

Functional and Structural Brain Differences Associated with Mirror-Touch Synaesthesia

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Abstract

Observing touch is known to activate regions of the somatosensory cortex but the interpretation of this finding is controversial (e.g. does it reflect the simulated action of touching or the simulated reception of touch?). For most people, observing touch is not linked to reported experiences of feeling touch but in some people it is (mirror-touch synaesthetes). We conducted an fMRI study in which participants (mirror-touch synaesthetes, controls) watched movies of stimuli (face, dummy, object) being touched or approached. In addition we examined whether mirror touch synaesthesia is associated with local changes of grey and white matter volume in the brain using VBM (Voxel-based Morphometry). Both synaesthetes and controls activated the somatosensory system (primary and secondary somatosensory cortices, SI and SII) when viewing touch, and the same regions were activated (by a separate localizer) when feeling touch – i.e. there is a mirror system for touch. However, when comparing the two groups, we found evidence that SII seems to play a particular important role in mirror-touch synaesthesia: in synaesthetes, but not in controls, posterior SII was active for watching touch to a face; activity in SII correlated with subjective intensity measures of mirror-touch synaesthesia (taken outside the scanner), and we observed an increase in grey matter volume within the SII of the synaesthetes' brains. In addition, the synaesthetes showed hypo-activity when watching touch to a dummy in posterior SII. We conclude that the secondary somatosensory cortex has a key role in this form of synaesthesia.

Introduction

Seeing somebody else being touched activates not only the visual regions of the brain as measured from fMRI but, additionally, parts of the somatosensory network (for a review see Keysers et al., 2010). This finding is consistent with the notion that we represent the thoughts, feelings and sensations (such as touch) of others via a process of simulation. However, there are many aspects of this process that are not fully understood. For instance, in the domain of observed touch there is inconsistency in whether the primary and/or secondary somatosensory cortices are activated by the sight of touch. There is also a lack of clarity as to what the functional contribution of these regions (and sub-regions within them) is in coding the observation of touch. For instance, there is evidence that somatosensory cortices are also activated by observing touch to inanimate objects as well as to humans (e.g. Keysers & Perrett, 2004; Ebisch et al., 2008) which raises questions about what this activity corresponds to: an anthropomorphic simulation of touch feeling; tactile activity linked to the touch-inducing action; or the coding of 'contact' between two solid bodies in some abstract sense. A related question is what prevents observed touch from giving rise to overt feelings of touch if both activate the same system. Some people do report tactile sensations from observing touch as a result of brain injury (Bradshaw & Mattingley, 2001; Halligan et al., 1996), amputation (Fitzgibbon et al., 2010; Goller et al., 2013), or in the developmental condition that we term mirror-touch synaesthesia (Banissy & Ward, 2007). In this study we examine the neural basis of mirror-touch synaesthesia and, in addition, explore the neural network for observing touch in the general population.

Mirror-Touch Synaesthesia (MTS)

Blakemore et al. (2005) reported the first case of mirror-touch synaesthesia, C, using an fMRI study. C reported that seeing someone else being touched triggered tactile sensations on the corresponding part of her own body. There was no known onset to this but there was a familial history of developmental synaesthesia (such as grapheme-colour synaesthesia). C did not report sensations when observing touch to objects. With this in mind, Blakemore et al. (2005) contrasted observed touch to the face versus an object in both C and controls. In controls, the comparison of face-touch versus object-touch activated a network of regions including regions within the primary and secondary somatosensory cortex, premotor cortex, intra-parietal area and superior temporal sulcus. C demonstrated hyper-activity within many of these same regions (and additional activity in anterior insula). This hyper-activity was interpreted as the neural correlate of her unusual conscious experience.

To date, this is the only study that has examined the neural (functional) basis of this type of synaesthesia and nothing is known about structural brain differences (if any) associated with it.

However, a series of behavioural studies have shed some light on the cognitive characteristics of the condition. Banissy and Ward (2007) found that observed touch to the face (and the synaesthetic touch that corresponds to it) affected the ability to discriminate the laterality of real touch in mirror touch synaesthesia. The same is not found for touch to objects (Banissy & Ward, 2007) or flashes of light projected onto a face (Banissy, Cohen-Kadosh, et al., 2009). The prevalence for this type of synaesthesia is estimated as 1.6% and falls into two spatial subtypes (Banissy, Cohen-Kadosh, et al., 2009). For those with the more common, specular spatial mapping observed touch to the right cheek is felt on the left cheek (as if looking in a mirror). For those with the, rarer, anatomical mapping observed touch to the right cheek is felt on the right cheek (as if rotated into an external perspective).

The profile of behavioural differences is broader and is by no means limited to observing touch. Tactile acuity on the fingertip (measured using gratings) is more sensitive (Banissy, Walsh, et al., 2009). Also, mirror-touch synaesthetes score higher on self-reported measures of empathy (Banissy & Ward, 2007) and perform better on expression recognition, but not identity recognition/memory, for faces (Banissy et al., 2011). These findings are consistent with a role for sensorimotor processes in wider aspects of social perception (Adolphs et al., 2000; Banissy et al., 2012; Banissy et al., 2010; Pitcher et al., 2008; Shamay-Tsoory et al., 2009). Finally, although most of the research has used facial stimuli, the basic phenomenology is preserved when other body parts are presented, including presenting stimuli from different perspectives (Holle et al., 2011). Interestingly, the intensity of the synaesthetic touch is reduced when dummy body parts and dummy faces are used (Holle et al., 2011). This suggests that the synaesthesia depends on inferred animacy (i.e. whether the touched object can experience touch) rather than visual appearance alone. This observation also motivated the design of the present study in which faces, dummy faces and objects are contrasted.

The Neural Network for Observed Touch in the General Population

Before considering the key studies, it is important to offer a brief overview of the functional and structural anatomy of the somatosensory system. The term 'primary somatosensory cortex' (SI) is used as a short-hand for a set of somatotopically organised regions lying posterior to the central sulcus and includes (from anterior to posterior) Brodmann areas (BA) 3, 1 and 2 (Kaas, 2004). BA3 receives cutaneous and proprioceptive input via the thalamus, whereas BA1 and BA2 represent a second processing stage beyond BA3 and connect with regions in posterior parietal cortex (Iwamura, 1998). Secondary somatosensory cortex (SII) is again typically used as a short-hand for a collection of regions lying in the parietal operculum. There are reciprocal connections between SI and SII,

although feedforward connections from SI to SII predominate over feedback (Pons et al., 1987). The receptive fields of SII neurons tend to be much larger than SI neurons (Sinclair & Burton, 1993). Within SII, several cytoarchitecturally distinct sub-areas have been identified recently (OP1 – OP4, Eickhoff, Grefkes, et al., 2007; Eickhoff, Paus, et al., 2007). Eickhoff et al. (2007) used fMRI for a functional characterization of these sub-areas and found that whilst OP1 is primarily somatosensory, OP4 is more involved with sensori-motor integration.

