NeuroImage 54 (2011) 2237–2249

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

A multisensory investigation of the functional significance of the "pain matrix"

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ARTICLE INFO

Article history:
Received 23 July 2010
Revised 10 September 2010
Accepted 28 September 2010
Available online 12 October 2010

Keywords:
Pain
Nociception
fMRI
Saliency
Multimodal

ABSTRACT

Functional neuroimaging studies in humans have shown that nociceptive stimuli elicit activity in a wide network of cortical areas commonly labeled as the "pain matrix" and thought to be preferentially involved in the perception of pain. Despite the fact that this "pain matrix" has been used extensively to build models of where and how nociception is processed in the human brain, convincing experimental evidence demonstrating that this network is specifically related to nociception is lacking. The aim of the present study was to determine whether there is at least a subset of the "pain matrix" that responds uniquely to nociceptive somatosensory stimulation. In a first experiment, we compared the fMRI brain responses elicited by a random sequence of brief nociceptive somatosensory, non-nociceptive somatosensory, auditory and visual stimuli, all presented within a similar attentional context. We found that the fMRI responses triggered by nociceptive stimuli can be largely explained by a combination of (1) multimodal neural activities (i.e., activities elicited by all stimuli regardless of sensory modality) and (2) somatosensory-specific but not nociceptive-specific neural activities (i.e., activities elicited by both nociceptive and non-nociceptive somatosensory stimuli). The magnitude of multimodal activities correlated significantly with the perceived saliency of the stimulus. In a second experiment, we compared these multimodal activities to the fMRI responses elicited by auditory stimuli presented using an oddball paradigm. We found that the spatial distribution of the responses elicited by novel non-target and novel target auditory stimuli resembled closely that of the multimodal responses identified in the first experiment. Taken together, these findings suggest that the largest part of the fMRI responses elicited by phasic nociceptive stimuli reflects non nociceptive-specific cognitive processes.

Introduction

A large number of neuroimaging studies have shown that when a nociceptive stimulus is applied to the skin, it elicits activity within a vast network of brain regions, often referred to as the "pain matrix", and including the primary (S1) and secondary (S2) somatosensory cortices, the insula, and the anterior cingulate cortex (ACC) (Bushnell and Apkarian, 2005; Peyron et al., 2002; Treede et al., 1999).

It is difficult to provide a unique and consensual definition of the "pain matrix" (reviewed in Iannetti and Mouraux, 2010). The term is derived from the "neuromatrix", which was originally proposed by Melzack in 1989. However, pain was viewed as only one of many possible perceptual outputs of this "neuromatrix", which was thus not considered to be pain-specific (Melzack, 2005). Only in later studies the label "pain" was added to the term "neuromatrix", leading to the current concept of a "pain matrix" (e.g., Avenanti et al., 2005; Boly et al., 2008; Borsook et al., 2010; Brooks and Tracey, 2005; Ingvar, 1999; Jones, 1998; Ploghaus et al., 1999; Talbot et al., 1991; Whyte, 2008). This relabeling introduced a fundamental deviation from the original concept, as it implied that the pattern of brain responses elicited by nociceptive stimuli reflects a pain-specific network and, hence, that functional neuroimaging could be used to "delineate the functional anatomy of different aspects of pain" (Ingvar, 1999). Some investigators have considered that it is the pattern of activation in the different structures of the "pain matrix" that constitutes, as an ensemble, the neural substrate for pain perception. In this population-coding view, the emergence of pain is not considered to result from the activation of one or more specific brain areas but to emerge "from the flow and integration of information" among these areas (Tracey, 2005). Therefore, this view differs from the original "neuromatrix" concept only in the fact that the experience of pain is considered as the only relevant output of the network. Other investigators have deviated further from the original "neuromatrix" concept, by considering the "pain matrix" as an enumeration of pain-specific brain structures. In such, the different structures constituting the

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doi:10.1016/j.neuroimage.2010.09.084

"pain matrix" are considered to have "specialized subfunctions" and, thereby, to encode self-standingly different aspects of the pain experience (Ingvar, 1999). For example, sensory-discriminative aspects of pain perception are proposed to be independently and specifically represented in S1 and S2, constituting the so-called "lateral pain system" or "somatosensory node" of the "pain matrix"; while affective aspects of pain perception are proposed to be independently and specifically represented in medial brain structures such as the ACC, constituting the "medial pain system" or "affective node" (Albe-Fessard et al., 1985; Avenanti et al., 2005). A large number of recent studies have relied on this "labeled-lines" interpretation of the "pain matrix" to interpret their data (e.g., Avenanti et al., 2005; Brooks and Tracey, 2005; Derbyshire et al., 1997; Frot et al., 2008; Garcia-Larrea et al., 2002; Gracely et al., 2004; Kakigi et al., 2004; Moisset and Bouhassira, 2007; Ploner et al., 2002; Schnitzler and Ploner, 2000; Singer et al., 2004).

It has been repeatedly demonstrated that the magnitude of activity in this network correlates robustly with the intensity of perceived pain, and this has been interpreted as evidence that this network is specifically involved in "encoding" pain intensity (Baliki et al., 2009; Coghill et al., 1999; Derbyshire et al., 1997; Iannetti et al., 2005). Several studies have characterized further the functional significance of this network. Using various experimental manipulations, they have suggested that it is possible to modulate selectively the magnitude of responses in different subregions of this network, a finding interpreted as evidence that different subregions process different aspects of the pain experience (Bushnell and Apkarian, 2005; Ingvar, 1999).

However, all these observations do not justify the conclusion that this network is *specifically* or *preferentially* involved in perceiving pain (Boly et al., 2008; Brooks and Tracey, 2005; Ingvar, 1999; Jones, 1998; Melzack, 1992; Whyte, 2008). Indeed, these observations are *compatible* but *not sufficient* to justify this conclusion, and, in fact, other observations showing (i) that it is possible to disrupt the correlation between the magnitude of activity in the "pain matrix" and the magnitude of perceived pain (Iannetti et al., 2008; Treede et al., 2003) and (ii) that stimuli that are not nociceptive may elicit responses in the different subregions of the "pain matrix" (Bamiou et al., 2003; Lui et al., 2008; Menon et al., 1997; Mouraux and Iannetti, 2009) suggest the opposite: that the "pain matrix" does not reflect neural mechanisms uniquely involved in nociception.

It is interesting to note that this possibility had already been put forward by a number of early studies (e.g., Bancaud et al., 1953; Carmon et al., 1976; Stowell, 1984) but has often been dismissed by recent studies, which have considered that because the stimulus elicits a sensation of pain, it is reasonable to assume that the elicited brain responses are at least partially pain-specific (e.g., Avenanti et al., 2005; Boly et al., 2008; Borsook et al., 2010; Brooks and Tracey, 2005; Ingvar and Hsieg, 1999; Jones, 1998; Ploghaus, 1999; Stern et al., 2006; Talbot et al., 1991; Whyte, 2008; Wiech et al., 2008).

Although objecting to the use of the term "pain matrix" could appear as an academic discussion only pertaining to the realm of scientific terminology, it actually reveals a practical and urgent issue in the field of pain neuroscience. Undeniably, the brain responses triggered by nociceptive stimuli, in particular, nociceptive laser-evoked brain potentials, are extensively used in clinical practice (Cruccu et al., 2004). Recently, the fMRI responses elicited by nociceptive stimuli have even been used as medico-legal evidence (Miller, 2009), or as evidence of pain perception in minimally conscious states (Boly et al., 2008). Similarly, they have been used to draw strong conclusions about how pain is "represented" in the brain (Bushnell and Apkarian, 2005; Tracey and Mantyh, 2007; Wiech et al., 2008). For example, a number of studies have shown that the brain areas responding to painful stimuli also respond when subjects experience empathy for pain (Singer et al., 2004), and these findings have been interpreted as evidence that such experiences are generated through a mirror activation of the "pain matrix" (Ogino et al., 2007).

The aim of the present study was to functionally characterize the "pain matrix" and determine whether at least a subset of the neural activity that it refers to is unique for nociception. We addressed this question by performing two different fMRI experiments.

