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ORIGINAL ARTICLE

Ipsilateral somatosensory responses in humans: the tonic activity of SII and posterior insular cortex

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Abstract

In the present study, we mapped the spatio-temporal dynamics of cortical responses to ipsilateral median nerve stimulation using intracerebral recordings (stereo-EEG) in 38 drug-resistant epileptic patients. Furthermore, we compared the pattern of responsiveness obtained in the same leads across ipsilateral and contralateral stimulations. Ipsilateral responses were found mostly confined to SII and posterior insula, while no activity was found in ipsilateral SI. By examining the temporal profiles of activation, ipsilateral SII showed a prominent tonic pattern, while contralateral SII exhibited both phasic and tonic responses. Beyond the localization of the active cortical nodes, these data contributed to identify the cortico-cortical connections carrying the somatosensory information to the ipsilateral hemisphere, with a major role of transcallosal projections from contralateral SII. In light of previous literature and of its localization, the functional role possibly covered by long lasting discharge in SII and insular cortex is also discussed. Overall, the presence of tonic activities was neglected so far due to the impossibility to identify deep sources along with a resolved description of their time course. The use of stereo-EEG, instead, allows one to achieve a four-dimensional characterization, complementing the classical view about the somatosensory system organization.

Keywords Stereo-EEG · Cerebral cortex · Touch · Perysilvian region · Median nerve

Introduction

In the recent decades, the cortical processing of somatosensory stimuli has been extensively investigated in humans by means of a variety of techniques such as magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), scalp electroencephalography (EEG) and, more rarely, intracranial electroencephalography (iEEG).

The results showed that, following unilateral tactile stimulation, there is a contralateral activation of the primary somatosensory cortex (cSI) and a bilateral activation of the secondary somatosensory cortex (SII) (Hari et al. 1993; Korvenoja et al. 1999; Backes et al. 2000; Wegner et al. 2000; Lin and Forss 2002). Bilateral activation is also observed in the posterior insular regions (Ferretti et al. 2007; Ruben et al. 2001) and in the frontal operculum (FO) (Hinkley at al. 2007).

The activation of SI following ipsilateral stimulation is not only controversial in terms of consistency across subjects and of topography (Korvenoja et al. 1995; Hari and Forss 1999; Nihashi et al. 2005; Hlushchuk and Hari 2006), but also its functional role in somatosensory perception is unclear. Indeed, previous studies proposed iSI activity as complementing a discriminative activity of cSI (Dijkerman and Haan 2007), while recent studies on primates opened to the possibility that iSI exerts an inhibitory modulation on cSI (Lipton et al. 2006).

As far as SII is concerned, the pathway mediating the ipsilateral response is still matter of debate. Simoes and Hari

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(1999) suggested that its activation results either from direct input from VP nuclei of the ipsilateral thalamus or from callosal input from cSII. In addition, a connectivity study based on Granger causality suggested that iSII receives a direct input from cSI (Gao et al. 2015). In a recent stereo-EEG study, Avanzini et al. (2016) mapped the activations of the contralateral hemisphere following stimulation of the median nerve. Activations were found in a large cortical region not limited to the areas described in previous fMRI studies (cSI, cSII and insular cortex, see Ferretti et al. 2007), but extending to dorsal premotor cortex (PMd) and middle temporal gyrus. Most interestingly, by taking advantage of the high temporal resolution of stereo-EEG (Lachaux et al. 2012), Avanzini et al. (2016) assessed the temporal activation pattern for each of the responsive areas. In particular, a dual time-course (phasic and tonic) was recorded from leads exploring cSII. While the phasic component (20–30 ms after the stimulus) is most likely related to touch detection, the significance of the tonic component, which has long latency (about 40 ms) and lasts until 200 ms, is open to different interpretations.

Given the procedures intrinsic to stereo-EEG—(the implantations are mainly unilateral as anatomo–electro-clinical indications often specify the laterality of the epileptogenic region to be investigated)—no information was available concerning the activations of the ipsilateral hemisphere. This information, however, is essential not only to map the overall cortical territories encoding somatosensory processing but also to clarify, according to their time-course, the functional connections between different areas. For these reasons, we complemented the battery of clinical tests by adding the stimulation of the median nerve ipsilateral to the implanted hemisphere.

The purpose of the present study is to obtain a comprehensive four-dimensional stereo-EEG mapping of the cortical areas responsive to the ipsilateral tactile stimulation. Furthermore, we compare the time-course of ipsilateral activations with the contralateral ones recorded in the same patients. This comparison should allow us to assess the cortico-cortical dynamics sustaining somatosensory processing, and to obtain insights on the functional properties of the different areas.

