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Stimulus-Independent Analysis of Affective Touch Using fMRI

--Manuscript Draft--

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Abstract:	Two types of sensory afferents (C-tactile and A-beta) respond to touch. C-tactile afferents respond to slow, gentle touch, which has been connected to "social brain" activation in neuroimaging studies 2. Viewing another person receiving this affective touch recruits a similar network of brain regions as when touch is experienced 3. This suggests that some aspects of touch processing do not require physical sensation. In particular, we aimed to investigate whether the affective component is associated with the physical sensation or whether the same brain response can be seen independent of all external stimulation. We built upon an established protocol, which dissociates between CT (affective) and Aβ targeted touch by comparing touch to the arm (hairy skin with CT afferents) and palm (lacking CT afferents). Here, we expanded this by adding a condition independent of all external stimuli: imagining the sensation of touch to each region. This created a four-condition block-design, comparing CT- vs. non-CT touch, imaging and experiencing tactile stimuli.
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New Haven, December 8, 2014

The Editors
Journal of Visualized Experiments

Dear Editor,

We ask you to consider for publication the enclosed manuscript titled, "**Stimulus-Independent Analysis of Affective Touch Using fMRI**" in the *Journal of Visualized Experiments*. Touch is a crucial facet of social interactions. Both direct contact through touch and witnessing others being touched provides valuable information about interpersonal relationships. Understanding how the affective components of touch are imbued will allow us to better understand nonverbal communication in humans (either healthy or when this process is disrupted). Some aspects of sensory processing can be replicated by imagining the stimulus (Grossman and Blake, "Brain activation evoked by inverted and imagined biological motion", *Vision Research*, 2001; Yoo et al., "Neural substrates of tactile imagery: a functional MRI study", *NeuroReport*, 2003). Our method builds upon previous work and allows researchers the ability to compare experiencing and imagining both C-tactile afferent targeted (affective) and non-CT-targeted touch.

While this protocol aims to study affective touch absent of vision, the methodology is best understood when visualized. India Morrison found that watching other people receiving slow, caress-like touch elicits similar brain activity to actually experiencing the same touch (Morrison et al., "Vicarious responses to social touch in posterior insular cortex are tuned to pleasant caressing speeds", *J Neurosci*, 2011). When describing touch experiments, technical descriptions of affective touch are often not well understood. However, as with Dr. Morrison's work, watching a demonstration of CT-targeted vs. non-CT-targeted touch resonates more strongly with viewers. JoVE's unique format capitalizes on our ability to understand social touch through vision, which allows for a better understanding of this method.

This manuscript was written by Molly Lucas. The experimental protocol was designed by Molly Lucas, Laura Anderson, Kevin Pelphrey, and Martha Kaiser. Data for the representative results was analyzed by Molly Lucas, Laura Anderson, Danielle Bolling, Kevin Pelphrey, and Martha Kaiser. JoVE Behavioral Editor, Emma Pennock, assisted during the submission process.

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Title:
Stimulus-Independent Analysis of Affective Touch Using fMRI

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Short Abstract:
C-tactile (CT) afferents respond to caress-like touch, which has been found to activate "social brain" regions [1]. Using fMRI, we compared neural responses of experiencing and imagining CT-targeted vs. non-CT-targeted touch to explore how the affective component of social touch is imbued.

Long Abstract:
Two types of sensory afferents (C-tactile and A-beta) respond to touch. C-tactile afferents respond to slow, gentle touch, which has been connected to "social brain" activation in neuroimaging studies [2]. Viewing another person receiving this affective touch recruits a similar network of brain regions as when touch is experienced [3]. This suggests that some aspects of touch processing do not require physical sensation. In particular, we aimed to investigate whether the affective component is associated with the physical sensation or whether the same brain response can be seen independent of all external stimulation. We built upon an established protocol, which dissociates between CT (affective) and Aβ targeted touch by comparing touch to the arm (hairy skin with CT afferents) and palm (lacking CT afferents). Here, we expanded this by adding a condition independent of all external stimuli: imagining the sensation of touch to each region. This created a four-condition block-design, comparing CT- vs. non-CT touch, imaging and experiencing tactile stimuli.

Introduction:
This method aimed to explore affective processing of touch absent of physical stimulus to better understand how the social component is attributed to touch. This technique combined two different tracks of research: comparing CT-targeted to non-CT-targeted touch and finding common activation from either experiencing or imagining touch. The results of the original study using this design have been published in Lucas *et al.* [4].

