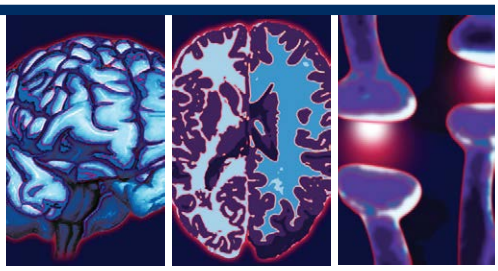

Gentle Touch Opens the Gate to the Primary Somatosensory Cortex

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ABSTRACT

Objective

Touch is a primary reinforcer strongly associated with motivational and affective processes that drive social behavior, and it also plays a critical role in massage therapy. Touch in massage is characterized by gentle touches of the skin involving light pressure effleurage and calm stroking movements intended to increase recipients' pleasure and relaxation. The relationships between basic physical parameters, such as patterns of the hand movements, and their neural bases are important for understanding the effects of gentle touch. However, such studies have not yet been performed. Here, we investigated these relationships and underlying neural mechanisms under two basic movement conditions.

Methods

Using functional Magnetic Resonance Imaging (fMRI), we investigated brain activity induced by Circular (C) and Back-and-forth (BF) massage of participants' left hands with the experimenter's right hand, ensuring that movements were not unpleasant. We assessed subjective feelings, and analyzed fMRI data with Principal Component Analysis (PCA) and correlation analyses to identify associated brain networks.

Results

In C compared with BF, participants felt more positive emotions. There was greater activation of the right primary Somatosensory Cortex (SI) and left cerebellum (CB), but lower activation of the Anterior Cingulate Cortex (ACC) and Periaqueductal Gray (PAG) in C compared with BF. There was no significant difference in unpleasant feelings between the conditions. Moreover, co-activation of the left mid-lateral Orbitofrontal Cortex (OFC), CB, and Rostral Ventromedial Medulla (RVM), and the right SI and posterior insula showed high loadings on Factor 1, which was negatively correlated with unnatural feelings. Meanwhile, co-activation of the ACC and PAG showed high loadings on Factor 2, which was positively correlated with unpleasant feelings.

Conclusion

Our findings suggest somatosensory afferents to the SI are regulated by the descending pain modulatory system under the control of the mid-lateral OFC and ACC, even with mild somatosensory stimulation.

Keywords

Somatosensation, Massage, fMRI, Somatosensory cortex, Anterior cingulate cortex, Orbitofrontal cortex, Descending pain modulatory system

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Introduction

Touch is a primary reinforcer, and one of the foundations of emotion and motivation [1]. Touch associated with positive affect is rewarding, i.e., individuals approach for it, and experience it as pleasant. In contrast, touch associated with negative affect is punishing, i.e., individuals avoid or escape from it, and experience it as unpleasant.

Inter-individual touch is frequently used to communicate positive messages, such as reassurance, comfort, sympathy, and support [2]. Touch from another person can be soothing [3,4], give rise to pleasurable feelings [5,6], and potentially suppress pain and negative emotion [7-10]. Skin-to-skin contact between individuals also has a pivotal role in social interactions, sub serving nonverbal communication of intentions and affect. A romantic caress is a primary expression of affiliative behavior that reflects the disposition of individuals to seek close contact with each other, promoting socio-emotional relationships, pair bonding, and reproduction [11-13]. Therefore, touch is a primary reinforcer strongly connected with motivational and affective processes that may drive social behavior [14].

Clinically, massage therapy is often used as an adjunct treatment for various conditions, including those involving chronic pain and distress [15-17]. Furthermore, it can enhance growth and cognitive functioning in preterm infants [18,19] and preschoolers [20]. Moreover, massage has beneficial effects in cancer patients by modulating immunity, alleviating depressive symptoms [21], and lessening pain and sleep disturbances [22-24].

Soft touch/stroking, including massage therapy, is characterized by gentle touches of the skin involving light pressure effleurage and calm stroking movements intended to increase the recipient's well-being [25], pleasure [26], and relaxation [27,28]. Therefore, understanding the influence of physical parameters including the softness, temperature, force, velocity, and movement patterns, is important to clarify their effects and underlying neural mechanisms.

As the human hand is intrinsically soft and warm, softness and temperature may remain within a certain limited range. In addition, force and velocity may also remain within a specific range with the intention to increase the recipient's well-being, pleasure, and relaxation. In contrast, movement patterns (e.g., how to move one's own hand over the back of the recipient's hand) are varied; circular movements may make individuals feel natural and comfortable, while mechanical movements may make them to feel unnatural and uncomfortable. Accordingly, even a subtle difference in the movement pattern may cause unexpected emotions. Based on these considerations, it is important to clarify the relationships between movement patterns and emotions, and the underlying neural mechanisms. However, such neuroscientific studies have not yet been performed.

