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ALE Meta-Analysis Reveals Dissociable Networks for Affective and Discriminative Aspects of Touch

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Abstract: Emotionally-laden tactile stimulation—such as a caress on the skin or the feel of velvet—may represent a functionally distinct domain of touch, underpinned by specific cortical pathways. In order to determine whether, and to what extent, cortical functional neuroanatomy supports a distinction between affective and discriminative touch, an activation likelihood estimate (ALE) meta-analysis was performed. This meta-analysis statistically mapped reported functional magnetic resonance imaging (fMRI) activations from 17 published affective touch studies in which tactile stimulation was associated with positive subjective evaluation ($n = 291$, 34 experimental contrasts). A separate ALE meta-analysis mapped regions most likely to be activated by tactile stimulation during detection and discrimination tasks ($n = 1{,}075$, 91 experimental contrasts). These meta-analyses revealed dissociable regions for affective and discriminative touch, with posterior insula (PI) more likely to be activated for affective touch, and primary somatosensory cortices (SI) more likely to be activated for discriminative touch. Secondary somatosensory cortex had a high likelihood of engagement by both affective and discriminative touch. Further, meta-analytic connectivity (MCAM) analyses investigated network-level co-activation likelihoods independent of task or stimulus, across a range of domains and paradigms. Affective-related PI and discriminative-related SI regions co-activated with different networks, implicated in dissociable functions, but sharing somatosensory co-activations. Taken together, these meta-analytic findings suggest that affective and discriminative touch are dissociable both on the regional and network levels. However, their degree of shared activation likelihood in somatosensory cortices indicates that this dissociation reflects functional biases within tactile processing networks, rather than functionally and anatomically distinct pathways. *Hum Brain Mapp 37:1308–1320, 2016.*

Key words: affective touch; discriminative touch; posterior insula; secondary somatosensory cortex; activation likelihood estimate; meta-analytic connectivity modeling

INTRODUCTION

Most people have experienced the potential of human touch to spark a cascade of emotion. This emotional aspect of touch has been called "affective touch," a category term capturing tactile processing with a hedonic or motivational component. It has been proposed as a relatively distinct category of touch, with qualitative and anatomical correlates distinguishable from the more well-mapped pathways of "discriminative touch" [Olausson et al., 2010; McGlone et al., 2014; Morrison et al., 2010]. In this perspective, affective touch is functionally distinct from discriminative touch, in that it preferentially weights tactile

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stimuli in affective, motivational, or hedonic terms, such as valence or reward value. This may be especially relevant in contexts in which touch can carry affective significance, particularly social interactions [Morrison, et al., 2010; Olausson et al., 2010].

Yet to what extent does the neuroanatomical organization of somatosensory cortices suggest a distinction between affective and discriminative touch? A parsimonious possibility is that processing in discriminative-associated networks such as primary somatosensory cortex (SI) can completely account for affective phenomena in the tactile domain. That is, discriminative terms could be sufficient for coding affectively-relevant variables. On this view, affective processing need not constitute an intrinsic component of the somatosensory domain—after all, affective processing of pictures does not imply a special system for "affective vision." A similar but less extreme possibility is that discriminative somatosensory networks, such as those involving SI, could play a direct role in hedonic evaluation [Gazzola et al., 2012].

On the other hand, emerging evidence supports the possibility that somatosensation *does* involve an intrinsic affective dimension, over and beyond the functional and anatomical scope of classical discriminative somatosensory networks. This evidence stems mainly from the discovery of unmyelinated afferents sensitive to light touch on the skin, called tactile C (CT) afferents [Nordin et al., 1990; Vallbo et al., 1993; Wessberg et al., 2003; Olausson et al., 2010]. In humans, the mean firing frequency of CT afferents correlates with the mean subjective pleasantness of skin stroking [Löken et al., 2009, Ackerley et al., 2014], and their signaling is associated with activation of the posterior insular cortex [PI; Olausson et al., 2002; Björnsdotter et al., 2009; Gordon et al., 2011; Morrison et al., 2011; Perini et al., 2015]. This evidence increases the plausibility of the hypothesis that affective and discriminative touch are indeed processed in the cortex in a dissociable manner.

This hypothesis was addressed here using an activation likelihood estimate (ALE) meta-analysis of 17 affective touch studies using functional magnetic resonance imaging (fMRI). This meta-analysis revealed peaks with significantly high probability of activation across studies, regardless of variations in methods, stimuli, and experimental paradigms. Its purpose was to identify likely activation hubs robustly implicated in affective touch. To discover the functional specificity of these activations, they were statistically compared to activations reported in studies involving discriminative tactile paradigms. It was predicted that areas consistently reported in affective touch studies, particularly posterior insula, would be dissociable from somatosensory regions activated by discriminative touch paradigms, such as SI. Another aim was to more closely explore any functional specificity of parietal opercular (PO) somatosensory regions, which have been reported in both discriminative and affective touch contexts.

Further, to determine whether these hubs are associated with different brain-wide networks, a meta-analytic connectivity modeling (MCAM) analysis was performed. The aim of the MCAM analysis was to assess differential degrees of functional co-activation across multiple study types, between the affect-related and discriminative-related regions identified by the ALE meta-analysis. Studies of anatomical connectivity in the insula suggest that PI has a relatively close relationship with PO somatosensory networks [Cerliani et al., 2012; Evrard et al., 2014; Kurth et al., 2010, Uddin et al., 2014]. The present study hypothesized that affectively- and discriminatively-biased regions, though each tactile-related and anatomically interconnected, are distinguishable by differential co-activations with other networks throughout the brain.