A unique component of CT targeted touch is that it has been associated with "social brain"[1] regions such as the medial prefrontal cortex, superior temporal sulcus, amygdala, posterior insula, and orbitofrontal cortex [2,3,5-7]. It is thought that these areas reflect processing related to social and communicative aspects of touch during human interactions [8]. Neuroimaging studies utilize two main paradigms to compare CT- to non-CT-targeted touch. Present in hairy skin, CT afferents respond to slow, gentle touch [9,10]. To selectively stimulate these afferents, the experimenter can vary either the velocity (CT afferents selectively respond to touch at a rate of 1-10 cm/s [11]) or location on the body, as CT afferents are found only in hairy skin [11]. Both techniques have been used with comparable results [2,3,5-7,11]. Recently, Voos and colleagues used the velocity method (CT afferents respond to 8 cm/s but not 32 cm/s) to replicate findings of an earlier study, which used the location method (forearm containing and palm lacking CT afferents) [2,6]. Through either method, CT targeted touch elicited greater activation in the superior temporal sulcus, medial prefrontal cortex, and amygdala. While the results are comparable between these studies, we believe varying location allows for greater consistency across subjects, as the slower velocity is easier to maintain for the experimenter. Here, we utilized the later, as it is easier for participants to imagine different regions being touched than a very specific velocity of touch.

Imagining visual stimuli has been found to show patterns of activation similar (though diminished) to actually viewing the same image [12,13]. Recently, this technique has been applied to touch studies. Imagining touch to the back of the hand can elicit similar somatosensory activation as experiencing being touched [14]. Descriptive words can change subjective experiences of being touched [15], suggesting that this affective component can be altered without any change in the physical stimulus. This is further supported by neuroimaging studies that show a similar pattern of activation while subjects view or experience affective touch [3]. In light of this study and of mirror neuron research, we questioned whether vision was required to "replace" the physical touch. This led to our combination of CT touch and imagination paradigms in order to assess affective touch absent of all external stimuli, including vision.

By combining these two approaches, we can study the neural response to a physical sensation absent of all physical stimulation. This method is particularly efficient in the use of four conditions to gain a broader understanding of how different aspects of touch contribute to the overall neural processing. We were able to evaluate various hypotheses using the same data set, as we were able to compare either CT to non-CT touch, experiencing vs. imagining, or combinations, such as experiencing and imagining CT-targeted touch.

Protocol:

The following procedure was approved by the Human Investigation Committee at Yale University.

1. Pre-Scan

1.1. Pre-screen subjects over the phone prior to visit.

1.1.1. Include subjects that are right-handed males between ages 18 and 25 to minimize variability. Exclude subjects for contraindications to fMRI such as medical conditions (i.e., cardiac pacemaker, electronic implants, prosthesis, metal implants), piercings that cannot be removed and participants that have worked with metal (to avoid metal shavings in eyes). Obtain written and verbal informed consent from each participant on the day of the scan.

1.2. Have participants complete a health screening form to ensure they did not have any medical conditions, which would prevent them from safely entering the scanner. Ask subjects to remove all metal from their person. Direct subjects to pass through a metal detector to verify this.

1.3. Measure an 8 cm area on the participant's right forearm with the palm facing upwards and mark this area using a water-soluble marker. Measure and mark a 4 cm area on the participant's right palm. During experience conditions, brush these areas with a 7 cm wide watercolor paintbrush. The soft bristles allow for consistent light pressure to be applied.

2. Pre-Scan Practice

2.1. Provide verbal instructions for each block to ensure clarity. Instruct subjects to focus on the touch during Experience blocks. Instruct subjects to imagine the touch during Imagine blocks. Emphasize that the attention should be to the sensation and not to imagine the experimenter performing the action. This specification aims to minimize the variance between conditions.

2.2. Practice each experimental condition (experiencing arm touch, imagining arm touch, experiencing palm touch, imagining palm touch) to ensure comprehension.

2.2.1. Blindfold the participant. Brush the marked arm area at a rate of 8 cm/s for 6 seconds. Rest for 12 seconds. Ask the participant to imagine the sensation they just experienced. Alert the participant at the end of 6 seconds that the block has ended. Rest for 12 seconds.

2.2.2. Brush the marked palm area at a rate of 8 cm/s for 6 seconds. Rest for 12 seconds. Ask the participant to imagine the sensation they just experienced. After 6 seconds, conclude the practice. Rest for 12 seconds.

2.2.3. Remove the participant's blindfold. Ask the subjects whether they understand the instructions. Repeat directions if necessary.