Functional imaging studies of observed touch in non-synaesthetes have revealed only partial agreement with the study of Blakemore et al. (2005) discussed earlier. Some of the differences may be methodological. One important difference is the choice of baseline stimuli. Whereas Blakemore et al. directly compared (observations of) face touch to object touch, almost all other studies use a no-touch baseline (e.g. in which an object approaches the stimulus but does not touch it). Such a baseline is not only better matched visually, but also avoids the problem that the sight of a body (touched or not) may affect somatosensory activity (e.g. Kennett et al., 2001). Keysers et al. (2004) compared observed touch to a leg (stroked with a stick) to observing the leg (a moving stick not making contact) and found activity in SII but not SI. They found similar results when a similar object was used (rolls of paper that were touched). One explanation for the absence of SI activity in the Keysers study might be the way in which touching occurred. In the stimuli of Keysers et al. (2004), body parts were touched with a stick whereas Blakemore et al. (2005) used a hand for this. Indeed, some of the SI coordinates reported by Blakemore et al. (2005) are in the hand area rather than face area. Other studies show that certain regions of SI (notably BA2 and BA1, but not BA3) are activated by the observation of actions (Gazzola & Keysers, 2009; Meyer et al., 2011) and, in their review, Keysers et al. (2010) conclude that “BA2 or BA1 activation relates to the toucher rather than to the sensations of the person being touched” (p. 421). In support of this, Ebisch et al. (2008) directly compared the object being touched (human arm v. chair) with the object doing the touching (human hand v. palm frond blowing against it). They found that the sight of touch activated SII in all conditions (suggesting that this codes a more abstract, semantic notion of touch) but only SI, and only weakly, when a human hand was doing the touching (and irrespective of what was touched). However, the perceptual qualities of the observed touch were not particularly well matched in the Ebisch study (the palm frond would be gentler). Furthermore, activity in SI relating to felt touch is generally greater when coming from another human than a stick (Kress et al., 2011). The same may apply to observed touch too.

Mirror touch synaesthesia could potentially inform theories of tactile consciousness given that the same visual stimulus gives rise to a reportable experience in this group but not controls. The notion that hyper-activity within the somatosensory system is linked to conscious tactile experiences (Blakemore et al., 2005) is underspecified in terms of which regions (if any) are

particularly important. Keysers et al. (2010) speculate that activity in BA3 (the earliest cortical region within SI) may be what discriminates mirror touch synaesthetes from controls. However, a case study of a different form of tactile-based synaesthesia points to a possible crucial role for SII. Beauchamp and Ro (2008) report a patient with an acquired lesion of the right thalamus that led to impaired tactile perception on her left side. Within a year or so of the lesion the patient began to report that sounds often triggered tactile sensations on her left hand/arm. Functional imaging showed that SII (both OP1 and OP4), but not SI, was associated with this: it showed greater activity for sounds that triggered a conscious tactile experience than sounds that did not (comparing within the patient) and responded less to real touch (comparing patient to controls).

The aims of the present research are to examine the neural correlates of observing touch to different classes of objects (human face, dummy, object). In addition, we include appropriate baseline stimuli (no-touch conditions) and the touch is not delivered by a hand (to reduce the possibility that somatosensory activity is related to observing hand actions). A further key aim is to understand the neural basis of mirror-touch synaesthesia, including any structural brain differences, and determine which functional regions may be linked to these unusual conscious experiences.

Methods

The basic design for the experiment was a 2 x 3 x 2 factorial, with the factors Touch (Sight of Touch, No-Touch) and Target (Face, Dummy, Object) within subjects and Group (control v. MTS) between subjects. The face was chosen as a target stimulus so that we could establish whether SI activity is related to the face, the hand, or both (i.e. the touched or the toucher). We also extended the design to include dummy faces. Dummies are visually more similar to real bodies than they are to objects, but in terms of their propensity to induce mirror-touch synaesthesia they rarely evoke mirror-touch sensations (Holle et al., 2011).

Participants

Ten participants with mirror-touch synaesthesia took part (2 male, age range 17 - 57). This did not include the previously reported case, C. All cases of mirror-touch synaesthesia were confirmed on a visual-tactile spatial congruity paradigm designed to provide evidence for the authenticity of the condition (Banissy, Cohen-Kadosh, et al., 2009; Banissy & Ward, 2007). All of them reported a specular spatial mapping. For the functional imaging study, 16 control participants took part (5 male, age range 20 - 43). For the VBM analysis, structural scans were taken from 42

non-synaesthetic controls (14 male, mean age: 24.1, range 19 – 43) including the 16 control participants from the fMRI study. One synaesthete participant was left-handed, all other participants were right-handed. All gave written informed consent and the study was approved by the Research Governance and Ethics committee of the Brighton and Sussex Medical School. Participants received financial compensation at a rate of £5 per hour.

fMRI Experiment

Stimulus Materials

All videos were edited to the same length (5 s) and depicted an event in which a paint brush continuously stroked a target stimulus (touch condition) or performed a stroking action next to the target (no-touch conditions). The hand controlling the paint brush was never visible. The targets consisted either of a human face (male or female), a dummy face (male or female face of a mannequin) or an object (a fan or a loudspeaker). The default movement of the paint brush in the videos was a slow vertical movement (e.g., from the top to the bottom of the cheek), with one complete cycle (up and down) taking about one second. In addition to these frequent vertical movements, some videos also contained a few horizontal movements (e.g., from the front to the back of the cheeks). For each of the six targets, we recorded two versions from two slightly different perspectives to create more variability in the stimulus set. Given the known laterality of the somatosensory system, and in order to increase our statistical power, the observed touch was always to the model's anatomical left side.

Procedure

The videos were presented in 23-second blocks by editing together four different video clips from the same condition. The order in which the four video clips were presented within each block was random. At the end of each block, following the four videos, participants were asked to indicate via button press whether they counted either '4 or less' or 'more than 4' horizontal brush movements in the preceding block (adapted from Schaefer et al., 2009). The display prompting them to respond remained on the screen for three seconds. During each of the two video runs, there was a total of 28 blocks, comprising four repetitions of each of the six experimental conditions and four repetitions of the 23-second fixation baseline block. The order of presentation of the blocks was counterbalanced within and between subjects.

We also included an 8-min touch localizer run. In this part, the experimenter touched either the left or the right cheek of the participant, similar to the stimuli in the video stimuli. The participants had their eyes closed during this part of the experiment. Stimulation was carried out

using a wooden stick covered with soft tissue. The touch localizer was a blocked fMRI experiment, alternating periods of stimulation (20 sec) with an equal amount of rest.

After the scanning session, the stimuli were shown again to the participants. This time they were asked to rate the intensity of any synaesthetic touch on a scale ranging from 0 (no sensation at all) to 10 (as intense as if I were the person in the video).

Data Acquisition

Participants were placed in the scanner in a supine position. Visual stimuli were presented on a computer screen outside of the scanner, which participants could see via mirror-glasses. To minimise signal artefacts originating from the sinuses, axial slices were tilted 30° from the inter-commissural plane. Thirty-six slices (3mm thickness, 0.75 mm inter-slice gap) were acquired on a 1.5 T MR Scanner (Siemens Avanto) with an in-plane resolution of 3 x 3 mm (TR = 3.3s per volume, TE = 50 ms).

Data Analysis

FMRI data were analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) and Matlab R2007b (The MathWorks Inc, Natick, MA, USA). Standard spatial pre-processing (realignment, coregistration, segmentation, normalization to MNI space, and smoothing with an 8 mm full-width at half-maximum, FWHM, Gaussian kernel) was performed. Voxel size was interpolated during pre - processing to isotropic 3 × 3 × 3 mm.

