NEURAL CORRELATES OF TACTILE LOCALIZATION IN EXTERNAL AND SOMATOTOPIC FRAMES OF REFERENCE

by

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DEDICATION

I dedicate this thesis to my parents Fabián Raigosa and Libia Posada. Thank you for your infinite love and for always watching over me. You are everything.

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ABSTRACT

Previous behavioral work has shown that tactile stimuli are represented in both somatotopic and external frames of reference. Our knowledge of the neural correlates of external representations of tactile stimuli is limited. For example, multi-voxel pattern analysis (MVPA) studies of tactile localization have not disambiguated between somatotopic and external reference frames. To examine this, we used MVPA in two fMRI experiments to identify brain regions involved in somatotopic and external tactile processing. Vibrotactile stimuli were presented to two possible somatotopic locations on the hand in two different postures. To examine hand-centered external processing, vibrotactile stimuli were presented to either the index or ring finger of the right hand while the palm was facing up or down (Experiment 1). In Experiment 2, we presented vibrotactile stimuli to either the left or the right index finger while the hands were crossed or uncrossed to examine trunk-centered external processing. Whole-brain MVPA analyses were used to decode activation patterns for somatotopic and external spatial representations. For both experiments, we found typical regions associated with somatotopic processing (contralateral S1, S2, and premotor cortex), with additional somatotopic regions in Experiment 2 (contralateral supramarginal gyrus, SMA). In Experiment 1, we found significant decoding of hand-centered space in contralateral anterior cingulate and surprisingly, in contralateral secondary visual cortex. However, we found no evidence for external body-centered processing in Experiment 2. Altogether, our results suggest a visual component relevant to tactile spatial representation in an external, hand-centered representation. We also demonstrate the presence of somatotopic representations of touch in areas beyond primary somatosensory cortex.

Keywords: neural correlates, fMRI, multi-voxel pattern analysis, touch localization, frames of reference, somatotopic, external space

Chapter 1

INTRODUCTION

Imagine a person is sitting on a park bench and sees a bee land on their hand. Localizing where the bee touched them is a complex process that would likely utilize sensory information from different systems. For example, they would use visual information from where they saw the bee land, knowledge of what posture their body is in, where the hand is in space, and information from sensory receptors on the skin of the hand to identifying where touch occurred. Integrating these various types of information, the location of a tactile stimulus can be represented based on different frames of reference. For example, the location of the contact with the bee could be described based on where it is on the person's body, or where it is in space. These reference frames can provide a framework for a coordinate system, each dependent on its particular origin and the type of information used to locate the stimulus. Following the bee example, the location of this tactile stimulus could be determined based on its coordinates with respect to the person's head, to its distance from the wrist, with respect to any particular object near this person, or to any other arbitrary origin. The location of the bee relative to the wrist could use visual and somatosensory information and would not depend on where the hand was in space. The location relative to the head would also have to additionally consider the position of the hand to

find how far it is from the head. In particular, the current study focuses on representations of touch in somatotopic and external frames of reference.

Somatotopic representations are based on the location of a touch on the skin surface relative to another and do not take into account information about location in space. This type of representation is concerned with where touch occurred on the skin surface, regardless of where this body part is in space. For example, the representation of touch on the left hand would be unchanged regardless of the location in space of this hand or its posture because it will be encoded as touch on the left hand wherever the hand happens to be. However, this is not enough information to localize touch.

Representing touch in an external frame of reference involves locating touch in a three-dimensional map of space where the body exists while being agnostic to what body part or skin surface receives the stimulus. If the left hand was touched while it was laying on the left leg of a sitting person, the location in an external frame of reference would be the same if the right hand was touched while placed at the same location on the left leg while in the same sitting posture. In this case, the somatotopic location would change from left to right hand and the arm posture would be different, but the external location would remain the same. There are a number of possible representations in external frames of reference based on where a origin of the reference frame is defined. In this example, the external frame of reference could be body-centered, meaning the locations in space are defined relative to the body midline. Other possible representations in external space could be centered on a particular body part, such as the hand or the head, or allocentric, centered on the stimulus itself

(Medina & Coslett, 2010). Proprioceptive information plays a role in terms of knowing where a particular body part is in space and is potentially integrated with somatotopic representations to form a representation of touch in three-dimensional external space.

There is evidence that somatotopic and external frames of reference are separate from behavioral, neuropsychological and neuroimaging studies. The behavioral evidence supporting this distinction in tactile representations frames of reference from eye-tracking (Groh & Sparks, 1996; Overvliet, Azañón & Soto-Faraco, 2011), temporal order judgments (Yamamoto and Kitazawa, 2001) and vibrotactile cueing studies (Azañón & Soto-Faraco, 2008).

Neuroimaging studies using GLMs and MVPA have identified areas that might represent touch locations but have not disambiguated representations in somatotopic and external frames of reference. Neural correlates of somatotopic localization of touch are fairly well established, but those of localization of touch in an external frame of reference are not yet fully understood. Direct stimulation of the cortex has showed that primary somatosensory areas like S1 are responsive to touch stimuli to a specific part of the skin and are organized somatotopically (Penfield & Boldrey, 1937). These areas, as well as the parietal cortex, have been implicated in localization of touch in a somatotopic frame of reference in TMS studies. Seyal, Siddiqui & Hundal (1997) tested touch localization on the thumb and index finger of the left hand. A tactile stimulus was presented before or after applying TMS over the part of sensorimotor cortex that optimally produced movement of the contralateral hand muscles.

Localization errors occurred when TMS was applied to sensorimotor cortex compared to a control area both when TMS happened before and after the tactile stimulus. Porro et al. (2007) found that applying TMS to the parietal cortex 150 ms after the onset of a non-noxious tactile stimulus significantly increased the errors in identifying the location of touch among four points on the right hand. However, the neural correlates of touch localization in external frames of reference are not well understood yet.

The neural correlates of external reference frames are less clear, although there are hints from differential activation when tactile stimulation is presented to the same body part at different spatial locations. Neuroimaging studies have identified areas that might represent touch locations but have not disambiguated representations in somatotopic and external frames of reference. Lloyd and colleagues compared activation when the right hand was stimulated passively at its canonical right side, and when it was stimulated in the left space, across the body midline (2003). In one comparison, participants kept their eyes closed and a general linear model (GLM) analysis showed activation patterns differed between the two hand positions, where the ipsilateral right ventral intraparietal sulcus (VIP) was significantly more active when the right hand was crossed over the body midline than when stimulation occurred while the hand was at its canonical right side. In this contrast, the somatotopic location and stimulation was the same in both conditions, but the location in external space was not. The same contrast of crossed minus uncrossed for the right hand was run for the eyes-open condition. Significantly higher activation was found in the left VIP and in other areas such as the left premotor cortex and the junction of the

left supramarginal and angular gyri. Activation in the ipsilateral right parietal cortex when the hand was in its canonical space shifted to the contralateral left parietal cortex when it was crossed over the body midline. The same contrast showed no significant results when stimulation on the right hand happened on two locations of the right hemispace, suggesting an effect of crossing the midline. When the left non-dominant hand was crossed into the right hemispace the eyes-open condition showed significantly higher activation in the right VIP, right premotor and parietal cortices, and medial occipital gyrus among other areas. Similarly, activation shifted from the ipsilateral left parietal cortex when the left hand was in its canonical left space, to the contralateral parietal cortex when the left hand was crossed over the body midline. Lloyd et al. (2003) interpret these results as evidence for visual cues coding for the anatomical space of the hand without taking into account the location in external space since this lateralization happened in the eyes-open conditions and only when crossing the body midline. If it was a representation of external space, it should have an effect when the right hand was tested in two different locations of the same hemispace. It is also possible that crossing the hand over the body midline was a stronger manipulation that the GLM could discern, while the two locations on the same hemispace were not. In this design the results could be interpreted in two ways; they could represent the location of touch in external space, or purely the posture of the hand regardless of whether it was stimulated or not. Additionally, the focus was on the comparison of observing the stimulated hand or not, and no analysis collapsed the data into crossed and uncrossed conditions.

Neuroimaging for TOJ tasks have also shown activation differences when arms are crossed. Takahashi et al. collected fMRI data for a temporal order judgment paradigm which required combining spatial representations and tactile perception of motion (2012). The behavioral task was similar to Yamamoto & Kitazawa and yielded similar behavioral results (2001). In the arms-crossed condition for temporal order judgements, they found greater activation of the left dorsal premotor cortex, left dorsolateral prefrontal cortex, left supramarginal gyrus, left superior parietal cortex and the right middle temporal gyrus compared to the uncrossed condition. Motion was perceived in both hand postures by presenting a tactile stimulus on one hand and then the other, meaning the differences in activation are likely related to the changes in limb position and external space location rather than to a lack of perception of movement. In the numerosity judgement (NJ) task that was used as a control, the same areas were found to be active in the crossed compared to the uncrossed condition although more spread out and less active than in the TOJ task. Similar to Lloyd et al. (2003), the increased activation in the crossed conditions in both the TOJ and NJ tasks could be representing changes in hand posture regardless of the task or other spatial information, and this paradigm is not disambiguating the two touch location representations, in somatotopic and external frames of reference. When contrasting the TOJ task, which requires information about the touch stimuli in external space, to the control NJ task which does not involve spatial judgments, an area in the parietal lobe was found. This area was close to the right VIP where Azañón, Longo et al. (2010) delivered TMS, and to the cluster found by Lloyd et al. in the crossed versus

uncrossed contrast (2003). Taken together, this suggests that the inferior parietal lobe is involved in touch localization in external space. Interestingly, more areas showed significantly greater activation in the crossed-arms conditions for both the TOJ and the NJ tasks than under the uncrossed-arms conditions. This could reflect the spatial conflict that arises between the somatotopic and external reference frames when the arms are crossed which could require more areas to be recruited. The behavioral results also support the idea that TOJs do not solely depend on a somatotopic representation of touch location in a similar way as Yamamoto & Kitazawa (2001) since posture would not affect TOJs if only somatotopic information was necessary. Instead, there was an effect of posture on TOJs, which require external space information, but not on NJs. If the results were due to postural changes alone, there would have been an effect of posture on NJs as well.

In fMRI studies about touch localization, a powerful tool that has been employed is multi-voxel pattern analysis (MVPA). GLM studies are informative in activation differences, but MVPA methods are better suited to address whether this activation is carrying information that encodes touch location in each reference frame. This type of analysis can have higher sensitivity since it compares patterns of activation rather than averaging overall activation between conditions. It consists of four main steps: feature selection, pattern assembly, classifier training and generalization testing (Norman et al., 2006). First, the voxels or regions of interest used to classify are chosen. Second, data from activation patterns is sorted based on experimental conditions. Third, a multivariate pattern classification algorithm is

trained to differentiate between two or more experimental conditions by using the exemplars and labels arranged in step two. Part of the data is excluded from training and saved for testing. Fourth, the classifier is fed activation patterns set aside for testing and its accuracy in identifying the experimental condition is tested. The result is a map of decoding accuracies showing how well brain areas perform in differentiating experimental conditions and allowing the identification of areas that can decode these conditions reliably.

Previous MVPA studies examining touch localization have found areas that are able to differentiate between stimulation of different body parts but have not disambiguated somatotopic and external reference frames. One study that used MVPA for touch localization was by Beauchamp, LaConte, & Yasar (2009). In their first experiment, participants received passive vibrotactile stimuli on their hands and feet using piezoelectric benders in an event related design. The regions of interest (ROIs) selected to perform the MVPA search in consisted of S1, S2 and area MST/STP. Activation patterns were sorted into four limb categories: left hand, right hand, left foot and right foot. A SVM classifier was trained to differentiate stimulation in these four categories. They found S1 and S2 decoded the location of touch among all four stimulus locations above chance, but not MST/STP. In another experiment, stimulation was presented on the thumb, middle and pinky fingers on the right hand. S1 and S2 were able to decode these locations, but not MST/STP. In this 3-way finger discrimination, S1 had a higher decoding accuracy than S2. However, since the posture never changed in either experiment, any given stimulus had the same location

somatotopically and in an external frame of reference, making it impossible to disambiguate the two representations. For example, when the left hand was stimulated, its location in external space was also on the left hemispace. There were no conditions where a spatial conflict was introduced between the somatotopic location and the external location. For example, the left side defined somatotopically by left hand stimulation corresponded to a left side defined by an external reference frame centered on the body midline. If the hands are crossed, the somatotopically-defined left would be at the externally-defined right hemispace. In these two studies there were no such conditions where this spatial conflict occurred.