3. Pre-Scan Ratings

3.1. Ask subjects to rate pleasantness of experienced arm touch using a Likert Scale (1 = not pleasant at all; 2 = slightly pleasant; 3 = moderately pleasant; 4 = very pleasant; 5 = extremely pleasant). Ask subjects to rate pleasantness of palm touch using the same scale.

4. fMRI Scan

4.1. Pre-Scan Procedure

4.1.1. Ask the subject again to check for and remove any metal objects. Bring the participant into the room with the fMRI scanner, and ask subject to lie on the table. Provide a blanket or cushion under subject's legs to ensure comfort during the scan.

4.1.2. Provide earplugs to dampen sounds of the fMRI and headphones to allow the experimenter to communicate with the subject via an intercom system. Blindfold the subject and secure his head in place with padding.

4.1.3. Attach the head coil. Check that participant's head is aligned properly, and move participant into the scanner. Ensure right arm is placed (palm up) such that experimenter can easily access both marked arm and palm areas without moving the subject.Using the intercom, establish that the sound is working, check that subject is comfortable, and remind him to remain still throughout the scan.

4.2. Collect anatomical and functional images using the 3T fMRI scanner.

4.2.1. Anatomical images

4.2.1.1. Conduct a localizer scan. Next, record high-resolution T_1-weighted anatomical images using an MPRAGE structural sequence (time repetition [TR] = 1900 ms; time echo [TE] = 2.96 ms; field of view [FOV] = 256 mm; image matrix = 256 mm^2, voxel size = 1 X 1 X 1 mm, 160 slices).

4.2.2. Functional images

4.2.2.1. Record whole-brain functional images using a single-shot, gradient-recalled echo planar pulse sequence (TR = 2000 ms; TE = 25 ms; flip angle = 60°; FOV = 220 ms), which is sensitive to blood-oxygenation-level-dependent (BOLD) contrast. Create an image matrix = 64 mm^2, voxel size = 3.4 X 3.4 X 4.0 mm, 34 slices. Acquire 306 successive brain volumes per run.

4.3. Alert participant that the experimenter will be entering the room to begin the study. Initiate the scan simultaneously with the software containing the experimental paradigm. Experimental program includes pre-recorded verbal instructions for participants, as well as silent countdown for experimenter to pace brushing velocity.

4.4. Counterbalance subjects so that half receive Arm blocks (Experience followed by Imagine) first and half receive Palm blocks (Experience followed by Imagine). Use the same experimenter to brush all participants to minimize variability. Test the four conditions using a block design. Follow the computer prompts to repeat each block 8 times and repeat the following sequence twice.

4.4.1. Experience Arm Touch Block

4.4.1.1. Listen to 6 seconds of pre-recorded verbal instruction: "You are entering an arm block. Focus on the touch." While a tone (identical in each condition) plays for 6 seconds, brush the pre-marked area on the subject's right forearm back and forth in the proximo-distal orientation at a consistent rate of 8 cm/s. Use the countdown on the projector screen (hidden from the blindfolded participant) as a metronome to keep constant pace of brushing. Ensure the full brush makes contact with the skin, and maintain consistent light pressure. Rest 12 seconds. Repeat 8 times.

4.4.2. Imagine Arm Touch Block

4.4.2.1. Listen to 6 seconds of pre-recorded verbal instruction: "Now, imagine how that same touch feels when you hear the cue." Listen to the tone play for 6 seconds. Rest 12 seconds. Repeat 8 times.

4.4.3. Experience Palm Touch Block

4.4.3.1. Listen to 6 seconds of pre-recorded verbal instruction: "You are entering a palm block. Focus on the touch." While a tone plays for 6 seconds, brush the pre-marked area on the subject's right palm back and forth in the proximo-distal orientation at a consistent rate of 8 cm/s. Use the countdown on the projector screen (hidden from the blindfolded participant) as a metronome to keep constant pace of brushing. Rest 12 seconds. Repeat 8 times.

4.4.4. Imagine Palm Touch Block

4.4.4.1. Listen to 6 seconds of pre-recorded verbal instruction: "Now, imagine how that same touch feels when you hear the cue." Listen to the tone play for 6 seconds. Rest 12 seconds. Repeat 8 times.

4.5. Scan for 20.13 minutes. Discard the initial 6 seconds of rest during analysis.

4.6. Post-Scan Procedure

4.6.1. Once the scan has concluded, remove participant from the scanner. Allow subject to remove the blindfold, and escort him from the scanner room.