Materials and methods

Participants

Stereo-EEG data were collected in 38 patients (19 females, 30.7 ± 10.8 years) suffering from drug-resistant focal epilepsy. As inclusion criteria, only patients presenting no anatomical alterations ($n = 34$) or little abnormalities not involving the sensorimotor areas ($n = 4$) in the pre-implantation MR were included. The four patients with positive MR showed minimal periventricular nodular heterotopia, three of them located in the temporal lobe and one in the orbito-frontal cortex. No patients presented sensorimotor deficits. Their pharmacological treatment was not modified during the 24 h prior the experimental tests and no epileptic seizures were observed during the recordings. All patients were stereotactically implanted with intracerebral electrodes as part of their presurgical evaluation at the "Claudio Munari" Center of Epilepsy Surgery, Ospedale Niguarda-Ca' Granda, Milan, Italy. Implantations sites were selected exclusively in relation to the electro-clinical data and neuroimaging examinations. This study received the approval of the Ethics Committee of Niguarda Hospital (ID 939-2.12.2013) and all the patients were fully informed regarding the electrode implantation and stereo-EEG recordings.

Electrodes implantation

Twenty-six of the 38 recorded patients were implanted unilaterally while the remaining 12 presented a bilateral implant, resulting in a total of 50 hemispheres analyzed (28 right, 22 left). A number of depth electrodes (range 8–18) were implanted into different regions of the hemisphere using stereotactic coordinates. Each electrode had a diameter of 0.8 mm and consisted of 8–18 2 mm-long contacts (leads), spaced 1.5 mm apart (DIXI®, Besancon, France). Immediately after the implantation, cone-beam computed tomography (CBCT) was obtained with the O-arm scanner (Medtronic, Minneapolis, Minnesota) and registered to pre-implantation 3D-T1-weighted MR images. Subsequently, multimodal scenes were built with 3D Slicer software package (Fedorov et al. 2012), and the exact position of each lead was determined, at the single patient level, looking at multiplanar reconstructions (Dale et al. 1999). Following clinical conventions, all leads were labeled by a letter corresponding to the electrode shaft, followed by a number sequentially increasing starting from the tip of the electrode.

Nerve stimulation

The stimulation of the median nerve is part of the clinical tests ordinarily administered by neurologists to map leads involved in somatosensory information processing. Stimulations were first delivered contralaterally to the recorded hemisphere, and subsequently also ipsilaterally, using 100 constant-current pulses (0.2 ms duration) at 1 Hz. Intensity for each patient was set at 10% above the motor threshold (range 3.2–5.3 mA), evaluated as the minimum threshold able to evoke twitches of the contralateral thumb.

Anatomical reconstruction of electrodes

The aim of the reconstruction was to localize the recording leads in the individual cortical surfaces and, via a 2D co-registration, to merge leads from all patients onto a common template. The procedure adopted in this study is the same as in Avanzini at al. (2016).

Stereo-EEG data recording and processing

The stereo-EEG trace was recorded with a Neurofax EEG-1100 (Nihon Kohden System) at 1-kHz sampling rate. The reference, chosen for each patient independently, is calculated as the average of two adjacent leads located in the white matter that do not respond to clinical stimulations (including somatosensory, visual and acoustical). In addition, their electrical stimulation does not evoke any sensory and/or motor behavior. The neurologists visually inspected the recordings and verified the absence of ictal epileptic discharges (IEDs) for all patients. Data from all leads in the grey matter were decomposed into time–frequency plots using Morlet's wavelet decomposition and power in the gamma frequency band was estimated for adjacent non-overlapping 10-Hz frequency bins (Vidal et al. 2010; Caruana et al. 2014a, b) between 55 and 145 Hz to avoid contamination from power-line noise. For both stimulations (ipsilateral and contralateral), the considered time-window spans 100 ms before and 500 ms after the stimulus delivery, and it was subdivided into 60 non-overlapping 10-ms bins. To obtain normalized data across patients and leads, power in post-stimulus bins was z scored relatively to the pre-stimulus interval. Leads responsive to median nerve stimulation were identified by comparing gamma band power in each post-stimulus bin against the baseline (t test, $p < 0.001$). Significance was Bonferroni corrected for the 50 comparisons and leads with at least 3 significant bins were considered as responsive. Overall responsiveness maps were computed according to the procedures detailed in (Avanzini et al. 2016) and visualized with Caret software (Van Essen et al. 2012). The brain template and the corresponding flat map are shown in Fig. 1. To group data according to their temporal pattern and regardless of amplitude modulations, gamma power time-courses of the reactive leads were first normalized between 0 and 1, and then

