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Differential human brain activity induced by two perceptually indistinguishable gentle cutaneous stimuli

Nobuhiro Watanabe[a], Kenji Ishii[b], Harumi Hotta[a], Keiichi Oda[b], Muneyuki Sakata[b], Jun Toyohara[b] and Kiichi Ishiwata[b]

We examined differences in brain activity in response to two types of mechanical stimulation, which have been reported previously as being perceptually indistinguishable but having different impacts on autonomic reflexes. As an indicator of brain activity, glucose metabolism was evaluated by PET with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG). Twelve healthy, young adult men participated in the study. Two types of cutaneous stimulation tools, soft elastomer discs with microcones (microcone disc) or flat surfaces (flat disc), were used in a crossover, randomized double-blind manner. Each type of cutaneous stimulation tool was applied on the cheeks and ^{18}F-FDG-PET scans were obtained. Greater ^{18}F-FDG uptake was observed in the right anterior cingulate cortex during microcone disc stimulation compared with flat disc stimulation. However, ^{18}F-FDG uptake during application of these two different stimuli was not different in the primary and secondary somatosensory cortices or insula. Stimulation using microcone discs and flat discs was noted by one and three participants, respectively, and there was no difference in the presence of perception between the stimulation tools. The results indicate that the right anterior cingulate cortex differentially responds to different types of cutaneous stimulation that are perceptually indistinguishable. *NeuroReport* 24:425–430 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: cingulate cortex, fluorodeoxyglucose, positron emission tomography, skin, somatosensory system, subliminal, touch

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Introduction

The cutaneous sensory system plays an important role in obtaining information on surrounding objects and the external environment, as well as in eliciting sensations. Cutaneous stimulation also induces biological reactions, including analgesia [1,2] and autonomic responses [3,4].

To clarify the central mechanisms involved in somatosensory information processing, various methods such as functional MRI [5–7] and PET [8] have been used to measure brain function accompanying perceptible tactile stimulation. In contrast, it seems that the influence of gentle, nonperceptible somatosensory stimulation has been overlooked.

Recently, we reported that gentle mechanical cutaneous stimulation inhibits somatically-induced autonomic responses in anesthetized rats [9,10] and conscious humans [11], independent of sensation and recognition. In these studies, cutaneous stimulation was applied using a brush with soft elastomer microcones and a flat disc made of the same material; only cutaneous stimulation with the brush inhibited the autonomic responses [9,11]. We found that the differences in texture between these cutaneous stimulations were not distinguished in conscious humans [11]. Our results indicate that subliminal somatic stimulation can have an impact on autonomic functions. However, responses of the brain to subliminal somatosensory stimulation are little known. Therefore, the present study aimed to compare brain activity during administration of perceptually indistinguishable gentle mechanical cutaneous stimuli using the two stimulation tools used in our previous studies [9,11].

To our knowledge, there is only one report stating that subliminal electrical stimulation elicits evoked potentials using recording electrodes placed on the pia-arachnoid surface of the primary somatosensory cortex (SI) [12]. There are a few studies that examined subliminal intensity on visceral stimulation, showing an increase in the blood oxygenation level-dependent (BOLD) signal in several brain regions [13,14]. A common brain region found in their studies to react to these stimuli is the anterior cingulate cortex (ACC). Gentle but perceptible cutaneous stimulation also increases BOLD signal or regional cerebral blood flow in the ACC [5,6], in addition to the SI [5–8], secondary somatosensory cortex (SII) [7,8], and insula [5,6]. Thus, in this study, we focused on the ACC, SI, SII, and insula as potential brain regions that may respond to mechanical cutaneous stimulation at a subliminal intensity.

The present study compared glucose metabolism in the ACC, SI, SII, and insula during administration of two different types of gentle mechanical cutaneous stimuli, which are perceptually indistinguishable, using PET with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG).

