

The cerebral representation of scratching-induced pleasantness

Hideki Mochizuki,¹ Satoshi Tanaka,² Tomoyo Morita,¹ Toshiaki Wasaka,¹ Norihiro Sadato,³ and Ryusuke Kakigi¹

¹Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Aichi, Japan; ²Center for Fostering Young and Innovative Researchers, Nagoya Institute of Technology, Nagoya, Aichi, Japan; and ³Department of Cerebral Research, National Institute for Physiological Sciences, Okazaki, Aichi, Japan

Submitted 22 May 2013; accepted in final form 19 October 2013

Mochizuki H, Tanaka S, Morita T, Wasaka T, Sadato N, Kakigi R. The cerebral representation of scratching-induced pleasantness. *J Neurophysiol* 111: 488–498, 2014. First published October 23, 2013; doi:10.1152/jn.00374.2013.—Itch is an unpleasant sensation with the desire to scratch. Although it is well known that scratching itchy skin is pleasurable, the cerebral mechanisms underlying this phenomenon are poorly understood. We hypothesized that the reward system is associated with scratching-induced pleasantness. To investigate this hypothesis, a functional magnetic resonance imaging study was performed in 16 healthy subjects. Pleasantness was evoked by scratching the wrists where itch stimuli were applied, while scratching the dorsal forearms, far from itch stimuli, did not evoke pleasantness. Interestingly, pleasantness evoked by scratching activated not only the reward system (i.e., the striatum and midbrain) but also key regions of perception (i.e., the primary somatosensory cortex) and awareness of subjective feelings (i.e., the insular cortex), indicating that a broad network is involved in scratching-induced pleasantness. Moreover, although itch was suppressed by scratching, motor-related regions such as the supplementary motor area, premotor cortex, and cerebellum showed significant activation when pleasantness was evoked. This activation could explain why scratching-induced pleasantness potentially reinforces scratching behaviors. This study is the first to identify networks activated by scratching-induced pleasantness. The results of the present study provide important information on the cerebral mechanisms underlying why scratching itchy skin evokes pleasurable feelings that reinforce scratching behaviors.

fMRI; itch; pleasantness of scratching; reward system; motor-related regions

ITCH IS AN UNPLEASANT SENSATION that triggers scratching behaviors. Scratching itchy skin can inhibit the itch sensation. Simultaneously, it evokes pleasurable feelings such as a pleasant somatic sensation perceived at the scratched skin. Hedonic experiences are associated with the reward system (Wise and Rompre 1989). The major brain regions of this system are the striatum, midbrain including the ventral tegmental area (VTA) and substantia nigra (SN), and medial frontal regions such as the medial prefrontal cortex (medial PFC) and medial orbitofrontal cortex (medial OFC) (Fibiger et al. 1987; Kühn and Gallinat 2012; Saper 2000; Tzschentke 2000). Thus we hypothesized that scratching-induced pleasantness also activates major brain regions of the reward system. Two functional magnetic resonance imaging (fMRI) studies have investigated the cerebral processing of scratching. One study investigated scratching without itch stimuli. The authors discussed possible

mechanisms of itch relief by scratching and itch-scratch cycle based on their finding (Yosipovitch et al. 2008). The other study measured brain activity while the itch sensation was suppressed by scratching and observed an increase in the blood oxygenation level-dependent (BOLD) signal in the striatum (Vierow et al. 2009). Unfortunately, since the previous study did not measure pleasantness, it remains uncertain whether the increased activity in the striatum during scratching reflected scratching-induced pleasantness. Brain regions associated with pleasantness evoked by scratching itchy skin have not yet been elucidated. Thus, in this study, we investigated the cerebral representation of scratching-induced pleasantness with fMRI.

MATERIALS AND METHODS

Subjects

Sixteen healthy subjects (10 men and 6 women) [mean age \pm standard deviation (SD): 31.6 \pm 8.1 yr] participated in this study. Written informed consent was obtained from all subjects. The study complied with the Declaration of Helsinki, and the Ethics Committee of the National Institute for Physiological Sciences (Japan) approved the experimental procedures.

Electrical Itch Stimulus

Electrical stimuli were used to evoke itch sensations in the present study (Ikoma et al. 2005; Mochizuki et al. 2008, 2009). Electrical stimuli were applied to the wrist by passing a weak current through an anode electrode 4.5 cm long and 2.1 cm wide (Vitrode, F-150M, Nihon Kohden, Tokyo, Japan). The anodal electrode was attached to the wrist so that the long side of the electrode was orthogonal to the forearm. The reference electrode was attached near the anodal electrode. The itch stimulus was applied for 4.5 s (frequency: 50 Hz; pulse width: 10 ms; number of pulses: 225) with a stimulator (SEN-7203, Nihon Kohden). The current intensity was determined for each subject with a visual analog scale (VAS) ranging from 0 (no itch) to 10 (unbearable itch sensation) so that a clear itch sensation (VAS 3 or more) was perceived. The current intensity for the electrical itch stimuli used during fMRI was 0.39 \pm 0.10 mA (mean \pm SD).

Scratching Stimulus

A previous study reported that an L-shaped copper plate can induce sensations comparable to those induced by fingernails (Vierow et al. 2009). In our preliminary experiments, we confirmed that scratching itchy skin with L-shaped copper plates could induce pleasurable feelings. Moreover, pleasurable feelings were much stronger when two L-shaped copper plates were used compared with when a single L-shaped copper plate was used. Thus, in this study, two L-shaped scratching plates were used as a scratching tool (thickness of the plate:

Address for reprint requests and other correspondence: H. Mochizuki, Dept. of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Aichi 444-8585, Japan (e-mail: motiz@nips.ac.jp).

0.6 mm; width: 1 cm; length: 13 cm) (Fig. 1A, left). Scratching stimuli were applied to either the wrist or distal forearm with the scratching tool. In the condition that included scratching of the wrist (the pleasant condition), the scratching tool was placed on the wrist so that the anodal electrode for the electrical itch stimulus was located between the two L-shaped copper plates (Fig. 1A, center). The wrist was then scratched by an experimenter for 5 s with the scratching tool. A tone was presented to the experimenter for 5 s through headphones so that the duration of scratching was always the same. The copper plates were moved between 1.5 cm lateral and 1.5 cm medial from the center of the electrodes (3 cm in total). In a pilot experiment, we confirmed that a pleasant sensation could be evoked by moving the scratching tool slowly with slight pressure on the skin where the electrical itch stimuli were applied. The force was 0.1–0.3 N, calculated using the weight measured while moving the tool on a balance (ASP413, AS ONE, Osaka, Japan). The speed was 5–8 cm/s, calculated by measuring the time while the tool was moved back (3 cm) and forth (3 cm) 10 times (60 cm in total) with a digital stopwatch (PC-GF15, Seiko, Tokyo, Japan). In the condition that included scratching of the distal forearm (the control condition), an experimenter scratched the skin

2–3 cm proximal from the reference electrode with the scratching tool in the same way as in the pleasant condition (Fig. 1A, right). In our preliminary experiment, we applied itching and scratching stimuli simultaneously. No itch sensation was evoked when scratching stimuli were applied to the wrists where itch stimuli were applied, whereas the itch sensation was perceived when scratching stimuli were applied to the forearm, far from the wrists. This difference in these conditions (i.e., with and without itch) was not suitable for our real experiment. On the other hand, when scratching stimuli were applied after the end of itch stimuli, the itch sensation was perceived during electrical itch stimuli in both conditions in the preliminary experiment. Fortunately, even after the end of electrical itch stimuli, pleasurable feelings were evoked in the condition in which scratching stimuli were applied to the wrists where itch stimuli were applied. On the other hand, when scratching stimuli were applied before and during itch stimuli, no pleasant sensation was evoked. Therefore, scratching stimuli were applied after electrical itch stimuli. Two experimenters performed the scratching in this study. One experimenter was the main scratcher, whereas the other experimenter was a secondary backup scratcher. The backup experimenter participated in the experiments twice as a

