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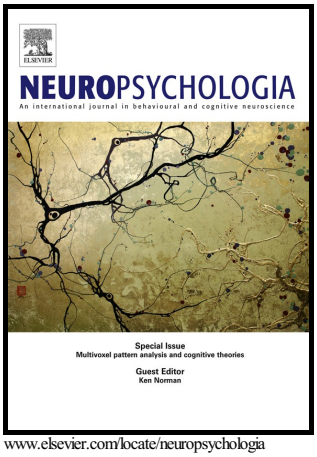

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F. Caruana, F. Gozzo, V. Pelliccia, M. Cossu, P. Avanzini

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SMILE AND LAUGHTER ELICITED BY ELECTRICAL STIMULATION OF THE FRONTAL OPERCULUM

Caruana F.[1,2*], Gozzo F.[3], Pelliccia V.[3], Cossu M.[3], Avanzini P.[1]

[1] Department of Neuroscience, University of Parma, Parma, Italy

[2] CNR Institute of Neuroscience, Parma, Italy.

[3] Claudio Munari Center for Epilepsy Surgery, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

* Correspondence should be addressed to:

Fausto Caruana, Department of Neuroscience, University of Parma, Via Volturno 39, 43125 Parma, Italy. Tel. +39 0521 903894; E-mail: fausto.caruana@unipr.it.

Abstract

Laughter and smile are typical expressions of mirth and fundamental means of social communication. Despite their general interest, the current knowledge about the brain regions involved in the production of these expressions is still very limited, and the principal insights come from electrical stimulation (ES) studies in patients, in which, nevertheless, laughter or smile have been elicited very rarely. Previous studies showed that laughter is evoked by the stimulation

of nodes of an emotional network encompassing the anterior cingulate, the superior frontal and basal temporal cortex. A common feature of these stimulation studies is that the facial expression was always accompanied by motor awareness and often by mirth, in line with the affective functions attributed to these regions. Little is known, in contrast, on the neural basis of the voluntary motor control of this expression. The objective of this study was to investigate the effect of ES of the frontal operculum (FO), which is considered a crucial node for the linkage of the voluntary motor system for emotional expression and limbic emotional network. We report the case of ES applied to the frontal operculum (FO) in four patients with drug-resistant focal epilepsy undergoing stereo-electroencephalographic (SEEG) implantation of intracerebral electrodes. In all patients, ES applied to the FO produced laughter or smile. Interestingly, in one patient, the production of a smiling expression was also clearly accompanied by the lack of motor awareness. Since the lack of motor awareness has been previously observed only after the stimulation of the voluntary motor network, we speculate that FO is involved in the voluntary control of facial expressions, and is placed at the interface with the emotional network, gating limbic information to the motor system.

Keywords: Emotional expression; Facial expression; Emotion; Stereo-EEG; Stimulation

1. Introduction

Laughter plays a fundamental role in our social and affective life. On one hand, emotional and involuntary laughter has been associated with a variety of social functions encompassing affection, enjoyment and agreement; on the other hand, voluntary and contrived laughter mediates several

communicative intents (Ruch and Ekman, 2001; Provine, 2000; Scott et al., 2014). It is common knowledge that its production is controlled by two interacting networks (Lauterbach et al., 2013). On one side, the emotional network, which includes the anterior cingulate, insular, mesial temporal and orbitofrontal cortices, as well as subcortical structures such as the amygdala, the hypothalamus and the periaqueductal gray, integrates social and motivational information to generate congruent emotional expressions. On the other side, the voluntary network is supposed to involve motor and parietal areas, and to provide conscious awareness and voluntary emotional regulation (Wortzel et al., 2008). Similar considerations are also valid for smile production (Niedenthal et al., 2010). According to a longstanding tradition, in facts, smile is a weaker form of laughter or its precursor, devoid of vocalizations but sharing with laughter the involvement of the same facial muscles, cortical networks and, most importantly, social and affective functions (Darwin, 1872; Frijda, 1986; Ramachandran, 1998; Niedenthal et al., 2010).

The distinction between voluntary and emotional laughter and smile has been classically suggested by the observed dissociation between emotional and voluntary facial paresis (Hopf et al., 1992), but it is difficult to describe the neural correlates of these behaviors by means of functional neurophysiological techniques. Indeed, despite its general interest, direct knowledge about the neural basis of the production of emotional facial expressions is still extremely limited, and mainly based on pathological laughter following brain lesions or gelastic seizures (Wild et al., 2003). These data, however, cannot clearly provide any precise anatomical information. Moreover, technical limitations related to the sensitivity to head movement prevent the use of non-invasive imaging techniques in studies investigating the production of emotional facial expressions. It follows that accurate anatomical information on this function largely depends on a small number of cortical electrical stimulation (ES) studies, performed during invasive EEG monitoring in patients candidate for surgical treatment of focal epilepsy. To date, smile and laughter have been

elicited in about 20 patients by ES of basal temporal (Arroyo et al., 1993; Satow et al., 2003; Yamao et al., 2015), superior frontal (Krolak-Salmon et al., 2006; Schmitt et al., 2006; Fried et al., 1998), inferior frontal (Fernandez-Baca Vaca et al., 2011) and, more consistently, pregenual anterior cingulate cortex (pACC) sites (Caruana et al., 2015; Sperli et al., 2006). In the large majority of these cases, patients reported a sense of mirth and merriment accompanying the induced emotional expression (see Table 1). Often they reported also a somatosensory feedback to the face and, most important, in all these cases patients were aware of producing a facial expression. Here we report the first evidence of four patients in whom ES applied to the frontal operculum (FO) produced laughter and smile. Notably, in one case the production of a smiling expression was clearly accompanied by the lack of motor awareness.

