The Contribution of Primary and Secondary Somatosensory Cortices to the Representation of Body Parts and Body Sides: An fMRI Adaptation Study

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Abstract

■ Although the somatosensory homunculus is a classically used description of the way somatosensory inputs are processed in the brain, the actual contributions of primary (SI) and secondary (SII) somatosensory cortices to the spatial coding of touch remain poorly understood. We studied adaptation of the fMRI BOLD response in the somatosensory cortex by delivering pairs of vibrotactile stimuli to the finger tips of the index and middle fingers. The first stimulus (adaptor) was delivered either to the index or to the middle finger of the right or left hand, and the second stimulus (test) was always administered to the left index finger. The overall BOLD response evoked by the stimulation was primarily contralateral in SI and was more bilateral in SII. However, our fMRI adaptation approach also revealed that both somatosensory cortices were sensitive to ipsilateral as well as to contralateral inputs. SI and SII adapted more after subsequent stimulation of homologous as compared with nonhomologous fingers, showing a distinction between different fingers. Most importantly, for both somatosensory cortices, this finger-specific adaptation occurred irrespective of whether the tactile stimulus was delivered to the same or to different hands. This result implies integration of contralateral and ipsilateral somatosensory inputs in SI as well as in SII. Our findings suggest that SI is more than a simple relay for sensory information and that both SI and SII contribute to the spatial coding of touch by discriminating between body parts (fingers) and by integrating the somatosensory input from the two sides of the body (hands). ■

INTRODUCTION

When coding the location of a tactile stimulus on the body, our brain needs to determine which body part and which body side was stimulated. This spatial disambiguation likely begins with neural processing in primary (SI) and secondary (SII) somatosensory cortices. The contribution of SI to the representation of body parts has been well established since the classical studies of Fritsch and Hitzig (1870) in dogs and the pioneering studies of Penfield and colleagues in humans (e.g., Penfield & Rasmussen, 1950). Many subsequent studies have confirmed the somatotopic organization of SI in humans using neuroimaging techniques (e.g., Sanchez-Panchuelo, Francis, Bowtell, & Schluppeck, 2010; Nelson & Chen, 2008; Overduin & Servos, 2004). Moreover, there is now evidence that a somatotopic organization also exists in SII, albeit to a lesser degree (e.g., Del Gratta et al., 2002; Ruben et al., 2001). The textbook description of the somatosensory cortices identifies SI as a cortical area with primarily contralateral afferents, whereas SII is an area in which bilateral afferents are denser. This suggests that integration of the somatosensory inputs from the two body sides should occur in SII, but not in SI. Thus, the contribution of the somatosensory cortices to the representation of the two body sides appears straightforward.

However, neurophysiological studies in monkeys and neuroimaging works in humans have recently challenged the notion that neural representations of the body in SI are purely contralateral (e.g., Sutherland, 2006). In monkeys, bilateral receptive fields have been found within SI, in BA 1 and BA 2 (Keysers, Kaas, & Gazzola, 2010; Lipton, Fu, Branch, & Schroeder, 2006; Iwamura, Tanaka, Iriki, Taoka, & Toda, 2002; Iwamura, Taoka, & Iriki, 2001; Killackey, Gould, Cusick, Pons, & Kaas, 1983). In humans, neuroimaging studies have documented neural activity in SI in response to tactile stimulation on the ipsilateral side of the body (e.g., Hlushchuk & Hari, 2006; Kanno, Nakasato, Nagamine, & Tominaga, 2004; Tan, Wühle, & Braun, 2004). Behavioral studies in humans also corroborate the notion that SI may hold sensory representations that are not fully

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separated between body sides. For instance, tactile localization errors at the hands, which reflect the somatotopic organization in SI (Schweizer, Braun, Fromm, Wilms, & Birbaumer, 2001), can be modulated by applying tactile stimuli to the fingers of the opposite hand (Braun, Hess, Burkhardt, Wühle, & Preissl, 2005). Similarly, participants trained to discriminate punctuate pressure or roughness stimuli on one finger of the right hand (e.g., the index) can transfer this training to the first neighboring finger of the same hand (i.e., the right middle finger) as well as to the homologous finger of the opposite hand (i.e., the left index finger; Harris, Harris, & Diamond, 2001; for earlier reports on perceptual learning, see Sathian & Zangaladze, 1997, 1998). Moreover, neuropsychological investigations in arm amputees and in brain-damaged patients with hemiparesis and hemisensory loss show contralateral referral of tactile sensations applied to the phantom body part (Ramachandran, Rogers-Ramachandran, & Cobb, 1995) or to the hand rendered anesthetic by stroke (Sathian, 2000). Finally, clear interactions between tactile stimuli delivered to opposite body sides were recently documented in a paradigm of tactile double simultaneous stimulation at the hands (Tamè, Farnè, & Pavani, 2011), in which participants detected tactile stimuli at a predefined target finger that could be stimulated alone or concurrently with another finger, either on the same or the opposite hand. For instance, when the target finger was the right index, the concurrent stimulation could be presented to the middle finger of the same hand, to the left index finger, or to the left middle finger. The results showed interference effects of tactile double simultaneous stimulation both within and between hands, which were more dependent upon the identity of the stimulated body part (i.e., which finger was touched) than body side (i.e., which hemibody was touched). These findings imply that at least some aspects of the processing of concurrent or subsequent tactile stimuli are integrated across body sides.

In this study, we examined the contribution of SI and SII to the spatial coding of touch at the fingers of the same or different hands, taking advantage of the fMRI adaptation paradigm. The adaptation paradigm relies on the hypothesized decrement of a neuronal response that results from the repeated presentation of a stimulus feature to which the neurons are selective. For instance, a population of neurons in the visual pathway selective to upward motion of visual stimuli would decrease its overall neuronal activity if the sequence of repeated stimuli contained the same feature (i.e., upward motion). This physiological response was initially described in single cell recordings (e.g., Tanaka, Saito, Fukada, & Moriya, 1991; Gross, Rocha-Miranda, & Bender, 1972) and has now been largely documented also using fMRI (e.g., Brozzoli, Gentile, Petkova, & Ehrsson, 2011; Lingnau, Ashida, Wall, & Smith, 2009; Krekelberg, Boynton, & van Wezel, 2006; Vuilleumier, Henson, Driver, & Dolan, 2002; Grill-Spector & Malach, 2001). In this study, we examined adaptation when successive vibrotactile stimuli were delivered to

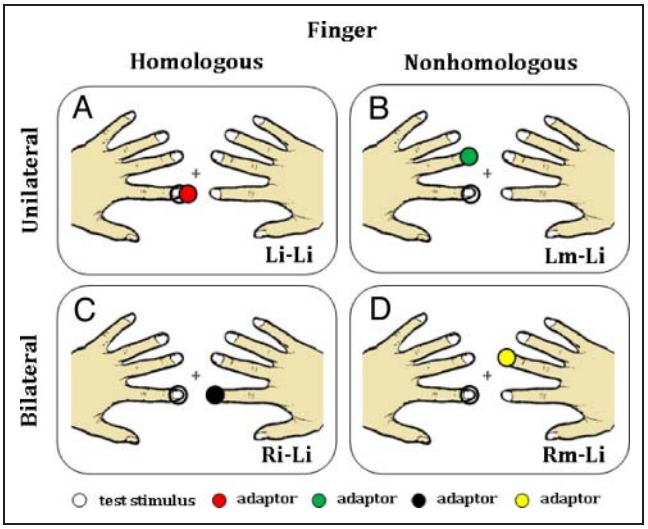

Figure 1. Schematic representation of all stimulation conditions as a function of whether the stimulation occurred to homologous or nonhomologous fingers and whether the stimulation was unilateral (i.e., same hand) or bilateral (i.e., both hands). (A) Homologous unilateral, the left index finger was stimulated twice (Li-Li). (B) Nonhomologous unilateral, the left middle and left index fingers were stimulated (Lm-Li). (C) Homologous bilateral, the right index and the left index were stimulated (Ri-Li). (D) Nonhomologous bilateral, the right middle and the left index fingers were stimulated (Rm-Li). The empty circle represents the test stimulus; the colored circles represent the adaptor. Note that the color code used for the adaptor stimuli is used in all subsequent plots.

the same or to different body parts (index or middle fingers), either on the same or on different body sides (left or right hands). Specifically, four different stimulation conditions were used (see Figure 1): (1) repeated unilateral stimulation of the same finger (i.e., left index finger, condition Li-Li; Figure 1A); (2) repeated unilateral stimulation of nonhomologous fingers (i.e., left middle and left index fingers, condition Lm-Li; Figure 1B); (3) repeated bilateral stimulation of homologous fingers (i.e., right index and left index fingers, condition Ri-Li; Figure 1C); (4) repeated bilateral stimulation of nonhomologous fingers (i.e., right middle and left index fingers, condition Rm-Li; Figure 1D). Note that the second stimulus (test) was always on the left index finger.