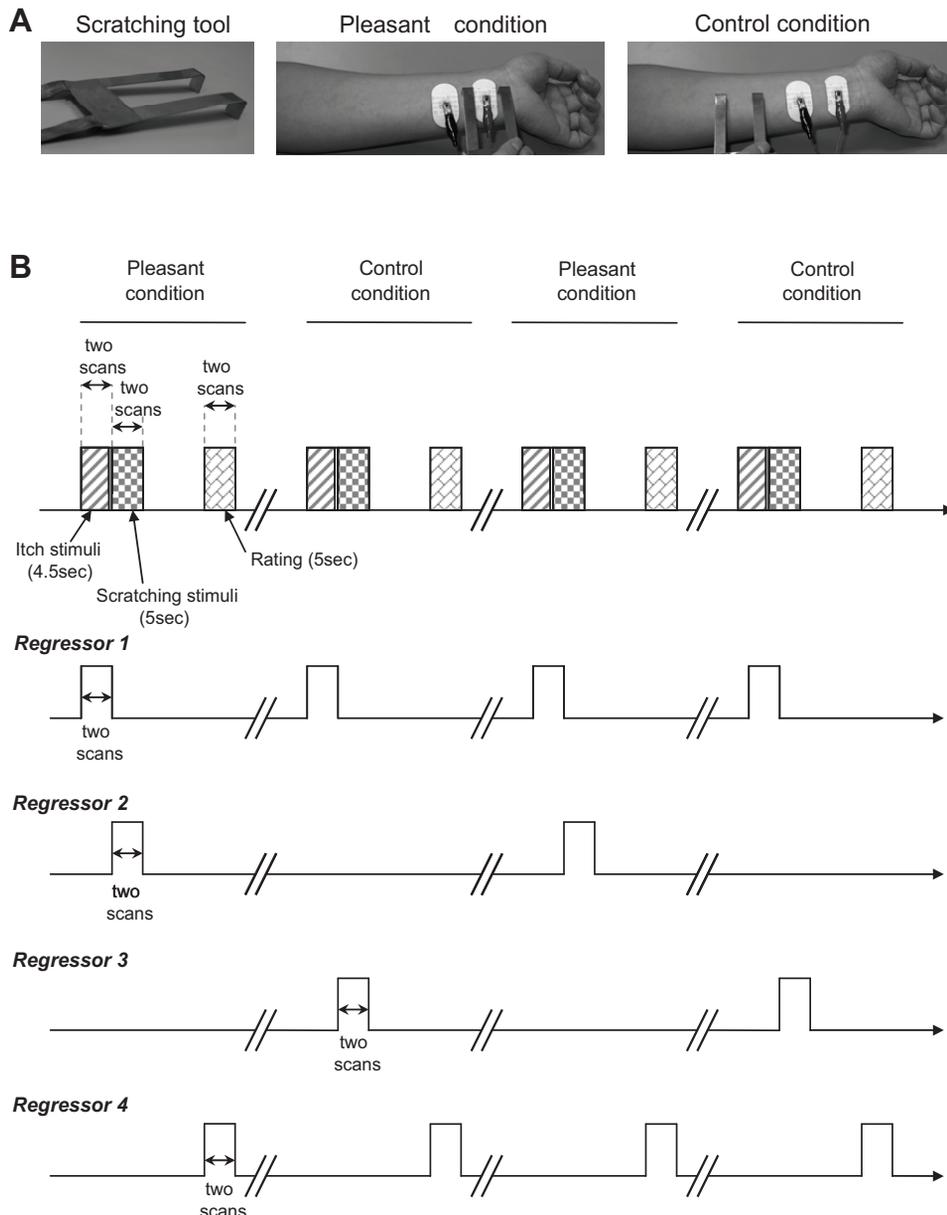


Fig. 1. Scratching tool and examples of the conditions used, an experimental session, and the regressors. *A*: the scratching tool used in this study (left) and locations used for scratching of the wrist in the pleasant condition (center) and the dorsal forearm in the control condition (right). *B*: example of a time course of presentation of stimuli and conditions. The interval between the electrical itch and scratching stimulus was 0.5 s. *Regressor 1*, the neural model associated with itch stimuli; *regressors 2 and 3*, the neural model associated with scratching stimuli in the pleasant (*regressor 2*) and control (*regressor 3*) conditions; *regressor 4*, the neural model associated with rating.

scratcher, whereas the main experimenter performed the scratching in all of the rest of the experiments in this study.

fMRI Experiment

Subjects participated in four sessions in the fMRI scanner. Two conditions were presented in each session. One was the pleasant condition, and the other was the control condition. In both conditions, electrical itch stimuli were applied to the wrist. The itch stimuli were always applied to the same wrist within a session. However, the wrist to which the itch stimuli were applied was changed between sessions. Specifically, if electrical itch stimuli were applied to the left wrist in one session, the opposite wrist (i.e., the right wrist) was stimulated with itch stimuli in the next session. In the pleasant condition, 0.5 s after the end of the electrical itch stimulus, the wrist to which the itch stimulus was applied (Fig. 1A, center) was scratched by an experimenter. In the control condition, the dorsal forearm, a few centimeters apart from the wrist to which the electrical stimulus was applied (Fig. 1A, right), was scratched by the experimenter in the same way. In both conditions, 10 s after the end of scratching, a cue ("How pleasurable was it?") was presented for 5 s. The subjects reported pleasantness with the fingers of the hand opposite to the side to which the itch stimuli were applied, using a VAS of pleasantness ranging from 0 (not pleasant) to 10 (scratching extremely pleasant). The two conditions were repeated four times in a session. The order of conditions was randomized among subjects. The interval between conditions was randomly changed between 75 s and 90 s.

Psychophysiological Experiment

All subjects also participated in the psychophysical experiment on a different day. One of the purposes of this experiment was to evaluate the duration of pleasantness evoked by scratching. Another purpose was to confirm that pleasantness was evoked by scratching the wrist only when itch stimuli were applied. In this experiment, the experimenter scratched the wrist to which the electrical itch stimulus was applied for 5 s after the end of the itch stimulus. The electrical itch and scratching stimuli used in this experiment were the same as those used in the fMRI experiment, except for the current intensity of the electrical itch stimuli (mean \pm SD: 0.44 \pm 0.10 mA). The subjects were asked to press a button if pleasantness was evoked after the beginning of scratching and to press the button again if pleasantness ended. The duration between the first and second pressing of the button was used as the dependent measure of the duration of pleasantness. In addition, they were asked to report the subjective intensity of pleasantness using a VAS. Moreover, the experimenter scratched the same wrist without applying the electrical itch stimuli to confirm that pleasantness was not greatly evoked by scratching in that condition. All trials mentioned above were repeated twice for each subject.

fMRI Measurements

The fMRI experiment was conducted with a 3-T MRI scanner (Allegra, Siemens, Erlangen, Germany). For functional imaging during each session, a series of 252 volumes was acquired with T2*-weighted, gradient-echo, echo-planar imaging (EPI) sequences. Each volume consisted of 39 transaxial slices, each having a thickness of 3.0 mm, with a 0.5-mm gap between slices to cover the entire cerebrum and cerebellum [repetition time (TR) \times 2,500 ms; echo time (TE) \times 30 ms; flip angle (FA) \times 80°; field of view (FOV) \times 192 mm; 64 \times 64 matrix]. Oblique scanning was used to exclude the eyeballs from images.

Data Analysis

The first three EPI volumes of each session were eliminated to allow for stabilization of the magnetization. Thus the fourth scan was

the first volume. The fMRI data were analyzed with statistical parametric mapping 8 software (SPM8, The Wellcome Trust Centre for Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). To reduce head motion artifacts, all volumes were realigned to the first volume. The first volume was normalized to the Montreal Neurological Institute (MNI) EPI image template using an affine transformation and a nonlinear basis function. The same parameters were applied to all EPI volumes, which were spatially smoothed in three dimensions with a Gaussian kernel with 6-mm full width at half-maximum.

Statistical analysis was conducted at two levels. First, individual activity associated with electrical itch stimuli (Fig. 1B, regressor 1), scratching in the pleasant condition (Fig. 1B, regressor 2), scratching in the control condition (Fig. 1B, regressor 3), and during rating (Fig. 1B, regressor 4) were evaluated (first-level analysis). In addition, to identify brain regions associated with scratching-induced pleasantness, brain activity associated with scratching in the pleasant condition was compared with that in the control condition [pleasant > control] in the first-level analysis. The regressors were convolved with a canonical hemodynamic response function.

