Cell Mol Neurobiol
DOI 10.1007/s10571-007-9228-z

ORIGINAL PAPER

Dynamic Changes in Brain Activations and Functional Connectivity during Affectively Different Tactile Stimuli

Qing-Ping Hua · Xiang-Zhu Zeng · Jian-Yu Liu · Jin-Yan Wang · Jian-You Guo · Fei Luo

Received: 28 August 2007 / Accepted: 22 October 2007

Abstract In the present study, we compared brain activations produced by pleasant, neutral and unpleasant touch, to the anterior lateral surface of lower leg of human subjects. It was found that several brain regions, including the contralateral primary somatosensory area (SI), bilateral secondary somatosensory area (SII), as well as contralateral middle and posterior insula cortex were commonly activated under the three touch conditions. In addition, pleasant and unpleasant touch conditions shared a few brain regions including the contralateral posterior parietal cortex (PPC) and bilateral premotor cortex (PMC). Unpleasant touch specifically activated a set of pain-related brain regions such as contralateral supplementary motor area (SMA) and dorsal parts of bilateral anterior cingulated cortex, etc. Brain regions specifically activated by pleasant touch comprised bilateral lateral orbitofrontal cortex (OFC), posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), intraparietal cortex and left dorsal lateral prefrontal cortex (DLPFC). Using a novel functional connectivity model based on graph theory, we showed that a series of brain regions related to affectively different touch had significant functional connectivity during the resting state. Furthermore, it was found that such a network can be modulated between affectively different touch conditions.

Keywords fMRI · Functional connectivity · Resting state · Pleasant touch · Unpleasant touch

Q.-P. Hua · F. Luo
Neuroscience Research Institute, Peking University, Beijing, P.R. China

Q.-P. Hua · J.-Y. Wang · J.-Y. Guo · F. Luo (✉)
Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences,
10A Datun Road, Chaoyang District, Beijing 100101, P.R. China
e-mail: luof@psych.ac.cn

X.-Z. Zeng · J.-Y. Liu
Department of Radiology, Peking University Third Hospital, Peking University, Beijing, P.R. China

Introduction

It is well known that touch is a multifaceted phenomenon. It comprises sensory-discriminative and affective components, which are processed by parallel neural systems (Francis et al. 1999; Vallbo et al. 1999; Olausson et al. 2002; Wessberg et al. 2003). Negative affective states such as unpleasantness, fear and anxiety have been studied more extensively than positive ones such as happiness, sexual arousal or 'pleasant' states provoked by tactile stimulation.

It is obvious that somatosensory stimulation can be rewarding and can produce pleasure, and seeking such stimulation could be beneficial to animals (including humans) in many ways (Rolls 1999). A series of examples come from the somatosensory stimulation produced by social contact. Indeed, the range of affiliative behaviours which involve somatosensory stimulation includes mother-infant interactions, grooming, play and sexual behaviour (Dunbar 1996; Panksepp 1998; Rolls 1999). However, the hedonic attributes of touch, especially in the central nervous system level, have rarely been studied.

Fortunately, a few pioneering neuroimaging studies have gained some insights into the brain regions mediating the pleasant touch. Specifically, using fMRI, Olausson et al. demonstrated that unmyelinated tactile afferents signal touch and project to insular cortex and that such a system may underlie emotional, hormonal and affiliative responses to caress-like, skin-to-skin contact between individuals (Olausson et al. 2002). It has been demonstrated in another fMRI study that pleasant touch gives rise to a different activation pattern in the human brain than neutral touch, notably activation of an area in the orbitofrontal cortex adjacent to areas responding to pleasant taste and smell (Francis et al. 1999). Furthermore, Rolls and colleagues provided 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 (Rolls et al. 2003). These convergent findings were interpreted to reflect the dissociation in discriminative and affective somatosensory cortical functions.

Nevertheless, it should be noted that these studies were concentrated on one or a few regions involved in representing affective components of touch. However, even the simplest cognitive procedures are supported by highly distributed neural circuits. In this context, we proposed that, even in resting state, some important brain structures (such as orbitofrontal cortex, insular cortex and cingulate cortex) constitute a network which contributes to emotion processing in the human brain and that the network can be modulated by affectively different touch. Therefore, understanding functional connectivity within the brain is crucial to understanding neural mechanisms underlying the processing of affectively different touch.

In this study, we adopted a novel method based on graph theory (Jiang et al. 2004) to investigate whether there exists a highly distributed functional connectivity network related to emotional processing for touch and how such a network can be modulated between pleasant, neutral and unpleasant touch. This method not only can completely characterize the joint interactions (i.e., functional connectivity) among multiple functionally related regions of the brain, but also can measure the functional modulation between different conditions.

Materials and Methods

Subjects

Twelve healthy, right-handed volunteers (six males six females; mean age 22 $\pm$ 2 years) participated in the fMRI study. There was no history of neurological or psychiatric disease in

any of the subjects, and none had any neurological deficits. All the subjects gave their written informed consent after the explanation of the experimental protocol, as approved by the ethical committee of Health Science Center, Peking University.

Affectively Different Tactile Stimuli

In order to investigate stimuli that might be used for the pleasant, neutral and unpleasant touch condition, we carried out a preliminary psychophysical investigation in nine subjects. A series of different stimuli were used of different textures, such as velvet, silk, cotton, terylene, soft plastic mesh and hard plastic mesh wrapped on a palmate resilient foam pad. The stimuli were manually applied by a practiced experimenter to the anterior lateral surface of subjects' lower leg with a force of about 400 g over an area of about 16 cm^2. All these stimuli were moved from proximal to distal at a velocity of about 10 cm/s. We note that these stimuli may fluctuate slightly in pressure, speed and duration due to technical limitations. Nevertheless, the aim of the study was not to perform a factorial analysis of variations of each of these parameters but to investigate the brain regions that respond to pleasant, neutral and unpleasant touch. Moreover, even to induce uniform subjective experiences, these touch stimuli cannot be matched on every physical parameter.