Abbreviations

ALE	Activation likelihood estimate
BOLD	Blood-oxygen-level-dependent
fMRI	Functional magnetic resonance imaging
MCAM	Meta-analytic connectivity modeling
PI	Posterior insula
PO	Parietal operculum
ROI	Region-of-interest
SI	Primary somatosensory cortex
SMA	Supplementary motor area
STT	Spinothalamic tract
TMS	Transcranial magnetic stimulation
VPI	Ventroposterior inferior thalamic nucleus

METHODS

Meta-Analysis Criteria

Affective touch map

The affective touch meta-analysis included published fMRI studies of affective touch (Table I). Studies published 1999 through early 2015 were identified through knowledge of the field, supplemented by PubMed literature search with keyword combinations "affective + touch," "pleasant + touch," "touch + emotion," and "fMRI." The inclusion criteria for "affective touch" were cutaneous tactile stimulation associated with a reported positive hedonic subjective rating (*e.g.*, pleasantness), regardless of stimulation site or stimulus type (*e.g.*, hand, soft velvet, lotion, etc). Studies involving drug manipulations or patient populations were included only if they reported contrasts *within* healthy, drug-free, adult control groups. Studies involving pain and pharmacological manipulations (eg, intranasal oxytocin spray) were excluded, as well as those involving semantic, graphic, or anticipatory manipulations without reporting tactile-only conditions or contrasts (*e.g.* word stimuli independent of tactile stimulation). The resulting dataset consisted of 17 papers (34 experimental contrasts) with a total N of 291 unique subjects (with an overall N of 552 across all contrasts), and 166 foci (See Table I). Of these, two studies reported coordinates based

TABLE I. Studies, stimulus, and foci information for affective touch meta-analysis

Reference	*N*	Tactile stimulus	Stimulus site	Skin type	Contrast(s)	Ipsilat foci	Contralat foci
Björnsdotter et al., 2009	6	Soft brush	R arm	Hairy	4 - 7.5 cm/s stroking vs baseline *	1	2
		Soft brush	R thigh	Hairy	4 - 7.5 cm/s stroking vs baseline *	1	2
Björnsdotter et al., 2014	22	Soft brush	R arm	Hairy	Stroking vs baseline	6	7
Björnsdotter et al., 2014	22	Soft brush	R palm	Glabrous	Palm stroking vs baseline	3	7
Cascio 2012	14	Soft brush	R arm	Hairy	Stroking vs baseline	0	9
Ebisch et al., 2011	19	Latex glove	R and L hand	Hairy	Stroking vs baseline	1	5
Francis et al., 1999	4	Velvet-covered dowel	palm	Glabrous		1	6
Gordon et al., 2013	22	Soft brush	R arm	Hairy	Stroking vs baseline	6	5
Gordon et al., 2013	17	Soft brush	R palm	Glabrous	Palm stroking vs baseline	6	3
Kress, 2011	14	Velvet-covered dowel	R arm	Hairy	Stroking vs tapping	0	1
		Hand	R arm	Hairy	Stroking vs tapping	1	2
		Hand	R arm	Hairy	Hand stroking vs other touch conditions	1	1
Krämer et al., 2007	12	Brush	L calf	Hairy	Stroking vs baseline	0	10
Lindgren, 2012	16	Hand	L arm	Hairy	Moving vs stationary stroking	0	2
		Hand	L arm	Hairy	Moving vs all stroking	1	0
Lovero et al., 2009	21	Hand and latex glove	L palm	Glabrous	Main effect real and latex hand stroking	1	3
Lucas et al., 2014	17	Soft brush	R arm	Hairy	Arm vs palm stroking	0	2
Lucas et al., 2014	17	Soft brush	R palm	Glabrous	Experience vs imagery stroking *	2	1
May, 2014	36	Soft brush	L arm	Hairy	Adults vs adolescents 2 cm/s stroking pleasantness interaction	3	5
	38	Soft brush	L arm	Hairy	Adolescents and young adults vs adults stroking	1	0
McCabe, 2008	12	Lotioned glove	L arm	Hairy	Rubbing vs baseline	2	2
			L arm	Hairy	Semantic label rich vs thin	1	0
			L arm	Hairy	All rubbing pleasantness positive correlation	1	0
			L arm	Hairy	All rubbing pleasantness negative correlation	0	2
			L palm	Glabrous	Rubbing vs baseline	0	4
Morrison et al., 2011	13	Soft brush	L arm	Hairy	3 cm/s vs 30 cm/s stroking	1	2
	18	Soft brush	L arm	Hairy	3 cm/s vs 30 cm/s stroking	0	2
Olausson et al., 2002	6	Soft brush	R arm	Hairy	Stroking vs baseline	5	1
Perini et al. 2015	18	Soft brush	L arm	Hairy	Preferred stroking vs baseline (3, 1, 10 cm/s)	0	1
		Soft brush	L arm	Hairy	Preferred arm vs palm	0	1
Perini et al. 2015	18	Soft brush	L palm	Glabrous	Preferred stroking vs baseline (3, 10 cm/s)	0	2
Voos et al., 2012	19	Soft brush	R arm	Hairy	Stroking vs baseline	4	6

Stimulation type, stimulation site, skin type (hairy or glabrous), are indicated, as well as ipsilateral and contralateral to stimulation side for each study. (Asterisk: small-volume correction not defined by whole brain contrasts.)

on mask or region-of-interest (ROI) restriction not defined by whole-brain contrasts within the same data set (marked in Table I).

Discriminate-detect map

BrainMap's Sleuth software (version 2.32) was used to identify all fMRI studies in the BrainMap database (http://www.brainmap.org) that reported activation for innocuous cutaneous tactile stimulation with task instructions to *detect* or to *discriminate* the stimulus, regardless of stimulation site or stimulus type (for example, a task to determine the orientation of a textured gradient, or the presence or absence of a tactile stimulus). The same exclusion criteria as the "affective touch" meta-analysis were applied. The resulting dataset consisted of 25 papers, with a total *N* of 1075 subjects across 91 experimental contrasts, and 683 foci (see Supporting Information for reference list). This dataset provided a representative (rather than exhaustive) sample of studies involving discriminative touch (see Supporting Information Fig. S1).