In this study, the stimulus onsets of itch and scratching stimuli were always the beginnings of fMRI scans. Thus the onset of each regressor was the scan corresponding to the stimulus onset. The duration for each regressor was two scans (i.e., 5 s). Even though the duration of the electrical itch stimulus was 4.5 s, the duration of regressor 1 to identify itch stimuli-related brain regions was two scans (i.e., 5 s).

The reason why the duration of electrical itch stimulus was 4.5 s was as follows. A clear pleasant sensation became weaker or was not evoked when the interval between itch and scratching stimuli increased (e.g., \sim 10 s) in our preliminary experiment. Thus the solution used was to apply scratching stimuli at the end of electrical stimuli. However, the scratching tool we used was copper, which conducts electricity. Therefore, if the tool accidentally touched the electrodes to which the electrical current was still conducting, the electrical current may have been passed to the scratcher, and the circuit could be closed by applying the scratching tool to the skin. This circuit changes the electrical properties of the skin, and the flow of electricity could change if the tool accidentally touched the electrodes through which the electrical current was still flowing. We reasoned that these accidents would probably not happen if the scratching stimuli were applied at the end of the electrical itch stimuli. However, it was safer to terminate the electrical itch stimuli several hundred milliseconds before starting the scratching. Thus electrical itch stimuli terminated 0.5 s before the end of two scans.

The duration of regressor 1 was set to two scans (i.e., 5 s) because of the slow conduction velocity of C fibers that mediate the itch sensations evoked by electrical itch stimuli (Mochizuki et al. 2008). The conduction velocity of C fibers is very low (0.4–2.0 m/s). Thus neural signals in the periphery evoked by an electrical itch stimulus were still reaching the brain several hundred milliseconds after stimulus offset. Here, the offset was 4.5 s after the stimulus onset. This delay differs in individuals, since the conduction velocity of C fibers varies with the individual. Thus it was impossible to make a neural model (i.e., regressor 1) with regard to the delay for each subject. We considered that a delay from stimulus offset of two scans (i.e., 5 s) was better suited to the duration of regressor 1 than 4.5 s. Thus the duration was set as two scans in this study.

To make inferences at a population level, individual data were summarized and incorporated into a random-effects model (second-level analysis) (Holmes and Friston 1998). To investigate whether brain regions were significantly activated during scratching in the pleasant condition compared with the control condition, we applied a masking procedure (i.e., an inclusive mask) to the second-level analysis of [pleasant > control]. Here brain regions significantly activated during scratching in the pleasant condition were used for the inclusive mask. In addition, we also investigated brain regions showing significantly more deactivation during the pleasant condition compared with the control condition. The statistical threshold for

significant change in activity was uncorrected $P < 0.001$ for intensity and false discovery rate (FDR) corrected $P < 0.05$ for cluster (whole brain) for the analyses mentioned above.

RESULTS

Behavioral Data

In the fMRI experiment, pleasantness was evoked by scratching in the pleasant condition, in which wrists were scratched by an experimenter for 5 s (mean \pm SD of VAS: 5.23 ± 1.70). All subjects reported clear pleasurable feelings in this condition. Conversely, pleasantness was not evoked in the control condition, in which the forearm, far from itch stimuli, was scratched (0.96 ± 1.19). There was a significant difference in pleasantness between the two conditions (paired t -test: $P < 0.0001$; Fig. 2A). In the psychophysical experiment, we investigated the duration of pleasantness evoked by scratching the wrist to which itch stimuli were applied. The duration was 5.18 ± 1.58 s (Fig. 2B). The intensity of the pleasantness was 4.52 ± 1.54 (Fig. 2C). In contrast, pleasantness evoked by scratching the wrist when no itch stimuli were applied was 1.45 ± 1.46 . There was a significant difference in pleasantness between the conditions with and without itch stimuli (paired t -test: $P < 0.0001$; Fig. 2C).

fMRI Data

Brain regions activated during scratching in pleasant and control conditions. In the pleasant condition, significant activation was observed in extended frontal areas, including the lateral PFC, lateral OFC, supplementary motor area (SMA), premotor cortex (PM), parietal cortex including the primary somatosensory cortex (SI), posterior part of the opercular cortex (pOPC), temporal cortex, precuneus, medial cingulate cortex (MCC), posterior cingulate cortex (PCC), insular cortex (IC), striatum, thalamus, cerebellum midbrain, and pons (Fig. 3A and Table 1). In the control condition, brain regions activated by scratching stimuli were the frontal regions including lateral PFC, lateral OFC, SMA, PM, parietal cortex including SI, pOPC, temporal cortex, precuneus, MCC, PCC, striatum, thalamus, and cerebellum (Fig. 3B and Table 1). Direct comparison of brain activity during scratching between the pleasant and control conditions showed significantly higher activity for the pleasant condition in the left SMA, bilateral inferior frontal gyrus (IFG)/PM, left PM, bilateral SI, right

MCC, bilateral IC, bilateral striatum, left thalamus, midbrain including VTA and SN, and left cerebellum (Fig. 3C and Table 1). As shown in Fig. 5, activity in the left striatum, midbrain, SMA, PM, thalamus, and cerebellum when pleasantness was evoked (pleasant $>$ control) did not significantly differ from that while itch stimuli were applied. Activity in the right striatum when pleasantness was evoked was significantly higher compared with that during itch stimuli. Similar results were also observed in the bilateral IFG/PM and SI. In contrast, the bilateral IC showed significantly higher activity during itch stimuli compared with when pleasantness was evoked.

Deactivation during scratching in pleasant and control conditions. Brain regions showing significant deactivation in the pleasant and control conditions were the primary motor cortex (MI)/PM, precuneus (Prec)/PCC, occipital cortex, medial OFC, and hippocampus (Fig. 4 and Table 2). There were no significant differences in deactivation between the pleasant and control conditions.

Brain regions associated with electrical itch stimuli and rating. Brain regions significantly activated during electrical itch stimuli were the lateral PFC, SMA, PM, SI, pOPC, precuneus, MCC, PCC, IC, striatum, thalamus, and midbrain (Fig. 3D and Table 3). Brain regions significantly activated during rating were the lateral PFC, SMA, PM, parietal cortex, pOPC, precuneus, MCC, PCC, IC, striatum, thalamus and cerebellum bilaterally, and midbrain (Table 4).

DISCUSSION

This is the first study to investigate the cerebral representation of scratching-induced pleasantness. As expected, scratching-induced pleasantness activated brain regions associated with the reward system such as the striatum and midbrain. Moreover, scratching-induced pleasantness also activated several other brain regions such as the SI, IC, SMA, PM, cerebellum, and IFG/PM. These results indicate that broad networks are associated with pleasurable feelings evoked by scratching.

Behavioral Data

Scratching wrists to which electrical itch stimuli were applied evoked pleasantness (Fig. 2A). However, scratching the dorsal forearm, away from where the electrical itch stimuli were applied, did not greatly evoke pleasantness (Fig. 2A). The difference in pleasantness between the pleasant (wrist) and