2. Material and methods

We report the case of ES in four patients with drug-resistant focal epilepsy undergoing stereo-electroencephalographic (SEEG) implantation of intracerebral electrodes on the frontal, parietal, and temporal lobes as part of the presurgical evaluation (Cardinale et al., 2013). The topographic strategy of implantations was based on hypotheses about the presumed Epileptogenic Zone (EZ), arising from clinical history and examination of non-invasive long-term video-EEG monitoring, and neuroimaging (Cossu et al., 2005). All the stereotactic electrode trajectories were planned on multimodal images, and the multicontact electrodes were implanted with the Neuromate robotic assistant (Renishawmayfield, Nyon, Switzerland), according to the technique detailed elsewhere (Cardinale et al., 2013). Immediately after the implantation, cone-beam computed tomography (CBCT) is obtained with the O-arm scanner (Medtronic, Minneapolis, Minnesota) and registered to pre-implantation 3D-T1-weighted MR images. Subsequently, multimodal scenes are built with the

3D Slicer software package (Gering et al., 1999), and the exact position of each contact is determined, at the single patient level, looking at multiplanar reconstructions and Freesurfer computed surfaces (Dale et al., 1999). In addition, the localization of all leads of interest on a brain template was reconstructed according to the procedure described in Avanzini et al. (2016) to ensure that all of them lied in the frontal operculum. All the electrodes were implanted only for clinical purposes. After the recordings of spontaneous seizures, electrical stimulations were performed through the electrodes in several cerebral structures, aimed at both inducing habitual seizures and functional mapping. Electrical bipolar stimulations of two adjacent contacts were carried out at high frequencies (HF, 50 Hz, pulse width 1ms, 5-6s, until 3mA), in order to elicit a part or the entire ictal subjective or objective symptomatology, and to map eloquent cortical areas (see Caruana et al., 2015). Patients were unaware of the timing of the stimulation and the anatomical location of the stimulated structure. During stimulations Patients 1-3 were requested to maintain the arms elevated and to name months aloud, to evaluate speech arrest and upper limbs atonia. The same procedure has not been adopted with Patient 4 because of the young age. HF stimulation has been systematically employed in neuroscientific research to map complex behavioral responses. It has been a recent debate whether the effect of HF stimulation is only at the site of stimulation or in larger regions (Desmurget et al., 2013; Borchers et al. 2012), and it has been suggested that HF stimulation likely produces a transynaptic spread of signal through a complex network of interconnected areas, with more effects at the site of stimulation (Desmurget et al., 2013; Selimbeyoglu and Parvizi, 2010; David et al., 2010; Graziano 2006). Accordingly, the presence of intradischarge during stimulation suggests an anatomical or functional connectivity between the region where intradischarge is recorded and the stimulated area. In addition to HF, stimulation was also carried out at low frequencies (LF, 1 Hz, pulse width 1ms, range 0.2-5mA). The aim of LF stimulation is to map primary motor and sensory (somatosensory, acoustic and visual) areas to

evoke simple clinical signs (e.g. jerks or visual or auditory simple hallucinations), while it is behaviorally unresponsive elsewhere. Any complex behavior or hallucination can be elicited by LF. The observations made in this study were incidental and no experimental design was on purpose planned. For this reason, we did not estimate a rate of laughter induced by ES. An appropriate strategy to investigate this issue would be to present a mapping of the entire operculum in a large dataset of patients, but this is beyond the scopes of the present report.

3. Results

3.1. Patient 1.

Patient 1 was a 23 years old woman, with left hemispheric dominance, investigated by a left fronto-temporo-parietal SEEG implantation. MRI data and neurological examination were unremarkable. HF electrical stimulation of contacts S'4-5, lying in the left FO between ventral BA6 and the dorsal insula (MNI [-46, 10, 6] see Fig.1), was performed at 3mA, for 5 seconds. The stimulation elicited a smile starting from the contralateral zygomaticus muscle and subsequently involving all the lower facial muscles, without interrupting the speech. The latency from the stimulation onset was ≅4.7s, in accord with previous stimulation studies on laughter production (Yamao et al., 2015). The facial expression was not accompanied by vocalization or any postural movement, resulting in a smile and not a laughter. Smile production was not accompanied by mirth and, more interestingly, the patient did not became aware that she produced a facial expression. More specifically, she did not spontaneously commented on her facial expression and, when explicitly asked whether she smiled, she responded negatively, stating that the stimulation was completely ineffective (see Movie1). Stimulation at lower intensity (1mA, 6 seconds) did not produced any response. The HF stimulation of the adjacent contacts Z'3-4 (MNI [-38, 8, 10] see

Fig.1) was performed at similar intensity (3mA, 6 seconds), and gave similar results. During the stimulation, the patient exhibited an evident smile (latency ≅4s) preserved after the end of the stimulation. No vocalizations accompanied the facial expression. The expression recovered suddenly and completely as the patient started to speak and answered questions. She reported only a very faint sensation behind the left ear and, when the neurologist explicitly asked whether she felt anything to the face, to the tongue or to the throat, the patient gave a negative answer (see Movie1). Given the close proximity, the two stimulated sites in Patient 1 virtually cover the same brain region and could be interpreted as a confirmation of the effect. During HF stimulations of both sites, we observed an intradischarge in the posterior insula, the inner and lateral aspects of the frontal operculum and, to a weaker extent, in the precentral cingulate and parietal operculum following S'4-5 stimulation, but no effects have been observed in the central and parietal cingulate cortex, pre-SMA, premotor cortex and inferior parietal lobule. A short afterdischarge (<3s) was recorded in the insular cortex, in the frontal operculum and in the precentral cingulate cortex (see Fig.2). The chance that the behavioral effect was triggered by the regions showing afterdischarge is very unlikely. Similar facial expressions were not elicited by the HF stimulation of any other contact (in total, 57 HF stimulations), including those in which intradischarge or afterdischarge were recorded. Furthermore, the onset of the behavioral response precedes the afterdischarge of about 2 seconds. As a consequence, the afterdischarge cannot explain the behavioral response. A possibility is that afterdischarge can at least explain the lack of motor awareness. Albeit this possibility deserves to be mentioned, we consider this interpretation very unlikely. First, the afterdischarge in this patient was very short (2-3 seconds), disappeared before the interview started and involved a limited number of contacts. Second, while HF stimulation-induced afterdischarges may be observed in our patients, their behavioral and cognitive correlates are rare

and difficult to be highlighted. In both sites, stimulations at low frequency (LF, 5mA, 30s) did not produce any effect.