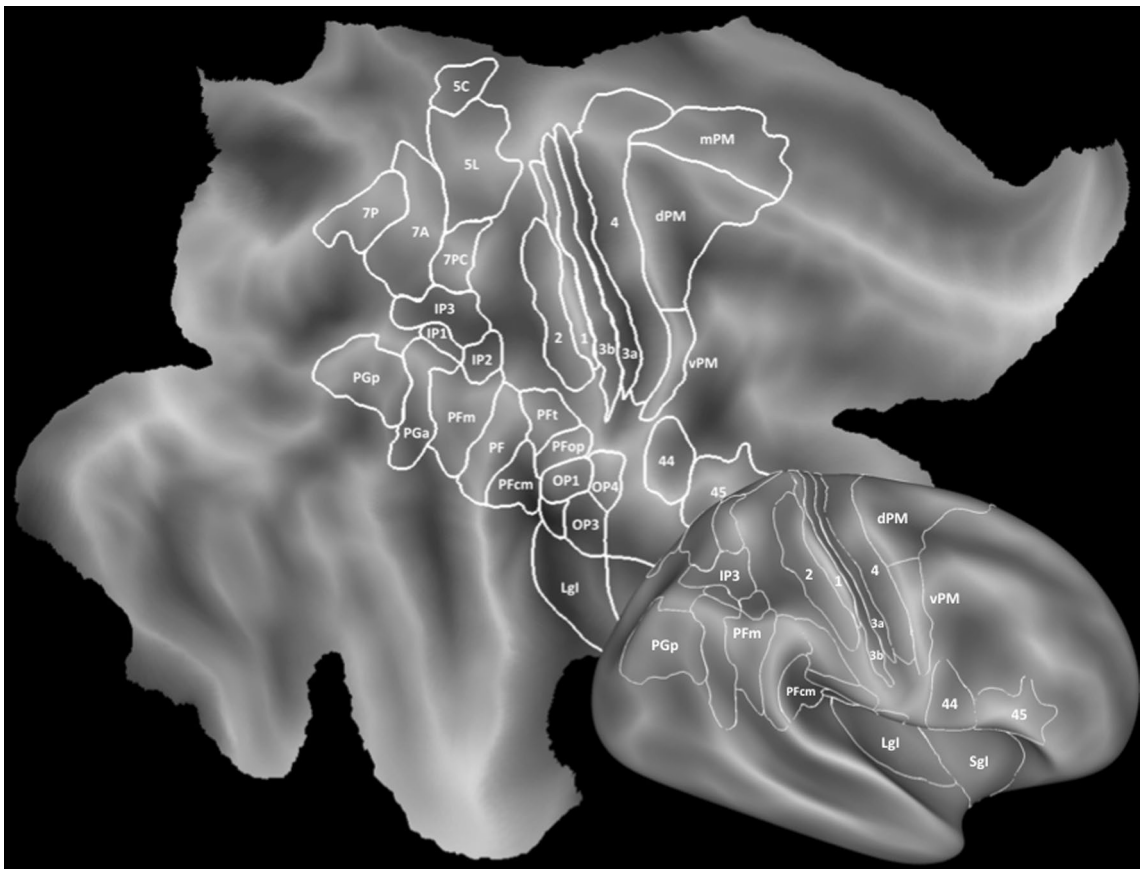

Fig. 1 Brain template. Flat map of fs-LR-average right hemisphere template (163.842 nodes), with cytoarchitectonic regions indicated. The bottom-right inset shows the inflated view of the same brain template. Borders for cytoarchitectonic areas are reported also in Figs. 2, 3 and 4

clustered with *k*-means algorithm, imposing an increasing number of clustering (3–20). For each, the maximal average silhouette value was computed and used to identify the optimal number of clusters. The described analysis, in line with (Avanzini et al. 2016), tested the presence of strong and highly significant responses in gamma band. While these are largely expected in the contralateral hemisphere, the ipsilateral activity might exhibit a lower strength. Starting from these premises, to avoid the presence of false negatives, we recalculated responsive leads removing the Bonferroni correction. Chi-squared tests were finally conducted to test for a possible lateralization effect on the number of reactive leads obtained in each stimulation condition for responsive areas.

Results

Overall, 5872 cortical sites have been explored of which 4466 were localized in the grey matter according to the anatomical reconstruction (2783 in the right hemisphere, 1683 in the left hemisphere). The sampling density maps (Fig. 2) show the extensive coverage of the cortical sheet except for the frontal and occipital tips of the hemispheres as well as the cortical crowns due to the obligatory orthogonal insertion of electrodes and to the anatomical and vascular constraints (presence of frontal bone sinus and superior sagittal sinus). A poor sampling was present also in the posterior parietal cortex (PPC); however, this region lies outside the areas responsive to median nerve stimulation as described in Avanzini et al. (2016).

Statistical analysis showed that 37 leads presented a significant broadband gamma power increase in response to the ipsilateral median nerve stimulation (19 in the right hemisphere, 18 in the left hemisphere). Responsive leads (Fig. 3) were almost exclusively located in the parietal operculum (8 right, 13 left) and in particular in its dorso-caudal part corresponding to area OP1 (5 right, 12 left). Active leads were found, at a smaller extent, bilaterally in the frontal operculum (FO) (4 right, 2 left), and in the long gyri of the right insular cortex (LgI, 4 leads) and one lead at the boundary with area OP2 (left). Six additional responsive leads were found in the right inferior parietal cortex (PFcm, 2), left short gyri of insular cortex (SgI, 2), right PMd (1) and right SI (1). Due to their sparsity, these latter activations will be not discussed further.

Following contralateral stimulation, 415 leads were found responsive (253 in the right hemisphere, 162 in the left hemisphere). The difference between the two hemispheres is merely linked to the different sampling (about 10% in both cases). The responsiveness maps, shown in Fig. 4, are in close agreement with those described by Avanzini et al. (2016). Of note, virtually all the leads reactive to the ipsilateral stimulation (34 out of 37) were found to be active also in response to the contralateral one.

