Representations of Pleasant and Painful Touch in the Human Orbitofrontal and Cingulate Cortices

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The cortical areas that represent affectively positive and negative aspects of touch were investigated using functional magnetic resonance imaging (fMRI) by comparing activations produced by pleasant touch, painful touch produced by a stylus, and neutral touch, to the left hand. It was found that regions of the orbitofrontal cortex were activated more by pleasant touch and by painful stimuli than by neutral touch and that different areas of the orbitofrontal cortex were activated by the pleasant and painful touches. The orbitofrontal cortex activation was related to the affective aspects of the touch, in that the somatosensory cortex (SI) was less activated by the pleasant and painful stimuli than by the neutral stimuli. This dissociation was highly significant for both the pleasant touch ($P < 0.006$) and for the painful stimulus ($P < 0.02$). Further, it was found that a rostral part of the anterior cingulate cortex was activated by the pleasant stimulus and that a more posterior and dorsal part was activated by the painful stimulus. Regions of the somatosensory cortex, including SI and part of SII in the mid-insula, were activated more by the neutral touch than by the pleasant and painful stimuli. Part of the posterior insula was activated only in the pain condition and different parts of the brainstem, including the central grey, were activated in the pain, pleasant and neutral touch conditions. The results provide evidence that different areas of the human orbitofrontal cortex are involved in representing both pleasant touch and pain, and that dissociable parts of the cingulate cortex are involved in representing pleasant touch and pain.

Introduction

Very little is known about the representation of affectively pleasant touch in the brain. Much more is known about the representation of pain in the brain, but it is not known whether the same or different areas represent affectively pleasant aspects of touch. This issue is of clinical relevance for, in so far as particular brain areas might be targeted (whether surgically or pharmacologically) therapeutically for pain relief, it is important to have evidence on whether a particular brain area is specifically involved in pain, or in affective somatosensory processing in general. In this paper we compare brain activations to pleasant, painful and neutral stimuli, to illuminate which parts of the brain represent affective aspects of touch.

It is clear that somatosensory stimulation can be rewarding (that is, worked for) and can produce pleasure, and seeking such stimulation could be advantageous to animals (including humans) in many ways (Rolls, 1999). One whole series of examples comes from the somatosensory stimulation produced by social contact and, indeed, the range of adaptive affiliative behaviours which involve somatosensory stimulation includes mother–infant interactions, grooming, play and sexual behaviour (Dunbar, 1996; Panksepp, 1998; Rolls, 1999). Another example of somatosensory stimulation that can be rewarding is that produced by the texture of a food in the mouth (Rolls, 1999; Rolls et al., 1999; Rolls and Scott, 2002). It is clearly adaptive therefore that some part of the brain should be involved in

representing the affectively positive aspects of somatosensory stimulation, as well as its aversive aspects, and some neuroimaging studies have been investigating the effects of tickling (Blakemore et al., 1998; Carlsson et al., 2000). Some evidence on the representation of affective somatosensory inputs comes from the finding that the texture of fat in the mouth activates a population of neurons in the macaque orbitofrontal cortex and that this population probably represents the reward value of the food, in that the responses to fat were decreased by feeding it to satiety (Rolls et al., 1999). In a pilot study we have shown that in humans pleasant touch to the hand (produced by velvet) produces relatively more activation of the orbitofrontal cortex than does neutral touch (produced by wood) when compared to the activation produced in the somatosensory cortex, SI (Francis et al., 1999). The present study builds on that pilot study, but includes a direct comparison with brain areas activated by painful touch, which was delivered to the hand to facilitate a direct comparison.

Somatic sensation depends on various types of receptors: mechanoreceptors, nociceptors, thermoreceptors, proprioceptors and various chemoreceptors, of which the first two are of special interest here. The mechanoreceptors of the skin in humans can be divided into four different types. Two of these (Meissner's corpuscles and Pacinian corpuscles) adapt rapidly, while the other two (Merkel's disks and Ruffini endings) adapt more slowly to constant skin indentation (Vallbo, 1995). This fragmented sensory information is subsequently integrated in the brain. Interestingly, there is some evidence that the C-mechanoreceptive units on hairy skin (although scarce on glabrous skin) have closer relations to limbic functions than to motor and cognitive functions (Vallbo et al., 1999).

Although much is known about the peripheral mechanisms and brainstem pathways involved in pain (Gardner and Kandel, 2000), somewhat less is known about cortical areas involved in pain. A lateral pain system projects via the somatotopically organized ventrobasal thalamic nuclei to the primary somatosensory area (SI; Brodmann's areas 1, 2 and 3) of the cerebral cortex and is believed to transmit spatially discriminative aspects of noxious stimuli (Ingvar, 1999; Gardner and Kandel, 2000). The primary somatosensory cortex then projects to a somatosensory area in the lateral sulcus of the inferior parietal cortex, which has been defined as the secondary somatosensory cortex – SII (Kaas, 1993). Other connections arise from SI to regions of the posterior parietal cortex (Kaas, 1993). The posterior and mid-insula receive somatosensory information through projections from SI and SII (Mufson and Mesulam, 1982; Friedman et al., 1986) and also directly from the thalamus (Craig et al., 1994). The orbitofrontal cortex receives somatosensory information from the granular insula and also directly from the primary and secondary somatosensory cortices (Barbas, 1988; Morecraft et al., 1992; Carmichael and Price, 1995). The anterior

cingulate cortex also receives somatosensory information, in particular direct nociceptive input (Vogt *et al.*, 1979; Van Hoesen *et al.*, 1993), but could also receive somatosensory information via the insula and orbitofrontal cortex, which are both well connected with the anterior cingulate cortex (Van Hoesen *et al.*, 1993). In addition, a medial pain system projects via the medial and intralaminar thalamic nuclei more diffusely to wide areas of the cerebral cortex and is believed to be mainly involved in the affective aspects of pain (Ingvar, 1999).