Activation Likelihood Estimate (ALE) Analysis

ALE analysis is a coordinate-based, probabilistic meta-analytic technique for assessing the co-localization of reported activations across studies [Eickhoff et al., 2009; Eickhoff et al., 2012; Fox et al., 2014; Turkeltaub et al., 2002, 2012]. A first step is the categorization of experiments in the literature, for example by stimulus and/or task. Based on this, whole-brain probability maps are created across the reported foci in standardized stereotaxic space (Talairach or MNI). The present meta-analysis used GingerALE software to create probability maps [www.brainmap.org; Eickhoff et al., 2009; Laird et al.., 2005; Turkeltaub et al.., 2002]. Here, probabilities are modeled by 3D Gaussian density distributions that take into account sample size variability by adjusting the FWHM for each study [Eickhoff et al., 2009]. For each voxel, GingerALE estimates the cumulative probabilities that at least one study reports activation for that locus. This voxelwise procedure generates a statistically thresholded ALE map, assuming and accounting for spatial uncertainty across reports. The resulting ALE values thus reflect the probability of reported activation at that locus, with high values for high probability estimates. This value is tested, using random effects, against the null hypothesis that activation is independently distributed across all studies in the meta-analysis [see Eickhoff et al., 2009, 2012; Turkeltaub et al., 2002, 2012].

Coordinates for all meta-analyses were transformed to MNI space (stereotaxic coordinates of the Montreal Neurological Institute), where necessary. For both meta-analyses here, the Lancaster et al. [2007] transform was applied (Laird et al., 2010); manually in the affective touch loci, and automatically via Sleuth software for the discriminative touch loci. To determine the likely spatial convergence of reported activations across studies, the resulting coordinates were submitted to an ALE analysis using GingerALE software [Laird et al., 2005; Eickhoff et al., 2009; Turkeltaub et al., 2002] and thresholded with a false discovery rate (FDR, pN; Genovese et al., 2002; Laird et al., 2005, wwwpersonal.umich.edu/~nichols/FDR/) of $q < 0.001$ with a 200 mm cluster size threshold. FDR pN does not assume independence and thus provides a strict threshold. Owing to the relatively small sample size of affective touch literature, relatively conservative thresholds were applied. The cluster size threshold applied exceeds the minimum estimated distribution of contiguous volumes across the whole brain [Eickhoff et al., 2012], and is therefore conservative with respect to FDR. Likewise, a conservative mask size was subsequently applied to the resulting statistical maps, to ensure restriction to activations within the brain. The statistical maps were visualized on the Montreal Neurological Institute (MNI) anatomical template using MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron).

RESULTS

ALE Maps

Affective touch map

The "affective touch" meta-analysis yielded 3 clusters with significantly high probability of activation across studies: right posterior insula (Ig2), 40, −14, 8 (max ALE score 0.028); two peaks in a cluster encompassing right posterior insula and adjacent parietal operculum (Ig2/OP1), 46, −26, 22 and 46, −16, 10 (max ALE score 0.039 and 0.032 respectively); and left parietal operculum (OP1), −54, −24, 20 (max ALE score 0.40). See Table II and Fig. 1.

Discrimination map

The detect-discriminate ("discrimination") touch meta-analysis yielded 11 clusters with significantly high probability of activation across studies. These cluster locations are summarized in Table II; see also Fig. 1. The largest of these fell in postcentral somatosensory-related regions: bilateral parietal operculum (OP4), 52, −24, 20 and −58, −20, 14 (max ALE scores 0.51 and 0.038 respectively); and right primary somatosensory cortex (SI), 48, −38, 44 (max ALE score 0.043).

Contrasts

Affective vs. discriminative touch

To discover clusters with a higher likelihood of activation by affective touch compared with discriminative touch, a contrast between the affective and discriminative ALE maps was performed [Eickhoff et al., 2011]. This contrast yielded a single cluster in right posterior insula (Ig2), 42,-14, 8 (max ALE score 3.71). See Table II and Fig. 1.

TABLE II. Clusters revealed by activation likelihood estimate (ALE) meta-analysis for affective touch, discriminative touch, and contrasts

Contrast/cluster	MNI xyz	mm^3	max ALE
Affective touch			
PI Ig2/PO OP3 (2 peaks)	46, −26, 22; 46, −16, 10	2,560	0.039
OP1	−54 − 24, 20	1,512	0.040
PI Ig2	40, −14, 8	728	0.028
Discriminative touch			
OP4/1	52, −24, 20	1,720	0.051
OP4	−58, −20, 14	1,032	0.038
SI	48, −38, 44	944	0.043
Lateral precentral gyrus	−40, −2, 34	928	0.045
AI	32, 20, 4	600	0.037
Pre-SMA	−2, −4, 50	544	0.034
AI	−32, 16, 4	472	0.035
Precentral sulcus	−40, −24, 54	408	0.031
IPL (PFop/SMG)	−54, −26, 30	392	0.030
Posterior superior parietal cortex	38, −62, 42	296	0.026
Lateral inferior frontal	38, 46, 2	232	0.032
Affective > discriminative			
PI Ig2	42, −14,8	304	3.71
Discriminative > affective			
SI	47, −39, 46	760	3.71
Precentral sulcus	−40, −4, 39	760	3.35
SMA	0, −1, 51	480	3.71
Affective ∩ discriminative			
OP3	48, −26, 22	488	0.032
OP1	−54, −20, 18	440	0.031
Affective glabrous skin bias			
OP1	46, −26,22	728	0.02
*Affective hairy skin bias **			
OP1	−54, −24,20	1,248	0.039
OP3	46, −16, 10	1,360	0.032
PI Ig2	−40, −14, 1	424	0.025

All maps thresholded at FDR (pN) $q < 0.001$, minimum cluster size 200 mm. (Asterisk: peak coordinates for "affective touch" clusters at $pN < 0.0001$.).

PI = posterior insula, Ig2 = granular insular area 2, PO = parietal operculum, OP1/3/4 = parietal opercular area 1/3/4, SI = primary somatosensory cortex, AI = anterior insula, pre-SMA = pre-supplementary motor area; IPL = inferior parietal lobule, PFop = opercular region PF.