Only one spontaneous seizure was recorded during the hospitalization period. During the seizure, which was recorded during sleep, the patient lifted her left leg and turned her chest to the left, with a dystonic posture of the right hemisoma. Head and gaze were turned to the left. Afterward, the seizure elicited guttural sounds, reddening of the cheeks, blink of the eyelids and sialorrhoea. The seizure did not elicited smile or facial expressions, albeit relatives described laughter as part of the spontaneous seizures, that were also characterized by afinalistic movements of the right arm and, subsequently, by goal directed movements of the left arm (grasping and mouth directed movements). From the electrical point of view, the onset of the recorded seizure started from contacts located in the fronto-parietal operculum and insula, and then spread to the cingulate cortex. The epileptogenic zone (EZ) was estimated to include the fronto-parietal operculum and the inferior parietal lobule but, since the patient refused to undergo surgical treatment, we have no surgical follow-up to confirm the location of the EZ.

3.2. Patient 2.

Patient 2 was a 30 years old woman, with left hemispheric dominance confirmed by language functional MRI, investigated by a right fronto-temporo-parietal SEEG implantation. MRI data and neurological examination were unremarkable. HF electrical stimulation of contacts R5-6, lying in the right FO (MNI [52, 6, 6] see Fig.1), was performed at 3mA, for 5 seconds. One second after the stimulation onset the patient interrupted her speech (anarthria) and smiled. Similar to Patients 1, the facial expression was not accompanied by vocalization or any postural movement, resulting in a smile and not a laughter. When explicitly asked by the neurologist why she arrested her speech

and started smiling, she answered that she was not able to speech anymore, and she was not able to explain the reason why she smiled. During HF stimulations, we observed an intradischarge in the contacts lying in the FO and in the adjacent insula. An afterdischarge was recorded in the operculum and the posterior insula (see Fig.3). Laughter or similar facial expressions were not elicited by the stimulation of any other contact (in total 37 HF stimulations), including those where the intradischarge was observed. LF stimulation of the same contacts did not produce any clinical effect.

Eighteen seizures were recorded during the hospitalization period. The seizures were characterized by a warmth sensation, staring, and a bottom right-hand gaze shift. In addition, during the seizures the patient was unable to speech correctly. From the electrical point of view, the seizure started from contacts located in the superior temporal gyrus, and then spread to the mesial temporal lobe. The epileptogenic zone was estimated to include the right temporal lobe and, accordingly, a right temporal lobectomy has been performed. The patient is seizure-free since surgery 3 months postoperatively.

3.3. Patient 3.

Patient 3 was a 39 years old woman, with left hemispheric dominance, investigated by a left fronto-temporo-parietal SEEG implantation. Neurological examination was unremarkable, while MRI data showed a focal cortical dysplasia in the left supramarginal gyrus. HF electrical stimulation of contacts X'6-7, lying in the left FO (MNI [-53, 13, 6] see Fig.1), was performed at 3mA, for 6 seconds. Five seconds after the stimulation onset the patient interrupted her speech and produced a laughter, the smiling facial expression being accompanied by air exhalation. Subsequently, the patient spontaneously reported that she arrested her speech because she was

laughing. During HF stimulations, we observed an intradischarge in contacts located in the insula. No afterdischarge was recorded (see Fig.3). Laughter or similar facial expressions were not elicited by the stimulation of any other contact (in total 35 HF stimulations), including the insular ones where the intradischarge was observed. LF stimulation (3mA, 15s) of the same contacts did not produce any clinical effect.

During the hospitalization period, we recorded only one seizure. The seizure was characterized by staring, leftward movements of the eyes and head, and by a hypertonic contraction of the right upper limb. Subsequently, the patient showed postictal aphasia. From the electrical point of view, the seizure was recorded from contacts located in the supramarginal gyrus. The epileptogenic zone was estimated to include the left supramarginal gyrus and, accordingly, a supramarginal lesionectomy has been performed. The patient is seizure-free since surgery 6 months postoperatively. The histological analysis of the resected region showed a focal cortical dysplasia (FCD IIb according to Blümcke et al., 2011).

3.4. Patient 4.

Patient 4 was a 4 years old boy, with a right manual laterality, investigated by a right frontal SEEG implantation. MRI data and neurological examination were unremarkable. HF electrical stimulation of contacts S4-5, lying in the right FO between ventral BA6 and the dorsal insula (see Fig.1), was performed at 1.4mA, for 6 seconds. Stimulation was delivered while the patient was at rest, in the lap of his mother. Four seconds after the stimulation onset the patient produced a laughter, the smiling facial expression being accompanied by air exhalation and postural movements. The expression was preserved after the stimulation offset. No clear vocalizations accompanied the facial expression. When the neurologist asked him what had happened, the

patient gave a negative answer, in line with the absence of motor awareness. However, because of the young age, it was difficult to assess in a reliable way whether the patient was aware of having produced a facial expression. During HF stimulations, we observed an intradischarge in contacts located in the insula while, after the stimulation an afterdischarge made up of non-focal slow waves (see Fig.3). Laughter or similar facial expressions were not elicited by the stimulation of any other contact (in total, 48 HF stimulations), including the insular ones where the intradischarge or afterdischarge was observed. LF stimulation (3mA, 15s) of the same contacts did not produce any clinical effect.

During the hospitalization period, we recorded two nocturnal seizures. The patient produced a deep breath followed by a retch-like opening of the mouth, and a wheeze. Afterward, the seizure elicited the lifting of the arms, followed by a hypertonia of the four limbs. From the electrical point of view, the seizure was recorded from contacts located in the lateral aspect of the frontal operculum, with a diffusion to the ventral aspect of the precentral gyrus, the inner face of the operculum and the anterior insula. After resection of the whole suprasylvian opercular cortex, the patient is not seizure-free 2 years postoperatively (Engel's class IIIa, according to Engel et al., 1993). The histological analysis of the resected region showed a focal cortical dysplasia (FCD IIa according to Blümcke et al., 2011).