Imaging studies have shown that SI and SII can be activated by painful stimuli (Ingvar, 1999; Petrovic *et al.*, 2000), while other brain imaging studies have been probing central pain pathways (Derbyshire *et al.*, 1997; Davis, 2000; Peyron *et al.*, 2000) and the effects of placebo (Petrovic and Ingvar, 2002). One clearly defined route for pain and thermosensory inputs to reach the cortex is via the ventral aspect of the basal ventral medial nucleus of the thalamus, which projects to the posterior insula (Craig *et al.*, 1994). Consistently, in humans the posterior insula can be activated by these stimuli (Craig *et al.*, 2000). In addition, almost all studies show activation by painful stimuli of the anterior cingulate cortex (BA 24/32), considered to be part of the medial pain system (Vogt *et al.*, 1996; Iadarola *et al.*, 1998; Ingvar, 1999; Rainville *et al.*, 1999; Petrovic *et al.*, 2000). Evidence that it is the affective qualities of the pain stimulus and not other aspects of the sensory stimulation that are represented in the anterior cingulate was provided by Rainville and colleagues (Rainville *et al.*, 1997), who used hypnotic suggestion to alter the subject's subjective pain ratings of a thermal stimulus. The hypnotic suggestion was used both to increase and decrease the subjective unpleasantness of the pain stimulation, which remained at the same physical intensity throughout the experiment. The activation in the anterior cingulate was found to increase following a suggested increase in the subjective unpleasantness and decrease following a suggested decrease in the subjective unpleasantness, indicating that the cingulate is involved in representing the affective qualities of the stimulus rather than its physical intensity. Further evidence consistent with the anterior cingulate playing a role in the affective component of pain is that neurosurgical operations to the cingulate in chronic pain sufferers result in some alleviation of the affective consequences of the pain. Patients with surgical lesions to this region commonly report that they are able to feel the pain, but that it no longer bothers them (Devinsky *et al.*, 1995). Further, in neurophysiological recordings made in the rabbit cingulate cortex, neurons were found which responded to noxious thermal and mechanical stimuli (Sikes and Vogt, 1992). Similar responses of single neurons in the cingulate cortex have been recently reported in humans. Hutchison and colleagues (Hutchison *et al.*, 1999) recorded from single neurons in the human cingulate cortex in patients who were undergoing bilateral cingulotomy as a psychosurgical treatment for chronic depression or obsessive compulsive disorder. A small number of neurons were found which responded to noxious thermal and mechanical stimulation, but that did not respond to non-noxious stimulation. Overall, this evidence does support the hypothesis that the anterior cingulate is particularly involved in the affective response to pain. Similarly, the orbitofrontal cortex has been reported to be activated by painful stimuli in a number of positron emission tomography (PET) imaging studies (Hsieh *et al.*, 1995; Rainville *et al.*, 1999; Petrovic *et al.*, 2000) and damage to the orbitofrontal cortex can lead patients to state that they still know that a painful stimulus is being applied, but that it no longer feels affectively painful (Freeman and Watts, 1950).

Given that it is of potential clinical relevance as well as of scientific interest to develop our understanding of which brain areas are involved in representing affectively pleasant as well painful aspects of touch and the extent to which the areas overlap with each other and with those involved in representing other, affectively neutral, aspects of touch, we performed the investigation described here. The investigation was designed to enable the areas activated by these affectively different touches to be compared. The investigation was also designed with high-field (3 T) fMRI in order to provide higher spatial resolution that that afforded by PET (in the in-plane), thus providing better evidence on whether the areas activated by painful and pleasant touch were separate. Another feature of the investigation is that it incorporated methodology (described below) to enable fMR imaging of the orbitofrontal cortex as well as areas such as the cingulate cortex, as we had reason to believe that the orbitofrontal cortex would be activated by the pleasant touch stimuli (Francis *et al.*, 1999) and have developed methods to minimize the effects of paramagnetic susceptibility in this region (Francis *et al.*, 1999; O'Doherty *et al.*, 2000; O'Doherty *et al.*, 2001a). This is the first study we know that has directly compared the cortical regions activated by pleasant touch and pain.

Materials and Methods

Design of the Stimuli
A preliminary psychophysical investigation was carried out in 12 naïve subjects in order to investigate stimuli that might be used for the pleasant touch condition. A range of different stimuli were used of different textures, such as very soft velvet (the softest stimulus), artificial fur, as well as three different grades of sandpaper presented on the end of a wooden dowel, each with a different level of coarseness which can be quantitatively defined: (1) smooth (grade 240); (2) medium (grade 140); and (3) rough (grade 60). The stimuli were externally applied to the palm of the subject's hand and rotated across the subject's palm at a frequency of ~1 Hz with a force of 67 g over an area of 3 cm^2. Subjective pleasantness ratings were assessed using a scale ranging from +2 = very pleasant, through 0 = neutral, to –2 = very unpleasant. This scale was used and validated in studies of the pleasantness of the taste, smell and texture of food (Rolls, 1981; Rolls *et al.*, 1983). Stimulus intensity ratings were assessed using a scale ranging from +2 (very strong) to –2 (very weak). A one-way analysis of variance (ANOVA) carried out on the subjective pleasantness ratings of each of the stimuli across the 12 subjects showed a significant effect of the different textures on the perceived pleasantness [$F(4) = 12.29$, $P < 0.0001$]. The mean pleasantness rating (± SEM) of the soft velvet was +1.2 ± 0.23, whereas that of the next most pleasant stimulus, the artificial fur was +0.69 ± 0.29. A *post hoc* one-tailed *t*-test showed that the velvet was rated as significantly more pleasant than the artificial fur ($t = 2.17$, $P < 0.03$). The pleasantness ratings of the sandpaper were related to the coarseness of the sandpaper: the rough sandpaper was rated as quite unpleasant (thought not really painful) by the subjects, with a mean pleasantness rating of –0.68 ± 0.20; the medium coarse sandpaper was given a mean pleasantness rating of –0.35 ± 0.19; and the smooth sandpaper was given a pleasantness rating of 0.0 ± 0.12 (which corresponds to a rating of affectively neutral).

This psychophysical investigation showed that the velvet was judged to be the most affectively pleasant by a considerable margin and for this reason it was used as the pleasant stimulus. Another reason for choosing the velvet stimulus was that it was successfully used as a positively affective stimulus in the previous investigation (Francis *et al.*, 1999). We suggest that it would potentially be of interest for future investigations to use graded tactile stimuli as a regressor in an imaging study.