Discriminative vs. affective touch

To discover clusters with a higher likelihood of activation by discriminative touch compared with affective touch, a contrast between the affective and discriminative ALE maps was likewise performed. This contrast yielded 3 clusters: postcentral gyrus (SI), 47,-39, 46 (max ALE score 3.71); precentral sulcus, −40,-4, 39 (max ALE score 3.35); and supplementary motor area (SMA), 0,-1, 51 (max ALE score 3.71). See Table II and Fig. 1.

Conjunction: affective and discriminative touch

In order to determine whether any areas made a statistically comparable contribution to both affective and discriminative likelihood maps, a conjunction (intersection) analysis was performed. Two clusters contributed to both maps, both in parietal operculum bilaterally: right OP4, 48,-26, 22 (max ALE score 0.032); and left OP4/1, −54,-20, 18 (max ALE score 0.031). See Table II and Fig. 2.

Spatial mapping by skin type

Of the 32 contrasts in the affective touch meta-analysis, 78% involved stimulation of hairy skin, whereas 22% involved stimulation of glabrous skin. To determine whether any region showed disproportionate specificity for glabrous skin inputs sufficient to overcome this sampling bias, the affective touch map was decomposed into separate ALE maps for stimulation on glabrous and hairy skin, applying the same thresholds as the overall map. This revealed a glabrous-specific cluster in right parietal operculum (46,-26, 22; Fig. 2), indicating that glabrous-related foci make a differential contribution to the activation likelihood of this region. The peak coordinates for this cluster coincided with the right PO peak in the overall

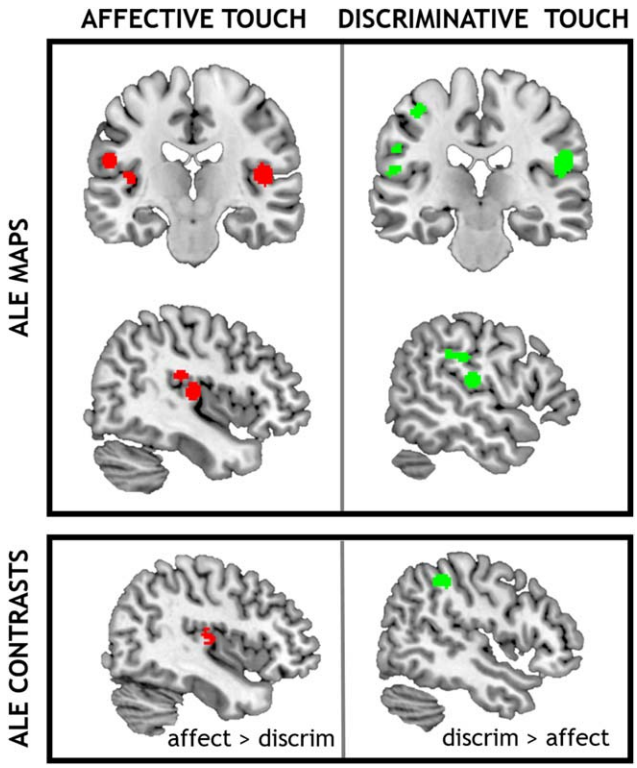

Figure 1.

Activation likelihood estimate (ALE) maps and contrasts for affective and discriminative touch. *Upper left panel*: Clusters in posterior insula (40, −14, 8) and parietal operculum (46, −26, 22; 46, −16, 10) with a significantly high likelihood of activation for touch stimulation associated with positive subjective ratings ("affective touch"). Map reflects reported activations across 17 studies ($N = 291$ unique subjects; see Table I). *Upper right panel*: Clusters in primary (48, −38, 44) and secondary (52, −24, 20; −58, −20, 14) somatosensory cortices with a significantly high likelihood of activation for touch stimulation associated with tactile discrimination tasks ("discriminative touch"). Map reflects reported activations across 25 studies, $N = 1075$. *Bottom left panel*: A cluster in posterior insula (42, −14, 8) had a significantly higher specific activation likelihood for affective touch, as revealed by a contrast between affective and discriminative ALE maps. *Bottom right panel*: A cluster in primary somatosensory cortex (47,-39, 46) had a significantly higher specific activation likelihood for discriminative touch, as revealed by a contrast between discriminative and affective ALE maps (see Table II for other clusters). All maps thresholded at FDR (pN) $q < 0.001$, minimum cluster size 200 mm. All coordinates reported in MNI space.

affective touch map, which fell in a cluster contiguous with the right PI peak (see Table II). It also overlapped with the right cluster for the conjunction between affective and discriminative maps (Table II; Fig. 2). Peak ALE coordinates for the remaining three clusters reflected contributions from hairy skin stimulation and coincided with the right PI peak, the left PI cluster, and the left PO cluster, respectively. See Table II and Fig. 2.

To confirm relative contributions of skin type (hairy, glabrous) for each of these clusters, the percentage of the foci contributions were calculated for hairy and glabrous skin stimulation on clusters resulting from the affective touch map. This was performed by tallying the foci contributions from reported contrasts involving hairy or glabrous stimulation for each cluster on the overall map. To separate the PO and PI-centered peaks from the contiguous right hemisphere cluster, the map was first re-thresholded at a higher threshold of $pN < 0.0001$. All previous clusters survived, with reduced extent (compare cluster sizes on Table II, "Affective touch" with "Affective glabrous skin bias" and "Affective hairy skin bias"). This exploration confirmed that the right PO cluster reflects a differential, disproportionate contribution from glabrous skin stimulation, with 67% contributing foci from glabrous skin stimulation and 33% from hairy skin stimulation. In contrast, 100% of the contributing foci to the right PI cluster were from hairy skin stimulation. 100% of foci contributions to the left posterior insula and left PO clusters also came from studies involving hairy skin stimulation.