To examine whether the temporal pattern of responsiveness differed between ipsi- and contra-lateral stimulations across OP1, LgI and FO, average time-courses of the gamma power were computed for the leads reactive in both stimulation conditions, for each area independently (Fig. 5). Following ipsilateral stimulation, all areas revealed a tonic long lasting response (see red traces in Fig. 5a–c). In contrast, following contralateral stimulation (black traces), the same leads might show two different behaviors. The majority of them (18 out of 28) presented simultaneously a dual pattern: phasic (a peak at around 20–30 ms) and tonic (long lasting response with low amplitude and peaking after 50 ms).

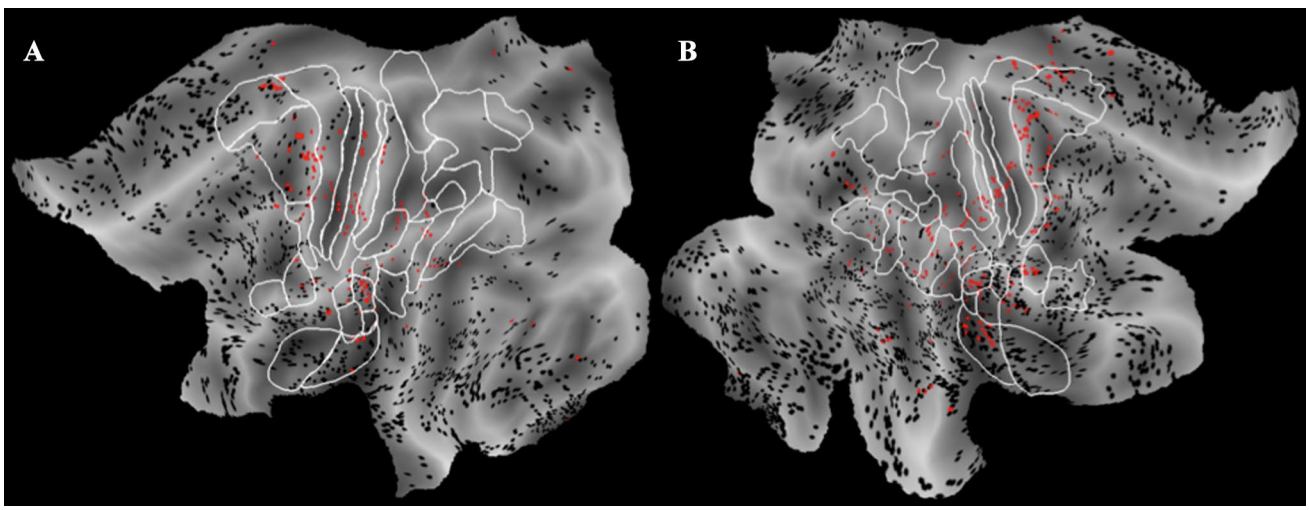

Fig. 2 Sampling density flat maps. Midthickness surface of the fs_LR brain template with all leads located in gray matter of the left (**a**) and right (**b**) hemispheres. Red dots correspond to leads active following the contralateral stimulation, black dots represent unresponsive leads

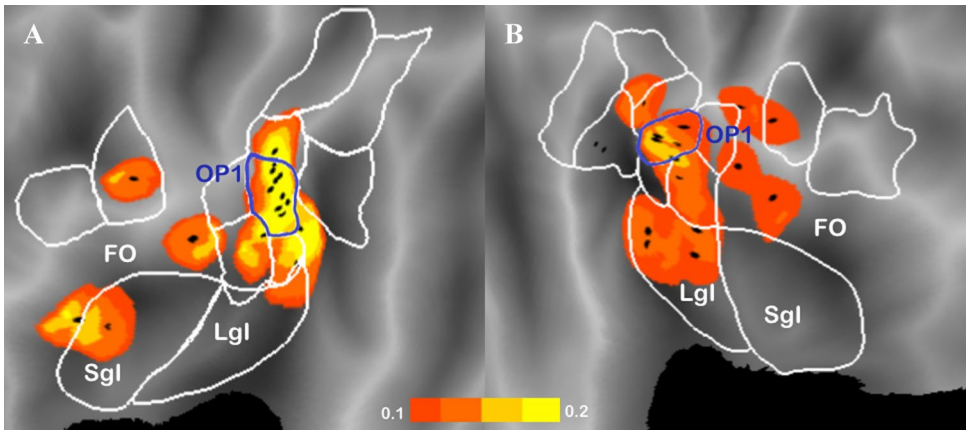

Fig. 3 Responsiveness to median nerve stimulation in the ipsilateral perisylvian regions. Responsive leads (black dots) and responsiveness maps are shown onto the midthickness surface of fs_LR_brain template for left and right hemispheres (**a, b**, respectively). The two reactive leads located in right PFcm do not generate a corresponding blob in the continuous map due to constraints on sampling. White borders refer to cytoarchitectonic areas of inferior parietal cortex (Caspers et al. 2006, 2008), parietal operculum (Eickhoff et al. 2006), and areas 44 and 45 (Amunts et al. 1999). In addition, long and short gyri of insula were anatomically defined using the gyral pattern