In a first experiment, we compared the brain responses elicited by a random sequence of intermixed nociceptive somatosensory, non-nociceptive somatosensory, auditory and visual stimuli presented in a similar attentional context and found that the brain responses triggered by nociceptive stimuli can be entirely explained by a combination of multimodal neural activities (i.e., activities elicited by all stimuli regardless of sensory modality) and somatosensory-specific but not nociceptive-specific neural activities (i.e., activities elicited by both nociceptive and non-nociceptive somatosensory stimuli). The magnitude of these multimodal brain responses was correlated with the subjective rating of stimulus saliency. To further explore the functional significance of these multimodal brain responses, and because previous studies have shown that the magnitude of the brain responses elicited by a nociceptive stimulus can be enhanced if subjects anticipate the occurrence of a possibly painful stimulus (Keltner et al., 2006; Koyama et al., 2005), we performed a second experiment in which we delivered only auditory stimuli using an oddball paradigm. We found that the spatial distribution of the responses elicited by novel and target (i.e., salient) auditory stimuli resembled closely the multimodal responses identified in the first experiment, thus indicating that these responses are elicited by salient non-nociceptive stimuli even in the absence of pain anticipation, and that their occurrence is largely determined both by the intrinsic saliency of the stimulus (bottom–up attention) and its task relevance (top–down attention). Taken together, these findings suggest that the largest part of the fMRI responses elicited by phasic nociceptive stimuli reflects non nociceptive-specific cognitive processes.

Materials and methods

Participants

Fourteen healthy right-handed volunteers took part in Experiment 1 (8 males, aged 20–36 years) and Experiment 2 (14 males, aged 20–32 years), under the following inclusion criteria: no history of brain injuries, hypertension, any psychiatric or neurological disease, alcohol abuse, or drug abuse. All volunteers gave written informed consent, and all experimental procedures were approved by the local Research Ethics Committees.

Experiment 1

Experimental design

The experiment consisted of a single fMRI acquisition, divided into four successive runs. Each run consisted of a stimulation period (~8-min duration), followed by a rating period (~2-min duration). Lights in the scanner room were dim and subjects lay supine in the scanner. During the stimulation period, participants received brief stimuli of four different sensory modalities: nociceptive somatosensory, non-nociceptive somatosensory, auditory, and visual. Within each stimulation period, each type of stimulus was delivered 8 times (8×4 stimulus modalities $= 32$ stimuli/period). All stimuli were delivered in a pseudo-random order, such that stimuli of the same sensory modality were not delivered consecutively more than twice. To ensure that observed differences were not related to differences in the spatial location of the stimulus or to spatial attention, all stimuli were delivered to or around the participant's right side. The inter-stimulus interval (ISI) was 10, 13, 16, or 19 s. ISIs were balanced across stimulus types, and the order of ISIs was pseudo-randomized such that the same ISI was not used consecutively more than twice. Throughout the stimulation sequence, participants were instructed to fixate on a white cross (~1.5° viewing angle) displayed at the center of

a screen. During the *rating period*, participants rated the saliency of each stimulus using a visual-analogue scale. This was done by adjusting the position of a cursor on four consecutively displayed scales labeled "laser," "electric," "visual," and "auditory", each displayed for 9 s. Left and right extremities of the scale were labeled "not salient" and "extremely salient". The order of presentation of the four scales was randomized across blocks. Stimulus saliency was explained to each subject as "the ability of the stimulus to capture attention". Therefore, it was expected to integrate several factors such as stimulus intensity, frequency of appearance, and novelty. Several studies have shown that human judgments of saliency correlate well with predicted models of saliency (Kayser et al., 2005; see also Mouraux and Iannetti, 2009).

Sensory stimuli

To ensure that observed differences were not related to differences in the spatial location of the stimulus or to spatial attention, all stimuli were delivered to the participant's right side. *Nociceptive somatosensory stimuli* were pulses of radiant heat (5-ms duration) generated by an infrared neodymium yttrium aluminium perovskite (Nd:YAP) laser (wavelength: 1.34 μm; ElEn Group, Italy). The laser beam was transmitted through an optic fibre, and focusing lenses were used to set the diameter of the beam at target site to ~7 mm. The energy of the stimulus (3 ± 0.5 J) was set to elicit a clear painful pinprick sensation, which has been shown to be related to the selective activation of Aδ skin nociceptors (Bromm and Treede, 1984). The stimulus was applied to the dorsum of the right foot, within the sensory territory of the superficial peroneal nerve. To prevent fatigue or sensitization of nociceptors, the laser beam was manually displaced after each stimulus (distance: ~2 cm). *Non-nociceptive somatosensory stimuli* were constant current square-wave electrical pulses (1-ms duration; DS7A, Digitimer Ltd., UK). The stimulus was delivered through a pair of skin electrodes (1-cm inter-electrode distance) placed at the right ankle, over the superficial peroneal nerve. For each participant, stimulus intensity (6 ± 2 mA) was adjusted to elicit a non-painful paresthesia in the sensory territory of the nerve. The intensity of electrical stimulation was above the threshold of Aβ fibers (which convey innocuous tactile sensations) but well below the threshold of nociceptive Aδ and C fibers (Burgess and Perl, 1967). Visual stimuli consisted of a bright white disk (~9° viewing angle) displayed on the projection screen, above the right foot, for 100 ms. Auditory stimuli were loud, right-lateralized 800 Hz tones (0.5 left/right amplitude ratio; 50-ms duration; 5-ms rise and fall times), delivered binaurally through custom-built pneumatic earphones bored into a set of low-profile ear defenders.

Data acquisition and pre-processing

Functional MRI data were acquired using a 3-T Varian-Siemens whole-body magnetic resonance scanner (Oxford Magnet Technology, UK). A head-only gradient coil was used with a birdcage radiofrequency coil for pulse transmission and signal reception. A whole-brain gradient-echo, echo-planar-imaging sequence was used for functional scanning (30-ms echo time, 41 contiguous 3.5-mm-thick slices, field of view 192×192 mm, matrix 64×64), with a repetition time (TR) of 3 s over 740 volumes, resulting in a total scan time of 37 min. The remainder of the ISIs (10, 13, 16, or 19 s) divided by the TR (3 s) was always equal to 1, thus allowing a 1-s effective temporal sampling of the stimulus-evoked BOLD (blood oxygen level-dependent) signal. The first four volumes were discarded to allow for signal equilibration. At the end of the experiment, a T1-weighted structural image (1-mm-thick axial slices, in-plane resolution 1×1 mm) was acquired for spatial registration and anatomical overlay of the functional data.

Each collected time-series of fMRI volumes was pre-processed using FEAT 5 (part of FSL, www.fmrib.ox.ac.uk/fsl). Brain extraction was performed using BET. Motion correction was applied using FLIRT. Spatial smoothing was applied using a Gaussian kernel of 5-mm full-width at half-maximum. High-pass temporal filtering was applied using a Gaussian-weighted least-squares straight line fitting ($\sigma = 100$ s), and signals were demeaned for normalization. Furthermore, denoising of each dataset was performed using a Probabilistic Independent Component Analysis (PICA) (Beckmann and Smith, 2004). Independent Components (ICs) containing clear artifacts related to slice dropouts, gradient instability, EPI ghosting, high-frequency noise, head motion, or field inhomogeneities (38 ± 11 out of 291 ± 53 ICs) were identified and removed (Beckmann et al., 2000).

General linear model analysis

Each single-subject fMRI dataset was modeled on a voxel-by-voxel basis, using a general linear model approach, with local autocorrelation correction (Woolrich et al., 2001). The fMRI time-series were modeled as a series of events convolved with a gamma hemodynamic response function (mean lag: 6 s; full-width at half-height: 6 s). The occurrences of each stimulus type were modeled as separate explanatory variables, including their temporal derivatives: (i) nociceptive somatosensory stimulation, (ii) non-nociceptive somatosensory stimulation, (iii) auditory stimulation, and (iv) visual stimulation. An additional explanatory variable was used to model BOLD responses related to the execution of the saliency rating task. Contrasts acting on each single regressor were used to assess the BOLD response associated with each sensory modality. In addition, differential contrasts were used to assess the difference in BOLD signal associated to different sensory modalities. Single-subject low-resolution functional images were co-registered to their corresponding high-resolution structural images and then co-registered to a standard brain (Montreal Neurological Institute 152 template) (Jenkinson et al., 2002). Group-level statistical analyses were carried out using a mixed-effect approach as implemented in FEAT (Woolrich et al., 2004). A Z-score > 2.3 was chosen as the significance threshold for the Z-statistic images from the group analysis. A cluster-based approach (threshold $p < 0.05$) was used to correct for multiple comparisons (Friston et al., 1994).