The General Design of the Investigation
The design of the experiment was to compare the activations of different brain regions to a soft and pleasant touch to the palm of the hand (produced by velvet) with an affectively neutral stimulus and a painful stimulus. The neutral stimulus was the textured end of a 4.5 cm diameter

wooden dowel (with a similar texture to the neutrally rated sandpaper) rotated on the palm of the left hand and applied with a force of 300 g. The rationale for the choice of these stimuli was that the more physically intense but neutral stimulus might be expected to relatively strongly activate parts of the somatosensory system concerned with representing the sensory details, including the intensity of a somatosensory stimulus, whereas the soft pleasant stimulus should relatively strongly activate parts of the brain concerned with representing the pleasantness of the touch. In the third condition, painful stimulation was applied to the palm of the hand using a pointed stylus, so that the activations produced by the painful stimulus could be compared to those produced by another perceptually intense, but neutral, stimulus – the wooden dowel. The painful stimulus chosen was used because it enabled pain to be rapidly turned on and off in the imaging experiment and could be easily adjusted quantitatively (with details of all the stimuli described below) to produce pain which was just bearable during the duration of each 16 s 'on' period. The pleasant velvet and neutral wood dowel stimuli were the same as those used previously (Francis *et al.*, 1999) and the present experiment builds on that investigation by providing a direct comparison with painful stimuli and by using more subjects. We confirmed by post-imaging investigations that the pleasantness and intensity of the stimuli were unchanging during the experiment.

Procedure

Imaging was conducted using a 3.0 T fMR scanner at the University of Nottingham. T_2-weighted coronal images were obtained using echo-planar imaging (EPI) with a 128×64 matrix size, in–plane resolution of 3 mm, 23 ms echo time and gradient switching frequency of 1.9 kHz. Twelve 10 mm slices were acquired with a T_R of 2 s. The slices covered an area of the brain ranging from the anterior orbitofrontal cortex (+60 A/P in Talairach coordinates) to the posterior parietal cortex (–60 A/P in Talairach coordinates). An inversion recovery EPI sequence was used to acquire an isotropic 3 mm T_1-weighted anatomical volume for each corresponding functional dataset.

The following parameters were carefully selected in order to minimize susceptibility and distortion artefacts in the orbitofrontal cortex (Wilson *et al.*, 2002). First, the data were acquired in a coronal rather than axial slicing direction, as this aligned the slices to be perpendicular to the predominant direction of the intrinsic susceptibility induced field gradients and helps to minimize through-plane dephasing. Secondly, the voxel resolution was kept relatively high by using 3 mm in-plane resolution and a 10 mm slice thickness. The probability of brain tissue within a voxel having different precession frequencies due to suscep-tibility induced field inhomogeneities is increased with larger voxel sizes and thus smaller voxels leads to less phase cancellation. Thirdly, a relatively low T_E of 23 ms was selected to decrease the signal dropout, as less phase dispersion is created across the voxels. Fourthly, each subject was individually shimmed using both linear and second-order shimming to minimize static field inhomogeneities in the orbitofrontal cortex. Finally, geometric distortion was minimized by using a specialist head insert gradient coil with a very high gradient switching frequency of 1.9 kHz.

The experiment was performed in three separate runs, corres-ponding to the three experimental conditions. Each condition consisted of a 16 s 'on' period, during which the somatosensory stimulus was applied to the subject's left hand and a 16 s 'off' period, during which no somatosensory stimulus was applied. This cycle was repeated 24 times, producing a total cycle time of 768 s, with 384 volumes being acquired in that time. The order in which the pleasant, painful and neutral conditions were run was varied across subjects. The subjects' subjective pleasant-ness ratings of the stimuli for each of the three conditions were also measured using the scale described above, ranging from +2 (very pleasant) through 0 (neutral) to –2 (very unpleasant/very painful).

Stimuli

The somatosensory stimulus used for the pleasant touch condition consisted of velvet fabric wrapped on a small 2 cm wooden dowel which was moved around the hand with an average force of 13 g at 1 Hz. The painful stimulus consisted of a pointed stylus, comparable to the styli used by Greenspan and McGillis (Greenspan and McGillis, 1991), which was attached to a pivot balance and applied to the hand with an average

force across subjects of 130 g. The actual force applied to an individual subject was adjusted for that subject's individual pain threshold and a force was found which corresponded to that which the subject found 'just tolerable'. The neutral stimulus consisted of the cut end of a 4.5 cm wooden dowel with exposed grain moved on the palm of the hand with an average force of 300 g. We note that these stimuli are different in size, pressure and speed, and that the aim of the study was not to perform a factorial analysis of variations of each of these parameters. Instead, the aim was to investigate with the relatively small number of stimulus types that can be used in a neuroimaging investigation the parts of the brain that respond to pleasant, painful and neutral stimuli, even if to obtain such affectively different stimuli, they can not be matched on every physical parameter.

Subjects

Nine right-handed subjects (five males and four females, average age 28 years) were scanned in all three conditions (pleasant, pain and neutral). However, the results of one subject had to be discarded due to a problem with the image acquisition and the pleasant condition from another subject had to be discarded due to that subject falling asleep during the stimulus application. This left seven subjects with all three conditions and one subject with both the pain and neutral conditions. The experiment was approved by the University of Nottingham ethics panel.

Image Analysis

Image analysis was performed using the MEDx (Sensor Systems Inc., VA) image analysis package. The datasets were corrected for motion using AIR (Woods *et al.*, 1992), spatial smoothing was applied using a Gaussian filter with a full width at half maximum (FWHM) of 7 mm and intensity normalization was also carried out. Standard low- and high-pass temporal filtering were applied to the data.

A serial *t*-test was then performed on the data using a MEDx TCL script. The serial *t*-test took a series of four sequential volumes (8 s) from seven different segments (early to late) of the 'on' period and a fixed series of four volumes from the 'off' period. This enabled the time-course of the maximal activations of voxels in different brain areas to be determined. The *t*-test which covered the section of the 'on' period starting at 6 s into the cycle was selected across subjects for subsequent analysis of the somatosensory activations and of other brain areas, while *t*-tests over sections of the cycle beginning at timepoints ranging from 6 to 10 s were selected for analysis of the orbitofrontal cortex activations, as the time-course of the blood oxygen level dependent (BOLD) signal in the orbitofrontal activation is in some subjects slower than that of other areas (Francis *et al.*, 1999; O'Doherty *et al.*, 2000).