4.6.2. Post-Scan Ratings

4.6.2.1. Ask participant whether if he was able to focus during imagine conditions or if his mind wandered during the task. Exclude subjects that slept during the scan from analysis.

4.6.2.2. Ask subject to rate difficulty of imagining arm touch using a Likert Scale (1 = not difficult at all; 2 = slightly difficult; 3 = moderately difficult; 4 = very difficult; 5 = extremely difficult). Ask subject to rate difficulty of imagining palm touch using the same scale.

4.6.3. Return metal items to participant. Provide payment for the subject's participation in the study, and allow the subject to depart.

5. Data Processing

5.1. Analyze data using analysis software package (here, BrainVoyager QX was used). Create a new FMR project using DICOM files (standard for most MRIs) uploaded from the scanner.

5.2. Preprocess FMR data using slice scan time correction (cubic spline interpolation, interleaved slice scanning order), 3D motion correction (trilinear / sinc interpolation), spatial smoothing (full-width half-maximum 4-mm Gaussian kernel), and temporal filtering (high-pass GLM Fourier basis of 2 cycles / time course). Exclude subjects with head motion greater than 3mm or 3° in any direction.

5.3. Co-register anatomical and functional brain data for each subject. Create and attach a time course plot based on the experimental design.

5.4. For each individual subject, perform a general linear model (GLM) based analysis using this stimulation protocol file. Identify each experimental condition as a separate boxcar function, using a value of 1 for each condition and 0 for each non-condition. Include the 6 parameters of motion as regressors that are predictors of no interest. Convolve regressors using a double-gamma hemodynamic response function (HRT).

5.5. Normalize each subject's data to Talairach space. Using the Montreal Neurological Institute template brain as a mask, run a group-level random-effects GLM analysis on all subjects.

5.6. Analyze contrasts of interest using a threshold of $p < 0.05$. Correct for multiple comparisons using a cluster threshold. Establish cluster threshold using a Cluster-level Statistical Threshold Estimator plug-in. Use 1000 iterations of a Monte Carlo simulation to find the relative frequency of cluster sizes for each contrast (set threshold at $\alpha < 0.05$).

5.6.1. Create a region of interest (ROI) using anatomically defined insula regions (anterior and posterior) previously established through a study of functional connectivity in this region [16].

Representative Results:

This study exemplifies how combining the CT-targeted touch paradigm with the sensory-independent conditions of imagining physical sensation allows us to better understand the affective component of a sensory mechanism. This procedure provides the flexibility to analyze various aspects of the data using multiple methodologies.

Highlighted in Figure 1, the data was analyzed using an anatomically defined region of interest (ROI) mask. The mask was created through a separate study of functional connectivity in the insula[16]. Within this region, we found a functional dissociation between the anterior and posterior insula bilaterally. Greater activation was seen in the posterior insula during the experience of touch (Experience Arm + Palm > Imagine Arm + Palm). The anterior insula response was seen during imagined touch (Imagine Arm + Palm > Experience Arm + Palm).

Using a separate analysis, we then sought overlapping active regions between experiencing and imaging CT-targeted touch, which can be see in in Figure 2. A two-level process was used to find overlapping regions selectively active during affective touch for both experiencing and imagining touch. The contrast Experience Arm >

Experience Palm was used to create a mask of the brain regions that have greater activation during CT-targeted vs. non-CT-targeted touch. The contrast Imagine Arm > Imagine Palm within this mask marks brain regions that overlap with those experience affective touch regions but show the same differential activation through imaging alone. The brain regions found in this mask have the same pattern of activation to both experiencing touch and stimulus-independent imagining of affective touch. Regions found are the right amygdala, right anterior insula, left temporal pole, and bilateral middle temporal gyri.

Figure legends:

Figure 1. Experience (Arm + Palm) > Imagine (Arm + Palm) contrast is shown using a bilateral insula mask (p = 0.05, k = 20). Left frame: sagittal view of the right insula. Right frame: axial view of the bilateral insula. Orange indicates Experience > Imagine, and blue denotes Imagine > Experience. Insula region was anatomically defined [16]. Modified from Lucas *et al.* [4].

Figure 2. Imagine Arm > Imagine Palm contrast is shown within Experience Arm > Experience Palm mask (p = 0.05, k = 10). Re-print with permission from Lucas *et al.* [4].

