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Ciclo XXXII

High order functions in secondary somatosensory cortex (SII)

Funzioni di alto livello nella corteccia somatosensoriale secondaria (SII)

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Abbreviations

AIP	Anterior Intraparietal Sulcus
APC	Anterior Parietal Cortex
CL	Central Lateral
cSI	contralateral Primary Somatosensory Cortex
cSII	contralateral Secondary Somatosensory Cortex
DLPFC	Dorso-Lateral Prefrontal Cortex
EEG	Electroencephalography
ERP	Event-Related Potentials
fMRI	functional Magnetic Resonance Imaging
FO	Frontal Operculum
IED	Ictal Epileptic Discharge
iEEG	Intracranial Electroencephalography
iSI	Ipsilateral Secondary Somatosensory Cortex
iSII	Ipsilateral Primary Somatosensory Cortex
LED	Light Emitting Diode
LgI	Long Gyri of Insular Cortex
MD	Medial Dorsal
MEG	Magnetoencephalography
MNS	Median Nerve Stimulation
MR	Magnetic Resonance
PMD	Dorsal Premotor Cortex
PO	Parietal Operculum
PV	Parietal Ventral
sEEG	Stereotactic Electroencephalography
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SgI	Short Gyri of Insular Cortex
SPL	Sound Pressure Level
UBLS	Upper Bank of the Lateral Sulcus
VS	Ventral Somatosensory
VP	Ventral Posterior
VPI	Ventral Posterior Inferior
VPL	Ventral Posterolateral
VPS	Ventral Posterior Superior

Sinossi

Le proprietà della corteccia somatosensoriale secondaria (SII) sono state largamente descritte in molteplici studi su primati umani e non umani, concludendo che quest'area riveste un ruolo di alto livello nella stimolazione tattile con funzioni che includono l'apprendimento e la memoria tattile **(Dijkerman and De Haan, 2007)**.

Inoltre, recenti studi sui primati non umani hanno suggerito che le funzioni di SII si estendono ben al di là della percezione tattile: sono state descritte risposte a seguito della stimolazione dello spazio peri-personale, dell'esecuzione di azioni, dell'osservazione di oggetti in movimento e di azioni **(Hihara et al. 2015)**.

Partendo dalla descrizione delle sue proprietà somatosensoriali nel tempo, questa Tesi si prefigge lo scopo di individuare lo specifico contributo di SII nella percezione degli stimoli visivi e durante l'esecuzione e l'osservazione di azioni. Tutti gli esperimenti presentati sono stati condotti attraverso la registrazione di elettroencefalografia stereotassica (stereo-EEG) su pazienti epilettici farmaco-resistenti. Questa tecnica, seppur invasiva, consente la registrazione di dati caratterizzati da un'elevata risoluzione spaziale e temporale **(Lachaux et al. 2003)**; in particolare, tra i diversi indicatori dell'attività neurale, ho selezionato la modulazione nella banda gamma (55 – 145 Hz), poiché questa correla direttamente con l'attività di spiking neuronale **(Manning et al. 2009)**.

Più in dettaglio, nel primo capitolo di questa Tesi ho investigato la distribuzione spaziale e il profilo temporale delle risposte intra-corticali alla

stimolazione del nervo mediano ipsilaterale e controlaterale. I risultati ottenuti indicano che le risposte bilaterali sono confinate alla corteccia somatosensoriale secondaria e all'insula posteriore, con un profilo tonico, la cui attivazione perdura sino a 200 ms dopo lo stimolo **(Avanzini et al. 2016)**.

Successivamente, per testare il possibile coinvolgimento dell'opercolo parietale nell'integrazione visuo-tattile, ho sottoposto 40 pazienti ad una stimolazione del nervo mediano controlaterale e visiva simultaneamente. Come controllo, entrambe le stimolazioni sono state amministrate anche singolarmente. L'ispezione del profilo di modulazione dell'attività in banda gamma a seguito della stimolazione bimodale sottolinea un aumento dell'attività tonica rispetto alla sola stimolazione tattile, localizzato nelle aree più rostrali dell'opercolo parietale e all'insula posteriore, mentre SII mantiene un profilo temporale inalterato. Tuttavia, poiché studi sul macaco riportano l'attivazione di SII a seguito della stimolazione visiva, sono necessarie ulteriori ricerche per comprendere quali specifiche caratteristiche siano in grado di attivare o modulare l'attività di quest'area. Con queste finalità, il secondo capitolo di questa tesi si conclude presentando un esperimento pilota finalizzato a studiare la modulazione dell'attività somatosensoriale di SII durante la visione di un video che mostra rispettivamente uno stimolo opto-cinetico, una porta che si apre (movimento non biologico) ed una azione di raggiungimento ed afferramento di un oggetto (movimento biologico). Risultati preliminari indicano che l'attività tonica di SII si modula prevalentemente durante la visione di questi due ultimi, suggerendo, dunque, che l'osservazione di un'azione che mostra o implica un'interazione tra mano ed oggetto possa rappresentare la peculiare caratteristica capace di determinare questa modulazione.

Infine, il terzo capitolo di questa Tesi presenta le risposte intracorticali registrate dalla corteccia somatosensoriale primaria (SI) e secondaria (SII) durante un compito motorio composto da una fase di preparazione motoria, una fase di raggiungimento-afferramento ed una fase di manipolazione, sia durante l'esecuzione da parte del paziente sia mentre quest'ultimo osservava lo sperimentatore nell'esecuzione del medesimo compito. I risultati ottenuti sottolineano che SII si attiva bilateralmente sia durante l'esecuzione sia durante l'osservazione di azioni, con un profilo temporale sincrono. Al contrario, SI si attiva solo durante l'esecuzione. Si ipotizza, dunque, che gli input ad SII durante l'osservazione non siano di natura somatosensoriale ma siano piuttosto sostenuti da circuiti visuo-motori capaci di operare simultaneamente ed indipendentemente da essi. Questo capitolo dimostra, così, la presenza di un meccanismo mirror in SII, specifico per quegli atti motori che richiedono funzioni di esplorazione aptica.

Abstract

The properties of the second somatosensory cortex (SII) have been largely described by many studies in both monkeys and humans, suggesting for this area a high-order role in tactile stimulation processing with functions including tactile learning and memory **(Dijkerman and De Haan, 2007)**. More interestingly, recent studies on non-human primates suggested that the functions of SII extend further beyond somatosensation, including a role in peripersonal space perception, active movements, observation of objects displacement and action observation **(Hihara et al. 2015)**.

Starting from the description of its somatosensory properties over time, this thesis aims to unravel the specific contribution of SII in visual stimuli perception and during action observation. The experiments presented in this thesis are carried recording stereotactic electroencephalography (stereo-EEG) on drug-resistant epileptic, a technique able to warrant high temporal and spatial resolution **(Lachaux et al. 2003)**. Furthermore, among different indicators of brain activity, I focused on gamma-band (55-145 Hz) power modulation, since it is reported to correlate with spiking activity and to be highly functionally and spatially specific in several studies **(Manning et al. 2009)**.

In the first chapter, I investigated the spatial distribution and the temporal profile of the intra-cortical responses to both contralateral and ipsilateral median nerve stimulation. Results indicated that the bilateral tactile responsiveness is confined to secondary somatosensory cortex and posterior insula with a tonic long-lasting temporal profile **(Avanzini et al. 2016)**.

In a second stage of the Thesis, to test the possible involvement of parietal operculum in visuo-tactile integration, I administered to patients a train of

concurrent contralateral median nerve stimulation and visual (i.e. flash) stimulation. As a control, both tactile and visual trains of stimulation were also delivered in isolation. The inspection of gamma-band time courses underlined an enhancement of the tonic components relative to tactile stimulation only, limited to the rostral areas of parietal operculum, with SII maintaining an unaltered behavior. Considering previous findings in non-human primates, which reported visual responsiveness in SII, further researches are needed to understand which visual features might activate or modulate this area. With this purpose, a pilot experiment was presented at the end of the second chapter. In this latter, I investigated the modulation of SII tonic response upon somatosensory stimulation delivered when the patient was viewing a video displaying a moving grating, an opening door or a reaching-to-grasp action. Preliminary results indicate that SII activates mostly during the view of the last two videos, thus suggesting that the observation of an action, displaying or implying a hand-object interaction, might represent the visual feature modulating SII activity.

Taking into account this preliminary evidence, the third part of this Thesis presents the intra-cortical responses of both SII to a motor task requiring reaching, grasping and manipulation, as well as to the observation of the same actions performed by another individual. The results obtained highlighted that SII activates bilaterally, during both the execution and the observation of actions, with a synchronous temporal profile. As SI activates only during the execution, inputs to SII during action observation cannot be somatosensory in nature, but rather they derive from visuo-motor circuits operating simultaneously and independently from SI.

Taken together all the evidence, this Thesis chapter demonstrates, thus, the pivotal role of SII not only in somatosensory functions but also in the integration of visuo-motor stimuli. Furthermore, it indicates the presence of a mirror mechanism in SII with a possible specificity for motor acts requiring haptic exploration.

It is then possible to conclude that SII might represent a key node in the brain perceptual network. In addition to its mirror properties, in fact, the displayed tonic activation converges with the features of the recurrent processing **(Lamme and Roelfsema, 2000)**, which is proposed to represent a peculiar element sustaining perceptual awareness **(Fisch et al. 2000)**.

Introduction

The presence of a region fulfilling somatosensory functions in the upper bank of the lateral sulcus (UBLS) has been described in mammals starting from the end of thirties **(Penfield and Boldrey 1937; Adrian 1940; Penfield and Jasper 1954)**. Due to its spatial contiguity and similarity in properties with the primary somatosensory cortex (SI), it has been called the secondary somatosensory cortex (SII). Because of its position, this region has been of difficult accessibility to attempts of stimulations and recordings both in monkeys and humans, limiting for years its characterization in terms of both functions and connectivity **(Kaas 2004)**. Later, several anatomical and physiological studies in monkeys **(Kribitzer and Kaas 1990; Burton et al. 1995; Krubitzer et al. 1995, Disbrow et al. 2000; Disbrow et al. 2001; Kaas and Collins, 2003)**. indicated that what was in principle referred as SII was the union of two distinct areas of primates parietal operculum: one more rostral, called PV (i.e. parietal ventral area) and another located caudally, which maintained the label SII, each one with a peculiar pattern of thalamic and cortical connections **(Disbrow et al. 2002)**. In addition, in the fundus of the lateral sulcus, the presence of a third subdivision was demonstrated **(Cusick et al. 1989)**, named ventral somatosensory area (VS). Later in time, the analysis of histological sections of post-mortem brains underlined the presence in humans of four cytoarchitectonic subdivisions in parietal operculum (OP1–4),which are functionally correspondent to monkey SII (OP1), VS (OP3) and PV (OP4) **(Eickhoff et al. 2005 [a,b])**

Over the years, several studies have then focused in describing connections and functional properties of perisylvian regions. SII is an area devoted to the processing of tactile stimuli **(see Dijkerman and De Haan for a review)**, but, if compared to anterior parietal cortex (APC), presents larger and bilateral receptive fields, **(Simoẽs and Hari 1999; Wegner et al 2000)** as well as reduced specificity to inputs **(Kaas 2004)**. The differences between primary and secondary somatosensory cortices also extend to diverse temporal behavior following tactile stimulation: while SI present only phasic responses (ending within 30 ms), SII displays a double-component pattern of responsiveness including both phasic and tonic (ending within 200 ms) activations **(Allison et al. 1989[a,b]; Avanzini et al. 2016, 2018)**. The nature of this peculiar behavior might find explanation considering lesional studies conducted in mammals. Lesions to SII, in fact, led to impairments in inter-manual transfer **(Taitelbaum et al. 1968; Ridley and Ettlinger, 1978)**, tactile discrimination learning **(Murray and Mishkin, 1984)** and retention **(Ridley and Ettlinger, 1976; Garcha and Ettlinger, 1980)**, thus suggesting that long-lasting responses might subtend to high-level tactile functions **(Avanzini et al. 2016, 2018)**.