The time to peak of the activation in the orbitofrontal cortex (between 6 and 10 s) was in general later than that often found by fMRI investi-gations in other brain areas, such as the primary visual or somatosensory cortex, in which a time to peak of between 4 and 6 s has commonly been reported (Miezin *et al.*, 2000). The relatively long latency of the BOLD response in the orbitofrontal cortex observed in the present study has been noted previously. In particular, using a somatosensory stimulation paradigm we observed that the activation in the orbitofrontal cortex peaked much later than did the activation in the primary somatosensory cortex (Francis *et al.*, 1999). A similar effect has also been observed in the anterior inferior prefrontal cortex (Buckner, 1998). Possible reasons for the slow haemodynamic response in the orbitofrontal cortex include the relatively low peak firing rates of neurons in the orbitofrontal cortex [frequently in the range 10–15 spikes/s (Rolls *et al.*, 1990; Rolls and Baylis, 1994), which contrasts with frequent peak responses of 60–120 spikes/s in the temporal lobe cortical visual areas (Rolls and Tovee, 1995)] and the sparseness of the representations found in the orbitofrontal cortex (Rolls and Baylis, 1994; Rolls, 2000b). A full understanding of this effect may only be possible when the relationship between the under-lying neural firing rate and the characteristics of the BOLD response is more completely understood (Rees *et al.*, 2000, Logothetis *et al.*, 2001).

A threshold for statistical significance of $P < 0.05$ (resel corrected) was applied to the individual data with an extent threshold of a minimum cluster size of three voxels. Resel correction takes into account the estimated spatial resolution of the data after spatial smoothing, as this reduces the effective spatial independence of the data. This is calculated by using the formula:

$$P_{corrected} = (Fw_x*Fw_y*Fw_z*P_{uncorrected})/N,$$

where Fw_x, Fw_y and Fw_z are the estimated FWHM of the Gaussian smoothing applied to the data in the x, y and z directions; N is the total number of voxels. The average percentage change in BOLD signal of all of the individual clusters within the z-maps was then determined using a specially built MEDx TCL script. The mean functional image from each subject was registered to the subject's corresponding inversion recovery anatomical volume, which in turn was normalized to MNI-space using the FMRIB Linear Registration Tool, FLIRT (Jenkinson and Smith, 2001). The normalized z-maps for each subject in each condition were used to form a group statistical model for each condition by calculating the sum of individual z-values divided by the square root of the number of subjects over each voxel in the brain. The group results were thresholded at $z = 4.5$ ($P < 0.05$, corrected for multiple comparisons).

Results

Subjective ratings

The mean pleasantness ratings for the pleasant touch stimulus across all subjects were 1.71 ± 0.17 (mean ± SEM), whereas those for the painful touch were –1.71 ± 0.15. The mean pleasantness rating for the neutral stimulus was 0.2 ± 0.11 (where +2 is very pleasant, 0 is neutral and –2 is very unpleasant/very painful).

Imaging Results

The results in the group analysis, fully corrected for multiple comparisons as described in the Materials and Methods section, are shown in Figure 1 for all three conditions in the primary somatosensory cortex, brainstem, rostral and dorsal parts anterior cingulate cortex, and orbitofrontal cortex. The regions of the orbitofrontal cortex activated in the pleasant and painful conditions are further illustrated by the coronal sections shown in Figure 2. We next describe in more detail the activations produced in each of the stimulus conditions and then explicitly compare statistically the activations produced in the pleasant touch, painful touch and neutral touch conditions.

Neutral Condition

The contralateral (to the hand of stimulation) primary somatosensory cortex (SI) was activated most strongly in the neutral condition – x, y, z = 42, –32, 68 in MNI space (Collins *et al.*, 1994); cluster size (cs in voxels) = 2559, $z > 8$ – but there was also some activation in the other two conditions (Fig. 1).

Strong ipsilateral activation of the primary somatosensory cortex was also seen in the neutral condition (–60, –28, 46; cs = 63, $z = 6.60$; not illustrated). There was also bilateral activation of the insular part of the secondary somatosensory cortex, SII (62, –22, 14; $z = 7.03$; and –60, –24, 8; $z = 6.20$) and activation of a brainstem region shown in the second row of Figure 1 (12, –24, –8; $z = 4.69$).

Pleasant Condition

Contralateral SI (36, –20, 72; cs = 204, $z = 6.65$) was activated in the pleasant condition, but to a lesser extent (in terms of significance and spread of activation) than in the neutral condition (middle column of Fig. 1). The secondary somatosensory cortex was activated in some individual subjects ($P < 0.001$ uncorrected), but was not significant in the group analysis.

The orbitofrontal cortex was significantly activated (bilaterally) by pleasant touch – 22, 52, –10; cs = 17, $z = 4.48$, SVC (small volume correction) (Worsley *et al.*, 1996) and –8, 58, –12; cs = 5, $z = 4.10$, SVC – as shown in the bottom row of Figure 1 and in Figure 2. In terms of individual subjects, the contralateral orbitofrontal cortex was significantly activated in

six of seven individual subjects, while the ipsilateral orbitofrontal cortex was activated in three subjects.

A rostral part of the anterior cingulate cortex was significantly activated by pleasant touch (10, 42, 16; cs = 5, $z = 4.93$; Fig. 1, row 3) as well as a dorsal part of anterior cingulate (–8, 12, 22; cs = 11, $z = 5.05$; not illustrated). In addition, a part of the brainstem was also activated (0, –26, –16; $z = 4.96$). Interestingly, activation was also produced by pleasant touch in a brain area in or near the amygdala (36, 4, –20; $z = 4.30$, SVC; not illustrated). (Although this was not significant corrected for all the degrees of freedom inherent in a whole brain analysis, it was significant at $P < 0.05$ when the SVC was applied. In addition, the amygdala activation was significant at $P < 0.001$ in 3/7 of the single subject analyses.)