The emotional aspects of touch have been explained as positive feelings elicited by activating specific C-tactile (CT) afferents in the skin that signal to areas in the brain involved in positive emotions [29]. Processing of body signals occurs *via* unmyelinated or thinly myelinated afferents, *via* interoceptive pathways that signal feelings rather than sensing states, as well as controlling organ functions that do not reach conscious perception. Stroking with a soft brush on hairy skin activates the contralateral posterior insular cortex, as well as the primary somatosensory cortex (SI). The insular cortex is a region of great interest in relation to affective mechanisms, and is considered as a gateway from sensory systems to the emotional systems of the frontal lobe [30,31]. The medial prefrontal cortex (mPFC)/anterior cingulate cortex (ACC) are also implicated in processing CT-targeted touch [32]. In addition, CTs are tuned to respond to tactile stimuli with the specific thermal characteristics of a gentle caress delivered at normal skin temperature [33]. Therefore, this reinforces their role in providing a peripheral mechanism to signal pleasant skin-to-skin contact in humans, thereby promoting interpersonal touch and affiliative behavior.

Moreover, an important neural mechanism exists that is known to exert top-down regulation of ascending somatosensory information. Placebo-induced enhancement of pleasant experiences involves upregulation of activity in the posterior insula and SI [34]. In contrast, placebo-induced analgesia involves downregulation of activity in these areas [35-37]. These results indicate that increased early sensory processing of a stimulus of positive valence (e.g., pleasant touch) underpins hyperhedonia, in a similar manner to which reduced processing of an aversive stimulus (e.g., painful touch) underpins analgesia [34]. Placebo-induced improvement of positive and negative hedonic feelings is underpinned by recruitment of common circuitry associated with emotion appraisal. This includes placebo-induced functional coupling between the ventromedial prefrontal cortex (vmPFC) and periaqueductal gray (PAG), which is correlated with increased sensory responses to stroking touch but decreased responses to painful touch [34]. Thus, similar modulatory circuits can either up- or down-regulate early sensory processing depending on whether the expectation is enhancement of positive or negative hedonic feelings. The PAG–rostral ventromedial medulla (RVM)–spinal cord axis is important for many forms of pro- and anti-nociception in non-human animals, paralleling involvement in human placebo and nocebo effects [38,39]. This axis is, in turn, governed by the ACC, vmPFC and mid-lateral orbitofrontal cortex (OFC) [36,40-45], which interact with the PAG–RVM pathway to mediate various pain-modulatory effects as part of the descending pain modulatory system (DPMS) [39].

The above neural mechanisms have been investigated by using highly unpleasant tactile stimuli such as those associated with pain, and by using top-down cognitive effects. Thus, whether similar neural mechanisms are activated with mild tactile stimulation such as affiliative and gentle touch remains unconfirmed. A recent fMRI study has shown that there is intrinsic functional connectivity in the DPMS in non-painful situations [46], and another one has shown that self-touch activates the DPMS in a pain-free and stress-free situation [47]. These studies may support the possibility that the DPMS regulates somatosensory afferents based on their emotive valence, even for mild somatosensory stimuli with subtly different movement patterns.

Based on these considerations, we focused in the current study on two basic movements: circular movement and back-and-forth movement. These movements are fundamental components constituting diverse movement patterns. Circular movement is associated with human and affiliative characteristics that would induce positive feelings, such as gentle, safe, and warm feelings. In contrast, back-and-forth movement has non-human and mechanical characteristics, which would make participants feel unnatural and nervous. We investigated differences in the activity of certain brain regions including the SI, cerebellum (CB), OFC, ACC, insula, and PAG. We conducted analyses to test our hypothesis that the DPMS regulates mild somatosensory afferent signals. We also hypothesized that the OFC activity would be associated with natural and positive emotions induced by circular rubbing, while the ACC activity would be associated with unnatural and nervous feelings induced by back-and-forth rubbing.

Materials and Methods

■ Participants

We recruited 12 healthy female participants (mean age: 31.5 ± 3.7 years). All participants were right-handed according to the Chapman test (13.3 ± 0.6) and had no history of neurological or psychiatric disorders. Participants provided informed consent to participate in the study. The Research Ethics Committee of Tokyo Metropolitan University approved this study and all methods were performed in accordance with approved guidelines.

■ Stimuli, trial protocol, and procedure

Each participant was instructed to relax and close her eyes without thinking about anything specific. We set two experimental conditions, in which one of the authors (TI) who is a professional esthetician, rubbed the back of the participant's hand in a circular motion (C) or rubbed it using a back-and-forth motion (BF). She practiced the rubbing so that she could rub the participant's hand with a maximum force of less than 0.3 N, and velocities between 6 cm/sec and 10 cm/sec. Within this range, CT-fibers respond optimally to stimulation [33,48,49], and parents naturally stroke their babies [50]. A session consisted of 8 trials (2 conditions × 4 times), with the trials counterbalanced across participants. A block-design paradigm was applied, with each trial lasting 32 sec interspersed with rest for 8 sec.

■ Analysis of subjective ratings

After the fMRI scans, participants were asked to rate their emotional state while being touched by TI in the same way during the fMRI experiment. We administered nine items to measure subjective feelings: "To what extent did you feel gentle ("gentle"), safe ("safe"), warm ("warm"), comfortable ("comfortable"), preferable ("preferable"), calm ("calm"), unnatural ("unnatural"), nervous ("nervous"), or unpleasant ("unpleasant")?". We used visual analog scaling for data collection (0%-100%). In addition, they were required to rate the perceived intensity on a five-point scale (1 = very weak, 2 = moderately weak, 3 = neutral, 4 = moderately strong, 5 = very strong). Statistical analyses were conducted with SPSS version 21.0 (SPSS, Inc., Chicago, IL).