We hypothesized that any brain areas that contain distinct neuronal populations for the index and middle fingers should adapt more when the index finger is stimulated twice as compared with when the middle and index fingers are stimulated in sequence. We expected this finger-specific adaptation in SI, which holds a strong somatotopic representation, and possibly to a lesser extent also in SII. Crucially, any brain area that integrates somatosensory inputs from the two hands should reveal finger-specific adaptation regardless of whether the stimulation occurs unilaterally or bilaterally. This finding should emerge in SII, which classically holds bilateral representations of somatosensory stimuli. However, it should emerge also in SI if a neural population

that integrates inputs from the two sides of the body exists in this brain area.

METHODS

Participants

Eighteen participants (mean age = 29, *SD* = 5 years; 7 women and 11 men) took part in the study. All reported normal or corrected-to-normal vision and normal somatosensation. Participants reported no history of psychiatric or neurological disorders and no current use of any psychoactive medication. All subjects were right-handed according to their self-report. Participants gave their written informed consent before their participation in the study, which was carried out according to the principles of the Declaration of Helsinki and was approved by the ethics committee of the University of Trento. One participant was discarded from the analysis because of several large, rapid head movements (>6 mm).

Apparatus and Procedure

During the experimental session, the participant's unseen hands rested palm down in a comfortable posture, one on each side of their abdomen. Subjects were instructed not to touch their hands together in order not to form a loop with their arms that might lead to the induction of electrical currents. Tactile stimuli were delivered to the index and middle fingertips of either hand using four magnetic resonance (MR) compatible vibrators (Quaerosys, Schotten, Germany). To avoid possible distortions caused by the stimulation equipment in the MR environment, a ferrite low-pass filter was applied to the signals entering the MR room. The stimulator consisted of a single rod (1 mm in diameter), protruding from a flat surface of 4 × 8 mm. The rod protruded and retracted at 20 Hz for 1000 msec, producing clearly perceivable skin indentations. Wave signal intensity was always set to the maximum level available except for 8% of the trials, in which signals were delivered at half-maximal intensity and served as fillers for the behavioral task. Vibrotactile stimulators were attached to the finger pads of the middle and index fingers of both hands using Velcro tape to ensure constant contact force between the fingers and the stimulation devices throughout the experiment.

Visual stimuli were delivered using a liquid crystal projector (Epson EMP 7900; Nagano, Japan, refresh rate: 60 Hz; resolution: 1280 × 1024 pixels) and were visible to the participants through a mirror positioned above the head coil. A fixation cross was presented at the center of the screen: The cross was green during the vibrotactile stimulation period and gray during the rest period. Occasionally, a written question appeared on the screen for 3000 msec probing the participants to answer whether they had just perceived a weak stimulation at the target finger.

Visual and vibrotactile stimulations were programmed using the in-house software "ASF" (Schwarzbach, 2011), based on the MATLAB (Mathworks, Natick, MA) Psychotoolbox-3 (Brainard, 1997) for Windows. A response box (Lumina LP-400 system by Cedrus, San Pedro, CA) was placed within reaching distance of the participant's right hand. Participants were instructed to press the button with the right thumb in response to the question presented on the screen. Closed-ear headphones (Serena Sound digital system: Resonance Technology, Inc., Los Angeles, CA) were used for reducing noise caused by the operation of the scanner. The noise made by the operation of vibrotactile stimulators was not audible.

fMRI Adaptation Paradigm

The experiment consisted of four event-related fMRI adaptation scans, consisting of 52 trials each. In each scan, the four experimental conditions were repeated 12 times resulting in 48 trials, and responses to fillers were probed in four additional trials. Responses in the filler condition were excluded from further analyses.

At the beginning of each trial a green fixation cross appeared at the center of the screen and remained visible for the entire duration of the trial. At 1000 msec after the appearance of the fixation cross, two consecutive vibrotactile stimuli were delivered to the participant's fingers, each lasting 1000 msec (S1, adaptation stimulus; S2, test stimulus). S1 and S2 were separated by a fixed ISI of 1200 msec. Fixed-interval designs have become an accepted standard for adaptation studies (e.g., Lingnau, Gesierich, & Caramazza, 2009; Wall, Lingnau, Ashida, & Smith, 2008; Ashida, Lingnau, Wall, & Smith, 2007; Weigelt, Kourtzi, Kohler, Singer, & Muckli, 2007; Grill-Spector & Malach, 2001), because any jittering of the S1–S2 interval would come at the cost of nonstationary adaptation effects not properly accounted for, which leads to increased error variance. The green fixation cross turned gray 3000 msec after the end of S2 to inform the participant of the end of the trial. The intertrial interval ranged randomly from 6000 to 8000 msec. A schematic description of the trial structure is shown in Figure 2.

Participants were instructed to pay attention to the left index finger throughout the experiment. To ensure that they were following the instructions, a written question appeared on the screen ("Did you feel the weak stimulation on your left index finger?") in four trials per scan, for a total of 16 trials in the whole experiment, excluded from the analysis.

The four experimental conditions were presented in a pseudorandom series. Specifically, it was assured that each condition was preceded equally often by any of the other conditions, including itself (Kourtzi & Kanwisher, 2000). Conditions that included the written question were randomly integrated in the sequence. At the start and at the end of each scan, a black screen was presented for 16 and 20 sec, respectively.

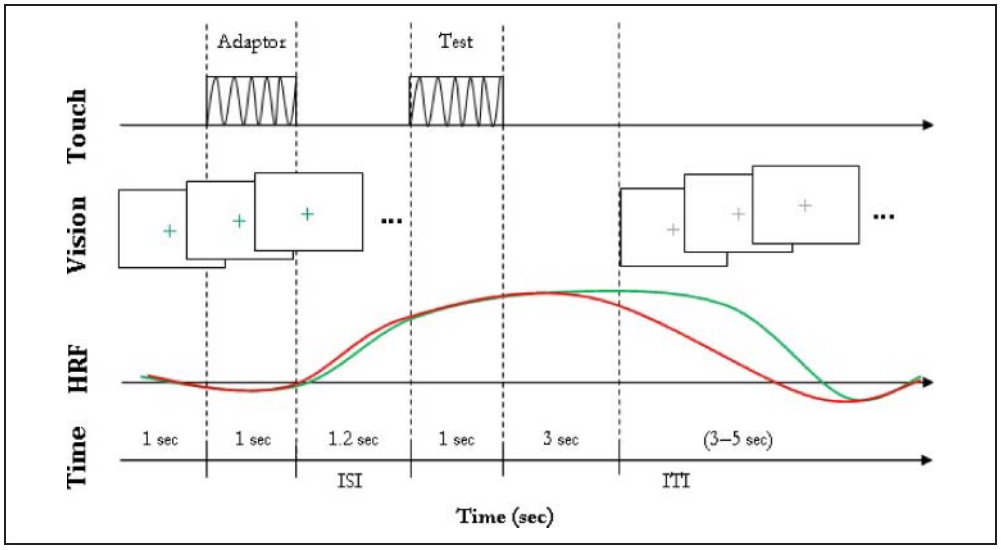

Figure 2. Schematic description of the time course of an experimental trial (see text for details), with a model of the hypothetical hemodynamic response function (HRF) to the adaptor (red line) and test (green line) stimuli.

