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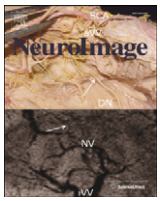

Activation of central sympathetic networks during innocuous and noxious somatosensory stimulation

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ABSTRACT

Although pain is accompanied by autonomic nervous system responses, the cerebral circuits involved in the autonomic pain dimension remain elusive. Therefore, we used functional magnetic resonance imaging (fMRI) and investigated brain processing associated with cutaneous sympathetic vasoconstrictor reflexes during noxious stimulation. When a classical fMRI analysis based on the applied block design was performed, we were able to detect activations well known to be engaged in the central processing of touch and pain. A parametric fMRI analysis in which cutaneous vasoconstrictor activity was correlated with MRI signals revealed two distinct patterns of brain activity. During (i) noxious stimulation itself, brain activity correlated with sympathetic activity in the anterior insula, ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex (ACC), and secondary somatosensory cortex (S2). During (ii) baseline, brain activity correlated with sympathetic activity in the VMPFC, dorsolateral prefrontal cortex (DLPFC), OFC, PCC, cuneus, precuneus, occipital areas, and hypothalamus. Conjunction analysis revealed significant similar responses during periods of noxious stimulation and periods of sympathetic activation in the anterior insula, ACC and VLPFC (activation) and VMPFC, OFC, PCC, cuneus and precuneus (deactivation). Therefore, we here describe a cerebral network which may be engaged in the processing of the autonomic subdimension of the human pain experience.

Introduction

The human pain experience is a complex sensation that is of paramount importance for maintaining body integrity and guaranteeing the survival of human beings. It is a multidimensional phenomenon including sensory-discriminative, affective–motivational, motor, and autonomic components. Remarkable efforts have been undertaken to explore the underlying cerebral processing, using non-invasive functional brain imaging techniques. There is evidence that the thalamus, primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insula, parts of the frontal cortices and anterior cingulate cortex (ACC) are crucially involved in the processing of human pain (Apkarian et al., 2005; Tracey and Mantyh, 2007). Furthermore, there is accumulating evidence that these areas process different aspects of pain. Processing in S1 and S2 determines the perception of sensory features of pain (Hofbauer et al., 2001; Treede et al., 1999), whereas the ACC and parts of the insula process affective–motivational aspects (Maihofner and Handwerker, 2005; Rainville et al., 1997; Treede et al., 1999). It is also of great clinical importance that pain is often accompanied by autonomic nervous system responses (Jänig, 1975; Jänig and Habler, 2003); it remains unclear however which brain areas are relevant for pain-related autonomic processing. Therefore, in the present study we used parametric functional magnetic resonance imaging (fMRI) to investigate brain processing associated with cutaneous sympathetic vasoconstrictor reflexes during noxious stimulation. Skin vasoconstrictor responses at the fingertip closely parallel central sympathetic outflow, as the abundant arteriovenous anastomoses of this area are subject to strict control from sympathetic vasoconstrictor neurons (Jänig and Habler, 2003; Wallin, 1990). We here report that increased activations of anterior insula, cingulate cortex and prefrontal cortices covary with pain-evoked sympathetic activity, providing a neural basis for the autonomic pain dimension.

Material and methods

Subjects

A total of 12 healthy subjects (6 male, 6 female, mean age 26.45 years ± 1.23 years) participated in the study. The volunteers were informed in advance about the procedures of the study. Informed consent was obtained from all participants, and the study adhered to the tenets of the Declaration of Helsinki. The study was

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approved by the local ethics committee. All subjects were already experienced in psychophysical studies.

Experimental protocol

The stimulation site in all subjects was the dorsum of the left hand. Two different stimuli (i.e. tactile and noxious stimulation) were applied in a randomized sequence. Mechanical impact stimuli were delivered using a ballistic apparatus as described previously (Kohlloffel et al., 1991; Maihofner et al., 2006b, 2007b). Briefly, a pneumatically driven plastic projectile (weight 0.5 g; diameter 5 mm) guided by a 31 cm long barrel provided phasically ballistic tactile or pain stimuli to the subjects' skin. Using this device, different pain intensities could be provoked by applying different velocities of the projectile (Kohlloffel et al., 1991). During fMRI experiments, impact stimulation was applied in a block design with a frequency of 1 Hz. Each stimulation block lasted 21 s, interrupted by a baseline of varying length (21–31 s), for a non-periodical stimulus protocol. Five stimulation blocks were applied for each psychophysical evaluation, i.e. tactile stimulation and mechanical impact pain.

Before fMRI sessions, psychophysical testing was performed to adjust pain intensities for noxious stimulation. The following velocities were applied: 12, 16, 20, 24, 28, and 32 m/s in ascending order. The ratings of tactile sensation and pain sensation were obtained using an NRS, ranging from 0 to 100. It was defined that 0 was no sensation, 10 was the beginning of pain, and 100 was the maximum of pain. NRS values were used to calculate stimulus response functions (Maihofner et al., 2007b). For fMRI measurement of brain activity during mechanical pain, only intensities of pain at NRS = 80 were used. Furthermore, during the fMRI experiments subjects were asked to rate the perceived pain and to give their ratings after the fMRI scanning procedure. The ratings were 8.1 ± 1.3 for tactile stimulation (thus, tactile stimulation was not painful) and 81.8 ± 4.5 for pain stimulation.