Conjunction analysis

To identify *multimodal* brain responses (i.e., responses elicited by all four categories of sensory stimuli), a conjunction analysis was performed on the group-level statistical volumes, using the method of Minimum Statistic compared to the Conjunction Null (MS/CN) (Nichols et al., 2005). For each Explanatory Variable (EV: nociceptive somatosensory, non-nociceptive somatosensory, auditory, and visual), the group-level z-statistic images were thresholded at $z > 2.3$, to construct a binary mask (0 = no significant activation, 1 = significant activation). We classified as *multimodal* the voxels in which nociceptive somatosensory and non-nociceptive somatosensory and auditory and visual stimulation all elicited a significant BOLD response. We classified as *somatosensory-specific* the voxels in which both nociceptive and non-nociceptive somatosensory stimuli elicited a significant response, whereas visual or auditory stimuli did not elicit a significant response. Finally, we classified as *nociceptive somatosensory-specific*, *non-nociceptive somatosensory-specific*, *auditory-specific*, and *visual-specific* the voxels that displayed a significant activation to only one category of sensory stimulation. In addition, it was examined whether a fraction of the voxels identified as multimodal responded *preferentially* to a particular modality of sensory stimulation. This was performed by computing, for each sensory modality, the conjunction of the three differential contrasts assessing the difference between the response to that modality of sensory stimulation and the response to each of the three other modalities of sensory stimulation. This conjunction revealed multimodal voxels showing greater activation to a particular modality of stimulation as compared to any of the other three modalities of stimulation.

Anatomically defined regions of interest

Anatomically defined regions of interest (ROI) circumscribed the left and right primary and secondary somatosensory cortices (S1 and S2), the primary and secondary auditory cortices (A1 and A2), the primary visual cortex (V1), the anterior and posterior insular cortices, and the anterior cingulate cortex (ACC). Two anatomical probabilistic atlases were used to define these ROIs. The Jülich probabilistic histological atlas (Eickhoff et al., 2005) was used to define the left and right S1 and S2, the left and right A1 and A2, as well as V1. The Harvard-Oxford probabilistic atlas was used to define the left and right insular cortices and the anterior division of the ACC. Each ROI was constructed by binarizing the corresponding probability volumes thresholded at $p>0.5$. The ROIs were then transformed into each participant's high-resolution structural space. For each participant, the boundaries of ROIs defining S1 were trimmed to include only the mesial hemispheric wall (i.e., the putative foot representation area of S1) (Penfield and Boldrey, 1937). Furthermore, the boundaries of the ROIs defining S2 were trimmed to exclude voxels located in the temporal lobe, while the boundaries of the ROIs defining A2 were trimmed to exclude any voxels located in the parietal lobe. Also, ROIs defining the insula were subdivided into an anterior and a posterior subdivision, using the position of the central sulcus as anterior/posterior boundary (Ture et al., 1999). Finally, all ROIs were transformed into each participant's low-resolution functional space.

Correlation between BOLD signal and subjective rating of stimulus saliency

For each ROI, the linear dependence between the magnitude of the BOLD response following each type of stimulation and the subjective rating of stimulus saliency was examined. The parameter estimates of the regressors used to model the BOLD response following each type of sensory stimulus were averaged across all voxels located inside the ROI, thus yielding an estimate of the size of the response (%BOLD signal change) as a function of the modality of the stimulus. For each subject, the distributions of the BOLD signal change and the ratings of stimulus saliency obtained for each type of stimulus were standardized (expressed as standard deviation from the mean, *z*-score). The standardized BOLD signal change and saliency ratings, pooled across stimulus types, were then correlated across participants (Pearson's correlation coefficient).

Model-free analysis of raw BOLD signal

A model-free analysis (i.e., free from any assumption about shape, latency, and duration of the BOLD response) was also performed, because the BOLD response has been shown to vary across different brain regions (e.g., Lee et al., 1995; Robson et al., 1998), and also according to the type of somatosensory stimulation (Lui et al., 2008). Peri-stimulus plots of the BOLD signal time course were computed for each ROI, subject, and stimulus type, thus allowing us to compare, within each anatomically defined ROI, the time course of the BOLD responses elicited by each type of sensory stimulus. For each acquired volume of the fMRI dataset, the signal intensity of all the voxels located inside the ROI was averaged, resulting in a single signal time course for each ROI. Peri-stimulus epochs were extracted (-4 s to $+11$ s relative to stimulus onset), and baseline-corrected (reference interval: -4 to 0 s). Epochs containing values deviating from the mean by more than four times the standard deviation of the whole time course were rejected (2.5 ± 3.9% of epochs). Remaining epochs were averaged across trials, yielding one peri-stimulus plot of the average BOLD time course for each ROI, subject, and stimulus type.

As these time courses were baseline corrected, Student's *t*-tests were used to compare the signal against zero, at each time point following stimulus onset (11 time points ranging from $+1$ to $+11$ s). A time point was considered as displaying significant post-stimulus activity if the average signal of that time point and the average signal of the preceding or following time point were both significantly different from zero ($p<0.01$, using Bonferroni correction for multiple comparisons).

Furthermore, for each ROI, the area under the curve of the post-stimulus time course ($+2$ to $+8$ s after stimulus onset) was used as an estimate of the size of the response. We thereby examined whether (1) the size of the response was dependent on the type of sensory stimulation and (2) whether the size of the response was significantly different in the contralateral vs. ipsilateral hemisphere. Response sizes in S1, S2, A1, A2, anterior insula, and posterior insula were submitted to a two-way repeated measures ANOVA with "stimulus" (four levels: nociceptive somatosensory, non-nociceptive somatosensory, auditory, and visual) and "hemisphere" (two levels: left, right) as within-subject factors. Response sizes in V1 and the ACC were analysed using a one-way repeated measures ANOVA with "stimulus" (four levels: nociceptive somatosensory, non-nociceptive somatosensory, auditory, and visual) as within-subject factor. When significant ($p<0.05$), paired *t*-tests were used to perform post hoc pairwise comparisons ($p<0.05$, using Bonferroni correction for multiple comparisons).

Experiment 2

Experimental design

The experiment consisted of a single fMRI acquisition, in which only auditory stimuli were presented using a typical oddball paradigm (Squires et al., 1975). The acquisition lasted 19 min. Three different types of stimuli were presented: frequent standard stimuli (a 1-kHz auditory tone lasting 100 ms, constituting 70% of the total number of stimuli), novel target stimuli (a 1.5-kHz auditory tone lasting 100 ms, constituting 15% of the total number of stimuli), and novel non-target stimuli (a random complex sound, e.g., a whistle, lasting 100 ms and constituting 15% of the total number of stimuli). All stimuli were presented binaurally through electrostatic headphones (NordicNeuroLabs electrostatic headphones) and delivered in a pseudo-random order, such that novel non-target and target stimuli were never delivered twice in a row. A total of 576 stimuli were delivered, separated by a constant 1.8-s inter-stimulus interval. Participants were asked to respond to the novel target stimuli by pressing a button held in the right hand and to not press the button following the standard stimuli or the novel non-target stimuli.

Data acquisition and processing

fMRI data were acquired using a 3-T GE HDx scanner. As for Experiment 1, a whole-brain gradient-echo echo-planar imaging was used for functional scanning (35-ms echo time, 50 contiguous slices, voxel size $3.25\times3.25\times3$ mm, matrix 64×64), with a repetition time (TR) of 3 s. At the end of the experiment, a T1-weighted structural image (voxel size $1\times1\times1$ mm) was acquired for spatial registration and anatomical overlay of the functional data. Collected time-series of fMRI volumes were pre-processed and analyzed using the different procedures described in the preceding section (motion correction, spatial smoothing, temporal high-pass filtering, and general linear modelling). To identify the differences between the brain responses elicited by novel non-target and target stimuli and the brain responses elicited by standard stimuli, contrasts between the conditions novel non-target vs. standard stimuli and novel target vs. standard stimuli were assessed as described for Experiment 1.

Results

Experiment 1

Behavioral data

The average ratings of stimulus saliency were as follows: nociceptive somatosensory: 6.1 ± 2.2; non-nociceptive somatosensory: 5.2 ± 2.2; auditory: 5.1 ± 3.0; visual: 5.0 ± 1.7. Although the nociceptive somatosensory stimulus elicited a sensation that was

qualified as clearly *painful* and *pricking*, the average ratings of saliency were not significantly different (repeated-measures ANOVA: $F=0.75$; $p=0.53$).

General linear model analysis

Nociceptive somatosensory, non-nociceptive somatosensory, auditory, and visual stimuli elicited consistent activity in a wide network of brain regions. A large amount of spatial overlap between the BOLD responses elicited by each of the four stimulus types was immediately noticeable (Fig. 1).