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Methods

Participants

Twelve healthy adult men [mean age ± SD: 22.6 ± 1.9 years (range: 21–26 years), mean BMI: 22.8 ± 2.3 kg/m^2] participated in the study. All participants met the following inclusion criteria: (i) nonsmoker; (ii) no history of diseases that may affect the cardiovascular and/or nervous system such as heart diseases, diabetes mellitus, or cancer; (iii) no facial or oral pain; and (iv) no regular administration of therapeutic drugs or drug use on the day of the experiment. According to the Japanese version of the Edinburgh Handedness Inventory, all participants were right-handed (laterality quotient score range, +60 to +100). No participant had any organic abnormality in the brain on MRI.

Written informed consent was obtained from all participants before the commencement of any experimental procedure. The experimental protocols of the study were in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committee of Tokyo Metropolitan Institute of Gerontology.

Participants fasted for at least 4 h before the experiment commenced. In addition, they were advised to avoid vigorous physical activity and abstain from alcohol on the day before their participation. The final intake time of food and caffeinated and alcoholic beverages was recorded using a pre-experimental questionnaire.

Cutaneous stimulation

Two types of cutaneous stimulation tools (used in our previous studies [9,11]) were used. The tools were made of soft elastomer and appeared to be identical discs (11 mm in diameter) with similar thicknesses. The contacting surface of the first type of disc had a brush with ~400 soft elastomer microcones and the other side was flat (microcone disc, Somareson II; gifted by Toyo Resin Corporation, Shizuoka, Japan); the second type of disc had flat surfaces on both sides (flat disc; custom-made for our research use by Toyo Resin). Each cutaneous stimulation tool was attached to the cheek bilaterally using an adhesive plaster.

Blinding and randomization

The order of cutaneous stimulation tool use was randomized. To blind the participant and experimenter from the type of tool used, both tools were placed in cartridges of the same color and shape before use, and the experimenter was not allowed to check the tool surface. The stimulation tools were packaged as two pairs (two sheets × two types), and the order of use was indicated on the cartridge. Each package of stimulation tools was allocated to a participant in advance and the probability of either type of stimulation tool being used first was 50%. After each session of the experiment, participants were questioned on whether they perceived any sensation from the cutaneous stimulation tools and were asked to describe the details of their perception using a questionnaire. After completion of the questionnaire, the cutaneous stimulation tools were removed.

Perception induced by the cutaneous stimulation tools was compared using Fisher's exact test (Prism 6; GraphPad Software Inc., La Jolla, California, USA), and the significance level was set at P less than 0.05. The identity of the cutaneous stimulation tools and the order of their use were not disclosed until the experimental period had ended.

Study overview

The study consisted of two experimental sessions and was carried out in a dimly-lit, quiet room with minimal sound from an air conditioner. Participants were supine on the bed and remained with their eyes closed and ears unplugged. To ensure that the participants remained awake, they were gently spoken to every 10 min during the experiment. After the right brachial vein was catheterized, a cutaneous stimulation tool was applied to the cheeks. Ten minutes later, ^{18}F-FDG (150 MBq) was injected intravenously. Participants were instructed to rest for the next 35 min. Thereafter, they walked to the PET scanner on foot after the catheter was withdrawn and transmission scanning was performed in the supine position for 5 min. A 6-min emission scan was then obtained at 45 min after ^{18}F-FDG injection.

PET scanning was performed between 3 and 5 p.m. for all participants. One week after the first experimental session, the experiment was conducted using the same protocol at the same hour with the other type of cutaneous stimulation tool.

Blood sampling was performed twice during an experimental session (at the time of venous catheter insertion and immediately before withdrawal) for measurement of blood glucose levels (Caresist; Roche Diagnostics Japan, Tokyo, Japan). The level of blood glucose was stable during each experiment and over both experimental days (first vs. second session; mean value ± SD: 83.7 ± 10.7 vs. 85.8 ± 12.5 mg/dl, respectively).

Image acquisition

The ^{18}F-FDG-PET scan images were acquired in the three-dimensional (3D) mode [reconstructed image resolution: transverse full-width at half-maximum (FWHM) = 4.4 mm, axial FWHM = 6.5 mm] using a PET scanner (SET 2400 W; Shimadzu, Kyoto, Japan) as described previously [15]. The emission scan parameters were as follows: matrix size, 128 × 128 × 63 voxels and size of one voxel, 2 × 2 × 3.125 mm. Attenuation correction was performed using a transmission scan with a ^{68}Ga/^{68}Ge source.