A study by Kim et al. has a similar limitation in terms of disambiguating representations of touch localization (2015). They used MVPA to find areas that decoded touch locations on the index, middle finger, ring finger and pinky on the right hand. Three locations on each of four right-hand fingers were passively stimulated (for 12 locations in total) but data was assembled into four categories based on the finger stimulated. The participants' task consisted of pressing a button with the left hand if they perceived a stimulus, regardless of location. A Gaussian Naïve Bayes classifier was trained and tested on differentiating what finger was stimulated. Kim et al. found that contralateral S1 decoded tactile stimulation compared to no stimulation but not locations of touch on different fingers. Contralateral posterior parietal cortex (PPC) and the supramarginal gyrus (SMG) decoded between different right-hand fingers. In the design by Kim et al. there were no changes in posture and therefore there is no spatial conflict between the stimulus location in somatotopic and external reference

frames. This means it is unknown whether the PPC and SMG were decoding touch location using somatotopic representations, external frame of reference representations, or both. Since some of the areas found to decode touch location are somatotopically organized, such as S1, and others might not be, it is important to disambiguate which areas are involved in somatotopic localization of touch and which are representing the location of touch in external frames of reference. Results differ from Beauchamp et al. (2009) where S1 and S2 were able to decode somatotopic locations. Several differences in the designs might relate to the difference in results. Kim et al. (2015) stimulated three locations in each of four fingers on the right hand: the index, middle, ring and pinky fingers. The data was binned into these four finger categories. In addition to testing fingers of the right hand, Beauchamp et al. (2009) tested decoding accuracies for each limb. These four locations are farther apart both somatotopically and in external space. Additionally, Beauchamp et al. (2009) used a SVM classifier, a rapid event-related design with 2-second stimulation, and there were catch trials during which participants were asked to direct their gaze toward a visual target following stimulation on the hip. On the other hand, Kim et al. (2015) used a Gaussian Naïve Bayes classifier, a block design with 30-second rest and stimulation periods, and task. Beauchamp et al. (2009) compared S1 and S2 decoding accuracies and found they were similar for distinguishing between the four limbs, but lower for S2 in decoding fingers of the right hand, which could be related to the larger receptive fields in S2, and poorer organization compared to S1. This could be one of the reasons

for the difference in results, along with the type of fMRI design, classifier choice and task.

In summary, there is evidence that two separate representations of touch location, one in a somatotopic frame of reference and one in an external frame of reference (Groh & Sparks, 1996; Yamamoto & Kitazawa 2001; Azañón, Longo et al., 2010). There is also evidence for a hand-centered external frame of reference (Liu et al., 2020). The neural correlates of the somatotopic representation of touch location are better understood given the somatotopic organization of primary somatosensory areas, but neural correlates of touch localization in external frames of reference are not well established. Neuroimaging studies that have investigated touch localization did not disambiguate both representations. In some, the contrasts of changing the external space location of the tactile stimulus could be because of these changes in location of tactile stimuli in external space or because of the postural change regardless of stimulation (Lloyd et al., 2003; Takahashi et al., 2012). Therefore, it is not possible to ascertain that the results are showing areas involved in touch localization in external space. Other studies have employed MVPA to search for areas that reliably decode the location on the skin where a tactile stimulus happens (Beauchamp et al., 2009; Kim et al., 2015). In these MVPA studies the posture was not changed and any given somatotopic location was always in the same external space location. Consequently, touch representations in somatotopic and external frames of reference cannot be disambiguated in these experimental paradigms and the resulting clusters could be using both representations to decode touch location.

This disambiguation of reference frames has been successfully done using MVPA in the vision literature to disambiguate object location representations in retinotopic and spatiotopic frames of reference. Golomb & Kanwisher (2012) used an MVPA approach to disambiguate object location representations in retinotopic and spatiotopic frames of reference. There were three possible locations where the stimuli were presented, one central and one at each side relative to the subject's body. Two possible fixation points were located in between the three stimulus locations such that each fixation point had a potential stimulus location on each side of the fixation point. This permitted conditions in which the spatial location of a stimulus was the same, but the retinotopic one was not and vice versa. For example, a stimulus in the central location would be on the right retinotopic location when the fixation point was on the left, but on the left retinotopic location when the fixation point was on the right. Golomb & Kanwisher (2012) found areas that decoded retinotopic location, but none that explicitly decoded spatiotopic locations. They offer two possibilities for why no spatiotopic decoding areas were found. The patterns elicited by spatiotopic representations could be finer or more distributed than what the MVPA can decode. Another possibility is that spatiotopic representations are extracted from a combination of retinotopic and other kinds of input and are not explicitly represented by a particular area of the brain.

The present study successfully disambiguated somatotopic and external space representations of touch location with MVPA in two experiments using a 2 by 2 design, with two somatotopic locations and two external space locations; experiment 1

targeted a hand-centered external reference frame and experiment 2 a body-centered one. The purpose of these experiments was to identify neural correlates of localization of touch in somatotopic and of spatiotopic frames of reference, and to answer whether body position modulates how touch is processed somatotopically. Additionally, it permits a comparison of brain areas that decode external space touch locations in hand-centered and in trunk-centered external frames of reference.

In the first experiment, vibrotactile stimuli were presented as a regular vibrotactile pulse either on the right index or the right ring finger, and the hand could be placed with the palm facing up or facing down. The hand was kept at its canonical right side. There were four conditions, which could be grouped by somatotopic location or by external space location. For example, the two conditions with stimulation on the index finger had the same somatotopic location, but in one the palm was facing up and in the other it was facing down, meaning the locations in external space with respect to the middle of the hand are opposite; one happens on the left of the hand and one on the right, respectively. Conversely, two conditions had the same location in external space at the left of the hand, but different somatotopic locations; when the index was stimulated with the palm facing down and when the ring finger was stimulated with the palm facing up, the location in external space is left of the hand in both cases. Two whole-brain searchlight MVPAs were run to find brain regions that represented touch location somatotopically and in external frames of reference. One was trained to differentiate patterns for each finger. Another was trained to differentiate patterns for external space locations. In each MVPA, each

category had trials with both hand postures, therefore the results of each could not be representing hand posture. The MVPA for somatotopic location had under each finger category both locations in external space. For example, data for the index category had trials where the index was on the left side of the hand and trials where it was on the right. For external space locations, the left space category included trials where the left index was stimulated in this location, as well as trials where the ring finger was stimulated in the same location. Additionally, whole-brain searchlight MVPAs decoding somatotopic and external space locations were run on the crossed- and uncrossed-arms data separately. A region of interest (ROI) MVPA decoding somatotopic locations was run to see if touch was processed differently when the hands were crossed compared to when they were uncrossed. If hand posture modulates somatotopic touch localization, decoding accuracies will decrease when the classifier is trained and tested in different postures. A GLM with 12 regressors was also run. Tactile stimulation was compared to baseline to ensure the stimulation and paradigm were effective. The left and right external space locations were contrasted, as well as the crossed and uncrossed postures. The second experiment was similar to the first in the methods and analyses but used a different postural manipulation. The vibrotactile stimulation was instead presented on either the right or left index fingers and hands could be either crossed or uncrossed. The arms-crossed and arms-uncrossed manipulation places one external space location on each side of the body midline rather than on a side of the hand. In this manipulation, the locations in external space were equidistant relative to a trunk-centered external frame of reference.

This study successfully found brain areas that represent touch in a somatotopic reference frame in both experiments, as well as areas capable of encoding touch in a hand-centered external reference frame. The GLM results confirmed that tactile stimulation was effective in eliciting activation in somatosensory regions for both experiments and results of the whole-brain searchlight MVPAs showed contralateral S1, and premotor cortex areas that reliably decoded somatotopic locations in both experiments. Additionally, the second experiment found clusters encompassing bilateral S2, SMA and left supramarginal gyrus that could differentiate stimulation on the left and right index fingers. In terms of neural correlates of external reference frames, the first experiment showed areas in contralateral anterior cingulate cortex and contralateral visual cortex that differentiated the relative left and right space in hand-centered external space, while no areas were found in the second experiment that could do the same for left and right space relative to the body midline. The ROI MVPA did not find any evidence for posture modulating somatotopic decoding for either experiment.

Chapter 2

EXPERIMENT 1

Experiment 1 was designed to disambiguate somatotopic and hand-centered external frames of reference, with stimulating presented to either the index or ring finger in different postures (palm-up, palm-down). Each trial type could be categorized by the somatotopic or hand-centered external space location (left-versus right-side of the hand) of the stimulus, disambiguating the two representations (see Figure 1). We then used MVPA to examine which brain regions encoded tactile stimuli in somatotopic and/or external, hand-centered frames of reference. Experimental data for Experiment 1 was collected by Yuqi Liu in 2019.

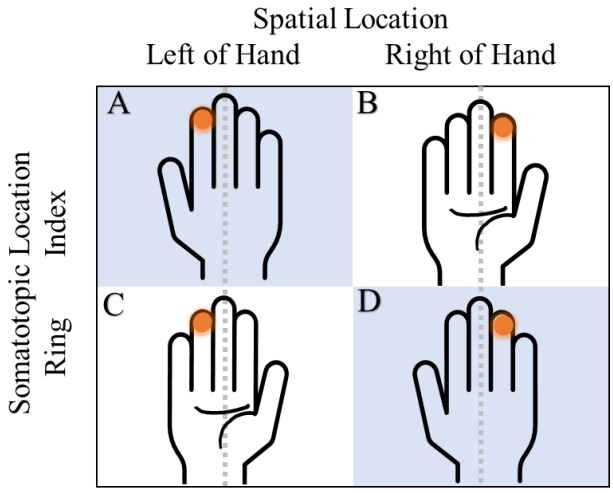

Figure 1 Experiment 1 conditions based on a 2×2 design. In conditions A and D, the hand is palm-down. In conditions B and C, the hand is palm-up. The dotted line represents the hand midline.

Methods

Participants

Sample sizes range from seven to ten in previous studies using MVPA to decode tactile locations (Kim et al., 2015; Beauchamp et al., 2009). Eight participants were recruited, and one was excluded due to chance performance on catch trials. A total of seven participants were included in the analysis (Age: 28 ±8.7, 4 males, 4 left-handed). Participants were University of Delaware students.

Materials

Piezoelectric MRI-compatible vibrotactile stimulators (PTS-C2, Dancer Design, St. Helens, UK) were attached to each participant's right index and ring finger. The right hand was placed on the MRI table by the participant's side. Posture was adjusted between runs by the experimenter. Participants responded using a standard MRI-compatible button box at their left hand.

Imaging parameters

Data was acquired at the University of Delaware's Center for Biomedical and Brain Imaging using a 3T Siemens Magnetom Prisma scanner and a 64-channel head coil. For the T1-weighted structural scans, an MPRAGE sequence was used (TR = 2080.0ms, TE = 4.64ms, flip angle = 7^{o}, voxel-size = 0.7 × 0.7 × 0.7 mm, 208 sagittal slices). Functional T2*-weighted images employed an EPI pulse multi-band sequence (TR = 1000ms, TE = 32.0 ms, flip angle = 61^{o}, voxel size = 2 × 2 × 2 mm, FOV = 192mm × 192 mm, slice number = 80, slice thickness = 2mm, matrix = 9216, slice order = interleaved, collection orientation = axial).

Procedure

Experiment 1 used a 2×2 design, with two somatotopic locations and two hand-centered, external spatial locations (Figure 1). MVPA studies generally include all experimental conditions in each functional run to avoid systematic differences that might affect decoding. However, changing hand posture during each run would have been time consuming and difficult to control. Therefore, this design randomized the two somatotopic locations of the stimuli in each functional run, meaning two of the four conditions were randomized in each run.

Each session had eight runs with 22 trials per run. Hand posture alternated between runs in an ABBAABBA manner, with first block posture counterbalanced across subjects. Each trial consisted of a 4-second stimulation period followed by an 8-second rest period. Vibrotactile stimulation was delivered as 30 Hz suprathreshold pulses on the fingertip of either the left or right index. Stimuli were presented as pulses rather than continuous stimulation to prevent tactile adaptation. Participants were presented with 18 test and 4 catch trials in each run, with an equal number of test and catch trials for each finger. Catch trials served the purpose of monitoring participant's attention, preventing sleepiness and maintaining their focus on the stimulation without overtly performing a touch localization task. This also kept participants naïve to the purpose of the study.