FMRI data analysis

Scanning was conducted with a 3.0T MRI system (Achieva Quasar Dual, Philips). BOLD T2*-weighted MR signals were measured with a gradient echo-planar imaging (EPI) sequence (TR = 4,000 msec, TE = 35 msec, flip angle = 90°, FOV = 23 cm^2, scan matrix = 128 × 128, total scan time = 324 sec, slice thickness = 5 mm, 25 slices per volume). Image processing was conducted with Statistical Parametric Mapping 8 (SPM8, Welcome Department of Imaging Neuroscience, London, UK; *http://www.fil.ion.ucl.ac.uk/spm/software/spm8*). EPI images were realigned and normalized to Montreal Neurological Institute (MNI) stereotactic space. Normalized images were smoothed with an 8 mm full-width half-maximum Gaussian kernel. The data were temporally convolved with the hemodynamic response function (HRF) and high-pass filtered with a cutoff period of 128 sec. Each C and BF condition was modeled with a separate regressor.

We set spherical regions of interest (ROI) in the right SI (40 -31 59) [51], left CB (-36 -61 -29) [52], left mid-lateral OFC (-24 36 -18) [53], right ACC (11 52 15) [54], right posterior insula (42 -31 21) [51], PAG (-6 -33 -18) [55], and RVM (-2 -38 -38) [47]. ROIs with a radius of 5 mm were set for each contrasts of C *vs.* baseline and BF *vs.* baseline. Subsequently, we tested differences in the eigenvariate values for each ROI between C and BF by using a paired *t*-test ($P<0.05$).

Furthermore, we conducted multiple regression analyses with each eigenvariate value for ROIs in the right SI, mid-lateral OFC, and ACC as dependent variable and those of the other ROIs as the independent variables ($P<0.05$). Multiple regression analyses were conducted for both C *vs.* baseline and BF *vs.* baseline. Moreover, we checked the residuals by performing the Shapiro-Wilks (S-W) test of normality ($P<0.05$), and calculated the Durbin-Watson (D-W) statistic for the null hypothesis of no autocorrelation.

Relationships between ROIs and subjective feelings

We conducted multiple regression analyses with each eigenvariate value for the ROIs as the dependent variable and subjective feelings as the independent variables ($P<0.05$). Moreover, we checked the residuals by performing the S-W test of normality ($P<0.05$), and calculated the D-W statistic for the null hypothesis of no autocorrelation.

Principal component analysis

We performed a principal component analysis (PCA) to classify all the ROIs into subgroups by using the Varimax rotation method with Kaiser Normalization. In addition, we checked the sampling adequacy by using Bartlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) test. We also performed multiple regression analyses with scores of each principal component as the dependent variable, and the subjective rating scores as independent variables ($P<0.05$). We then checked the residuals for all regression analyses by performing the S-W test of normality ($P<0.05$), and calculated the D-W statistic for the null hypothesis of no autocorrelation.

Furthermore, to confirm whether simultaneous activation of the RVM and deactivation of the PAG is positively correlated with right SI activity, we performed PCA and calculated the principal component scores for the simultaneous reverse activity and a simple regression analysis between the scores and right SI activity ($P<0.05$). In addition, we checked the sampling adequacy by using Bartlett's test of sphericity and the Kaiser-Meyer-Olkin test, the residuals for all regression analyses by performing the S-W test of normality ($P<0.05$), and calculated the D-W statistic for the null hypothesis of no autocorrelation. These statistical analyses were conducted with SPSS version 21.0.

Results

Subjective ratings

Participants showed significantly higher scores for "gentle", "safe", "warm", "comfortable", "preferable", and "calm" in C compared with BF. In contrast, they showed significantly higher scores for "unnatural" and "nervous" in BF compared with C. There was no significant difference in "unpleasant" feeling **(Figure 1).** Moreover, there was also no significant difference in the perceived intensity by Wilcoxon signed-rank test at $P<0.05$ (C 2.833 ± 0.697; BF 2.833 ± 0.333).

Differences in brain activity between the C and BF condition

The right SI (t=3.077, P=0.011) and left CB (t=3.587, P=0.004) showed significantly higher activity in C compared with BF. In contrast, the ACC (t=-2.248, P=0.0461) and PAG (t=-2.492, P=0.029) showed significantly higher activity in BF compared with C **(Figure 2).**