Furthermore, recent studies on macaque monkeys demonstrated that besides tactile stimulation, SII responds to a wide number of stimuli, including peri-personal space stimulation, active hand movements, proprioception, observation of objects displacement and observation of reaching and grasping actions **(Fitzgerald et. al 2004; Ishida et al. 2013; Hihara et al. 2015).** These data are in agreement with both monkey and human fMRI studies, reporting SII activation during the observation of another individual's body being touched **(Keysers et al. 2004; Raos et al. 2004; Ferri et al. 2015; Sharma et al. 2018).**

Although SII has been largely and consistently studied across years, some points concerning its connections and behavior has not been addressed yet. The first concerns the pathway mediating SII ipsilateral responses. In **Simoẽs and Hari (1999)** it is suggested that its activation results either from direct input from ventral posterior (VP) nuclei of the ipsilateral thalamus or from callosal input from contralateral SII. In addition, another connectivity study suggested that ipsilateral SII receives a direct input from contralateral SI **(Gao et al. 2015)**. Furthermore, the analysis of similarities and differences between contralateral and ipsilateral responses would be beneficial for the comprehension of SII behavior.

Secondly, the discover of SII responsiveness to object displacement and action observation open to several questions: a) which visual stimuli may elicit responses in this area; b) if and how visual stimuli act if delivered in combination with tactile stimulation; c) if there are specific features in visual stimulation that triggers or modulate the activation of SII; d) how SII responds to the execution and observation of complex action.

All this issues will be addressed in this Doctoral Dissertation by recording the stereotactic electroencephalographic signal (sEEG) in drug-resistant epileptic patients admitted to Ca' Granda-Niguarda Hospital (Centro per la Chirurgia dell'Epilessia "Carlo Munari", Milan, Italy) for their presurgical evaluation. Stereo-EEG recordings combine both a strong localization power and a high temporal resolution **(Lachaux et al. 2003)**, allowing the description of temporal events with a ms-time scale. Among the different indicator of brain activity, in this Thesis I will concentrate on gamma-band (55-145 Hz) power modulation, as it is reported to reflect spiking activity **(Manning et al. 2009)** and to be highly functionally and spatially specific in several studies **(see Jerbi et al. 2009 for a review)**.

More in detail, chapter 1 contains a comprehensive mapping of the cortical areas responsive to the ipsilateral tactile stimulation. Furthermore, it analyzes the time-course of ipsilateral activations of SII (as well as surrounding opercular and insular areas) with the contralateral ones recorded in the same patients. This chapter will then discuss the cortico-cortical dynamics sustaining somatosensory processing and it will give insights about functional properties of parietal operculum.

Chapter 2 presents the analysis of gamma-band time-courses in response to the concurrent visuo-tactile stimulation of patients whose implantation covered right parietal operculum. This choice has been driven considering a recent study on patients affected by tactile extinction, which identified in the rostral part of parietal operculum (OP3-OP4) the more frequent origin of the lesion. These patients were found to improve their contralateral tactile detection by delivering proximal visual stimuli **(Fossataro et al., *under review*)**. This chapter will also report a pilot test in which I investigated the modulation of gamma activity to different tactile stimuli intensities when delivered in combination with a video displaying optokinetics, non-biological and biological movements. The aim is to understand if a specific class of visual stimuli might interact with somatosensory activity in SII.

Finally, in chapter 3, I analyze the SII activity in response to a motor task requiring reaching, grasping and manipulation, as well as the observation of the same actions performed by another individual. As a control, we functionally characterized this area administering a set of clinical tests, including tactile, acoustical and visual stimuli. The results obtained will elucidate the involvement of SII, not only in somatosensory functions, but also during the execution and observation of actions involving haptic control.

CHAPTER 1

The bilateral tonic activity of SII

Introduction

The cortical processing of somatosensory stimuli has been extensively investigated in humans by means of different 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 also extends to posterior insular regions **(Ferretti et al. 2007; Ruben et al. 2001)** and to frontal operculum (FO) **(Hinkley at al. 2007)**.

Relatively to SII, the pathway mediating the ipsilateral response is still debated. **Simoẽs and Hari (1999)** identified two possible hypothesis: the first is that iSII receives direct input from VP nuclei of the ipsilateral thalamus while the second explain its responsiveness as a callosal input from cSII.

Recently, a connectivity study based on Granger causality also suggested that iSII receives a direct input from cSI **(Gao et al. 2015)**. In a 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, a dual time-course (phasic and tonic) was recorded from leads exploring cSII (**Avanzini et al. 2016**). 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 still an unsettled issue. In a recent work of **Avanzini et al. (2018)**, authors measured the intracranial responses to contralateral median, tibial and trigeminal nerves stimulation and reported a widespread tonic multi-nerve activity in the entire perysilvian region. Following previous ERP studies, which identified in the enhancement of long lasting components the neural correlate of conscious perception (**Shubert et al. 2006**), Avanzini and coworkers linked the tonic component with the process underlying tactile awareness.

This chapter will extend the analysis of the temporal behavior to ipsilateral median nerve stimulation. The comparison of the subsequent profiles of activation with the contralateral ones, jointly with the mapping of ipsilateral responsiveness, might give further insight on the functional properties subserving tactile perception.

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 in relation to the electro-clinical data and neuroimaging examinations. 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).

Median 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. Stereo-EEG data recording and processing The stereo-EEG trace was recorded with a Neurofax EEG1100 (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 processing

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. 2014[a, 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. Significance was Bonferroni corrected ($p < 0.001$) and leads with at least 3 significant bins were considered as responsive.

Finally, a procedure of electrodes reconstruction is performed to localize the recording leads in the individual cortical surfaces and to merge leads from all patients onto a common template. This, along with maps of responsiveness, are compliant with the one described in **Avanzini at al. (2016)**. Their visualization on a flat map is obtained with Caret software **(Van Essen 2012).** The correspondences between the areas depicted on a flat map with an inflated model of brain are reported in Figure A1 of the Appendix.

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). 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 (Figure 1) 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.

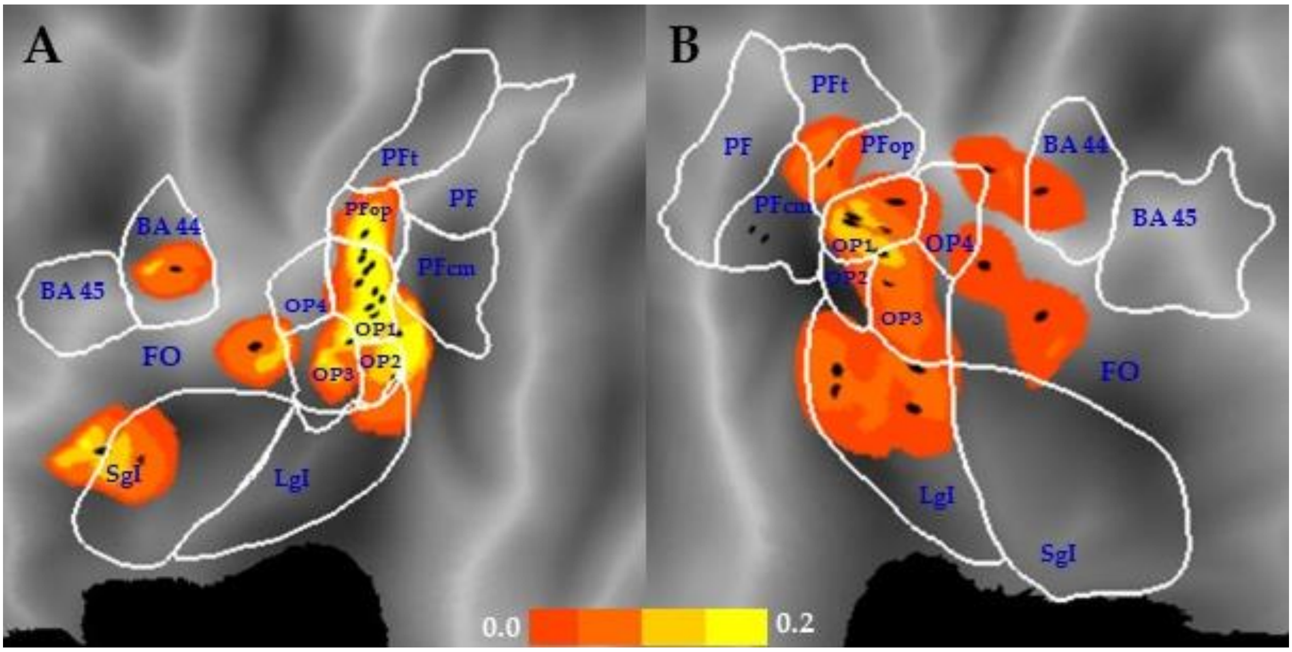

Figure 1: Responsiveness to median nerve stimulation in the ipsilateral perisylvian regions. Responsive leads (black dots) and responsiveness maps are shown onto the midthickness surface of fs_LR_brain template for left **(A)** and right (B) hemispheres. The two reactive leads located in right PFcm do 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. 2005^{a,b})**, and areas 44 and 45 **(Amunts et al. 1999)**. In addition, long and short gyri of insula were anatomically defined using the gyral pattern. The correspondences between the areas depicted on a flat map with an inflated model of brain are reported in Figure A1 of the Appendix. Adapted from Del Vecchio et al. **(2019)**.

Following contralateral stimulation, 415 leads were found responsive (253 in the right hemisphere, 162 in the left hemisphere). Sampling density flat maps and leads responsive to contralateral stimulation are shown in Figure 2.

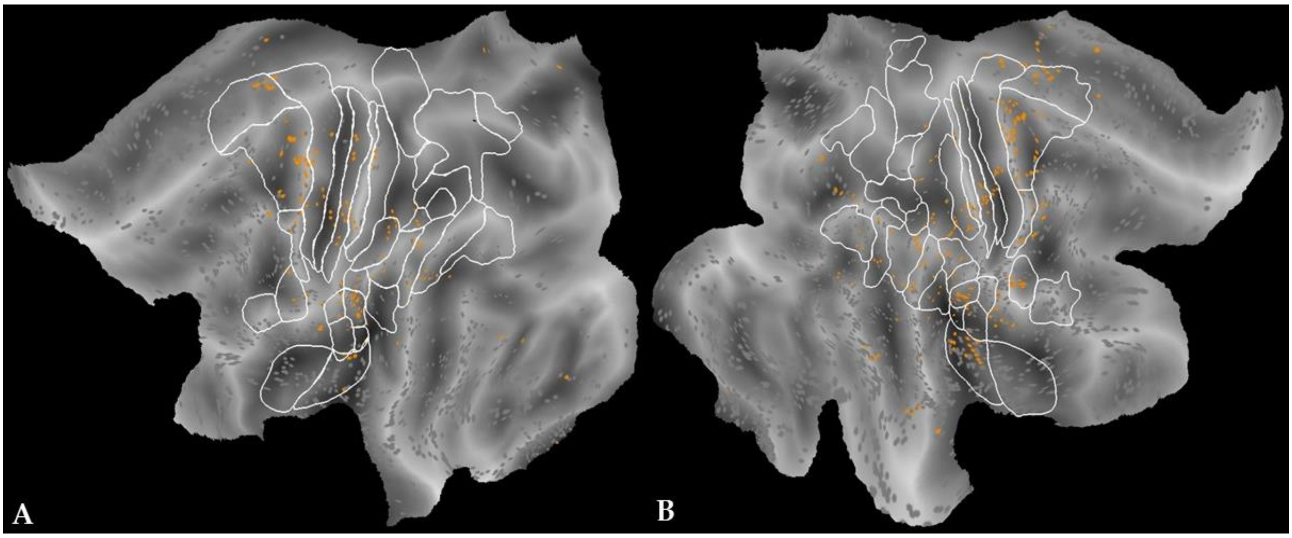

Figure 2. **Sampling density flat maps.** Midthickness surface of the fs_LR brain template with all leads located in gray matter of the left (A) and right (B) hemispheres. Colored dots correspond to leads responsive to contralateral stimulation, grey dots represent unresponsive leads The correspondences between the areas depicted on a flat map with an inflated model of brain are reported in Figure A1 of the Appendix. Adapted from Del Vecchio et al. **(2019)**.