For the statistical model, we included regressors for each experimental condition, covering the duration of the tactile or visual blocks (20 s each). We also included six movement regressors to regress out any residual variance due to head movement. Group analyses were carried out using the Full Factorial procedure of SPM8. To protect against false-positives, a double threshold was applied, by which only regions with a Z -score exceeding 2.58 ($p < 0.005$, uncorrected) and a volume exceeding 15 voxels (equivalent to 405 mm³) were considered (corresponding to $p < 0.05$, corrected). This was determined in a Monte Carlo simulation using a Matlab script provided by Scott Slotnick (see <http://www2.bc.edu/~slotnics/scripts.htm>).

Anatomical Localization of Group Differences

We were particularly interested in whether an observed group difference was located within the somatosensory system or outside of it. For this we used three localization strategies. First, we tested whether the peak coordinate of a cluster was within an anatomical mask of the somatosensory system (see supplementary online material). This mask consisted of BA3a, BA3b, BA1, BA2, OP1 and OP4, as defined by the SPM Anatomy Toolbox (Eickhoff, Paus, et al., 2007). For activations that fell within the primary somatosensory system, we then additionally checked for

somatotopy (i.e., whether an activation fell within the hand or face area of SI; (see Eickhoff et al., 2008). Finally, we checked whether a peak was within a mask defined by our face touch localizer (see Results).

Voxel-Based Morphometry (VBM)

Data Acquisition

High-resolution anatomical images were acquired using a T1-weighted MPAGE sequence (voxel size 0.9 x 0.9 x 0.9 mm) on the scanner described above.

Data Analyses

The T1-weighted images were prepared for voxel-based morphometry using the 'estimate & write' option of the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/download/>) which is itself an extension of the 'New Segment Toolbox' implemented in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). Using the default options of the VPM8 toolbox, images were segmented into grey matter (GM) and white matter (WM). The GM and WM images of each subject were then transformed to MNI space using an existing high-dimensional DARTEL template derived from 550 healthy brains of the IXI-database (www.brain-development.org). Subsequently, the GM and WM images were spatially smoothed (FWHM = 8mm). The pre-processed GM and WM images from all participants were then analyzed statistically with two-sample t-tests using age and gender as additional regressors of no interest. A significance threshold corrected for multiple comparisons was determined using the above-mentioned Monte Carlo simulation ($Z > 3.09$; $p < 0.001$, uncorrected and extent greater than 60 voxels (or 202 mm³), corresponding $p < 0.05$, corrected).

Results

For the contrasts reported below RF and LF refer to actual touch to the right and left face respectively (during the tactile localizer); PT, DT and OT refer to observed touch to a person, dummy and object respectively; and PN, DN and ON refer to observing no-touch to a person, dummy and object respectively.

Behavioral Results

Within the scanner, most participants found the task of counting the number of horizontal strokes easy. However, one synaesthete and one control participant were excluded from the fMRI analysis because of an excessive amount of errors on the behavioural task (> 30% errors). For the remaining participants, the synaesthetes scored 93.7 % correct ($SD = 7.04$), on average, and the

controls scored 89.5 % correct ($SD = 6.33$). Accuracy did not differ significantly between the two groups ($t(22) = 1.51, p = .145$).

Outside of the scanner, the synaesthetes rated the subjective intensity of any felt touch in response to viewing the previously shown movies. These ratings are summarised in Figure 1 for the 9 synaesthetes included in the fMRI analysis. An ANOVA using the factors Touch (Touch, No-Touch) and Target (Person, Dummy, Object) revealed main effects of Touch ($F(1,8) = 10.33, p = .12$) and Target ($F(2,16) = 8.61, p = .003$). Additionally, there was a trend towards an interaction between both factors ($F(2,16) = 2.73, p = 0.09$). Given this trend and previous research indicating that real body parts are particularly important (Holle et al., 2011), we conducted post-hoc tests comparing the three touch conditions with each other (PT, DT, OT). These tests indicated that observing touch to a person elicited significantly more intense experiences than observing touch to a dummy ($t(8) = 2.84, p = 0.02$) or an object ($t(8) = 2.78, p = 0.02$). The difference between Dummy Touch and Object Touch was not significant ($t(8) = 1.78, p = 0.11$).

INSERT FIGURE 1 ABOUT HERE

fMRI data: Touch Localizer

We first report activations elicited by actual touch, collapsed across both groups (synaesthetes and non-synaesthetic controls).

Main effect of touch–baseline: [(RF + LF) – baseline]

The comparison of the two actual touch conditions relative to rest resulted in bilateral activation of a number of somatosensory regions, including the more ventral face area and the more dorsal hand area of the primary somatosensory cortex (see Fig. 2a; Supplementary Table, 1). Secondary somatosensory cortex (OP1) was also activated bilaterally. Other regions activated by the actual experience of touch included the left premotor cortex (BA6), middle temporal gyrus, putamen and the cerebellum.

INSERT FIGURE 2 ABOUT HERE

fMRI data: Observing Touch – No Touch

Activations to the observation of touch in the control group

The main effect of observing touch, relative to observing no-touch was calculated as follows: [(PT + DT + OT) – (PN + DN + ON)]. In the non-synaesthetic group, observing the touch videos,

relative to no-touch videos, produced bilateral activations in the postcentral gyrus, intraparietal sulcus and lateral occipital cortex, as well as the left precentral gyrus and posterior insula (see Fig. 2b).

Common activations between observed and actual touch in the control group

Areas that are active both for observing touch, relative to observing no-touch, as well as for touch to subject's face were identified using the following contrast: $[(PT + DT + OT) - (PN + DN + ON)] \cap [(RF + LF) - \text{baseline}]$. This contrast resulted in activation of the face area of SI, bilaterally, as well as the left hand area of SI (see Table 1, Figure 2b). Additionally, left OP1 and the cerebellum were activated.

Activations to the observation of touch in the synaesthetic group

Similar to the pattern in the non-synaesthetic group, the synaesthetes showed bilateral activations to the observation of touch in the following areas: Postcentral gyrus, intraparietal sulcus and lateral occipital cortex, as well as the posterior insula (see Fig. 2c). However, synaesthetes showed no activation in the left precentral gyrus.

Common activations between observed and actual touch in the synaesthetic group

Areas that are active both for observing touch, relative to observing no-touch, as well as for touch to subject's face were calculated as previously done for controls. In the synaesthetic group, this contrast showed significant activations in the face area of SI, bilaterally. Additionally, the left hand area of SI, left OP1 and the right cerebellum (see Fig. 2c, Table 1) were activated.

Common activations across stimulus types to the observation of touch

In this conjunction analysis, we isolated areas showing an effect of observing touch relative to observing no-touch for each of the three stimulus types: $(PT - PN) \cap (DT - DN) \cap (OT - ON)$. This analysis revealed significant activation in the left middle occipital gyrus (MNI: -33 -94 -5) and a portion of SI (MNI: -54 -19 43, 90% BA2*, 80% BA1; see Figure 3f). The SI activation was localized to the left ventral face area suggesting that this aspect of SI responds both to touch to a face (real and dummy) delivered by an inanimate object and, in some contexts, to touch between two inanimate objects (e.g. a stereo speaker and a paintbrush).