Laterality and body part contributions to somatosensory clusters

Similarly to the "affective" dataset, low and/or unequal contributions from different body sides and sites limited the statistical power required for refined tests of somatotopic mapping through direct contrasts. Right-side stimulation was predominant in the "discriminative" dataset (67% right, 12% left, and 21% both/midline). However, laterality and body part contributions to the three postcentral (putatively somatosensory) clusters yielded by the "discriminative" ALE map were examined *post hoc*. Left OP4 (which extended to SI) showed 100% foci contributions from studies in which contralateral body sites were stimulated, with 38% contribution from hand/finger stimulation and 62% contribution from other non-hand sites (*e.g.* arm, foot, leg, wrist, esophagus). Right OP4/1 showed more heterogeneity, with 25% contralateral and 75% ipsilateral contributions, and 32% from hand stimulation and 39% contributions from other sites. The right SI cluster showed 40% foci contributions from studies involving contralateral stimulation and 60% from ipsilateral stimulation, with 100% contributions from studies in which the hand or fingers (glabrous skin) were stimulated. See the Supplementary bibliography for side and site information per study.

Meta-Analytic Connectivity Modeling (MCAM) Analysis

To discover any task-independent, stimulus-independent, and network-wide functional coactivations with the clusters revealed by the affective and discriminative

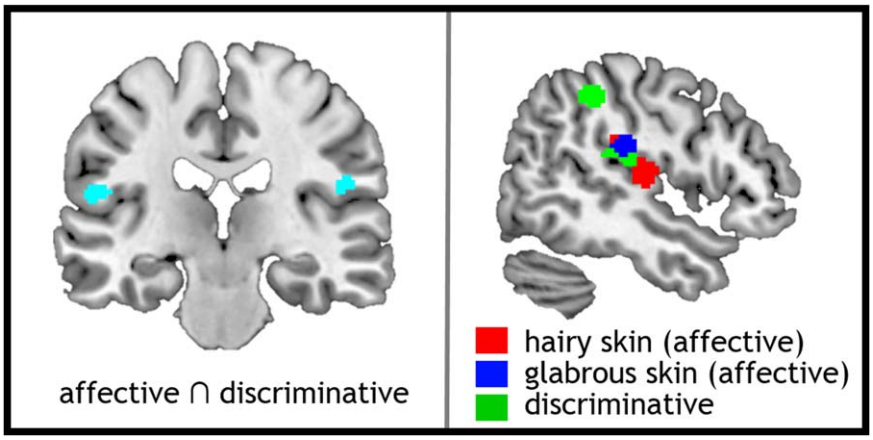

Figure 2.

Selectivity and bias in somatosensory activation likelihood maps for aspects of affective touch. *Right*: Nonselective secondary somatosensory clusters (48, −26, 22; −54, −20, 18) significantly likely to be activated in both affective and discriminative touch paradigms, as revealed by a conjunction of affective and discriminative touch ALE maps. *Left*: Relative contributions of stimulated skin type (hairy, red; or glabrous, blue) to the affective touch ALE map. Despite an overall sampling bias toward hairy skin stimulation in affective touch studies (78%), 67% of the contributing foci in a PO cluster (46, −26, 22) reflect glabrous skin stimulation. All other clusters in the affective touch map reflected a 100% contribution of hairy skin stimulation. Contributions to the right PO cluster (52, −24, 20) from the discriminative touch map (overlaid in green) were exclusively from glabrous skin stimulation. All maps thresholded at FDR (pN) $q < 0.001$, minimum cluster size 200 mm. All coordinates reported in MNI space.

touch contrast maps, two MCAM analyses were performed [Robinson et al., 2010]. Each used the BrainMap database via Sleuth software (http://www.brainmap.org/sleuth/). This analysis included 402 experimental contrasts (total $N = 4913$), yielding 6352 foci. Relative to the whole BrainMap database, the profile of the contributing studies reflected a high contribution from the domain categories of action execution, somatosensation, pain, audition, and sexual interoception (see Supporting Information Fig. S2).

For affective touch, the right PI cluster from the "affective > discriminative" contrast was used as a seed for the MCAM analysis. For discriminative touch, the right SI cluster from the "discriminative > affective" contrast was used as a seed (see Table II). This resulted in two maps of significantly likely task- and stimulus-independent co-activations across studies: an "affective touch" and a "discriminative touch" MCAM map (Fig. 3). These maps were then contrasted using GingerALE software, thresholded at $pN < 0.01$ with a minimum cluster size threshold of 100 mm. A conjunction map was also created, yielding clusters shared by both the "affective" and "discriminative" MCAM maps.

The "affective" MCAM map yielded two large contiguous clusters (13,552 mm^3 in the left hemisphere and 11,848 mm^3 in the right) with significantly high probability of co-activation with the PI seed region. These large bilateral clusters encompassed peaks in posterior and anterior insula, postcentral primary and secondary somatosensory regions, striatum (putamen), thalamus, frontal operculum, and medial prefrontal cortex (dACC, SMA, and pre-SMA). The maximum ALE value for this map was 0.35.

The "discriminative" MCAM map yielded 9 clusters with significantly high probability of co-activation with the SI seed region. The largest (> 1000 mm^3) included: left lateral inferior premotor cortices, inferior parietal cortex (area 2/PF), SMA, and bilateral angular gyri, medial prefrontal cortex. The maximum ALE value for this map was 0.30.

The "conjunction" map between the affective and discriminative MCAM maps yielded 16 clusters. The largest (> 1000 mm^3) of these were: left SII/SI, left SMA, bilateral striate cortex, bilateral AI, putamen, thalamus, right caudate nucleus, and right inferior parietal cortex (area 2/PF). See Fig. 3.

DISCUSSION

The ALE meta-analysis revealed dissociable regions for affective and discriminative tactile stimulation (Fig. 1). Namely, PI is more likely to be activated by touch stimuli with a positive hedonic rating than by tasks involving the detection or discrimination of tactile stimuli. In contrast, SI cortices are more likely to be activated by discriminative than affective touch. Secondary somatosensory cortices in parietal operculum, however, share similar activation likelihoods for both affective and discriminative touch (Fig. 2).