Conjunction analysis

The conjunction analysis showed that all four stimuli elicited strikingly similar BOLD responses in the ipsilateral and contralateral parietal operculum (areas corresponding to S2), insula, posterior parietal cortex, ACC, and thalamus, thus indicating that the largest part of the BOLD response elicited by all four stimuli was *multimodal* (Fig. 2). In addition to this multimodal activity, nociceptive and non-nociceptive somatosensory stimuli elicited a joint, *somatosensory-specific* response in the medial portion of the post-central gyrus, corresponding to the foot area of S1 (Figs. 2 and 3), while auditory stimuli elicited an *auditory-specific* response in the ipsilateral and contralateral temporal operculum (areas corresponding to A1), and visual stimuli elicited a visual-specific response in the occipital lobes (areas encompassing V1). In contrast, *nociceptive-specific* activity was extremely sparse, forming small patches in the ipsilateral and contralateral frontal operculum, as well as in the ipsilateral medial prefrontal cortex. Most of these nociceptive-specific voxels were located at the margins of large multimodal clusters of activity.

As detailed in Materials and methods, we examined whether the voxels exhibiting multimodal activity responded preferentially to stimuli belonging to a particular sensory modality (Fig. 4). This analysis showed that multimodal voxels located at the junction between the parietal operculum and the insula displayed a significantly greater response following nociceptive and non-nociceptive somatosensory stimulation, especially in the hemisphere contralateral to the stimulated side. This finding suggests that these voxels at least partially reflected neural activity *preferentially* involved in processing somatosensory input.

Correlation between BOLD response and subjective rating of stimulus saliency

Independently of sensory modality, a significant positive correlation between the ratings of stimulus saliency and the magnitude of the stimulus-evoked BOLD response was found in all the regions of interest (ROI) exhibiting multimodal activity (Fig. 5, right panel): S2 ($r^2=0.38$, $p<0.0001$), A2 ($r^2=0.27$, $p<0.0001$), posterior insula ($r^2=0.45$, $p<0.0001$), anterior insula ($r^2=0.47$, $p<0.0001$), and ACC ($r^2=0.50$, $p<0.0001$).

Model-free analysis of raw BOLD signal

Average peri-stimulus plots of the obtained raw BOLD signal time courses are displayed in Figs. 3 and 5.

ROIs displaying modality-specific activity

In S1 contralateral to the stimulated side, the time courses of BOLD signals displayed a significant increase following nociceptive (from 5 to 9 s after stimulus onset) and non-nociceptive somatosensory stimulation (from 2 to 8 s after stimulus onset), but not following auditory or visual

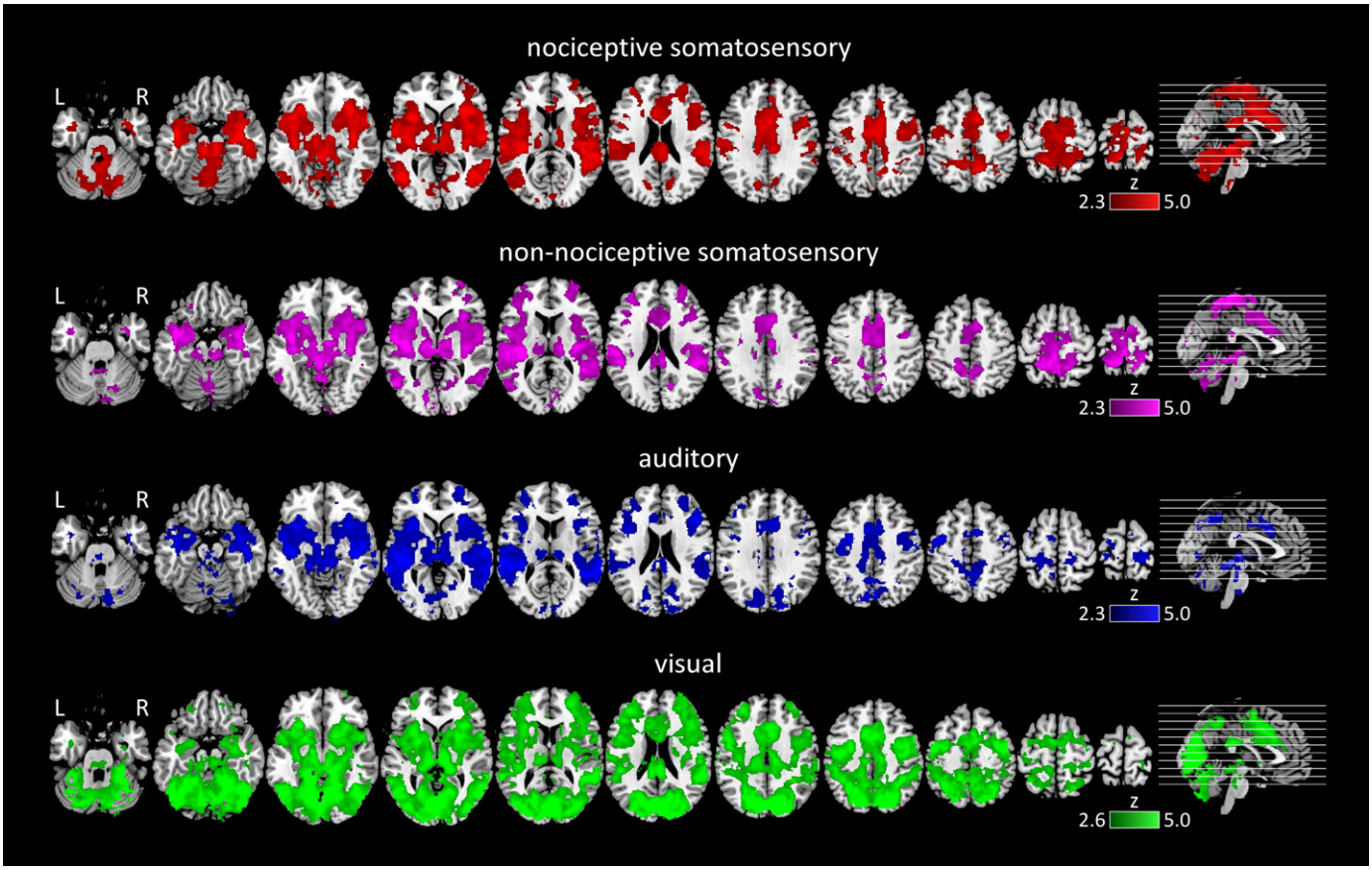


Fig. 1. BOLD response to nociceptive somatosensory (red), non-nociceptive somatosensory (purple), auditory (blue), and visual (green) stimulation. Random-effect group analysis, voxel threshold $Z>2.3$ and cluster threshold $p<0.05$, corrected for multiple comparisons across the whole brain. L: left, R: right. Significant clusters are overlaid onto an average structural scan. Note the large amount of spatial overlap between the responses elicited by all four modalities of sensory stimulation.