Data Acquisition

MR scans were acquired using a 4T BrukerMedSpecBiospin MR scanner and an eight-channel birdcage head coil. Functional images were acquired using T2*-weighted gradient-recalled EPI. An additional scan was performed to measure the point-spread function of the acquired sequence, which served for the correction of the distortions expected with high-field imaging (Zeng & Constable, 2002). We used 31 slices, acquired in ascending interleaved order providing almost full-brain coverage, with a repetition time of 2200 msec (voxel resolution = 3 × 3 × 3 mm; echo time = 33 msec; flip angle = 75°; field of view = 192 × 192 mm; gap size = 0.45 mm). In addition, a fat saturation pulse was used to avoid EPI artifacts. Each participant performed four EPI scans, with the number of volumes varying between 360 and 391. These variations were due to the partially randomized duration of the intertrial interval in the trial generation.

To perform spatial normalization of functional data between participants, we acquired a T1-weighted anatomical scan (MPRAGE; 1 × 1 × 1 mm; field of view = 256 × 224; 176 slices; GRAPPA acquisition with an acceleration factor of 2; repetition time = 2700 msec; echo time = 4.18 msec; inversion time = 1020 msec; flip angle = 7°) for each participant.

Data Analysis

Data analysis was performed using BrainVoyager QX 2.0 (Brain Innovation, Maastricht, The Netherlands). Before analysis, the first two volumes of the functional data of each scan were discarded. Distortion correction was applied on the basis of the point-spread function, acquired before each EPI scan, to correct distortion derived from the EPI images. Functional data preprocessing was performed applying a three-dimensional motion correction referred to the first volume in the scan and a temporal high-pass filter with a cutoff of three cycles/scan. A Gaussian kernel of 4.5 mm was applied to smooth the images spatially. Next, functional data were coregistered with a high-resolution deskulled anatomical scan for each participant in their native space. For group analysis, echo-planar and anatomical images were transformed into Talairach and Tournoux space for each participant (Talairach & Tournoux, 1988). Participants' mean coordinates for each ROI are reported in Table 1.

As mentioned above, the interval between S1 and S2 was fixed. Because parameters for events that have a fixed short ISI and stimuli with a very short duration cannot be estimated independently due to superposition of their hemodynamic responses (see Ashby, 2011), we modeled the compound response to S1 and S2 as a function of the relation between S1 and S2 (e.g., same finger vs.

Table 1. Talairach Coordinates of Peaks of BOLD Signal Change in the ROIs

	Right			*Left*		
	Talairach Coordinates (mm)			*Talairach Coordinates (mm)*		
ROIs	*x*	*y*	*z*	*x*	*y*	*z*
SI	53	−20	37	−55	−29	40
SII	50	−17	15	−49	−20	18
Thalamus	8	−14	6	−10	−14	6
PPC	41	−35	36	−43	−41	39
rIFG	37	6	24			
M1	28	−27	48	−30	−28	48

Talairach coordinates of peaks of BOLD signal change in the right and left hemisphere.

different finger), this being the classical method of compound measure adopted for the statistical analysis of fMRI adaptation in these circumstances (i.e., Lingnau, Ashida, et al., 2009; Lingnau, Gesierich, et al., 2009; Grill-Spector et al., 1999).

Whole-brain Analysis: Identification of ROIs

Functional data were analyzed using the general linear model. Experimental events (mean duration = 14.2 sec) were convolved with a standard dual gamma hemodynamic response function. There were four regressors of interest (corresponding to the four experimental conditions) and seven regressors of no interest, corresponding to the six motion correction parameters obtained during preprocessing and the response trials.

To identify the brain regions involved in the processing of unilateral and bilateral stimuli, group analysis ($n = 17$) was performed using a random-effects (RFX) general linear model.

To control for family-wise error, we thresholded our statistical maps using a false discovery rate of 0.05 and a cluster threshold of four voxels. False discovery rate describes the expected proportion of false positive findings among all the rejected hypotheses (Genovese, Lazar, & Nichols, 2002; Benjamini & Hochberg, 1995). ROIs were defined using an RFX contrast including only bilateral experimental conditions compared with baseline (i.e., [Ri-Li + Rm-Li] > Baseline). The baseline was estimated from all the periods in the time course that were not explicitly modeled in the design matrix. The rationale for including only bilateral stimulation conditions in the RFX contrast was that the inclusion of all stimulation conditions would have biased the resulting statistical map toward one hemisphere (i.e., right hemisphere). This is because the stimulation of the two fingers of the same hand elicit a different level of activation in the two hemispheres due to the presence of primarily contralateral projection. By contrast, bilateral stimulation conditions are balanced in terms of energy generated in the two hemispheres. Note that this condition selection was applied only for identification of the ROIs.

In accordance with our hypothesis, ROIs of primary interest included the contralateral and ipsilateral primary and secondary somatosensory cortices (cSI and cSII, iSI and iSII, respectively). Note that the terms "contralateral" and "ipsilateral" always refer to the side of the body to which the adaptor stimulus was applied. For instance, with bilateral homologous stimulation (i.e., right index and then left index fingers stimulated) cSI refers to the left SI. In addition to SI and SII, we defined other ROIs of secondary interest deriving from the activation maps. We defined ROIs on the basis of both functional and anatomical criteria (Gallivan, McLean, Valyear, Pettypiece, & Culham, 2011; Cavina-Pratesi et al., 2010; Dinstein, Gardner, Jazayeri, & Heeger, 2008). A detailed description of the identification procedure for ROIs of primary interest is provided in the Identification of SI, SII, and Other Vibrotactile Responsive Brain Areas section.

Event-related Averaging Analysis

Event-related averaged responses of the four stimulation conditions were extracted for each ROI (i.e., cSI, cSII, iSI, iSII). For completeness, we also extracted the event-related averages from the other significantly active regions defined as ROIs of secondary interest (e.g., right inferior frontal gyrus [rIFG], bilateral thalamus [cT and iT], and posterior parietal cortex [PPC]). We computed the percent BOLD signal change with respect to the baseline, which was defined as the mean signal over the period between −2 and 0 sec.

Considering that the average of the peak latencies for each condition differs depending on the ROI (i.e., difference in brain response between contralateral and ipsilateral tactile stimulation), we determined the peak latency of each of the four stimulation conditions and took the peak amplitude as an index of the event-related deconvolved BOLD response. For statistical analysis, peak amplitudes for all conditions were considered as dependent variables. In particular, the activation peak values of the percent BOLD signal change from the baseline were entered into two separate repeated-measures ANOVAs: one for SI and one for SII, with Hand (within, between), Hemisphere (contralateral, ipsilateral), and Finger (homologous, nonhomologous) as within-participant factors. Tukey's HSD test was used for all post hoc comparisons. On the basis of our strong a priori assumption regarding the presence of an adaptation effect in SI and SII cortices, the critical p value of the event-related data of these areas has been Bonferroni-corrected ($p_{\text{corrected}}$: .05/4 = .0125) for multiple comparisons with respect to the numbers of ROIs of primary interest (cSI, iSI, cSII, and iSII). For completeness, we also reported the p values of the event-related data of the remaining regions (ROIs of secondary interest) uncorrected.

RESULTS

Figure 3 shows the statistical map resulting from the t contrast obtained when comparing the bilateral stimulation conditions against baseline, (Ri-Li + Rm-Li) > (baseline), $t(16) > 3.14$; $p < .0063$. Several clusters of activation were identified within the somatosensory cortices and in other regions of the brain (see Identification of SI, SII, and Other Vibrotactile Responsive Brain Areas section), both in the right (Figure 3A–C) and the left (Figure 3B–D) hemisphere. This statistical map served to compute all of the subsequent analyses, which include the event-related averaging of the defined ROIs. The results are organized in two sections: (1) identification of SI, SII, and other vibrotactile responsive brain areas and (2) description of the fMRI adaptation effects.