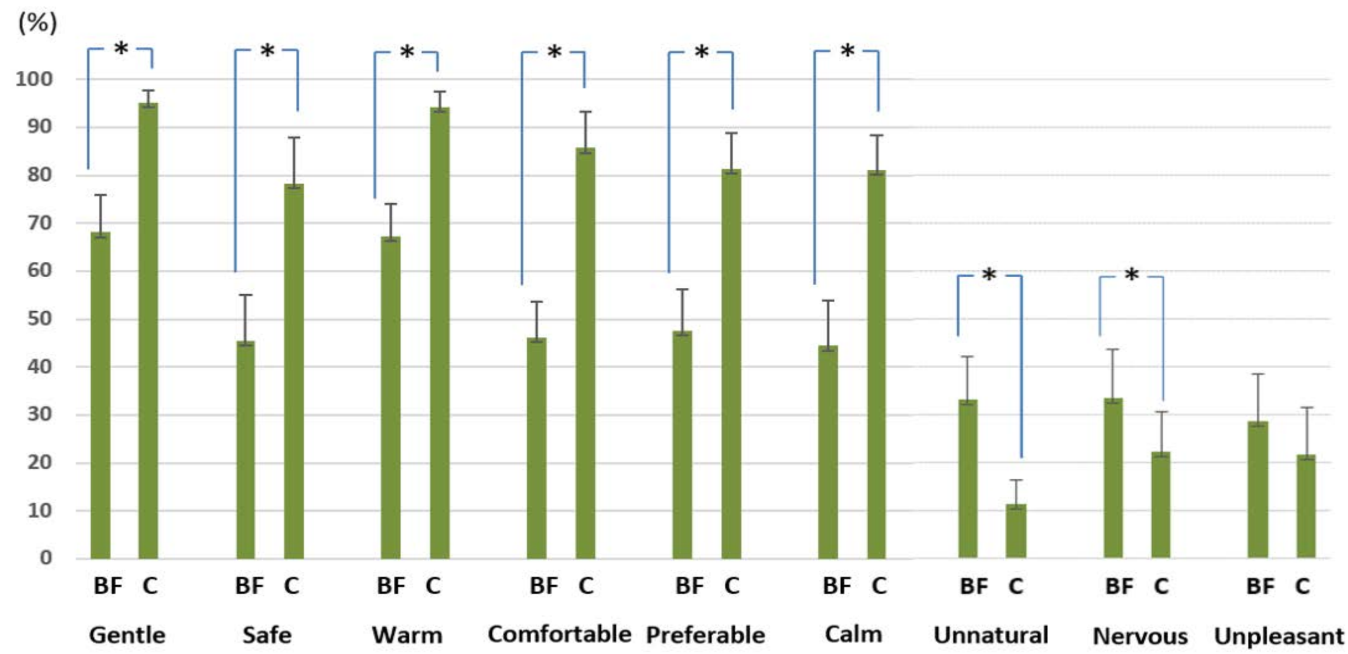

Figure 1: Differences in subjective feelings between C and BF.

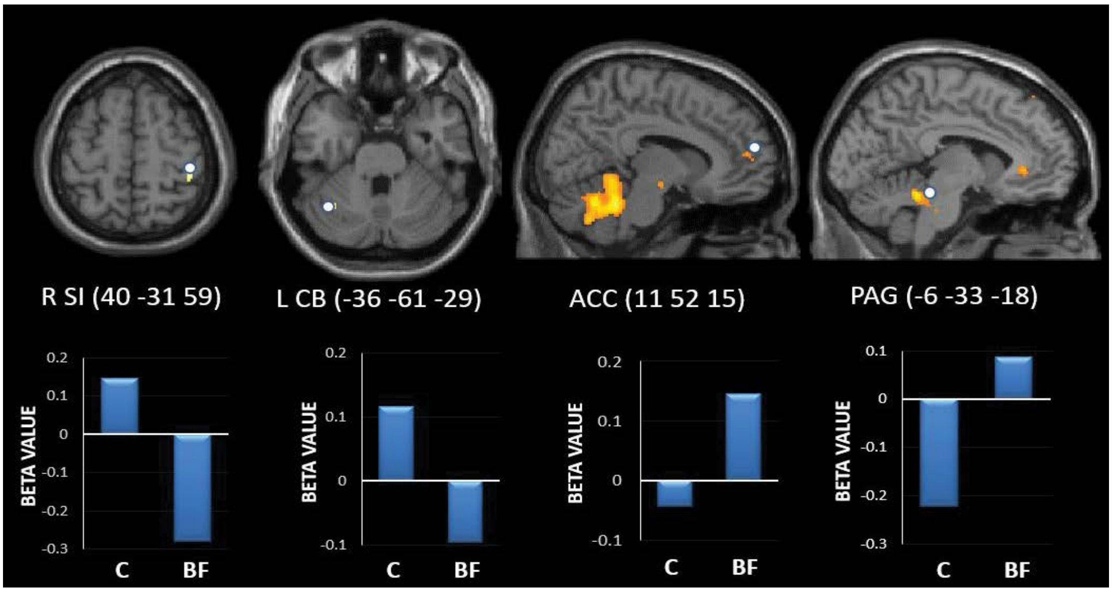

Figure 2: Relationships between ROIs and subjective feelings.

■ Relationships between ROIs and subjective feelings

Activity in the left CB, right posterior insula, and PAG were positively correlated with feeling "safe" (CB: t=2.380, P=0.026, adjusted R^2=0.169; S-W statistic=0.949, P=0.255; D-W statistic=2.578; posterior insula: t=3.233, P=0.004, adjusted R^2=0.291; S-W statistic=0.919, P=0.054; D-W statistic = 1.783), and "unpleasant" (PAG: t=2.825, P=0.010, adjusted R^2=0.233; S-W statistic=0.972, P=0.720; D-W statistic=1.829) **(Figure 3)**.