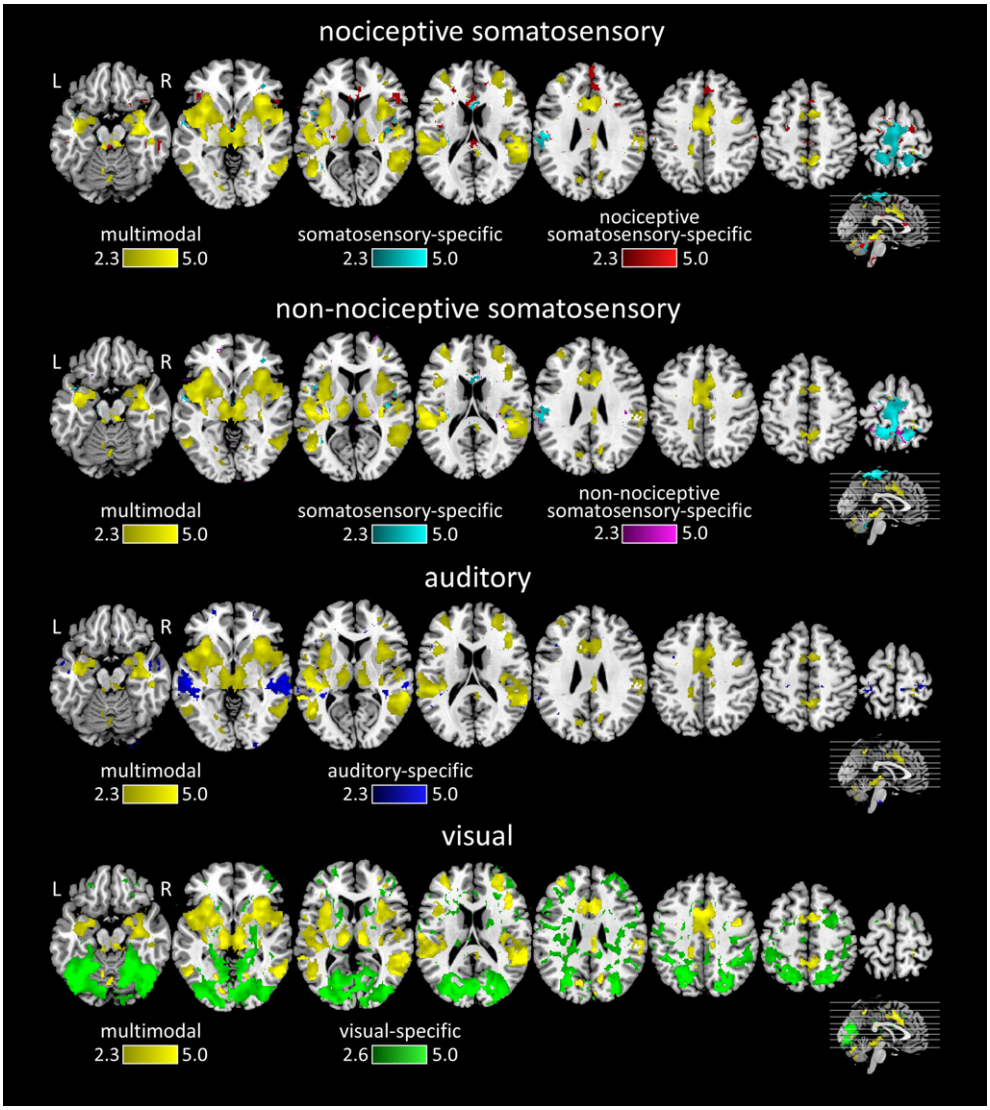


Fig. 2. Conjunction analysis. To dissociate modality-specific from multimodal brain responses, a conjunction analysis was performed using the MS/CN procedure (see Materials and methods). Multimodal voxels (i.e., voxels displaying a significant activation to all four types of sensory stimuli) are shown in yellow. Somatosensory-specific voxels (i.e., voxels displaying significant activation to nociceptive and non-nociceptive somatosensory stimulation, but not to auditory or visual stimulation) are shown in cyan. Nociceptive-specific voxels (i.e., voxels displaying significant activation only to nociceptive somatosensory stimuli) are shown in red. Non-nociceptive somatosensory-specific, auditory-specific, and visual-specific voxels are shown in purple, blue, and green respectively. L: left, R: right.

stimulation (Fig. 3, right panel). The two-way ANOVA performed on the estimate of response magnitude in the ipsilateral and contralateral S1 revealed a significant effect of the factor "stimulus" ($F=4.5$, $p=0.008$), as well as a significant interaction between the factors "stimulus" and "hemisphere" ($F=18.9$, $p<0.001$). Post hoc comparisons showed that in S1 contralateral to the stimulated side, both nociceptive and non-nociceptive somatosensory stimuli elicited responses of greater magnitude than auditory or visual stimuli (Fig. 3, right panel).

In A1, BOLD signals displayed a significant increase following auditory stimuli (2–9 s after stimulus onset. The two-way ANOVA performed on the estimates of response magnitude showed a significant effect of the factor "stimulus" ($F=12.1$, $p<0.001$), but no effect of "hemisphere" and no interaction. Post hoc comparisons showed that in both the ipsilateral and contralateral A1, auditory stimuli elicited responses of greater magnitude than nociceptive or non-nociceptive somatosensory stimuli, as well as visual stimuli (Fig. 3, right panel).

Finally, in V1, BOLD signals displayed a significant increase only following visual stimuli (2–9 s after stimulus onset). The one-way ANOVA performed on response magnitudes showed a significant effect of "stimulus" ($F=8.5$, $p<0.001$). Post hoc comparisons showed that in V1, visual stimuli elicited a greater response than any other type of stimulus (Fig. 3, right panel).

ROIs displaying multimodal activity

In S2, A2, the anterior insula, and the ACC, BOLD signals displayed a significant increase following all four modalities of stimulation (see Fig. 5, left panel for latencies). In the posterior insula, BOLD signals displayed a significant increase following nociceptive and non-nociceptive somatosensory stimulation, auditory stimulation, but not visual stimulation.

The two-way ANOVA performed on the magnitude of the responses estimated in the ipsilateral and contralateral S2, A2, posterior insula, and anterior insula showed a significant effect of "stimulus" (S2: $F=3.5$, $p=0.024$; A2: $F=9.2$, $p<0.001$; posterior insula: $F=6.4$, $p=0.001$; anterior insula: $F=4.2$, $p=0.011$), but no effect of "hemisphere", and no interaction between the two factors. The one-way ANOVA performed on the magnitude of the responses estimated in the ACC did not show a significant effect of "stimulus" ($F=2.4$, $p=0.083$). Post hoc comparisons showed that the magnitude