The difference between the two hemispheres might be attributed to the different sampling (about 10% in both cases). 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. Following ipsilateral stimulation, all areas revealed a tonic long lasting response (Figure 3). In contrast, following contralateral stimulation (blue 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). 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 (Figure 3A) while LgI showed only a tonic response (Figure 3B). Finally, a more unclear pattern was obtained for FO (Figure 3C), where, however, the latency of the earliest peak is compatible with a phasic behavior preceding a tonic response.

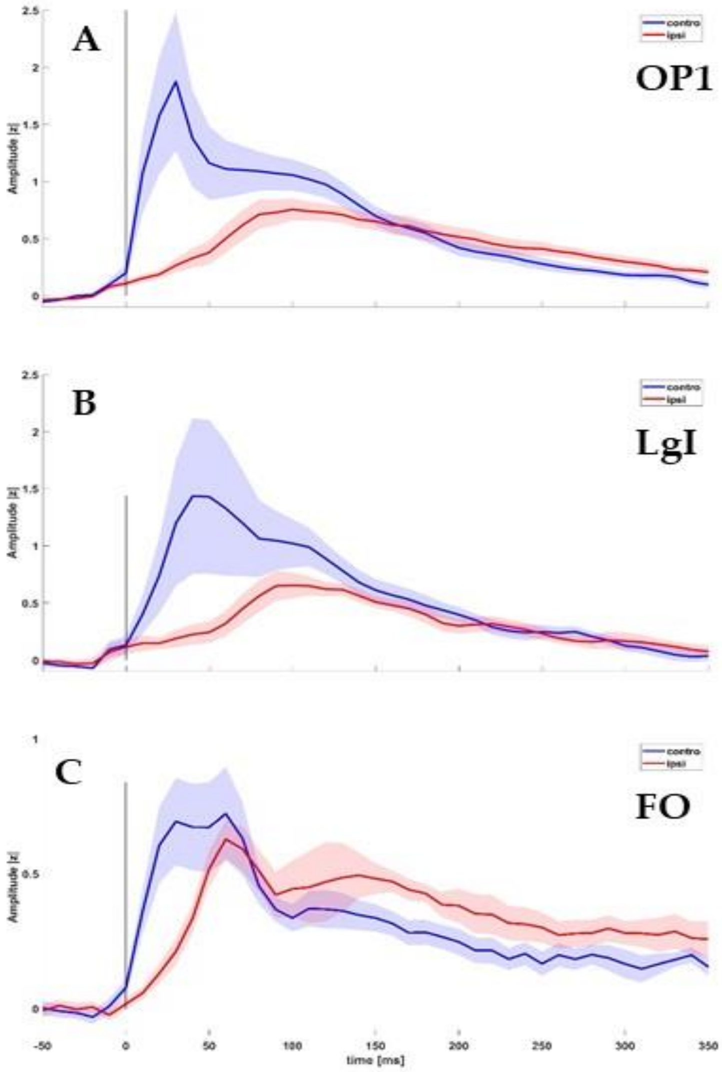

Figure 3: **Gamma-band time course of regions active for both ipsi- and contra-lateral median nerve stimulation.** Average time-courses (± SE) are shown separately for OP1 (A), LgI (B), and FO (C) based only on leads active for both stimulations.

The pathway mediating ipsilateral tactile responses

The 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. 2016)**, and the predominance of the tonic response in the ipsilateral hemisphere might represent the signature of diverse functions mediated by SII in somatosensory processing.

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 **(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 **(Simoẽs 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 **(Avanzini et al. 2016)** which peaks around 20 ms and ends within 50 ms. The tonic response from iSII, 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 **(Simoẽs and Hari 1999)**.

The bilateral tonic response in SII

The results of the previous section together with recent sEEG studies (**Avanzini et al. 2016, 2018)** 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 thalamo-cortical 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. 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.

CHAPTER 2

Visuo-tactile integration in the parietal operculum

Introduction

The knowledge of how the brain integrates sensory inputs of different modalities has been strongly impacted by studies conducted on superior colliculus in nineties **(Stein and Meredith 1993)**. This structure, involved in controlling gaze shifts, contains, in fact, neurons able to respond to visual, auditory and even somatosensory inputs. Also several cortical areas have been proven to contribute to multisensory integration such as, for example, the superior temporal sulcus **(Barraclough et al. 2005, Oh et al. 2018)**, the intraparietal sulcus **(Schlack et al. 2005, Avillac et al. 2007, Regenbogen et al. 2018)** and regions in the frontal lobe **(Ehrsson et al. 2019, Cao et al. 2019)**.

Starting from the description of the properties of the neurons in abovementioned structures and cortical areas, three principles in cross-modal integration were derived and commonly adopted:

- the principle of spatial coincidence (cross-modal integration is more effective when stimuli of different sensory modalities arise from the same location, **Stein 1998**);
- the principle of temporal coincidence (the effect of sensory integration is more evident when different stimuli are presented simultaneously in time, **Stein and Wallace 1996**)

- the principle of inverse effectiveness (cross-modal integration is stronger when unisensory inputs are not informative by themselves, **Stein and Wallace 1996**).

It is also worth to distinguish between the concepts of cross-modal integration (or convergence) and cross-modal interaction. The first refers to areas that can respond to stimuli of different sensory modalities also when presented in isolation; the second, instead, pertains to neurons whose activity can only be modulated by the presence of a second modality **(Kayser and Logothetis, 2007)**.

Besides classical associative areas (e.g. parietal cortex, superior temporal sulcus), peculiar functions of cross-modal integration or modulation might be also extended to parietal operculum, as suggested by its heterogeneous pattern of cortical and subcortical connections. SII, in fact, plays a role in tactile-motor integration, contributing to tactile discrimination and motor control during object manipulation **(Huttunen et al., 1996; Hinkley et al., 2007, Ishida et al. 2013)**. In addition to this, recent studies on macaque monkeys report that SII responds also to specific visual stimuli such as moving objects and manipulative actions **(Hihara et al. 2015),** thus suggesting a possible role for this area in visual processing. PV, instead, presents connections with posterior parietal cortex and premotor cortices **(Disbrow et al. 2003)**, both involved in reaching and grasping functions as well as in object perception **(see Goodale 2001 for a review)** in human and non-human primates.

Complementing these functional and anatomical considerations, a recent study conducted by Fossataro and coworkers identified in 10 patients presenting tactile extinction **(Remy et al. 1999, Chechlaz et al. 2013[a,b], Chechlaz**

et al. 2014) the post-stroke lesional site in right rostral parietal operculum, matching in particular its human cytoarchitectonic subdivision OP3 (**Fossataro et al. 2019, *under review*).**

These patients are reported to maintain an unaltered somatosensory sensitivity when passively stimulated unilaterally, but an altered perception if they are instead stimulated bilaterally. These same patients are, however, able to recover their bilateral tactile sensitivity when a LED is flashing near the stimulated hand. This result might be linked with a previous fMRI study that reported PO activity as modulated by the spatial congruence of visuo-tactile stimuli when both delivered at the same contralateral location (**Macaluso et al. 2005**).

Taking together these premises, I investigated whether the presence of a basic visual stimulation (i.e. flash) interacts with the neural response of PO to a concurrent contralateral MNS. The high spatial and temporal resolution of intracranial EEG data will give insight on parieto-opercular contribution to visuo-tactile integration, possibly complementing the view about functional properties of different cytoarchitectonic subdivisions in PO.

Methods

Participants

Data were collected from 40 drug-resistent epileptic patients (19 males, 21 females, age 27 ± 11) whose implantation explored right OP1-4. For all patients, neurological examination was unremarkable and, in particular, no patient presented any motor or sensory deficit. Procedure used for electrodes implantation and their anatomical reconstruction are fully consistent with (**Avanzini et al. 2016**). For each patient, intracranial reference was chosen among leads exploring the white matter, which did not present any response to clinical stimulations, including somatosensory, acoustical and visual. The sEEG trace was recorded with a Neurofax EEG-1100 (Nihon Kohden System) at 1-kHz sampling rate.

Stimulations

Following the implantation each patient underwent to:

- *Tactile Stimulation*: the median nerve opposite to the recorded hemisphere was stimulated at the wrist, using 100 constant-current pulses (0.2-ms duration) at 1 Hz while the patient lied in bed with eyes closed. The intensity and site of stimulation were varied until an observable thumb twitch was obtained. The stimulation intensity was set at 10% above the motor threshold.

- *Visual stimulation*: patients wearing goggles received 100 bilateral visual stimulations (i.e. flash) at a rate of 1 Hz.
- *Bimodal stimulation*: patients received 100 concurrent tactile and visual stimulations with the same procedure described above.

Data processing

The recordings from all leads in the gray matter were decomposed into time–frequency plots using complex Morlet's wavelet decomposition. Power in the gamma (55 to 145 Hz) frequency band was extracted in a window extending from 100 ms before to 500 ms after the electrical stimulation, and subdivided into 60 non-overlapping 10-ms bins. Thus, gamma power was estimated for 10 adjacent non-overlapping 10-Hz frequency bands. To identify the leads responsive to median nerve stimulation, the gamma band power in each post-stimulus bin was compared with baseline using a t test ($p < 0.001$), and, to decrease the false-positive ratio, only leads with significant gamma increases in at least three consecutive time bins were designated as responsive.

Furthermore, to assess statistical differences between bimodal and tactile stimulation, I performed a two-tailed t-test ($p<0.05$) for all leads designated as responsive in at least one of the trains of stimulations. Finally, to evaluate if/when the bimodal stimulation displays an increase in term of z-score across time I computed the cumulative sum for each lead responsive at least to bimodal or MNS alone. A right-tail t-test ($p<0.05$) was then performed to assess statistical significance of the results.

Results

For each of the area sampled, I evaluated the number of exploring leads jointly with the number of leads responsive for each kind of stimulation administered. Overall, the sampling provided is extensive for each of the areas of interest (Figure 1).

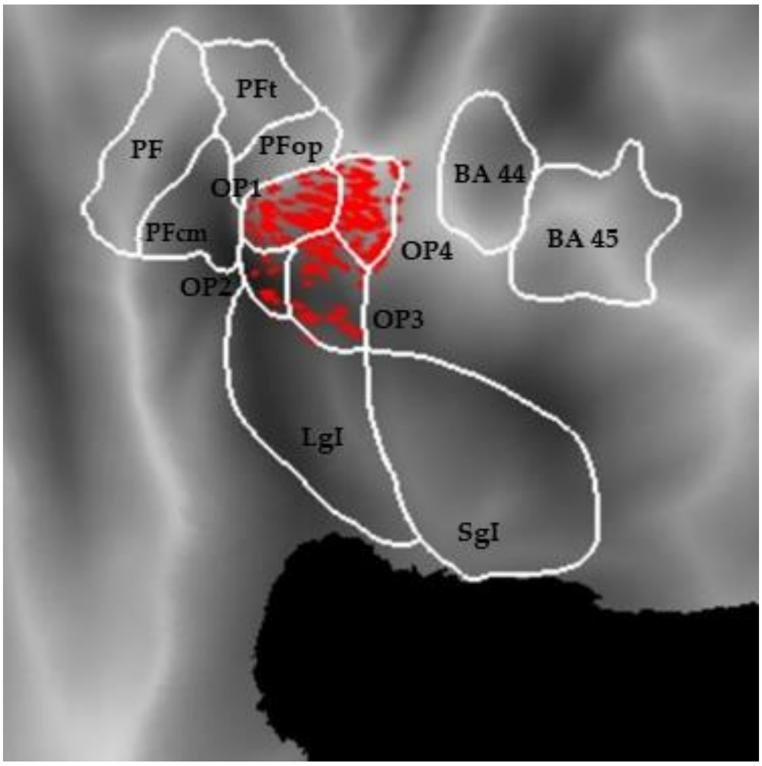

Figure 1: **Sampling density flat map.** Sampling density flat map of leads exploring right PO. White borders refer to cytoarchitectonic areas of inferior parietal cortex **(Caspers et al. 2006, 2008)**, parietal operculum **(Eickhoff et al. 2005[a,b])**, and areas 44 and 45 **(Amunts et al. 1999)**. In addition, long and short gyri of insula were anatomically defined using the gyral pattern. The correspondences between the areas depicted on a flat map with an inflated model of brain are reported in Figure A1 of the Appendix.