In contrast, activity in the right SI, RVM, mid-lateral OFC, and ACC was negatively correlated with feeling "unnatural" (SI: t=-3.726, P=0.001, adjusted R^2=0.359; S-W statistic=0.935, P=0.126; D-W statistic=2.012; RVM: t=-2.214, P=0.037, adjusted R^2=0.145; S-W statistic=0.950, P=0.272; D-W statistic=1.797), "unpleasant" (OFC: t=-2.835, P=0.010, adjusted R^2=0.234; S-W statistic=0.924, P=0.070; D-W statistic=1.924), and "comfortable" (ACC: t=-2.395, P=0.026, adjusted R^2=0.171; S-W statistic=0.954, P=0.329; D-W statistic=1.633) **(Figure 3)**.

■ PCA results

We extracted two principal components: 1) brain activity associated with positive emotion (48.544% of the total variance); and 2) brain activity associated with negative emotion (21.902% of the total variance). A subsequent exploratory factor analysis including seven predictors for the ROI activity scores revealed that these predictors converged on two factors **(Figure 4)**. The first (Factor 1) included activity in the SI, CB, posterior insula, mid-lateral OFC, and RVM. The second (Factor 2) included activity in the ACC and PAG **(Table 1 and Figure 4)**.

We confirmed the sampling adequacy with Bartlett's test of sphericity (χ^2=89.556, d_f=21, P<0.0001) and KMO's test (KMO measure=0.627). Moreover, the score for Factor 1 was negatively correlated with "unnatural" feelings (t=-2.870, P=0.009; adjusted R^2=0.239; S-W statistic=0.982, P=0.936; D-W statistic=2.132). In addition, the score for Factor 2 was significantly positively correlated with "unpleasant" feelings (t=2.478, P=0.021; adjusted R^2=0.183 S-W statistic =0.980, P=0.900; D-W statistic=1.366). Furthermore, there was a significant positive correlation between the score for simultaneous activation of the RVM and deactivation of the PAG (55.954% of the total variance) and right SI activity (t=4.361, P<0.0001, adjusted R^2=0.439; S-W statistic=0.940, P=0.165; D-W statistic=2.705) **(Figure 5)**.