Summary

Observing touch activates a network of regions that are involved in the perception of actual touch. Within SI, this activity is found within the face area (as functionally defined) suggesting that

SI activity relating to observed touch is not a sole reflection of the simulation of hand actions (Keysers et al., 2010). However, simulation of hand actions – even when the hand is not visible – may additionally occur (there is a separate cluster of activity within the hand region). One cluster of activity found within the left ventral face area of SI was associated with all three kinds of stimuli suggesting this area may code the contact between two bodies in some abstract sense, or that objects can sometimes be incorporated within bodily representations. In this first analysis, both synaesthetes and controls showed quite similar activation patterns for the observation of touch. This may be due to the fact that we collapsed across stimulus types, although observed touch to faces is much likely to induce synaesthetic touch than observed touch to dummies or objects (see Figure 1). The next analysis therefore directly targeted group differences separately for each stimulus type.

INSERT TABLE 1 ABOUT HERE

fMRI data: Synaesthetes v. Controls

Significant group differences for the observation of touch to a human face

To identify brain regions showing stronger activation for the observation of face touch in synaesthetes, relative to controls, we calculated the interaction between Group and Touch for all face stimuli: $\text{SYN}(\text{PT} - \text{PN}) - \text{CON}(\text{PT} - \text{PN})$. The results are summarised in Table 2 and Figure 3. This contrast showed activation in the left SII (OP1), the left dorsal face area of SI, as well as the right posterior temporal lobe. While both of the left-hemispheric activations were within our anatomical mask of the somatosensory system (see Methods), only left OP1 was additionally activated by the touch localizer. Thus, when synaesthetes are presented with visual stimuli that typically elicit synaesthetic experiences of touch (observing touch to a human face), one component of their ‘tactile mirror system’, namely the left OP1, shows increased activation, relative to controls.

No significant activations were observed for the reverse interaction: $\text{CON}(\text{PT} - \text{PN}) - (\text{SYN}(\text{PT} - \text{PN}))$.

Significant group differences for the observation of touch to a dummy face

We first tested for brain regions showing stronger activation to the observation of touch to a dummy in synaesthetes, relative to controls. No significant activations were observed in the corresponding interaction contrast: $\text{SYN}(\text{DT} - \text{DN}) - \text{CON}(\text{DT} - \text{DN})$.

In the reverse interaction, we observed a number of significantly activated regions, including the supramarginal gyrus (PFt, PFop) and superior temporal gyrus bilaterally (PF, PFm), as well as the left pre- and postcentral gyri (BA6, BA4p, BA3b). We also observed activations in the right supplementary motor area and the left inferior frontal gyrus. Some of these regions are part of the somatosensory network. The left SI (BA3b) cluster was within our somatosensory mask but was assigned to the hand area and was not activated by the touch localizer (see Table 2, Fig. 3). Two regions were activated by the touch localiser, namely left BA6 (premotor) and left PF/PFop (which lies next to the OP1 region of SII).

Thus, although dummy faces and real faces share a superficial resemblance, observing touch to a dummy face elicits quite distinct response patterns in mirror-touch synaesthetes: Less intense experiences of synaesthetic touch (see Figure 1), and at the neural level, significantly less activation in the left SI (BA3b), premotor (BA6) and inferior parietal cortex (PF) of synaesthetes, relative to controls.

Significant group differences for the observation of touch to an object

The interaction testing for greater activation to the observation of touch to an object in synaesthetes, relative to controls [SYN(OT – ON) – CON(OT- ON)] showed activation in the right hand area of SI as well as left ventral SI. Additionally, the cerebellum, the right precentral gyrus (BA6) and rolandic operculum (PFt), supramarginal gyrus (PFt) and SMA (BA6) were activated. None of these regions were activated during the touch localizer.

No significant activations were observed for the reverse interaction CON(OT – ON) – SYN(OT – ON).

Summary

The previous account of mirror-touch synaesthesia was in terms of hyper-active cortical somatosensory response to observing human touch (Blakemore et al., 2005). Although the present results offer some support for this, they also suggest that the explanation needs to be refined. A more accurate account is that the synaesthetes show greater modulation of somatosensory activity within left SI and SII that includes both up-regulation (for humans) and down-regulation (for dummies).

INSERT TABLE 2 ABOUT HERE

INSERT FIGURE 3 ABOUT HERE

Correlating fMRI data with Intensity of Synaesthetic Touch

To identify brain areas correlating with the intensity of the synaesthetic experience, we performed another analysis using only the data from the synaesthetes. For this analysis, each participant (N=9) contributed 3 contrast images (FT – FN, DT – DN and OT – ON), as well as the corresponding 3 difference measures of the post-hoc intensity rating (see Figure 4).

The subjective intensity ratings were entered as a regressor at the second level, in addition to the three regressors for the contrast images. The analysis for the intensity regressor revealed an almost exclusively left-lateralised network of medial and lateral prefrontal, temporal and parietal areas (see Fig. 4), with one peak (MNI coordinates: -57 -10 7) falling within the somatosensory mask (ventral OP4 region of SII, extending into auditory TE 1.2) although no area fell within the mask defined by the touch localizer.

INSERT FIGURE 4 ABOUT HERE

Structural Brain Differences

The results of the VBM analysis are summarised in Table 3 and Figure 5. The statistical analysis indicated four regions where synaesthetes relative to controls displayed significant increases in grey matter volume: The medial and lateral aspect of the right temporal pole, the dorsal part of the right precentral gyrus (localized to BA6) and a region within secondary somatosensory cortex (localized to right OP4). Note that the OP4 coordinates are virtually identical to those that were found when subjective synaesthetic intensity is correlated with brain activity (albeit in left OP4). In the reverse contrast, we also observed two regions where synaesthetes display significantly less grey matter volume than controls, namely at the superior medial gyrus and the right angular gyrus. With regards to white matter, there was one region associated with significant increases in synaesthetes and this was in the right temporal lobe, immediately posterior to the regions linked to grey matter increases. It does not fall into one of the labelled tracts in the Anatomy Toolbox. There were no significant white matter differences in the reverse contrast.

INSERT TABLE 3 and FIGURE 5 ABOUT HERE

General Discussion

In this section we consider the implications of our findings for the neural circuits for observing touch in general. We then consider how differences in this network may be related to mirror-touch.

Neural Circuits for Observing Touch in the Normal Population

Observing touch (relative to approaching stimuli) activated primary and secondary somatosensory cortices bilaterally, but activations were more pronounced and extended in the left hemisphere (see Fig. 2b). This is consistent with a specular mapping that is reported, phenomenologically, in our synaesthetes and is typically found, behaviourally, in controls (Serino et al., 2008). (Recall: observing touch to the left side of a face would be mapped to the right side of the observers' body in a specular mapping, and would be linked to greater activity in left SI than right SI, as found here).

A surprising finding, perhaps, is that the face-sensitive region of SI is not functionally homogeneous in its response to observed touch. We observed that the latero-ventral aspect of face SI is relatively insensitive to what type of touch is being observed. This area showed a significant activation increase, regardless of what type of touch was observed (real face, dummy face or object, see yellow cluster in Fig. 3). This suggests that the latero-ventral aspect of face-sensitive SI may code the contact between two solid bodies in some abstract sense or, otherwise, become incorporated into body-related processes.¹ It would be interesting for future research to determine whether the same objects become associated with hand-related SI activity if they are presented alongside movies of hands instead of faces. In contrast, the response to observed touch in more dorso-medial aspects of face SI seems more narrowly tuned, and showed stimulus-specific up- and down-regulations depending on the touched stimulus (see below).