More interestingly, the number of responsive leads following the bimodal stimulation is higher in almost the whole PO, if compared to tactile stimulation only, without virtually reporting any activation to the mere visual stimulation (3 leads out of 225). This result might indicate that opercular areas might act in response to bimodal stimulation with a more complex behavior than an adder of inputs of different sensory modalities. Table 1 reports the number of responsive leads respect to the overall number of sampled leads for each cytoarchitectonic subdivision within PO.

AREA	**BIMODAL**		**TACTILE**		**FLASH**	
OP1	**37/81**	**45,7%**	**32/81**	**39,5%**	**1/81**	**1,2%**
OP2	**5/11**	**45,5%**	**5/11**	**45,5%**	**1/11**	**9,1%**
OP3	**21/45**	**46,7%**	**16/45**	**35,6%**	**0/46**	**0%**
OP4	**16/87**	**18,4%**	**13/87**	**14,9%**	**1/87**	**1,1%**

Table 1: Table 1 reports the number of responsive leads respect to the overall number of sampled leads (first column) and the relative percentage of responsiveness (second column) for each cytoarchitectonic subdivision within PO.

The performed two-tailed t-test ($p<0.05$) underlines an enhancement of the tonic component in the interval 60-100 ms following bimodal stimulation limited to OP4 (panel D, Figure 2), with OP1 and OP2 maintaining an unaltered behavior (panel A and B, Figure 2). Concerning OP3, the inspection of the gamma-band time courses reveals however an amplitude increase in the interval 0-150 ms, with a statistical trend toward significance at 120 ms when lowering the threshold ($p<0.08$).

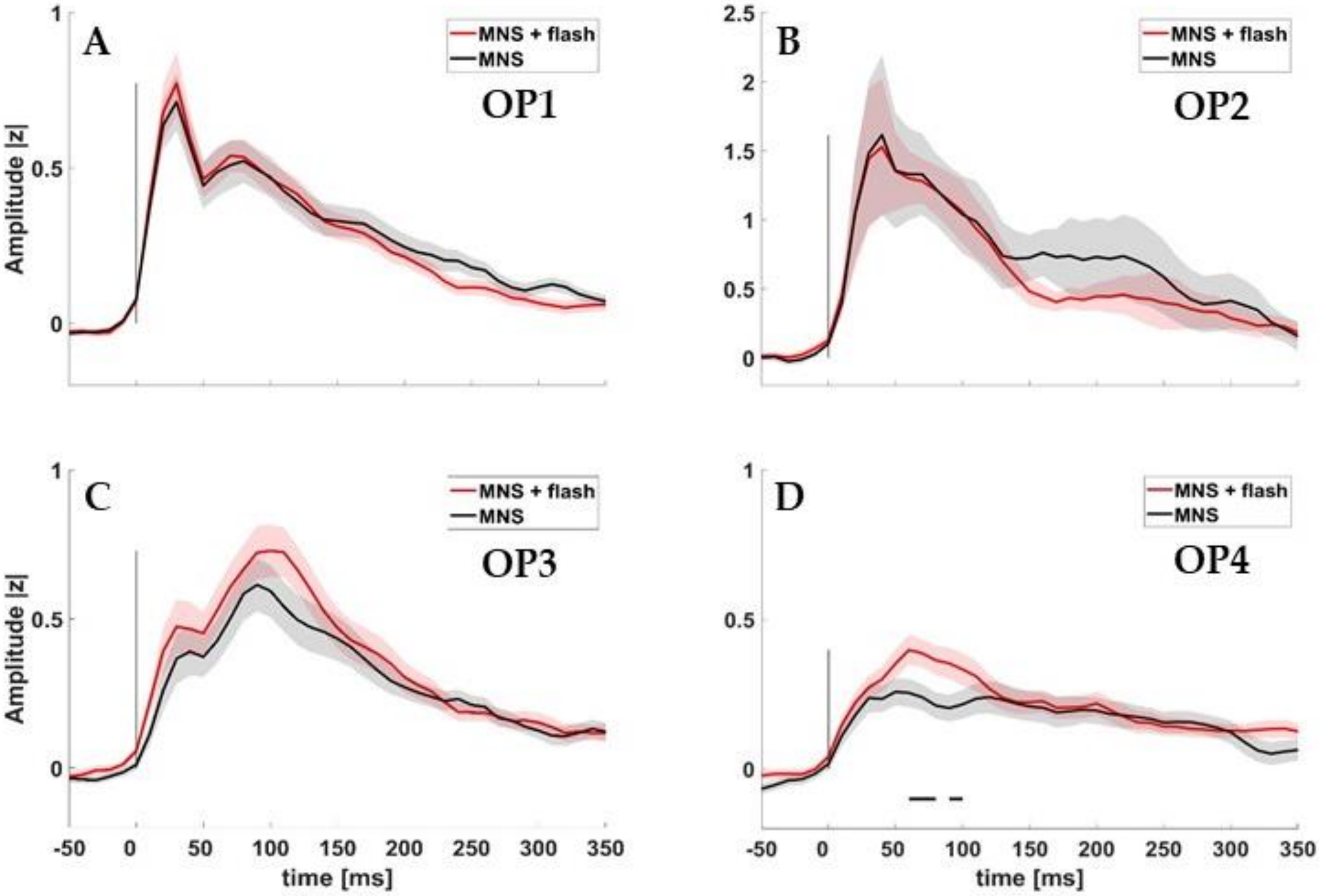

Figure 2: Gamma-band time courses of PO cytoarchitectonic subdivision in response to bimodal and tactile stimulation. Average time-courses (± SE) are shown separately for OP1 (A), OP2 (B), and OP3 (C) and OP4 (D) based on leads responsive in at least one train of stimulations. The statistical comparison (two-tailed t-test, p<0.05) underlines significant differences only for OP4 (60-100 ms).

To further estimate when the enhanced tonic modulation is statistically significant I performed a right-tailed t-test (*p<0.05*) between the *z*-score cumulative sum of the bimodal versus the tactile stimulation. Significance is presented in OP4 (60-120 ms), thus overlapping the comparison between the gamma-band time modulation following the two trains of stimulations.

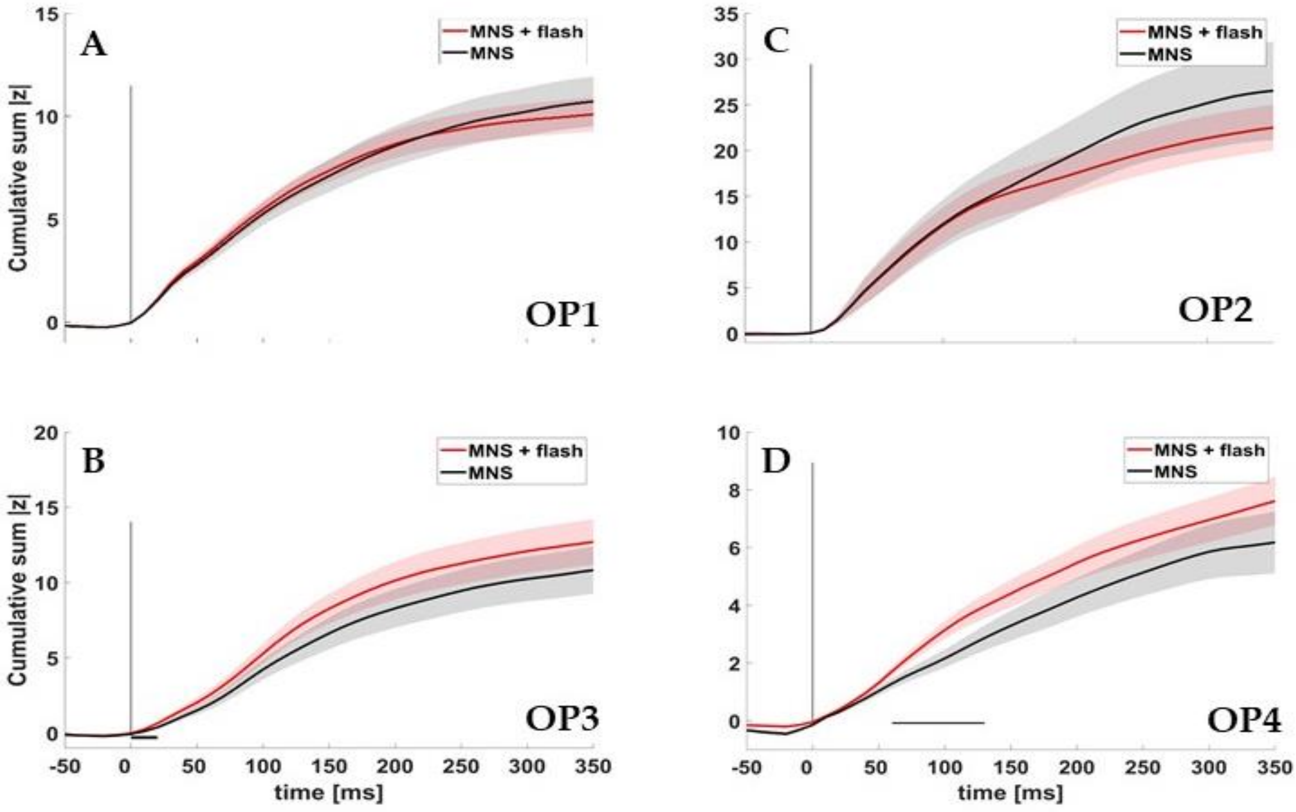

Figure 3: **Cumulative sum of the gamma-band time-courses in response to bimodal and tactile stimulation.** Cumulative sum of the gamma band time-courses (± SE) for OP1 (A), OP2 (B), and OP3 (C) and OP4 (D) based on leads responsive in at least one train of stimulations. The statistical comparison (one-tailed t-test, $p<0.05$) underlines significant differences only for OP4 (60-120 ms).

Therefore, the collected intracranial data identified in rostral PO location where visuo-tactile modulation occurs. This outcome finds a partial convergence with post-stroke lesional mapping of patients affected by tactile extinction, suggesting that the enhanced tonic component following bimodal stimulation might reflect the neural correlate of the visual input magnifying the tactile perception, and possibly underlying the visuo-tactile integration **(Fossataro et al. 2019,** ***under review*****)**.

The modulation of the tonic component: the neural signature of cross-modal interaction?

In this chapter, I investigated if/how a visual stimulus interacts with the simultaneous somatosensory activity in parieto-opercular cortex. In particular, patients included in this study presented a right stereotactic implant coveringthe four cytoarchitectonic subdivision of parietal operculum. The choice of the inspected hemisphere is related to previous studies reporting phenomena of tactile extinction as occurring more frequently after right-brain lesions **(Remy et al. 1999, Fossataro et al.,** ***under review*****)**.

The analysis of the gamma-band time courses revealed that all the investigated areas did not respond to mere visual stimulation, thus ruling out the presence of direct afferences from visual cortices to parietal operculum. Furthermore, rostral operculum (OP3-4) showed a significant gamma-band modulation following bimodal stimulation if compared to tactile only, matching the tonic component of the time-course (60-120 ms)**.** More caudally located portions of PO, instead, show an unaltered behavior during bimodal stimulation, thus indicating that visual responsiveness shown by SII in previous studies **(Avaikainen et al. 2002, Hihara et al. 2015)** might be strongly linked with some specific features of the delivered visual stimulus.

This different behavior is in line with previous studies comparing set of thalamic inputs and cortical connections of SII and PV**.** Tracer injections in macaque SII resulted in connections with SI, PV and 7b **(Disbrow et al. 2003)** while concerning its thalamic afferences they are limited to nuclei processing deep inputs **(Disbrow et al. 2002)** such as VPI and VPS. PV, instead, has connections with cortices subserving sensory system beside somatosensation and the motor system such as the auditory belt area, the intraparietal sulcus, the premotor cortices and the Frontal Eye Field region (FEF). Finally, PV has access to non-sensory inputs from the Medial Dorsal Nucleus (MD) and Central Lateral Nucleus (CL) of the thalamus. Due to its connections with the prefrontal cortex **(Bechevalier et al. 1997),** the first is considered to play a crucial role in attention and active memory **(Hunt and Aggleton, 1991)** and it is also presumed to play a role in monitoring internal eye movements. CL nucleus, instead, is thought to play a role in arousal, executive cognitive functioning and awareness **(Smythies, 1997)**. This pattern of cortical and thalamic connections might be explainatory of the enhancement of the tonic component following visuo-tactile stimulation, which finds a convergence with the post-stroke lesional study of patients showing tactile extinction. However, although the enhancement of the tonic component might be the candidate to be neural correlate of the recovering from tactile extinction, our data cannot address if this process is due to an increase of attentional process or rather to a lowering of the sensory threshold triggered by the visual stimulus **(Vaishnavi et al. 1999)**. MNS was, in fact, delivered at 10% above the motor threshold, and being the somatosensory the predominant sensory modality in PO, it has not been possible to evaluate if the concurrent visual stimulation altered patients' perception of the tactile stimulus (*principle of inverse effectiveness*). Ad-hoc experimental paradigms are, thus, needed to disentangle this issue, possibly clarifying the neural substrate sustaining tonic activity.