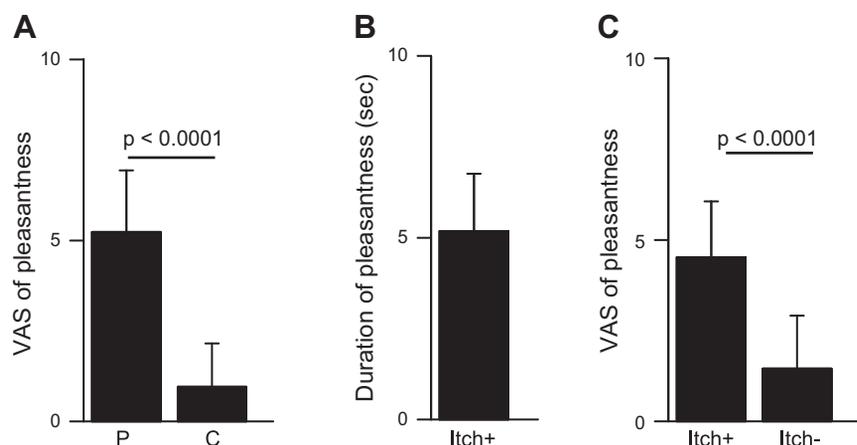
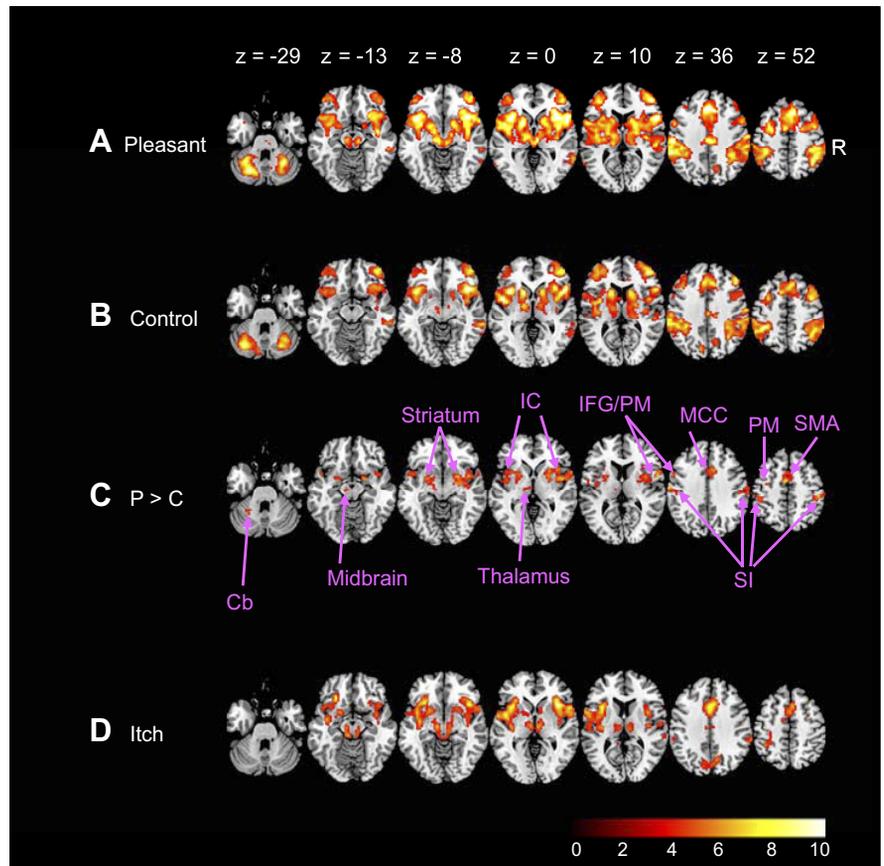


Fig. 2. Intensity and duration of evoked pleasantness. A: visual analog scale (VAS) rating of pleasantness evoked by scratching in the pleasant and control conditions in the fMRI experiment. P, pleasant condition; C, control condition. B: duration of pleasantness evoked by scratching the wrist to which itch stimuli were applied (Itch+) in the psychophysical experiment. C: VAS ratings of pleasantness evoked by scratching in the condition in which itch stimuli were applied (Itch+) and the condition in which no itch stimuli were applied (Itch-) in the psychophysical experiment.

Fig. 3. Brain activation during scratching and itch stimuli. *A* and *B*: brain regions significantly activated while scratching stimuli were applied in the pleasant (*A*) and control (*B*) conditions. R, right hemisphere. *C*: brain regions that showed significantly higher activity in the pleasant condition compared with the control condition within the brain regions significantly activated in the pleasant condition. *D*: brain regions significantly activated during itch stimuli. Threshold for statistical significance: uncorrected $P < 0.001$ for intensity and false discovery rate (FDR) corrected $P < 0.05$ for cluster (a whole brain). $P > C$, pleasant $>$ control; Cb, cerebellum; IC, insular cortex; IFG/PM, inferior frontal gyrus; PM, premotor cortex; MCC, medial cingulate cortex; SMA, supplementary motor area; S1, primary somatosensory cortex.



control (dorsal forearm) conditions was not due to a difference in the location of scratching, since scratching the wrist did not greatly evoke pleasantness in the absence of electrical itch stimuli (Fig. 2C). Thus pleasantness observed in this study was associated with scratching itchy skin. The duration of pleasantness was about 5 s (Fig. 2B), indicating that subjects continuously felt pleasantness during scratching.

In this study, a strong itch sensation disappeared soon after the electrical itch stimuli terminated, but a weak itch sensation still remained on the wrist for ~ 10 s. In contrast, previous itch studies reported that itch sensation disappeared as soon as electrical itch stimuli were terminated (Ikoma et al. 2005; Mochizuki et al. 2008). In the previous studies the area to be stimulated was just a tiny spot, while it was much larger in this study ($4.5 \text{ cm} \times 2.1 \text{ cm}$). Moreover, the duration of electrical stimuli in the previous studies was 400 ms and 1,000 ms, while it was much longer (i.e., 4,500 ms) in this study. The larger the area to be stimulated and the longer the stimulus duration becomes, the longer the residual effects of stimulation last. This is a possible interpretation of the discrepancy between this study and previous studies. The remaining weak itch sensation was the main factor leading to the induction of pleasantness.

Key Brain Regions of the Reward System

Key brain regions of the reward system such as the striatum and midbrain were activated when pleasantness was evoked (Fig. 3C). Other pleasurable somatosensory stimuli such as warming, gentle touch, cold pain, and sexual tactile stimuli also activate similar brain regions (Georgiadis et al. 2006; Holstege et al. 2003; Lindgren et al. 2012; Mohr et al. 2009;

Rolls et al. 2008). We considered that the main component of scratching-induced pleasantness was the pleasant somatic sensation. Thus we suggest that the significant activation of the reward system observed in this study was mainly associated with the pleasant somatic sensation. However, some subjects reported not only pleasant somatic sensations but also delight at the moment when they recognized the wrists were scratched. In these subjects, the pleasant condition (scratching itchy skin) was preferred, whereas the control condition (scratching far from itchy skin) was not (i.e., an adverse event). This type of pleasure was included in our measure of scratching-induced pleasantness. Previous studies have reported that activity in the reward system significantly increased when preferred events occurred to subjects compared with when no preferred events or adverse events occurred (Leknes et al. 2011; Seymour et al. 2005). Considering these previous studies, we suggest that the significant activation of the reward system observed in this study was also associated with the delight evoked at the moment when preferred events (i.e., the pleasant condition) occurred to the subjects. In the study by Vierow et al. (2009), activity in the striatum during scratching itchy skin was significantly higher compared with that during scratching normal skin. In our psychophysical experiment, pleasantness was evoked by scratching when itch stimuli were applied to the wrists but not in the absence of itch stimuli (Fig. 2C). Thus the subjects felt pleasantness only when itchy skin was scratched. We speculate that the significant activation of the striatum observed by Vierow et al. was associated with pleasantness evoked by scratching itchy skin. In our study, activity in the left striatum and midbrain during pleasantness was not signif-