Table legends:

Table 1. Contrast of Experience > Imagine using an Insula Mask. Coordinates are reported in Talairach space and represent voxel peak activation within the region. Region extents are reported in structural voxels ($1mm^3$), and statistics correspond to peak voxel. Re-print with permission from Lucas *et al.*[4].

Table 2. Imagine Arm > Palm contrast within Experience Arm > Palm mask (p = 0.05, k = 10). Coordinates are reported in Talairach space and represent voxel peak activation within the region. Region extents are reported in structural voxels ($1mm^3$), and statistics correspond to peak voxel. Re-print with permission from Lucas *et al.* [4].

Discussion:

Using this method, our experience conditions replicated previous touch studies, finding greater activation in the mPFC pSTS, and the amygdala for CT-targeted than non-CT-targeted touch (Experience Arm > Experience Palm contrast). Looking at the insula region of interest, we found a functional dissociation where greater activation was seen in the posterior insula during experienced touch (Experience > Imagine contrast) and the anterior insula showed greater activation during imagined touch (Imagine > Experience contrast). A component of this difference may be due to the difference in bodily location, not just the differences from CT versus non-CT touch. However, experience CT touch results (Experience Arm > Experience Palm) are consistent not only with a study of CT touch using this varied location method but also with a study that varied the velocity of brushing on the forearm; therefore, we do not believe the differing locations contributed significantly to our findings.

This procedure allows for a more complete analysis of the affective component of touch. Previous methods have explored differences in the neural response to CT-targeted and non-CT-targeted touch through the same brushing paradigm utilized here [2,6]. It has been shown that people can elicit similar somatosensory activation by imagining touch more generally [14]. A previous study by Morrison and colleagues looked at vicarious responses to social touch through watching others being touched [3], suggesting that the affective component of touch, not just the somatosensory aspects, can be replicated without the physical action. Our method combines aspects of these prior works allowing us to explore how imagining the sensory experience of CT-targeted touch elicits activation in social regions of the brain.

A significant aspect of this method is how, because of the multiple conditions (CT vs. non-CT touch, experience vs. imagine), we were able to analyze the same data set in numerous ways to address multiple hypotheses and gain a better understanding of how different facets of touch interact. We utilized this method for two purposes: first, we found regions showing a differential response for CT-targeted (arm) and non-CT-targeted (palm) touch, which demonstrated regions selectively actively during affective touch. Second, we explored how the affective component of this type of touch is integrated with the sensory experience.

Two critical aspects of the protocol were the velocity of the brushing speed and the clarity in instructing the participant for the imagine blocks. To keep the brushing consistent, one experimenter performed this task on all participants. A projector screen with a visual countdown (unseen by participants) was used as a metronome to pace the brushing. CT afferents will not be stimulated if brushing velocity is too fast, making it crucial to keep this step consistent and accurate across all subjects. The most difficult aspect to control for was the attention to task during the imagine conditions. Prior to the scan, participants underwent a practice session and were given thorough instructions. Subjects were asked to rate difficulty of imagining and report if they fell asleep or let their mind wander in order to ensure focus during the experiment. If participants were unable to focus on the imagination task, we would not see significant results consistent with our hypothesis. The ratings of difficulty imagining were a potential troubleshooting measure to compare activation patterns in subjects that had little or no difficulty imaging compared to those that found it incredibly difficult to maintain task attention. This would allow us to determine whether results were seen in the focused group but not the unfocused group. We did not resort to this troubleshooting technique in our study, as all subjects reported little difficulty in imagining tasks (no significant difference between arm and palm) and there was very little variance between subject ratings.

A potential future direction building on this technique would be to focus on whether stronger imaginative capacity elicits activation in the posterior insula comparable to that associated with the experience of being touched. This would suggest that individual difference in subjective experience could better recreate a physical sensation in the mind. The two major limitations to determining this were 1) that we did not have a measure of imaginative ability to correlate with the activation seen in the anterior insula, and 2) the fMRI analysis used did not allow us to infer directionality of the functioning between the anterior and posterior insula. Our findings were consistent with work studying the nerve afferents, which suggests that anterior insula is involved in affective feelings of body states, and posterior insula is more directly connected to the nerves and therefore signals from the physical stimulus [17]; however, the current method cannot prove that greater activation in the anterior insula specifically leads to greater activation in the posterior insula.

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Disclosures:
The authors declare no conflict of interest.