How informative sight modulates touch perception in SII: a pilot study

The absence of a response modulation to the concurrent visuo-tactile stimulation in SII seems not to dovetail with previous findings reporting that SII responds to visual stimuli (**see Keysers et al. 2010 for a review**). Several studies, in fact, reported the activation of SII following the sight of humans and even objects being touched (**Keysers et al. 2004, Blakemore et al. 2005, Ebisch et al. 2008, Schaefer et al. 2009, Ferri et al. 2015**), identifying in the embodiment of the tactile experience the possible reasons of this activation. Other studies, instead, describe that SII responds to the observation of reach-to-grasp and manipulative actions (**Avikainen et al. 2002, Hihara et al. 2015**), suggesting that this activation might be linked with the existence of an intrinsic haptic component in the observed action. Taken together, these results indicate that some specific properties of the visual stimulus elicit/modulate SII activity rather than the visual stimulus per se. One first hypothesis might be linked with the motion content in the stimulus: Antal and coauthors **(2008)** reported the activation of PO to pattern-organized motion visual stimuli. In **Kennett et al. (2001)**, authors identified behaviorally another form of visuo-tactile interaction in humans: the view of body improves tactile perception in the viewed skin region, if compared to the view of an object placed in the same location. Tactile modulation operated by the view of the body is also reported in other several studies **(Haggard et al. 2003, Longo et al. 2008, Cardini et al. 2011, Cardini et al. 2012, Konen and Haggard 2012).**

However, the timing of such modulatory activity is still a matter of debate. Two are the most relevant hypothesis: the first is that the tactile modulation emerges rapidly after the body sight, thus reflecting a cross-modal integration of visual and somatosensory information **(Cardini et al. 2012)**. The other identifies the sustaining mechanism in a plastic reorganization of visual-tactile links, which might require few minutes to obtain efficacy in the modulation **(Facchini and Aglioti, 2003)**.

To address a) if there is a content-related processing of visual stimuli able to modulate activity in SII and b) which is the eventual timing of cross-modal interaction I delivered to one drug-resistant epileptic patient (male, 18 years old, right implantation) a train of contralateral MNS (motor threshold, 6.4 mA) during the vision of a short video-clip (duration 2 s), displaying respectively a moving grating, an opening door and a hand performing a reaching-to-grasp action toward a ball (Figure 4). Contralateral MNS occurred 1 second after the beginning of the video in each condition. Videos were randomized across trials (7 trials for each video condition)

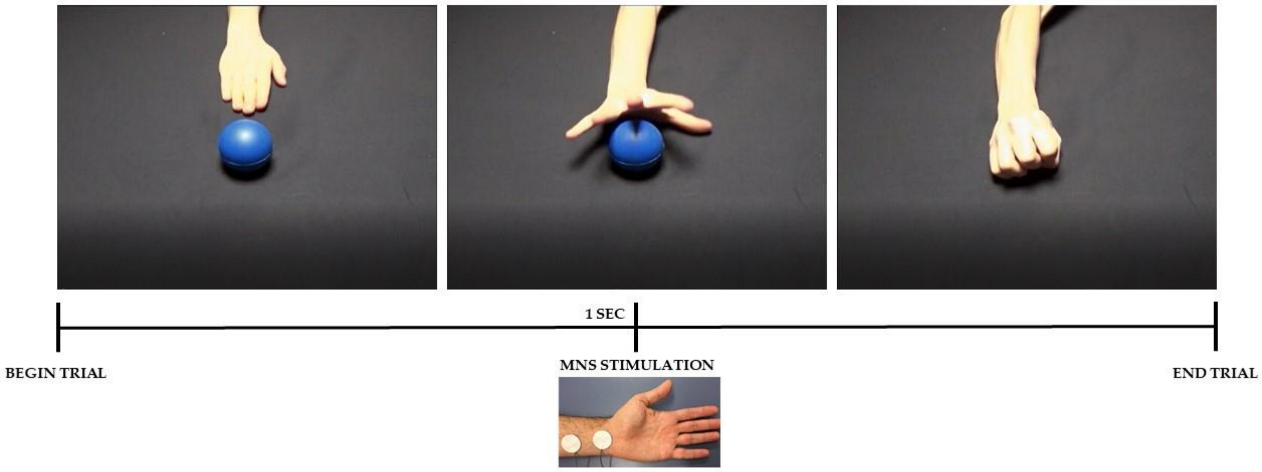

Figure 4: **The experimental paradigm.** The patient was required to watch carefully a short video-clip. After 1 second, the patient's contralateral median nerve was stimulated at motor or sensory threshold.

Results

The procedure of electrode reconstruction *(***see Avanzini et al. 2016 for further details***)* on a common template returned a number of two leads located caudally in OP1, near the border with PFcm (*see figure A1*).

Gamma-band time-courses for these two leads were averaged together according to the content of the video and the intensity of the tactile stimulus are shown in Figure 5. A time-wised statistical comparison (two-tailed t-test, $p<0.05$) is performed for each pair of conditions and shown below the traces. When the MN is stimulated at the motor threshold, stronger statistical differences were found between the optokinetics and hand video, virtually covering most of the interval between 110 and 380 ms after the stimulation, thus suggesting that the sight of a biological movement may elicit the strongest somatosensory modulation. Sparser significances were also found between optokinetics and the non-biological movement and between this latter and the hand video. Interestingly, the interval of significance between the optokinetics and the other two conditions fits with the timing of the tonic, late component, peculiarly depicted in SII.

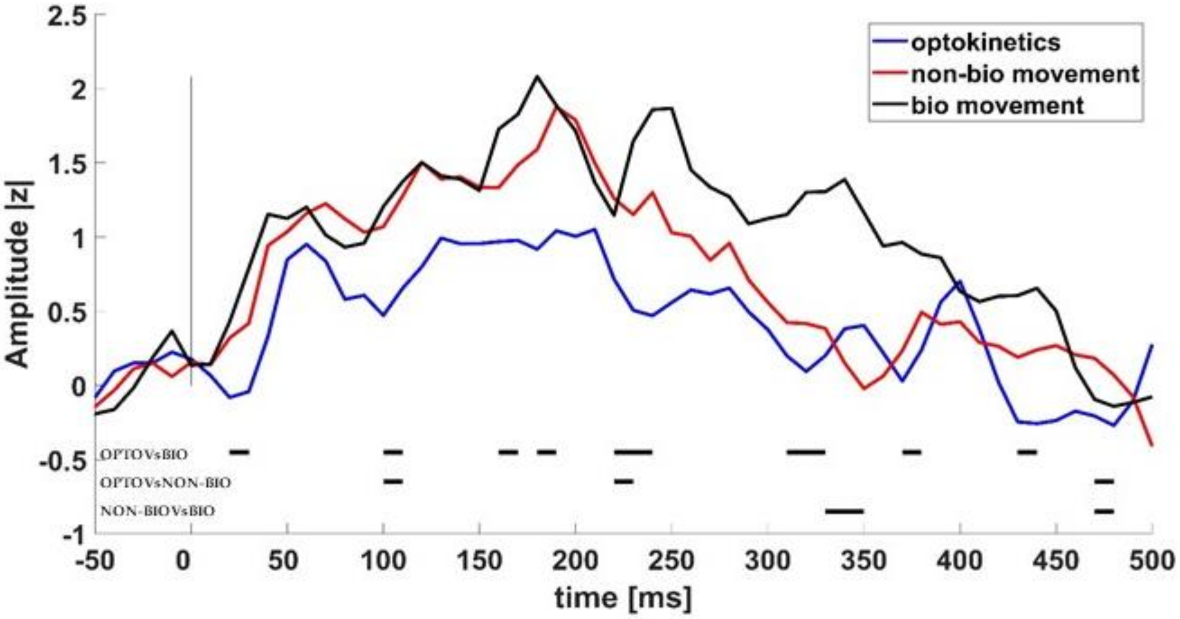

Figure 5. Gamma-band time course of the two leads sampling OP1 following contralateral median nerve stimulation. Average time-courses of the two leads sampling OP1 are shown accordingly the video-clip shown during the stimulus delivery.

Tonic activity and awareness in PO: a tentative link

This pilot study represents a preliminary attempt to understand if some content-specific feature of a visual stimulus might modulate the somatosensory activity in OP1. The inspected gamma-band time-course displayed that, at a fixed intensity of stimulation, the responses are statistically different in terms of z-score. In particular, when MNS is delivered at the motor threshold together with a video displaying optokinetics, the obtained response is significant lower than the other two, thus favoring the hypothesis that a possible cause of modulation might be related to the meaningfulness of the content rather than to the presence of motion in the stimulus. However, although the examined sample is extremely limited, we failed to identify statistical differences in the interval 40-200 ms between the video displaying an opening door and the reaching-to-grasp action.

This finding might be in principle in line with previous single-neuron recordings on macaques reporting that SII responds to both object displacement and action observation **(Hihara et al. 2015);** furthermore, although no effector is shown in the door video, it might implicitly evoke an action representation. Then, it is possible to speculate that a modulation of the somatosensory activity in SII is mostly related to the observation of an action, displaying or even implying a hand-object interaction.

Concerning the timing, this pilot study underlines that the modulation already occurred within 200 ms after the stimulus delivery, thus suggesting a convergence with the work of **Cardini et al. (2012)**; however due to the limited amount of trials delivered, it is not possible to exclude that a further modulation of the SII tonic component might also occur after a longer trains of stimulation.

Together with previous data, this pilot experiment, indicates that the tonic responses occurring in the perysilvian region might represent the neural signature of processes sustaining tactile awareness. It is non-earliest, long-lasting, low-amplitude, bilateral **(Del Vecchio et. al 2019)** and non somatotopically arranged **(Avanzini et al. 2018)**. Furthermore, it may be enhanced/modulated by the presence of a concurrent visual stimulus, possibly corresponding to a process of information retention supplied for integration with inputs of different sensory modalities.

Enhanced, long-lasting activation occurring in the interval 150-200 ms after the stimulus onset has been already proposed to play a key role in the emergence of perception in conscious awareness **(Fisch et al. 2009)**; moreover this temporal behavior converges with recurrent processing, which is proposed to be the key element sustaining perceptual awareness (**Lamme and Roelfsema, 2000, Chang et. al 2019, Kar et al. 2019**).

CHAPTER 3

The role of SII in action observation

Introduction

As previously introduced in this Thesis, single neurons recording on Macaque monkeys reported that SII responds to a wide number of stimuli, including peri-personal space stimulation, active hand movements, proprioception, observation of objects displacement and observation of reaching and grasping actions **(Fitzgerald et al. 2004, Ishida et al. 2013, Hihara et al. 2015)**. These data are in agreement with human and non-human fMRI studies, reporting SII activation during the observation of another individual's body being touched **(Keysers et al. 2004, Raos et al. 2004, Ferri et al. 2015, Sharma et al. 2018**). Together, these results suggest that the functions of SII extend further beyond somatosensation.

Despite these evidences, which is the specific contribution of SII during action execution and observation remains an unsettled question. This lack might be explained with some intrinsic constraints in electrophysiological studies: these, in fact, are limited in terms of poor localization power and sensitivity to movements artifacts preventing, thus, to investigate the neural dynamics sustaining complex actions. Stereo-electroencephalography, instead, provides data with high temporal and spatial resolution **(Lachaux et al. 2003)** as well as out-of-the-lab like recording conditions, allowing for setting ecological experimental paradigms able to clarify the role of this area during executed and observed hand actions.