For all participants, 3D-MRI images of the brain with T1-weighted contrast were obtained in a sagittal orientation using a 1.5 T Signa Excite HD scanner (GE, Milwaukee,

Wisconsin, USA) with a matrix size of $256 \times 256 \times 98$ voxels and a voxel size of $0.8984 \times 0.8984 \times 1.8$ mm. The images were obtained using the 3D spoiled gradient echo (TR/TE = 21/6 ms).

Image processing and data analyses

Image processing was performed as per the procedures described previously [15]. All ^{18}F-FDG-PET images were spatially normalized to the standard anatomical space created by the Montreal Neurological Institute using an institutionally-designed ^{18}F-FDG template, resampled (matrix size: $79 \times 95 \times 80$ voxels; voxel size, $2 \times 2 \times 2$ mm), and smoothed with a Gaussian kernel of 12 mm FWHM in the x, y, and z axes using SPM8 (Functional Imaging Laboratory, London, UK) implemented on MATLAB (The MathWorks, Natick, Massachusetts, USA). A threshold of 20% of maximal pixel values in the averaged image of all individual images was set, and the subthreshold signals in each PET image were excluded in order to eliminate the influence of extracerebral signals (using Dr View software; AJS, Tokyo, Japan). The ^{18}F-FDG uptake was expressed as a standardized uptake value [body weight (g) × tissue concentration (Bq/ml)/total injected dose (Bq)]. To eliminate the effect of global variation, the average intracerebral ^{18}F-FDG uptake was normalized to be 50.

On the basis of our hypothesis, ^{18}F-FDG uptakes in the ACC, SI, SII, and insula were compared between the microcone and flat disc stimulation tools. To test a priori hypotheses (see the Introduction section) and quantify the differences in ^{18}F-FDG uptake, a volume of interest (VOI) analysis was performed. Five VOIs (in this case, a sphere of 5 mm radius) were placed in each hemisphere: two in the ACC and one each in the SI, SII, and insula. The location of the VOI was determined on the basis of previous brain imaging studies, which examined the effect of somatosensory stimulation applied to the face [7,16–19]. VOI locations are shown in Table 1 and Fig. 1. The values obtained using SPM 8 were compared using two-way analysis of variance (factors: cutaneous stimulation and brain region) with repeated measures between cutaneous stimulation (microcone and flat disc), followed by Bonferroni's correction for multiple comparisons ($P < 0.05$, Prism 6; GraphPad Software Inc.).

In addition, we conducted a global search over the entire brain for a comparison of ^{18}F-FDG uptake between the microcone and flat disc stimulation tools. The threshold of statistical significance was set to P less than 0.001 uncorrected, and the extent threshold, k, was 100 voxels (SPM 8).

Results

Comparison of ^{18}F-FDG uptake between microcone and flat disc stimulation tools

Table 1 summarizes the values of ^{18}F-FDG uptake during application of cutaneous stimulation tools. Analysis of variance revealed a significant main effect of cutaneous stimulation. ^{18}F-FDG uptake in the right ACC tended to be greater during application of microcone stimulation compared with flat disc stimulation (Table 1). In particular, ^{18}F-FDG uptake in a part of the ACC was significantly higher during microcone stimulation (Fig. 2a and b, Table 1). In contrast, there was no significant difference in ^{18}F-FDG uptake in the other brain regions on microcone and flat disc stimulation: the left ACC or SI, SII, or insula in either hemisphere (Table 1).