4. Discussion

In the present study, we reported about four patients in whom ES of the frontal operculum produced smiling and laughing. The frontal operculum is deemed to play a crucial role in the voluntary control of facial expressions. Imaging studies showed that the this region is active during the observation (Jabbi and Keysers, 2008) and the voluntary imitation of smiles (Leslie et

al., 2004; Hennenlotter et al., 2005; van der Gaag et al., 2007), and during the production of voluntary, involuntary and inhibited laughter, with a slight preference for the first condition (Wattendorf et al., 2013). Furthermore, lesions inducing volitional facial paresis typically involve the operculum (see Wild et al., 2003). Studies on primates showed that the ES of the frontal operculum elicits non-emotional and typically voluntary orofacial movements, such as chewing or mouthing (Jezzini et al., 2012), but not emotionally-driven facial expressions, which are encoded in the ACC (Livneh et al., 2012; West and Larson 1995; Smith 1945) and in the ventral insula (Caruana et al., 2011), two key nodes of the emotional network (Jezzini et al., 2015; Lauterbach et al., 2013; Hopf et al., 1992). Finally, laughter has been elicited by ES of the opercular part of the left inferior frontal gyrus in one patient (Fernández-Baca Vaca et al., 2011), a region likely corresponding to the FO reported in the present study. These evidences are in line with our data that the stimulation of the frontal operculum elicits facial expressions, further suggesting that this region could be mainly involved in the voluntary production or inhibition of laughter.

A confirmation of this hypothesis is related to the lack of motor awareness that characterizes the effect of ES in Patient 1. This aspect singles out the present case from all other cases in the literature, since laughter elicited from nodes of the emotional network was always accompanied by awareness (Caruana et al., 2015; Yamao et al., 2015; Fernandez-Baca Vaca et al., 2011; Schmitt et al., 2006; Krolak-Salmon et al., 2006; Sperli et al., 2006; Satow et al., 2003; Fried et al., 1998; Arroyo et al., 1993; see also Lauterbach et al., 2013). A first possibility is that the lack of motor awareness is an effect of the afterdischarge that followed ES. We consider this interpretation very unlikely, given the rare correlation between afterdischarge and behavioral effects, and the characteristics (duration, latency and spread) of afterdischarge in this patient. A more convincing interpretation comes from the evidence that motor production without motor awareness has been occasionally reported after the stimulation of the voluntary motor system in the premotor cortex. Desmurget

and coworkers (2009) showed that the electrical stimulation of premotor sites elicit mouth and limb movements devoid of conscious intention and awareness, suggesting that motor awareness does not arise from proprioceptive feedback signals, but rather generates from the predicted consequences of a prior voluntary intention to act (see Desmurget and Sirigu 2009; see also Bolognini et al., 2016; Berti et al., 2005). Accordingly, they speculated that the lack of motor awareness is an expected consequence of the stimulation of the voluntary motor system.

The functional similarity between the effects of frontal operculum and premotor cortex stimulation, and their close anatomical localization, are in line with the hypothesis that the frontal operculum is part of a premotor network specialized in the voluntary control of emotional facial expressions (Jabbi and Keysers, 2008). The evidence that mirth is not clearly manifest after FO stimulation also supports this interpretation. It is however unlikely that the FO is sharply segregated from the emotional network. Anatomical studies identify FO as the main hub linking the emotional network and the premotor cortex (Jezzini et al., 2015; Gerbella et al., 2016; Morecraft et al., 2012), and recent data show that mirthful smiling induced by ventral striatal deep brain stimulation impacts on the frontal operculum BOLD signal (Gibson et al., 2016). Hence, a more reasonable conclusion is that the FO plays as interface between voluntary and emotional networks, gating limbic information to the motor system.

There has been a debate whether laughter and smile are left lateralized in the cortex. The majority of reports of laughter induced by ES of the frontal areas was left lateralized (Fried et al., 1998; Schmitt et al.., 2006; Krolak-Salmon et al., 2006; Fernandez-Baca Vaca et al., 2011). Reports of laughter elicited by ES of the basal temporal lobe showed a left lateralization in all cases (Arroyo et al., 1993; Satow et al., 2003; Yamao et al., 2015), and stimulated sites were typically located adjacent to the basal temporal language area. Taken together, these evidences leaded to the hypothesis that

laughter and language processing have a very close relationship, and that laughter can be elicited mainly in the dominant hemisphere and in close spatial proximity to language (Fernandez-Baca Vaca et al., 2011; Yamao et al., 2015). Nevertheless, laughter was also elicited from the right supplementary motor area in one patient (Schmitt et al., 2006) and, more recently, from the pregenual anterior cingulate area (pACC) in seven out of eleven stimulation sites (Caruana et al., 2015), questioning this hypothesis. The current report further challenge this view. Despite the left FO lies in close proximity with the Broca's area, half of our stimulation sites were located in the right hemisphere, albeit patients had left hemispheric dominance. Accordingly, despite the role of smiling and laughing in social communication is well established (Scott et al., 2014 Niedenthal et al., 2010; Provine, 2000; Frijda 1986), any attempt to link laughter and language processing should be cautious.

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References

Arroyo S, Lesser RP, Gordon B, Uematsu S, Hart J, Schwerdt P, et al. (1993). Mirth, laughter and gelastic seizures. Brain; 116(Pt 4): 757e780.

Avanzini P, Abdollahi RO, Sartori I, Caruana F, Pelliccia V, Casaceli G, Mai R, Lo Russo G, Rizzolatti G, Orban GA. (2016). Four-dimensional maps of the human somatosensory system. Proc Natl Acad Sci USA; 113(13):E1936-43.

Berti A, Bottini G, Gandola M, Pia L, Smania N, Stracciari A, Castiglioni I, Vallar G, Paulesu E. (2005). Shared cortical anatomy for motor awareness and motor control. Science; 309(5733):488-91.

Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, Jacques TS, Avanzini G, Barkovich AJ, Battaglia G, Becker A, Cepeda C, Cendes F, Colombo N, Crino P, Cross JH, Delalande O, Dubeau F, Duncan J, Guerrini R, Kahane P, Mathern G, Najm I, Ozkara C, Raybaud C, Represa A, Roper SN, Salamon N, Schulze-Bonhage A, Tassi L, Vezzani A, Spreafico R. (2011). The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia; 52(1):158-74.

Bolognini N., Zigiotto L., Izzadora Souza Carneiro M., Vallar G. (2016). "How Did I Make It?": Uncertainty about Own Motor Performance after Inhibition of the Premotor Cortex, Journal of Cognitive Neuroscience, 28(7):1052-61.