Measurement of skin perfusion as a marker for sympathetic activity

Cutaneous blood flow in the glabrous skin (of the left index finger) was measured during fMRI experiments using an MRI-suitable laser Doppler flowmeter (LDI, Moore Instruments, UK). The fingertip was selected for investigation because it is known that the abundant arteriovenous anastomoses of this area are under strict sympathetic vasoconstrictor control (Jänig and Habler, 2003; Wallin, 1990). Therefore, changes mediated by central sympathetic outflow are very prominent, and vasomotor reflexes are extensive. During all experiments, laser Doppler signals were recorded online (IBM-compatible computer) using an analog digital converter (Moore Instruments, UK) along with a custom-made data acquisition software (Maihofner et al., 2006a) for subsequent analysis. The sampling rate was 1 Hz. Skin blood flow is expressed in arbitrary perfusion units (Wasner et al., 1999). The baseline blood flow was set at a value of "1" (representing 100%), and corresponding evoked vasoconstrictor responses are presented as signal changes relative to the baseline flux. Data were baseline corrected, and periods of 3 s were averaged to account for the repetition time of fMRI experiments. The MRI scanner was inside an air-conditioned room in which the temperature was kept between 21 and 23 °C. Subjects had to acclimatize inside the room for at least 25 min. In addition an infrared thermometer was used to guarantee that the temperature at the index finger did not drop below 30 °C. If necessary, the arm and trunk of the subjects were covered by woollen blankets until a stable temperature situation at the hand was achieved.

fMRI image acquisition

Echoplanar images were collected on a 1.5 T MRI scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany) using the standard head coil. For each subject two time series (tactile and noxious stimulation in a randomized order) of 93 whole-brain images were obtained, using a gradient-echo, echo-planar scanning sequence (EPI; TR 3 s, time to echo 40 ms, flip angle 90°; field of view 220 mm², acquisition matrix 64×64, 20 axial slices, slice thickness 4 mm, gap 1 mm). The first 3 images were discarded to account for spin saturation effects. A T1-weighted three-dimensional magnetization prepared rapid acquisition gradient echo sequence (MPRAGE) scan (voxel size = 1.0 × 1.0 × 1.0 mm^3) was recorded in the same session as the functional measurements for the recording of the individual brain anatomy.

fMRI study design and MRI sequence order

MRI sequences were assessed in the following order: anatomical scout, MPRAGE, EPI in randomized order (i.e. tactile and noxious stimulation).

fMRI data analysis

Data analysis, registration, and visualization were performed using the fMRI software package BrainVoyager QX (www.brainvoyager.com) (Maihofner et al., 2007a; Maihofner and Handwerker, 2005; Seifert and Maihofner, 2007). Data were motion-corrected using sinc interpolation. Preprocessing also included Gaussian spatial (FWHM = 4 mm) and temporal (FWHM = 3 volumes) smoothing of the functional data. Afterwards, the functional data were transformed into a standard stereotactic space and linear-interpolated to 3 × 3 × 3 mm (Talairach and Tournoux, 1988). During fMRI, a block design with two conditions (stimulus and baseline) was applied, with each stimulation block lasting 21 s and seven images being acquired. In a first analytical approach, the stimulation protocol served to obtain appropriate reference functions reflecting experimental and baseline conditions (stimulus = 1 and baseline condition = 0). The stimulation protocol was convoluted with a canonical haemodynamic response function (Boynton et al., 1996). Group analysis was performed resulting in T-statistical activation maps for the conditions (i) tactile stimulation and (ii) pain stimulation. A T-statistical contrast map (tactile stimulation *versus* pain stimulation) was calculated.

In a second analytical approach, we took the evoked patterns of sympathetic mediated vasoconstriction as recorded online during fMRI (see above) and used them as predictors in the GLM in order to identify brain regions covarying with sympathetic activity during (i) painful stimulation within corresponding stimulation blocks, (ii) baseline segments between painful stimulation outside the stimulation blocks, (iii) tactile stimulation within corresponding stimulation blocks, and (iv) baseline segments between tactile stimulation outside the stimulation blocks. Thus, we correlated changes in BOLD signal with changes in skin blood flow during (i) the stimulus blocks only and (ii) during the baseline periods only. For correlation of sympathetic vasoconstrictor activity with BOLD signal during painful or tactile stimulation the baseline segments were removed (by introducing an additional dummy-predictor masking the baseline condition). For correlation of changes in skin blood flow with changes in BOLD signal during baseline the stimulus block segments were removed (by introducing an additional dummy-predictor masking the stimulus condition).

All reference functions served as independent predictors for a general linear model (GLM). As implemented in the BrainVoyager software package, a z-transformation of the functional volume time courses for each subject was applied to take the varying baseline signal levels into account. For all contrasts, a threshold of $p < 0.05$ (false discovery rate [FDR] corrected) was used. Furthermore, a minimum cluster size of 150 mm^3 was used. The cluster size criterion was used as a conservative measure to minimize false positive activations (Maihofner and Handwerker, 2005; Mailis-Gagnon et al., 2003).