Table 1 Comparisons of 2-[^{18}F]fluoro-2-deoxy-D-glucose uptake during microcone and flat disc stimulation

	Side	MNI coordinates (x, y, z)	Microcone	Flat disc
ACC	R	6, 30, 30	71.0±0.81*	69.7±0.75
	L	−6, 30, 30	66.5±0.56	66.0±0.64
pgACC	R	6, 44, 6	69.3±0.87	68.4±0.77
	L	−6, 44, 6	66.2±0.66	66.1±0.68
SI	R	62, −10, 38	51.0±0.59	51.0±0.42
	L	−58, −14, 42	53.6±0.33	53.8±0.51
SII	R	60, −26, 20	68.9±0.60	68.5±0.51
	L	−60, −26, 20	64.1±0.42	64.3±0.39
Insula	R	40, −16, 10	70.6±0.45	70.8±0.65
	L	−40, −16, 10	73.0±0.41	72.6±0.65

Coordinate values of x, y, and z for each VOI are given in millimeters (MNI space). Values were extracted using a VOI, which is a sphere 5 mm in radius. Data are expressed as mean±SEM.
*Significant difference in ^{18}F-FDG uptake between the microcone and the flat disc stimulation ($P < 0.05$); two-way analysis of variance with repeated measures between the cutaneous stimulation (microcone and flat disc), followed by Bonferroni's correction for multiple comparisons.
ACC, anterior cingulate cortex; L, left; MNI, Montreal Neurological Institute; pgACC, pregenual ACC; ^{18}F-FDG, 2-[^{18}F]fluoro-2-deoxy-D-glucose; R, right; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; VOI, volume of interest.

The result of the global search showed that there was no difference in ^{18}F-FDG uptake between the stimuli.

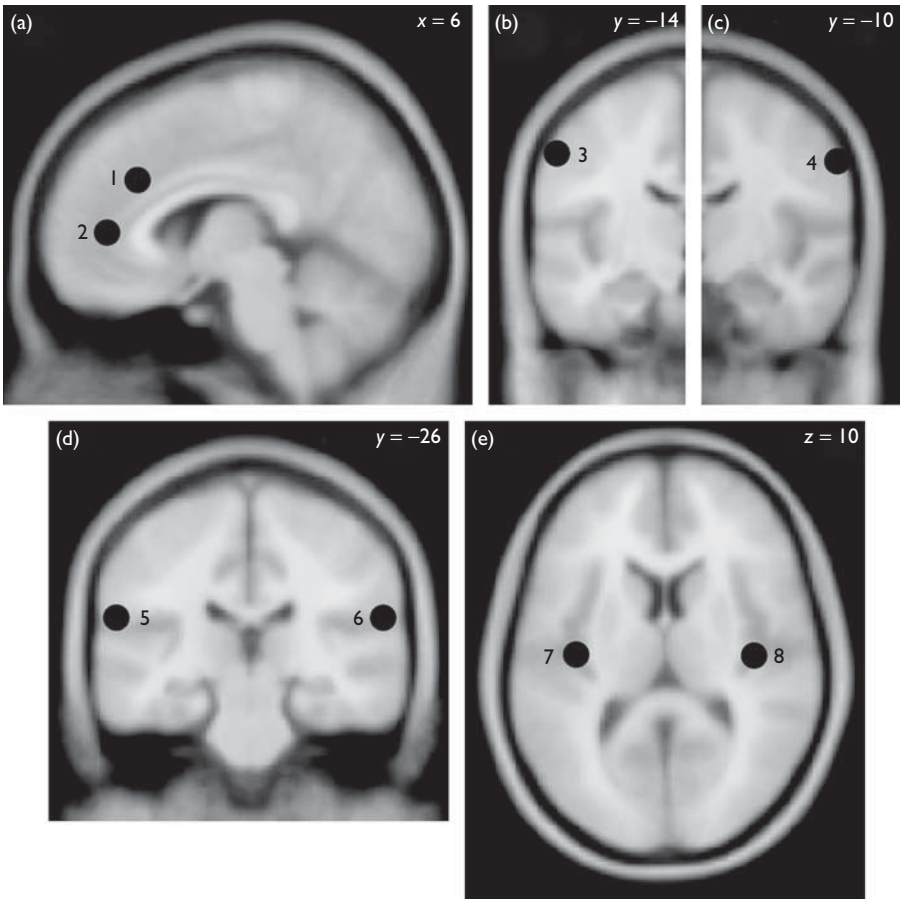
Perception of touch

One of the 12 participants perceived sensation by touch on microcone stimulation and described the sensation as 'only left cheek was itchy but no problem'. Three other participants reported sensations by touch on flat disc stimulation, and they described the sensation as: 'I felt some stimulation like pins and needles although it is not bothering', 'I felt like a little pressure on the cheek for a little while after the application', and 'I felt tingling only on the left'. There was no significant difference in the presence of perception by touch between the microcone and flat disc stimulation tools. The results of ^{18}F-FDG uptake were not different between participants who perceived the touch and those who did not.