Subjective pleasantness ratings were assessed using a visual analogue scale (VAS) ranging from +10 = "maximum pleasant", through 0 = "neutral", to −10 = "maximum unpleasant". Since the selected unpleasant touch stimuli also produced slight pain-sensation, pain intensity ratings were also assessed using a VAS scale with the endpoints 0 = 'no pain' and −10 = 'worst imaginable pain' under the unpleasant touch condition. Consistent with Essick's work (Essick et al. 1999), we found that the materials that are soft and smooth are unanimously reported as pleasant; those that were stiff, rough or coarse are reported as unpleasant. Among these materials, velvet, terylene and hard plastic mesh can produce stable pleasant (7.08 ± 1.16, mean ± SD), neutral (1.29 ± 1.52) and unpleasant (-7.60 ± 0.96) touch stimuli, respectively and were selected in the following imaging studies.

Experimental Protocol

The experiment was performed in four separate runs (all the four separate runs were performed on the same volunteer) corresponding to the resting condition and three touch conditions (pleasant, neutral and unpleasant touch respectively). Each touch condition consisted of a 30 s 'on' period, during which the tactile stimulus was stroked across the anterior lateral surface of subject's lower leg (left and right side, six subjects respectively) and a 30 s 'off' period, during which no stimulus was applied. This cycle was repeated six times, producing a total cycle time of 360 s, with 190 volumes being acquired in that time (additional five volumes at starting). The order in which the pleasant, neutral and unpleasant touch conditions were run was arranged randomly and counterbalancedly across subjects. Before the three touch conditions, the resting condition which lasted for 380 s was performed. Subjects were instructed to keep their eyes closed, relax their mind and remain motionless as much as possible.

Immediately after MRI scanning, all subjects were asked to rate the averaged extent of pleasantness (and pain intensity for unpleasant touch condition) using the VAS scale mentioned above. We also ascertained verbally whether the pleasantness and intensity of the stimuli were unchanging during the experiment. Subjects who reported an obvious change in pleasantness or intensity would be excluded from the analysis.

Imaging Data Acquisition

All MRI experiments were performed using either a 1.5 T Sonata or a 3.0 T Trio (6–6 split) MRI scanner (Siemens, Germany) with a standard head coil. Functional T_2*-weighted images were acquired using a gradient echo planner imaging (EPI) sequence (TR/TE/FA: 2000 ms/40 ms/90° FOV: 220 × 220 mm^2; Matrix: 64 × 64 pixels). Twenty-five consecutive axial slices (thickness = 5 mm, gap = 0.5 mm) covering the entire cortex and cerebellum were acquired.

For anatomical reference, a magnetization prepared rapid gradient echo imaging (MPRAGE) sequence was selected and the images (128 sagittal slices, voxel size = 1.7 × 0.86 × 0.86 mm^3) were used for Talairach transformation and functional mapping during data analysis later. Another set of turbo spin-echo (TSE) T_1-weighted images (25 axial slices, voxel size = 0.86 × 0.86 × 5) with identical position of functional acquisition was obtained for image registration.

Image Processing And Statistical Analysis

Imaging processing and statistical analyses were performed using AFNI (Medical College of Wisconsin, Milwaukee; http://www.afni.nimh.nih.gov/afni/index.shtml) (Cox 1996). The first five volumes of each fMRI session were discarded because of unsteady magnetization and the remaining 185 volumes per session (740 volumes per subject) were used for analysis. Slice time was corrected and reconstructed data were realigned, spatially normalized, and smoothed with a 5 mm FWHM Gaussian kernel to decrease spatial noise and residual differences (Friston et al. 1995). Specifically, for the resting state data, a low-pass frequency filter ($f < 0.08$ Hz) was applied to remove physiological high-frequency noise, e.g., respiratory and cardiac (Biswal et al. 1995) and low frequency fluctuations (LFFs) were further analyzed.

For each touch conditions, preprocessed MRI data were analyzed statistically by using multivariable linear regression model. Neural activities that related to affectively different touch stimulation were modeled using a boxcar function convolved with a hemodynamic response function (HRF) as employed by AFNI. To reduce the risk that brain activation could be movement-correlated, movement parameters derived from the realignment procedure were included as covariates of no interest.

To make statistic inferences at the population level, individual beta-coefficient data were then pooled and the statistical maps of those subjects with left-sided stimulation were mirrored along the *y*-axis (L-R flipped) so as to spatially overlay activation in homologue brain areas for both sides of stimulus application. After this procedure, all these data were incorporated into a random-effect model that estimates the error variance for each condition of interest across subjects, rather than across scans (Holmes and Friston 1998). In this random-effect analysis, one-sample *t* test (d.f. = 11) at each voxel was performed across subjects and the *t* threshold was set to $P \leq 0.001$ (uncorrected). The minimal cluster requirement was 8 voxels, hence the overall significance of the results (alpha) is < 0.05 as calculated with AlphaSim.

Conjunction analysis can be used to find out the overlapping regions in the brain among a set of contrasts. Those regions can be obtained through 3 dcalc in AFNI, a general purpose program for performing logic and arithmetic calculations.

Region-of-interest (ROI) Delineation And Functional Connectivity Analysis

For some bilaterally activated regions (based on the preliminary inspection of the group activation t-map), we only selected the contralateral ones. Therefore 16 ROIs were selected for further functional connectivity analysis. Taking into account the anatomical variance across

subjects, subject-specific ROIs were defined based on their own beta-coefficient maps as follows. First, we calculated the averaged group activation t-map of three touch conditions. The individual mean beta-coefficient map across three touch conditions was also calculated for all subjects. Each peak voxel and its nearest 26 neighbours in the averaged group t-map were defined as a group ROI then the group ROI was taken as a mask. Based on the individual mean beta-coefficient map, the voxel with largest mean beta-coefficient-value within this mask together with its six nearest neighbours were taken as a subject-specific ROI. Subject-specific mean time series were extracted by averaging the time series of 7 voxels in the subject-specific ROI. For each of the resting and touch conditions, 16 such subject-specific mean time series were calculated leading to further functional connectivity analysis.