Test trials lasted 4 seconds and delivered eight equally spaced 400 ms vibrotactile pulses, separated by 100 ms pauses. Catch trials had the same duration but had a one-second gap at a random timepoint during the 4 seconds that interrupted the regular pulses. To minimize eye movements, participants were instructed to fixate on a square at the center of the screen. This square was white during the four second stimulation period and changed to black during the eight second rest period (Figure 2).

Subjects were asked to respond to catch trials by pressing the left foot pedal during the eight-second rest period to avoid overlap between tactile and motor processes. Before starting data collection, participants were shown examples of test and catch trials to ensure they understood the task and that they felt the tactile stimulation. Presentation of fixation squares and delivery of vibrotactile stimuli was done using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997) on Matlab (Version R2021a; 2021). To ensure synchronization with the scanner, there was a pause at the beginning of every run to allow for experimenters to adjust hand position, after which the scanning was resumed manually and the scanner trigger signaled the stimulus computer to begin the run, starting with six dummy scans that were excluded from data analysis.

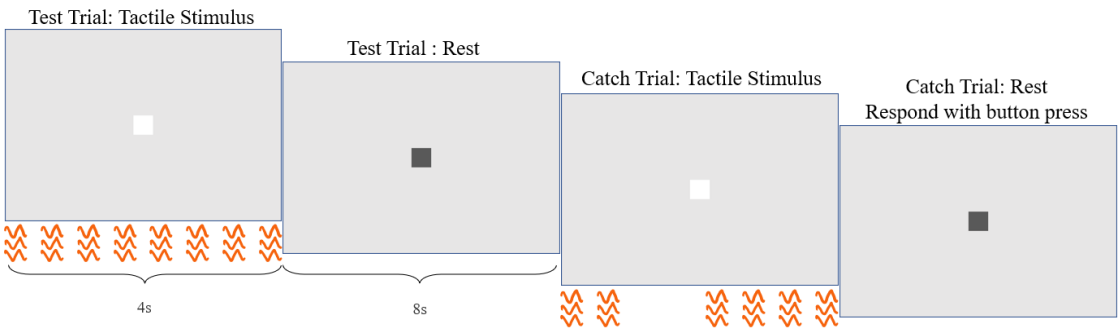

Figure 2 Test and catch trials presentation.

Data Analysis

Preprocessing

Preprocessing was done in the FSL toolbox (FSL 6.0, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) and consisted of motion correction using MCFLIRT,

brain-extraction using BET, temporal filtering with a high-pass filter of 100s, spatial smoothing with a 2 mm full-width-half-maximum Gaussian kernel, co-registration to the subject's T1 image, and normalization using a standard 1 mm MNI152 brain image and a linear transformation with 12 DOF. The small smoothing kernel keeps the spatial resolution high for MVPA, while reducing spatial noise. Data was scrutinized for excessive head motion. No slice timing correction was done given the multi-band sequence collects several volumes simultaneously.

General linear model (GLM) analysis

We ran a GLM analysis to verify the efficacy of the design in eliciting activation in primary somatosensory areas by contrasting tactile stimulation versus baseline. To examine if brain areas showing higher activation for one hand-centered external space location were different to those with higher activation for the other location, we ran two contrasts comparing trials when tactile stimuli were presented in the left space of the hand versus the right space regardless of posture, and vice versa. A second contrast compared activation in the palm-up versus palm-down posture.

The 12 regressors used included test trials on the index finger, test trials on the ring finger, catch trials on the index finger, catch trials on the ring finger, foot pedal presses, and the six motion parameters obtained during motion correction. For participants with false alarms, trials where a button press was recorded during a test trial were included in an additional regressor and these trials were excluded from the test trial regressors. This ensured they were not considered in the baseline or in the test trials to be analyzed. At the subject-level, runs were combined with a fixed-effect analysis. A mixed-effects analysis was used at the group-level using FSL's

FLAME1+2 option given the smaller sample size. Results were thresholded at a FWE-corrected α of .05.

Tactile stimulation compared to baseline

Since activation in the somatosensory cortex is expected from vibrotactile stimulation, the contrast of tactile stimulation versus baseline serves to verify whether the stimulation was effective in inducing activation in S1. With the purpose of confirming that the stimuli on the left and right index fingers were eliciting a response in their corresponding hand areas of the primary somatosensory cortex, two contrasts comparing stimulation in each index finger versus baseline were included.

External left space compared to right space

To see if external, hand-centered tactile locations are processed in lateralized manner, two contrasts comparing the left and right external space locations were run. If there are areas that are more active when stimulation happens on the left space but not on the right, and vice versa, this would suggest that there might be separate areas representing each spatial location, rather than one area representing both.

Palm-up versus palm-down contrast

The purpose of comparing crossed and uncrossed conditions was to examine if there were changes in activation patterns due to body position when the same somatosensory stimulus was presented in either the canonical side or in the opposite side. Uncrossed and crossed conditions were contrasted for tactile stimulation on both index fingers to find any areas that could represent the location of tactile stimuli with crossed versus uncrossed hand postures regardless of the somatotopic location. One analysis collapsed somatotopic targets and instead grouped trials by posture. The same

contrasts were run separately for each index finger. Separating the data by somatotopic location and then contrasting uncrossed and crossed conditions would show whether areas that are involved in hand posture changes for the left and right index fingers overlap, or whether there is homotopy, such that the same areas with higher activation in one hemisphere in response to stimulation of one index finger are also present in the homologous location on the opposite hemisphere in response to stimulation of the other index finger.

Multi-voxel pattern analysis (MVPA)

Whole-brain MVPA for Somatotopic and External Space Decoding

Two whole-brain searchlight MVPAs were run to find brain regions that represented touch location in somatotopic and external, hand-centered frames of reference. The somatotopic MVPA aimed to find areas able to decode between ring and index finger stimulation. The external space MVPA aimed to find areas able to decode tactile stimuli presented to the left- versus right-side of the hand, regardless of hand posture.

Two whole-brain searchlight MVPAs with spherical 200-voxel searchlights were run for each participant using the CoSMoMVPA toolbox (Oosterhof, Connolly, & Haxby, 2016). Each searchlight moves throughout the entirety of the brain and analyzes how well each voxel within the searchlight is able to decode between conditions. The voxel at the center of the spherical searchlight is then assigned a decoding accuracy based on the performance of all voxels in the spherical searchlight. The result is a whole-brain map of decoding accuracies. From this, any areas that can perform above chance in decoding between conditions can be identified. One whole-

brain MVPA tested decoding between the two somatotopic locations: left index finger and right index finger. Trials were separated into these two categories based on which finger was stimulated. The second MVPA decoded between two locations in external space, one to the left and one to the right of the body midline. Trials were separated based on the external location regardless of whether stimulation happened on the left or right index.

Since the neural correlates of touch localization in external, hand-centered space are not well established, choosing specific areas to run a region of interest analysis for the external-space MVPA would be difficult. Therefore, a whole-brain searchlight was used instead to capture any areas that might be coding for external space touch locations aside from primary and secondary somatosensory areas.

Only the preprocessed data from test trials was included; catch trials were excluded from both MVPAs. Each voxel was normalized along the temporal dimension to its own time series mean and standard deviation for every functional run. The normalized BOLD signal in each trial was averaged across the eight volumes acquired during the eight-second rest period to account for the delay in the hemodynamic responses (Harrison & Tong, 2009). Trials within each run were combined to yield a 4D dataset where each trial is a point on the 4th dimension. This 4D data was used to train and test the classifier in the two MVPAs. For each MVPA, a linear discriminant analysis (LDA) classifier was trained and then tested on two runs set aside for this purpose. In order to keep conditions balanced, a leave-two-out cross-validation method was used. If only one run is taken out, then there would be four blocks for one hand position and three for the other position and therefore the training data would be unbalanced. For example, if a run with the palm-up posture was taken

out, there would be overall more trials with palm-down posture, meaning more trials with stimulation on the index finger at the left external location than at the right one, and more trials with stimulation on the ring finger at the right external location than at the left one. This overrepresentation would be problematic because it could train the classifier to systematically misclassify external locations.

Aside from the two decoding accuracy maps for each subject, 100 null maps were generated by shuffling the finger labels randomly in each run following the approach in Stelzer et al. (2013). The same set of null maps was used in both group level analysis. Within each posture, finger and external space labels were coupled, meaning that randomizing finger labels within a run had the same effect as randomizing external space labels. Subject-level decoding accuracy maps for each frame of reference were registered to MNI 1mm space and merged, resulting in two group-level decoding accuracy maps. These were corrected for multiple comparisons using the previously generated null maps as simulated decoding accuracy maps assuming a null hypothesis where decoding performance was at chance. A one-sample *t*-test was run on each voxel for decoding accuracy in each frame of reference across participants using 0.5 as the null hypothesis. Each resulting map, one for somatotopic decoding and one for external space decoding, was thresholded at $p < .005$ and corrected for multiple comparisons by implementing a cluster-based Monte Carlo simulation with 10,000 iterations (cosmo_montecarlo_cluster_stat; Oosterhof et al., 2016; Vannuscorps et al., 2018). In each iteration, a *t*-test was run on each voxel across participants, where a null map was randomly drawn from each participant's null map set. The resulting null map was thresholded at $p < .005$ and the process was repeated 10,000 times for each type of representation, somatotopic and external space.

From these 10,000 null hypothesis maps, a distribution of maximum cluster sizes was calculated and compared to the original thresholded map. The resulting maps show cluster-corrected two-tailed *z*-scores from which we can see areas that decode for touch locations significantly above chance, one for somatotopic frames of reference and one for external frames of reference.

Somatotopic-decoding ROI MVPA

The purpose of these analyses was to examine if encoding changes as a function of posture in brain regions shown to encode somatotopically. Two ROIs were defined in S1, and premotor cortex based on the clusters found in the somatotopic-decoding whole-brain MVPA. These clusters were transformed back into each subject's native space before running subject-level ROI MVPAs.

Four ROI MVPAs were run for each ROI at the subject level. In two of them, the classifier trained and tested on the same posture. In the other two, the classifier was trained to decode for index and ring fingers on data from one hand posture and tested on another. Since there were four runs on with each hand posture, the classifier for same-posture ROI MVPAs was trained on three runs and tested on one. The two decoding accuracies for each same-posture ROI MVPAs were averaged to get an overall same-posture decoding accuracy value. For the different-posture ROI MVPAs, the classifier was trained on three runs of the palm-up posture and tested on one run of the palm-down posture. This ensured that any differences between the two are not due to unbalanced training sample sizes. For different-posture ROI MVPAs, the three training runs were randomly selected from one posture and the single run for testing was randomly selected from the second posture. The average decoding accuracy was calculated from all possible combinations. The same was done training on the palm-

down and testing on palm-up postures. Then an average of the two different-posture ROI MVPAs was extracted. The different-posture average decoding accuracy was subtracted from the same-posture one in each subject. Each subject's decoding accuracy difference value was then included in a group average. If hand posture has no effect on somatotopic decoding, the decoding accuracies will neither improve or worsen when the classifier is trained and tested on different postures. If it does have an effect, the decoding accuracies will change.

To determine if this was significant, a two-step permutation method was used. The process for all four ROI MVPAs was repeated 100 times in each subject using permutated somatotopic location labels. In other words, the ring and index finger labels were randomized within each run to simulate 100 decoding accuracy difference values at chance. A null distribution was generated by randomly selecting one of these 100 decoding accuracy difference values for each subject and averaging them. This was repeated 10000 times. This null distribution was then compared to the group average of decoding accuracy differences and generated a *p*-value.

Whole-brain MVPA separating hand posture

Two additional whole-brain MVPAs were run with the goal of investigating differences in the brain areas that can encode somatotopic location when the hand is placed palm-up compared to when it is placed palm-down. A similar procedure as the other whole-brain MVPAs was followed, but the data was split into palm-up and palm-down runs. In both cases the somatotopic and external space locations were correspondent. In other words, when the hand was placed palm-down, the index finger somatotopic location necessarily corresponded to the left location in external space. When the hand was placed palm-up, the index finger somatotopic location was

necessarily the right location in external space. Therefore, only one MVPA was run for each postural condition. As with the initial whole-brain somatotopic MVPA, an LDA classifier was trained to differentiate index and ring fingers at the subject-level. The resulting decoding accuracy maps of all subjects were registered to MNI 1mm space. In this analysis, the decoding accuracy map for the palm-up condition was subtracted from the palm-down accuracy map for each subject and then merged. Null maps were generated for each posture for each subject. To generate 100 null difference maps, we subtracted one null map from one posture from a null map from the other. These difference maps were then used to correct for multiple comparisons using the same Monte Carlo simulation with 10,000 iterations, as the previous whole-brain MVPAs. The result was a map of *z*-scores based on whether the difference between postures from the experimental data was significantly different from differences generated from a null distribution.