Discussion

The present study examined differences in brain activity in response to mechanical stimulation using two types of cutaneous stimulation tools – microcones and flat discs – attached to the face bilaterally. On microcone stimulation, greater ^{18}F-FDG uptake was observed in the right ACC. However, there was no difference in ^{18}F-FDG uptake in the bilateral SI, SII, or insula, supporting the

Fig. 1



The locations of volumes of interest (VOIs). Filled circles with numbers in each panel indicate the location of each VOI. (a) 1, right anterior cingulate cortex (ACC); 2, right pregenual ACC (pgACC). VOIs were placed in mirrored coordinates for the left ACC and left pgACC. (b) 3, left primary somatosensory cortex (SI). (c) 4, right SI. (d) 5, 6, left and right secondary somatosensory cortices (SII), respectively. (e) 7, 8, the left and the right insula, respectively.

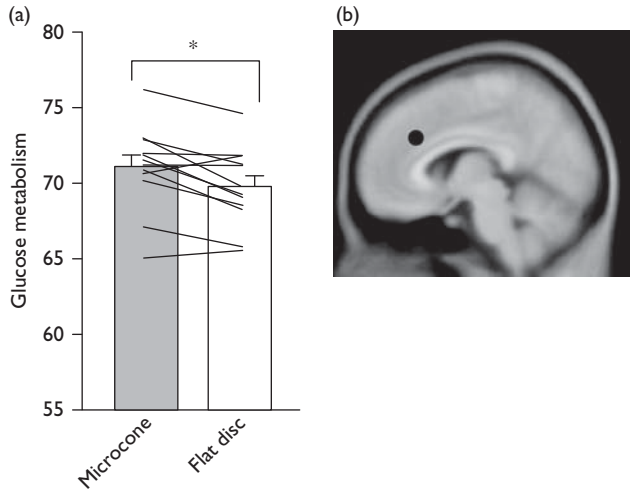
fact that the texture of the two stimulation tools was not perceptually distinguishable in this study, as observed in our previous study [11].

There are reports that the brain responds to imperceptible (subliminal) sensory stimulation. For example, brain activity in response to subliminal visceral stimulation was examined by functional MRI [13,14]. These studies showed that an increase in the BOLD signal was observed in the cingulate cortex, associated with rectal distension at subliminal pressure. The cingulate cortex findings, in which we observed a significant difference, are spatially similar to the findings from a previous study report on activation by subliminal visceral stimulation [14]. Therefore, the cingulate cortex may relate to mechanisms of the subliminal effect of somatovisceral stimuli. So far, little is known about the effect of somatosensory stimulation at subliminal intensity on brain activity; however, one study reports that subliminal electrical stimulation elicits a somatosensory evoked potential [12]. Hence, the present study is the first to localize a difference in brain activity in response to two types of somatosensory stimuli, both of which were perceptually indistinguishable.

In contrast to that in the ACC, ^{18}F-FDG uptake in the SI, SII, and insula was not different on microcone and flat disc stimulation. This supports the conclusion that there is no perceptual difference between the stimulation tools. However, it could be argued that the absence of a difference in ^{18}F-FDG uptake in these regions is because of both stimulation tools altering glucose metabolism in the brain regions by similar amounts. Further studies are needed to clarify this matter.

The differences in brain responses must be attributed to differences in responses of cutaneous sensory units. We have demonstrated that touch with microcone stimulation induces low frequency (< 4 Hz) activities of Aβ, Aδ, and C afferent units, and the myelinated A afferent units are classified as rapidly adapting (RA) and slowly adapting

Fig. 2



A difference in ^{18}F-FDG uptake in the right anterior cingulate cortex. (a) Each line indicates an individual comparison of 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) uptake (glucose metabolism) between the microcone and the flat disc stimulation. Bar graph and error bars express mean±SEM. $N=12$. $^*P<0.05$. (b) The location of the volume of interest (VOI) used for data extraction is presented as a filled circle (the *x*, *y*, and *z* coordinates=6, 30, 30).