Differences Between Mirror-Touch Synaesthetes and Controls

Across stimuli types, the synaesthetes activated a similar 'mirror touch' network to that found in controls (see Fig. 2c). However, there are also between-group differences in a number of

¹ The suggestion that SI and not SII with its larger receptive fields may code the contact between two solid objects may seem at odds with the findings from Keyers et al. (2004). Note, however, that they only performed a test for stimulus specificity with respect to SII (their selected Region of Interest), whereas such a test was not performed for SI. This raises the possibility that any generalization effects in SI may have been missed in that study.

regions (depending on the visual stimulus being touched). Here we focus our discussion on three key regions: SI, SII and premotor cortex.

With regards to SI, Keyzers et al. (2010) speculate that the earliest cortical processing stage within SI (BA3) may distinguish MTS from others. We did find that the dorsal aspect of face-sensitive SI (at the BA3/BA2 boundary, see Fig. 3a) showed a significant modulation of activity when MTS saw touch to a face, relative to controls, and that a very nearby aspect of SI (see Fig. 3b) is less active in MTS for touch to a dummy, relative to controls. However, this part of SI is not active during actual touch to the face (as defined by our tactile localizer), the Group x Touch interaction for faces does not show the anticipated pattern (it is driven by condition PN, rather than condition PT, see Fig. 3a) and SI activity did not correlate with self-reports of tactile intensity (see Fig. 4). The left SII complex (see Table 2, Figure 3c), on the other hand, showed hyper-activity when MTS observed touch to faces in a region also activated by real touch to the face. A directly adjacent region (see Fig. 3d) showed hypo-activity to dummies'. Finally, another region of SII correlated with self-reported tactile intensity and was linked to structural differences (discussed later). As such, we suggest that the SII region (rather than SI) may have a central role in this form of synaesthesia presumably via its connectivity to other tactile, motor and sensory regions. It is to be noted that different regions of SII (OP1 and OP4) are implicated in different analyses that we conducted.

OP1 has been suggested to be a somatosensory 'perceptive' area (Eickhoff et al., 2010). It typically shows a contralateral activation pattern to tactile stimulation (Burton et al., 2008). It has been suggested that its strong connections to the anterior parietal cortex, the thalamus and the contralateral hemisphere may pre-dispose OP1 to perform more integrative somatosensory processing (Eickhoff et al., 2010), such as stimulus discrimination (Burton et al., 2008). In contrast, OP4 is more involved in sensory-motor integration, such as incorporating sensory feedback into motor actions (Halsband & Lange, 2006; Rizzolatti & Wolpert, 2005). Relative to OP1, OP4 has stronger anatomical and functional connections to the postcentral gyrus, premotor and motor cortices, and well as inferior frontal areas (Eickhoff et al., 2010). OP4 typically shows a bilateral activation pattern to tactile stimulation (Burton et al., 2008). These findings could explain why we observed a more-stimulus driven up- and down regulation of activity in OP1 (see Fig. 3c and d), whereas less stimulus-specific modulations of activity driven by the intensity of synaesthetic touch were observed in OP4.

Finally, the left premotor cortex was active in controls but not in synaesthetes when observing touch. Further analyses suggested that this reflects reduced activity in the MTS group specifically when observing touch to dummies (see Fig. 3e). The premotor cortex is known to be activated by passive touch (e.g. Zhang et al., 2005) and receives tactile input via SII (Disbrow et al.,

2003). As such, we speculate that these functional differences when observing touch may be a consequence of core differences in SII functioning in MTS.

When designing our experiment, we were especially interested in studying the role of tactile areas in MTS, based on the findings by Blakemore and colleagues (2005). Of course, this does not preclude that other areas not activated by the actual experience of touch might nonetheless play an important role in MTS. In particular, the right posterior temporal lobe and the left dorsal face area (see Fig. 3) showed a significant interaction of Group by Face Touch. However, because of their lack of activation to tactile stimulation during our touch localizer, an interpretation of these interactions is less straightforward and has to remain speculative. Given that MTS, but not controls, tend to experience touch when observing touch to a human face, one possible explanation is that these activations reflect attentional differences. The coordinates of the activation in the posterior temporal lobe are close to the face-sensitive part of the lateral occipital complex (Grill-Spector et al., 2004) and thus may reflect a more attentive processing of observed face touch in MTS, relative to controls. The second region lies within SI but more dorsal to the face area that was activated by real touch. This may suggest that the spatial extent of SI activity for observed touch to faces is larger in synaesthetes. It will require further examination to delineate exactly what functional contribution each area is playing in MTS.

In terms of structural brain differences, there is some similarity to the functional differences observed. Namely, there is increased grey matter volume in a region of SII (OP4) and premotor cortex (both on the right side) but no structural differences within SI. The absence of a comparable effect on the left could reflect our small sample size, but note that no statistical trend was found in the left homologous regions. Also, the difference between left sided functional activity but right sided structural difference is trivial to explain because the observed touch was always lateralised and participants had a specular mapping. The right-sided anatomical differences are, however, of theoretical interest in the context of prior work highlighting the dominant role of the right hemisphere in wider aspects of social perception that mirror-touch synaesthetes have been shown to differ on. For example, previously we have shown that individuals with mirror-touch synaesthesia outperform non-synaesthetes in their perception of facial expressions, but not facial identity (Banissy et al. 2011). In non-synaesthetes, neural activity in right somatosensory cortices has been shown to be crucial to facial expression processing (e.g. Pitcher et al. 2008; Adolphs et al. 2000); therefore our findings of increased gray matter volume in SII of mirror-touch synaesthetes is consistent with right hemisphere somatosensory regions playing a role in broader aspects of social perception (for review of somatosensation in social perception see Keysers et al. 2010).

Furthermore, the right-sided laterality of other regions showing structural differences between synaesthetes and controls is potentially of interest given the important role of this

hemisphere in bodily awareness and self-other representations. For example, the right angular gyrus region where we observed differences in gray matter volume between synaesthetes and non-synaesthetes has been termed the right temporo-parietal junction (rTPJ) in a number of studies. This region is considered to be important in aspects of empathy (Decety & Lamm, 2007) and self-other distinctions (Brass et al., 2009). Differences in the rTPJ, may therefore reflect a correlate of broader differences in mirror-touch synaesthete's abilities to distinguish between the self and other (Banissy, Cohen-Kadosh, et al., 2009). Moreover, some have suggested that the atypical functional activity within the somatosensory cortices shown by mirror-touch synaesthetes when observing touch to others may be a consequence of faulty self-other monitoring (e.g. Banissy, Cohen-Kadosh, et al., 2009; Fitzgibbon et al., 2012); the findings of atypical gray matter volume in the rTPJ are consistent with this possibility.

In this context, it is also of note that structural differences observed in the superior medial gyrus are also consistent with the possibility of atypical self-other representations in mirror-touch synaesthesia. This region corresponds to more dorsal regions of the medial prefrontal cortex (mPFC). The mPFC has commonly been linked to self-representations (e.g. Benoit et al., 2010; Northoff et al., 2006; Sugiura et al., 2012) and is thought to contribute to atypical self-representations in a variety of groups (e.g. see Lombardo et al., 2010; Wang et al., 2011). While these studies tend to implicate more ventral aspects of the mPFC to self-representations, prior functional neuroimaging work has indicated that the dorsal mPFC plays an important role in processing self-other discrepancy (Tamir & Mitchell, 2010). Moreover, the degree of functional activity in the dorsal mPFC has been shown to correlate with the extent to which a target individual is perceived to be dissimilar from the self (e.g. Tamir & Mitchell, 2010). Evidence of reduced brain volume in dorsal mPFC of individuals with MTS may therefore also be consistent with the suggestion that faulty self-other monitoring mechanisms contribute to the generation of synaesthetic experiences.