Results

Contrasting vibrotactile stimulation against no stimulation

To ensure that we could elicit expected changes in BOLD signal due to tactile stimulation, we contrasted stimulation for each finger compared to rest. GLM contrasts for tactile stimulation minus baseline found expected areas in bilateral S1, S2, Premotor Cortex and SMA (Figure 3 and Table 1). Additional regions found to be significant included bilateral cerebellum areas, right superior frontal gyrus and left intra-parietal sulcus (See Table 1). Overall, these results confirm that tactile stimulation elicited activity in expected brain regions.

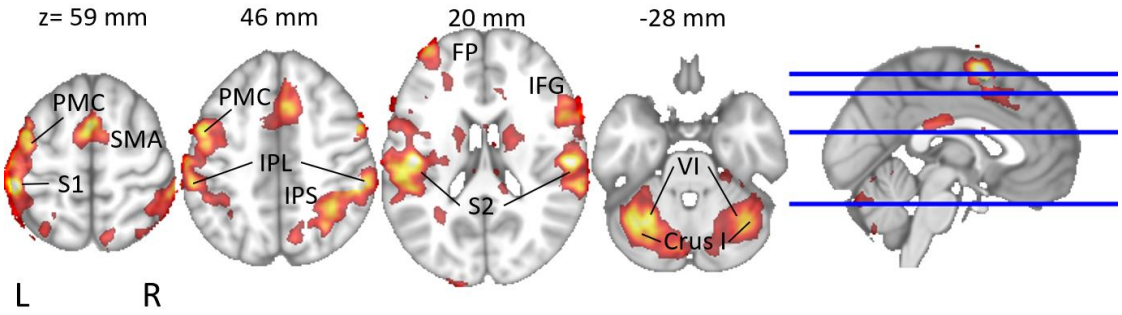

Figure 3 Brain areas activated by tactile stimulation on the left and right index fingers during test trials compared to baseline. Statistical maps show *z*-scores and are thresholded at FWE corrected $p < .05$. Slices in MNI coordinates. PMC: premotor cortex. SMA: supplementary motor area. IPL: inferior parietal lobule. IPS: Intra-parietal sulcus. FP: frontal pole. IFG: inferior frontal gyrus.

Table 1 Cluster list for the group level contrast of tactile stimulation versus baseline. Side indicates hemisphere (R = right, L = left, B = bilateral).

			Max Z MNI Coordinates				
Cluster Index	**Regions**	**Side**	**x**	**y**	**z**	**Voxels**	**Z**
13	S1, S2, Premotor Cortex, Insular Cortex, Intra-parietal sulcus	L	-49	-20	23	82960	25.1
12	Cerebellum Crus I, VI and VIIIa	B	-31	-60	-26	77515	19.5
11	S2, Inferior Frontal Gyrus, Premotor Cortex, Superior Parietal Lobule, Broca's area, and Thalamus	R	59	-18	21	66938	21.3
10	SMA and Premotor Cortex	B	-1	3	61	21685	20.5
9	Callosal body and Posterior Cingulate Gyrus	B	4	-28	26	5085	10.4
8	Middle Temporal Gyrus	L	-43	-53	2	1761	8.85
7	Frontal Pole	R	43	59	10	1636	10.6
6	Inferior Temporal Gyrus	R	60	-44	-15	991	7.33
5	Optic radiation	L	-48	-41	-8	899	6.58
4	V1	R	4	-86	-6	764	8.91
3	Planum Polare	L	-43	-13	-12	581	6.5
2	Callosal body	L	-29	-56	21	547	5.71

1	Middle Temporal Gyrus	R	52	-22	-5	539	7.23

Decoding somatotopic touch locations

One whole-brain searchlight MVPA aimed to decode tactile stimulation in two somatotopic locations: right index finger versus the right ring finger. This whole-brain somatotopic MVPA found a cluster able to decode somatotopic touch locations above chance after correcting for multiple comparisons. It encompassed left S1 and extended slightly into left M1 and premotor cortex (Figure 4; 3520 voxels, peak mean accuracy across participants = 94%, cluster-corrected $z = 3.72$, $p = .0001$).

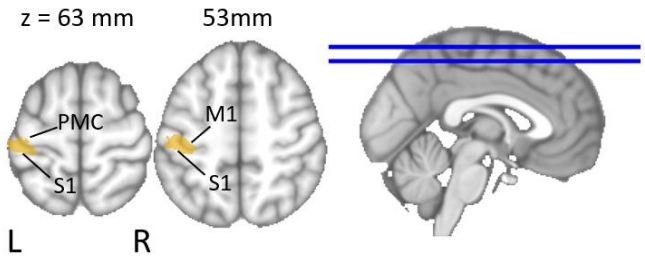

Figure 4 Brain areas decoding right index finger and right ring finger. Slices shown in MNI coordinates. PMC: premotor cortex.

Decoding external space touch locations

The whole-brain external space MVPA found brain areas that decode above chance in contralateral anterior cingulate cortex and contralateral visual cortex. One cluster was found in contralateral (left) anterior cingulate cortex and extended to a small part of right anterior cingulate cortex as well as to the genu of the corpus callosum on both hemispheres. (Figure 5; 1224 voxels, peak mean accuracy across participants = 59%, cluster-corrected $z = 2.21$, $p = .01$). An additional cluster was found in the left occipital lobe (Figure 5; 966 voxels, peak mean accuracy across

participants = 58%, cluster corrected $z = 1.75$, $p = .04$). Without retinotopic mapping, it is difficult to determine the exact location in visual cortex, but it is likely to encompass the inferior and superior divisions of lateral occipital cortex, and occipital pole.

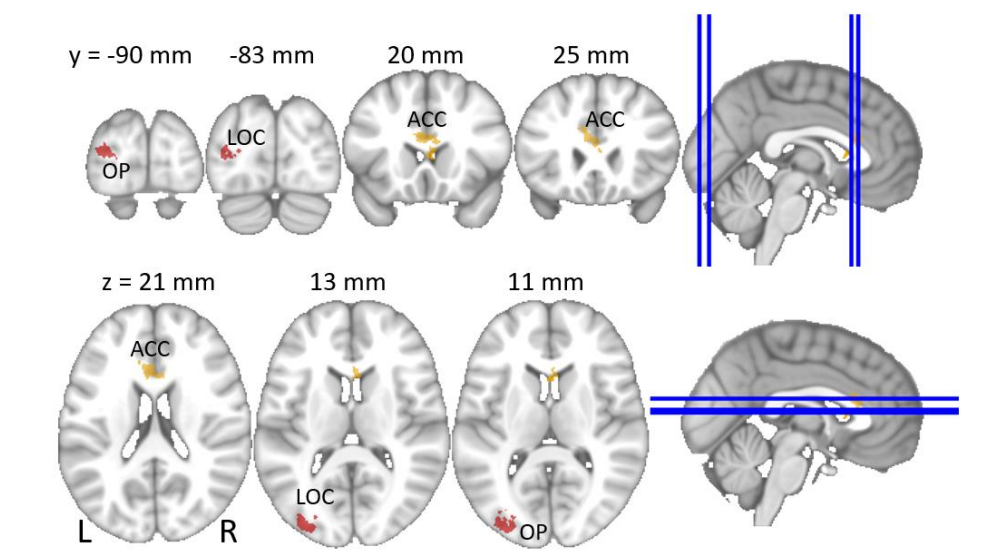

Figure 5 Brain areas decoding for left and right index fingers. Slices shown in MNI coordinates. OP: occipital pole. LOC: lateral occipital cortex. ACC: anterior cingulate cortex.

Effect of posture on somatotopic touch localization

ROI MVPA

To test whether there was an effect of posture on somatotopic decoding within two pre-defined ROIs, a two-step permutation method was used. Within each ROI, the difference between same- and different-posture decoding was calculated for the experimental data and compared to a distribution of 10000 values generated under the

null hypothesis. The ROI MVPA showed no significant differences in either S1 (t (7) = -.28, p = .785) or premotor cortex (t (7) = 1.03, p = .335), providing no evidence that somatotopic representations in these areas are modulated by hand posture.

Somatotopic MVPA in each posture

To compare somatotopic decoding under the palm-up versus the palm-down conditions, two whole-brain searchlight MVPAs for somatotopic decoding were run separately, one on data for each posture. The group decoding accuracy map for the palm-up condition was subtracted from the palm-down one. The resulting map was corrected for multiple comparisons using a Monte Carlo simulation with 10,000 iterations. The results of the additional whole-brain somatotopic and external space MVPAs for the palm-up posture were not significantly different from those for the palm-down posture.

GLM spatial and postural contrasts

The contrasts between stimulation in palm-up and palm-down postures aimed to investigate whether there were differences in activation patterns based on postural changes in the right hand. The GLM contrast comparing palm-up and palm-down postures found some areas where activation was significantly higher for the palm-down condition than palm-up. These included bilateral superior parietal cortex, V2, V4, left LOC, left cingulate gyrus, among others (See Figure 6 and Table 2).

Trials where stimulation was presented on the left side in the hand-centered external space were contrasted with trials on the right space to determine whether any brain areas show increased activation when vibrotactile stimulation is presented to one

spatial location compared the other. The contrasts comparing left and right space did not show significant differences.

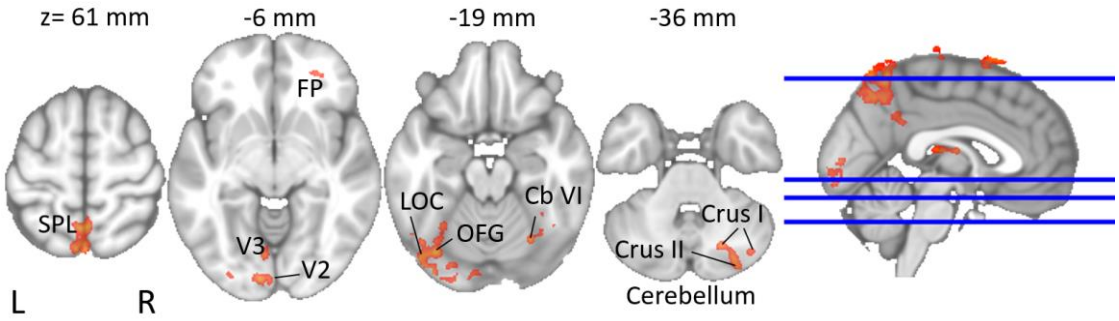

Figure 6 Brain areas activated by tactile stimulation when the hand was palm down compared to palm up. Statistical maps show *z*-scores and are thresholded at FWE corrected $p < .05$. Slices shown in MNI coordinates. SPL: superior parietal lobule. FP: frontal pole. LOC: lateral occipital cortex. Cb; cerebellum.

Table 2 Cluster list for the group level contrast of tactile stimulation when the right hand was placed palm-down versus palm-up. Side indicates hemisphere (R = right, L = left, B = bilateral).

Cluster Index	Regions	Side	Max Z MNI coordinates			Voxels	Z
			x	y	z		
14	Superior Parietal Lobule	B	1	-57	61	4770	4.95
13	V1, V2, V3, V4	L	-9	-91	-6	2067	4.95
12	Fusiform Gyrus, Lateral Occipital Cortex	L	-35	-73	-19	1562	4.78
11	Cerebellum Crus I	R	47	-65	-40	1054	5.36
10	Cerebellum Crus I, Crus II	R	21	-68	-34	728	4.46
9	Premotor Cortex, M1	B	7	-25	78	602	4.12
8	Corpus Callosum, Frontal Pole	R	33	42	-4	594	4.25
7	SMA, Premotor Cortex	L	-1	12	74	526	4.29

6	Thalamus	B	-3	-24	13	477	4.5
5	Caudate, Superior Occipito-Frontal Fascicle	R	22	12	20	400	4.75
4	Posterior Cingulate Gyrus	L	-8	-48	37	394	4.19
3	Cerebellum VI, Temporal Occipital Fusiform Cortex	R	28	-64	-19	382	4.58
2	V3	L	-5	-75	-5	368	4.64
1	Caudate	L	-7	16	1	338	4.34

Discussion

Experiment 1 successfully found regions where touch locations are represented in different reference frames. For the MVPA analyses, we were able to disambiguate somatotopic and hand-centered external reference frames and found initial evidence for brain areas representing touch in both from the whole-brain somatotopic and external space MVPAs. However, there are multiple types of "external" frames of reference for tactile processing. As Experiment 1 involved stimuli on the hand, one possibility is that the brain regions active for external coding were specific to a hand-centered external representation. In the next experiment, we examined whether the same (or other) regions would encode for external, trunk-centered space using a hand crossing manipulation.