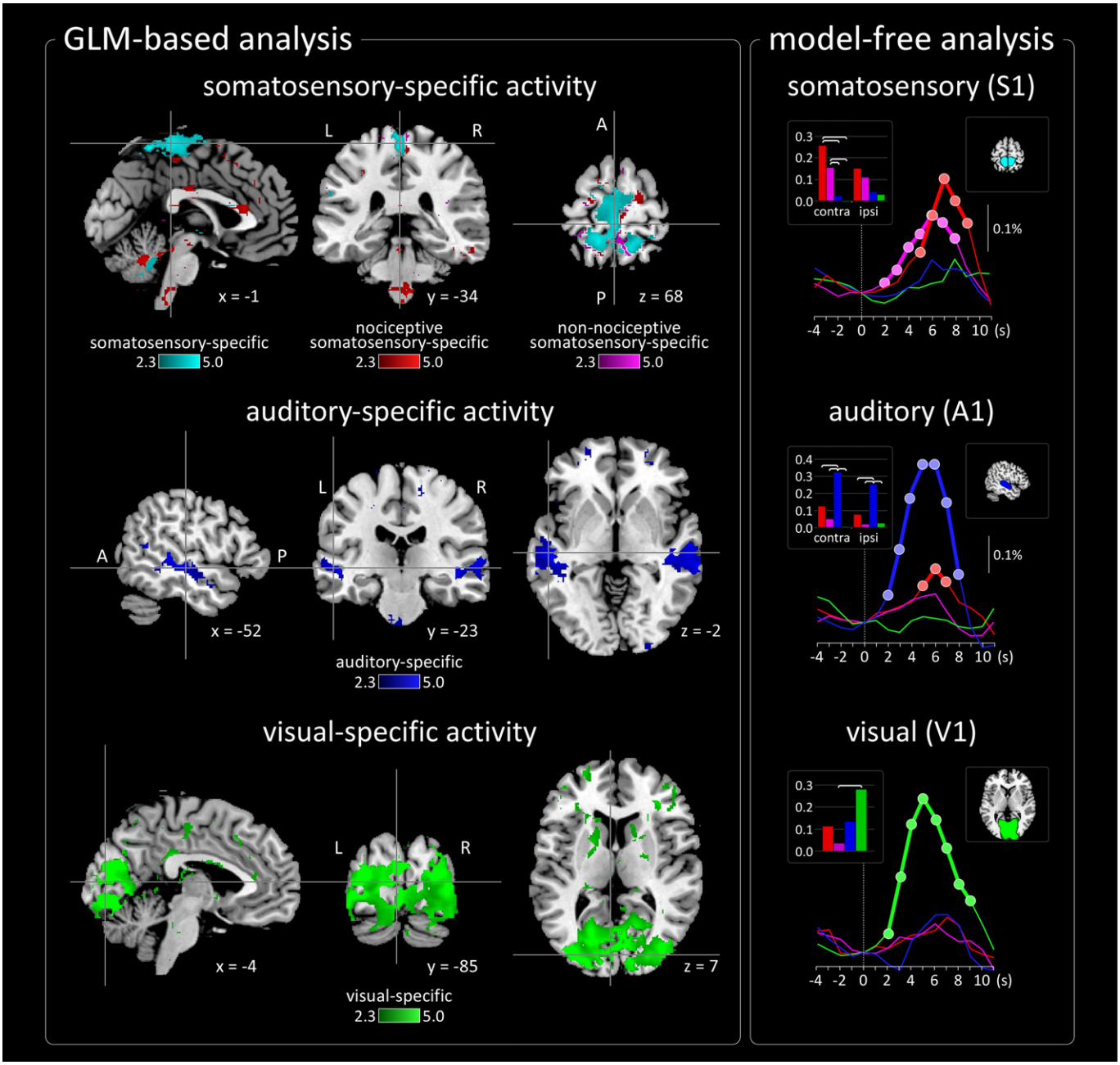


Fig. 3. Modality-specific brain responses. *Left panel.* GLM analysis: somatosensory-specific voxels (in cyan) correspond to voxels showing significant activation to nociceptive and non-nociceptive somatosensory stimulation but not to auditory or visual stimulation. Note that these are located in the medial part of the post-central gyrus, corresponding to the foot area of S1. Auditory-specific voxels (in blue) and visual-specific voxels (in green) correspond to voxels showing significant activation only to auditory or visual stimulation. Note how these encompass A1 and V1, respectively. Coordinates are in Montreal Neurological Institute space. L: left, R: right, A: anterior, P: posterior. *Right panel.* Raw BOLD-signal time courses, averaged relative to the onset (vertical dashed line) of nociceptive somatosensory (red), non-nociceptive somatosensory (purple), auditory (blue), and visual (green) stimuli (group-level average). *x* axis: time (s); *y* axis: %signal change averaged across all voxels located in the S1, A1, and V1 ROI contralateral to the stimulated side. The time intervals showing a significant increase relative to baseline are highlighted by colored disks and thick segments. Upper left graphs show the average %signal change to stimuli of each sensory modality in the contralateral and ipsilateral ROI (area under the curve of the BOLD-signal between +2 and +8 s). The thick connecting segments highlight significant differences between stimuli of different modalities.

of the BOLD response in S2, the posterior and anterior insula, and the ACC was significantly greater following nociceptive vs. non-nociceptive stimulation (Fig. 5, left panel). To clarify the significance of these differences, and because the correlation analysis had shown that the magnitudes of these responses were positively correlated with the ratings of saliency (Fig. 5, right panel), subjects were divided into two groups of equal size according to how they had rated the saliency of each stimulus type (median split between low and high ratings of stimulus saliency, expressed within each participant as standard deviation from the mean). This procedure showed that the magnitude of the BOLD response was strongly conditioned by the saliency of the stimulus and not necessarily greater following nociceptive stimulation (Fig. 5, middle panel). Indeed, when nociceptive stimuli were perceived as less salient than non-nociceptive stimuli, the magnitude of the BOLD response following nociceptive stimulation was, in fact, *smaller* than the magnitude of the BOLD response following non-nociceptive stimulation.

Experiment 2

As compared to standard auditory stimuli, both novel non-target and novel target stimuli elicited a significantly greater BOLD response

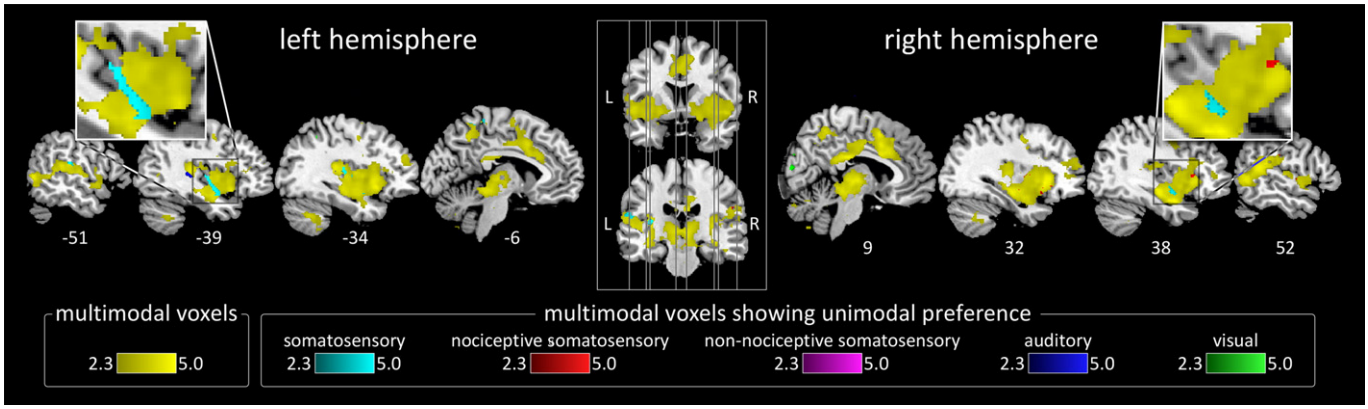


Fig. 4. Multimodal brain responses. Within multimodal voxels (in yellow), it was examined whether some showed a preference to stimuli of a particular modality. Voxels responding preferentially to somatosensory stimuli are shown in cyan, while voxels responding preferentially to nociceptive somatosensory, non-nociceptive somatosensory, auditory, or visual stimuli are shown in red, purple, blue, and green, respectively. Coordinates are in Montreal Neurological Institute space. L: left, R: right.

in a wide array of brain regions (Fig. 6, upper panel). Indeed, the differential contrast between novel non-target and standard auditory stimuli revealed significantly greater BOLD responses in the left and right thalamus, temporal lobes (areas corresponding to A1 and A2), posterior parietal cortices, and the mid-portion of the ACC. The differential contrast between novel target and standard auditory stimuli revealed an even more widespread pattern of greater activation, this time also including the parietal and frontal operculum, as well as the insula.

This network of brain regions was largely overlapping with the network of brain regions displaying the multimodal BOLD responses identified in Experiment 1 (Fig. 6, lower panel).

Discussion

Our study yielded four main findings. First, at least at the macroscopic level of fMRI, nociceptive and non-nociceptive somatosensory stimuli, auditory stimuli, and visual stimuli elicited extremely similar responses in the thalamus, S2, the insula, and the ACC (Fig. 2), thus indicating that a significant fraction of the neural activities determining the BOLD response within these structures are multimodal (i.e., they are elicited by all stimuli regardless of sensory modality). Second, nociceptive and non-nociceptive somatosensory stimuli elicited spatially indistinguishable responses in S1 (Fig. 3) as well as in a restricted portion of S2 (Fig. 4), thus indicating that a fraction of the neural activities determining the BOLD response in these two structures are somatosensory-specific, but not nociceptive-specific (i.e., they are elicited by all somatosensory stimuli, regardless of whether they are nociceptive or non-nociceptive). Taken together, these first two findings suggest that the network of regions identified using fMRI that is commonly labeled as the "pain matrix" is equally involved in processing nociceptive and non-nociceptive stimuli.

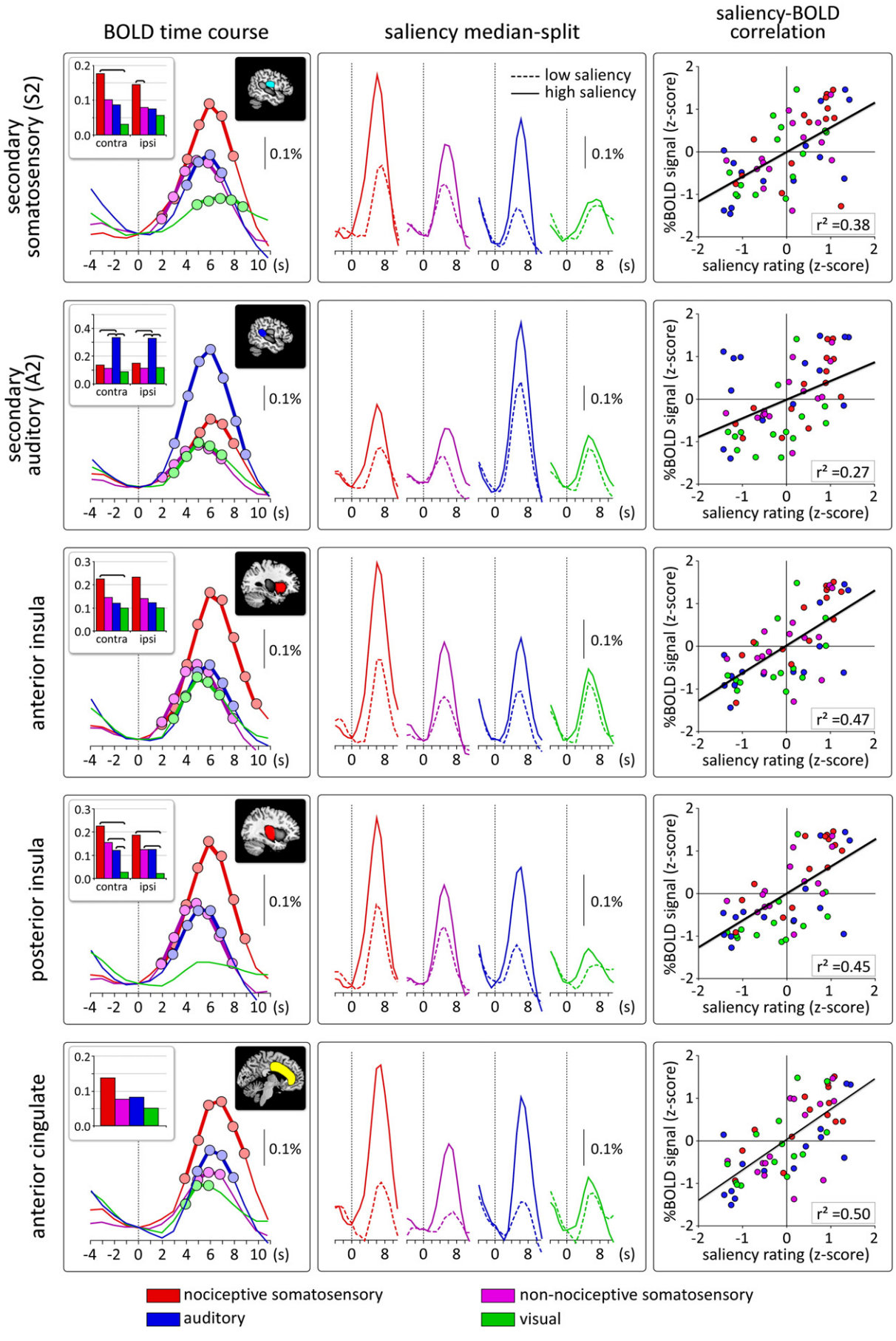
Third, the magnitude of the multimodal responses in the insula, ACC, and S2 correlated significantly with the perceived saliency of the stimulus, regardless of its sensory modality (Fig. 5, right panel). This finding suggests that the multimodal brain responses that represent the greater part of the "pain matrix" is partly, if not entirely, related to bottom–up cognitive processes involved in saliency detection, arousal, and/or attentional capture (Downar et al., 2000, 2002).