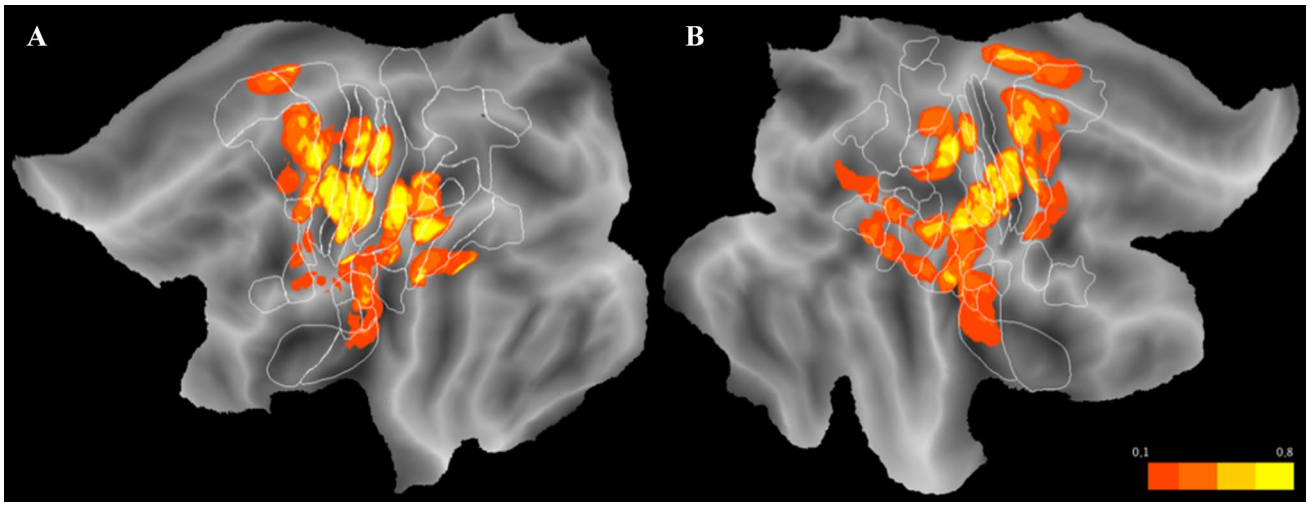

Fig. 4 Overall responsiveness maps following contralateral stimulation. Overall responsiveness (responsive leads as a percentage of total explored leads per disk) for left (**a**) and right (**b**) hemispheres. Only surface nodes with values exceeding 10% were shown

The remaining 10 leads showed an exclusively tonic course, whose temporal profile was comparable with the one found for the ipsilateral stimulation. As a result, OP1 was characterized by a dual time course, with both phasic and tonic activity (Fig. 6a), while LgI showed only a tonic response (Fig. 6c). Finally, a more ambiguous pattern was obtained for FO (Fig. 6b), where, however, the latency of the earliest peak is compatible with a phasic behavior preceding a tonic response.

A similar pattern was obtained also when considering all the leads responsive to the contralateral stimulation regardless their response to the ipsilateral one; in this case, however, a small phasic component seems to be present also in LgI (Fig. 6c). Centroids resulting from the clustering procedure are available in Fig. 5d. Comparing the areas responsive to ipsilateral versus contralateral stimulation, SI and PMd resulted to respond only to contralateral stimuli. In total 78 leads (42 right, 36 left) were explored in SI complex, including areas 3a(15), 3b(27), 1(14), 2(22). Among these, 64 (82%) were found responsive to the contralateral stimulation, while only one to the ipsilateral stimulation. Furthermore, 133 leads (75 right, 58 left) were recorded in PMd, of which 62 (46%) responsive to the contralateral stimulation and only one to the ipsilateral stimulation.

The removal of Bonferroni correction for the ipsilateral stimulation increased the number of responsive leads to 6 in