Chapter 3

EXPERIMENT 2

Experiment 2 was similar in design to Experiment 1 but examined body-centered external representations of tactile stimuli, as opposed to the hand-centered representations in Experiment 1. Like Experiment 1, it used a 2×2 design, with two somatotopic locations and two body-centered external space locations (Figure 7). This again allowed data to be separated into two categories of external space or two categories of somatotopic location in order to disambiguate the two reference frames. In Experiment 2, the stimuli were presented on either the left or right index fingers and responses were made with a foot pedal. The hands could be crossed or uncrossed.

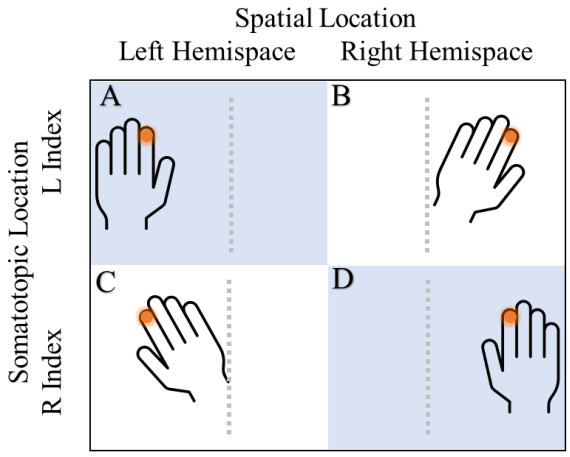

Figure 7 Experiment 2 conditions based on a 2×2 design. In conditions A and D, the hands are uncrossed. In conditions B and C, the hands are crossed. The dotted line represents the body midline.

Methods

Participants

In total 15 participants were recruited. One was excluded due to excessive misses on catch trials, and another did not complete the study, leaving 13 participants for analysis. Participants were University of Delaware students (Age: 25 ±5.4, 5 males, 4 left-handed). Participants with a history of neurological conditions were excluded. Recruiting was done through student organizations at the University of Delaware.

Materials

The same stimulators were used as in Experiment 1. Piezoelectric MRI-compatible vibrotactile stimulators (PTS-C2, Dancer Design, St. Helens, UK) were attached to each participant's right and left indexes using MR-compatible medical tape. Stimulators were secured to a Velcro strip on a single foam wedge where both hands rested. The stimulator positions were adjusted between runs while keeping each stimulator on its assigned finger (Figure 8). The two locations on the foam wedge were marked to ensure the external spatial locations did not shift as the stimulators were moved. In Figure 8, a red rectangle marked the location on the wedge where the vibrating part of the stimulator were placed. The foam wedge was placed on the participant's lap in a position where they were able to reach the stimulators when their arms were crossed or uncrossed. For crossed runs, additional MRI-compatible foam pads were placed under both elbows for support since the hands had to stretch forward slightly more than when uncrossed to reach the stimulators. Participants used MRI-compatible foot pedals (HHSC-2x1-FP-1, Current Design, Philadelphia, US) for responses. They were instructed to use only the left pedal.

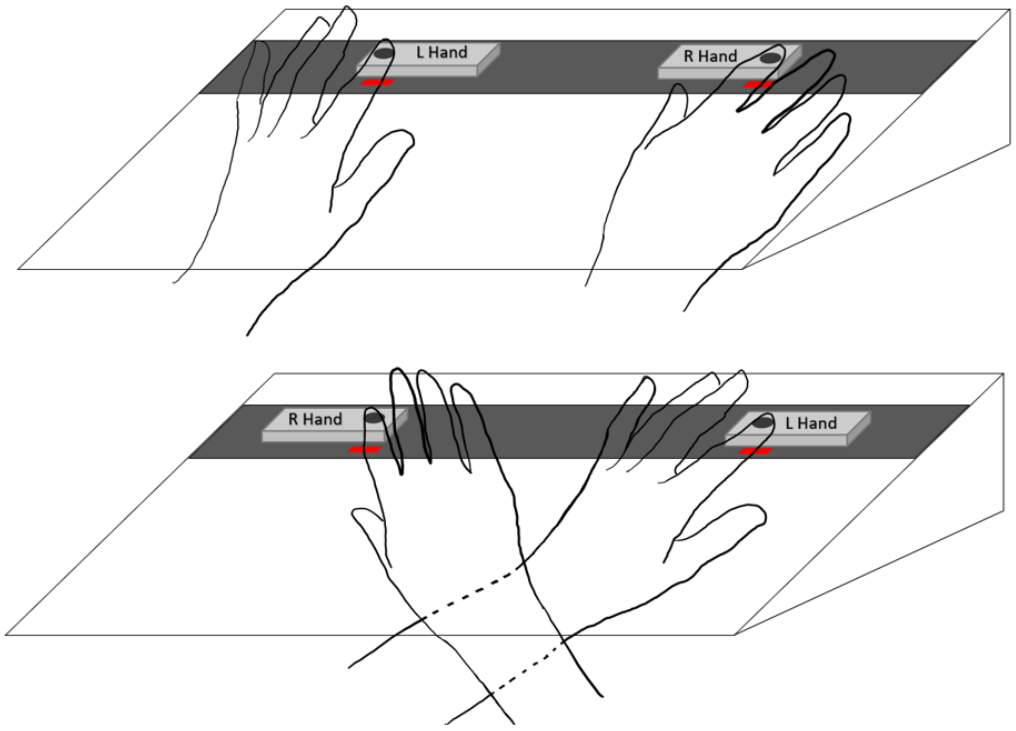

Figure 8 Stimulators and participant indexes are secured to the foam wedge when hands are crossed or uncrossed. Each stimulator is assigned to one hand and kept with that hand when changing positions.

Imaging parameters

Data was acquired at the University of Delaware's Center for Biomedical and Brain Imaging using a 3T Siemens Magnetom Prisma scanner and a 64-channel head coil. For the T1-weighted structural scans, an MPRAGE sequence was used (TR = 2080.0ms, TE = 4.64ms, flip angle = 7°, voxel-size = 0.7 × 0.7 × 0.7 mm, 208 sagittal slices). Functional T2*-weighted images employed an EPI pulse multi-band sequence (TR = 1000ms, TE = 32.0 ms, flip angle = 61°, voxel size = 2 × 2 × 2 mm, FOV = 192mm × 192 mm, slice number = 80, slice thickness = 2mm, matrix = 9216, slice order = interleaved, collection orientation = axial).

Procedure

The design and procedure of Experiment 2 was similar to Experiment 1 except for the postural manipulation and response mode. It used a 2×2 design with two hand postures (crossed or uncrossed) and two somatotopic locations (left and right index fingers) design that allowed for four conditions (Figure 7). By separating data by either somatotopic location or by body-centered external space location, this experiment also disambiguated the two reference frames.

Like Experiment 1, eight runs with 22 randomized trials each were acquired. Hand position, crossed or uncrossed, alternated between runs in an ABBAABBA fashion and the hand position for the first block was counterbalanced across subjects. Trials were kept the same for Experiment 2, with a 4-second 30 Hz pulse stimulation period followed by an 8-second rest period. The same catch trial format of a 1-second gap with a random onset time were used. Stimulation was presented on the fingertip of either the left or right index finger. Participants fixated on a central white square during stimulation, which changed color to black during rest when they were allowed to respond after a catch trial using the left foot pedal (Figure 9). Each run consisted of 18 test trials and 4 catch trials in a random order. Half of the test and catch trials happened on the left index finger and half on the right index finger. Participants were shown a sample trial and asked to confirm they felt the vibrotactile stimuli in each finger. Experiment presentation was done using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997) on Matlab (Version R2021a; 2021).

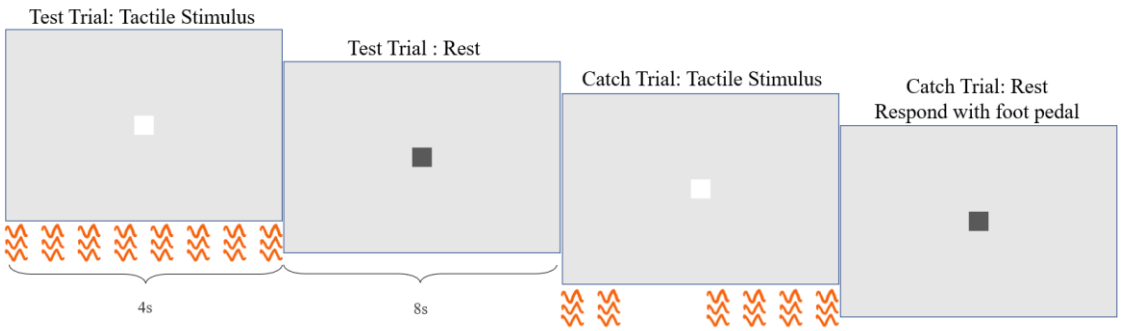

Figure 9 Test and catch trials presentation.

Data Analysis

The same analyses were performed as in Experiment 1 with experimental data collected between 2020 and 2021.

Preprocessing

Preprocessing was done in the same manner as Experiment 1 through FSL toolbox (FSL 6.0, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) and consisted of motion correction using MCFLIRT, brain-extraction using BET, temporal filtering with a high-pass filter of 100s, spatial smoothing with 2 mm full-width-half-maximum Gaussian kernel, co-registration to the subject's T1 image, and normalization using a standard 1 mm MNI152 brain image and a linear transformation with 12 DOF. No slice timing correction was done given the multi-band sequence.

General linear model (GLM) analysis

A GLM with 12 regressors was run in the same way as Experiment 1 in order to verify the paradigm effectiveness in eliciting a response in somatosensory areas. At the subject-level, runs were combined with a fixed-effect analysis. A mixed-effects

analysis was used at the group-level using FSL's FLAME1+2 option. Results were thresholded at a FWE-corrected α of .05.

Tactile stimulation compared to baseline

A contrast comparing tactile stimulation of each finger to baseline was run to confirm that the stimulation was effectively activating the expected somatosensory areas.

External left space compared to right space

A contrast comparing left and right body-centered external space tested whether there were areas with significantly higher activation for either external location.

Uncrossed versus crossed hands contrast

An uncrossed versus crossed hands contrast compared activation for each posture regardless of the finger stimulated. Additionally, the same contrasts were run separately for each index finger to examine whether areas involved in hand posture changes for the left and right index fingers overlap or are mirrored in each hemisphere.

Multi-voxel pattern analysis (MVPA)

Whole-brain MVPA for somatotopic and external space decoding

Two whole-brain MVPAs were run to determine if the results of Experiment 1 would replicate and to test a body-centered external frame of reference. One MVPA decoded somatotopic locations and another decoded body-centered external space locations.

Somatotopic-decoding ROI MVPA

ROI-based MVPAs similar to those in Experiment 1 were run to see if changes of body posture (i.e., crossing the hands over the midline) modulate somatotopic decoding in regions previously associated with somatotopic processing. A similar process was followed where classifiers were trained and tested on the same posture, and two were trained on one posture and tested on another. In this case, one trained on crossed-hands data and tested on uncrossed-data and vice versa. If changing hand posture modulates somatotopic decoding, decoding accuracies will significantly change when the classifier is trained and tested on different postures.

The ROIs were chosen based on the results of the somatotopic MVPA and included S1, S2, SMA and premotor cortex. The S1 ROI was functionally and anatomically defined based on the group results of the contrast of stimulation versus baseline for each index finger and the Jülich atlas (Eickhoff et al., 2007; Geyer et al., 2000; Grefkes et al., 2001). The voxel with the peak activation in each hemisphere was identified and the areas of S1 within a 20-voxel radius were included in each hemisphere. The S2 ROI was anatomically defined based on the Jülich atlas (Eickhoff et al., 2007; Eickhoff, Schleicher, Zilles & Amunts, 2006; Eickhoff, Amunts, Mohlberg & Zilles, 2006). The premotor cortex ROI was anatomically defined based on the Jülich atlas (Eickhoff et al., 2007; Geyer, 2000). The SMA was defined based on the Harvard-Oxford cortical atlas and subtracted from the premotor cortex mask (Desikan et al., 2006). ROI masks were transformed back into each participant's functional space. The four ROI MVPAs, two for same-posture somatotopic decoding and two for different-posture somatotopic decoding, were run in each ROI. Like in Experiment 1, there were 4 runs for each posture, meaning the same-posture MVPAs could train on three runs and test on one. The resulting decoding accuracies for the

two same-posture ROI MVPAs were averaged. In order to prevent unbalanced samples in same- and different-posture ROI MVPAs, three training runs and one testing run were randomly selected for the different-posture ROI MVPA. All possible combinations were included, and an average was calculated. The two decoding accuracy values for the different-posture ROI MVPAs were averaged. In order to examine whether the decoding accuracy changed when the classifier was trained and tested on different postures, we calculated the difference between same- and different-posture decoding accuracies was calculated by subtracting the different-posture decoding accuracy from the same-posture accuracy. The decoding accuracy differences of all subjects were averaged to get a group-level experimental value.