With this aim, I investigated the response of bilateral SII in a motor task requiring action planning, object reaching, grasping and manipulation. Subsequently, I compared all these responses with those recorded during the observation of the same actions performed by an experimenter.

Aiming to obtain a more comprehensive picture of the functional role of SII, I extended the study also to contralateral SI (3a, 3b, 1) which is largely reported to be the main input for tactile inputs for cSII **(Friedman et al. 1980, Pons and Kaas 1986, Barbaresi et al. 1994, Disbrow et al. 2003)**.

Finally, to functionally characterize the leads sampling the areas, all patients underwent to a set of train of stimulations including tactile, visual, optokinetics and acoustic stimulations.

Taking together, this chapter aims to elucidate the temporal profile exhibited by SII (and SI) during the execution and observation of complex actions. The inspection of the temporal dynamics will elucidate about the functional role of SII, also in comparison with SI.

Methods

Participants

Stereo-EEG data were collected from 18 right-handed patients (12 males, 6 females) suffering from drug-resistant focal epilepsy (age 36±7)

Neurological examination was unremarkable for all patients and, in particular, no patient presented any motor or sensory deficit.

Electrode implantation

Six patients were implanted in the left hemisphere, eight patients in the right one and 4 were implanted bilaterally, resulting in a total of 22 hemispheres explored.

Experimental paradigm

Patients performed two experimental sessions: in the first they were required to perform a reach-grasp task and an ecological manipulation on different objects set in a workbench (i.e. tighten a screw, beat a nail or screw a bolt with the hand). In the second session, patients were asked to carefully observe the same task performed by an experimenter. Both patients and the experimenter performed all the experimental session with the right hand.

Session were composed by 60 trials (20 for each object, randomly sorted), each comprising three different phases whose onset and offset were signaled by digital events. While sitting in front of the workbench, the subject had first to press a button box with the right hand (four fingers, except the little finger posed on the button box) as initial position.

- *'movement preparation' phase (duration 2 s)*: The initial position triggers the instruction about which object the patient/experimenter will have to manipulate. This information is administered by turning on a LED under the object to-be-manipulated, remaining turned on for 2 seconds;
- *a 'reaching' phase (variable duration):* as far as the LED turns off, the patient is free to start the action. The beginning of the reaching phase is identified by the button box signaling when all the buttons are unpressed, while the end is identified by a photocell on the top of the workbench estimating the onset of the hand/object interaction. The duration of this phase varied within and across patients;

a 'manipulation' phase (duration 2 s): In this phase the patient/experimenter is required to manipulate the object (beating the nail, screwing the bolt, and tighten the screw). The end of the manipulation was signaled by an acoustical tone, delivered 2 seconds after manipulation onset, after which the agent has to return in the starting position. During the whole experiment, both the patient and the experimenter were required to minimize their postural adjustments. The described experimental paradigm is detailed in Figure 1.

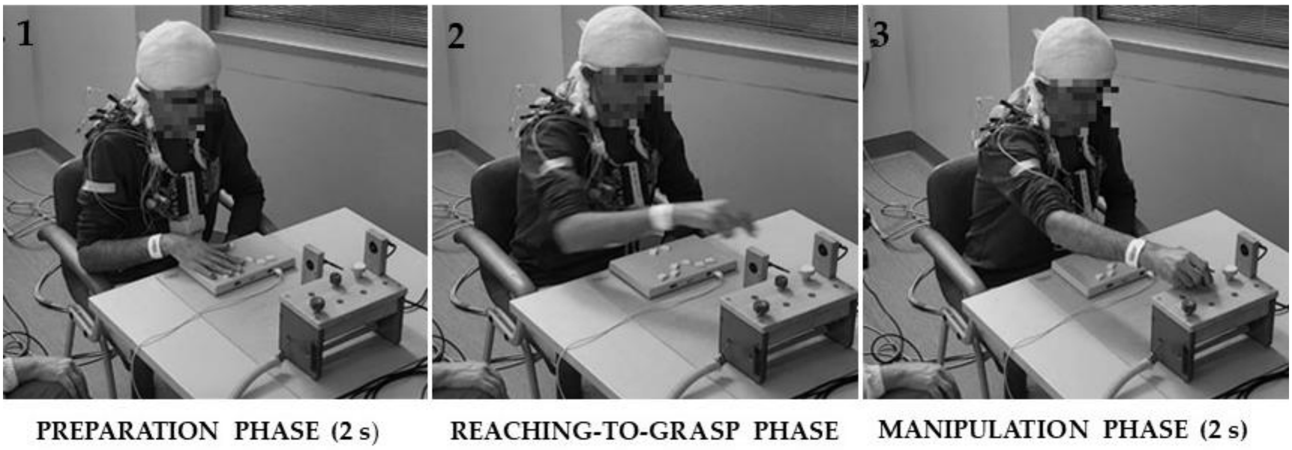

Figure 1: The experimental paradigm. The figure shows the experimental procedure. In the first phase (panel 1), the subject is required to keep a button box pressed with the right hand and to fixate a LED signalling the object to be manipulated (2 s). When the led turns off (panel 2) the subject may lift the hand (self-paced) from to the button box to reach the object (reaching-to-grasp phase). When the subject's hand crosses the photocell placed just above the objects (hand-object interaction), the reaching-to-grasp phase ends. In the last phase (manipulation phase) the subject is required to manipulate the object continuously for two seconds until the end of the trial. Adapted from Del Vecchio et al. (*under review*)

Clinical and neurophysiological tests

Median Nerve Stimulation: the median nerve opposite to the recorded hemisphere was stimulated at the wrist, using 100 constant-current pulses (0.2-ms duration) at 1 Hz while the patient lied in bed with eyes closed. The intensity and exact site of stimulation were varied until an observable thumb twitch was obtained. The motor threshold in our sample ranged from 3.2 to 5.8 mA. The stimulation intensity was set at 10% above the motor threshold.

Acoustic stimulation: patients wearing earphones were required to listen to 100 click acoustical stimulation (contralateral to the implanted hemisphere) of respectively 40 and 85 dB SPL (Sound Pressure Level).

Visual stimulation: patients wearing goggles received 100 bilateral visual stimulations (i.e. flash) at a rate of 1 Hz.

Optokinetic stimulation: patients were required to sit in front of a computer screen and watch a sequence composed by six images representing concentric curves enlarging at each image and thus indicating an anterograde progression in space. The duration of the whole sequence was set to 320 seconds; the number of trials was 90.

SEEG data recording and processing

Recordings. For each patient, the initial recording procedure included the selection of an intracranial reference, which was chosen by using both anatomical and functional criteria. The reference was computed as the average of two adjacent leads both exploring white matter. These leads were selected time-by-time because they did not present any response to standard clinical stimulations, including somatosensory (median, tibial, and trigeminal nerves), visual (flash), and acoustical (click) stimulations. Nor did the leads' electrical stimulation evoke any sensory and/or motor behavior

Data processing. The data from all leads in the gray matter were decomposed into time–frequency plots using complex Morlet's wavelet decomposition. To avoid power-line contamination, power in the gamma frequency band was extracted from 55 to 145 Hz for each of three phases separately (preparation, reaching, and manipulation) in execution and observation conditions. Gamma-band power was also computed for baseline condition ranging from 350 ms to 50 ms before the led lighting. In median nerve, acoustical and visuo-motor stimulation, the selected window for gamma-band power computation ranged from 100 ms before to 500 ms after the stimulus delivery. Finally, gamma power was subdivided into non-overlapping 10-ms bins and estimated for 10 adjacent 10-Hz frequency bands **(Vidal et al. 2010, Caruana et al. 2014[a])**.

To compare the gamma-band power dynamics during the reaching phase within and across subjects, the estimation in each frequency band has been linearly interpolated in a fixed number of points (n=155).

Statistical analysis.

To identify the responsive leads, the gamma band power in each post-stimulus bin was compared with baseline using a t-test. Significance was corrected for 50 comparisons ($p < 0.001$), and to decrease the false-positive ratio, only leads with significant gamma increases in at least three time bins were designated as responsive. Note that significance for the reaching phase was computed limiting the comparison at the minimum common duration across trials for each patient, independently for execution and observation conditions. To normalize data across patients and leads, power in post-stimulus bins was transformed into z-scores relative to the baseline interval. For each phase, significance was Bonferroni corrected. Finally, we estimated the delay between responses following action execution and observation as the first significant bin of activation after hand lifting.

Mapping of spatial sampling and responsiveness maps were computed according to the procedures detailed in **(Avanzini et al. 2016)** and visualized on a flat map with Caret software **(Van Essen 2012).**

Results

Reactivity of SII

In the execution phase, about half of the SII sites showed a significant gamma power increase during both the reach-to-grasp (18 left, 16 right) and the manipulation phase (19 left, 16 right) while only 3 leads were responsive in the preparation phase (2 left, 1 right). Most of the leads active during reach-to-grasp were active also during manipulation (15 left, 15 right).

In the observation condition, 19 (7 left, 12 right) leads showed a significant gamma power increase during the reach-to-grasp phase, and 13 (6 left, 7 right) did the same for the manipulation phase. Overall 9 leads were active in both phases (5 left, 4 right). No leads were responsive during the preparation phase.

Interestingly, the large majority (96%) of the leads active during action observation were also active during action execution, thus suggesting a link between visual and sensori-motor functions of SII. Figure 2 shows the gamma-band time-course for both execution (blue trace) and observation (red trace) for left SII (panel A) and right SII (panel B). Curves were computed by averaging all the leads active in at least one phase of the experimental paradigm, for both execution and observation. For each condition, significance against the baseline is shown below the traces in the corresponding color code.

During action execution, the significant activity in left SII (Figure 2A) starts before hand lifting. This was followed by an activity decrease during reaching, and by a strong power increase preceding the hand-object interaction, which lasted for the entire manipulation phase. The activity pattern during action observation was highly similar to that observed during action execution, but characterized by a lower amplitude of the activations during hand-object interaction and manipulation phase and a response onset following the hand lifting (delay of 50 ms relative to action execution in terms of earliest significance for leads active both during execution and observation conditions).

The biphasic temporal pattern is present also in right SII during both action execution and observation (Figure 2B). However, virtually no differences in amplitude were observed if comparing action execution and observation.