(SAI, SAII) units by single unitary afferent recording in rats [9]. Response of the RA and SAI units depends on the texture of the surface of the contacting objects [20]. In addition, afferent activities of the SAII unit and the low-threshold mechanosensitive C unit, which are sensitive to skin stretch [21] and slow, gentle stroking stimulation [22], respectively, may be different between the stimulation tools, because of presumed vibration of the microcones [9].

There are several reports that tactile cutaneous stimuli activate various brain regions including the SI and the ACC region, as well as the SII region and insula [5–8]. Of these studies, that by Lindgren *et al.* [6] compared BOLD effects in response to perceptible touch by a human bare hand with that by a hand wearing a rubber glove. The study showed the increase in BOLD signal on touch by a bare hand in the ACC, but not in the SI or insula, was greater than that on other types of touch. As the microcone arrangement (0.4 mm) of the stimulation tool used in the present study is similar to the width of a fingerprint ridge in humans, touch with the microcones or flat disc is considered to be equivalent to touch with a bare hand and rubber glove hand, respectively, in the previous study [6]. Microcones are suggested to be a tool that can apply finger touch-like stimulation continuously.

There are various biological meanings of touch. One of those may be a modulation of nociceptive transmission. It is a common experience that pain is reduced on placing hands near the region in which the pain is located. Touch stimulation is used for pain management in clinical situations [1,2]. We have reported that gentle mechanical cutaneous stimulation with microcones, but not flat discs, inhibits somatically-induced autonomic responses in anesthetized rats [9] and conscious humans [11], independent of sensation and recognition. Our animal studies suggest that touch can promote release of endogenous opioids in the central nervous system, as the inhibitory effect was significantly attenuated [9] or blocked [10] by intravenous naloxone. There are high-density μ-opioid receptors in the ACC [23]. Systemic injection of remifentanil (μ-opioid receptor agonist) dose-dependently increased cerebral blood flow in the regions including the ACC [24]. There is evidence that the right hemisphere tends to be more predominant on processing of somatosensory information using brain imaging techniques [25]. Collectively, higher glucose utilization in the right ACC on microcone stimulation may be due to opioid release evoked by direct stimulation in this region or indirectly in other regions, such as trigeminal nerve nuclei.

Together with our previous studies [9,11], the present study suggests that there are differences in brain activity, depending on the type of mechanical cutaneous stimuli, which are indistinguishable but have different impacts on autonomic reflexes.

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Conflicts of interest

H.H. received cutaneous stimulation tools from Toyo Resin Corporation. For the remaining authors there are no conflicts of interest.

References

1 Johnston CC, Stevens B, Pinelli J, Gibbins S, Filion F, Jack A, *et al.* Kangaroo care is effective in diminishing pain response in preterm neonates. *Arch Pediatr Adolesc Med* 2003; **157**:1084–1088.

2 Yildirim G, Sahin NH. The effect of breathing and skin stimulation techniques on labour pain perception of Turkish women. *Pain Res Manag* 2004; **9**: 183–187.

3 Fujimoto T, Budgell B, Uchida S, Suzuki A, Meguro K. Arterial tonometry in the measurement of the effects of innocuous mechanical stimulation of the neck on heart rate and blood pressure. *J Auton Nerv Syst* 1999; **75**: 109–115.