A two-step permutation method was used for group analysis. The same process to calculate the difference between same- and different-posture decoding accuracies was repeated 100 times for each of the four ROI MVPAs using permutated somatotopic labels. That is, the index finger labels were randomized within each run to generate values under a null hypothesis where the decoding accuracy is at chance. The two same-posture decoding accuracies, and the two different-posture decoding accuracies were averaged, and the difference was calculated for each of the 100 permutations. The result was 100 null decoding accuracy difference values for each subject based on the permutation of finger labels. To generate a null distribution to compare the experimental value against, one null decoding accuracy difference value was randomly chosen from each subject and a group average calculated. This process was repeated 10000 times to generate a distribution under the null hypothesis. The experimental decoding difference between same- and different-posture conditions was

then compared to this null distribution and the p-value calculated to determine if the difference was significant.

Whole-brain MVPA separating hand posture

Additionally, whole-brain somatotopic and external space MVPAs were run on each posture separately and the decoding accuracies compared. The same procedure was followed as in Experiment 1, where the decoding accuracy maps of the uncrossed condition was subtracted from the accuracy map of the crossed condition to create a difference map. This was then compared to a null distribution of difference maps. As in Experiment 1, by separating data by posture, the somatotopic and external space locations are aligned and therefore only one MVPA was run per posture. For example, when the hands are uncrossed, the left index finger necessarily corresponds to the left space and the right index finger to the right space.

Results

Contrasting vibrotactile stimulation against no stimulation

As in Experiment 1, GLM contrasts for tactile stimulation minus baseline confirmed that the experimental design was successful in targeting activation in somatosensory areas. There was significant bilateral activation of S1, S2, SMA, and premotor cortex. Other areas included putamen, thalamus, frontal cortex, left lateral occipital cortex, and insular cortex, among others (See Figure 10 and Table 3).

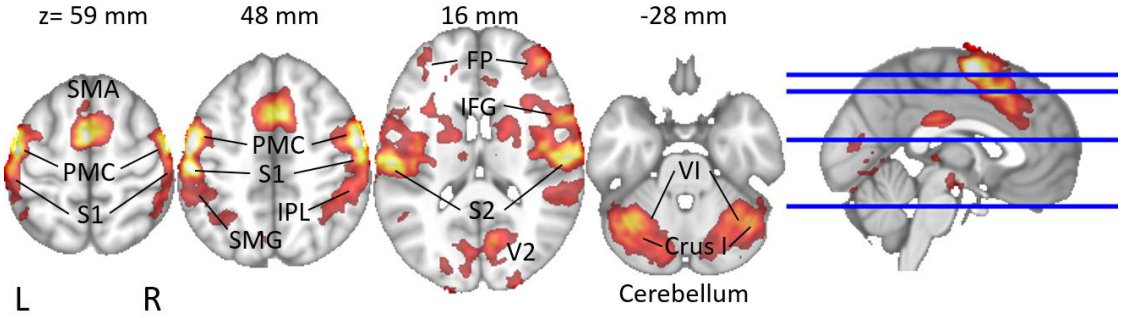

Figure 10 Brain areas activated by tactile stimulation on the left and right index fingers during test trials compared to baseline. Statistical maps show *z*-scores and are thresholded at FWE corrected $p < .05$. Slices in MNI coordinates. SMA: supplementary motor area. PMC: premotor cortex. IPL: inferior parietal lobule. SMG: supramarginal gyrus. FP: frontal pole. IFG: inferior frontal gyrus.

Table 3 Cluster list for the group level contrast of tactile stimulation versus baseline. Side indicates hemisphere (R = right, L = left, B = bilateral).

Cluster Index	Regions	Side	Max Z MNI Coordinates			Voxels	Z
			x	y	z		
13	S1, S2, Premotor Cortex, Insular Cortex, Intra-parietal sulcus	L	-49	-20	23	82960	25.1
12	Cerebellum Crus I, VI and VIIIa	B	-31	-60	-26	77515	19.5
11	S2, Inferior Frontal Gyrus, Premotor Cortex, Superior Parietal Lobule, Broca's area and Thalamus	R	59	-18	21	66938	21.3
10	SMA and Premotor Cortex	B	-1	3	61	21685	20.5
9	Callosal body and Posterior Cingulate Gyrus	B	4	-28	26	5085	10.4
8	Middle Temporal Gyrus	L	-43	-53	2	1761	8.85
7	Frontal Pole	R	43	59	10	1636	10.6
6	Inferior Temporal Gyrus	R	60	-44	-15	991	7.33
5	Optic radiation	L	-48	-41	-8	899	6.58
4	V1	R	4	-86	-6	764	8.91
3	Planum Polare	L	-43	-13	-12	581	6.5

2	Callosal body	L	-29	-56	21	547	5.71
1	Middle Temporal Gyrus	R	52	-22	-5	539	7.23

Decoding somatotopic touch locations

The whole-brain somatotopic MVPA found brain areas that decode somatotopic touch locations above chance in five clusters encompassing bilateral S1, left supramarginal gyrus, bilateral premotor cortex, bilateral S2 and SMA. One cluster was in left S1 extending to the supramarginal gyrus, premotor cortex and S2 (Figure 11; 31394 voxels, peak mean accuracy across participants = 76%, cluster-corrected z = 3.72, p = .0001). On the right hemisphere, the whole-brain MVPA found a cluster in right S1 extending to premotor cortex and including S2 (Figure 11; 19362 voxels, peak mean accuracy across participants = 80%, cluster-corrected z = 3.72, p = .0001). A smaller cluster was found in the supplementary motor area and premotor cortex (Figure 11; 1298 voxels, peak mean accuracy across participants = 63%, cluster-corrected z = 3.72, p = .0001). Two additional clusters with smaller z-values were found in left S2 (Figure 11; 430 voxels, peak mean accuracy across participants = 64%, cluster-corrected z = 1.88, p = .03) and right cerebellum lobules VIIIa and VIIIb (Figure 11; 374 voxels, peak mean accuracy across participants = 60%, cluster-corrected z = 1.66, p = .048).

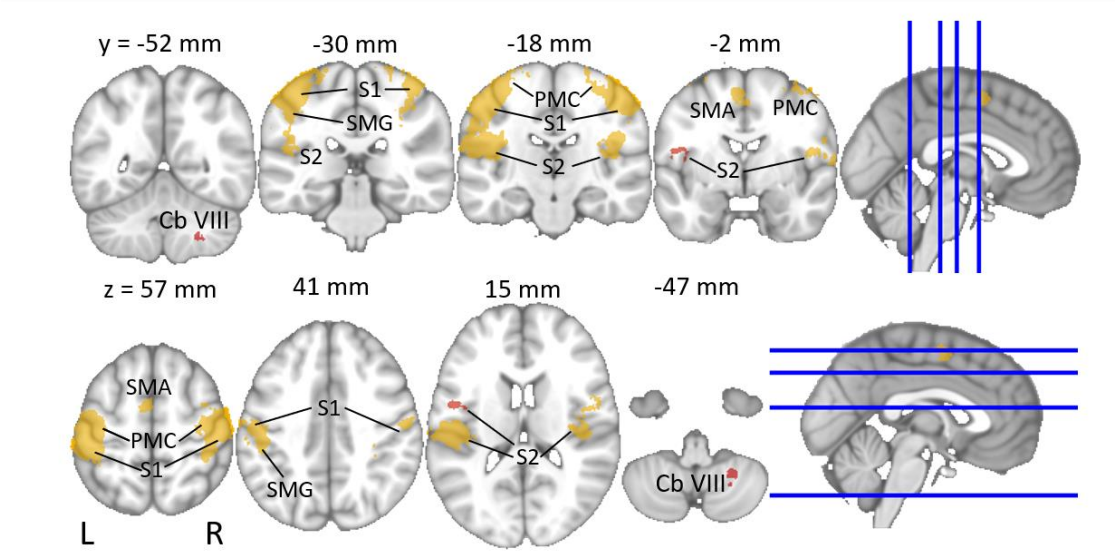

Figure 11 Brain areas decoding for left and right index fingers. Slices shown in MNI coordinates. SMG: supramarginal gyrus. SMA: supplementary motor area. PMC: premotor cortex. STG: superior temporal gyrus.

Decoding external space touch locations

The external space whole-brain MVPA did not find any areas able to decode left and right spatial locations in a body-centered external reference frame after correcting for multiple-comparisons.

Effect of posture on somatotopic touch localization

ROI MVPA

For the ROI MVPA, the difference between same- and different-posture decoding within each ROI was compared to a distribution of 10000 values generated under the null hypothesis. There was no significant difference between the experimental decoding difference and the null distribution for S1 (*p*-value = 0.5), S2 (*p*-value = 0.3), SMA (*p*-value = 0.3) or premotor cortex (*p*-value = .09).

Somatotopic MVPA in each posture

In order to compare somatotopic decoding between the two postural conditions, two additional whole-brain somatotopic MVPAs were run, one for each posture. The group decoding accuracy maps were compared by subtracting the palm-up map from the palm-down one. The resulting map was corrected for multiple comparisons using a Monte Carlo simulation with 10,000 iterations. The results of the hands-crossed postural condition were not significantly different from those for the hands-uncrossed posture.

GLM spatial and postural contrasts

The purpose of contrasting tactile stimulation with the hand uncrossed versus crossed was to examine whether there were areas that showed differential activation based on posture alone. The GLM contrasts comparing hands-crossed and hands-uncrossed postures found one cluster spanning parts of the superior frontal gyrus on both hemispheres where activation was significantly higher when the arms were crossed than when uncrossed (1040 voxels, $z = 4.79$).

Trials where stimulation was presented on the left side in the body-centered external space were contrasted with trials on the right space to examine whether any brain areas show increased activation in response to one spatial location over the other. The GLM contrasts comparing left and right space did not show significant differences.

Chapter 4

GENERAL DISCUSSION AND CONCLUSION

The main goals of this study were to disambiguate somatotopic and external reference frames for touch localization and search for brain areas that were able to decode the location of a tactile stimulus in each frame of reference. Additionally, we wanted to test whether posture modulated somatosensory representation in somatosensory-processing areas. We used both univariate and multivariate approaches to investigate these issues. The designs of both experiments manipulated spatial locations in an external reference frame and somatotopic locations so that the data could be separated by somatotopic location or by external space location in order to disambiguate the two. The ring and index fingers of the right hand were the somatotopic locations in Experiment 1, while Experiment 2 presented stimuli on the index finger of each hand. Experiment 1 targeted a hand-centered manipulation for external space using palm-up and palm-down postures for the right hand, while Experiment 2 used hands crossed and uncrossed postures to target a trunk-centered external reference frame.

For each experiment, a GLM contrast of stimulation versus baseline confirmed the effectiveness of the tactile stimulation presented and a whole-brain searchlight MVPA tested decoding of touch locations in each frame of reference. For testing a postural modulation, an ROI MVPA was run in each area found to decode somatotopic location. Additional GLM contrasts compared activation for one posture versus the other and between the relative left and right external space in each experiment.

Experiments 1 and 2 verified the expected areas involved in somatosensory processing, such as S1 and S2, utilizing GLM contrasts of stimulation versus baseline. In disambiguating somatotopic and external reference frames using MVPA, both experiments provided evidence for somatotopic encoding in contralateral S1 and premotor cortex. Experiment 2 additionally found evidence for somatotopic decoding between the hands in left SMG, bilateral S2 and bilateral SMA.