We adopted a novel functional connectivity model, which takes into account n-to-1 connectivity using 1-to-1 connectivity measures instead of conventional pairwise connectivity (Jiang et al. 2004). A brief review of the procedures and corresponding mathematic explanations is provided in Appendix.

Results

Subjective Ratings

The mean pleasantness ratings for the pleasant touch stimulus across all subjects were 7.00 ± 1.11 (mean $\pm$ SD), whereas those for the unpleasant touch were -7.54 ± 1.03. The mean pleasantness for the neutral stimulus was 1.33 ± 1.39 (where +10 is maximal pleasant, 0 is neutral and -10 is maximal unpleasant). In addition, the pain intensity ratings for the unpleasant touch condition were -4.42 ± 1.35. ANOVA showed significant differences in the mean pleasantness ratings across three touch conditions ($F = 456.5$, $P < 0.0001$).

Functional Imaging Results

The results in the group analysis, fully corrected for multiple comparisons as described in the Materials and methods section, are shown in Table 1 and Fig. 1 for all three touch conditions.

Following the neutral touch stimulation, the contralateral primary somatosensory area (SI), bilateral secondary somatosensory area (SII), contralateral middle insular cortex (mIC) and posterior insular cortex (pIC) were significantly activated (Table 1 and Fig. 1a).

Unpleasant touch stimulation led to several increased activations in pain-related regions that are known to be activated during the perception of nociceptive stimulation, namely, bilateral SI, SII, pre-motor cortex (PMC), mIC, contralateral pIC, medial dorsal thalamic nucleus (MD), supplementary motor area (SMA), dorsal parts of the bilateral anterior cingulate cortex (dACC), bilateral putamen and cerebellum (Table 1 and Fig. 1b). Additionally, an increased activation was located in the posterior parietal cortex (PPC) in both hemispheres. At a more liberal threshold, additional activations were observed in contralateral anterior insular cortex (aIC) and bilateral caudal anterior cingulate cortex (cACC).

Different patterns of brain activations were revealed during the pleasant touch condition as compared with other conditions (Table 2 and Fig. 1c). There were activations in bilateral SI, SII, PMC, contralateral PPC, mIC, pIC, bilateral intraparietal cortex (IP), lateral orbitofrontal cortex (LOFC), posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) (Table 1 and Fig. 1c).

In order to assess whether there exists laterality in brain activation, we also performed group analyses on original (i.e., unmirrored) individual beta-coefficient data. Most

Table 1 Talairach co-ordinates (average centres of mass) and *t* score of peak voxel of activations produced by three touch conditions*

ROINo.	Region	Hemi.	*x*	*y*	*z*	*t* score of peak voxel		
						Unpleasant touch	Neutral touch	Pleasant touch
1	SI	contra	−20	−31	73	9.8	12.5	10.5
	SI	ipsi	17	−31	70	5.8	–	6.4
2	SII	contra	−52	−24	25	11.7	10.5	11.6
	SII	ipsi	48	−23	24	10.2	11.1	6.9
3	PPC	contra	−47	−35	55	6.1	–	6.1
	PPC	ipsi	45	−34	61	5.1	–	–
4	PMC	contra	−52	13	14	5.1	–	4.7
	PMC	ipsi	56	12	14	6.8	–	4.0
5	mIC	contra	−39	−2	10	5.8	5.7	4.2
	mIC	ipsi	41	0	7	6.2		
6	pIC	contra	−36	−20	18	7.0	6.8	8.0
7	SMA	contra	−7	−3	61	6.8	–	–
8	dACC	–	−2	5	46	4.8		
9	MD	contra	−11	−17	8	4.9	–	–
10	Pu	contra	−21	−2	12	5.1	–	–
	Pu	ipsi	19	−2	12	5.5	–	–
11	Declive	contra	−19	−70	25	5.8	–	–
	Declive	ipsi	20	−70	30	5.8	–	–
12	IP	contra	−40	−54	40	–	–	4.8
	IP	ipsi	43	−55	34	–	–	5.7
13	LOFC	contra	−40	43	4	–	–	4.9
	LOFC	ipsi	44	45	4	–	–	4.6
14	PCC	–	1	−38	29	–	–	4.4
15	DLPFC	left[a]	−28	20	45	–	–	5.6[a]
16	mPFC	–	−3	40	36	–	–	5.1

* Abbreviations: contra, contralateral; ipsi, ipsilateral; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; PPC, posterior parietal cortex; PMC, premotor cortex; mIC, middle insular cortex; pIC, posterior insular cortex; SMA, supplementary motor area; dACC, dorsal parts of anterior cingulate cortex; MD, medial dorsal nucleus; Pu, Putamen; IP, intraparietal cortex; LOFC, lateral obito-frontal cortex; PCC, posterior cingulate cortex; DLPFC, dorsal lateral prefrontal cortex; mPFC, medial prefrontal cortex

[a] Laterality activation revealed by group analysis using original (i.e., un-mirrored) individual data

intriguingly, we found that there was an apparent laterality activation during pleasant touch condition located in left dorsal lateral prefrontal cortex (DLPFC) (Table 1). The individual beta-coefficient maps of two subjects (Fig. 2a) and corresponding mean time series (Fig. 2b) were shown in Fig. 2.