The MCAM analysis indicated that these dissociable regions also involve dissociable general brain-wide networks (Fig. 3). Affective-touch-specific regions are

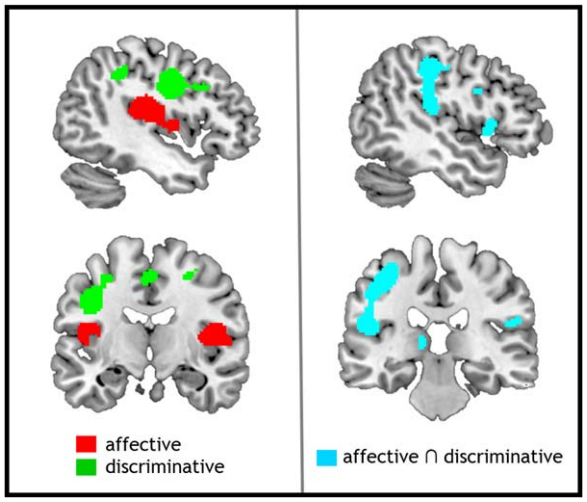

Figure 3.
Task- and stimulus-independent network co-activation likelihoods as revealed by meta-analytic connectivity modeling (MCAM) analysis. *Left panel*: Regions with a significant likelihood of co-activation with the posterior insula seed region defined by the affective > discriminative touch ALE map, encompassing clusters in somatosensory regions and insula (red; see Table III). Regions with a significant likelihood of co-activation with the primary somatosensory seed region defined by the discriminative > affective touch ALE map, encompassing clusters in somatosensory and lateral premotor regions (green; see Table III). *Right panel*: Regions with a significant likelihood of co-activation in common between "affective" and "discriminative" seed regions, encompassing somatosensory cortices, anterior insula, and medial premotor regions. MCAM analysis included 406 fMRI contrasts ($N = 4913$). All maps thresholded at $pN < 0.01$, minimum cluster size 100 mm.

functionally related to insular networks across a range of studies, while regions more likely to respond in discriminative touch tasks consistently co-activate sensorimotor networks. These dissociable networks also overlap in primary and secondary somatosensory cortices, underscoring that affective and discriminative touch recruit common components of a sensory network, despite different activation likelihoods within each tactile dimension.

AFFECTIVE TOUCH AND POSTERIOR INSULA

The ALE meta-analysis indicated that the posterior insula has a high likelihood of selective activation for touch stimuli associated with positive hedonic ratings. The cluster with high activation likelihood for affective touch in this meta-analysis fell in cytological subdivision Ig2 of granular insular cortex. Alongside adjacent granular subregion Ig1, Ig2 has been broadly implicated in a range of somatosensory, visceral, and nociceptive stimulation in humans [Kurth et al., 2010; Segerdahl et al., 2015].

In the past two decades, categorical dichotomies between affective and discriminative touch systems [McGlone et al., 2014; Olausson et al., 2010] have drawn on anatomical and physiological distinctions between tactile information carried via two relatively distinct afferospinal pathways. To a great extent, these pathways correspond to the classical "lemniscal" and "extralemniscal" pathways. Tactile signaling in the well-studied lemniscal pathway is fast-conducting and spatially acute, projecting via the dorsal column of the spinal cord, with major terminations in postcentral primary somatosensory cortex. In contrast, extralemniscal cutaneous tactile signaling involves slowly-conducting, spatially-diffuse coding, with

TABLE III. Task- and stimulus-independent network co-activation clusters revealed by meta-analytic connectivity modeling (MCAM) analysis for affective touch posterior insula (PI) seed region, discriminative touch primary somatosensory (SI) seed region, and contrasts

Contrast/cluster	MNI xyz	mm^3
PI > SI		
Operculoinsular cortex	−49, −20, 16	10,432
Operculoinsular cortex	46, −17, 14	9,688
SI > PI		
Lateral IFC	−39, −2, 35	7,800
Area 2/PF	40, −43, 42	3,824
SMA	0, −3, 52	2,480
Angular gyrus	27, −65, 43	1,136
Angular gyrus	−25, −65, 35	1,088
Precentral gyrus	41, 2, 33	1,048
MFG/IFG	27, −6, 52	880
SMG	−43, −41, 41	816
MFG/IFG	43, 30, 28	792
SI ∩ PI		
ACC	5, 9, 44	200
Postscentral gyrus	−36, −30, 52	10,616
SMA	−6, −10, 56	9,488
Striate cortex	−12, −18, 6	5,144
AI	34, 14, 6	4,520
AI	−32, 14, 10	2,768
Striate cortex	10, 16, 8	1,864
Caudate	20, 0, 8	1,128
Area 2/PF	50, −36, 40	1,128
Cerebellum	20, −48, −22	1,064
Lateral frontal gyrus	34, 36, 30	424
IPL	56, −28, 22	400
MFG	−52, 4, 24	352
SMG	−38, 34, 20	56
Precentral gyrus	42, −8, 46	32
MFG	−42, 32, 20	16
Precentral gyrus	46, −4, 44	16

All maps thresholded at $pN < 0.01$, minimum cluster size 100 mm.
FC = inferior frontal cortex, SMA = supplementary motor area, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, SMG = supramarginal gyrus, ACC = anterior cingulate cortex, AI = anterior insula

predominant projections via the dorsal horn of the spinal cord and major terminations in posterior insula [Andrew, 2010; Craig and Zhang, 2006].