Primary somatosensory cortex is known to be organized somatotopically and respond to tactile stimuli on the skin surface (Penfield & Boldrey, 1937). It is therefore a logical candidate area to represent somatotopic touch locations. S1 has also been found to show activation patterns discernible enough to decode between different fingers on the same hand presented with tactile stimulation (Beauchamp et al., 2009). Premotor cortex plays a role in planning movement in response to sensory cues in both humans and non-human primates (Toni, Rushworth, & Passingham, 2001). In the monkey brain, premotor cortex follows a somatotopy similar to that found in M1 (Godschalk et al., 1995). Furthermore, it activates in a somatotopically organized fashion in perceptual-attentional tasks that do not require executing or imagining a movement, in particular if they require spatial attention or object-directed attention (Schubotz & von Cramon, 2003). With regards to tactile stimulation, the premotor cortex has been found to be activated in fMRI studies involving pattern and frequency tactile discrimination (Li Hegner et al., 2010) and during tactile stimulation of the index fingers compared to rest (Van Boven et al., 2005). Notably, previous MVPA studies on tactile localization did not find clusters in PMC that were able to differentiate between touch locations. Beauchamp et al (2009) did not choose this region as an ROI, and Kim et al. (2015) used a whole-brain approach but did not find

PMC to differentiate activation patterns from tactile stimulation on different fingers of the right hand. Although participants are not instructed to make hand movements in this experiment, one possibility is that PMC is implicitly decoding somatosensory location information in order to plan a motor response more accurately to both experiments' vibrotactile stimuli.

Significant decoding in SMG was found only in Experiment 2 but in a previous MVPA study was found to differentiate between fingers of the right hand (Kim et al., 2015). The supramarginal gyrus has also been implicated in discriminating tactile patterns and sensation (Li, Hegner et al., 2010; Van Boven et al., 2005). Secondary somatosensory cortex was also only found to differentiate somatotopic touch locations in Experiment 2. In previous MVPA studies, S2 decoded with higher accuracy between limbs than between fingers of the same hand (Beauchamp et al., 2009). Beauchamp et al. (2019) additionally tested the decoding accuracy of S2 in distinguishing between the left hands, right hand, left foot and right foot. They found accuracy was higher than when discriminating between fingers of the same hand. Furthermore, in the 4-way discrimination task, S2 showed a similar decoding accuracy as S1, but in the finger-discrimination task the accuracy was lower than that of S1. They suggest this is due to the larger receptive fields and less organized nature of S2 compared to S1, making S2 better at differentiating somatotopic locations that are farther apart, and S1 more sensitive to locations that are closer together. One possible explanation as to why Experiment 2 but not Experiment 1 found S2 to decode somatotopic touch locations is that the larger receptive fields of S2 and more diffuse somatotopy makes it better suited for discrimination and representation of touch locations on two hands rather than closer ones on fingers on the same hand. A third

cluster that was able to decode somatotopic location in Experiment 2 but not Experiment 1 was located in supplementary motor area. This area has been involved in tasks requiring planning internally generated movement that depends on sensory stimuli (Beurze et al., 2007). This could be an effect of the task demand that required participants to attend carefully to the vibrotactile stimuli on the hands to decide when to press a foot pedal in catch trials. Although there has been some controversy on the organization of the supplementary motor area, correlations between the location of surgically removed sections of SMA and patterns of motor deficits in postoperative patients suggests somatotopic organization since removing a particular part of the SMA correlated with a motor deficit in a specific area of the body rather than a generalized deficit (Fontaine, Capelle & Duffau, 2002). Somatotopic organization in the supplementary motor area supports the possibility of it showing activation patterns that allow for decoding of different somatotopic locations.

The univariate GLM analysis comparisons of tactile stimulation to baseline found clusters in S1and PMC, like the somatotopic MVPA for both experiments. This contrast also found S2 and SMA in both experiments, which were also found in the somatotopic MVPA for Experiment 2. In the context of the MVPA analyses, this suggests that patterns of activation elicited in these regions by tactile stimulation on the one finger are discernible from those elicited by tactile stimulation on another finger, which in turn might suggest that these areas are representing touch in a somatotopic frame of reference. In the context of the univariate GLM analysis, these brain regions are those that respond to tactile stimulation regardless of the differentiability of the activation patterns, which speaks to their involvement in perceiving the tactile stimuli but not to whether they represent different locations of

touch in any given frame of reference. Apart from these areas coinciding with the somatotopic MVPA results, several other brain regions were found in the GLM contrast of stimulation versus baseline, including insular cortex, cerebellum and IPS. Overall, both experiments successfully utilized MVPA to find areas representing touch locations in somatotopic reference frames under two conditions with varying distance between stimuli and provide novel evidence of PMC being among these areas.

In terms of external frames of reference, Experiment 1 found brain areas that differentiated between external space location in contralateral anterior cingulate cortex and contralateral visual cortex. This finding provides initial evidence for explicit representations of touch locations in external, hand-centered frames of reference. The anterior cingulate cortex has been involved in response selection and conflict monitoring (Walton et al., 2007; Botvinick, Cohen, & Carter, 2004), particularly related to making manual motor selections (Turken & Swick, 1999). Areas in close proximity to the cingulate cortex cluster found in Experiment 1 have also been implicated in a covert spatial attention network (Gitelman et al., 1999). It is surprising that this area would represent external space locations of touch when the task did not involve spatial conflicts that might require explicit dissociation of the relative left and right of the hand. We are unsure of why this region is associated with external, hand-centered processing, and believe this is worth further exploration.

The visual cortex is particularly interesting given the stimuli were solely vibrotactile and there were no overt visual cues about spatial locations. This finding in Experiment 1 opens the possibility of visualization element in localizing touch in an external, hand-centered frame of reference. Furthermore, this cluster is partially overlaps with areas in occipito-temporal cortex that have previously been found to

have a topographic representation of the human body (Orlov, Makin & Zohary, 2010). Additionally, the visual cortex cluster in Experiment 1 coincides with brain regions in the visual body network (Longo et al., 2012). Although the cluster in visual cortex is likely in LOC and possibly overlaps with the extrastriate body area (EBA), it is important to note that without retinotopic mapping, it is difficult to be certain. There is evidence for the LOC representing visual hand-centered space (Makin, Holmes & Zohary, 2007) and for the EBA to be selectively responsive to human bides or body parts (Downing et al., 2001).

Given that Experiment 1 found two areas that represent touch locations in external space, Experiment 2 aimed to replicate these findings using a postural manipulation of hand crossing over the body midline that would target a body-centered reference frame as well as increase the spatial distance between the touch locations in order to make activation patterns more discernable for the MVPA classifiers. The MVPA analysis did not show any areas that were able to decode touch in external space better than chance, and the GLM contrasts for left versus right space did not brain regions with significantly more activation for one side of space versus the other. It is surprising that we find areas that decode two very close points in space in Experiment 1, but no areas able to decode between two points separated by a larger distance on either side of the body midline, especially considering the hands-crossed manipulation of Experiment 2 has been shown to elicit strong effects in the behavioral, EEG and fMRI literature and given that the much larger sample size in Experiment 2.

One reason the results of both experiments differ could be the type of external reference frame on which touch was localized, where Experiment 1 used a hand-centered reference frame while Experiment 2 used a body-centered one. The main

distinction between the two studies is the manipulation of external space locations. Experiment 1 used only the right hand, which was always on its canonical side at the right hemispace and the changes in posture consisted of having the palm facing up or down. On the other hand, Experiment 2 utilized both hands and the change in posture involved having each hand at its corresponding canonical side or crossed along the body midline. Although the latter manipulation does increase the absolute distance between the two locations, both somatotopically and externally, the relative left and right are anchored to a different midline. In Experiment 2, that midline was trunk-centered and aligned with the body midline. In Experiment 1, the left and right external locations were relative to a hand-centered midline whose center ran through the middle of the right hand. It could be the case that each experiment elicited one particular external reference frame; alternatively, it is also possible that both external reference frames were being generated simultaneously in both experiments and differed in which reference frame was being prioritized based on the demands and context of the task.

There is evidence for both hand-centered and body-centered external space representations in previous literature. A case study with a patient following a stroke that affected pathways from the thalamus to the frontal eye fields and superior frontal gyrus on the right hemisphere showed intact tactile detection on the contralesional left hand but impaired tactile localization relative to a hand-centered midline; tactile stimuli delivered to the right side of the left hand were perceived as happening towards the left side and this pattern persisted regardless of whether the palm of the hand was facing up or down, or tilted by 90 degrees (Liu et al., 2020). If this bias was relative to a somatotopic frame of reference, then a bias towards the pinky when the

left hand was facing palm-down would be observed in conditions where the hand was facing up. Instead, with the palm facing up, the bias shifted towards the thumb. Additionally, when the left hand was facing down and tilted by 90 degrees clockwise, the bias remained towards the pinky. If the bias was relative to a different external frame of reference, such as a trunk-centered one, responses should have shifted towards the wrist, which would be the left side of the hand relative to the body midline. Instead, the bias was observed towards the pinky suggesting that the external frame of reference was hand-centered since the bias was still towards the left of the hand relative to its own midline. A similar pattern was seen in a patient with left tactile extinction who did not perceive stimuli presented to the relative contralesional side (Tinazzi et al., 2000). In one manipulation, stimuli were delivered to the thumb and pinky of the right hand in two postures, palm facing up and palm facing down. When the right hand was facing down, the patient extinguished stimuli on the thumb, meaning it was not perceived. When the right hand was facing up, stimuli on the pinky were extinguished instead. This also points to an external frame of reference that is not body-centered, but hand-centered. However, in both of these studies it is also possible that it is allocentric, meaning that stimuli locations are represented relative to each other. The same is true for the unilateral neglect patients tested in a study by Moscovitch and Behrman (1994). Stimulation was presented simultaneously on the left and right of one wrist when the palm of the hand was facing up and when it was facing down. In both conditions, the neglected side was dependent on a spatial frame of reference rather than a somatotopic one since the contralesional side of the wrist was neglected regardless of the hand position, but these results could be explained by a hand-centered or an allocentric external frame of reference. Considering this

evidence for hand-centered representations of touch in external space, the areas found to decode locations of touch in external space in Experiment 1 could be relying on this type of external space representation of touch rather than on a body-centered one.

Given the previous evidence for the existence of both hand- and body-centered external reference frames, each experiment could be relying on a different one. Both experiments could be tapping into body-centered reference frames, but it is unlikely since the larger distance in Experiment 2 would have probably replicated the Experiment 1 findings and improved discriminability of activation patterns. Both experiments could be utilizing an allocentric reference frame, but once again the larger distances in Experiment 2 should have at least replicated Experiment 1 findings. Therefore, it is likelier that Experiment 1 and Experiment 2 tapped into two different representations, each with their own frames of reference. Experiment 1 presented stimuli on the relative left and right side of the hand, suggesting a hand-centered frame of reference. Experiment 2 presented stimuli on the left and right of the body midline, suggesting a body-centered frame of reference. However, there is no way to determine whether one external reference frame was used exclusively in each experiment, or both were generated and the more relevant to the task was given priority. This phenomenon has been documented previously in a tactile Simon effect where multiple reference frames co-occurred and drove the effect to different degrees based on the experimental context (Medina et al., 2019). The Simon effect consists of faster response times when the stimulus and response occur on the same spatial side and was fist tested in the auditory domain (Simon & Small, 1969). Medina and colleagues (2019) attached tactile stimulators to both pinky fingers and thumbs of participants and stimuli were presented under different conditions across a series of experiments

where they were asked to judge whether the stimulus was low- or high-intensity using foot pedals. By manipulating whether the hands were placed palm-up or palm-down and whether they were crossed or uncrossed over the body midline, it was possible to test multiple reference frames. In one experiment, they tested the tactile Simon effect with crossed and uncrossed hands and found significant somatotopic and hand-centered Simon effects. This suggests the simultaneous existence of two reference frames while performing the task. In another experiment they compared presenting stimuli to one hand only versus two hands in order to tease out hand- and trunk-centered reference frames. In both conditions there was a hand-centered Simon effect, but the trunk-centered Simon effect was absent from the one-hand condition, suggesting the task demands can affect whether a given spatial coding is generated or not. In this case a somatotopic or trunk-centered coding was not spatially salient. It is therefore possible that Experiment 1 in the present study elicited a hand-centered reference frame and an absent or weakened trunk-centered one because the latter was less salient since all stimuli were confined to one hand, while Experiment 2 instead required a trunk-centered spatial coding alone or in conjunction with a weaker hand-centered one.