To sum up, by comparing mirror touch synaesthetes with controls, our study set out to investigate what prevents observed touch from giving rise to overt feelings of touch in controls, but not in synaesthetes. The findings provide some important clues to the mechanisms that contribute to synaesthetes' experiencing overt feelings of touch when observing touch to others. Our functional data imply that the synaesthetes show hyper-activation of the secondary somatosensory system which is in line with prior suggestions that the degree of activation in the mirror-touch system may mediate the extent to which observed touch gives rise to overt feelings of touch (Blakemore et al. 2005). Our structural brain imaging findings indicate that synaesthetes show broader differences in neural regions that play a crucial role in distinguishing between the self and other (e.g. right TPJ; mPFC), which would be consistent with suggestions that faulty self-other monitoring may lead to

disinhibition of normal somatosensory mirror mechanisms (e.g. Aimola-Davies & White, 2012; Banissy, Cohen-Kadosh, et al., 2009; Fitzgibbon et al., 2012).

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Figure Captions

Figure 1: Reported intensity of synaesthetic touch to the movie stimuli used in the fMRI study (from N=9 mirror-touch synaesthetes). Error bars show 1 SEM. Horizontal lines indicate significant differences between touch conditions ($p < 0.05$).

Figure 2: (a) Results from the touch localizer shown in dark blue; (b) shows the contrast of observed touch vs observed no-touch (in green) as well as its conjunction (cyan) with actual touch in controls; (c) Observed touch vs. Observed no-touch (green) and its conjunction (cyan) with actual touch in MTS.

Figure 3: Surface rendering of areas showing significant Group X Touch interactions. Areas marked in red, blue and green show a significant interaction of Group x Person Touch, Dummy Touch and Object touch, respectively. Yellow areas indicate significant activation for the conjunction $(PT - PN) \cap (DT - DN) \cap (OT - ON)$. a) – f) illustrate the interaction for selected key regions. Bar graphs for conditions that are relevant to the particular interaction shown are highlighted by thick black borders. Light grey bars indicate synaesthetes, dark grey bars indicate controls. Asterisks indicate whether the contrast estimate is significantly different from 0 (fixation baseline). Error bars show 1 SEM. * $p < .05$, ** $p < .01$, *** $p < .005$.

Figure 4: Regions showing significant correlations between BOLD signal and intensity of synaesthetic touch (measured outside of the scanner) considering all types of stimuli.

Figure 5: Results of Voxel-based morphometry analysis showing group differences in Grey Matter (GM) and White Matter (WM) volume.

Table 1 List of regions activated both by observed touch as well as actual touch

Anatomical Region	Cluster size (voxels)	Z	x	y	z
<i>Common activations between observed and actual touch in the control group: [(PT + DT + OT) – (PN + DN + ON)] ∩ [(RF + LF) – baseline]</i>					
right postcentral gyrus (BA1*) ^{s,f}	37	4.38	60	-13	43
left postcentral gyrus (50% BA2*, 50% BA3b) ^{s,h}	29	4.14	-30	-37	58
left postcentral gyrus (40% PFt*, 40% BA1, 40% BA2) ^{s,f}	319	6.05	-57	-19	37
left postcentral gyrus (60% OP1*) ^s		4.82	-51	-19	22
left postcentral gyrus (50% OP1*, 40% OP4) ^s		4.60	-60	-16	22
Left precentral gyrus (70% BA6*)		4.41	-57	2	34
right cerebellum	35	3.92	15	-67	-50
<i>Common activations, synaesthetic group: [(PT + DT + OT) – (PN + DN + ON)] ∩ [(RF + LF) – baseline]</i>					
left postcentral gyrus (40% PFt*, 40% BA1, 40% BA2) ^{s,f}	218	6.05	-57	-19	37
right postcentral gyrus (90% BA1*) ^{s,f}	38	4.31	60	-13	40
left postcentral gyrus (60% BA2*) ^{s,h}	22	3.47	-30	-40	55
left postcentral gyrus (60% OP1*) ^s		5.51	-51	-19	16
right cerebellum	40	4.86	12	-70	-50

Note. . In addition to gross anatomical region, we provide the most probable cytoarchitectonic area as defined in the SPM Anatomy Toolbox 1.8. * indicates assigned regions. Percentages indicate probability of peak falling within defined area. BA: Brodmann Area. OP: Operculum Parietale. For a definition of area PFt, see (Caspers et al., 2006). ^s indicates a peak within the somatosensory mask (see Methods). ^f indicates a peak within the face area of SI (Eickhoff et al., 2008), ^h a peak within the hand area of SI.

Table 2: List of regions where significant group differences were observed.

Anatomical Region	Cluster				
	size (voxels)	Z	X	y	z
<i>Human faces: Interaction of Group and Touch SYN(PT – PN) – CON(PT – PN)</i>					
left supramarginal gyrus (40% OP1*, 30% PFop) ^{s,t}	15	3.11	-48	-28	25
left postcentral gyrus (60% BA2*, 50% BA3b) ^{s,f}	16	3.05	-45	-25	49
right posterior middle temporal lobe	16	3.85	36	-64	4
<i>Dummy faces: Interaction of Group and Touch CON(DT – DN) – SYN(DT – DN)</i>					
left postcentral gyrus (60% BA3b*, 40% BA2) ^{s,h}	24	3.17	-36	-34	52
left precentral gyrus (50% BA4p*)	172	4.07	-45	-10	37
left precentral gyrus (80% BA6*, 40% BA4a) [†]		3.40	-39	-10	52
left superior frontal gyrus (60% BA6*)		3.33	-21	-10	67
left supramarginal gyrus (40% PFop*, 20% OP1) [†]	26	3.21	-51	-31	25
left superior temporal gyrus (70% PF*, 40% PFcm) [†]		3.16	-57	-37	22
left posterior middle temporal gyrus	70	3.63	-48	-55	19
right supramarginal gyrus (40% PFt*)	34	3.56	51	-25	34
supplementary motor area	46	3.56	0	-16	67
right superior temporal gyrus	29	3.39	48	-43	16
right superior temporal gyrus (30% PFm*)		2.68	57	-46	19
left inferior frontal gyrus	22	3.24	-36	26	25
left precentral gyrus (40% BA44*)	29	3.15	-51	5	25
left inferior frontal gyrus (p. Triang. 70% BA44*)		2.78	-57	14	31
<i>Objects: Interaction of Group and Touch SYN(OT – ON) – CON(OT – ON)</i>					
right precentral gyrus (50% BA6*)	32	3.07	63	-1	34
right rolandic operculum (30% BA3b*) ^s		2.84	63	-1	13
left postcentral gyrus (40% BA3b*) ^{s,h}	24	3.24	-24	-34	67
left supramarginal gyrus (50% PFt*)	32	3.58	-45	-28	34
right cerebellum	23	3.19	33	-58	-50
right cerebellum	15	3.22	45	-58	-32
right cerebellum	29	3.52	12	-73	-32

left cerebellum	32	4.52	-21	-58	-50
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Note. . In addition to gross anatomical region, we provide the most probable cytoarchitectonic area as defined in the SPM Anatomy Toolbox 1.8. * indicates assigned regions. Percentages indicate probability of peak falling within defined area. BA: Brodmann Area. OP: Operculum Parietale. For a definition of area PF, PFcm, PFm, PFop, PFt, see (Caspers et al., 2006). ^s indicates a peak within the somatosensory mask (see Methods). ^f indicates a peak within the face area of SI (Eickhoff et al., 2008), ^h a peak within the hand area of SI.