Functional Connectivity Analysis

Figure 3 shows the normalized total connectivity degree ($\bar{\Gamma}$, see Appendix) of each brain region in the resting state across all subjects. A larger $\bar{\Gamma}$ suggests that there exists significant functional connectivity between the brain region and others and it is therefore considered as an

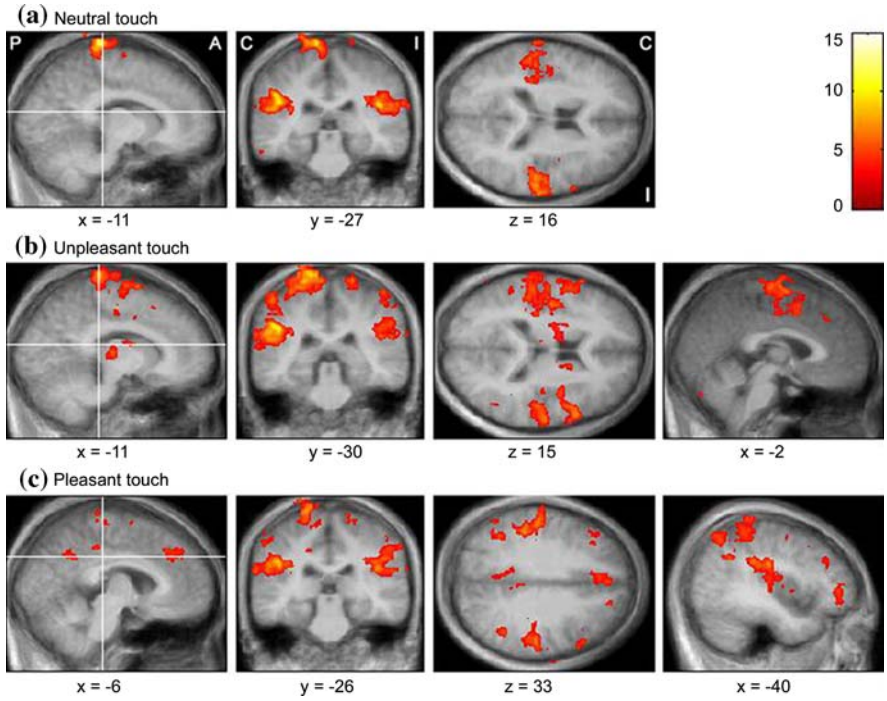

Fig. 1 Group activation t-maps of three touch conditions ($P < 0.001$, uncorrected, clusters with size > 8 voxels), smoothed with an additional 2-mm FWHM Gaussian kernel. Characters C, I, A, P indicates contralateral, ipsilateral, anterior, posterior respectively. (**a**) Neutral touch condition. (**b**) Unpleasant touch condition. (**c**) Pleasant touch condition

Table 2 The top 8 of the selected brain regions based on their $\bar{\Gamma}$

Conditions	Ranking of the brain regions
Resting state	dACC, SI, mIC, PPC, PMA, SMA, mPFC, LOFC
Neutral touch	pIC, SII, SI, dACC, MD, PPC, SMA, Pu
Unpleasant touch	pIC, SI, SII, dACC, SMA, MD, mPFC, PPC
Pleasant touch	SII, pIC, mPFC, PPC, mIC, PMC, SI, dACC

important node in the network. The top eight of the selected brain regions based on their $\bar{\Gamma}$ value are listed in Table 2 for all conditions (results of a two-way ANOVA on the data were shown in Fig. 4).

For all conditions, $\bar{\Gamma}$ values had an approximate Gaussian distribution (Jarque-Bera test: $j = 1.92$, $P = 0.38$). Two-way ANOVA shows that the differences in $\bar{\Gamma}$ among the selected brain regions were significant in the three touch conditions ($F = 112.4$, $P < 0.0001$). In addition, there exists a significant interaction between factor A (i.e., conditions) and factor B (i.e., brain regions) ($F = 14.98$, $P < 0.0001$). Notably, Bonferroni post-tests (paired t-tests) show significant differences in $\bar{\Gamma}$ for some pairs of ROIs between two of the three conditions, e.g., the contralateral PMC ($P < 0.001$) between unpleasant and neutral touch conditions.

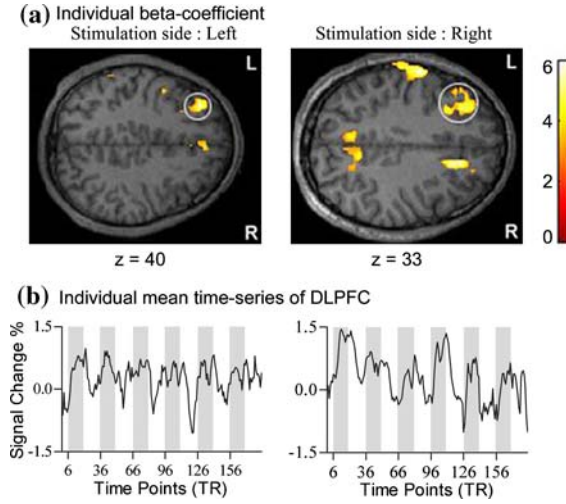

Fig. 2 Laterality activation located in DLPFC and their corresponding mean time series. Vertical grey bars indicate stimulation "on" periods. L/R indicates the left/right hemisphere of the brain respectively. (**a**) Individual beta-coefficient map showed laterality activation in DLPFC. (**b**) Mean time series extracted from DLPFC

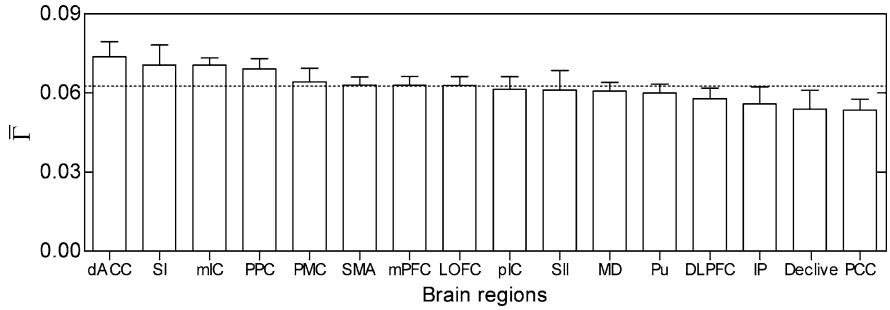

Fig. 3 Ranking of the selected brain regions based on their $\bar{\Gamma}$ (mean $\pm$ SEM) in the resting state. Dotted line indicates the chance value of $\bar{\Gamma}$ (i.e., 0.625)