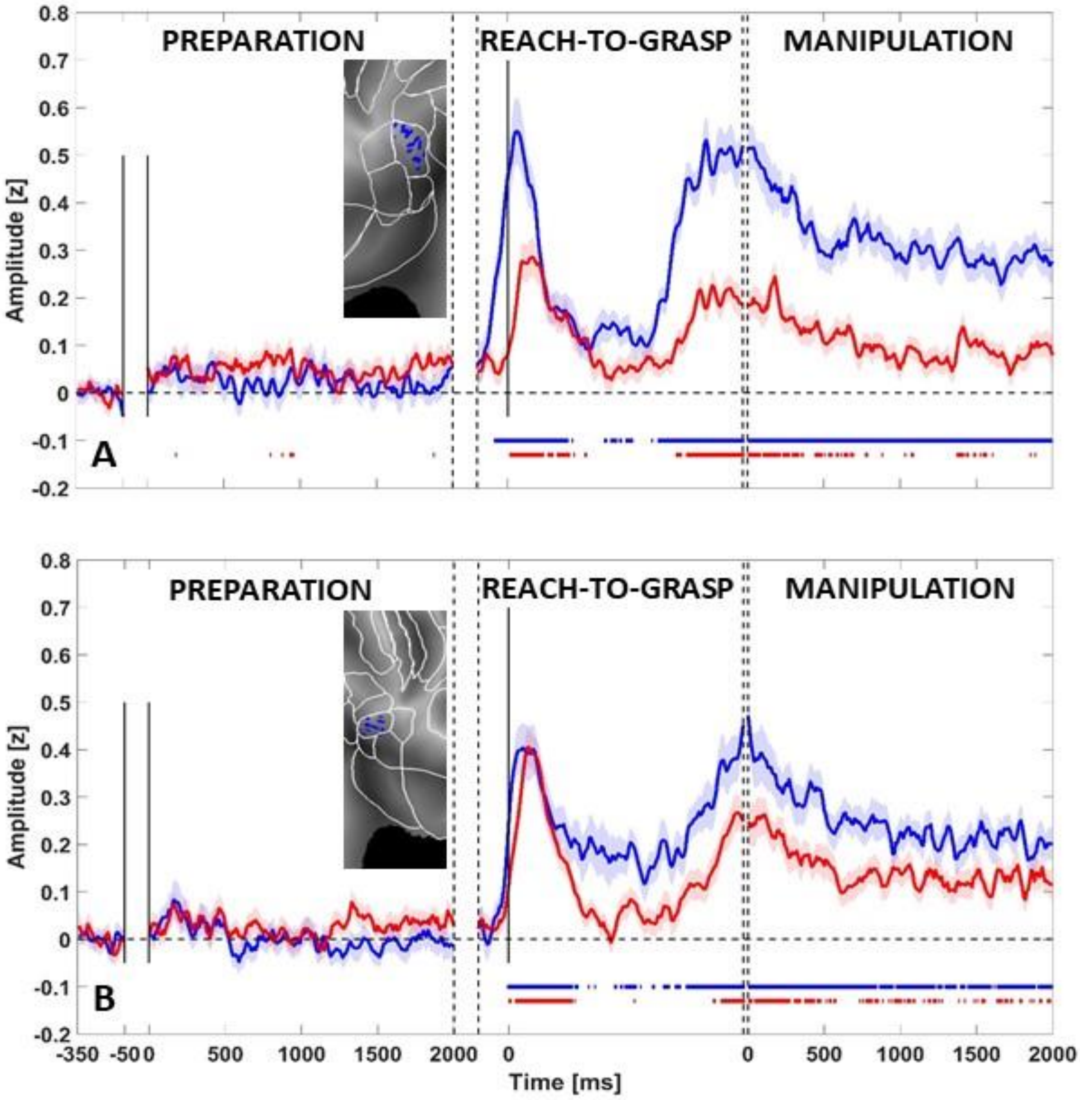

Figure 2: Contralateral and ipsilateral SII gamma responses to action execution and observation. The figure depicts for the contralateral SII (panel A) and ipsilateral SII (panel B) the average time-course (±SE) for execution (blue trace) and observation condition (red trace). The averaged amplitude is computed in terms of z-score respect to the baseline for each trial, including all leads responsive in at least one phase (22 left, 19 right). Significance respect to the baseline is shown below the traces in the same color code. For each hemisphere, the panel includes an inset showing the localization of responsive leads on a flat map (*see Appendix*). Adapted from Del Vecchio et al. **(*under review*)**.

Reactivity of SI

Figure 3 shows the time course of left SI activity during action execution and observation. The analyzed leads, all responsive during the execution of reach-to-grasp and manipulation phases, exhibit a phasic response at the hand lifting preceded by a decrease of gamma power respect to the baseline period, covering most of the preparation phase. Before the hand-object contact and during the whole manipulation period, activity was continuously sustained.

It is important to note that both left and right SI show no activation during the observation, ruling out a mirror function for this area.

Finally, the contralateral SI activation before the hand lifting, in common with SII during the execution condition, might reflect either a proprioceptive input or a tactile-off signal **(Onishi et al. 2010)**; however the source of this same SII activation during action observation remains unclear.

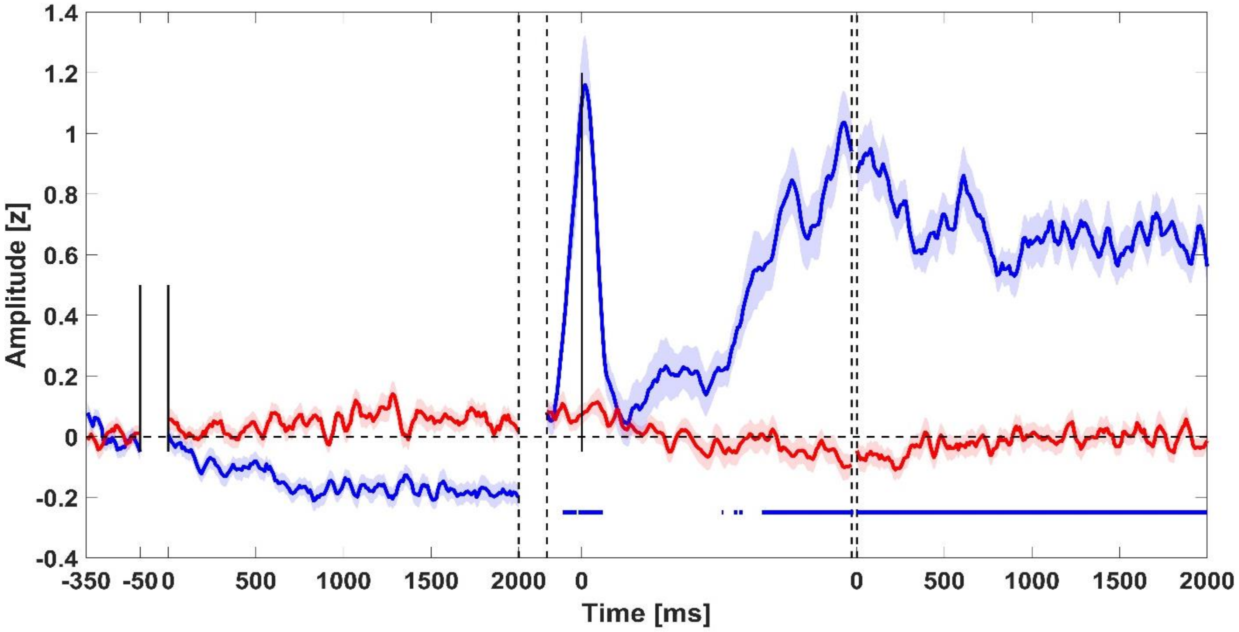

Figure 3: Contralateral SI gamma responses to action execution and observation. The figure depicts for the contralateral SI (including area 3a, 3b, 1) the average time-course (±SE) for execution (blue trace) and observation condition (red trace). The average is computed including all leads responsive in at least one phase (12). Significant increase respect to the baseline is shown below the traces in the same color code. The panel includes an inset showing the localization of responsive leads on a flat map (*see Appendix*). Adapted from Del Vecchio et al. ***(under review)***.

Clinical and neurophysiological tests

All patients examined in this study completed a stimulation set aimed at depicting the responsiveness to clinical tests including contralateral median nerve, acoustic (40 dB and 85 dB) and bilateral visual stimulation (both static and dynamic). Percentage of responsiveness respect to leads active in at least one phase of the paradigm are reported in Table 1.

STIMULATION	PERCENTAGE RESPECT TO LEADS RESPONSIVE IN AT LEAST ONE PHASE	
	LEFT	RIGHT
CONTRALATERAL MEDIAN NERVE STIM.	95% **(21/22)**	74% **(14/19)**
CONTROLATERAL ACOUSTIC STIM. (40 DB)	27% **(6/22)**	0% **(0/19)**
CONTROLATERAL ACOUSTIC STIM.(85 DB)	27% **(6/22)**	26% **(5/19)**
VISUAL STIMULATION	0% **(0/22)**	0% **(0/19)**
OPTOKINETIC STIMULATION	0% **(0/22)**	0% **(0/19)**

Table 1: Table 1 indicates the results of clinical and neurophysiological tests administered to patients. Each column reports the percentage of responsive leads respects to leads showing a significant response in at least one phase of the experimental paradigm.

The most relevant information emerging from this analysis is that no lead exploring SII, which is responsive to action execution or observation is also responsive to visual stimulation, even though the stimulus is suggestive of a motion, like in the optokinetic stimulation, excluding that a visual stimulus is able to activate this area. Figure 4 shows the gamma band temporal course of all leads responsive to at least one phase of the experimental paradigm following contralateral median nerve stimulation (panel A), static (panel B) and dynamic (panel C) visual stimulation and acoustic stimulation at 40 dB (panel D) and 85 dB (panel E).

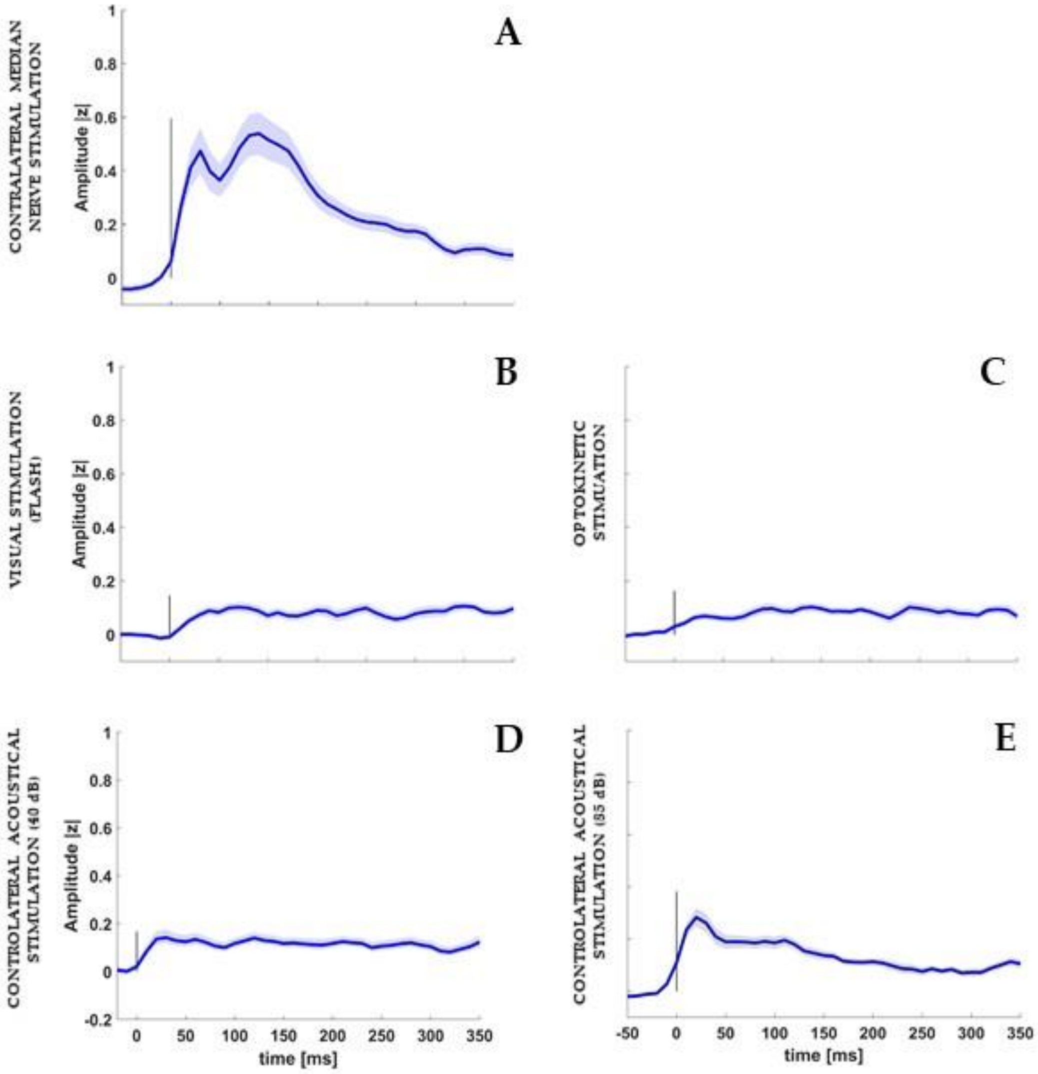

Figure 4: Gamma band time-course following neurophysiological tests of SII leads responsive in at least one phase of the experimental paradigm. Figure 4 shows the normalized (z-score) gamma band temporal course (±SE) following to contralateral median nerve stimulation (panel A), to visual (panel B), to optokinetic (panel C), to acoustical stimulation (panel D and E, respectively to 40 and 85 dB SPL). The average has been computed taking into account all leads (22 left, 19 right) with a statistically significant response to at least one phase of the experimental paradigm (*see Methods*). Adapted from Del Vecchio et al. (***under review***).