Table 1. *Brain regions activated during scratching*

	Pleasant Condition				Control Condition				Pleasant > Control			
	MNI coordinate				MNI coordinate				MNI coordinate			
	x	y	z	z Score	x	y	z	z Score	x	y	z	z Score
<i>Left hemisphere</i>												
Lateral PFC	-44	34	22	4.83	-46	40	24	5.23				
	-54	8	6	5.87	-54	10	0	4.59				
	-52	8	32	4.7								
Lateral OFC	-38	46	-12	4.52	-30	46	-12	4.31				
SMA	-2	20	52	4.78	-8	14	48	4.99	-4	-2	54	4.77
PM	-26	-4	48	5.52	-30	-4	46	4.29	-36	-8	54	4.05
IFG/PM									-54	6	36	3.77
SI	-58	-20	38	6.06	-40	-42	50	5.11	-62	-12	36	4.94
	-36	-40	52	5.17					-48	-26	48	4.62
Parietal cortex	-40	-32	40	5.69	-44	-34	40	4.92				
	-60	-42	34	6.02								
pOPC	-58	-18	24	5.82	-54	-24	16	5.63				
Temporal cortex	-62	-62	6	4.95								
MCC	-6	32	32	5.69	-4	30	38	5.11				
PCC	-4	-28	28	6.47	-2	-24	28	5.81				
IC	-40	14	-4	6.13	-36	14	2	5.51	-42	0	-4	4.05
Striatum	-18	8	0	5.9	-14	14	0	5.64	-24	2	-10	4.19
Precuneus					-10	-78	36	4.33	-26	4	10	3.83
Thalamus	-16	-8	6	5.08	-16	-8	2	4.65	-10	-16	6	3.44
Cb	-26	-68	-30	5.42	-32	-60	-36	5.72	-20	-62	-26	4.44
Midbrain	-10	-20	-8	5.14					-10	-18	-14	3.61
<i>Right hemisphere</i>												
Lateral PFC	46	44	10	5.89	44	34	26	6.19				
	60	10	30	5.62	52	18	0	5.87				
Lateral OFC	44	48	-8	4.92	42	46	-16	5.21				
SMA	6	24	50	5.73	8	28	50	5.16				
PM	32	0	48	4.82								
IFG/PM									62	10	28	4.11
SI	50	-30	42	5.47					48	-28	52	4.53
	60	-14	30	5.78					64	-14	34	3.66
Parietal cortex	42	-42	44	5.78	60	-40	48	5.39				
	62	-42	32	5.36								
pOPC	54	-30	24	5.76	60	-30	22	5.66				
Temporal cortex	64	-50	0	4.51	58	-38	-10	4.74				
Precuneus	8	-72	44	4.38	8	-72	44	4.79				
MCC	2	30	38	6.46	12	26	38	5.36	10	14	36	4.42
PCC	4	-22	28	5.99								
IC	34	24	2	6.05	44	18	-6	6	46	0	0	4.56
Striatum	16	8	-6	5.13	16	12	6	5.12	26	4	-4	4.68
									24	4	-8	4.54
Thalamus	14	-22	8	4	16	-22	12	4.15				
Cb	30	-56	-30	5.4	32	-54	-34	5.16				
Midbrain	4	-20	2	5.74								
Pons	8	-18	-36	4.18								

MNI, Montreal Neurological Institute; PFC, prefrontal cortex; OFC, orbitofrontal cortex; SMA, supplementary motor area; IFG, inferior frontal gyrus; PM, premotor cortex; SI, primary somatosensory cortex; pOPC, posterior opercular cortex; MCC, middle cingulate cortex; PCC, posterior cingulate cortex; IC, insular cortex; Cb, cerebellum.

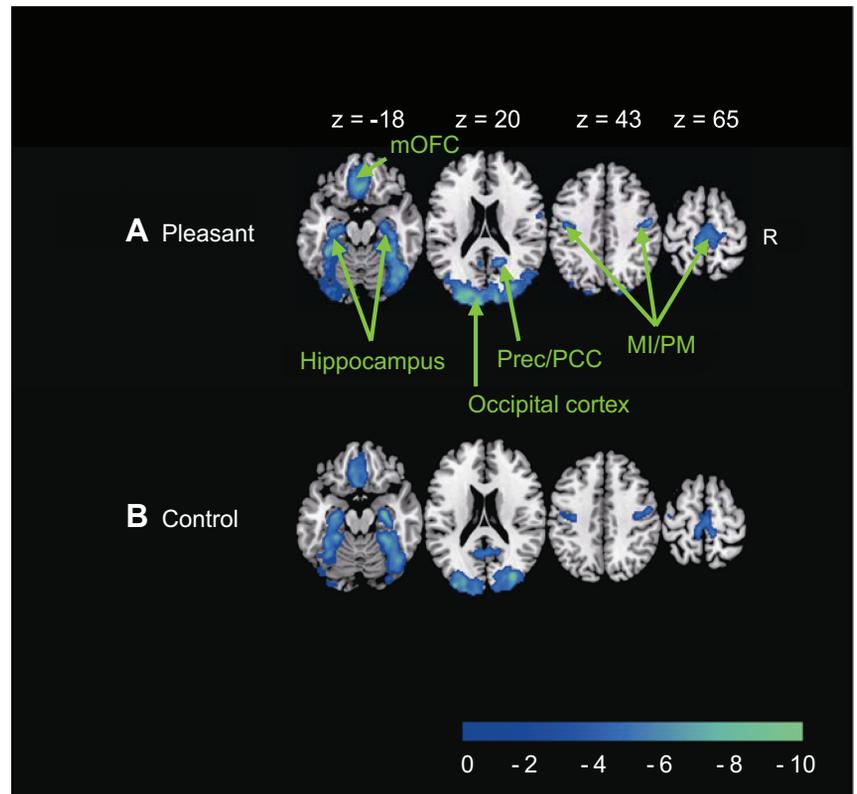
icantly different from that during itch stimuli (Fig. 5, top row). However, this result is not surprising, as itch evokes the desire to scratch, and the striatum and midbrain are associated with not only pleasantness but also craving (see, e.g., Berridge and Robinson 1988; Martin-Sölch et al. 2001, 2003; McClernon et al. 2009; Volkow et al. 2006). It was suggested that activation of the striatum and midbrain during itch stimuli was associated with the desire to scratch to remove unpleasantness caused by itch, whereas activation during pleasantness was associated with scratching-induced pleasantness.

Pleasantness-related activation (i.e., pleasant > control) of the right striatum was significantly higher compared with

activity in the same region during itch stimulation (Fig. 5, top row). This difference likely reflects processes specific for pleasantness.

SI. SI activity in the pleasant condition was significantly higher compared with the control condition. We suggest that this was not related to differences in location to be scratched (i.e., wrist vs. forearm), since their anatomical locations in the SI are almost identical and it is difficult to distinguish them in SI (Krakauer and Ghez 2000). It could be that higher activity in the SI was associated with an increased arousal level or attention caused by pleasantness. If so, activity in the same region should also have increased when the itch stimuli were

Fig. 4. Brain deactivation during scratching: brain regions significantly deactivated when scratching stimuli were applied in the pleasant (A) and control (B) conditions. Threshold for statistical significance: uncorrected $P < 0.001$ for intensity and FDR corrected $P < 0.05$ for cluster (whole brain). mOFC, medial orbitofrontal cortex; Prec, precuneus; PCC, posterior cingulate cortex; MI, primary motor cortex.



applied, since unpleasantness caused by itch stimuli also increases arousal and attention. However, activity in the SI decreased during itch stimuli (Fig. 5, third row). Similar results were also observed in a pain study. Mohr et al. (2009) compared activity in the SI while unpleasantness was evoked by application of cold pain stimuli to normal skin, with pleasantness evoked by application of the same stimuli to burning skin caused by capsaicin pretreatment. They observed that activity in the SI decreased during the unpleasant condition but significantly increased during the pleasant condition. This difference

was not due to pretreatment with capsaicin, since such a significant difference in SI activity was not observed when, instead of cold pain stimuli, nonnoxious cold stimuli were applied to normal and burning skin. Specifically, the SI showed pleasantness-specific activation in the previous study and the present study. However, such a pleasantness-specific activation pattern was not observed in the SI in previous studies of other pleasurable somatic stimuli, such as gentle touch, warming, and sexual stimuli (Holstege et al. 2003; Komisaruk et al. 2004; Lindgren et al. 2012; Rolls et al. 2003, 2008). It may be that the SI plays

Table 2. Deactivation by scratching

	Pleasant Condition				Control Condition			
	MNI coordinate			z Score	MNI coordinate			z Score
	x	y	z		x	y	z	
<i>Left hemisphere</i>								
MI/PM	50	-10	42	-4.54	38	-14	46	-4
	10	-26	68	-3.98	12	-34	60	-4.29
Precuneus/PCC	14	-56	18	-5.05				
Occipital	14	-92	34	-5.7	16	-92	34	-5.22
mOFC	4	54	-16	-4.6	2	34	-20	-4.14
Hippocampus	26	-16	-22	-4.74	28	-12	-20	-5.57
Cb	8	-50	-46	-4.58				
<i>Right hemisphere</i>								
MI/PM	-44	-12	48	-4.29	-42	-16	50	-5.09
	-6	-34	64	-4.24	-6	-28	64	-4.1
Precuneus/PCC					-2	-58	14	-4.72
Occipital	-10	-96	26	-5.99	-34	-92	18	-5.31
mOFC	-2	30	-18	-4.84	-10	34	-16	-4.47
Hippocampus	-32	-18	-20	-4.79	-28	-14	-22	-5.08

MI, primary motor cortex; mOFC, medial orbitofrontal cortex.