Discussion

In the present study, we compared brain activations to unpleasant, neutral and pleasant touch stimuli, to illuminate which parts of the brain represent affective aspects of touch. We hypothesized that these brain regions, including orbitofrontal cortex, insular cortex and cingulate cortex, constitute a network which contributes to emotion processing in the human brain. Notably, using functional connectivity analysis, we showed the existence of a high distributed functional connectivity network related to affective touch in the resting brain. More importantly, we found that such a network can be modulated between pleasant, neutral and unpleasant touch.

The results of conjunction analysis (Table 1) showed that the brain regions including the contralateral SI, bilateral SII, contralateral middle insula cortex and posterior insula cortex were commonly activated to three touch conditions. They are the most commonly activated regions in sensory-discriminative, pleasant touch and pain studies (Peyron et al. 2000; Olausson et al. 2002; Rolls et al. 2003; Stoeckel et al. 2003). The primary somatosensory area

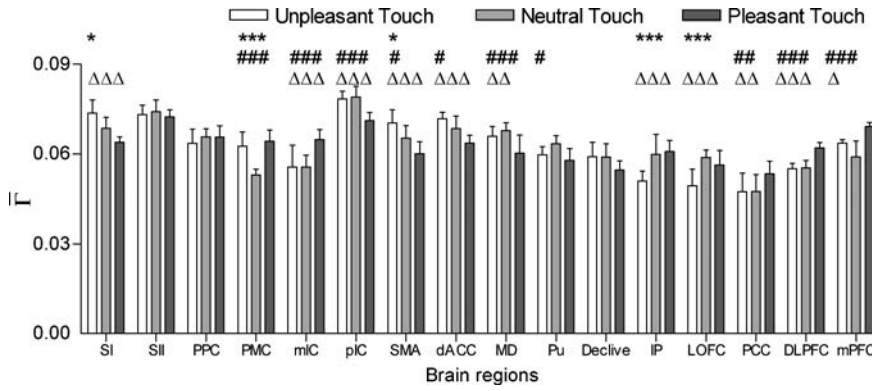

Fig. 4 Two-way ANOVA (touch conditions × brain regions) on $\bar{\Gamma}$ (mean ± SEM). Bonferroni post-tests (paired *t*-tests): *unpleasant touch vs. neutral touch; # pleasant touch vs. neutral touch; Δ unpleasant touch vs. pleasant touch. *, #, Δ $P < 0.05$; **, ##, ΔΔ $P < 0.01$; ***, ###, ΔΔΔ $P < 0.001$

(SI) receives somatosensory information through somatosensory relay nuclei of thalamus [ventroposterior lateral nucleus (VPL) and ventroposterior inferior nucleus (VPI)] and is believed to transmit spatially discriminative aspects of tactile or noxious stimuli (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). The middle and posterior parts of insula cortex receive somatosensory information through projections from SI and SII (Friedman et al. 1986) and also directly from thalamus (Craig et al. 1994).

In addition, pleasant and unpleasant touch conditions shared a few brain regions—contralateral PPC and bilateral PMC. It is suggested that the role of PPC is to integrate afferent information from multimodalities, such as touch, vision and proprioception, and to convert it into common spatial representations (Andersen et al. 1997). It is clear that the PMC has potential roles in selection of movement (Deiber et al. 1991) and motor programming of sequential and rhythmic patterns (Halsband et al. 1993). Cortical sensory-motor "mirror" networks are thought to play a key role in primate communication. Warren and colleagues demonstrated that a network of human premotor cortical regions activated during facial movement is also involved in auditory processing of affective nonverbal vocalizations (Warren et al. 2006). More speculatively, PMC activation may be interpreted to reflect more requirements of interaction during pleasant and unpleasant touch conditions.

Unpleasant touch specifically activated a set of pain-related brain regions including contralateral SMA, MD, aIC, bilateral dACC, putamen, declive and caudal ACC (for an overview on pain-related activations, see Peyron et al. 2000). MD and ACC belong to medial pain pathways, and the nociceptive projections to ACC come mainly from medial thalamic nuclei (midline and intralaminar nuclei) (Vogt et al. 1987). Rainville et al. demonstrated that ACC was specifically related to the pain unpleasantness but not pain sensation (Rainville et al. 1997). Buchel and colleagues (Buchel et al. 2002) demonstrated that the caudal ACC is associated with pain intensity, and dorsal parts of the aACC are associated with cognitive processing like attention and working memory and stimulus awareness related to pain. In addition, the dorsal ACC also plays important roles in cognition, motor control and emotional processing (Bush et al. 2002). In fact, ACC is also involved in other functions unrelated to pain, which include coding for the reward properties of particular behaviours (Bush et al.

2002; Rolls et al. 2003) and activation during romantic love (Bartels and Zeki 2000). Putamen is known to represent behaviourally relevant nociceptive information and hence to make available for pain-related motor responses (Bingel et al. 2004).

Oibitofrontal activation has been reported in previous studies on acute (Derbyshire et al. 1997; Rainville et al. 1999; Craig et al. 2000; Petronic et al. 2000), chronic (Hsieh et al. 1995; Apkarian et al. 2001), and capsaicin-induced pain (Lorenz et al. 2002) but was absented in the present study. This inconsistency was probably caused by the difference in the method of stimulation used.