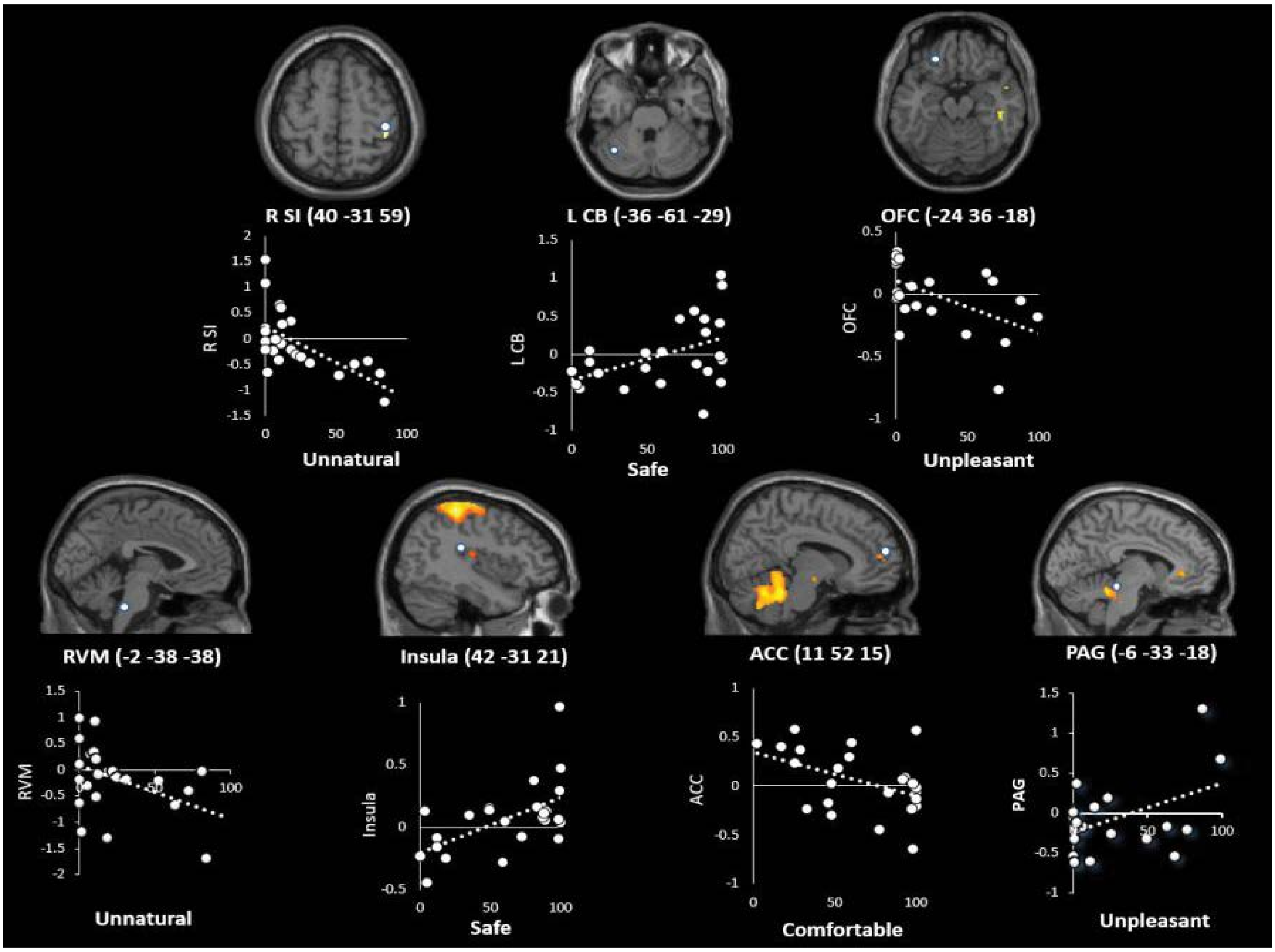

Figure 3: Correlations between brain activity and subjective feelings.

Table 1: Exploratory factor structure of brain activity.

Factor analysis		Factor 1	Factor 2
	Brain regions	**Factor loading**	**Factor loading**
	RVM	0.926	0.157
	R SI	0.906	-0.204
	L CB	0.801	0.023
	Mid-lateral OFC	0.787	-0.245
	R posterior insula	0.546	0.056
	ACC	0.109	0.734
	PAG	-0.190	0.924
Regression analysis	feeling	unnatural	unpleasant
	correlation	negative (-)	positive (+)

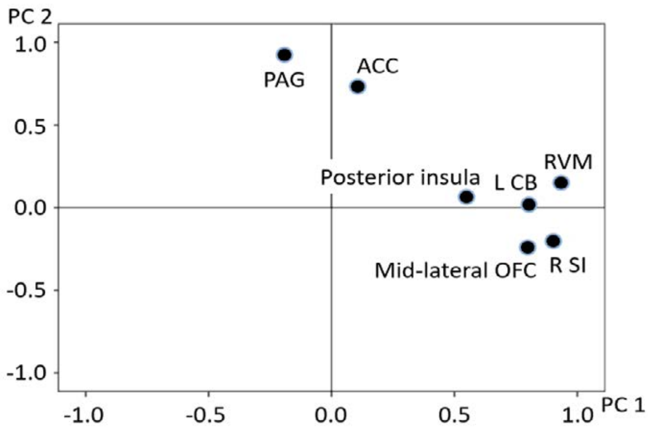

Figure 4: 2D scatter plot of principal components (PCs) of brain activity. The x-axis and the y-axis represent PC1 and PC2, respectively.

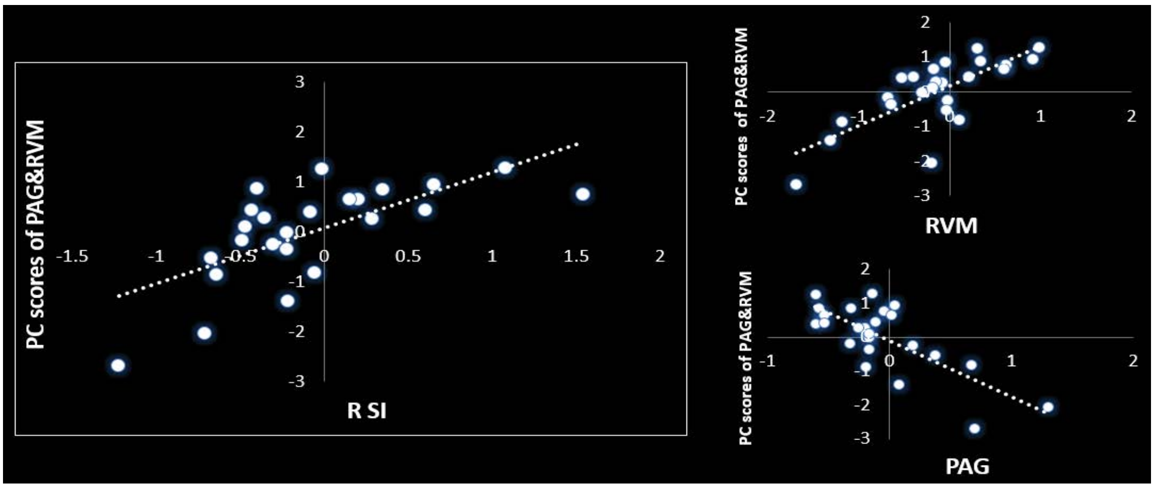

Figure 5: Significant positive correlation between the score for simultaneous activation of the RVM and deactivation of the PAG and right SI activity.