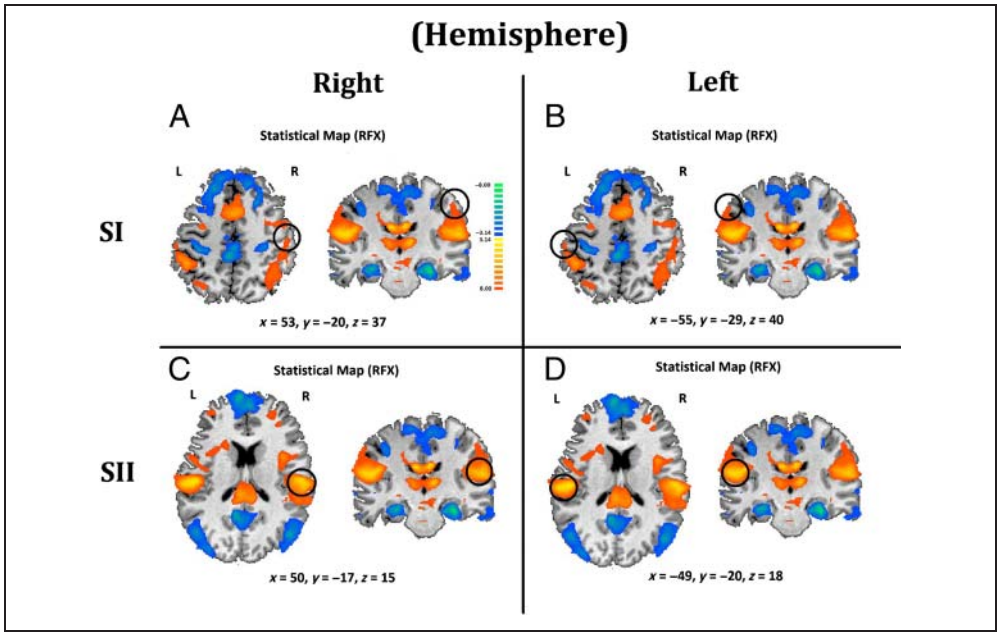

Figure 3. ROIs of primary interest. Black empty circles highlight the primary somatosensory cortex in the right (A) and left (B) hemispheres and the secondary somatosensory cortex in the right (C) and left (D) hemispheres. The statistical maps are overlapped on the anatomy of one participant.

Identification of SI, SII, and Other Vibrotactile Responsive Brain Areas

SI Localization

As shown in the functional activation map in Figure 3A–B, in both hemispheres the activated cluster of voxels within SI was quite large and spread into the PPC. The peak of activation of this large cluster of voxels (i.e., SI + PPC) was clearly located outside the anatomical SI region. However, visual inspection of the statistical map along the axial plane showed two clear segregated clusters of activation: one compatible with the anatomical location of SI and the other that included a wide portion of the PPC. To confirm the anatomical location of the presumed SI cluster, three approaches were used. First, we submitted the x, y, z coordinates of the activation peak of the cluster to the Talairach Client software (www.talairach.org/; see Lancaster et al., 1997, 2000), which labeled the coordinates as BA 1 or BA 2. Second, we verified that the coordinates of the activation peak fell within the probabilistic map for SI obtained from a meta-analysis of fMRI data on 126 articles (see Nelson & Chen, 2008; Hlushchuk & Hari, 2006; Mayka, Corcos, Leurgans, & Vaillancourt, 2006). Third, we checked the location of this functional activation against the structural images of various participants. As a result of these inspections, we selected a cube of 10 × 10 × 10 mm around the identified peak as ROI for SI. Note that, although we inspected the location of the ROI on various participants, the ROIs for SI were then identified on the statistical map derived from the overall contrast. This procedure was adopted also for all other ROIs.

Notably, the location of SI in the two hemispheres was not completely symmetrical. SI was slightly more posterior in the left as compared with the right hemisphere. Although this activation resulted from stimulation occurring on both hands, it should be noted that, in our protocol, the left hand was stimulated more often and was constantly attended. Left SI was thus ipsilateral to this salient tactile stimulation. In this respect, this asymmetrical finding seems to parallel the results of recent work that detected ipsilateral SI activation using fMRI with unilateral median nerve stimulation and found that the position of this activation was located more posteriorly with respect to the homologous area in the contralateral hemisphere (Nihashi et al., 2005).

Finally, we also identified the peak of the activation in PPC (see Figure 5) and compared its event-related averages with those extracted for SI.

SII Localization

Similar to SI localization, the localization of SII was based on both functional and anatomical criteria (see Figure 2C–D). SII activation was well defined in space and clearly separated from other activation clusters. Therefore, we selected the peak of activation in those voxels identified by the RFX contrast located in the region of the operculum and defined a cube of 10 × 10 × 10 mm around this point. SII localization was, as for SI, checked with the Talairach Client software, which confirmed that the selected region may be SII (see also Ploner, Schmitz, Freund, & Schnitzler, 2000).

Other Active Regions

In addition to the activations in somatosensory areas, a series of other brain areas showed a significant BOLD response to tactile stimulation (see Figure 3). These areas include the right IFG, the ACC, bilateral thalamus, bilateral

PPC (cPPC and iPPC), and in particular bilateral angular gyrus, bilateral supramarginal gyrus, and bilateral inferior parietal lobule.

fMRI Adaptation Effect in the Somatosensory Cortices

Figure 4 shows the BOLD response in SI. Overall, BOLD response in SI was more pronounced for the contralateral (mean = 0.645%, *SE* = 0.16%) compared with the ipsilateral (mean = 0.438%, *SE* = 0.14%) hemisphere with respect to the adaptor stimulus (main effect of Hemisphere, $F(1, 16) = 34.52$, $p < .0001$; see Figure 4). This is an expected finding and reflects the primarily contralateral response to tactile stimulation in SI (e.g., Nelson & Chen, 2008; Overduin & Servos, 2004; Ruben et al., 2001). Most importantly, the BOLD response was modulated as a function of which finger served as the adaptor and which hemisphere was considered. As shown in Figure 4B, in the hemisphere contralateral to the adaptor, the BOLD