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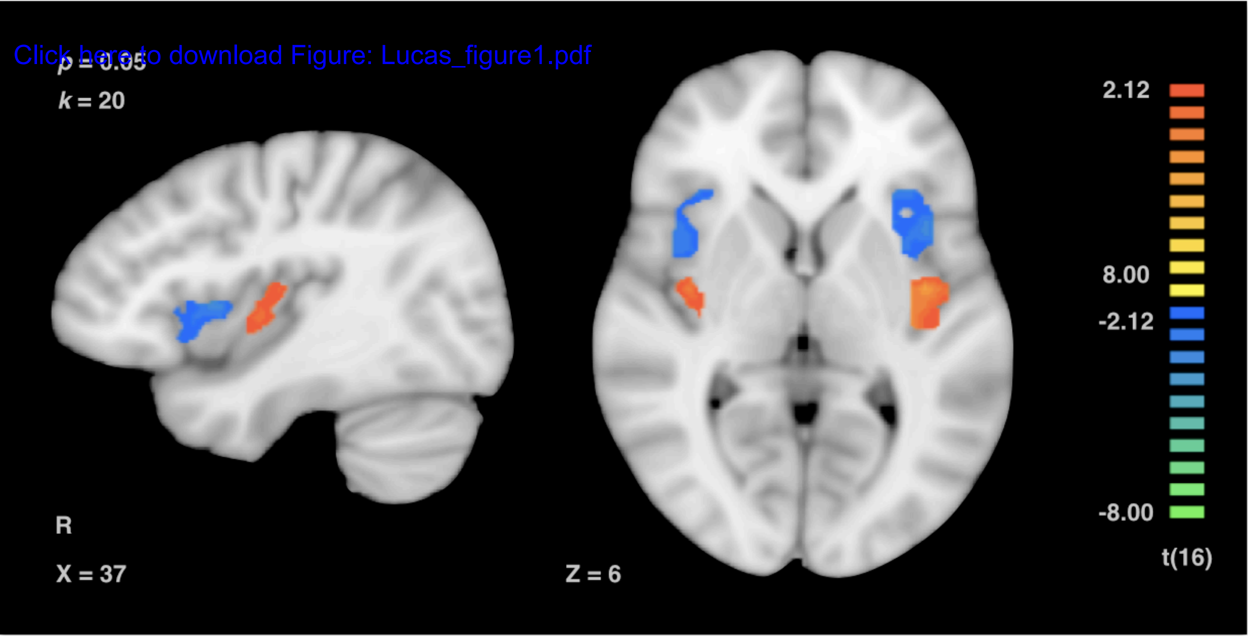

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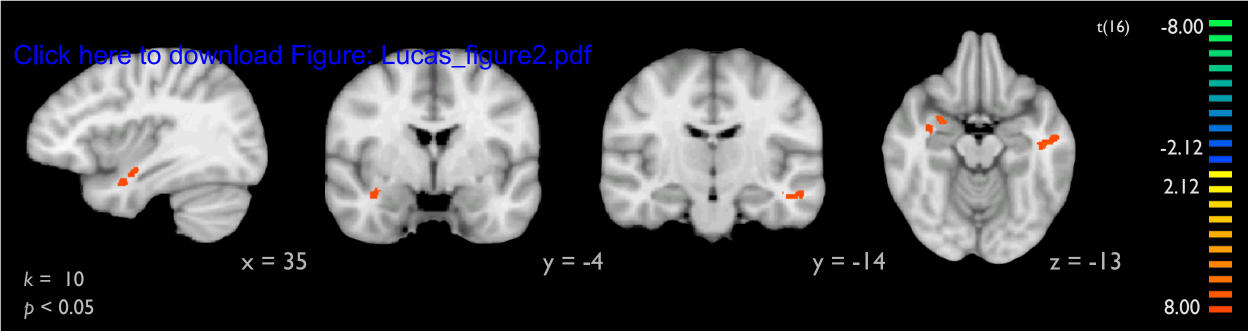

Table1
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Region	Peak X	Peak Y	Peak Z	*t*	*p*	Number of Voxels
R Posterior Insula	36	-7	4	4.26	<0.001	869
R Anterior Insula	30	23	0	-3.89	<0.01	1545
L Anterior Insula	-40	11	7	-4.17	<0.001	2466
L Posterior Insula	-35	-16	13	7.21	<0.0001	2470

Table2
Click here to download Table: Lucas_table2.xls

Region	Peak X	Peak Y	Peak Z	*t*	*p*	Number of Voxels
R Middle Temporal Gyrus, R Amygdala, & R Anterior Insula	39	-2	-20	4.08	<0.001	700
L Middle Temporal Gyrus & L Temporal Pole	-51	-10	-14	4.23	<0.001	312