Brain regions specifically activated by pleasant touch comprised bilateral lateral OFC, PCC, medial PFC, intraparietal cortex and left dorsal lateral PFC. The orbitofrontal cortex has been proposed to be involved in sensory integration, in presenting the affective value of reinforcers and in decision-making and expectation. Recent neuroimaging studies (O'Doherty et al. 2000; Gottfried et al. 2003; Kringelbach et al. 2003; McClure et al. 2004) have found that the reward value, the expected reward value and even the subjective pleasantness of foods and other reinforcers (including pleasant touch) are represented in the orbitofrontal cortex. In contrast to Francis and Rolls's findings, the OFC activation in the current study was located more laterally (BA47/12). This difference was presumably resulted from the difference in the site of stimulation applied. The posterior cingulated cortex is one of the most commonly activated regions in emotional studies, and is considered responsible for assessing the self-relevance of emotional events and stimuli (Vogt et al. 2005). McClure and colleagues showed that PCC is engaged in decisions involving immediately available rewards (McClure et al. 2004). Phan et al. carried out a meta-analysis of simple emotions and found that vPCC shows a high level of activity during happiness (Phan et al. 2002).

Rowe and colleagues have related DLPFC and IP to working memory (Rowe et al. 2000). They demonstrated that dorsal lateral prefrontal cortex (BA 46) is associated with selection of an item from working memory. In contrast, intraparietal cortex is involved in maintenance within working memory. Intriguingly but not singularly, DLPFC activation identified here had an obvious laterality. A number of neuroimaging studies on working memory have supported such a functional laterality of frontal cortex (Fletcher et al. 2001; Stoeckel et al. 2003). Otherwise, McClure et al. have related DLPFC and IP to delayed monetary rewards (McClure et al. 2004). Notwithstanding remaining uncertainties, there is no doubt that DLPFC and IP can be activated by pleasant touch and may contribute to either working memory or evaluation of reward.

The above-mentioned discrepancy between the brain activation pattern of pleasant touch and that of unpleasant touch raises the chance that the two affective touch stimuli are processed in two diverse brain networks, and result in very different affective outcomes. The two brain networks share a few cortical regions related to discriminative components of touch. Alternatively, there is a possibility that all these brain regions constitute a large organized functional connectivity network, and such a network can be modulated between affectively different touches. We prefer the latter because of its consistency with a global hypothesis advanced by Craig on the role of the small-diameter primary afferents and recent findings about functional role of tactile C afferents. Craig (1996) recently has proposed that the small-diameter afferents, which include nociceptive and thermoreceptive afferents as well as afferents from deep structures and viscera, have the function in common to contribute information to "a larger limbic network involved in homeostatic and behavioural maintenance of the integrity of the self" and "provide the underpinnings for basic emotional and motivational states." Furthermore, several observations have suggested that tactile C afferents which signal pleasant touch could be part of such a system (Vallbo et al. 1999; Olausson et al. 2002; Wessberg et al. 2003).

Many studies have demonstrated that there exists very low frequency fluctuations (LFFs; <0.08 Hz) in MR signals measured in the resting brain (Biswal et al. 1995; Lowe et al. 1998; Greicius et al. 2003). In functionally related regions of the brain, these fluctuations are synchronous and exhibit high temporal coherence, even in those regions located remotely, which suggests the existence of neuronal connectivity coordinating activity in the human brain. Till now, functional connectivity in the resting brain has been found in motor regions (Biswal et al. 1995; Lowe et al. 1998; Cordes et al. 2000), auditory regions (Cordes et al. 2001), visual regions (Biswal et al. 1995; Lowe et al. 1998; Cordes et al. 2000) and the language system (Hampson et al. 2002). In the present study, we showed that a series of brain regions related to affectively different touch have significant functional connectivity during the resting state. Based on graph theory, brain regions with larger $\bar{\Gamma}$ values indicate stronger interactions with other brain regions and were considered as important nodes implicated in the resting state network (Jiang et al. 2004). In this context, we considered dACC, SI, mIC, PPC and PMC as important nodes and such an idea fits well with the functional roles and anatomic connections of these brain structures:

The anterior cingulate cortex is considered as limbic motor cortex, because of its association with autonomic and emotional control (Devinsky et al. 1995). ACC receives somatosensory information, in particular direct nociceptive input (i.e., from ventrocaudal part of the medial dorsal nucleus) (Vogt et al. 1979; Van Hoesen et al. 1993), but could also receive somatosensory information indirectly via the ventrally directed cortico-limbic somatosensory pathway (i.e., from insula cortex and orbitofrontal cortex, which are both well connected with the ACC) (Van Hoese et al. 1993).

The insula cortex is regarded as limbic sensory cortex, and recent findings suggested that, mid-posterior insula may provide a primary 'interoceptive cortex', specialized for perception of internal bodily states incorporating pain, sensual touch, temperature, itch, as well as autonomic arousal (Critchley et al. 2002; Craig et al. 2003). Insula cortex and ACC are the intersections of direct and cortico-limbic somatosensory pathways and both of them are strongly interconnected with amygdala, hypothalamus, orbitofrontal cortex and brainstem homeostatic regions.

The posterior parietal cortex that integrates somatosensory information with other sensory modalities and with learning and memory are located at the origin of the ventrally directed cortico-limbic pathway (Friedman et al. 1986). In addition, the posterior parietal cortices have strong connections with the prefrontal cortex and transfer information from specific unimodal processing areas to the prefrontal cortex when information has to be kept online.

If the network can be modulated between affectively different touch conditions, we expect that there exist significant differences in $\bar{\Gamma}$ values for some particular brain regions among the conditions. Statistical analysis (viz. two-way ANOVA) in $\bar{\Gamma}$ values has strongly supported such a hypothesis.