The contribution of the extralemniscal system may be particularly relevant for the affective touch map. This system includes the spinothalamic tract (STT) projections from the dorsal horn of the spinal cord to the brain, via specific suprageniculate thalamic nuclei [Craig and Zhang, 2006; Friedman and Murray, 1986]. This pathway also receives afferent input from skin receptive fields from CTs, a subtype of unmyelinated C afferent nerve which responds to light, moving touch. CT afferents exhibit increased firing frequency to stroking speeds of around 3 cm/s, which are also rated as most pleasant [Ackerley et al., 2014; Löken et al., 2009]. A majority (41%) of projections from the STT pathway have a first cortical synapse in granular insula in the macaque [Dum et al.., 2009]. Consistent with the STT as a CT projection pathway [Andrew, 2010], a relationship between CT afferent stimulation by light, pleasant touch and PI activation in humans has been indicated by evidence from patient studies [Olausson et al., 2002, 2009]. In healthy subjects, PI activation preferentially increases for CT optimal vs. CT-non-optimal stroking speeds [Björnsdotter et al., 2009, 2010; Morrison et al., 2011], which subjects prefer to receive at above-chance levels [Perini et al., 2015].

The correlative relationship between a hedonically-positive subjective experience of touch and CT afferent activity may at least partially account for the high likelihood of PI activation in this meta-analysis. However, it is important to note that velocity-dependent CT firing and hedonic processing may be only indirectly related, or related instead to a common cortical-level variable (for example, specific neurotransmitter release) rather than directly related to each other. Blood-oxygen-level-dependent (BOLD) activations in PI for CT-targeted touch have consistently failed to correlate with touch pleasantness measures [Ebisch et al., 2011; Morrison et al., 2011; Perini et al., 2015]. Likewise, positive tactile ratings do not necessarily imply CT-related signaling. The affective touch ALE map included contributions from stimulation of the palm skin, where CTs are absent, and palm stimulation has also been associated with subjective touch pleasantness [Etzi et al., 2014; Klöcker et al., 2014; Löken et al., 2011; Perini et al., 2015]. Yet whether directly or indirectly, the granular region of posterior insular cortex may have a high probability for activation by affective touch by virtue of a critical role in efficient network-wide processing of affectively-relevant somatosensory information [Lovero et al., 2009; Lucas et al., 2014; Perini et al., 2015].

AFFECTIVE TOUCH AND PARIETAL OPERCULAR REGIONS

The ALE meta-analysis also revealed that somatosensory regions on the PO have a high likelihood of being activated for affective touch. However, this activation was not selective, in contrast to the PI cluster. Rather, PO had a similar activation likelihood for both affective and discriminative touch, as revealed by a conjunction between the affective and discriminative ALE maps.

The clusters with highest shared activation likelihood for affective and discriminative touch fell in two subregions of opercular somatosensory cortex, OP1 and OP3 [Baumgartner et al., 2010; Eickhoff et al., 2006; Kurth et al., 2010]. OP1 lies posterior to OP3, and is the likely human homologue of "classical" secondary somatosensory (SII) cortex in the monkey [Eickhoff et al., 2006]. It responds to innocuous tactile stimuli as well as nociceptive and vestibular stimulation [Zu Eulenburg, 2013]. OP3 lies deeper in the Sylvian fissure and is the likely homologue of the primate "ventral somatosensory" area (VS), which is not functionally well-characterized [Eickhoff et al., 2006; Krubitzer and Kaas, 1992]. It has been speculated that thalamic inputs to SII and PV are modulatory rather than relaying strictly sensory information [Krubitzer and Kaas, 1992; Qi et al., 2002].

Given its known functional characteristics, how might PO cortex contribute to the processing of positively-valenced touch? One possibility is that its role may involve higher-order aspects of discriminative somatosensory information (for example, sensorimotor, visuomotor, spatial, etc, integration) that is processed in parallel with more general affective network-wide evaluative processing. Another possibility is that PO regions could process certain aspects of affective touch, integrated via direct cortico-cortical connections with more selective populations in nearby PI [zu Eulenberg, etc; Cauda et al., 2011; Cerliani et al., 2012; Deen et al., 2010; Ebisch et al., 2010; Wei and Bao, 2013[. Though insular and opercular areas have distinct receptive fields and cytological characteristics, they are closely adjacent and highly interconnected [Evrard et al., 2014; zu Eulenburg et al., 2013].

Like PI, secondary somatosensory cortices on the PO receive major input from the STT, via anatomical projections from ventroposterior inferior (VPI) nucleus, and minor input from the posterior-suprageniculate complex [Po-Sg; Friedman and Murray, 1986]. In nonhuman primates such as the macaque (*Macaca mulatta)* and the marmoset (*Callithrix jacchus*), SII receives major projections from VPI, whereas this is not clearly the case for VS [Qi et al., 2002]. More generally, PO cortex in the macaque receives 29% of STT inputs, in second place behind granular insular cortex [Dum et al., 2009].

The role of human SII cortex in affective touch requires further experimental investigation. For example, quantitative rather than qualitative differences may contribute to its nonselective activation likelihood in this analysis. It is also possible that distinct populations within the operculum have varying degrees of specificity with respect to affective touch processing. A hint of such potential heterogeneity was provided by the decomposition of the affective touch map, which revealed an "island" of

disproportionate contribution from glabrous skin stimulation in the right OP3 peak (Fig. 3).

FUNCTIONAL NETWORKS

If cortical-level relationships between affective and discriminative touch are highly interpenetrating and context-dependent, as is likely, approaching the cortical mapping solely with respect to stimulus and afferent input classes will yield limited insight. Instead, clues to more specific functional differences lie at the network level. The MCAM analysis assessed functional connectivity through identifying statistically robust whole-brain coactivations with the PI and PO clusters, respectively, across studies in the whole BrainMap database. This approach focuses on co-activation likelihood with respect to regions of interest, rather than to domains, stimuli, or tasks of interest, and thus uncovers network relationships with a high degree of generality. Importantly, though, a high co-activation likelihood *across* experiments also implies a high co-activation likelihood *within* a given subset or domain [Toro et al., 2008], such as somatosensation, Indeed, the profile of the MCAM dataset showed a large contribution from studies in the somatosensory domain (Supporting Information Fig. S2).

The MCAM analysis revealed that the PI region identified by the affective touch map and the SI region identified by the discriminative touch map are associated with different network-wide activations. A selective "affective touch" network based on the PI seed involves inter-insula activations bilaterally. This suggests that insular processing is a selective driver of affective touch network activation. In contrast, a selective "discriminative touch" network based on the SI seed involves a wider range of co-activation likelihoods. Many of these fall in premotor regions in inferior lateral frontal, medial frontal, and inferior parietal areas. This implies that SI is pivotal within selective discriminative touch networks associated with sensorimotor processing.