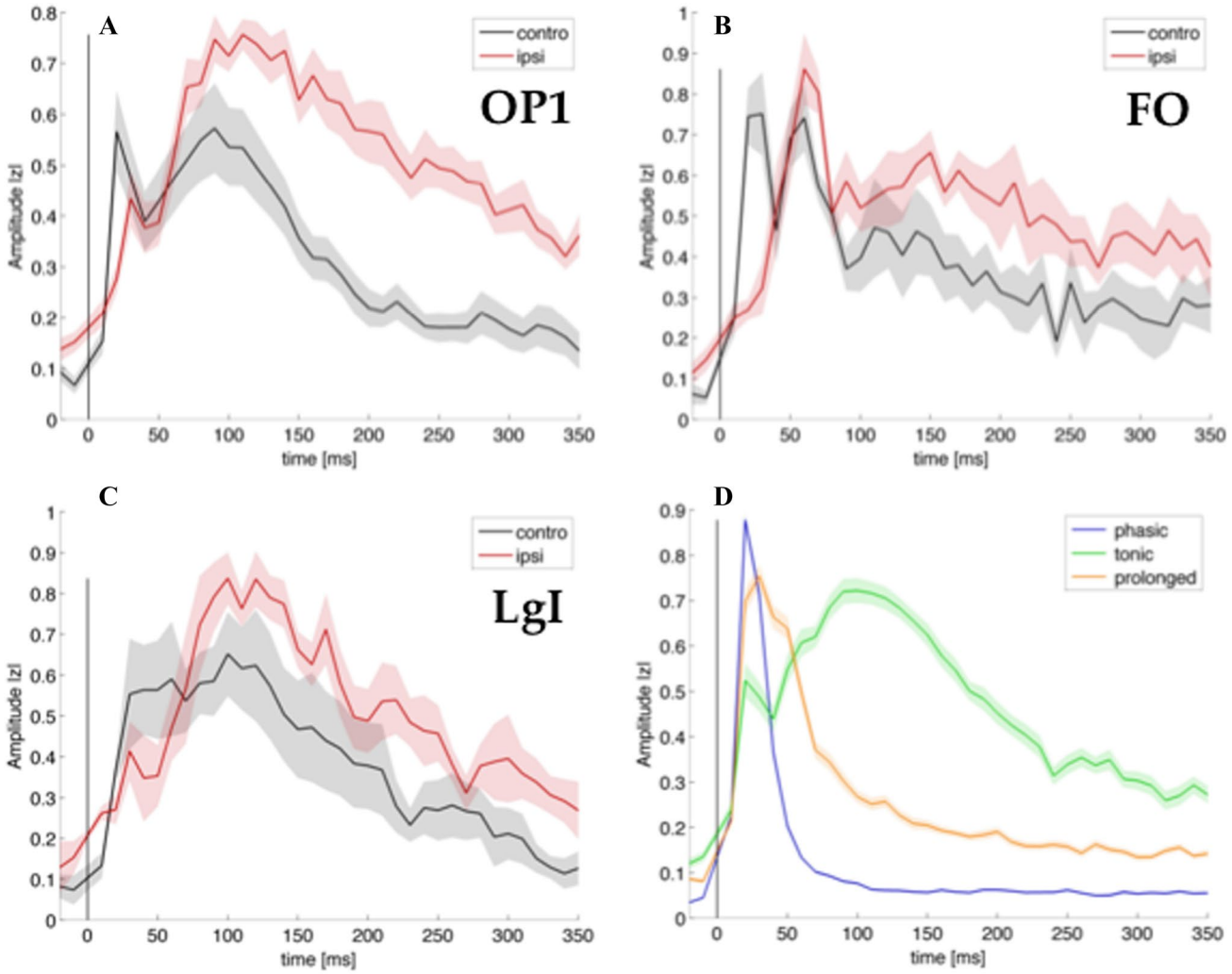

Fig. 5 Normalized gamma-band time course of regions active for both ipsi- and contra-lateral median nerve stimulation. Average time-courses (±SE) are shown separately for OP1 (**a**), FO (**b**) and LgI (**c**), based only on leads active for both stimulations and after a normalization to the [0,1] range. **d** The centroids resulting from *k*-means clustering applied on normalized responses to contralateral stimulation. The labels assigned to clusters follow Avanzini et al. (2016): phasic (peak around 20–30 ms and return to baseline level within 50 ms from stimulation), prolonged (rising similar to phasic but longer duration of the activation) and tonic (activation lasting more than 200 ms with a peak lower than other clusters)

SI (4 patients; 2 in area 1, 3 in area 2 and 1 in area 3b) and 5 in PMd (3 patients), all located in the right hemisphere. Earliest latency and number of significant bins for each of these leads are reported in Table 1.

Chi-square tests reveal that the distribution of responsive leads in both stimulation conditions do not differ significantly across implanted hemispheres for SI complex, PMd, OP1, LgI, FO and these three latter taken together.

Discussion

Ipsilateral cortical responses to somatosensory stimulation

In the present study, we used stereo-EEG to obtain a four-dimensional picture of the cortical areas active following