To compare the behavior of SII with SI following MNS, Figure 5 shows the gamma band temporal course of responsive leads in left SI (12 out of 12 sampled, panel A) and of both left (23 out of 31) and right SII (21 out of 33) (panel B). It is worth nothing that these two areas show a completely different temporal behavior: SI depicts a phasic time-course while bilateral SII has a long-lasting tonic behavior ending after 200 ms after the stimulus.

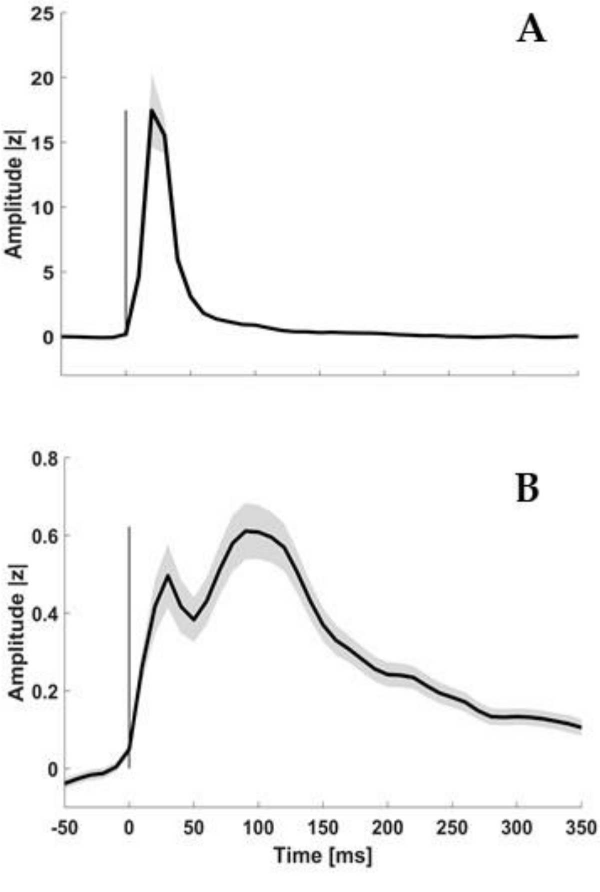

Figure 5: Gamma band time-course following contralateral median nerve stimulation. Panel A shows the gamma band temporal course of leads responsive to contralateral median nerve stimulation by leads sampling SI (12 out of 12) with error bar corresponding to standard error. Panel B shows the response to contralateral median nerve stimulation in both left and right SII (±SE). The average has been computed taking into account all leads (23 left, 21 right) with a statistically significant response to the stimulation. Adapted from Del Vecchio et al. **(*under review*).**

Action execution in SI and SII

During action execution, SI and SII present an overlapping temporal profile. Initially, both areas failed to show a gamma power increase during the motor planning. While this is an expected finding as far as SI is concerned, the lack of activation in SII is less trivial, considering that this area is anatomically connected with dorso-lateral prefrontal (DLPFC) and pre-supplementary motor areas, known to be recruited during action preparation **(Cipolloni and Pandya 1999, Borra et al. 2011, Gerbella et al. 2012, Gerbella et al. 2017)**

The gamma power of both SI and SII during the reaching phase is observed only at the action onset and just before the hand-object interaction, but it is virtually absent during arm movement, hence failing to reveal a contribution specific for reaching. This result is in line with a long-standing model assessing that the circuits controlling the integration subserving reaching movements are located more dorsally relatively to SII **(Jeannerod, 1988)**.

The most interesting result concerns the hand-object interaction, which shows a very strong gamma power response in both SI and SII. While SI activity is compatible with its tactile or proprioceptive functions, the activation of SII could also be compatible, in principle, with a motor control. This last hypothesis is supported by recent single neuron studies in the monkey. Indeed, Ishida and coworkers **(shida et al. 2013)** reported that some SII neurons activate during active manipulation also when tactile and proprioceptive fields are absent, and similar results have been also reported by Hihara and coworkers **(2015)**. The hypothesis that the same temporal course of SI and SII during action execution might underlie different functional roles is in line with the different reactivity of these regions to basic somatosensory stimulation. The median nerve stimulation determines a short-lasting, phasic response in the contralateral SI, whereas the same stimulation elicits a prolonged, tonic activity in both contralateral and ipsilateral SII. This evidence is in line with previous studies (**Avanzini et al. 2016, Avanzini et al. 2018, ,Del Vecchio et al. 2019**), and is suggestive of a segregation between SI and SII somatosensory processing, with SII playing higher order functions, likely including haptic control **(Sathian 2016)**.

Action observation in SII

During action observation, SII is active, while SI does not show any significant increase in gamma power respect to the baseline period, thus indicating a lack of neural recruitment in this area **(Lachaux et al. 2008)**. The possible activity of SI during action observation is a debated issue in social neuroscience **(Raos et al. 2004, Ebisch et al. 2008, Meyer et al. 2011)**. In our study, intracranial recordings were performed from areas 3a, 3b and 1, sparing area 2. This is in line with the distinct functional roles of these sub-regions within SI complex, with visual responses limited to area 2, as indeed suggested by Keysers et al. **(2010)**

The temporal pattern exhibits by SII during action observation represents the most relevant result of this study. Indeed, during action observation, the temporal course of SII activation follows a temporal pattern virtually superimposable to that recorded during action execution. One hypothesis to explain this congruence might be that our data simply reflect a visual processing of the action, which occurs both when the action is observed and when it is performed by the subject. However, no response was found in secondary somatosensory cortex following presentation of visual stimuli, neither when they contained visual motion, excluding the possible involvement of SII in basic visual processing. Furthermore, a recent study on monkeys identified a common coding for grasping execution and observation in SII, maintained also when the primates performed actions in the dark **(Fiave et al. 2018)**.

The exclusion of SII in the processing of visual stimuli contributes to formulate the hypothesis that the visual information reaching this area might come from the inferior parietal lobule, which is known to be involved in the processing of other's actions **(Fogassi et al. 2005)**. Furthermore, SII is a pivotal node of the so-called lateral grasping network endowed with the mirror mechanism, and its anatomical connections with the hand fields of F5, AIP, and PFG have been largely reported in the monkey **(Rozzi et al. 2005, Borra et al. 2007, Gerbella et al. 2011).** Thus, it is not unlikely that it plays a role also in action observation. The time course simultaneity and similarity shown by SII during action execution and observation is even more remarkable considering that the networks conveying visual and somato-motor information to SII are different.

The involvement of SII in action mirroring has been previously suggested by single neuron **(Hihara et al. 2015)** and fMRI **(Raos et al. 2004, Sharma et al. 2018)** studies in the monkey. While the functional role of SII activation during action observation requires further investigations, previous human fMRI studies indicated that specific actions, i.e. those depicting haptic movements, drive the strongest SII activation **(Ferri et al. 2015)**. This view is in line with the reliable response shared by execution and observation during the object manipulation, i.e. the action phase with the strongest haptic component. The notion that SII encodes more than just somatosensory information during executed actions is further supported by a recent study by Limanowsky and coworkers **(2019)**. They reported that tactile inputs activate SII more strongly when in concomitance with active movements, proposing for SII a role in instantiating long-lasting sensorimotor responses to be further used by higher-order motor regions for motor adjustments.

Conclusion

The role of secondary somatosensory cortex in high level tactile functions has been acknowledged over the years, clarifying its peculiar contribution in tactile discrimination learning and memory**.** This view has been strongly reinforced if considering its specific pattern of responsiveness to tactile stimulation: its bilateral, non-earliest, long-lasting tonic responses well matches with the features of recurrent processing, a mechanism proposed to sustain perception and conscious awareness.

In addition, the data presented in this Doctoral Dissertation demonstrate that, besides tactile processing, SII modulates its responsiveness and even activates during the observation of grasping and manipulative actions. Interestingly, SII shows a temporal profile synchronous with that depicted during action execution, with SI activation limited to this latter. This indicates the presence of a mirror-like mechanism also in SII, sustained by a neural circuit able to operate simultaneously and independently from the somatosensory input of SI and with a peculiarity for motor acts requiring haptic exploration.

Together, this Thesis indicates that SII, even though maintaining a specificity for somatosensation, fulfills higher-order functions for perception and awareness.

Ethical committee

All the studies presented in this Thesis received the approval of the Ethics Committee of Niguarda Hospital (ID 939-2.12.2013). All the patients were fully informed regarding the electrode implantation and stereo-EEG recordings.

Appendix

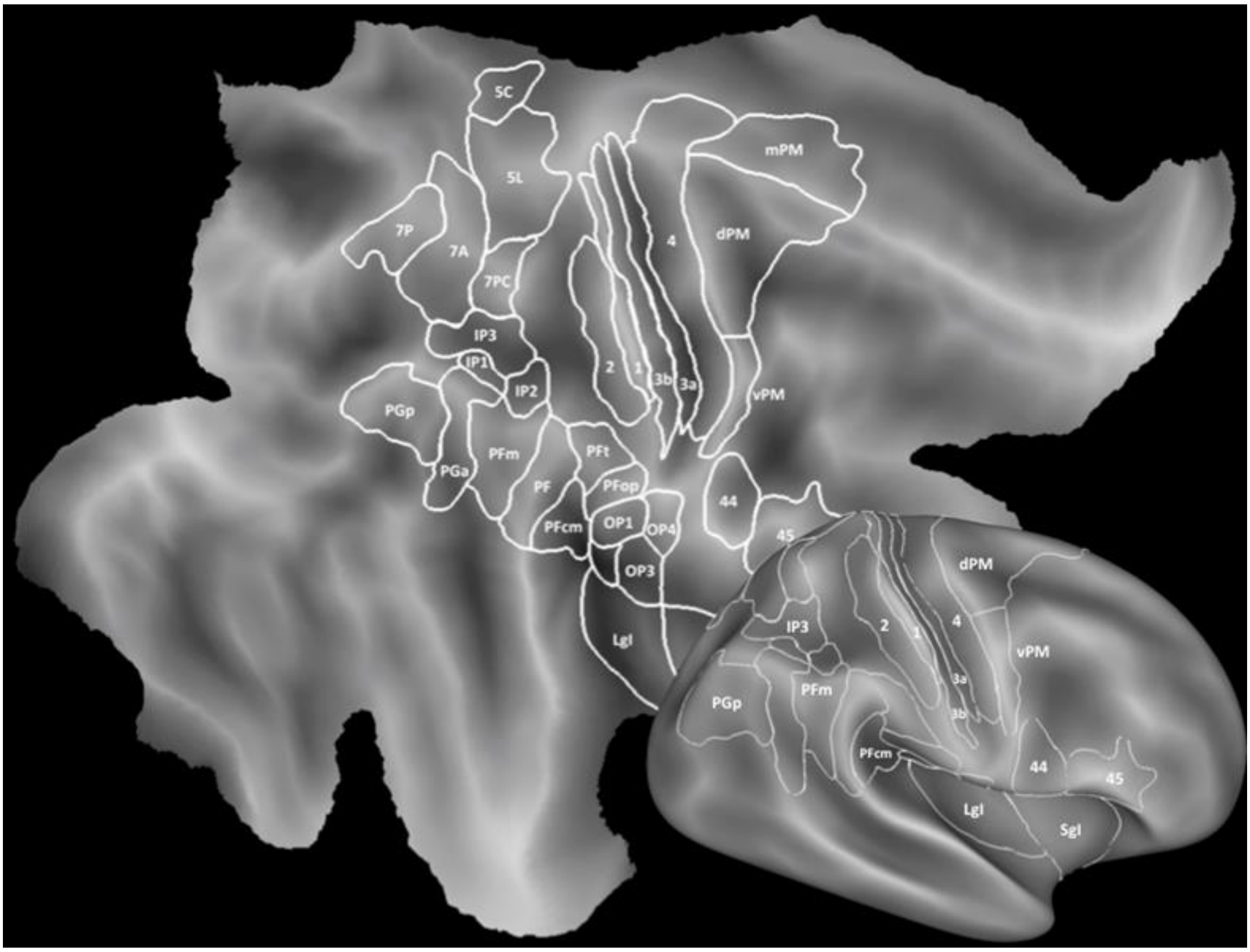

Figure A1: Brain template. Flat map of fs-LR-average right hemisphere template (163.842 nodes), with cytoarchitectonic regions indicated. The bottom-right inset shows the inflated view of the same brain template. Adapted from Del Vecchio et al. **(2019)**

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