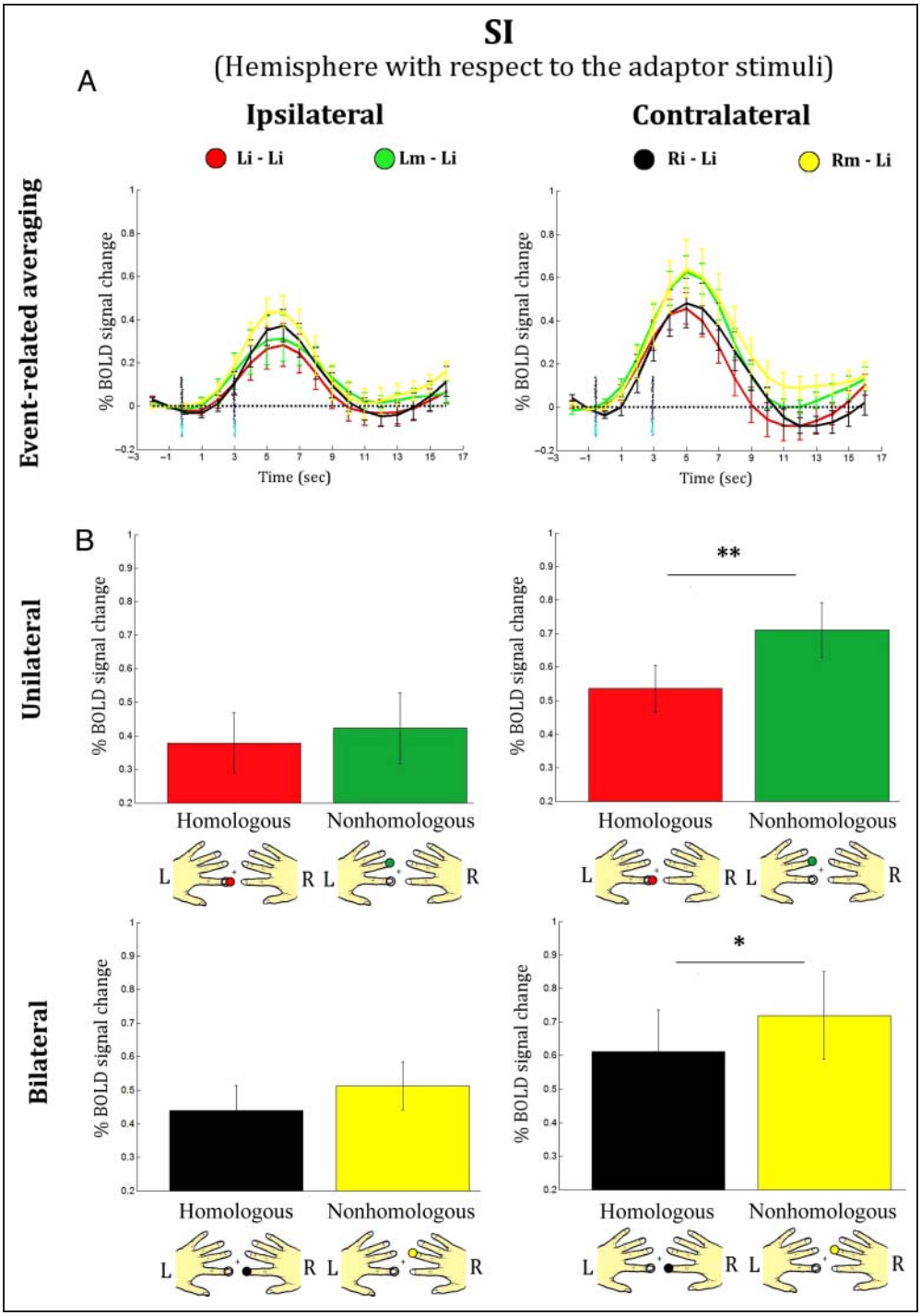

Figure 4. BOLD response in SI. (A) Event-related averaging and the mean percentage of BOLD signal change from the baseline in the four vibrotactile stimulation conditions in the hemisphere ipsilateral and contralateral with respect to the adaptor. The vertical dotted lines represent the onset time of the first (adaptor) and second (test) stimuli. (B) Percentage of BOLD signal change of the peak of activation, as a function of hemisphere and hand. Error bars represent *SEM*.

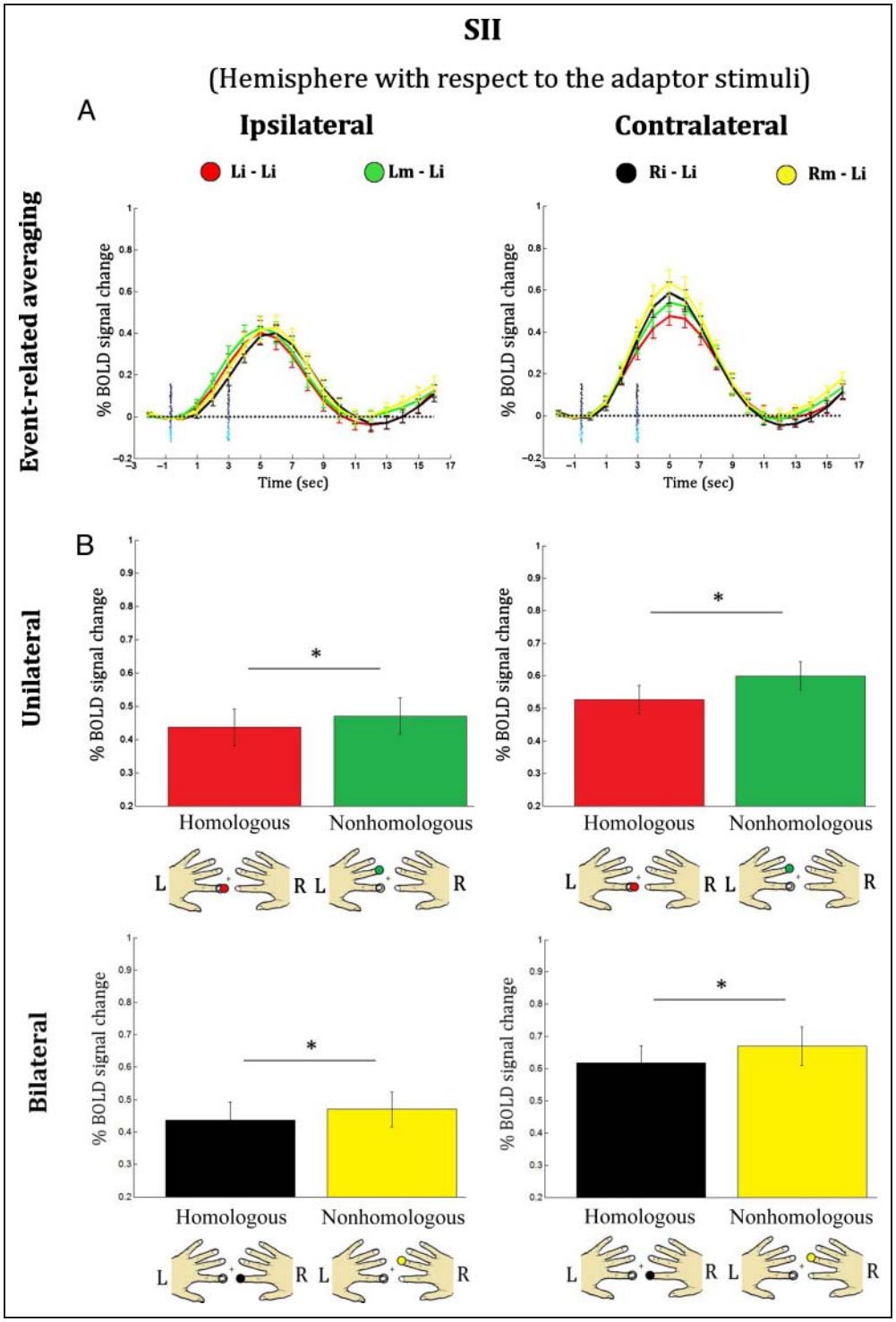

Figure 5. BOLD response in SII. (A) Event-related averaging and the mean percentage of BOLD signal change from the baseline in the four vibrotactile stimulation conditions in the hemisphere ipsilateral and contralateral with respect to the adaptor. The vertical dotted lines represent the onset time of the first (adaptor) and second (test) stimuli. (B) Percentage of BOLD signal change of the peak of activation, as a function of hemisphere and hand. Error bars represent *SEM*.

response was reduced when the stimulation was delivered to the homologous (mean = 0.574%, *SE* = 0.11%) compared with the nonhomologous fingers (mean = 0.715%, *SE* = 0.12%; $p < .0001$). This reduction was not significant in the hemisphere ipsilateral to the adaptor, resulting in a two-way interaction between Hemisphere and Finger, $F(1, 16) = 9.99$, $p < .006$. This shows a finger-specific adaptation that emerged selectively in SI contralateral to the adaptor.

Interestingly, there were no significant interactions involving the Hand factor. As can be noted from the visual comparison of bar plots for unilateral and bilateral stimulation (Figure 4B), the decreased BOLD response for the homologous in comparison with the nonhomologous finger in the hemisphere contralateral to the adaptor was present for both unilateral and bilateral vibrotactile stimulation conditions. No other significant effects or interactions were found (all ps $> .08$), apart from a main

effect of Finger, $F(1, 16) = 9.58, p < .007$, which was, however, subsidiary to the higher order interaction described above.