Painful Condition

Painful stimulation with the pointed stylus activated the contralateral primary somatosensory cortex (46, –28, 66; cs = 10, $z = 5.84$), but with a smaller spatial extent than for the pleasant and neutral conditions. In contrast to the pleasant condition, significant activation was also produced by the painful stimulus in mid-insular parts of SII bilaterally (–58, –14, 8; $z = 6.13$ and 56, –2, 16; $z = 5.28$) and in a more anterior part of the insula (36, 0, 8; $z = 5.46$ and –44, –2, 10; $z = 5.35$). In addition, activation was also found in a posterior part of the insula (–60, –32, 18; $z = 5.13$), which is illustrated in Figure 2 and which may be the region described by Craig *et al.* (Craig *et al.*, 1994).

Activation by the painful stimulus was also found in parts of the brainstem, including the periaqueductal grey (–6, –20, 16; $z = 5.72$ and 10, –22, –18; $z = 4.53$; see Fig. 1, row 2) and (not illustrated) in the primary motor cortex (24, –6, 66; $z = 4.61$), the basal ganglia/ventral striatum (22, 10, –4; $z = 7.65$) and in the thalamus (12, –6, 4; $z = 5.02$).

Furthermore, significant activation of the orbitofrontal cortex bilaterally was also found (–26, 40, –20; cs = 9, $z = 4.88$ and 16, 32, –24; cs = 18, $z = 5.14$) as shown in Figure 1 row 4 and in Figure 2. Activations were also seen in the mid/anterior (or dorsal) cingulate cortex (10, –6, 34; cs = 113, $z = 6.12$) and pre-SMA (8, 4, 52; cs = 34, $z = 5.64$; Fig. 1, third row).

Comparison of the Three Stimulus Conditions

To determine whether the pleasant and painful touches caused relatively greater activation of the orbitofrontal cortex than the somatosensory cortex and than the affectively neutral condition, two-way, within-subjects ANOVAs were performed on the BOLD signals from significantly activated clusters of voxels in the orbitofrontal cortex and somatosensory cortex, which was one factor, with the second factor being stimulus condition. A very significant interaction effect [$F(1,6) = 18.37$, $P < 0.006$] between the effects of pleasant versus neutral touch as one factor and brain area (orbitofrontal cortex versus somatosensory cortex) as the second factor was found using the two-way, within-subjects ANOVA. This result indicates that the less intense but affectively pleasant stimulus caused relatively greater activation of the orbitofrontal cortex across subjects than did the more intense but affectively neutral stimulus, yet the affectively neutral stimulus resulted in relatively greater activation of the somatosensory cortex than did the pleasant stimulus.

Similarly, a two-way ANOVA carried out on the mean percentage change in BOLD signal to determine the effects of painful versus neutral touch, with one factor being type of stimulation (painful versus neutral) and the second factor being brain area (orbitofrontal cortex versus somatosensory cortex), showed a significant interaction effect [$F(1,7) = 12.03$, $P < 0.02$].
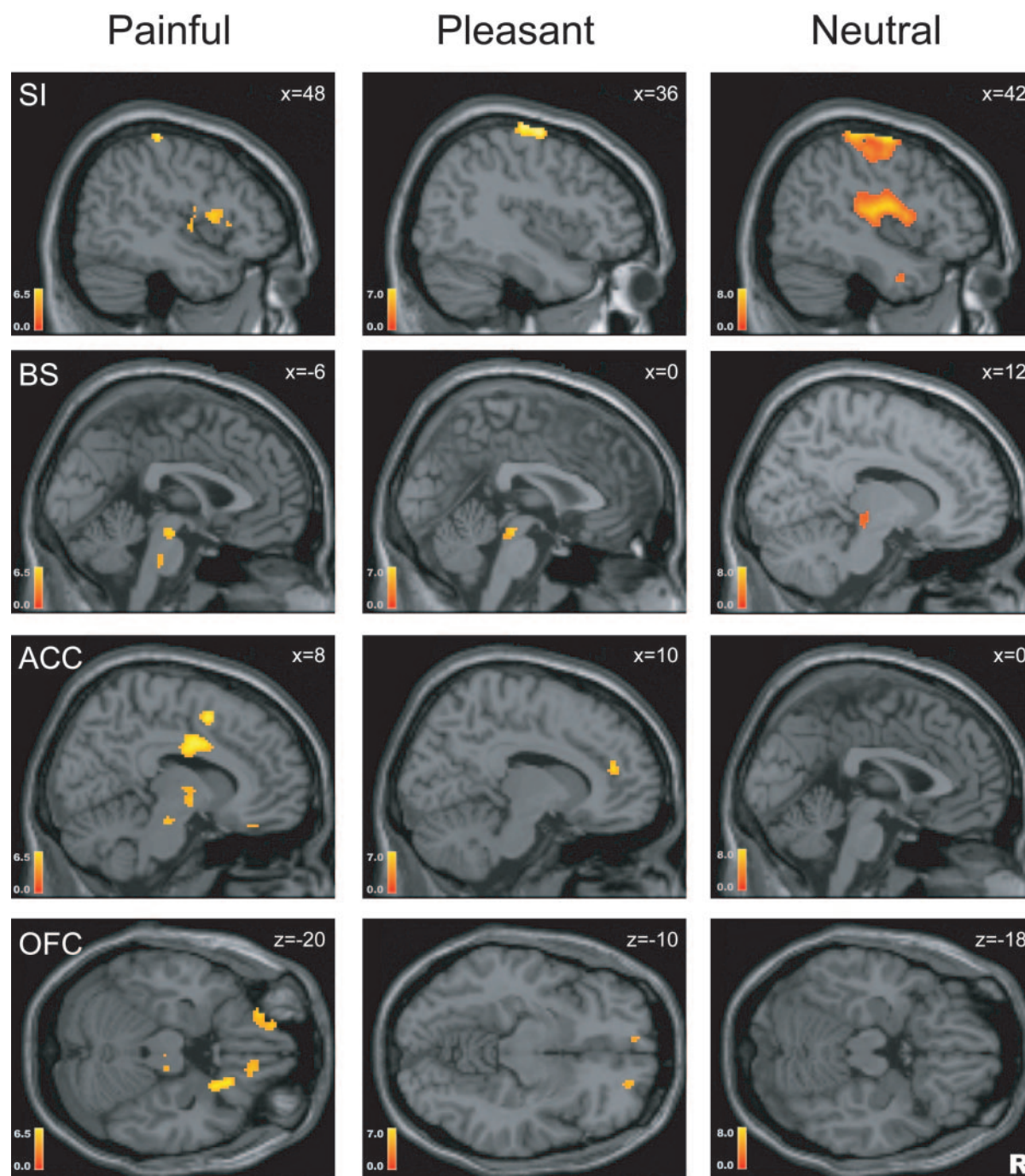
Figure 1. Brain activation to somatosensory stimulation. Sagittal slices are shown for each of the three conditions (depicted in each of the columns) with the group activation significant at $P < 0.05$ corrected for multiple comparisons of the contralateral (right) somatosensory cortex (SI) as well as sagittal slices showing activation in brainstem (BS). Furthermore, for the painful and pleasant conditions are shown sagittal slices of activations in the mid/anterior cingulate cortex (ACC) and axial slices of activations in the orbitofrontal cortex. The activations have been thresholded at $P < 0.0001$ to show the extent of the activations. The scale shows two values (corrected).