Fourth, novel non-target and novel target auditory stimuli delivered in Experiment 2 elicited a BOLD response whose spatial distribution resembled closely that of the multimodal brain activity identified in Experiment 1 (Fig. 6). This finding indicates that the multimodal activities identified in Experiment 1 cannot be attributed to pain anticipation, i.e., to the fact that subjects were expecting the possible occurrence of a painful stimulus. Furthermore, because saliency and behavioral relevance were the key factors differentiating novel non-target and target stimuli from standard stimuli delivered in the auditory oddball paradigm, this finding provides further evidence suggesting that the greater part of the "pain matrix" is likely to reflect cognitive brain processes involved in the detection and processing of salient sensory input.

Primary somatosensory cortex

Our results show that nociceptive and non-nociceptive somatosensory stimuli elicit an identical pattern of activity in S1. This activity was located in the medial part of the post-central gyrus, a location compatible with the foot of the somatosensory homunculus (Penfield and Boldrey, 1937). Importantly, this result does not necessarily imply that nociceptive and non-nociceptive somatosensory stimuli activate the same population of S1 neurons. Indeed, these stimuli could elicit activity within two subpopulations of S1 neurons that are spatially indistinguishable at the macroscopic level of BOLD signals (Logothetis, 2008). In agreement with this view, single-cell recordings in animals have shown that S1 neurons responding to nociceptive stimuli are sparsely distributed and intermingled with non-nociceptive neurons having similar receptive fields (Kenshalo and Isensee, 1983). In fact, nociceptive-specific neurons are not even organized into nociceptive-specific cortical columns. Furthermore, neurons responding to nociceptive stimuli can either respond *uniquely* to nociceptive stimuli ("nociceptive-specific" neurons, NS) or respond to *both* nociceptive

Fig. 5. *Left panel.* Group-level time courses of the BOLD-signal recorded in multimodal brain regions, averaged relative to the onset (vertical dashed line) of nociceptive somatosensory (red), non-nociceptive somatosensory (purple), auditory (blue), and visual (green) stimuli. *x* axis: time (s); *y* axis: % signal change. Time intervals showing a significant increase relative to baseline are highlighted by colored disks and thick segments. Graphs (upper left insets) show the average % signal change in the contralateral and ipsilateral ROIs (area under the curve of the BOLD signal between +2 and +8 s). The black connecting segments highlight significant differences between stimuli of different modalities. Note that, in all ROIs, stimuli of different sensory modalities elicited a significant BOLD response. Also note that in S2, anterior insula, posterior insula, and the ACC, nociceptive stimuli elicit a greater response than non-nociceptive stimuli. *Middle panel.* Participants were divided into two groups of equal size according to their saliency rating, for each stimulus type. Note that the magnitude of the response to nociceptive stimuli perceived as less salient is smaller than the magnitude of the responses to non-nociceptive stimuli perceived as more salient. *Right panel.* Correlation between stimulus saliency and the average magnitude of the BOLD response to each type of sensory stimulation. *x* axis, saliency rating; *y* axis, BOLD response. Both rating and magnitude of the BOLD response are expressed as *z*-scores relative to the mean rating and response magnitude of each participant. The linear regression across all values, significant in all ROIs, is represented as a thick black line. Each colored disk represents the response of one participant to stimuli of one sensory modality.


BOLD time course
saliency median-split
saliency-BOLD correlation
secondary somatosensory (S2)
secondary auditory (A2)
anterior insula
posterior insula
anterior cingulate
contra
ipsi
0.1%
----- low saliency
—— high saliency
%BOLD signal (z-score)
saliency rating (z-score)
r² =0.38
r² =0.27
r² =0.47
r² =0.45
r² =0.50
(s)
nociceptive somatosensory
non-nociceptive somatosensory
auditory
visual

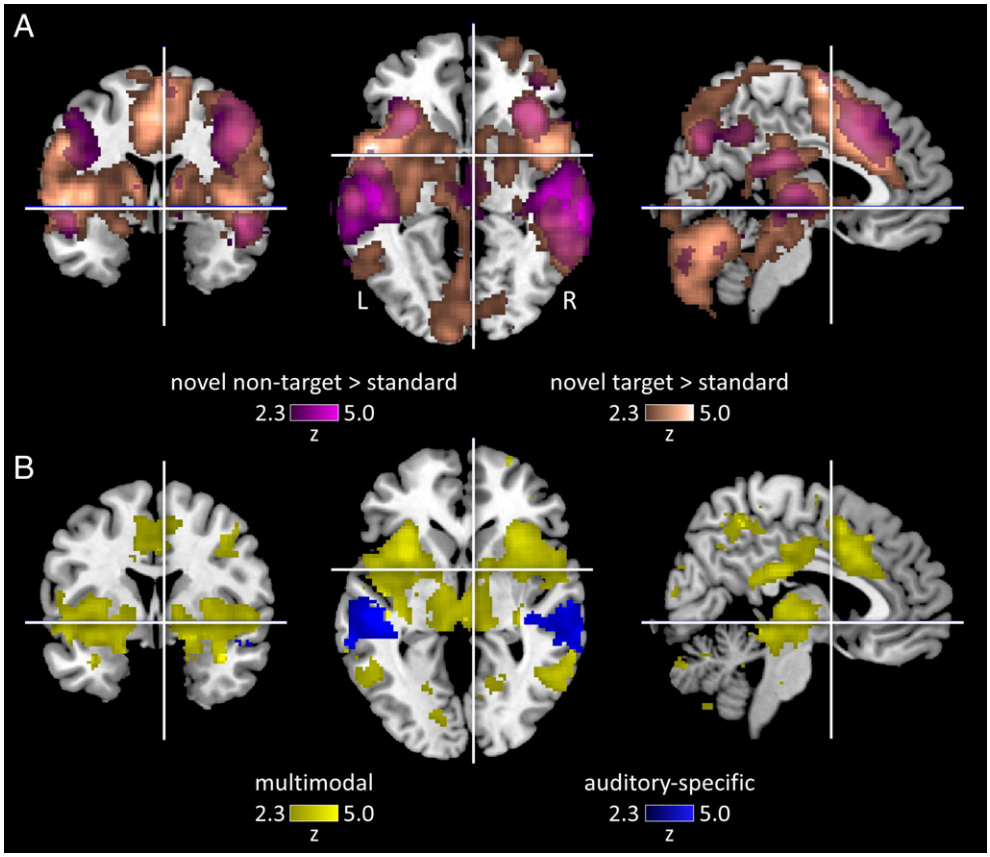


Fig. 6. BOLD-fMRI responses elicited by auditory stimuli presented using an oddball paradigm (Experiment 2). A. Voxels displaying significantly larger responses to novel non-target vs. standard stimuli are shown in purple, whereas voxels displaying significantly larger response to novel target vs. standard stimuli are shown in pink. Coordinates are in Montreal Neurological Institute space. L: left, R: right. B. The pattern of multimodal responses (yellow) and auditory-specific responses (blue) recorded in Experiment 1 are shown in the same reference space. Note the large spatial overlap between the brain responses triggered by novel and target auditory stimuli in Experiment 2, and the multimodal brain responses identified in Experiment 1.

and non-nociceptive stimuli ("wide dynamic range" neurons, WDR). Notably, not only in S1 but also in other regions of the "pain matrix", the ratio between WDR and NS neurons is largely in favor of WDR neurons (Dong et al., 1994; Kenshalo and Douglass, 1995). Furthermore, following nociceptive stimulation, WDR neurons exhibit much higher firing rates than NS neurons (Kenshalo and Isensee, 1983). Therefore, we suggest that, at least in S1, the bulk of the BOLD response following nociceptive stimulation originates from WDR neurons also responding to non-nociceptive somatosensory stimulation.