The regional and network activation likelihood differences here can be tentatively viewed in terms of sensorimotor and "somatovisceral" [Norman et al., 2014] systems, respectively. Sensorimotor networks handle complex integration of tactile and motor processing in order to produce goal-directed or exploratory behavior. In primates, distal effectors (hands and feet) and glabrous surfaces (like palms and lips) loom large in sensorimotor processing, as reflected by their disproportionate representation on cortical sensory and motor maps [Penfield and Boldrey, 1937], with scope for dynamic plastic changes during behavior [Schaefer et al., 2005]. Goal-directed and exploratory behaviors are also often visually-guided and occur within peripersonal space, making integrated visual, spatial, and body-centered spatial mapping important. Quick and highly-refined online updating of sensory and motor variables is also crucial for such systems during ongoing behavior. Parietal and premotor circuits are primarily associated with these functions [Gallivan and Culham, 2015].

In contrast, affective touch may involve broad evaluative appraisals that do not necessarily call for millisecond-scale updates. It also involves the integration of different types of information that influence behavior via affective and motivational dispositions, such as preferences [Perini et al., 2015] or hedonic expectations [Ellingsen et al., 2013; Lovero et al., 2009]. It may also involve autonomic and/or visceral efference within the body, such as changes in heartbeat and respiration, or attenuation of threat anxiety [Coan et al., 2006]. The insula's central involvement in the meta-analysis results is consistent with its role in integrating sensory information into higher-level, subjective representations [Craig, 2002], as well as its relationship to autonomic efference [Harrison et al., 2010; Seth and Critchley, 2013]. In particular, the posterior-anterior insula axis may contribute to affective evaluation in terms of salience [Menon and Uddin, 2010; Pessoa, 2014], certainty, and/or risk, as has been postulated for the case of pain [Mouraux et al., 2011; Morrison et al., 2013; Perini et al., 2013].

The MCAM analysis also showed overlap in primary and secondary somatosensory cortices. This suggests that whereas regional activation likelihoods may differ depending on stimulus or behavioral parameters, tactile stimulation recruits somatosensory networks regardless of any affective or discriminative bias. For example, although the affective-touch-associated CT pathway may privilege certain information based on specific ranges of speed [Löken et al., 2009] and temperature [Ackerley et al., 2014] variables, any tactile stimulation anywhere on the body will also activate the large myelinated Aβ afferents that project predominantly to somatosensory cortices.

VALUE AND LIMITATIONS OF ALE META-ANALYSIS

ALE meta-analysis represents an estimation of the probability of spatial co-activations, based on coordinates reported in the literature. It provides a way of applying statistical thresholds to large sets of coordinate data, in order to identify the most consistently-activated and reproducible activation loci across many studies. Its value thus lies in spatially mapping those activations which survive the numerous differences in methodology, experimental paradigms, scanner hardware, analysis techniques and software, and sample sizes, as well as differences in individual functional neuroanatomy and stereotaxic normalization procedures. In the present meta-analysis, PI and PO emerged as robust and reproducible regions implicated in affective touch, and these results can provide *a priori* hypotheses for further experimental testing. But by the same token, ALE and MCAM meta-analysis filter out less robust or infrequently-reported foci that may have a greater dependence on the details of individual studies.

For example, here SI showed no significant likelihood of activation for affective touch. However, it has previously been shown to use visuotactile cues to distinguish between videos of male and female strokers during tactile stimulation of the leg [Gazzola et al., 2012], and it receives high-acuity information from the palm, which is an active "touch-seeking" surface during social interactions [Ackerley et al., 2012; McGlone et al., 2014; Perini et al., 2015]. Further, transcranial magnetic stimulation (TMS) selectively over right SI has slowed reaction times on a go-no go task following affective touch [Bolognini et al.., 2011]. The likelihood of activation for SI may increase as the body of literature grows.

Other areas previously implicated in affective touch networks include the superior temporal gyrus and sulcus [STG and STS; Bennett et al., 2014; Gordon et al., 2011; Kaiser et al., 2015; Singh et al., 2014; Voos et al., 2013]. However, any contribution of STS to affective touch has not been sufficient to produce a high likelihood of activation here. Posterior STS regions implicated in caress stimulation have been engaged by social-specific and biological movement information [Deen et al., 2015], as well as polymodal integration [Beauchamp et al., 2008], sensory imagery [Berger and Ehrsson, 2014], and convergent auditory and visual facial information [Ghazanfar et al., 2008]. Any role of superior temporal areas may thus lie in the integration of tactile information with sensory and spatial information from other modalities. For example, posterior STS might contribute to structuring a coherent representation of the touch by via visuospatial imagery for tactile biological motion [Kilintari et al., 2014].

CONCLUSIONS

The different activation likelihoods for affective and discriminative touch render it improbable that "discriminative" (*e.g.* primary) somatosensory regions are sufficient for affective touch processing. Depending on the context, tactile stimulation may enlist spatially and temporally acute, goal-directed sensorimotor guidance of behavior, or contribute to context-dependent, hedonic or emotional appraisals with influences on bodily regulation. The former is more likely to recruit classical "discriminative" cortical sensory regions and networks; while the latter is more likely to recruit insular and PO cortices. However, this does not imply a wholesale distinction between affective and discriminative touch. Rather, cortical processing of the relevant stimulus and task properties may fall along a continuum, with the categories "affective" and "discriminative" at the extremes. Or, like pain, they may represent experimentally dissociable dimensions despite operating together inextricably during normal processing ["sensory" and "affective" components; Kulkarni et al., 2005; Rainville et al., 1999]. In daily life, tactile interactions with other people may prompt both simultaneously, providing means for not only reaching out and touching someone, but also for feeling and evaluating their touches in return.

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