Figure 5 shows the BOLD response in SII. Overall, a larger BOLD response in contralateral (mean = 0.603%, *SE* = 0.09%) compared with ipsilateral SII (mean = 0.456%, *SE* = 0.10%) was found; main effect of Hemisphere, $F(1, 16) = 98.83, p < .0001$). Figure 5B shows a general reduction in the BOLD response for the homologous (mean = 0.505%, *SE* = 0.09%) compared with the nonhomologous fingers (mean = 0.554%, *SE* = 0.10%; main effect of Finger, $F(1, 16) = 7.83, p < .01$). This difference occurred regardless of whether the stimulation was unilateral or bilateral (as in SI) and was also equally present in both hemispheres (unlike in SI). No other significant effects or interactions were observed (all *p*s > .09).

BOLD Response Outside the Somatosensory Cortices

Outside the somatosensory cortices, only two vibrotactile responsive regions were modulated as a function of which finger was stimulated: the primary motor cortex (M1) and the right IFG (see Figure 6). In M1, an overall negative BOLD response was detected (Intercept representing the baseline, $F(1, 16) = 69.30, p < .0001$), and the ANOVA revealed a significant interaction between Hemisphere and Finger, $F(1, 16) = 5.94, p < .03$. In M1 ipsilateral

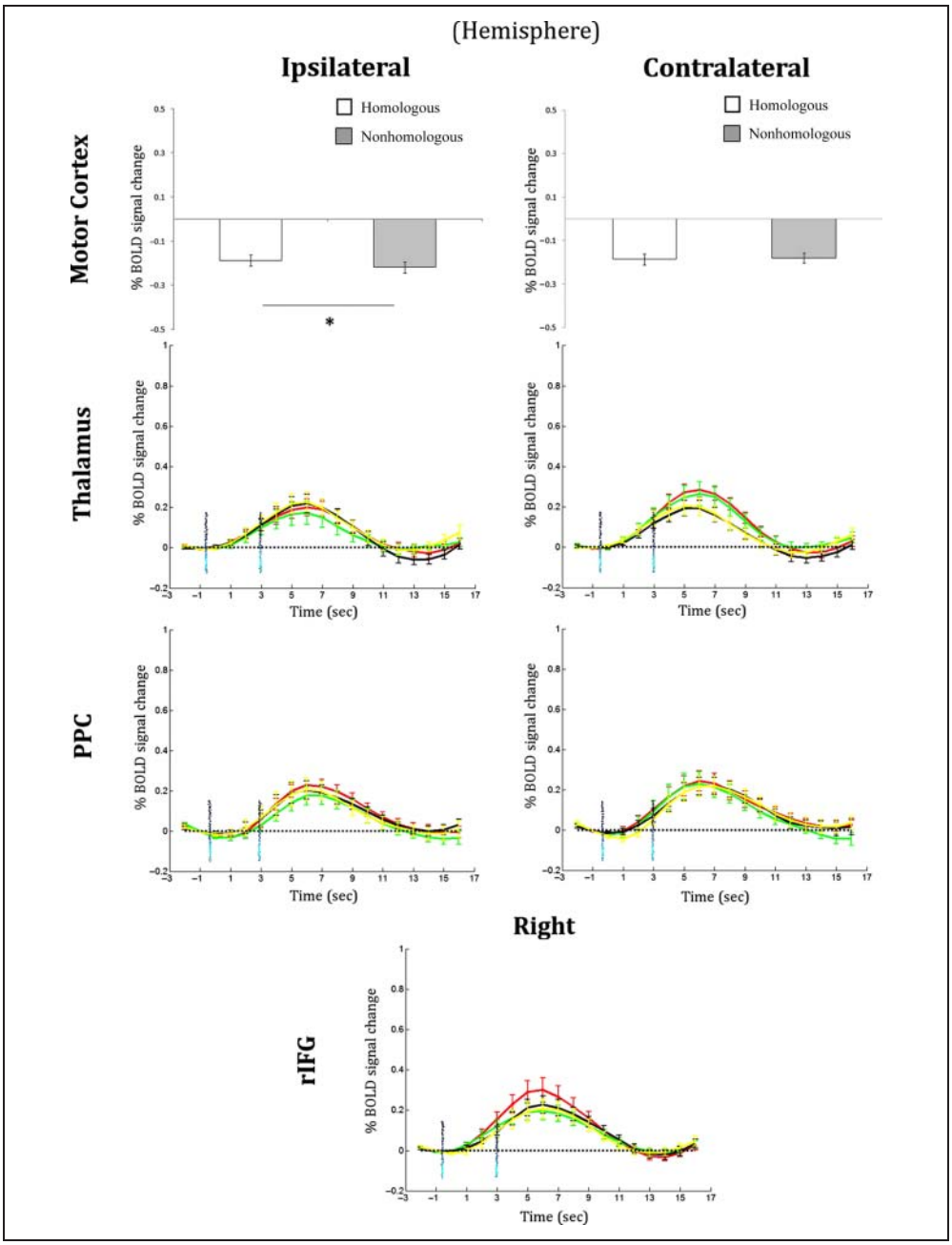

Figure 6. BOLD activity in other tactile responsive regions. The vertical dotted lines in the event-related averaging represent the onset time of the first (adaptor) and the second (test) stimulus.

to the adaptor, negative BOLD response was smaller for homologous (mean = −0.187%, *SE* = 0.04%; $p = .05$ corrected) than nonhomologous finger stimulation (mean = −0.218%, *SE* = 0.04%). By contrast, M1 contralateral to the adaptor showed no difference between homologous (mean = −0.186%, *SE* = 0.04%) and nonhomologous stimulation (mean = −0.179%, *SE* = 0.04%; $p = .93$).

In the right IFG, we ran two separate ANOVAs, one for each side of stimulation (i.e., within and between hands). This analysis revealed a greater BOLD response for the homologous (mean = 0.339%, *SE* = 0.05%) than nonhomologous (mean = 0.229%, *SE* = 0.04%) finger when the stimulation was within the same hand (main effect of Finger, $F(1, 16) = 21.68$, $p < .0003$), but not when it was between the hands ($p > .3$). Note that in this brain region we found an increase rather than a decrease in the BOLD response for the homologous finger stimulation.

The analysis on the thalamus and PPC showed that these brain areas were not modulated as a function of finger. In particular, the ANOVA on the thalamus revealed a greater BOLD response for the contralateral (mean = 0.286%, *SE* = 0.08%) than ipsilateral (mean = 0.265%, *SE* = 0.07%) hemisphere with respect to the adaptor (main effect of Hemisphere, $F(1, 16) = 11.37$, $p < .004$), the same was true also for the PPC (main effect of Hemisphere, $F(1, 16) = 8.45$, $p < .01$). Moreover, for the thalamus the BOLD response in the contralateral hemisphere was greater with unilateral (mean = 0.327%, *SE* = 0.06%) rather than bilateral (mean = 0.246%, *SE* = 0.05%; $p < .001$) fingers stimulation (interaction between Hemisphere and Hand $F(1, 16) = 33.22$, $p < .0001$). No other significant effects or interactions were observed (all ps $> .13$).

DISCUSSION

We used an fMRI adaptation approach to examine the contribution of SI and SII in the response to vibrotactile stimuli, delivered to fingers of same or different hands. Our results show that the overall BOLD response in SI and SII was stronger in the hemisphere contralateral to the adaptor stimuli. This finding is consistent with the well-established fact that afferent inputs to somatosensory cortices (i.e., SI and SII) are primarily contralateral. Our fMRI adaptation approach, however, allowed acquiring finer grained insights into the nature of the representations contained in the somatosensory cortices. SI and SII adapted more strongly when the stimulation was applied over homologous than nonhomologous fingers, thus showing that both these brain regions can clearly distinguish between the different fingers. Strikingly, our findings also show that, in both somatosensory regions, this adaptation effect occurred regardless of whether touches were delivered unilaterally or bilaterally. In other words, stronger adaptation to homologous than nonhomologous finger stimulation emerged even when the touched fingers belonged to different hands. This result implies that both SI and SII can integrate ipsilateral and contralateral signals originating from the hands. No other tactually responsive area of the brain showed such a pattern of adaptation for homologous than nonhomologous finger stimulation. This further indicates that the effects we observed in the somatosensory cortices are unlikely the result of modulations originating from other (earlier or later) stages of tactile stimulus processing. Instead, they most likely reflect the specific contribution of somatosensory cortices during tactile perception.