Secondary somatosensory cortex

In contrast to the somatosensory-specific response in S1, our results indicate that the largest part of the BOLD response in S2 is multimodal. Indeed, nociceptive and non-nociceptive somatosensory stimuli, and also auditory and visual stimuli, elicited a similar response in the ipsilateral and contralateral S2. This finding is compatible with the accumulating experimental evidence indicating that S2 integrates inputs across multiple sensory modalities (Brett-Green et al., 2004; Menzel and Barth, 2005; Robinson and Burton, 1980).

We also observed that in a small subregion of S2, located at the junction between the parietal operculum and the insula, the BOLD response following nociceptive and non-nociceptive somatosensory stimulation was significantly stronger than the BOLD response following auditory or visual stimulation, thus indicating that part of S2 may be preferentially involved in processing somatosensory input. This somatosensory-specific (but, crucially, non-nociceptive-specific) response was prominent in the hemisphere contralateral to the stimulated side. This finding is compatible with the results of previous studies suggesting a somatotopical organization of S2, where the foot area would lie in its most medial part (Del Gratta et al., 2002).

Insula

Such as in S2, our results show that the largest part of the BOLD signal both in the anterior and posterior insula reflects multimodal neural activities. This finding questions the classical view that the posterior insula is primarily involved in somatosensation and nociception (Augustine, 1996; Craig et al., 2000) and that part of the posterior insula may even constitute a primary "thermosensory cortex" (Craig et al., 2000). In contrast, this finding agrees well with the results of a number of recent studies, suggesting a central role of the anterior insula in human perception (independently of sensory modality), cognition, and attention (e.g., Brass and Haggard, 2010; Menon and Uddin, 2010; Sterzer and Kleinschmidt, 2010).

Anterior cingulate cortex

A robust BOLD response to nociceptive stimulation in the ACC is a consistent finding across fMRI studies (Peyron et al., 2000). This response is often considered to play a key role in generating the affective dimension of pain. However, Vogt et al. (1996) suggested

that the affective reactions associated with pain unpleasantness are confined mainly to the peri-genual region of the ACC, whereas most neuroimaging studies show pain-related activity located in the mid-cingulate, a region which is thought to be involved in attentional orienting processes and premotor functions (Bancaud et al., 1976; Berns et al., 1997; Botvinick et al., 2004; Clark et al., 2000; Devinsky et al., 1995). For this reason, investigators have hypothesized that the mid-cingulate component of the "pain matrix" may reflect a specific function of "orienting attention to pain" (Peyron et al., 2000). Our results, showing that nociceptive and non-nociceptive stimuli elicit a similar response in the ACC, indicate that there is no reason to consider this orienting function specific for nociception.

Stimulus saliency

The ability to discriminate the different qualities of a painful percept elicited by a nociceptive stimulus is certainly sufficient to postulate the existence of "pain-specific" cortical activity. However, the results of the present study indicate that this cortical activity does not constitute the bulk of the BOLD fMRI response elicited by a transient nociceptive stimulus.

The saliency of a given sensory stimulus is commonly defined as its ability to stand out relative to both the background sensory environment and the preceding sensory events (Itti and Koch, 2001). Therefore, the saliency of a stimulus is not determined by a particular feature of the stimulus but by how much each of its different features contrast with the surrounding (Fecteau and Munoz, 2006; Itti and Koch, 2001; Knudsen, 2007; Yantis, 2008). It is generally recognized that the ability to detect, reorient attention, and prioritize the cortical processing of salient sensory input is crucial for survival (Legrain et al., 2009; Van Damme et al., 2010). Indeed, this ability allows individuals to adapt swiftly and efficiently their behavior to the changing environment. Because of their noxious nature, nociceptive stimuli have an intrinsically high saliency content, and, for this reason, this ability to detect and react to salient sensory input is often considered as one of the most important function of nociception.

In addition to showing that the bulk of the fMRI responses constituting the pain matrix are multimodal (i.e., S2, the insula, the ACC), our results also suggest that stimulus saliency is an important determinant of their magnitude, for two reasons. First, the magnitude of the multimodal responses identified in Experiment 1 was not dependent on the nociceptive nature of the stimulus but, instead, was significantly related to the subjective rating of the saliency of the stimulus, regardless of sensory modality. Second, the same response pattern was revealed in Experiment 2 when contrasting the BOLD response triggered by novel non-target and novel target auditory stimuli with the BOLD response triggered by standard auditory stimuli. In this experiment, the increase in BOLD response associated with novel *non-target* stimuli may be considered to be related exclusively to the novelty of the stimulus and, hence, to reflect brain processes that are largely driven by bottom–up factors that determine the saliency of the stimulus. In contrast, the more widespread increase in BOLD response associated with novel *target* stimuli may be considered to also reflect brain processes that are driven by goal-oriented, top–down factors.

Therefore, these multimodal responses are likely to reflect brain processes related, directly or indirectly, to the process of detecting salient and/or behaviorally relevant sensory events, *regardless of the sensory modality through which these events are conveyed*. This interpretation would agree with the results of previous studies indicating that some of these brain structures are part of a "multimodal network for the detection of changes in the sensory environment" (Downar et al., 2000). Obviously, at least part of these multimodal brain responses could reflect brain processes that are likely to follow the detection of salient sensory input, such as neural activity related to motor preparation and action or neural activity related to the emotional expression.

Importantly, this reinterpretation of the functional significance of the "pain matrix" (see also, for a detailed discussion on the topic, Iannetti and Mouraux 2010) would constitute a viable alternative explanation as to why, in most cases, the magnitude of the "pain matrix" response correlates strongly with the intensity of the noxious stimulus or the intensity of pain perception (Baliki et al., 2009; Coghill et al., 1999; Derbyshire et al., 1997; Iannetti et al., 2005). Indeed, when stimuli of graded energy are presented within the same attentional context, the stimuli of greater energy are also more salient (i.e., they are more contrasted relative to the surrounding environment).

Conclusion

We conclude that the network of brain areas exhibiting a significant BOLD fMRI response to nociceptive stimulation, often referred to as the "pain matrix", can also respond to any salient or behaviorally relevant stimulus, regardless of whether it is nociceptive in nature.

This conclusion has one crucial implication: the observation that a given stimulus elicits a pattern of BOLD fMRI response similar to that elicited by a nociceptive stimulus, or that a given experimental manipulation modulates the activity within this pattern, cannot be considered as unequivocal evidence that the stimulus or the applied experimental manipulation engage pain-specific cortical processes. Indeed, such observations could often result from an activation or a modulation of multimodal neural activities, i.e., neural activities that are largely independent of nociceptive processing. In many instances, this possibility can be fairly easily examined using an experimental design that includes, for example, control stimuli of similar saliency content.

Importantly, our findings do not imply that the neural activities subserving the fMRI brain responses to nociceptive stimuli are not important for the experience of pain. Instead, they suggest that these responses mainly reflect multimodal brain processes that are likely to be crucial for all sensory systems, as they relate to the ability to detect and react to salient or behaviorally relevant sensory input, and thereby trigger swift and appropriate behavioral responses.

Novel approaches to analyze fMRI data, such functional connectivity methods aiming to characterize how information flows across this network of brain regions could provide more specific information about how pain sensations are generated at the level of the cerebral cortex.

Acknowledgments

A.M. is a Marie-Curie post-doctoral Research Fellow and a "*chargé de recherches*" of the Belgian National Fund for Scientific Research (FNRS). A.D., M.C.L., and R.G.W. are supported by the Medical Research Council. G.D.I. is University Research Fellow of The Royal Society and acknowledges the support of the BBSRC.

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