Excel Spreadsheet- Table of Materials/Equipment

Click here to download Excel Spreadsheet- Table of Materials/Equipment: Lucas_materials_revised.xls

Material	**Description**
Watercolor paintbrush	7 cm wide, soft bristle
Blindfold	
Water-soluble marker	
BrainVoyager QX	Brain Innovation, Maastricht, the Netherlands
3T fMRI	Siemens MAGNETOM Trio

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Article Title: Stimulus-Independent Analysis of Affective Touch

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We thank the reviewers for your helpful comments. We believe each has been addressed in the manuscript and a response to each comment is written below.

Editorial comments:

1.In the SW doc: Please make sure the Step # corresponds to a step in the protocol. Make sure the text in the SW doc aligns exactly with the protocol step. Please include all highlighted steps in the SW doc, but not the unhighlighted material.

This has been corrected in the SW document.

2. Results: Please transfer the first parts of the 2nd and 3rd paragraphs to the figure legend. Discuss what the figure shows in the main body of the Results.

These sections were transferred to the legend, and the results section was rewritten.

3. Please keep the editorial comments from your previous revisions in mind as you revise your manuscript to address peer review comments. For instance, if formatting or other changes were made, commercial language was removed, etc., please maintain these overall manuscript changes.

The original changes were maintained throughout this editing.

4. Please take this opportunity to thoroughly proofread your manuscript to ensure that there are no spelling or grammar issues. Your JoVE editor will not copy-edit your manuscript and any errors in your submitted revision may be present in the published version.

The manuscript was proofread for spelling and grammar.

5. If your figures and tables are original and not published previously, please ignore this comment. For figures and tables that have been published before, please include phrases such as "Re-print with permission from (reference#)" or "Modified from.." etc. And please send a copy of the re-print permission for JoVE's record keeping purposes.

This was corrected in the manuscript.

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All available DOIs were added to the references.

Reviewers' comments:

Reviewer #1:
The authors propose to have a video produced which depicts a procedure for using functional magnetic resonance imaging to investigate the neural correlates of experienced and imagined, affective and non-affective, touch.
The proposed video will comprise a timely and novel contribution to the literature. I have just a few comments for clarification:

Line 306 mentions that activation within an insula region of interest (ROI) will be investigated. Can the authors state, in the methods section, how the ROI will be defined?

This description was added as step 5.6.1 as follows:

> **Create a region of interest (ROI) using anatomically defined insula regions (anterior and posterior) previously established through a study of functional connectivity in this region [14].**

In the discussion, where the authors comment on CT-targeted and non-CT-targeted touch they should refer to the relevant contrasts from the results section (for clarity). In addition they should highlight that a component of this activation might reflect differences in the bodily location of touch stimulation, not just CT versus non-CT differences.

This was corrected in the manuscript.

A note about the differences in location was added to the discussion as follows:

> **A component of this difference may be due to the difference in bodily location, not just the differences from CT versus non-CT touch. However, these results are consistent not only with a study of CT touch using this varied location method but also with a study that varied the velocity of brushing on the forearm; therefore, we do not believe the differing locations contributed significantly to our findings.**

It would be useful if the authors could compare and contrast their approach to CT-targeting with the approach of varying velocity.

The following was added to the introduction to address this issue:

> **To selectively stimulate these afferents, the experimenter can vary either the velocity (CT afferents selectively respond to touch at a rate of 1-10 cm/s) or location on the body, as CT afferents are found only in hairy skin [7]. Both techniques have been used with comparable results [2,3,7-9]. Recently, Voos and colleagues used the velocity method (CT afferents respond to 8 cm/s but not 32 cm/s) to replicate findings of an earlier study, which used the location method (forearm containing and palm lacking CT afferents) [2,8]. Through either method, CT targeted touch elicited greater activation in the superior temporal sulcus, medial prefrontal cortex, and amygdala. While the results**

are comparable between these studies, we believe varying location allows for greater consistency across subjects, as the slower velocity is easier to maintain for the experimenter. Here, we utilize the later, as it is easier for participants to imagine different regions being touched than a very specific velocity of touch.

Reviewer #2:
Manuscript Summary:
This is an interesting methods article describing use of real versus imagined touch to elicit brain activation in different areas of the insula. The detailed methods seem useful to others trying to create touch-related fMRI studies. In fact, while much of the focus is on methods comparing real versus imagined touch, I recommend the authors place more emphasis simply on the difficulty of examining response to touch in the scanner, as it can be quite difficult to standardize and time correctly. Other minor recommendations are outlined below.