Table 3: Whole brain analysis ($p < .05$ corrected) examining regions of increased grey and white matter volume in synaesthetes relative to non-synaesthetic controls.

Anatomical Region	Cluster				
	size (mm ³)	Z	x	y	z
<i>Grey Matter: MTS > Controls</i>					
right lateral temporal pole	310	3.4	55.5	13.5	-15
right medial temporal pole	209	3.6	43.5	4.5	-31.5
right precentral gyrus (40% BA6*)	267	3.6	27	-12	73.5
right superior temporal gyrus (OP4*)	#	3.1	59	-13	9
<i>Grey Matter: Controls > MTS</i>					
superior medial gyrus	368	3.6	-1.5	51	19.5
right angular gyrus (30 % PFm, 20 % PGa)	243	3.5	48	-45	25.5
<i>White Matter: MTS > Controls</i>					
right middle temporal gyrus	290	3.9	51	-6	-21

Note. . In addition to gross anatomical region, we provide the most probable cytoarchitectonic area as defined in the SPM Anatomy Toolbox 1.8. * indicates assigned regions. Percentages indicate probability of peak falling within defined area. BA: Brodmann Area. OP: Operculum Parietale. For a definition of areas PGa and PFm, see (Caspers et al., 2006). #: Significant ($p < 0.05$, corrected) using a small volume correction. The volume used for correction was the right OP4 area, as defined in the Anatomy Toolbox.