Borchers S, Himmelbach M, Logothetis N, Karnath HO (2011). Direct electrical stimulation of human cortex - the gold standard for mapping brain functions? Nat Rev Neurosci; 13(1):63-70.

Cardinale F, Cossu M, Castana L, Casaceli G, Schiariti MP, Miserocchi A, Fuschillo D, Moscato A, Caborni C, Arnulfo G, Lo Russo G. (2013). Stereoelectroencephalography: surgical methodology, safety, and stereotactic application accuracy in 500 procedures. Neurosurgery; 72(3):353-66.

Caruana F, Jezzini A, Sbriscia-Fioretti B, Rizzolatti G, Gallese V. (2011). Emotional and social behaviors elicited by electrical stimulation of the insula in the macaque monkey. CurrBiol.; 21(3):195-9.

Caruana F, Avanzini P, Gozzo F, Francione S, Cardinale F, Rizzolatti G. (2015). Mirth and laughter elicited by electrical stimulation of the human anterior cingulate cortex. Cortex; 71:323-31.

Cossu M, Cardinale F, Castana L, Citterio A, Francione S, Tassi L, Benabid AL, Lo Russo G. (2005). Stereoelectroencephalography in the presurgical evaluation of focal epilepsy: a retrospective analysis of 215 procedures. Neurosurgery; 57(4):706-18.

Dale AM, Fischl B, Sereno MI. (1999). Cortical surface-based analysis, I: segmentation and surface reconstruction. Neuroimage; 9(2):179-194.

Darwin C. (1872). The expressions of the emotions in men and animals. London: John Murray.

Desmurget M, Song Z, Mottolese C, Sirigu A.(2013). Re-establishing the merits of electrical brain stimulation. Trends Cogn Sci; 17(9):442-449.

Desmurget M, Reilly KT, Richard N, Szathmari A, Mottolese C, Sirigu A. (2009). Movement intention after parietal cortex stimulation in humans. Science; 324(5928):811-3.

Desmurget M, Sirigu A. (2009). A parietal-premotor network for movement intention and motor awareness. Trends CognSci; 13(10):411-9.

Engel J, Van Ness PC, Rasmussen TB, Ojemann LM. (1993). Outcome with respect to epileptic seizures. In: Engel J. Surgical Treatment of the Epilepsies. 2nd ed. New York: Raven Press.

Fernandez-Baca Vaca G, Lüders HO, Basha MM, Miller JP. (2011). Mirth and laughter elicited during brain stimulation. Epileptic Disorders; 13: 435-440.

Fried I, Wilson CL, MacDonald KA, Behnke EJ. (1998). Electric current stimulates laughter. Nature; 391(6668):650.

Frijda N. (1986). The emotions. Cambridge University Press.

Gerbella M, Borra E, Rozzi S, Luppino G. (2016). Connections of the macaque Granular Frontal Opercular (GrFO) area: a possible neural substrate for the contribution of limbic inputs for controlling hand and face/mouth actions. Brain Struct Funct; 221(1):59-78.

Gering DT, Nabavi A, Kikinis R, Grimson WE, Hata N, Everett P, Ferenc J, Wells WM (1999). An integrated visualization system for surgical planning and guidance using image fusion and interventional imaging. Proceedings from the International Conference on Medical Image Computing and Computer Assisted Intervention; 809-819.

Gibson W.S., Cho S., Abulseoud O.A., Gorny K.R, Felmlee J.P., Welker K.M., Klassen B.T., Min H.K., Lee K.H. (2016). The Impact of Mirth-Inducing Ventral Striatal Deep Brain Stimulation on Functional and Effective Connectivity, Cereb Cortex. 2016 Mar 21. [Epub ahead of print]

Graziano M (2006). The Organization of Behavioral Repertoire in Motor Cortex. Ann Rev Neurosci; 29:105-34.

Hennenlotter A, Schroeder U, Erhard P, Castrop F, Haslinger B, Stoecker D, Lange KW, Ceballos-Baumann AO. (2005). A common neural basis for receptive and expressive communication of pleasant facial affect. Neuroimage; 26(2):581-91.

Hopf HC, Müller-Forell W, Hopf NJ. (1992). Localization of emotional and volitional facial paresis. Neurology; 42(10):1918-23.

Jabbi M, Keysers C. (2008). Inferior Frontal Gyrus Activity Triggers Anterior Insula Response to Emotional Facial Expressions. Emotion; 8, 6:775-780.

Jezzini A, Caruana F, Stoianov I, Gallese V, Rizzolatti G. (2012). Functional organization of the insula and inner perisylvian regions. Proc Natl Acad Sci USA; 109(25):10077-82.

Jezzini A, Rozzi S, Borra E, Gallese V, Caruana F, Gerbella M.(2015). A shared neural network for emotional expression and perception: An anatomical study in the macaque monkey. Front. Behav. Neurosci; 9:243. doi: 10.3389/fnbeh.2015.00243.

Krolak-Salmon P, Hénaff MA, Vighetto A, Bauchet F, Bertrand O, Mauguière F, et al. (2006). Experiencing and detecting happiness in humans: the role of the supplementary motor area. Annals of Neurology; 59: 196-199.

Lauterbach EC, Cummings JL, Kuppuswamy PS. (2013). Toward a more precise, clinically--informed pathophysiology of pathological laughing and crying. Neurosci Biobehav Rev.; 37(8):1893-916.

Leslie KR, Johnson-Frey SH, Grafton ST. (2004). Functional imaging of face and hand imitation: towards a motor theory of empathy. Neuroimage; 21(2):601-7.

Livneh U, Resnik J, Shohat Y, Paz R. (2012). Self-monitoring of social facial expressions in the primate amygdala and cingulate cortex. Proc. Natl. Acad. Sci. U.S.A; 109: 18956–18961.

Morecraft RJ, Stilwell-Morecraft KS, Cipolloni PB, Ge J, McNeal DW, Pandya DN. (2012). Cytoarchitecture and cortical connections of the anterior cingulate and adjacent somatomotor fields in the rhesus monkey. Brain Research Bulletin, 87(4-5): 457-497.

Niedenthal PM, Mermillod M, Maringer M, Hess U. (2010). The Simulation of Smiles (SIMS) model: Embodied simulation and the meaning of facial expression. Behav Brain Sci; 33(6):417-33.