Table 3. Brain regions activated during itch stimuli

	MNI Coordinate			z Score
	x	y	z	
<i>Left hemisphere</i>				
Lateral PFC	-60	6	10	5.13
SI	-32	-24	58	3.75
pOPC	-50	-28	20	5.6
Precuneus	-10	-80	42	4.24
PCC	-8	-44	18	4.3
IC	-36	14	8	5.14
	-36	-18	16	4.37
Striatum	-20	8	-12	4.4
Thalamus	-6	-14	-2	4.27
Midbrain	-10	-18	-10	4.55
<i>Right hemisphere</i>				
SMA	4	16	52	4.4
PM	26	4	58	3.8
pOPC	58	-30	16	5.6
Precuneus	8	-74	44	4.28
MCC	2	10	40	5.32
PCC	8	-32	26	4.5
IC	38	18	0	5.66
	40	-12	4	4.43
Striatum	24	8	-8	3.83
Thalamus	4	-16	2	4.42
Midbrain	8	-22	-8	4.08

an important role in the perception of pleasurable somatic sensation only in specific situations, such as the application of somatosensory stimuli to suppress pain and itch.

IC. The IC was significantly activated when pleasantness was evoked in this study (Fig. 3C). The IC was also activated when itch stimuli were applied (Fig. 3D). The IC is considered to be a key brain region involved in the awareness of changes happening in the body and the mind (Craig 2002, 2009, 2010). For example, bodily sensations such as itch, pleasure, thirst, hunger, and others are thought to be represented in the IC. It has been reported that pleasurable feelings such as chills evoked by listening to favorite music are associated with activation of the reward system (Salimpoor et al. 2011). However, chills disappear if the IC is lesioned (Griffiths et al. 2004). These studies indicate that pleasurable feelings require the IC to be brought into one's consciousness. The importance of the IC in the awareness of subjective feelings is also supported by other studies (Berthier et al. 1988; Bird et al. 2010; Siliani et al. 2008). Thus it is likely that the IC in subjects in the present study was associated with awareness of pleasurable feelings that subjects felt during scratching itchy skin.

Motor-related regions. Comparison of brain activity between the pleasant and control conditions showed significantly higher activity in motor-related regions such as the SMA, PM, and cerebellum for the pleasant condition (Fig. 3C). Motor-related region activity has not been frequently observed in previous studies of pleasantness (Anderson et al. 2003; Blood et al. 1999; de Araujo et al. 2003; Filbey et al. 2008; Frank et al. 2003; Grabenhorst et al. 2007, 2010; Grabenhorst and Rolls 2008; Heinzel et al. 2005; Izuma et al. 2008; Kühn and Gallinat 2012; McCabe and Rolls 2007; McLean et al. 2009; Plassmann et al. 2008; Rolls et al. 2003, 2008; Salimpoor et al. 2011). Thus it is unlikely that activation of motor-related regions was associated with pleasantness. This interpretation is partly supported by the fact that activity in the SMA, PM, and cerebellum

during pleasantness was not significantly different compared with that during itch stimuli (Fig. 5, second row). The activation of the SMA, PM, and cerebellum during itch stimuli was interpreted to be caused by the desire to scratch to remove the itch (Drzezga et al. 2001; Mochizuki et al. 2003). However, this interpretation would not be applicable for activation of these regions during pleasantness, as itch was already suppressed by scratching. Scratching itchy skin may unconsciously or consciously induce a different type of desire such as the desire to scratch to get further pleasantness. This interpretation is consistent with observations in patients with atopic dermatitis who scratch until it no longer provokes pleasant sensations rather than until itch has subsided (Ikoma et al. 2006). Motor-related regions such as the SMA, PM, and cerebellum are regulated by striatal dopaminergic neurons (DeLong 2000; Krakauer and Ghez 2000; Kupfermann 1995; Nieuwenhury et al. 1988; Wise and Rompre 1989). Importantly, reinforcement and motivation are partly regulated by dopamine (Berridge and Robinson 1998; Fibiger et al. 1987; Wise and Rompre 1989). In this study, we observed significant activation of the midbrain when pleasantness was evoked. This region is rich in dopaminergic neurons (see, e.g., DeLong 2000), implying that significant activation of the midbrain observed in this study reflected increased dopamine release. Indeed, pleasantness increases dopamine release (see, e.g., Salimpoor et al. 2011). Thus enhanced activity in motor-related regions observed in this study was likely associated with

Table 4. Brain regions activated during rating

	MNI Coordinate			z Score
	x	y	z	
<i>Left hemisphere</i>				
Lateral PFC	-34	50	24	4.7
SMA	-8	4	62	5.72
	-6	10	48	5.59
PM	-36	-12	58	5.91
Parietal cortex	-32	-36	48	5.94
pOPC	-54	-24	24	5.52
Precuneus	-8	-78	44	3.55
MCC	-6	26	30	5.28
PCC	-4	-26	28	5.26
IC	-40	0	-4	5.74
Striatum	-34	4	-10	6.28
Thalamus	-12	-12	0	6.74
Cb	-30	-52	-26	6.39
Midbrain	-10	-10	-8	6.83
<i>Right hemisphere</i>				
Lateral PFC	32	48	24	5.45
SMA	16	12	68	5.51
	4	12	48	5.95
PM	38	-16	56	5.87
Parietal cortex	40	-36	48	5.32
pOPC	52	-20	16	6.08
Precuneus	8	-58	56	4.4
MCC	4	32	34	4.94
PCC	6	-34	26	5.43
IC	36	6	0	5.85
Striatum	26	12	0	5.27
Thalamus	12	-26	4	6.58
Cb	36	-44	-32	6.39
Midbrain	2	-24	-12	6.48