■ Multiple regression analyses with the right SI, mid-lateral OFC, or ACC as the dependent variable

Activity in the right SI was positively correlated with that in the left CB (t=2.199, P=0.040), RVM (t=2.783, P=0.012), and right posterior insula (t=2.561, P=0.019). In contrast, activity in the right SI was negatively correlated with that in the PAG (t=-2.709, P=0.014; adjusted R^2=0.761; S-W statistic=0.393, P=0.393; D-W statistic=1.707) **(Figure 6)**. Moreover, activity in the mid-lateral OFC was positively correlated with that in the RVM (t=5.327, P<0.0001), and negatively correlated with that

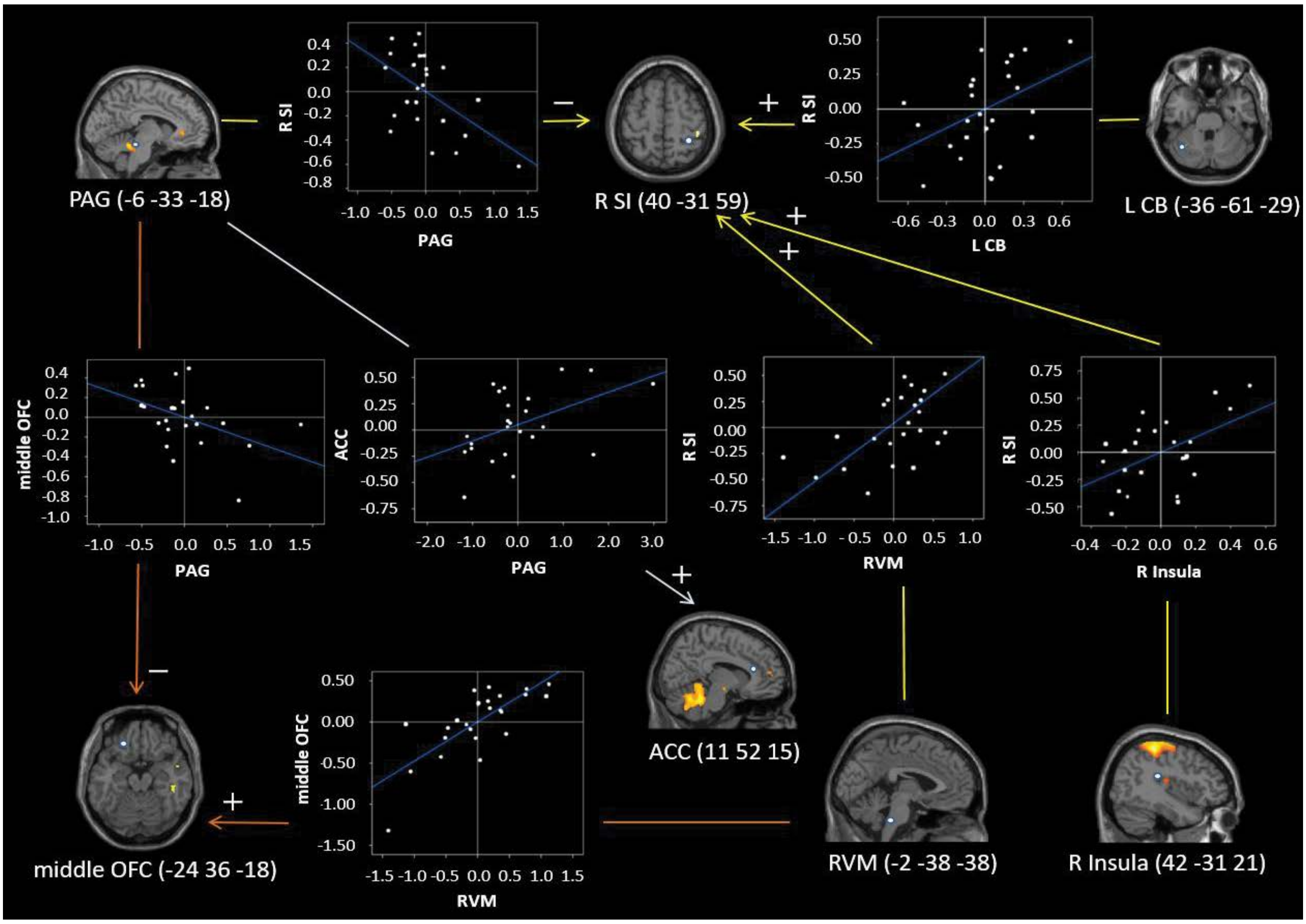

Figure 6: Multi-regression analyses with the right SI, mid-lateral OFC, or ACC as the dependent variable. Each arrow represents the correlation, and the tail and the head represent an independent variable and the dependent variable, respectively.

in the PAG (t=-2.375, P=0.027; adjusted R =0.607; S-W statistic=0.742, P=0.742; D-W statistic=1.540) **(Figure 6)**. Activity in the ACC was positively correlated with that in the PAG (t=2.581, P=0.017; adjusted R^2=0.197; S-W statistic=0.928, P=0.088; D-W statistic=2.873) **(Figure 6)**.

Discussion

In the present study, participants reported that they felt more positive feelings when circularly rubbed on the back of the left hand compared with being rubbed back and forth on the same hand. In contrast, they reported that they felt more unnatural and nervous when rubbed back and forth compared with being circularly rubbed. Moreover, there was no significant difference in feelings of unpleasantness. As back-and-forth linear movements have non-human and mechanical characteristics, they might make participants feel unnatural and nervous. In contrast, circular movements have human and affiliative characteristics, which might make participants experience positive feelings.