This finding indicates that, across subjects, the affectively unpleasant pain stimulus resulted in relatively greater activation of the orbitofrontal cortex than did the affectively neutral stimulus, whereas the neutral stimulus produced relatively greater activation of the somatosensory cortex than did the painful stimulus.

These dissociations are illustrated in Figure 3, which shows the mean percentage changes in the orbitofrontal cortex and somatosensory cortex in these clusters for all three conditions averaged across subjects. The BOLD measure used in these statistical comparisons was fully supported by a measure of the extent of the two brain regions activated by the different stimuli — the number of voxels in the significant clusters within each brain area activated in the different stimulus conditions, reported above as the cluster size. Thus, either measure of the activation of these brain regions, the percentage change or the number of activated voxels, showed the type of dissociation captured in Figure 3.
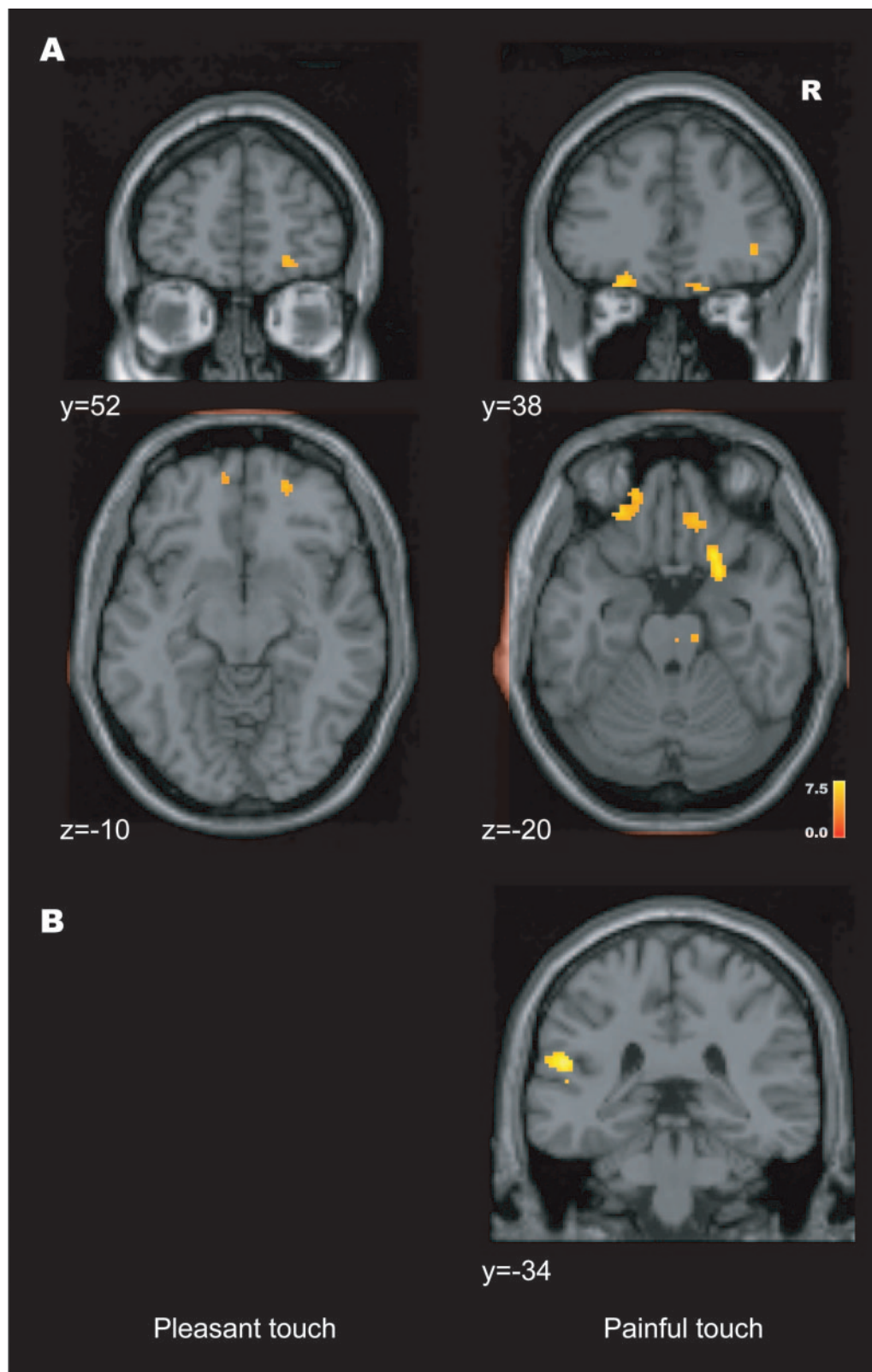
Figure 2. Painful and pleasant touch in the orbitofrontal cortex. (*A*) Two slices (coronal and transverse) show the group results in the orbitofrontal activations to pleasant (left) and painful (right) touch. (*B*) A coronal slice showing the activation to painful touch in the posterior insula. The activations are significant at *P* < 0.05 corrected for multiple comparisons, but are thresholded at *P* < 0.0001 for extent. The scale shows two values (corrected).
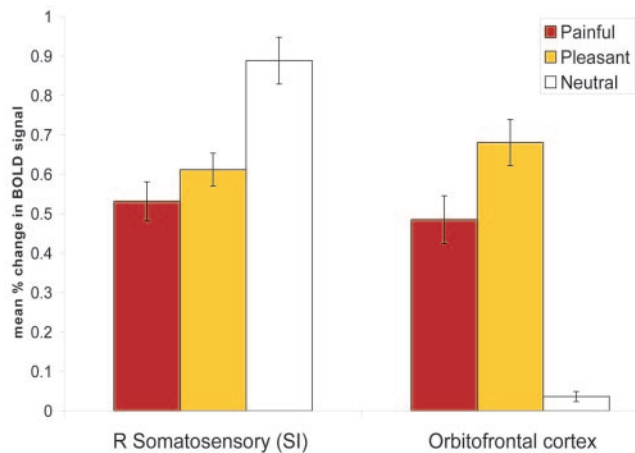
Figure 3. Average percentage change in brain areas following somatosensory stimulation. Plot of the average percentage change in BOLD signal of the contralateral somatosensory cortex and orbitofrontal cortex averaged across each individual subject for the painful, pleasant and neutral conditions. Painful and pleasant stimuli result in significantly greater activation of the orbitofrontal cortex than in the neutral condition, whereas the neutral stimulus results in significantly greater activation of the somatosensory cortex. The error bars depict the standard error of the mean.