Figure 1

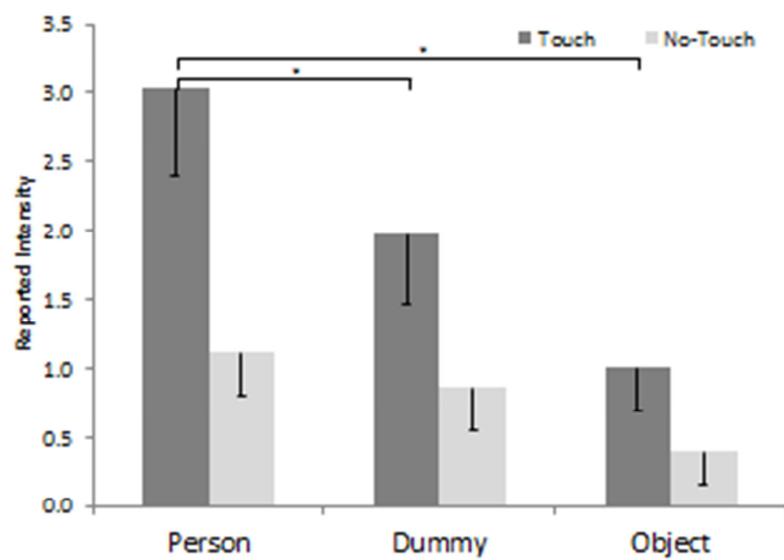


Figure 2

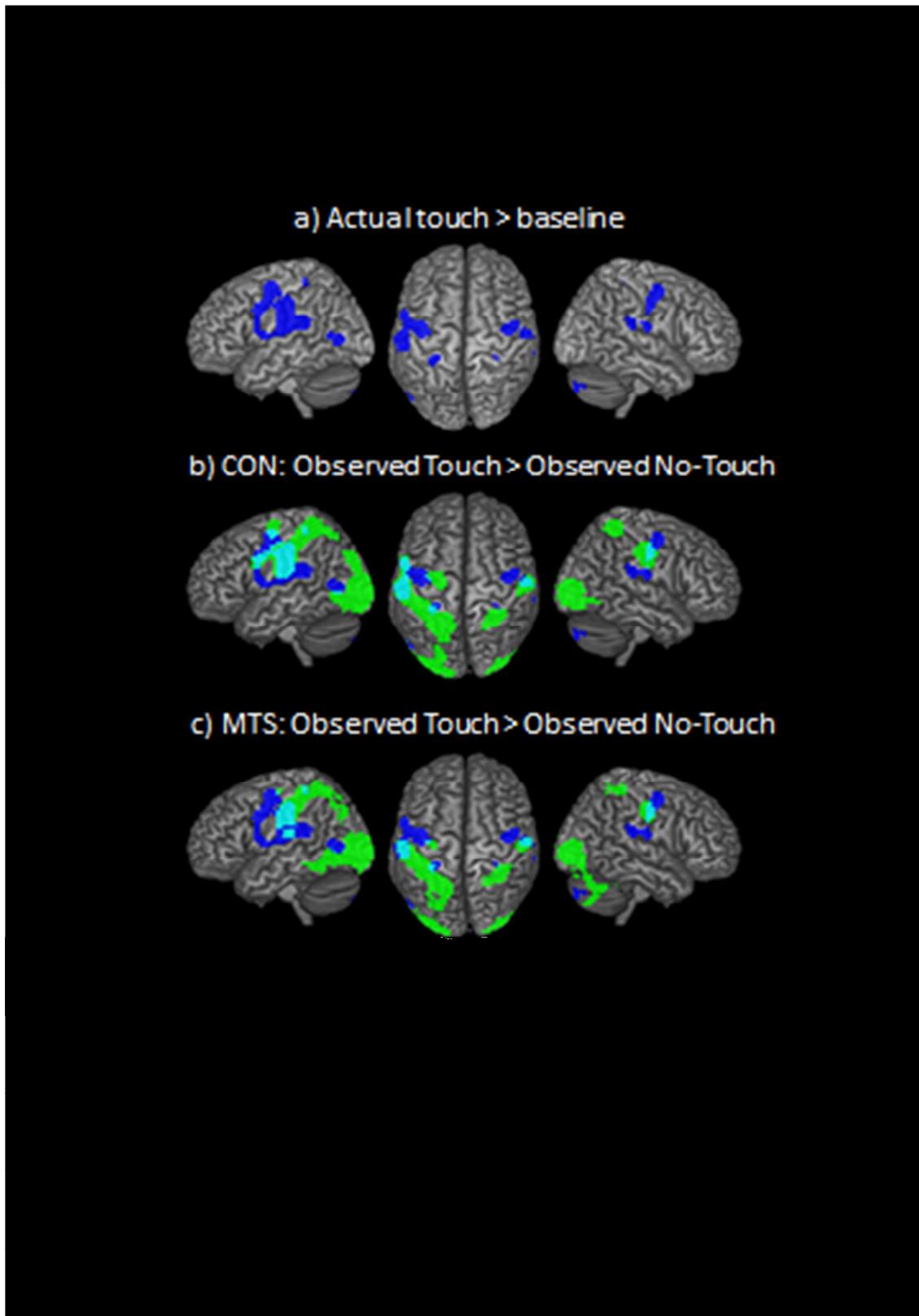


Figure 3

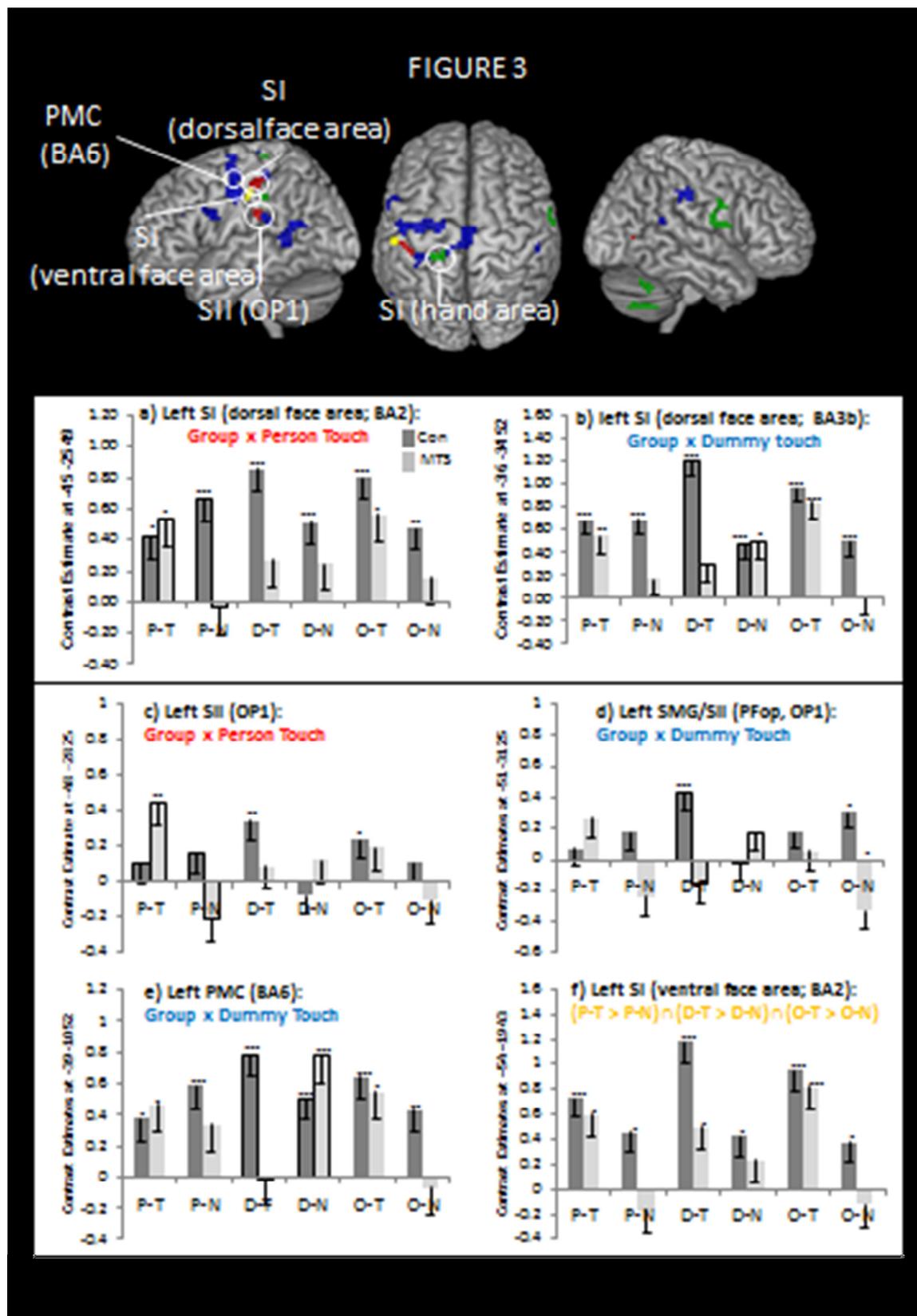


Figure 4

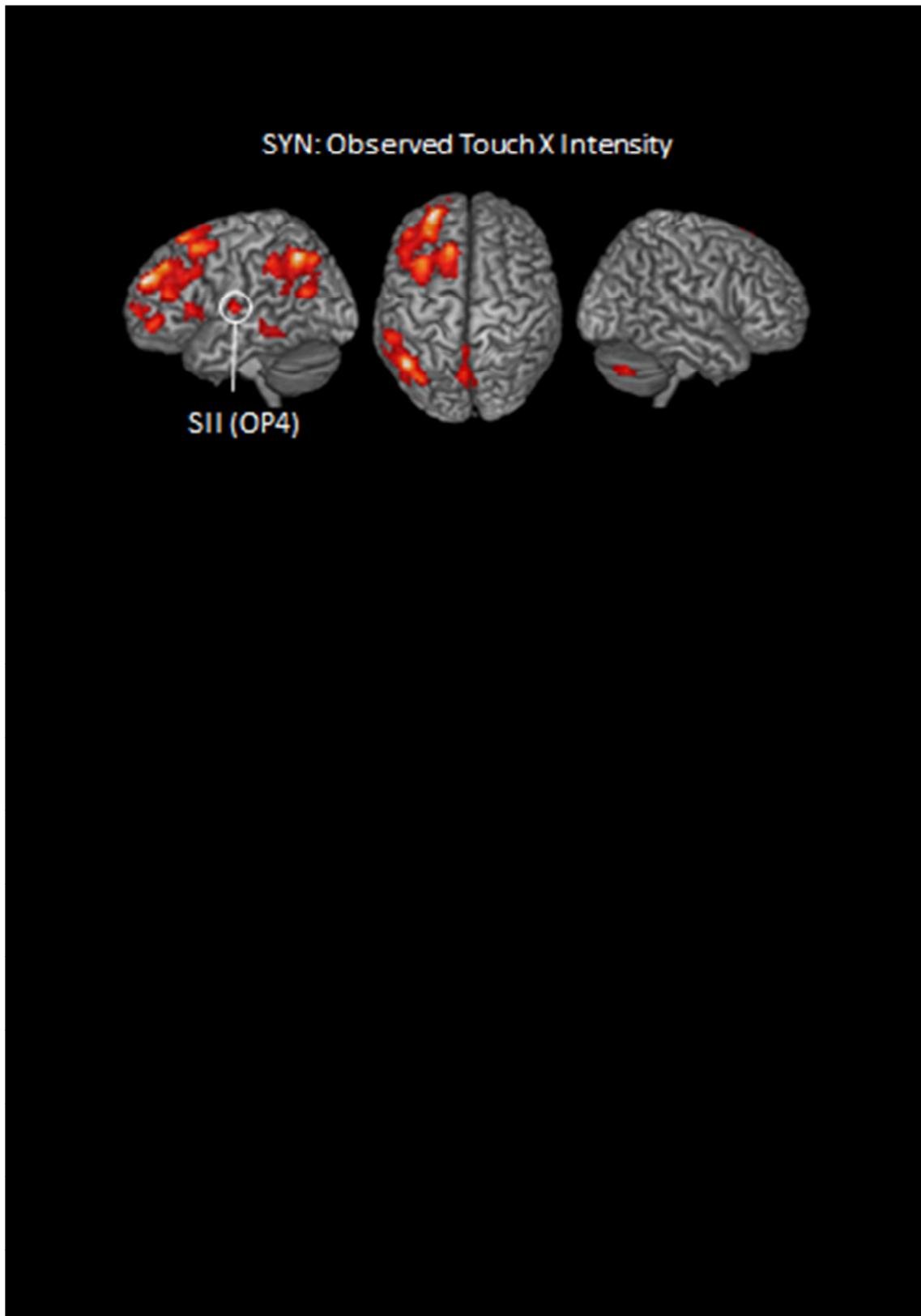


Figure 5