Adaptation Effect in the Somatosensory Cortices

Adaptation effects in the somatosensory modality have been reported previously using fMRI. Li Hegner and colleagues (2007; see also Li Hegner, Lee, Grodd, & Braun, 2010) asked participants to discriminate two vibrotactile stimuli applied sequentially to the same finger (left middle fingertip). In half of the trials, the same frequency was repeated twice, whereas in the remaining trials, two different frequencies were used. Within the somatosensory cortices, fMRI adaptation emerged in SI contralaterally and in SII bilaterally. Our findings extend this result by showing that fMRI adaptation for tactile stimuli to the fingers can also emerge when the repeating feature of the stimulus is its spatial location (i.e., which finger was stimulated) rather than its frequency. In our study, adaptation emerged as a reduced BOLD response in homologous compared with nonhomologous finger stimulation. Similar to Li Hegner et al. (2007), we found that this adaptation effect was lateralized in SI and bilateral in SII.

Our finger-specific adaptation effect was expected for the vibrotactile stimuli confined to a single hand (i.e., unilateral stimulation). Touches delivered twice to the same fingertip (unilateral homologous condition) stimulate the same region of skin and—to a large extent—the same population of tactile receptors. By contrast, touches delivered to adjacent fingers (unilateral nonhomologous condition) stimulate two distinct regions of skin and entirely different receptors. Thus, homologous finger stimulation likely activates the same population of neurons in the somatosensory cortex twice, whereas nonhomologous finger stimulation activates populations of neurons that are—at best—partially overlapping in the somatosensory cortex (for evidence of partially overlapping cortical regions of the index and middle finger see Krause et al., 2001; Kurth et al., 2000).

Strikingly, stronger adaptation for homologous than nonhomologous finger stimulation also emerged when the same stimuli were applied bilaterally. In this condition, no region of skin and no tactile receptors were shared between the two successive stimulations. The only common feature was the homology of body parts across sides (i.e., left and right index fingers). The present findings show that the only brain regions that were sensitive to this homology were the somatosensory cortices (both SI and SII), whereas no other brain region changed its BOLD response

as a function of finger identity (with the notable exception of M1 and to some extent the rIFG, see below). When considered in terms of neural coding, this finding implies the existence of neural populations in both SI and SII that code for finger identity irrespective of side. Although this notion is compatible with the existence of bilateral afferents and bilateral receptive fields in SII, it is more intriguing when considered within the well-known prevalence of contralateral afferents and contralateral receptive fields in SI.

Before discussing the implications of this key finding of bilateral integration in SI, two methodological concerns arising from our selection of ROIs based on bilateral stimulations should be addressed. The first concern is that the ROIs were extracted from a set of data also used for subsequent analysis, namely, the bilateral stimulation conditions. Kriegeskorte, Simmons, Bellgowan, and Baker (2009) argued that all data should be used for selection and statistical analysis, maximizing statistical power, provided that the contrast used for ROIs definition is orthogonal to subsequent analyses. The contrast vectors used here for ROIs definition and subsequent analyses were indeed orthogonal,[1] and the design with respect to the homologous versus nonhomologous conditions was balanced (see supplementary discussion in Kriegeskorte et al., 2009). The second concern is whether the key finding of bilateral integration emerged precisely because ROIs were selected from bilateral stimulation conditions. However, if this bilateral contrast for ROIs selection were to bias results toward an activation of bilateral integration brain areas, we should not find any evidence (or weaker evidence) of adaptation effects in the unilateral condition. This is clearly not the case. Most importantly, ROIs identified through bilateral stimulation conditions were localized in both hemispheres. Instead, the adaptation effect revealed in the bilateral condition clearly emerged for SI only in the hemisphere contralateral to the adaptor.

Bilateral Representations of the Body in SI and SII

Although BOLD responses in SI and SII were overall larger in the hemisphere contralateral to the adaptor stimuli than the ipsilateral one, our finger-specific adaptation effects were limited to the contralateral hemisphere in SI but were bilateral in SII. This is in line with the magnetoencephalographic (MEG) literature on tactile perception, which shows a primarily contralateral response in SI and a bilateral response in SII when adopting the classical approach of median nerve stimulation (e.g., Maldjian, Gottschalk, Patel, Detre, & Alsop, 1999; Hari et al., 1993). Bilateral representations of the two sides of the body in SII (e.g., Hari et al., 1993) are ascribed to more dense bilateral afferent inputs in SII in comparison with SI (e.g., Lin & Forss, 2002; Maldjian et al., 1999; Forss, Jousmäki, & Hari, 1995).

However, neurophysiological studies in monkeys and neuroimaging studies in humans have now pointed out that neural representations of the body in SI are probably not only contralateral. Bilateral receptive fields have been found in the Monkey Somatosensory Area 2 (Keysers et al., 2010; Iwamura et al., 2001, 2002; Killackey et al., 1983).[2] Moreover, when stimuli were presented to both paws, interhemispheric interactions have been revealed in Area 3b of the primary somatosensory cortex of owl monkeys (Reed, Qi, & Kaas, 2011; Reed et al., 2010). In rats, it has been demonstrated that SI can integrate inputs from the contralateral and ipsilateral whisker pads (Shuler, Krupa, & Nicolelis, 2001). In particular, Shuler and colleagues (2001) found that the neuronal responses in SI of one hemisphere (e.g., contralateral) after whisker pad stimulation were affected by a previous stimulus that reached the other hemisphere (e.g., ipsilateral). This effect was modulated as a function of the spatial location and the relative timing at which the whisker stimuli were presented. In humans, SI responses ipsilateral to a tactile stimulus have been shown using neuroimaging (Hlushchuk & Hari, 2006; Tan, Wühle, & Braun, 2004; Staines, Graham, Black, & McIlroy, 2002). In addition, bilateral BOLD responses in both SI and SII have been recorded under unilateral sensory stimulation conditions (Blatow, Nennig, Durst, Sartor, & Stippich, 2007). Finally, behavioral studies in humans have corroborated these observations by showing that tactile representations may not fully differentiate between body sides (Tamè, Farnè, & Pavani, 2012; Tamè et al., 2011; Braun et al., 2005; Harris et al., 2001; Sathian, 2000; Sathian & Zangaladze, 1997, 1998; Ramachandran et al., 1995).

Interactions between ipsilateral and contralateral inputs in SI may derive from different anatomical pathways, which are not mutually exclusive (Sutherland, 2006). One first possibility is that ipsilateral somatosensory inputs are conveyed transcallosally from the contralateral SI (Allison, McCarthy, Wood, Williamson, & Spencer, 1989). In rats, for instance, the pharmacological inactivation of SI in one hemisphere using muscimol eliminates the ipsilaterally evoked whisker responses in the unaffected SI in the other hemisphere (Shuler et al., 2001), supporting the hypothesis of information exchange between SI in the two hemispheres. A second possibility is the existence of direct projections from the receptor surface to ipsilateral SI (Kanno et al., 2004; Kanno, Nakasato, Hatanaka, & Yoshimoto, 2003), mediated by uncrossed afferent fibers (Kanno et al., 2003; Noachtar, Lüders, Dinner, & Klem, 1997). An MEG study on two patients with left hemispheric lesions found ipsilateral activation of the right SI after stimulation of the median nerve of the right arm, despite impaired somatosensory responses in the left hemisphere (Kanno et al., 2003). This clinical finding potentially obviates the need for transcallosal pathways for the ipsilateral activation of SI. Finally, cortico-cortical modulations of SI could also emerge via transcallosal connections between homotopic SII regions (Tommerdahl, Simons, Chiu, Favorov, & Whitsel, 2006; Schnitzler, Salmelin, Salenius, Jousmäki, & Hari, 1995).