Discussion

This study provides evidence that there is a dissociation between the brain areas that represent the affective aspects of touch from those that represent other, non-affective, aspects of touch. The dissociation is sufficiently strong that it was clear and statistically significant in a group analysis. The study shows that both affectively positive (pleasant) touch and affectively negative, in particular painful, touch produce strong activation of parts of the orbitofrontal cortex, relative to a touch which was physically strong but neutral, which produced more activation of the somatosensory cortex. Moreover, the study shows in the group analysis that different parts of the orbitofrontal cortex are activated by affectively pleasant touch and by pain. An implication of the study is thus that the orbitofrontal cortex is involved in representing both positive and negative affect produced by touch, as it is for affect produced by stimulation through other sensory modalities (Rolls, 2000b).

The study also showed that pain produced activation of three regions that were not activated by the pleasant touch, namely the midbrain central grey, part of the dorsal anterior cingulate cortex that is relatively posterior, and a posterior part of the insula implicated in pain and temperature (Craig et al. (1994). The part of the dorsal anterior cingulate cortex activated by pain is part of the cingulate motor area and activation of this area by pain may have reflected the necessity for the subjects to inhibit withdrawal of the hand from the painful stimulus in the present study. In addition, a rostral part of the cingulate cortex was activated by the pleasant and not by the neutral touch or by pain; this is part of the cingulate that contains other affective representations (Bush et al., 2000) and that may be involved in the generation of some autonomic and emotional responses.

The design of the study and the results obtained provide evidence that it is the affective aspects of the touch and not some other correlate that is represented in the orbitofrontal cortex. For example, the perceived and physical intensity as the relevant correlate for orbitofrontal cortex activation can be ruled out, given that the rated intensity and the physical force (300 g) of the neutral stimulus (the 4 cm wood texture dowel) was high, whereas the perceived and physical intensity (13 g) of the velvet

was low and the perceived intensity of the moderate physical (130 g) painful stimulus was high; additionally, different parts of the orbitofrontal cortex were activated by the pleasant and painful stimuli, so that a single property such as physical force cannot account for the orbitofrontal cortex activations found. The comparison provides clear evidence that it is not just stimuli that are physically and psychophysically weak, such as velvet, that activate the orbitofrontal cortex (Francis et al., 1999), but that it is an affective correlate that most clearly relates to orbitofrontal cortex activation. The neutral but physically intense (300 g) wood texture stimulus may have produced strong activation of SI partly because it was physically intense and partly because it covered a reasonable area of the hand (4 π cm²), though again it is not the area of the stimulus that was relevant in this study, in that this surface area was intermediate between that of the pleasant touch (which covered most of the palm of the hand), and the painful touch, which was applied to a very small area of the hand using a stylus.

One of the interesting points of the results described in this paper is that there is sufficient that is common between subjects in the activation produced by painful and by pleasant stimuli in the orbitofrontal cortex to obtain significant group effects. We have elsewhere addressed the issue of the variation between subjects in at least the pleasant condition in the orbitofrontal cortex (Francis et al., 1999), where we give the Talairach coordinates from individual subjects.

The findings described here provide further evidence on the representations in the orbitofrontal cortex that are relevant to understanding emotion. Rolls (Rolls, 1990, 1999) has noted that emotions can be considered as states elicited by reinforcers; that is, roughly, by rewards [stimuli such as pleasant touch for which an animal will work (Taira and Rolls, 1996)] and by punishers (stimuli that produce pain that an animal will work to escape from or avoid). Reinforcers can be primary, that is unlearned (for example the taste of food, or pleasant or painful touch), or secondary, that is learned (for example the sight of food, which becomes a secondary reinforcer by learned association with the primary reinforcer, the taste of food). The present results provide new evidence that two primary reinforcers, pleasant touch and pain, are represented in the human orbitofrontal cortex. The results add to previous evidence that:

the reward value of the primary reinforcer taste is represented in the primate orbitofrontal cortex — in that orbitofrontal cortex taste neurons in monkeys decrease their responses as a monkey is fed to satiety (Rolls et al., 1989);

the reward value of the secondary reinforcer, the odour of food, is represented in the orbitofrontal cortex — in that orbitofrontal cortex olfactory neurons in monkeys decrease their responses to the odour of a food that has been ingested to satiety (Rolls et al., 1996) and in that fMRI-measured activation of the human orbitofrontal cortex decreases in response to the odour of a food with which humans have been fed to satiety (O'Doherty et al., 2000), as does the pleasantness of the odour (Rolls and Rolls, 1997);

the reward value of the secondary reinforcer, the sight of food, is represented in the orbitofrontal cortex in that orbitofrontal cortex visual neurons in monkeys decrease their responses to the sight of the food that has been ingested to satiety (Critchley and Rolls, 1996) and in that separate areas of the human orbitofrontal cortex are activated in proportion to the magnitude of an abstract (monetary) reward received and of an abstract (monetary) punishment (O'Doherty et al., 2001a).