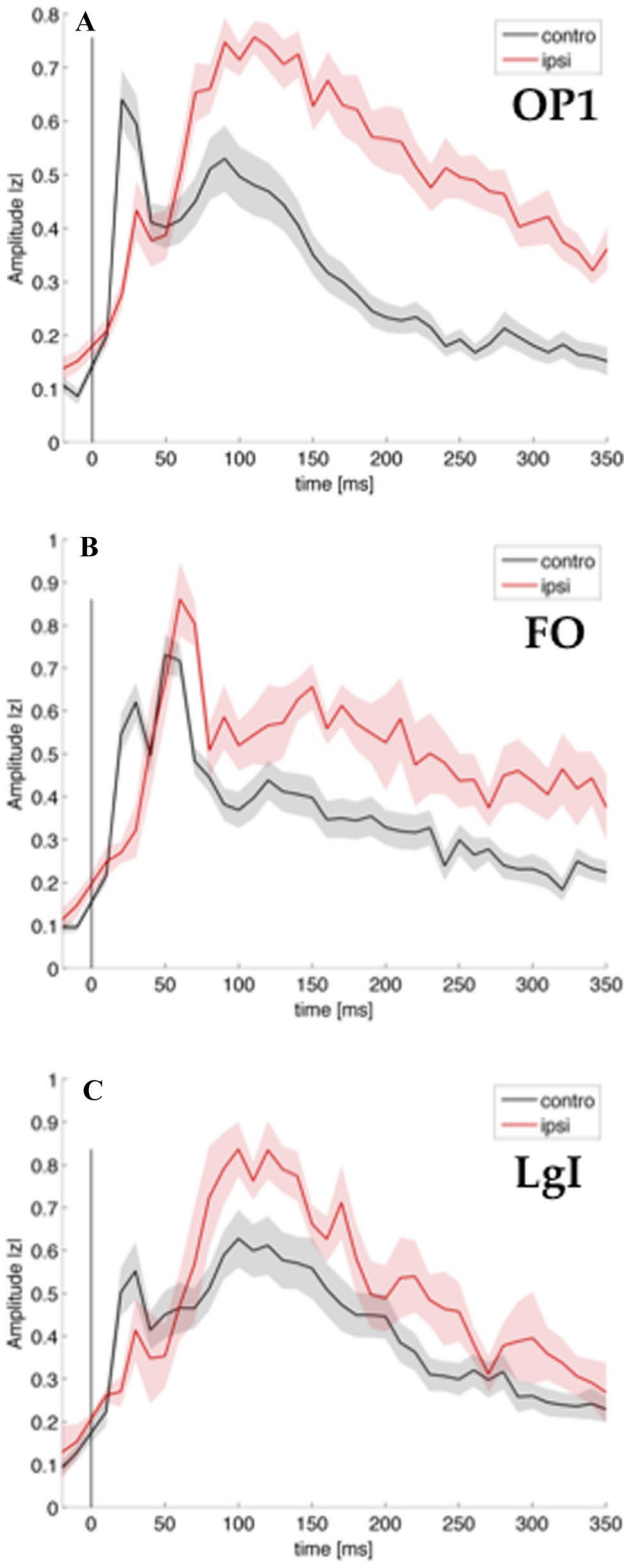

Fig. 6 Normalized gamma-band time course of regions active to ipsi- and contra-lateral median nerve stimulation. Average time-courses (± SE) are shown separately for OP1 (**a**), FO (**b**) and LgI (**c**), based on all leads active in each stimulations and after a normalization to the [0,1] range

ipsilateral median nerve stimulation. To this purpose, we used the gamma activity (50–150 Hz), elicited by nerve stimulation, as an index of neuronal recruitment (see Lachaux et al. 2007) in both space and time (Jerbi et al. 2009; Vidal et al. 2010). Note that, given the millisecond time-scale resolution of stereo-EEG, we were able to evaluate the time-course of each active region and to compare it with the responses recorded from the contralateral hemisphere (see also Avanzini et al. 2016).

Our results confirmed previous findings that bilateral somatosensory responses are mostly confined to SII, and less extensively to long insular gyri (LgI), with the unilateral somatosensory responses being always contralaterally located (Dijkerman and Haan 2007). In agreement with Wegner et al. (2000), ipsilateral SII responses were found in the same SII leads activated by contralateral stimulation. However, the inspection of the gamma time-course revealed clear differences between cSII and iSII activation pattern. While iSII exhibits an almost exclusively tonic behavior, the cSII shows a large phasic response at 20–30 ms followed by a sustained tonic one. The co-existence of two different patterns of responsiveness for cSII, earlier described in (Avanzini et al. 2017), and the predominance of the tonic response in the ipsilateral hemisphere might represent the signature of diverse functions mediated by SII in somatosensory processing (see below).

Summing up, the activation in the ipsilateral hemisphere following somatosensory stimulation is virtually limited to perisylvian regions, and its tonic time-course seems in line with what highlighted for same regions in the contralateral hemisphere. In the next section, we will discuss how this spatio-temporal evidence might provide a significant contribution to the issue concerning the anatomo-functional pathways recruited during non-nociceptive somatosensory processing.

How does somatosensory information reach iSII?

The bilateral activation of SII is consistently reported in previous literature (Hari et al. 1993; Korvenoja et al. 1999; Backes et al. 2000; Wegner et al. 2000; Lin and Forss 2002). One debated point is how peripheral somatosensory information reaches not only cSII but also iSII. Several hypotheses have been advanced, and namely: (1) via uncrossed afferent fibres reaching the ipsilateral thalamus, which then projects to iSII, (2) callosal connections from cSII and (3) callosal connections from cSI; (4) connections from iSI, which in turn might receive callosal connections from cSI.

The long average latency found for iSII relative to cSI and cSII, along with the almost complete absence of phasic activity, renders very unlikely a contribution of the ipsilateral thalamus, contrary to what suggested by Kanno et al. (2003). This conclusion is also in line with previous studies

Table 1 Responsive leads to ipsilateral stimulation without Bonferroni correction

Lead (area)	Latency (ms)	Num. of significant bins
Lead 1 (BA1)	50	19 (responsive also with Bonferroni correction)
Lead 2 (BA2)	40	3
Lead 3 (BA2)	100	6
Lead 4 (BA2)	60	4
Lead 5 (BA2)	30	3
Lead 6 (BA3b)	60	3
Lead 1 (PMd)	50	4 (responsive also with Bonferroni correction)
Lead 2 (PMd)	50	4
Lead 3 (PMd)	60	6
Lead 4 (PMd)	190	3
Lead 5 (PMd)	10	4

Latency value represents the first significant time bin after the stimulus delivery

(Fabri et al. 1997, 1999), revealing that patients with partial or complete callosotomy show a normal pattern of activation of the contralateral hemisphere, but a complete absence of activation of the ipsilateral one.