David O, Bastin J, Chabardès S, Minotti L, Kahane P (2010). Studying network mechanisms using intracranial stimulation in epileptic patients. Front. Syst. Neurosci.; 4:148. doi: 10.3389/fnsys.2010.00148

Provine RR. (2000). Laughter: a scientific investigation. New York: Viking.

Ramachandran VS (1998). The neurology and evolution of humor, laughter, and smiling: the false alarm theory. Med Hypotheses; 51(4):351-4.

Ruch W, Ekman P. (2001). The expressive pattern of laughter. In A.W. Kaszniak (Eds.) Emotion qualia, and consciousness. Word Scientific Publisher. Tokyo. 426-443.

Satow T, Usui K, Matsuhashi M, Yamamoto J, Begum T, Shibasaki H, et al. (2003). Mirth and laughter arising from human temporal cortex. Journal of Neurology, Neurosurgery, and Psychiatry; 74: 1004-1005.

Schmitt JJ, Janszky J, Woermann F, Tuxhorn I, Ebner A. (2006). Laughter and the mesial and lateral premotor cortex. Epilepsy Behaviour; 8: 773-775.

Scott SK, Lavan N, Chen S, McGettigan C. (2014). The social life of laughter. Trends Cogn Sci; 18(12):618-20.

Selimbeyoglu A, Parvizi J. (2010). Electrical stimulation of the human brain: perceptual and behavioral phenomena reported in the old and new literature. Front Hum Neurosci.;4:46. doi: 10.3389/fnhum.2010.00046.

Smith WK. (1945). The functional significance of the rostral cingulate cortex as revealed by its responses to electrical excitation. J Neurophisiol.; 8: 241–255.

Sperli F, Spinelli L, Pollo C, Seeck M. (2006). Contralateral smile and laughter, but no mirth, induced by electrical stimulation of the cingulate cortex. Epilepsia; 47: 440-443.

van der Gaag C, Minderaa R, Keysers C. (2007). Facial expressions: What the mirror neuron system can and cannot tell us. Social Neuroscience; 2: 179–222.

Wattendorf E, Westermann B, Fiedler K, Kaza E, Lotze M, Celio M. (2013). Exploration of the neural correlates of ticklish laughter by functional magnetic resonance imaging. Cereb. Cortex; 23: 1280–1289.

West RA, Larson CR (1995). Neurons of the anterior mesial cortex related to faciovocal activity in the awake monkey. J Neurophysiol.; 74: 1856–1869.

Wild B, Rodden FA, Grodd W, Ruch W. (2003). Neural correlates of laughter and humour. Brain; 126: 2121-2138.

Wortzel HS, Oster TJ, Anderson CA, Arciniegas DB. (2008). Pathological laughing and crying. Epidemiology, pathophysiology and treatment. CNS Drugs; 22: 531–545.

Yamao Y, Matsumoto R, Kunieda T, Shibata S, Shimotake A, Kikuchi T, Satow T, Mikuni N, Fukuyama H, Ikeda A, Miyamoto S. (2015) Neural correlates of mirth and laughter: A direct electrical cortical stimulation study. Cortex; 66:134-40.

Table 1. Summary of ES studies in which smiling or laughter were induced by electrical cortical stimulation

Author	Patients	Region	Hem.	Emotion
Arroyo et al., 1993	2	Basal inferior temporal	Left	Mirth
Satow et al., 2003	1	Basal inferior temporal	Left	Mirth
Yamao et al., 2015	1	Basal inferior temporal	Left	Mirth
Sperli et al., 2006	1	Rostral ACC	Right	No mirth
Fried et al., 1998	1	SFG	Left	Mirth
Schmitt et al., 2006	1	SFG	Left	NA
Schmitt et al., 2006	1	SMA	Right	No Mirth
Krolak-Salmon et al., 2006	1	SMA	Left	Mirth
Fernandez-Baca Vaca et al., 2011	1	IFG	Left	Mirth
Caruana et al., 2015	5	Rostral ACC	Left=3 Right=2	Mirth
Caruana et al., 2015	5	Rostral ACC	Left=1 Right=4	No Mirth
Current study	4	Frontal Operculum	Left=2 Right=2	No Mirth/Mirth

Figure 1. Contacts whose stimulation elicits smile are shown for the four patients. A yellow cross indicates the external contact employed for the bipolar stimulation. Contact localization is obtained by the coregistration of a pre-implantation anatomical MR with a post-implantation cone-beam computed tomography (CBCT).

Figure 2. Left panel indicates the entry/target points of each electrode on a 3D reconstruction of the brain of Patient 1. Target points of electrodes sampling the deep structures (insula and hippocampus) are not visible. Right panel shows the reactivity of SEEG recordings from contacts lying in the most salient regions during HF stimulation of both S'4-5 and Z'3-4. During stimulation, low-voltage fast activity is visible in the inner and lateral aspects of the frontal operculum, the posterior insula, and, to a weaker extent, in the precentral cingulate and parietal