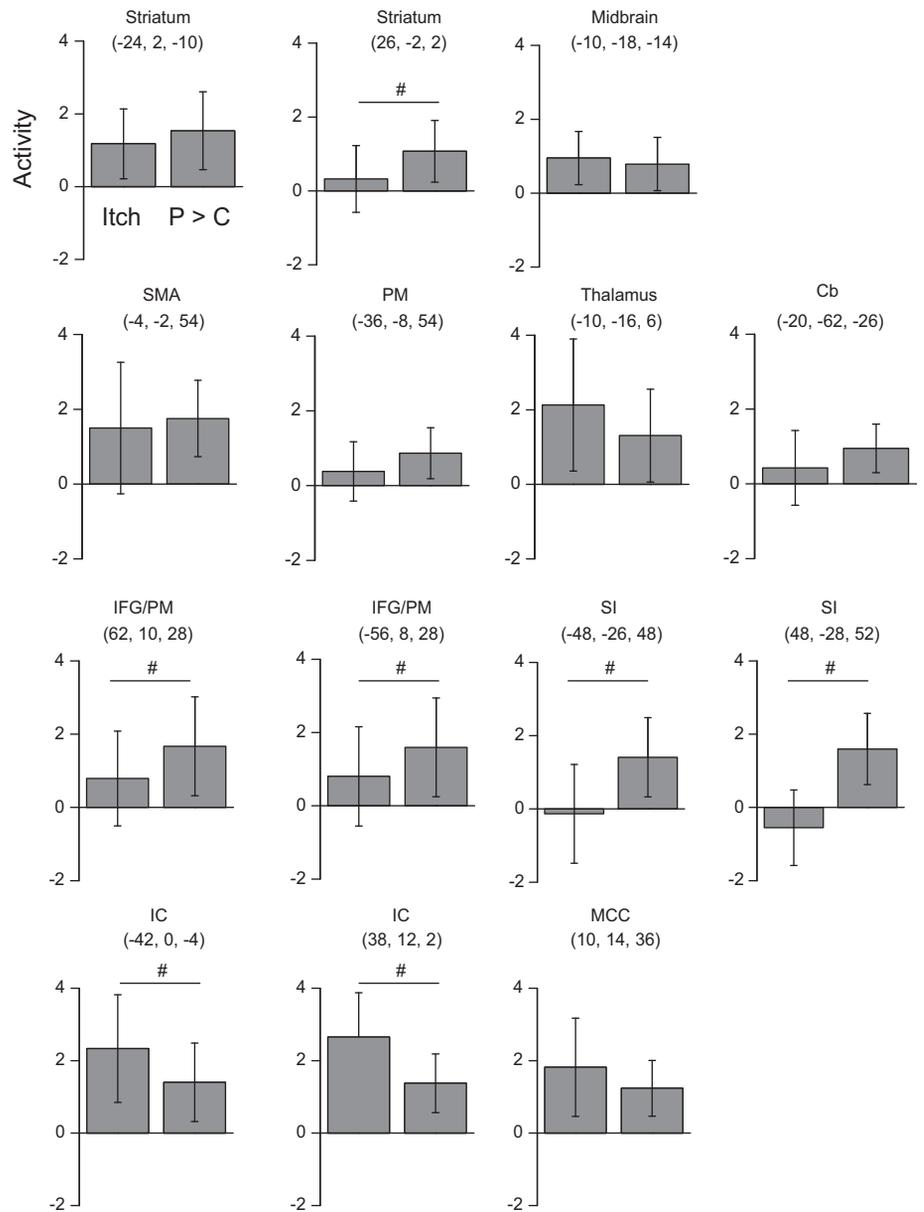


Fig. 5. Activity during the perception of pleasantness and during itch stimulation. Regions of interest (ROIs) were placed on brain areas significantly activated in the pleasant condition compared with the control condition. Each ROI was a sphere with a 3-mm radius. The centers of the ROIs were the statistical peaks of significant activation (see also Table 1). Parameter estimates in the pleasant and control conditions within the ROIs were obtained. The parameter estimates in the control condition were then subtracted from those in the pleasant condition. This represents activity during pleasantness (“P > C” in the graph). In contrast, activity during itch stimuli was obtained as parameter estimates within ROIs during itch stimuli (“Itch” in the graph). $^{\#}P < 0.05$, paired *t*-test.

activation of the reward system caused by scratching-induced pleasantness.

Itch stimuli-related brain regions. In this study, itch sensation was evoked soon after stimulus onset of electrical itch stimuli and rapidly weakened soon after stimulus offset. Thus we speculate that neural activity in brain regions associated with itch also show a similar temporal profile, such as a square wave. Because the conduction velocity of C fibers varies individually, the temporal profile of neural activity (i.e., the square wave) in brain regions associated with itch may have been delayed by several hundred milliseconds from the neural model associated with itch stimuli (i.e., *regressor 1*) for each subject. In addition, the short-lasting weak itch sensation after the termination of itch stimuli (i.e., ~ 10 s) did not include the model, since it was impossible to measure how long the weak itch sensation lasted after every itch stimulus. These are limitations of this study. However, these factors were not a significant concern in this study, as itch stimulus-related brain regions observed in this study were similar to those observed in

previous itch studies using PET and fMRI (Darsow et al. 2000; Drzezga et al. 2001; Herde et al. 2007; Hsieh et al. 1994; Ishiuchi et al. 2009; Leknes et al. 2007; Mochizuki et al. 2003, 2007, 2009; Papoiu et al. 2011; Walter et al. 2005).

Other brain regions. We also observed significant activation of IFG/PM regions bilaterally while pleasantness was evoked (Fig. 3C). In addition, this activation was significantly higher compared with itch stimuli-evoked activation of the same region (Fig. 5, third row). Similar to motor-related regions, activation of this region has not been frequently observed in previous studies of pleasantness, indicating that significant activation of the IFG/PM is likely independent of pleasantness evoked by scratching. Unfortunately, the role of these regions was unclear. Further study will be needed to clarify the role of this region when pleasantness is evoked by scratching itchy skin.

Brain regions showing significant deactivations during scratching were the MI/PM, Prec/PCC, occipital cortex, medial OFC, and hippocampus. Similar regions were also observed in

previous studies (Vierow et al. 2009; Yosipovitch et al. 2008). There was no significant difference in deactivation between the pleasant and control conditions. This result suggested that the most important brain regions associated with scratching-induced pleasantness are those that show significantly increased activity in the pleasant condition compared with the control condition.

Conclusions

Scratching itchy skin evokes pleasurable feelings. As expected, the key brain regions of the reward system such as the striatum and midbrain were significantly activated. In addition, several other brain regions, such as SI, IC, motor-related regions, and IFG/PM, were also activated when pleasurable feelings were evoked by scratching. We presented several interpretations of activation of these regions. For example, the SI and IC would likely be involved in processing pleasurable feelings evoked by scratching. The activation of motor-related regions could explain why scratching-induced pleasantness potentially reinforces scratching behaviors. This is the first study to identify brain regions activated when pleasantness is evoked by scratching itchy skin. The findings contribute to our understanding of why scratching itchy skin evokes pleasurable feelings that can reinforce scratching behaviors.

ACKNOWLEDGMENTS

The authors thank Dr. Clemens Forster for technical support in producing the L-shaped copper plates used in this study and Yasuyuki Takeshima for preparation for experiments.

GRANTS

This study was partly supported by the Takeda Science Foundation and a Grant-in-Aid for Scientific Research (B) (no. 22300135) and Young Scientist (B) (no. 24791584).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: H.M., S.T., and T.W. conception and design of research; H.M., S.T., T.M., and T.W. performed experiments; H.M. and T.M. analyzed data; H.M., N.S., and R.K. interpreted results of experiments.

REFERENCES

- Anderson AK, Christoff K, Stappen I, Panitz D, Ghahremani DG, Glover G, Gabrieli JD, Sobel N. Dissociated neural representations of intensity and valence in human olfaction. *Nat Neurosci* 6: 196–202, 2003.
- Berthier M, Starkstein S, Leiguarda R. Asymbolia for pain: a sensory-limbic disconnection syndrome. *Ann Neurol* 24: 41–49, 1988.
- Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev* 28: 309–369, 1998.
- Bird G, Silani G, Brindley R, White S, Frith U, Singer T. Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain* 133: 1515–1525, 2010.
- Blood AJ, Zatorre RJ, Bermudez O, Evans AC. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. *Nat Neurosci* 2: 382–387, 1999.
- Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 3: 655–666, 2002.
- Craig AD. How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci* 10: 59–70, 2009.
- Craig AD. The sentient self. *Brain Struct Funct* 214: 563–577, 2010.
- Darsow U, Drzeżdżga A, Frisch M, Munz F, Weilke F, Bartenstein P, Schwaiger M, Ring J. Processing of histamine-induced itch in the human cerebral cortex: a correlation analysis with dermal reactions. *J Invest Dermatol* 115: 1029–1033, 2000.
- de Araujo IE, Rolls ET, Kringelbach ML, McGlone F, Phillips N. Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. *Eur J Neurosci* 18: 2059–2068, 2003.
- DeLong MR. The basal ganglia. In: *Principles of Neural Science* (4th ed.), edited by Kandel ER, Schwartz JH, Jessell TM. New York: McGraw-Hill, 2000, p. 853–867.
- Drzeżdżga A, Darsow U, Treede RD, Siebner H, Frisch M, Munz F, Weilke F, Ring J, Schwaiger M, Bartenstein P. Central activation by histamine-induced itch: analogies to pain processing: a correlational analysis of O-15 H₂O positron emission tomography studies. *Pain* 92: 295–305, 2001.
- Fibiger HC, LePiane FG, Jakubovic A, Phillips AG. The role of dopamine in intracranial self-stimulation of the ventral tegmental area. *J Neurosci* 7: 3888–3896, 1987.
- Filbey FM, Claus E, Audette AR, Niculescu M, Banich MT, Tanabe J, Du YP, Hutchison KE. Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. *Neuropsychopharmacology* 33: 1391–1401, 2008.
- Frank GK, Kaye WH, Carter CS, Brooks S, May C, Fissell K, Stenger VA. The evaluation of brain activity in response to taste stimuli—a pilot study and method for central taste activation as assessed by event-related fMRI. *J Neurosci Methods* 131: 99–105, 2003.
- Georgiadis JR, Kortekaas R, Kuipers R, Nieuwenburg A, Pruim J, Reinders AA, Holstege G. Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. *Eur J Neurosci* 24: 3305–3316, 2006.
- Grabenhorst F, Rolls ET. Selective attention to affective value alters how the brain processes taste stimuli. *Eur J Neurosci* 27: 723–729, 2008.
- Grabenhorst F, Rolls ET, Margot C, da Silva MA, Velasco MI. How pleasant and unpleasant stimuli combine in different brain regions: odor mixtures. *J Neurosci* 27: 13532–13540, 2007.
- Grabenhorst F, Rolls ET, Parris BA, d'Souza AA. How the brain represents the reward value of fat in the mouth. *Cereb Cortex* 20: 1082–1091, 2010.
- Griffiths TD, Warren JD, Dean JL, Howard D. “When the feeling’s gone”: a selective loss of musical emotion. *J Neurol Neurosurg Psychiatry* 75: 344–345, 2004.
- Heinzel A, Bermpohl F, Niese R, Pfennig A, Pascual-Leone A, Schlaug G, Northoff G. How do we modulate our emotions? Parametric fMRI reveals cortical midline structures as regions specifically involved in the processing of emotional valences. *Cogn Brain Res* 25: 348–358, 2005.
- Herde L, Forster C, Strupf M, Handwerker HO. Itch induced by a novel method leads to limbic deactivations—a functional MRI study. *J Neurophysiol* 98: 2347–2356, 2007.
- Holmes AP, Friston KJ. Generalizability, random effects, and population inference. *Neuroimage* 7: S754, 1998.
- Holstege G, Georgiadis JR, Paans AM, Meiners LC, van der Graaf FH, Reinders AA. Brain activation during human male ejaculation. *J Neurosci* 23: 9185–9193, 2003.
- Hsieh JC, Hägermark O, Staehle-Bäckdahl M, Ericson K, Eriksson L, Stone-Elander S, Ingvar M. Urge to scratch represented in the human cerebral cortex during itch. *J Neurophysiol* 72: 3004–3008, 1994.
- Ikoma A, Handwerker H, Miyachi Y, Schmelz M. Electrically evoked itch in humans. *Pain* 113: 148–154, 2005.
- Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. The neurobiology of itch. *Nat Rev Neurosci* 7: 535–547, 2006.
- Ishijima Y, Coghill RC, Patel TS, Oshiro Y, Kraft RA, Yosipovitch G. Distinct patterns of brain activity evoked by histamine-induced itch reveal an association with itch intensity and disease severity in atopic dermatitis. *Br J Dermatol* 161: 1072–1080, 2009.
- Izuma K, Saito DN, Sadato N. Processing of social and monetary rewards in the human striatum. *Neuron* 58: 284–294, 2008.
- Komisaruk BR, Whipple B, Crawford A, Liu WC, Kalnin A, Mosier K. Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the vagus nerves. *Brain Res* 1024: 77–88, 2004.
- Krakauer JK, Ghez C. Voluntary movement. In: *Principles of Neural Science* (4th ed.), edited by Kandel ER, Schwartz JH, Jessell TM. New York: McGraw-Hill, 2000, p. 756–781.
- Kühn S, Gallinat J. The neural correlates of subjective pleasantness. *Neuroimage* 64: 289–294, 2012.

