Garcia-Larrea L (2007): Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. *NeuroImage* 34:310–321.
- Ploghaus A, Becerra L, Borras C, Borsook D (2003): Neural circuitry underlying pain modulation: Expectation, hypnosis, placebo. *Trends Cogn Sci* 7:197–200.
- Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, et al. (2001): Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci* 21:9896–9903.
- Ploghaus A, Tracey I, Clare S, Gati JS, Rawlins JN, Matthews PM (2000): Learning about pain: The neural substrate of the prediction error for aversive events. *Proc Natl Acad Sci USA* 97:9281–9286.
- Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN (1999): Dissociating pain from its anticipation in the human brain. *Science* 284:1979–1981.
- Price CJ, Devlin JT (2003): The myth of the visual word form area. *NeuroImage* 19:473–481.
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. *Proc Natl Acad Sci USA* 98:676–682.
- Scheperjans F, Eickhoff SB, Homke L, Mohlberg H, Hermann K, Amunts K, Zilles K (2008a) Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. *Cereb Cortex* 18:2141–2157.
- Scheperjans F, Hermann K, Eickhoff SB, Amunts K, Schleicher A, Zilles K (2008b) Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. *Cereb Cortex* 18:846–867.
- Schultz W (2000): Multiple reward signals in the brain. *Nat Rev Neurosci* 1:199–207.
- Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27:2349–2356.
- Seminowicz DA, Davis KD (2007): Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. *J Neurophysiol* 97:3651–3659.
- Shulman GL, Corbetta M, Fiez JA, Buckner RL, Miezin FM, Raichle ME, Petersen SE (1997): Searching for activations that generalize over tasks. *Hum Brain Mapp* 5:317–322.
- Shulman GL, McAvoy MP, Cowan MC, Astafiev SV, Tansy AP, d'Avossa G, Corbetta M (2003): Quantitative analysis of attention and detection signals during visual search. *J Neurophysiol* 90:3384–3397.
- Shulman GL, Ollinger JM, Akbudak E, Conturo TE, Snyder AZ, Petersen SE, Corbetta M (1999): Areas involved in encoding and applying directional expectations to moving objects. *J Neurosci* 19:9480–9496.
- Simpson JR, Drevets WC, Snyder AZ, Gusnard DA, Raichle M (2001): Emotion induced changes in human medial prefrontal cortex. II. During anticipatory anxiety. *Proc Natl Acad Sci USA* 98:688–693.
- Sokolowski CJ, Giovannitti JA Jr, Boynes SG (2010): Needle phobia: Etiology, adverse consequences and patient management. *Dent Clin North Am* 54:731–744.
- Sridharan D, Levitin DJ, Menon V (2008): A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci USA* 105:12569–12574.
- Tranel D, Damasio H, Damasio AR (1997): A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia* 35:1319–1327.
- Vogt BA (2005): Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci* 6:533–544.

- Vogt BA, Laureys S (2005): Posterior cingulate, precuneal and retrosplenial cortices: Cytology and components of the neural network correlates of consciousness. *Prog Brain Res* 150:205–217.
- Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, et al. (1998): The emotional counting Stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry* 44:1219–1228.
- Wiech K, Lin C, Brodersen KH, Bingel U, Ploner M, Tracey I (2010): Anterior insula integrates information about salience into perceptual decisions about pain. *J Neurosci* 30:16324–16331.
- Yan C, He Y (2011): Driving and driven architectures of directed small-world human brain functional networks. *PLoS ONE* 6:e23460.
- Yu C, Zhou Y, Liu Y, Jiang T, Dong H, Zhang Y, Walter M (2011): Functional segregation of the human cingulate cortex is confirmed by functional connectivity based neuroanatomical parcellation. *NeuroImage* 54:2571–2581.
- Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, Nichols TE, Stohler CS (2005): Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci* 25:7754–7762.