Concerning the contralateral origin of the input to iSII, the candidate pathways to mediate its activation are callosal projections either from cSI (Allison et al. 1989; Gao et al. 2015) or from cSII (Simoes and Hari 1999). However, the first hypothesis seems unlikely, given the completely different temporal patterns of response of cSI and iSII. Contralateral SI has only a phasic response (blue trace in Fig. 5d) which peaks around 20 ms and ends within 50 ms. The tonic response from iSII (red trace in Fig. 5a), instead, shows a delay of about 40 and 60 ms in terms of onset and peak timing, respectively, which is not compatible with transcallosal transmission timing as measured by Bashore (1981). On the contrary, the response pattern recorded from cSII constitutes the ideal bridge between cSI and iSII: cSII has a clear phasic component paralleling the main feature of cSI. Most importantly, cSII shows also an evident tonic component that is the dominant feature of iSII.

A remaining hypothesis—transcallosal communication between cSI and iSI—can be ruled out as no activity in iSI is detected in the present study. In conclusion, the findings of the present study strongly support the hypothesis that iSII activity following somatosensory stimulation is mediated by direct callosal communication coming from cSII, as also hypothesized in (Simoes and Hari 1999).

Tonic responses in SII and insular cortex

The results of the previous section together with recent sEEG studies (Avanzini et al. 2016, 2017) suggest that different time-courses might reflect different aspects of the cortical somatosensory processing.

Phasic activity (fast and short-lasting), shared by cSI and cSII, seems the best candidate to reflect somatosensory functions such as simple somatosensory detection, which is common to cSI and cSII (see Preusser et al. 2014) as well as more complex functions such as discrimination of texture and haptic processing, which are peculiar for cSII (Sathian et al. 2011; Sathian 2016). Phasic activity most likely reflects thalamic inputs from VPL in the case of cSI, and from VPI in the case of cSII (Burton et al. 1990; Friedman et al. 1986), although a cortico-cortical contribution cannot be excluded. This conclusion is in line with previous physiological evidence, confining early responses to cSI and cSII (Barba et al. 2002).

The origin of a tonic long-lasting response might, in principle, be consistent with the transmission via unmyelinated and the smallest myelinated fibres. This, however, appears unlikely because the median nerve stimulation in the present study did not produce any painful sensation, thus indicating the lack of recruitment of C fibres, and of the smallest myelinated fibres carrying first sharp pain. In addition, Olausson et al. (2002) showed that in a patient lacking myelinated fibers, a light tactile stimulation produced activation of contralateral insular cortex, but not of cSI, cSII and iSII. Our results, instead, depicted a tonic behavior both in contralateral and ipsilateral SII regions, highly comparable in terms of latency and patterns.

The tonic activity in response to a single shock nerve stimulation has been observed in our study in two areas: SII and posterior insular cortex. Both of them were more responsive following contralateral stimulation than ipsilateral one. However, a trend favoring responses of the right hemisphere—regardless from the stimulation side—was observed only for the insular cortex. Considering that tonic activity could not be determined either by SI input, which is exclusively phasic, or by slow-conducting fibres (see above), it appears that the tonic activity is generated either endogenously inside the cortex or by recurrent thalamocortical activity.

The presence of the tonic activity opens a question about what could be the functional role of this prolonged activation. Romo et al. (2002) administered macaques with two different unilateral vibratory stimuli, each 500 ms long, and interspersed by 3 s, while neuronal activity was recorded from SI and SII. In SI, neural activity followed faithfully the features of the single stimulus. In contrast, SII responses to the second stimulus changed according to the features of the first one. These findings suggest that this area is involved in the integration of somatosensory activities over time, and this process could require a long lasting recurrent activity to take place.

Due to the high unspecificity in terms of topography and timing of the posterior insular cortex (see Avanzini et al. 2017), the hypothesis that the insular tonic activity may reflect the cortical processes sustaining tactile awareness seems to be the most convincing. There is clinical evidence indicating that insula plays a role in corporeal awareness: insular lesions may determine somatoparaphrenia (Cereda et al. 2002), while insular seizures may cause somatic hallucinations (Roper et al. 1993). These conclusions are in line with Tsakiris et al. (2007), who showed that our sense of limb ownership is sustained by a network composed by right posterior insula and right frontal operculum. A similar role for posterior insula was also advanced by Karnath and Baier (2010).

Despite further studies are needed to conclude about the functional role of tonic responses in somatosensory processing, we propose that the long-lasting tonic activity observed in our experiment might represent the neural substrate for maintaining somatosensory information in time, allowing for comparison and integration between stimuli and for the instantiation of a sense of tactile awareness.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards and they were approved by the Ethics Committee of Niguarda Hospital (ID 939-2.12.2013) and all the patients were fully informed regarding the electrode implantation and stereo-EEG recordings.

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