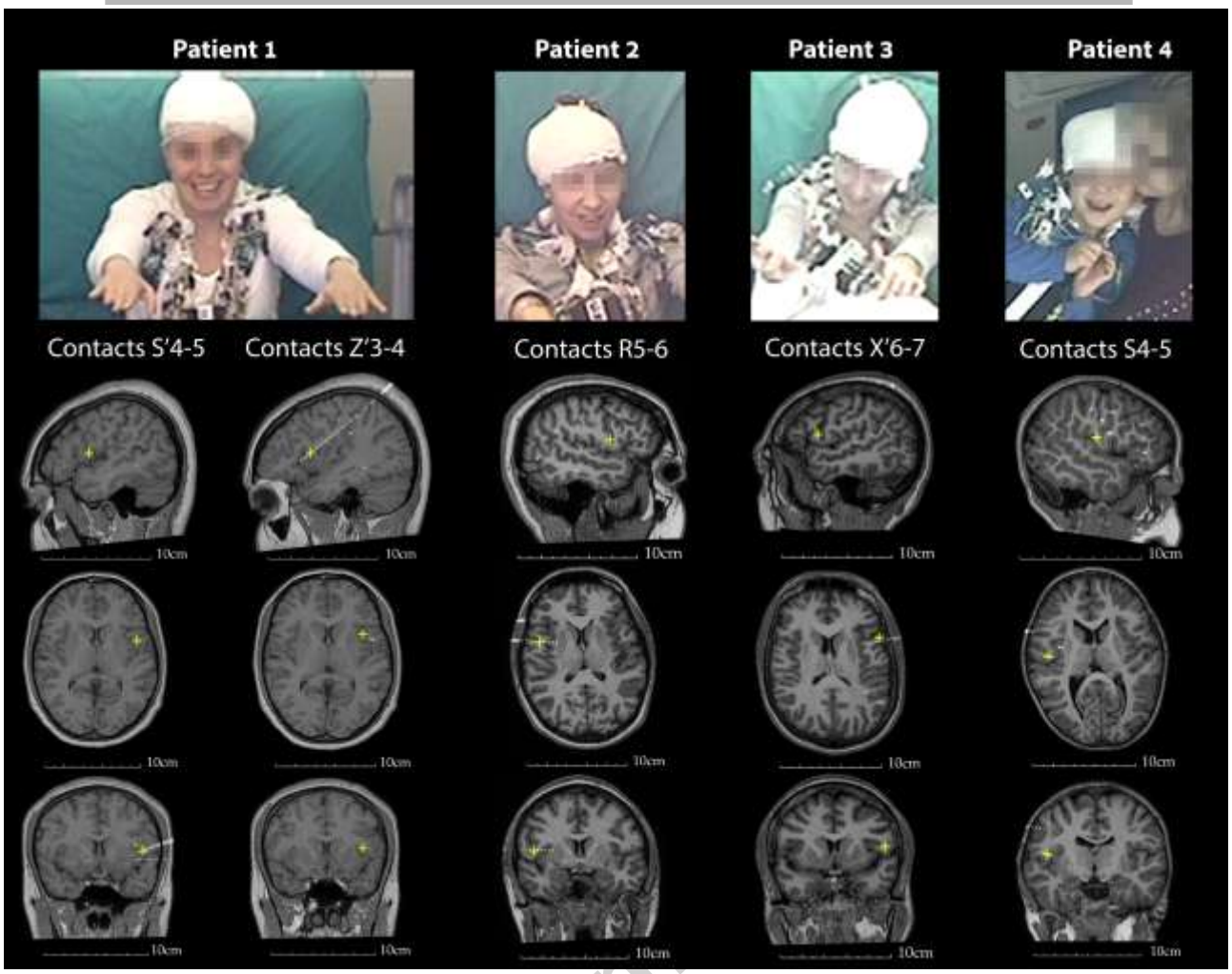
operculum (following S'4-5 HF), but no effects have been observed in the central and parietal cingulate cortex, pre-SMA, premotor cortex and inferior parietal lobule. An afterdischarge is visible in the insular cortex, the frontal operculum and, to a weaker extent, in the precentral cingulate cortex. Abbreviations: pre-SMA=pre-supplementary motor area; PMd=dorsal premotor cortex; PCC= posterior cingulate cortex; MCC= midcingulate cortex; IPL=inferior parietal lobule; PMv=ventral premotor cortex; LG=long gyri; PO=parietal operculum; STG=superior temporal gyrus; Hip=hippocampus; MTG=middle temporal gyrus.

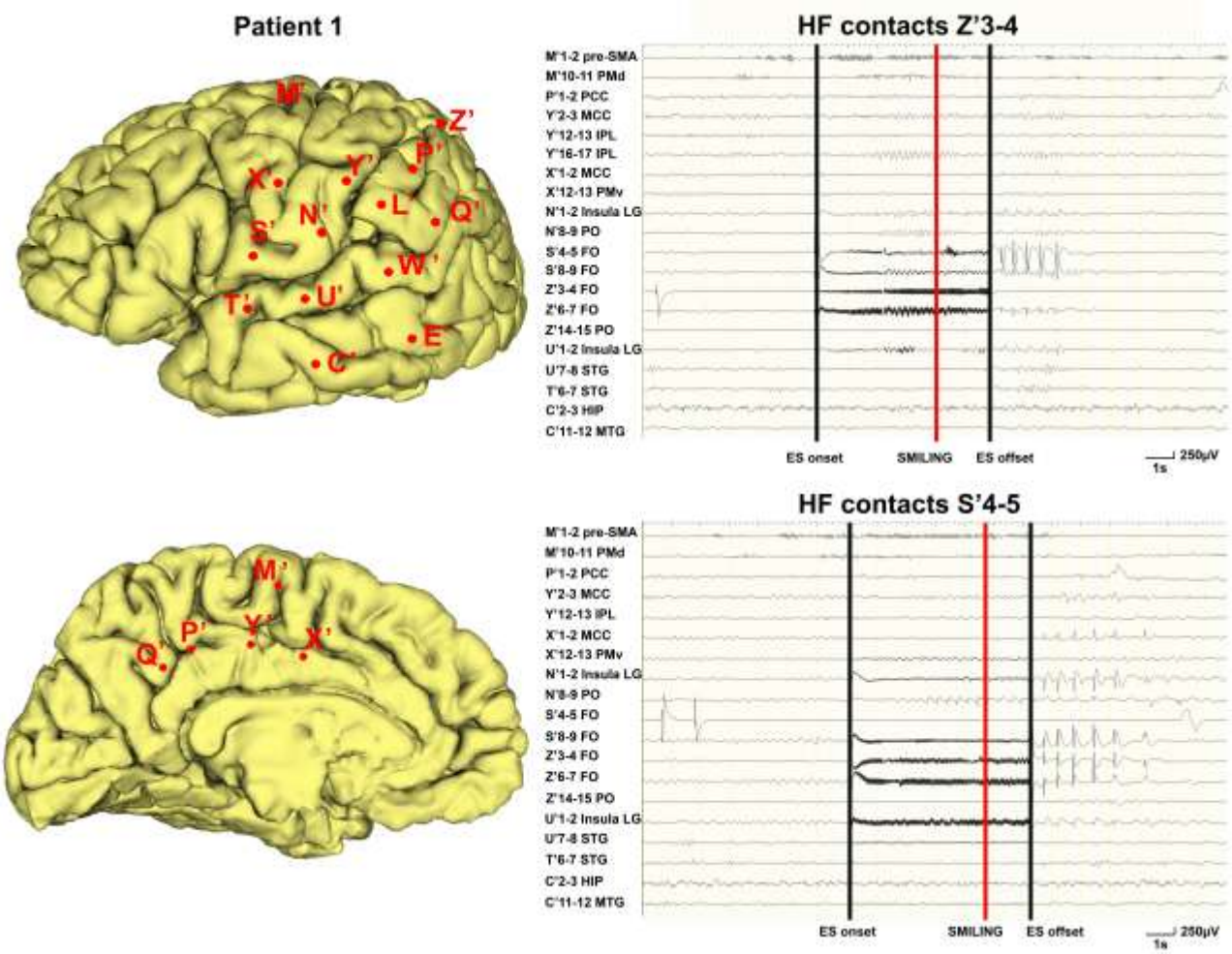
Figure 3. Left panel indicates the entry points of each electrode on a 3D reconstruction of the brain of Patients 2-4. Right panel shows the reactivity of SEEG recordings from contacts lying in the most salient regions during HF stimulation. All captions as in Figure 2. Additional abbreviations: SFG=superior frontal gyrus; MFG=middle frontal gyrus; IFG=inferior frontal gyrus; OF=orbitofrontal; IPL=inferior parietal lobule; SMG=supramarginal gyrus; AG=angular gyrus; MTG=middle temporal gyrus; STS=superior temporal sulcus; PHIP=parahippocampus; TO=temporo-occipital junction; TP=temporal pole.