4 Sato A, Sato Y, Schmidt RF. The impact of somatosensory input on autonomic functions. *Rev Physiol Biochem Pharmacol* 1997; **130**:1–328.
5 Gordon I, Voos AC, Bennett RH, Bolling DZ, Pelphrey KA, Kaiser MD. Brain mechanisms for processing affective touch. *Hum Brain Mapp* 2013; **34**:914–922.
6 Lindgren L, Westling G, Brulin C, Lehtipalo S, Andersson M, Nyberg L. Pleasant human touch is represented in pregenual anterior cingulate cortex. *Neuroimage* 2012; **59**:3427–3432.
7 Kopietz R, Sakar V, Albrecht J, Kleemann AM, Schöpf V, Yousry I, *et al*. Activation of primary and secondary somatosensory regions following tactile stimulation of the face. *Klin Neuroradiol* 2009; **19**:135–144.
8 Hagen MC, Pardo JV. PET studies of somatosensory processing of light touch. *Behav Brain Res* 2002; **135**:133–140.
9 Hotta H, Schmidt RF, Uchida S, Watanabe N. Gentle mechanical skin stimulation inhibits the somatocardiac sympathetic C-reflex elicited by excitation of unmyelinated C-afferent fibers. *Eur J Pain* 2010; **14**:806–813.
10 Watanabe N, Uchida S, Hotta H. Age-related change in the effect of gentle mechanical cutaneous stimulation on the somato-cardiac sympathetic C-reflex. *J Physiol Sci* 2011; **61**:287–291.
11 Watanabe N, Miyazaki S, Mukaino Y, Hotta H. Effect of gentle cutaneous stimulation on heat-induced autonomic response and subjective pain intensity in healthy humans. *J Physiol Sci* 2012; **62**:343–350.
12 Libet B, Alberts WW, Wright EW Jr, Feinstein B. Responses of human somatosensory cortex to stimuli below threshold for conscious sensation. *Science* 1967; **158**:1597–1600.
13 Andresen V, Bach DR, Poellinger A, Tsrouya C, Stroh A, Foerschler A, *et al*. Brain activation responses to subliminal or supraliminal rectal stimuli and to auditory stimuli in irritable bowel syndrome. *Neurogastroenterol Motil* 2005; **17**:827–837.
14 Lawal A, Kern M, Sidhu H, Hofmann C, Shaker R. Novel evidence for hypersensitivity of visceral sensory neural circuitry in irritable bowel syndrome patients. *Gastroenterology* 2006; **130**:26–33.
15 Kawasaki K, Ishii K, Saito Y, Oda K, Kimura Y, Ishiwata K. Influence of mild hyperglycemia on cerebral FDG distribution patterns calculated by statistical parametric mapping. *Ann Nucl Med* 2008; **22**:191–200.
16 Moulton EA, Pendse G, Morris S, Aiello-Lammens M, Becerra L, Borsook D. Segmentally arranged somatotopy within the face representation of human primary somatosensory cortex. *Hum Brain Mapp* 2009; **30**:757–765.
17 Brooks JCW, Zambreanu L, Godinez A, Craig AD, Tracey I. Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage* 2005; **27**:201–209.
18 Moulton EA, Pendse G, Becerra LR, Borsook D. BOLD responses in somatosensory cortices better reflect heat sensation than pain. *J Neurosci* 2012; **32**:6024–6031.
19 Albuquerque RJC, de Leeuw R, Carlson CR, Okeson JP, Miller CS, Andersen AH. Cerebral activation during thermal stimulation of patients who have burning mouth disorder: an fMRI study. *Pain* 2006; **122**:223–234.
20 Phillips JR, Johansson RS, Johnson KO. Responses of human mechanoreceptive afferents to embossed dot arrays scanned across fingerpad skin. *J Neurosci* 1992; **12**:827–839.
21 Johnson KO. The roles and functions of cutaneous mechanoreceptors. *Curr Opin Neurobiol* 2001; **11**:455–461.
22 Nordin M. Low-threshold mechanoreceptive and nociceptive units with unmyelinated (C) fibres in the human supraorbital nerve. *J Physiol* 1990; **426**:229–240.
23 Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci* 2005; **6**:533–544.
24 Wagner KJ, Willoch F, Kochs EF, Siessmeier T, Tölle TR, Schwaiger M, *et al*. Dose-dependent regional cerebral blood flow changes during remifentanil infusion in humans: a positron emission tomography study. *Anesthesiology* 2001; **94**:732–739.
25 Coghill RC, Gilron I, Iadarola MJ. Hemispheric lateralization of somatosensory processing. *J Neurophysiol* 2001; **85**:2602–2612.