By and large, brain regions specifically activated by unpleasant touch have higher $\bar{\Gamma}$ values during unpleasant touch condition. Likewise, brain regions specifically activated by pleasant touch have stronger $\bar{\Gamma}$ values during pleasant touch condition. This result confirmed our brain activation results. Secondly, pIC and SII have stronger $\bar{\Gamma}$ values during the three touch conditions than during the resting condition. We considered that it is probably caused by that more brain regions are involved in touch conditions than in the resting state and that SII and pIC are upriver brain structures in the ventrally direct cortico-limbic pathways. Thirdly, some brain regions, such as SI, SMA and dACC, exhibit descending $\bar{\Gamma}$ values across three touch conditions (unpleasant $>$ neutral $>$ pleasant). Last but most important, most of the brain regions (besides SI, PMC, IP, LOFC and SMA) had similar $\bar{\Gamma}$ values ($P > 0.05$) between during neutral touch condition and

unpleasant touch condition. In addition, the ranking of brain regions were analogical during the two conditions. More speculatively, this finding may reflect that, during neutral touch condition, the network operates in a 'vigilant' pattern similar to that during unpleasant touch, in order to make immediate defence and withdraw behaviour against pain events. Reversely, during pleasant touch condition, the network operates in an 'easy-going' pattern.

To the best of our knowledge, this is the first neuroimaging study of humans to investigate the functional connectivity network involved in conveying and processing affective components of touch. These findings suggested that there is a highly distributed functional network related to emotion processing for touch. This network can be modulated between affectively different touch, producing different subjective experiences. Our findings provide new insights into the neural mechanisms related to affective aspects of touch and might be useful to explain why pleasant touch could be lenitive and hedonic.

Acknowledgements This work was supported by 211 project to JYL, a grant from National Natural Science Foundation of China (30700223) to JYW, NNSF grants (30370461, 30570577, and 30770688), the 100 Talented Plan of the Chinese Academy of Sciences, and the 863 project (2006AA02Z431) of China to FL. The authors would like to thank Prof. Tianzi Jiang, Institute of Automation, Chinese Academy of Science, for his functional connectivity analysis algorithm and insightful discussions.

Appendix

In this study, functional connectivity network analysis is based on graph theory. Therefore, the nodes denote the brain regions (ROIs) and the links denote the connections or information flow. In this way, we can define the total connectivity degree Γ_i of node i in a graph as the sum of all the connectivity degrees between i and all other nodes, i.e.,

$$\Gamma_i = \sum_{j=1}^{n} \eta_{ij}$$

where η_{ij} is the connectivity degree between the node i and the node \, defined by the exponential function of the distance between them (Lopez and Sanjuan 2002),

$$\eta_{ij} = e^{-\xi d_{ij}}$$

where, ξ is a real positive constant, measuring how the strength of the relationship decreases with the distance between the two nodes [ξ is a subjective selection and discussed by Lopez and Sanjuan (2002) and is here fixed to $\xi = 2$], and d_{ij} is the distance between the two nodes, calculated as a hyperbolic correlation measure (Golay et al. 1998),

$$d_{ij} = (1 - c_{ij})/(1 + c_{ij})$$

where c_{ij} represents the Pearson correlation coefficient between the two nodes (i.e., cross-correlating two mean time series of the above).

In addition, as there are different touch conditions and different preprocessing in this study, we normalized Γ_i of a node i, namely,

$$\bar{\Gamma}_i = \Gamma_i / \sum_{j=1}^{n} \Gamma_j$$

The normality of the distribution of the $\bar{\Gamma}_i$ values for all conditions was tested using the Jarque-Bera test.

References

Andersen RA, Snyder LH, Bradley DC, Xing J (1997) Multimodal representation of space in the posterior parietal cortex and its use in planning movements. Annu Rev Neurosci 20:303–330

Apkarian AV, Thomas PS, Krauss BR, Szeverenyi NM (2001) Prefrontal cortical hyperactivity in patients with sympathetically mediated chronic pain. Neurosci Lett 311(3):193–197

Bartels A, Zeki S (2000) The neural basis of romantic love. NeuroReport 11:3829–3834

Bingel U, Glascher J, Weiller C, Buchel C (2004) Somatotopic representation of nociceptive information in the putamen: an event-related fMRI study. Cereb Cortex 14:1340–1345

Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planner MRI. Magn Reson Med 34:537–541

Buchel C, Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C (2002) Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulated cortex: a parametric single-trial laser functional magnetic resonance imaging study. J Neurosci 22:970–976

Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR (2002) Dorsal anterior cingulated cortex: a role in reward-based decision making. Proc Natl Acad Sci USA 99:523–528

Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, Quigley MA, Meyerand ME (2000) Mapping functionally related regions of brain with functional connectivity MRI (fcMRI) Am. J Neuroradiol 21:1636–1644

Cordes D, Haughton V, Arfanakis K, Carew JD, Turski PA, Moritz CH, Quigley MA, Meyerand E (2001) Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. Am J Neuroradiol 22:1326–1333

Cox RW (1996) AFNI software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173

Craig AD, Bushnell MC, Zhang ET, Blomqvist A (1994) A thalamic nucleus specific for pain and temperature sensation. Nature 372:770–773

Craig AD (1996) Pain, temperature and the sense of the body. In: Franzen O, Johansson R, Terenius L (eds) Somesthesis and the neurobiology of the somatosensory cortex. Birkhauser, Basel, pp 27–39

Craig AD (2003) Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 13(4):500–505

Craig AD, Chen K, Bandy D, Reiman EM (2000) Thermosensory activation of insular cortex. Nat Neurosci 3(2):184–190

Critchley HD, Melmed RN, Featherstone E, Mathias CJ, Dolan RJ (2002) Volitional control of autonomic arousal: a functional magnetic resonance study. Neuroimage 16(4):909–919

Deiber MP, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RSJ (1991) Cortical areas and the selection of movement: a study with positron emission tomography. Exp Brain Res 84:392–402