- Kupfermann I.** Cognition and the cortex. In: *Essentials of Neural Science and Behavior*, edited by Kandel ER, Schwartz JH, Jessell TM. Norwalk, CT: Appleton and Lange, 1995, p. 347–366.
- Leknes S, Lee M, Berna C, Andersson J, Tracey I.** Relief as a reward: hedonic and neural responses to safety from pain. *PLoS One* 6: e17870, 2011.
- Leknes SG, Bantick S, Willis CM, Wilkinson JD, Wise RG, Tracey I.** Itch and motivation to scratch: an investigation of the central and peripheral correlates of allergen- and histamine-induced itch in humans. *J Neurophysiol* 97: 415–422, 2007.
- Lindgren L, Westling G, Brulin C, Lehtipalo S, Andersson M, Nyberg L.** Pleasant human touch is represented in pregenual anterior cingulate cortex. *Neuroimage* 59: 3427–3432, 2012.
- Martin-Sölich C, Magyar S, König G, Missimer J, Schultz W, Leenders KL.** Changes in brain activation associated with reward processing in smokers and nonsmokers. A positron emission tomography study. *Exp Brain Res* 139: 278–286, 2001.
- Martin-Sölich C, Missimer J, Leenders KL, Schultz W.** Neural activity related to the processing of increasing monetary reward in smokers and nonsmokers. *Eur J Neurosci* 18: 680–688, 2003.
- McCabe C, Rolls ET.** Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain. *Eur J Neurosci* 25: 1855–1864, 2007.
- McCleron FJ, Kozink RV, Lutz AM, Rose JE.** 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology (Berl)* 204: 25–35, 2009.
- McLean J, Brennan D, Wyper D, Condon B, Hadley D, Cavanagh J.** Localisation of regions of intense pleasure response evoked by soccer goals. *Psychiatry Res* 171: 33–43, 2009.
- Mochizuki H, Inui K, Tanabe HC, Akiyama LF, Otsuru N, Yamashiro K, Sasaki A, Nakata H, Sadato N, Kakigi R.** Time course of activity in itch-related brain regions: a combined MEG-fMRI study. *J Neurophysiol* 102: 2657–2666, 2009.
- Mochizuki H, Inui K, Yamashiro K, Otsuru N, Kakigi R.** Itching-related somatosensory evoked potentials. *Pain* 138: 598–603, 2008.
- Mochizuki H, Sadato N, Saitoh D, Toyoda H, Tashiro M, Okamura N, Yanai K.** Neural correlates of perceptual difference between itching and pain using functional magnetic resonance imaging. *Neuroimage* 36: 706–717, 2007. [Erratum. *Neuroimage* 39: 911–912, 2008.]
- Mochizuki H, Tashiro M, Kano M, Sakurada Y, Itoh M, Yanai K.** Investigation of the central itch modulation system using positron emission tomography. *Pain* 105: 339–346, 2003.
- Mohr C, Leyendecker S, Mangels I, Machner B, Sander T, Helmchen C.** Central representation of cold-evoked pain relief in capsaicin induced pain: an event-related fMRI study. *Pain* 139: 416–430, 2009.
- Nieuwenhury R, Voogd J, Huijzen CV.** *The Human Central Nervous System*. New York: Springer, 1988.
- Papou AD, Coghill RC, Kraft RA, Wang H, Yosipovitch G.** A tale of two itches: common features and notable differences in brain activation evoked by cowhage and histamine induced itch. *Neuroimage* 59: 3611–3623, 2011.
- Plassmann H, O’Doherty J, Shov B, Rangel A.** Marketing actions can modulate neural representations of experienced pleasantness. *Proc Natl Acad Sci USA* 105: 1050–1054, 2008.
- Rolls ET, Grabenhorst F, Parris BA.** Warm pleasant feelings in the brain. *Neuroimage* 41: 1504–1513, 2008.
- Rolls ET, Kringelbach ML, de Araujo IE.** Different representations of pleasant and unpleasant odours in the human brain. *Eur J Neurosci* 18: 695–703, 2003.
- Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ.** Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat Neurosci* 257: 257–262, 2011.
- Saper CB.** Brain stem modulation of sensation, movement, and consciousness. In: *Principles of Neural Science* (4th ed.), edited by Kandel ER, Schwartz JH, Jessell TM. New York: McGraw-Hill, 2000, p. 889–909.
- Seymour B, O’Doherty JP, Koltzenburg M, Wiech K, Frackowiak R, Friston K, Dolan R.** Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. *Nat Neurosci* 8: 1234–1240, 2005.
- Silani G, Bird G, Brindley R, Singer T, Frith C, Frith U.** Levels of emotional awareness and autism: an fMRI study. *Social Neurosci* 3: 97–112, 2008.
- Tzschentke TM.** The medial prefrontal cortex as a part of the brain reward system. *Amino Acids* 19: 211–219, 2000.
- Vierow V, Fukuoka M, Ikoma A, Dörfler A, Handwerker HO, Forster C.** Cerebral representation of the relief of itch by scratching. *J Neurophysiol* 102: 3216–3224, 2009.
- Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C.** Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* 26: 6583–6588, 2006.
- Walter B, Sadlo MN, Kupfer J, Niemeier V, Brosig B, Stark R, Vaitl D, Gieler U.** Brain activation by histamine prick test-induced itch. *J Invest Dermatol* 125: 380–382, 2005.
- Wise RA, Rompre PP.** Brain dopamine and reward. *Annu Rev Psychol* 40: 191–225, 1989.
- Yosipovitch G, Ishiuiji Y, Patel TS, Hicks MI, Oshiro Y, Kraft RA, Winnicki E, Coghill RC.** The brain processing of scratching. *J Invest Dermatol* 128: 1806–1811, 2008.