Major Concerns:
N/A

Minor Concerns:
Abstract: the authors sometimes switch between past and present tense…please be consistent.

This correction was made.

Introductions: Can the authors be more specific about "patterns of activation" in response to touch? What brain areas usually respond to touch? Are there different areas that respond to CT touch versus other touch? I know this is a methods article but it still seems relevant if the purpose of the method is to elicit brain response in different areas.

This information has been added to the introduction:

> **A unique component of CT targeted touch is that it has been associated with "social brain"[1] regions such as the medial prefrontal cortex, superior temporal sulcus, amygdala, posterior insula, and orbitofrontal cortex [2,3,5-7]. It is thought that these areas reflect processing related to social and communicative aspects of touch during human interactions [8].**

Methods
2.1.1 It's not clear what the difference is in instructing subjects to focus on the "sensation of being touched" during Experience compared to the "sensation of the touch" in the Imagine blocks? Are they supposed to be focusing on the same or different things?

The goal of this distinction was only to emphasize that the person focus on the feeling and not try to imagine the action of the person interacting with them. The imagination should be focused on touch not visual imagery. This section was re-written to clarify as:

Instruct subjects to focus on the touch during Experience blocks. Instruct subjects to imagine the touch during Imagine blocks. Emphasize that the attention should be to the sensation and not to imagine the experimenter performing the action. This specification aims to minimize the variance between conditions.

4.5.1.1. The authors clearly put a lot of consideration into how to keep brushing speed consistent. What was done to keep pressure consistent? And what kind of pressure was used? For example, a lighter pressure would feel more like a tickling sensation.

There is less variation in pressure when using the watercolor brush than one would predict. The bristles are soft enough that as long as full contact is made with the skin, the pressure is fairly consistent. Participants were asked to describe the sensation without prompts following the experiment, and most used adjectives such as "tickles, soft, smooth".

A description of this was added to the manuscript in step 1.4:

The soft bristles allow for consistent light pressure to be applied.

A second description was added to the manuscript in step 4.5.1.1:

Ensure the full brush makes contact with the skin, and maintain consistent light pressure.

Figures:
I noticed that the figures are reprinted with permission from Oxford University Press. Has this study been previously published in another format? If so, this should be referenced to/cited in the introduction.

The study in which the experience/imagine methodology was created is published in Cerebral Cortex. The representative results are a component of the results of that study.

This reference has been added to the introduction as follows:

The results of the original study using this design have been published in Lucas *et al.* [4].

The citation of the original paper is as follows:

Lucas, M. V., Anderson, L. C., Bolling, D. Z., Pelphrey, K. A. & Kaiser, M. D. Dissociating the Neural Correlates of Experiencing and Imagining Affective Touch. *Cereb Cortex*, doi:10.1093/cercor/bhu061 (2014).

Discussion:

Line 361 "One study looked at" It's unclear if the authors are referring to their own study or a previous study? Can you clarify?

This previous study is not referring to our own study but one by India Morrison's group.

The following is the citation for her paper:

> **Morrison, I., Bjornsdotter, M. & Olausson, H. Vicarious responses to social touch in posterior insular cortex are tuned to pleasant caressing speeds. *J Neurosci* 31, 9554-9562, doi:10.1523/JNEUROSCI.0397-11.2011 (2011).**

This has been clarified in the manuscript as:

> **A previous study by Morrison and colleagues looked at vicarious responses to social touch through watching others being touched [3], suggesting that the affective component of touch, not just the somatosensory aspects, can be replicated without the physical action.**

Line 397 there is a typo: it should read, "focus ON whether"

This correction was made.

While the focus of the discussion is on the methods, it again seems worth at least mentioning the brain areas activated, e.g., that this method effectively activated different areas of the insula. As it is, it is confusing that the insula is not mentioned until the final paragraph of the discussion.

A summary of the results was added to the discussion:

> **Using this method, our experience conditions replicated previous touch studies, finding greater activation in the mPFC pSTS, and the amygdala for CT-targeted than non-CT-targeted touch (Experience Arm > Experience Palm contrast). Looking at the insula region of interest, we found a functional dissociation where greater activation was seen in the posterior insula during experienced touch (Experience > Imagine contrast) and the anterior insula showed greater activation during imagined touch (Imagine > Experience contrast).**

Additional Comments to Authors:
N/A

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