Derbyshire SWG, Jones AKP, Gyulai F, Clark S, Townsend D, Firestone LL (1997) Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 73:431–445

Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulated cortex to behaviour. Brain 118:279–306

Dunbar R (1996) Grooming, gossip, and the evolution of language. Faber & Faber, London

Essick GK, James A, McGlone FP (1999) Psychophysical assessment of the affective components of non-painful touch. Neuroreport 10:2083–2087

Fletcher PC, Henson RNA (2001) Frontal lobes and human memory—insights from functional neuroimaging. Brain 124:849–881

Francis S, Rolls ET, Bowtell R, McGlone F, O'Doherty J, Browning A, Clare S, Smith E (1999) The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. NeuroReport 10:453–459

Friedman DP, Murray EA, O'Neill JB, Mishkin M (1986) Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. J Comp Neurol 252:323–347

Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SC, Frackowiak RS, Turner R (1995) Analysis of fMRI time-series revisited. Neuroimage 2:45–53

Gardner EP, Kandel ER (2000) Touch. In: Kandel ER, Schwartz JH, Jessell TM (eds) Principles of neural science, 4th edn. McGraw-Hill, New York, pp 451–470

Golay X, Kollias S, Stoll G, Merier D, Valavanis A, Boesiger PA (1998) New correlation-based fuzzy logic clustering algorithm for fMRI. J Magn Res Med 40:249–260

Gottfried JA, O'Doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdale and orbitofrontal cortex. Science 301:1104–1107

Greicius MD, Krasnow B, Reiss AL, Menon v (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 100:253–258

Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC (2002) Detection of functional connectivity using temporal correlations in MR images. Hum Brain Mapp 15:247–262
Halsband U, Ito N, Tanji J, Freund HJ (1993) The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. Brain 116:243–266
Holmes AP, Friston KJ (1998) Generalisability, random effects and population inference. Neuroimage 7:754
Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M (1995) Central presentation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 63:225–236
Jiang T, He Y Zang Y, Weng X (2004) Modulation of functional connectivity during the resting state and the motor task. Hum Brain Mapp 22:63–74
Kass JH (1993) The functional organization of the somatosensory cortex in primates. Anat Anz 175:509–518
Kringelbach ML, O'Doherty J, Rolls ET, Andrews C (2003) Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex 13:1064–1071
Lopez L, Sanjuan MAF (2002) Relation between structure and size in social networks. Phys Rev E 65:036107
Lorenz J, Cross D, Minoshima S, Morrow T, Paulson P, Casey K (2002) A unique representation of heat allodynia in the human brain. Neuron 35(2):383–393
Lowe MJ, Mock BJ, Sorenson JA (1998) Functional connectivity in single and multisclice echoplannar imaging using resting state fluctuations. Neuroimage 7:119–132
McClure SM, Laibson DI, Loewenstein G, Cohen JD (2004) Separate neural systems value immediate and delayed monetary rewards. Science 306:503–507
O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 11:893–897
Olausson H, Lamarre Y, Backlund H, Morin C, Wallin BG, Starck G, Ekholm S, Strigo I, Worsley K, Vallbo AB, Bushnell AC (2002) Unmyelinated tactile afferents signal touch and project to insular cortex. Nat Neurosci 5(9):900–904
Panksepp J (1998) Affective neuroscience: the foundations of human and animal emotions. Oxford University Press, New York
Petrovic P, Petersson KM, Ghatan PH, Stone-Elander S, Ingvar M (2000) Pain-related cerebral activation is altered by a distracting cognitive task. Pain 85:19–30
Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 30:263–288
Phan KL, Wager T, Taylor SF, Liberzon I (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16:331–348
Rainville P, Duncan GH, Price DD (1997) Pain affect encoded in human anterior cingulated but not somatosensory cortex. Science 277:968–971
Rainville P, Hofbauer RK, Paus T, Duncan GH, Bushnell MC, Price DD (1999) Cerebral mechanisms of hypnotic induction and suggestion. J Cogn Neurosci 11(1):110–125
Rolls ET (1999) The brain and emotion. Oxford University Press, New York
Rolls ET, O'Doherty J, Kringelbach ML, Francis S, Bowtell R, McGlone F (2003) Representations of pleasant and painful touch in the human orbitofrontal and cingulated cortices. Cereb Cortex 13(3):308–317
Rowe JB, Toni I, Josephs O, Frackowiak RSJ, Passingham RE (2000) The prefrontal cortex: response selection or maintenance within working memory? Science 288:1656–1660
Stoeckel MC, Weder B, Binkofski F, Buccino G, Shah NJ, Seitz RJ (2003) A fronto-parietal circuit for tactile object discrimination: an event-related fMRI study. Neuroimage 19:1103–1114
Vallbo AB, Olausson H, Wessberg J (1999) Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. J Neurophysiol 81:2753–2763
Van Hoesen GW, Morecraft RJ, Vogt BA (1993) Connections of the monkey cingulated cortex. In: Vogt BA, Gabriel M (eds) The neurobiology of the cingulated cortex and limbic thalamus: a comprehensive handbook. Birkhauser, Boston, pp 249–284
Vogt BA (2005) Pain and emotion interactions in subregions of the cingulated gyrus. Nat Rev Neurosci 6:533–544
Vogt BA, Pandya DN (1987) Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents. J Comp Neurol 262:256–270
Vogt BA, Rosene DL, Pandya DN (1979) Thalamic and cortical afferents differentiate anterior from posterior cingulated cortex in the monkey. Science 204:205–207
Warren JE, Sauter DA, Eisner F, Wiland J, Dresner MA, Wise RJS, Rosen S, Scott SK (2006) Positive emotions preferentially engage an auditory-motor "mirror" system. J Neurosci 26(50):13067–13075
Wessberg J, Olausson H, Fernstrom KW, Vallbo AB (2003) Receptive field properties of nmyelinated tactile afferents in the human skin. J Neurophysiol 89:1567–1575