Video caption: "HF electrical stimulation of contacts S'4-5 and Z'3-4, lying in the left FO, in Patient 1. The red dot indicates the onset/offset of the stimulation."

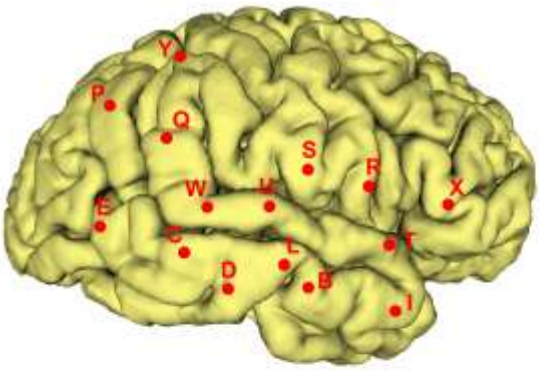
Highlights

- ES applied to the FO produced laughter or smile in four patients
- In one patient the production of smiling was accompanied by the lack of motor awareness
- ES effects were elicited from both hemispheres
- FO plays as interface between voluntary and emotional networks

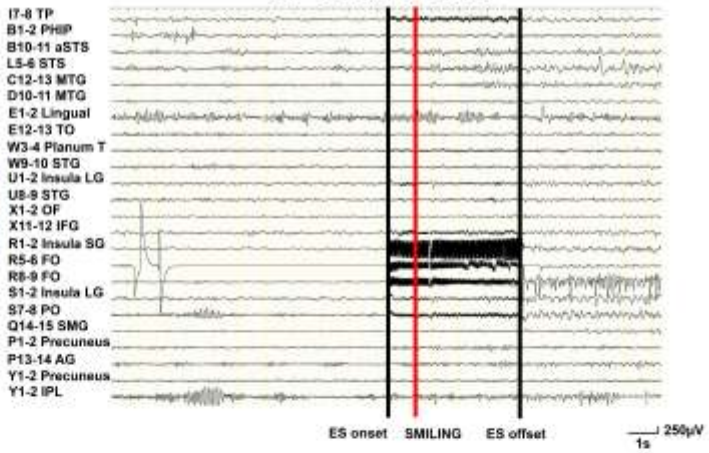




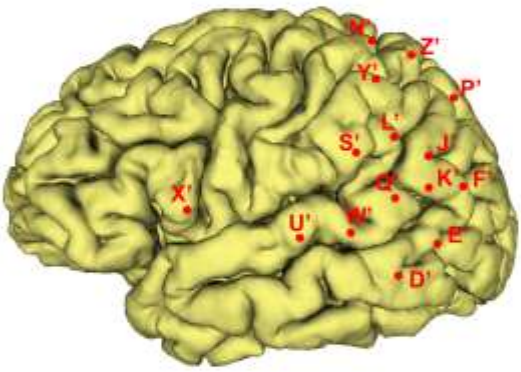
Patient 2



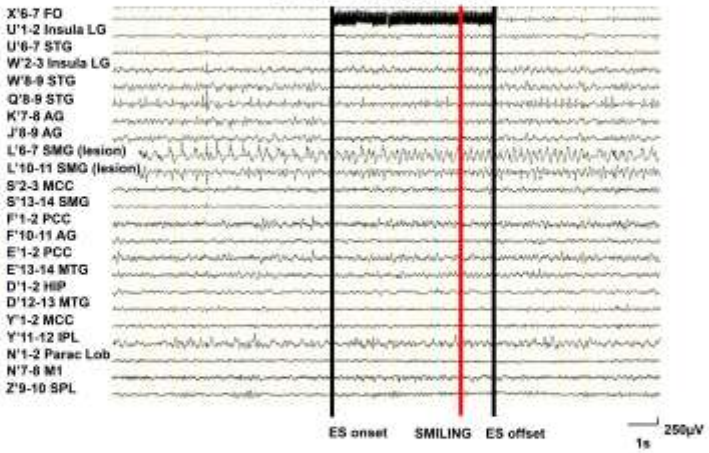
HF contacts R5-6



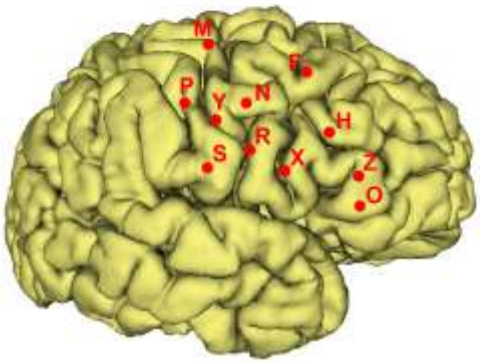
Patient 3



HF contacts X'6-7



Patient 4



HF contacts S4-5