Furthermore, in BF compared with C, there was significantly more activation in the ACC and PAG, but significantly less in the right SI and left CB. Furthermore, ACC activity was negatively correlated with “comfortable” feelings and PAG activity was positively correlated with “unpleasant” feelings. Meanwhile, right SI activity was negatively correlated with “unnatural” feelings and left CB activity was positively correlated with “safe” feelings. These results suggest that ACC and PAG activity is related to negative emotions associated with being rubbed, while right SI and left CB activity are related to the positive emotions evoked by rubbing.

The ACC receives somatosensory information via the insula and OFC, which are both well connected with the ACC [56]. ACC activation was observed to increase following a suggested increase in subjective unpleasantness, but to decrease following a suggested decrease in subjective unpleasantness [57]. This indicates that the ACC is involved in representing affective qualities of a stimulus rather than its physical intensity. In fact, there was no significant difference in the perceived intensity between C and BF. Activity in the ACC is also positively correlated with unpleasantness of pain in healthy individuals [58], indicating that this region is particularly involved in affective responses to pain. Moreover, the ACC controls the brainstem, including the PAG and RVM [59,60] , during both opioid and placebo analgesia [39,61]. The ACC has one of the highest levels of opioid receptor binding in the cortex [62], and positron emission tomography (PET) studies indicate that the binding potential is specifically highest in the ACC [63,64].

The PAG plays a pivotal role in the DPMS [65]. It is functionally connected with the ACC [46], and participates in the descending modulation of pain. Indeed, our results that ACC activity is positively correlated with PAG activity, which in turn was negatively correlated with right SI activity, suggests involvement of the DPMS. Moreover, the DPMS can function even in the absence of painful/stressful stimulation, because intrinsic functional connectivity among DPMS regions (including the ACC and RVM) has been demonstrated in such situations [46]. Moreover, the DPMS is activated during self-touching behaviors in pain-free and stress-free situations [47].

A positive correlation has been observed between behavioral opioid analgesia and opioid-induced suppression of neuronal responses to noxious stimuli in the RVM [66]. The RVM plays a critical role in both inhibition and facilitation of pain through interactions with the spinal cord. Both off- and on-cells in the RVM project to the spinal dorsal horn, indicating that they exert modulatory influences on nociceptive/non-nociceptive inputs [67]. RVM on-cells are directly inhibited by opioids, and it is suggested that these cells express mu-opioid receptors [68]. Moreover, increased RVM neuronal responses to noxious stimuli observed in human imaging studies indicate on-cell activity [69,70]. In fact, we observed a positive correlation between RVM activity and right SI activity in the present study. Furthermore, simultaneous activation of the RVM and deactivation of the PAG was positively correlated with right SI activity. This suggests that PAG activity inhibits on-cell activity in the RVM, which suppresses right SI activity. In fact, PAG neurons modulate nociception by directly inhibiting on-cells in the RVM *via* GABAergic neurons [71].

Conversely, somatosensory afferent signals were enhanced (facilitated) by circular rubbing compared with back-and-forth rubbing. We suggest that the mid-lateral OFC downregulates PAG activity, which inhibits RVM activity and/or directly upregulates RVM activity, based on reward/saliency evaluation processes in the mid-lateral OFC. This suggestion is supported by results indicating that mid-lateral OFC activity is negatively correlated with PAG activity, and positively correlated with RVM activity. Moreover, the mid-lateral OFC showed a negative correlation with "unpleasant" feelings. Furthermore, co-activation of the left mid-lateral OFC, CB, and RVM, and of the right SI and posterior insula showed high factor loading on Factor 1, which was negatively correlated with "unnatural" feelings. However, these co-activations showed low factor loading on Factor 2, which was positively correlated with "unpleasant" feelings. The posterior and mid-insula receive somatosensory information through projections from the SI [72,73] and directly from the thalamus [74]. The OFC receives somatosensory information from the granular insula and directly from the SI [75-77]. As such, the OFC can mediate integration of such information and evaluate its rewarding (salient) characteristics. Indeed, a meta-analysis has suggested that sensory pleasure is most faithfully represented within a mid-lateral OFC site [78].

Neuroimaging studies of placebo effects on physical pain suggest that activation of the ACC, OFC, and vmPFC influences pain by activating the descending pain regulatory pathways in the brainstem, especially opioidergic mechanisms in the PAG [39,45,79-83]. The DPMS is important for many forms of pro- and anti-nociception in non-human animals, paralleling involvement in human placebo and nocebo effects. The present findings show that somatosensory afferents to the SI are regulated by the DPMS under the control of the mid-lateral OFC and ACC, even under mild somatosensory stimulation situations.

Conclusion

The principal component and regression analyses of brain activity and subjective feelings showed that somatosensory afferents to the primary somatosensory cortex contralateral to the rubbed hand were regulated by the descending pain modulatory system under the control of the mid-lateral orbitofrontal cortex and anterior cingulate cortex, even under mild (pain-free) rubbing situations.

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