The low temporal resolution of fMRI does not allow us to determine the time course of the interaction between contralateral and ipsilateral tactile stimulation in SI and SII, thus preventing any definite conclusion about the pathway leading to the interactions between ipsilateral and contralateral signals observed here in SI. Interestingly, our data showed a trend toward a delayed activation peak of the overall BOLD response in the ipsilateral compared with the contralateral SI. This trend may have failed to reach significance due to the adopted repetition time (2.2 sec), which does not provide sufficient temporal precision to characterise this temporal difference. It would be relevant to assess this pattern in a dedicated study, as this could speak in favour of a transcallosal interaction from SII to ipsilateral SI. In this respect, preliminary evidence we collected with MEG, using a similar paradigm to the one described here, suggest that transcallosal interactions may be more likely than direct ipsilateral afferent projections (Braun, Tamè, Papadelis, Farnè, & Pavani, 2011). Particularly, transcallosal interactions at the level of SII are also possible due to its strong anatomical connections with SI (Manzoni, Conti, & Fabri, 1986; Caminiti, Innocenti, & Manzoni, 1979), implying quite a local top–down modulation within the somatosensory cortex. As noted by Shuler et al. (2001), ipsilateral evoked activity in primary sensory cortices has been largely accounted for by transcallosal pathways in other sensory systems and species (e.g., Iwamura et al., 2001; Schnitzler et al., 1995; Swadlow, 1990; Manzoni, Barbaresi, Conti, & Fabri, 1989; Berlucchi, Gazzaniga, & Rizzolatti, 1967). Whatever the particular pathway the tactile inputs travel to join ipsilateral SI, this study indicated that integration of inputs from the two body sides can occur in SI as well as in SII.

A final aspect that deserves to be addressed is the nature of the neural mechanisms subserving the contralateral and ipsilateral fMRI response in SI. The contralateral response is commonly associated with an excitatory process (activation: increment of the BOLD response), whereas the ipsilateral one has been reported to be associated with both excitatory (e.g., Blatow et al., 2007) or inhibitory (e.g., Hlushchuk & Hari, 2006, deactivation: reduction of the BOLD response) processes. In this respect, Lipton and Colleagues (2006), using fMRI and electrophysiology to investigate the hand representation in the SI (Area 3b) of macaque monkeys, showed bilateral responses at an early stage of cortical somatosensory processing. In particular, these authors reported a clear hemodynamic evidence of an ipsilateral response in Areas 1 and 2 and surprisingly also in Area 3b of SI. Furthermore, they demonstrated that the ipsilateral inputs in SI were mainly inhibitory (Lipton et al., 2006). In relation to our work, this interesting finding suggests that the neural mechanism underlying our finger-specific adaptation effect (in Areas 1 and 2) is likely to result from a stronger inhibitory response of the ipsilateral SI, when bilateral homologous rather than nonhomologous fingers were stimulated. In turn, this different amount of inhibition could reflect a "preferential" finger-specific homotopic pathway or a different ipsilateral inhibitory weight assignment as a function of the body parts homology (e.g., homologous or nonhomologous) between the two sides of the body.

Adaptation Effects Outside the Somatosensory Cortex

Outside somatosensory regions, none of the brain areas responsive to vibrotactile stimuli showed specific adaptation for homologous in comparison with nonhomologous fingers. The fact that the adaptation pattern does not come from the previous stages (e.g., thalamus) and that it cannot be observed at other stages (e.g., areas within the PPC) of tactile processing suggests that the distinction between fingers and the interaction between body sides originates in the somatosensory cortex.

The only two exceptions were the right IFG and M1. The rIFG showed an increased BOLD response when the target finger was stimulated twice (i.e., left index twice) compared with when nonhomologous finger of the same hand was stimulated (i.e., left middle and left index). rIFG is a well known region of the brain network activated during stimulus-driven attentional orienting (e.g., Corbetta & Shulman, 2002). Thus, this effect is likely attributable to attentional cueing to the test finger, when the preceding stimulation occurred exactly in the same location. More relevant to the purpose of this study and directly related to the adaptation effects examined for the somatosensory cortices is the modulation of BOLD response we found in the M1 ipsilateral to the adaptor. M1 showed a general deactivation pattern for all stimulation conditions. Previous studies in humans reported inhibition of M1 during sensory–motor interactions (e.g., Bikmullina, Kičić, Carlson, & Nikulin, 2009; Tokimura et al., 2000; for a review, see Chen, 2004; Chen, Corwell, & Hallett, 1999). Furthermore, studies in awake monkeys showed that many neurons in the primary motor cortex respond to cutaneous stimulation (e.g., Lemon, 1981) and that BA 1 and BA 2 are strongly anatomically connected with M1 (Stepniewska, Preuss, & Kaas, 1993). The deactivation pattern we revealed in left M1 was exactly mirror symmetric to the finger-specific adaptation effect we reported in somatosensory cortices. This suggests a very close and low-level inhibitory interaction between the somatosensory and motor cortices, indicating that the study of M1 can be informative about the representation of touch in somatosensory regions and particularly SI. It is unclear why the effect in M1 was only present in the hemisphere ipsilateral to the adaptor. However, one previous study on a patient with Klippel–Feil syndrome and mirror movements of the hand muscles (Farmer, Ingram, & Stephens, 1990) reported that digital nerve stimulation produced an inhibitory response only in the muscles ipsilateral to the stimulus, meaning that low-level interactions between the somatosensory and the motor cortices of opposite hemispheres are possible.

Conclusions

Using fMRI adaptation to study the spatial coding of touch, the present work shows that the primary somatosensory cortex can homotopically integrate somatosensory inputs from the two sides of the body, despite its prominent contralateral response. This finding extends the contribution of SI to spatial coding of touch beyond the mere distinction of body parts (i.e., somatotopy). The involvement of SI in the processing of somatosensory stimuli from both sides of the body is in accordance with a growing body of evidence in animals and humans that suggest that SI can be "an actual site of integration, rather than merely a conduit for sensory information that is integrated at higher processing stages" (Shuler et al., 2001, p. 2967). As such, it may play a role in the integration of bilateral somatosensory input required, for instance, during bimanual exploration of objects.

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Notes

1. For ROI selection, we computed the following contrast: $c_{\text{selection}} = [0\ 0\ 1\ 1]^T$. To compare homologous and nonhomologous unilateral conditions, we computed the following test contrast: $c_{\text{unilateral}} = [1\ -1\ 0\ 0]^T$. To compare homologous and nonhomologous bilateral conditions, we computed the following test contrast: $c_{\text{bilateral}} = [0\ 0\ 1\ -1]^T$. The selection contrast and the two test contrasts are orthogonal contrast vectors because their inner product is zero: $c_{\text{selection}}{}^T \cdot c_{\text{unilateral}} = 0$, and $c_{\text{selection}}{}^T \cdot c_{\text{bilateral}} = 0$.

2. Although it was beyond the scope of the present work to identify sub-areas in SI and SII cortices, we nonetheless examined peak of activation and centroids in our somatosensory ROI using the SPM anatomy toolbox. To this aim, we converted the coordinates from Talairach and Tournoux space (the coordinate system we adopted) to MNI space (SPM anatomy toolbox coordinates) by applying the MTT transform proposed by Lancaster et al. (2007). This inspection identified the following subareas: right SI was associated with area 3b; left SI was equally associated with Areas 1 and 2; SII in both hemispheres were primarily associated with subareas OP1 and OP4. As discussed in the manuscript, in monkeys bilateral receptive fields in SI were observed selectively in Area 2 (Keysers et al., 2010; Iwamura et al., 2002; Killackey et al., 1983). Although probabilistic subarea identification should be treated with caution, it is most interesting to note that our key finding of bilateral integration in SI emerged precisely in the left hemisphere, which the SPM anatomy toolbox associates with Areas 1 and 2. Instead, the right SI was associated with Area 3b. Furthermore, there is good correspondence between the subareas we identified for SII and the regions typically associated with SII in monkey neurophysiology (e.g., Eickhoff, Grefkes, Fink, & Zilles, 2008).

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