In conclusion, this study provides evidence for neural correlates of touch localization in somatotopic and external frames of reference and suggests differences in the representation of body-centered and hand-centered external frames of reference for touch location. It also opens the possibility of a visual component in localizing touch in external space. We found contralateral S1, and premotor cortex encoded somatotopic touch locations regardless of hand or arm posture, as well as additional areas in S2, SMG and SMA when stimuli were presented across both hands rather than

within the same hand. These results are in agreement with previous studies that used MVPA to decode touch location when somatotopic and external frames of reference were confounded (Beauchamp et al., 2009; Kim et al., 2015) and offer initial evidence of premotor cortex encoding somatotopic touch locations. With regards to the neural correlates of tactile location representation in external reference frames, we found areas of contralateral anterior cingulate cortex and visual cortex that were able to encode these locations in hand-centered external space. Surprisingly, we did not find areas that explicitly encoded touch locations in trunk-centered external space.

In the future, it would be important to further disambiguate hand-centered and body-centered frames of reference, possibly by designing a 4-way MVPA classification paradigm with 4 spatial locations and 4 somatotopic ones. Future research could disambiguate hand-centered or allocentric external frames of reference from a body-centered one using a similar paradigm as Experiment 1 with palm-up and palm-down conditions on the hand's canonical side and also testing these two hand postures when the hand is on the opposite side of the body midline. This would allow the data to be grouped somatotopically, and in two types of external frames of reference: hand-centered and body-centered.

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Appendix

IRB/HUMAN SUBJECTS APPROVAL

University of Delaware *IRB Approved From: 07/11/2020 to: 07/21/2021*

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

Title of Project: Neural networks underlying the integration of knowledge and perception: MRI studies

Principal Investigators: Timothy Vickery, Ph.D

You are being invited to participate in a research study. This consent form tells you about the study including its purpose, what you will be asked to do if you decide to take part, and the risks and benefits of being in the study. Please read the information below and ask us any questions you may have before you decide whether or not you agree to participate.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to learn more about human perception. We are interested in how knowledge and context influences the way sensory information is processed and in turn neural functions underlying perceptual experiences of the world and the body. To examine these questions, we will examine your behavior during tasks as well as your neural activity, as measured using MRI, during tasks.

You are being asked to take part in this study because we are interested in how normal adult humans learn about the world and the body. You must be between the ages of 18 and 40, have normal or corrected to normal vision, normal hearing, are not pregnant, have no history of psychological or neurological conditions, are not currently taking psychoactive drugs, and have no non-removable metal in or on your body.

WHAT WILL YOU BE ASKED TO DO?

The experiment will take place at the Center for Biomedical and Brain Imaging. You will first be asked to complete instructions. You will be interviewed and asked to fill out forms. Before the actual experiment, you may be seated in front of a computer to complete practice. Next, we will complete a series of brain scans while you either rest or do tasks. You will be asked to perform a variety of tasks, including see visual stimuli and making simple choices using the keyboard and mouse; receiving tactile stimuli on your hand or arm and reporting if and where you felt stimuli and/or other body states. You will lie on your back inside the MRI machine while images of your brain are collected. A projector or monitor will be viewed via a mirror. You will hold one or two button boxes in order to make responses. You will also be fitted with a belt that measures respiration and a finger sleeve that measures heart rate. The experiment will take no more than 120 minutes to complete in one session, with no more than 90 minutes taking place in the MRI machine. You will be given frequent breaks (approximately every 10 minutes) to rest in between tasks.

What is involved in the study?

This study involves measuring the anatomy and activity of your brain using magnetic resonance imaging (MRI). You will be required to lie completely still on the bed that will slide into the bore of the MRI scanner. Functional MRI (fMRI) is an MRI scan of your head/brain that measures the activity of your brain

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while you do specific tasks. An MRI head coil will surround your head (a head coil is an apparatus that is used to measure signals emitted from your brain). Your head will be supported with foam pads to make you more comfortable and to help you to keep your head still. Pillows and other cushions may be used (e.g., under your knees) to make you more comfortable. Several scans will be taken and you will need to remain still on the table for about 10 minutes at a time. You will be given periodic breaks, in which you will be able to relax but you will be asked to remain on the scanner bed for the duration of the session, which should last about 90 minutes.

We may monitor your eye positions using a camera mounted at the bore of the magnet. This eye recording is non-invasive and will require only short calibration and validation procedures occasionally during the experiment. These procedures involve simply moving your eyes to targets marked on the stimulus display screen.

You may additionally be asked to wear devices, such as a small clip on your finger to measure your heart rate, and/or a belt around your torso (over the clothing) to measure your breathing rate. You will be able to communicate with us via a built-in intercom. You will also be provided with an emergency bulb that you can squeeze at any time to let us know you want to come out of the MRI scanner. If at any time you feel uncomfortable or unwilling to continue, no matter what the reason, you can request to immediately stop the study, and the operator will remove you from the scanner. All scans are conducted by a certified MRI Technologist or other experienced personnel with relevant safety training.

During scans, you will need to leave your belongings in the control room. The control room is secure and accessible only to the researchers.

This is not a clinical evaluation

The images of your brain collected in this study are not intended to reveal illness, in part because this research protocol is not designed for clinical diagnosis. Your images will not be routinely examined by a clinical radiologist. The personnel at the MRI Center are not qualified to medically evaluate your images. However, if, in the course of collecting images, we have any concerns, we may show your scans to a clinical radiologist, who may suggest that you obtain further diagnostic tests. Do not rely on this research MRI to detect or screen for abnormalities.

At the investigator's discretion, you may view your images and receive digital copies of them. These images will show the inside of your body and you should be aware of the potential distress or discomfort that may occur by viewing these type of images.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

MRI is an imaging technique that uses radio waves and magnetic fields to produce images of internal structures in your body. While it is commonly used in hospitals, the MRI scanning used in this study is not part of a medical evaluation. Unlike X-rays, the MRI does not use any ionizing radiation, and it does not use radioactivity, so there is no radiation related risks from having an MRI scan done on you. Below there is a description of MRI related risks and what is being done to reduce any possible risks associated with them:

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Metal: The MRI scanner produces a constant strong magnetic field, which may cause any metal implants, clips, or implanted medical devices within your body to shift position or malfunction. You will not be allowed to participate in this study if you have any implanted metal, clips or devices. You will be screened to make sure that it is safe for you to enter a strong magnetic field. Please provide us with as much information as you can, for example if you had surgery in the past, so that we may decide whether it is safe for you to be a participant. Metallic objects brought into the MRI environment can become hazardous projectiles and can also interfere with the data quality. To minimize this risk, metal earrings, other piercings, necklaces and any other metal in contact with your body must be removed prior to the study. You must also remove all items from your pockets, including coins, electronics (including cell phones and hearing aids) and wallets. You must remove belts with metal buckles, and you may be asked to change into a gown that we will provide if your clothing contains significant metal, including metal underwire bras.

Pregnancy: Exposure to MRI scanning might be harmful to an unborn child. Although there are no established guidelines at this time regarding MRI and pregnancy, you should be informed that there is a possibility of a yet undiscovered pregnancy related risk. If you know or suspect you may be pregnant or if you do not want to expose yourself to this risk, you will be excluded from participating in this study.

Inner ear damage: MRI scanning produces loud noises that can cause damage to the inner ear if appropriate hearing protection is not used. Earplugs and/or headphones will be provided to protect your ears.

Claustrophobia: When you are inside the MRI scanner, the "bore" of the scanner will surround your head and torso. We are interested in brain structure and activity, and your head will be centered inside a close-fitting scanning coil positioned in the bore of the scanner. If you feel anxious in confined, spaces you may not want to participate. If you are unsure, you can try our "mock" scanner to evaluate your comfort level with the enclosed space of the magnet bore. If you decide to participate and begin to feel claustrophobic, you will be able to tell us via the intercom or the squeeze ball and we will discontinue the study immediately.

Burns: In rare cases, contact with the MRI transmitting and receiving coil, conductive materials such as wires or other metallic objects, or skin-to-skin contact that forms conductive loops may result in excessive heating and burns during the experiment. The operators of the MRI scanner will take steps, such as using foam pads when necessary, to minimize this risk. Tattoos with metallic inks can also potentially cause burns. In addition, please let the MRI operator know immediately if you experience any heating or burning sensations during a scan. The scanning session will be stopped as soon as you tell the operator.

Nerve or muscle stimulation. While the scanner is operating, there is a small chance that the rapidly changing magnetic fields could cause a slight tingling sensation or a muscle twitch, usually felt in the upper arms or torso. While these sensations may be startling, they are not dangerous or a health risk, and they have no lasting consequences. The sensations should stop when the scan ends. Because these sensations may nevertheless be distracting or even possibly uncomfortable, please squeeze the signal bulb to alert the scanner operator if you feel tingling or muscle twitching, and we will immediately stop the scan. You will then have the opportunity to choose to withdraw from the study or to continue.

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Other Risks. Besides the risks listed above, there are no other known risks from the magnetic field or radio waves at this time. Although functional MRI scanning has been used for more than 20 years, long-term effects are unknown.

WHAT ARE THE POTENTIAL BENEFITS?

You will not benefit directly from taking part in this research. However, the knowledge gained from this study may contribute to our understanding of human cognitive function.

HOW WILL CONFIDENTIALITY BE MAINTAINED? WHO MAY KNOW THAT YOU PARTICIPATED IN THIS RESEARCH?

All information obtained during the study will be held in strict confidence to the fullest extent possible by law. In no case will your personal information be shared with any other individuals or groups without your expressed written consent. Your images will be stored on secured computer servers and will be archived indefinitely. The experimental data acquired in this study may, in an anonymized form that cannot be connected to you, be used for teaching purposes, be presented at meetings, published, shared with other scientific researchers or used in future studies. Your name or other identifying information will not be used in any publication or teaching materials without your specific permission. Your research records may be viewed by the University of Delaware Institutional Review Board, which is a committee formally designated to approve, monitor, and review biomedical and behavioral research involving humans. Records relating to this research will be kept for at least three years after the research study has been completed.

Your behavioral data and images will be de-identified and linked to a non-identifying alphanumeric code. The link between that code and your identity will be stored in a secure, password-protected document, along with the time and date of your participation, your name, and contact info (telephone and email). This document will only be accessible only to approved researchers on this protocol. The linking information will only be used in case of the need to contact you regarding any incidental findings on your brain images, or in the case that that your scans are used as part of a future study (with your consent). The linking information will never be shared with researchers who are not approved as part of this protocol.

WILL THERE BE ANY COSTS TO YOU FOR PARTICIPATING IN THIS RESEARCH?

There are no costs associated with participating in the study.

WILL YOU RECEIVE ANY COMPENSATION FOR PARTICIPATION?

You will receive a minimum of $5 per half hour of participation on completion. The amount will be prorated according to the time spent participating if you decide to withdraw from the study for any reason. If you were required to park in a municipal lot for a fee, we will pay for your parking fee for the duration of your time participating in the study.

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USE OF DATA COLLECTED FROM YOU IN FUTURE RESEARCH:

The research data we will be collecting from you during your participation in this study may be useful in other research studies in the future. Your choice about future use of your data will have no impact on your participation in this research study. Do we have your permission to use in future studies data collected from you? Please write your initials next to your preferred choice.

_____ **YES** _____ **NO**

DO YOU HAVE TO TAKE PART IN THIS STUDY?

Taking part in this research study is entirely voluntary. You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide not to participate or if you decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which you are otherwise entitled. Your decision to stop participation, or not to participate, will not influence current or future relationships with the University of Delaware.

As a student, if you decide not to take part in this research, your choice will have no effect on your academic status or your grade in the class.

If, at any time, you decide to end your participation in this research study, please inform our research team by telling the investigator(s). If you do not complete all procedures listed in this form, you will only receive compensation for the tasks you finish.m

WHO SHOULD YOU CALL IF YOU HAVE QUESTIONS OR CONCERNS?

If you have any questions about this study, please contact Principal Investigator Dr. Timothy Vickery at 302-831-1511, or e-mail him at tvickery@psych.udel.edu.

If you have any questions or concerns about your rights as a research participant, you may contact the University of Delaware Institutional Review Board at hsrb-research@udel.edu or (302) 831-2137.

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`Q1QBN WaTHYour signature on this form means that: 1) you are at least 18 years old; 2) you have read and understand the information given in this form; 3) you have asked any questions you have about the research and the questions have been answered to your satisfaction; and 4) you accept the terms in the form and volunteer to participate in the study. You will be given a copy of this form to keep.

_____	_____	_____
Printed Name of Participant	Signature of Participant	Date
_____	_____	_____
Person Obtaining Consent (PRINTED NAME)	Person Obtaining Consent (SIGNATURE)	Date

Participant's Initials _____