Other neuroimaging studies have also reported activation in the human orbitofrontal cortex to different types of primary

and secondary (learned) rewards and punishers, including predictability of taste (Berns *et al.*, 2001), pleasant and aversive odors (Zatorre *et al.*, 1992; Zald and Pardo, 1997), sexually arousing stimuli (Redouté *et al.*, 2000), positive and negative feedback (Elliott *et al.*, 1997), induced emotions (Damasio *et al.*, 2000), pleasant music (Blood *et al.*, 1999) and monetary reward (Thut *et al.*, 1997; Knutson *et al.*, 2001; O'Doherty *et al.*, 2001a). Taken together with other findings, these results provide a foundation for understanding the functions of the orbitofrontal cortex in emotion in terms of its functions in decoding and representing primary reinforcers and in learning associations between these and secondary reinforcers (Rolls, 1990, 1999).

The findings of the present study not only confirm previous findings that the anterior cingulate cortex is activated more by pain than by neutral control stimuli (Vogt *et al.*, 1996; Rainville *et al.*, 1997; Iadarola *et al.*, 1998), but also extend these findings by showing that different parts of the cingulate cortex are activated by painful and by pleasant touch stimuli, with the painful stimuli in this study activating a relatively posterior part of the anterior cingulate cortex (see Fig. 1, row 3), which is in or close to the cingulate motor hand area (Paus, 2001), and the pleasant touch a considerably more anterior part of the anterior cingulate cortex (Fig. 1, row 3), within or close to cingulate areas activated in affective tasks such as the Emotional Stroop task, as shown by various meta-analyses (Picard and Strick, 1996; Bush *et al.*, 1999, 2000; Koski and Paus, 2000).

Activation of the insula was most pronounced to the neutral touch, although an anterior part of the insula (including and anterior to the activation shown in Fig. 1, row 1) was activated by the painful stimuli. An anterior part of the insula has been implicated by imaging studies in other emotional responses, including: facial expressions of disgust- and recall-generated sadness (Phillips *et al.*, 1997); during stimulation of the thenar eminence of the hand using either a warm (and non-painful) or hot (and painful) contact thermode (Brooks *et al.*, 2002); during processing of itch (Drzezga *et al.*, 2001); and in healthy males experiencing visually evoked sexual arousal (Stoleru *et al.*, 1999). It is probably a more anterior area that is activated by taste (Francis *et al.*, 1999; Small *et al.*, 1999; O'Doherty *et al.*, 2001b) and olfactory (Jones-Gotman and Zatorre, 1988; Francis *et al.*, 1999; O'Doherty *et al.*, 2000) stimuli. Critchley *et al.* (Critchley *et al.*, 2000) found that activation in an anterior insula region (and caudal orbitofrontal cortex) mirrored changes in the subjects' autonomic arousal as indexed by galvanic skin response, a finding consistent with a role for this region in the cortical representation of autonomic feedback and of the internal visceral state. One possibility is that activity in the insula produced by pain may be due to an increase in autonomic arousal that could follow from painful stimulation or, alternatively, the insular area activated could be more a somatosensory area (Mufson and Mesulam, 1982; Friedman *et al.*, 1986).

We have reported what we believe to be some very interesting activations in the brainstem to touch, but note that it would be prudent to exercise extreme caution in interpreting these activations because of the well-known pulsatile motion artefacts. Further studies may well need to use new techniques to reduce or control for these motion-related artefacts, such as cardiac gating (Guimaraes *et al.*, 1998). It may also be of interest to use alternating conditions (painful, pleasant, neutral and resting) such that direct comparisons can be made.

It is intriguing that a brain region in or near the amygdala was found to be activated by pleasant touch. While most studies of the amygdala have tended to concentrate on its role in negative emotions such as fear (Morris *et al.*, 1998), other imaging studies

have found amygdala activations to affectively positive stimuli such as the taste of glucose (O'Doherty *et al.*, 2001b), happy faces (Breiter *et al.*, 1996) and happy mood induction (Schneider *et al.*, 1997). This is consistent with single-neuron studies demonstrating that neurons in the amygdala respond to sweet tastes (Scott *et al.*, 1993; Nishijo *et al.*, 1998) and to visual stimuli associated with reward (Sanghera *et al.*, 1979; Rolls, 2000a).

Given that involvement of the orbitofrontal cortex (as well as part of anterior cingulate and posterior insula) has been found in the representation of painful touch, a further issue is the extent to which the orbitofrontal cortex and cingulate cortex are involved in responding to non-painful but unpleasant touch. An example of such a stimulus is rough sandpaper. As described in the Materials and Methods section, this stimulus was perceived to be quite unpleasant by the subjects. Nevertheless, it was not perceived as painful. [The mean pain rating (±SEM) of the rough sandpaper across the subjects in the psychophysics investigation was 0.18 ± 0.09, where 0 = not at all painful and +2 = very painful. The mean pain rating given to the pointed stylus in the psychophysics experiment (the results for the painful stimulus were not described previously) was, in contrast, +1.22 ± 0.16.] In a future study, it would be interesting to investigate the effects of such a stimulus and compare the results to those found with painful touch, to determine if the role of the orbitofrontal cortex and anterior cingulate in painful and non-painful but aversive touch can be differentiated.

The findings described here are relevant to understanding the effects of brain damage. The implication that the orbitofrontal cortex is involved in pain is consistent with the evidence that patients with orbitofrontal cortex damage may report that pain stimuli no longer bother them. The findings are also potentially relevant to a better understanding of the role of reward in drug abuse behaviour. The evidence that both positive and negative tactile stimuli are represented in the orbitofrontal cortex is also consistent with the evidence that emotions may be altered by damage to this region, in that representing and learning about the primary reinforcers rewarding and punishing tactile stimuli may be one of the foundations of the brain's emotional systems (Rolls, 1999). The findings also are consistent with neurological evidence that cingulate cortex damage may decrease affective responses to pain and go beyond this by suggesting that affective responses to pleasant touch may be affected by damage to some other parts of the cingulate cortex.

Notes

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