Clinical Neurophysiology 128 (2017) 780–791

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

How can we explain the frontal presentation of insular lobe epilepsy? The impact of non-linear analysis of insular seizures

Koichi Hagiwara [a,b,c,e,*], Julien Jung [b,c,f], Romain Bouet [b,f], Chifaou Abdallah [c], Marc Guénot [b,d,e], Luis Garcia-Larrea [e,g], François Mauguière [b,c,e], Sylvain Rheims [b,c,e], Jean Isnard [b,c,e]

[a] Department of Clinical Neurophysiology, Neurological Institute, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan
[b] Université Lyon 1, Lyon F-69000, France
[c] Hospices Civils de Lyon, Neurological Hospital, Department of Functional Neurology and Epileptology, Lyon F-69003, France
[d] Hospices Civils de Lyon, Neurological Hospital, Department of Functional Neurosurgery, Lyon F-69003, France
[e] Central Integration of Pain (NeuroPain) Lab—Lyon Neuroscience Research Center, INSERM U1028, CNRS, UMR5292, Université Claude Bernard, Bron F-69677, France
[f] Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR5292, Brain Dynamics and Cognition Team, Lyon F-69000, France
[g] Centre D'évaluation et de Traitement de la Douleur, Hôpital Neurologique, Lyon F-69000, France

A R T I C L E I N F O

Article history:
Accepted 26 January 2017
Available online 13 February 2017

Keywords:
Insular lobe seizure
Mesial frontal propagation
Stereoelectroencephalography (SEEG)
Non-linear regression analysis
Directed functional coupling

H I G H L I G H T S

- Non-linear regression analysis was applied to insular seizures with/without frontal presentation.
- Seizures propagation to the mesial frontal/cingulate regions is common in insular lobe epilepsy.
- Frontal presentation is mediated by strong functional coupling to the mesial frontal regions.

A B S T R A C T

Objective: For a decade it has been known that the insular lobe epilepsy can mimic frontal lobe epilepsy. We aimed to clarify the pattern of functional coupling occurring during the frontal presentation.
Methods: We analyzed five insular lobe epilepsy patients. Frontal semiology was predominant for three of them, whereas insular semiology was predominant for the two others. We applied the non-linear regression analysis to stereoelectroencephalography-recorded seizures. A directed functional coupling index was calculated during clonic discharge periods that were accompanied either with frontal or insular semiology.
Results: We found significant functional coupling between the insula and mesial frontal/cingulate regions, with the former being a leader region for seizures propagation. Extra-insular regions showed significantly less or even no coupling with the mesial hemispheric regions. The three patients with frontal semiology showed strong couplings with the mesial frontal as well as cingulate regions, including the medial orbitofrontal cortex, pre-SMA/SMA, and the anterior to posterior cingulate. The two patients with the insular semiology only showed couplings between the insula and cingulate regions.
Conclusions: The frontal semiology was expressed by strong functional couplings between the insula and mesial frontal regions.
Significance: The insular origin of seizure should be considered in cryptogenic mesial frontal epilepsies.

1. Introduction

Insular lobe epilepsy is one of the least understood focal epilepsies. This is attributable to the difficulty to explore insular epileptic foci and, consequently, to the slow accumulation of clinical experience. Stereo-electroencephalography (SEEG) has played a critical role for identifying insular lobe seizures (Isnard et al., 2000, 2004; Ryvlin et al., 2006), allowing definitive spatiotemporal

* Corresponding author at: Department of Clinical Neurophysiology, Neurological Institute, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Fax: +81 92 642 5545.
E-mail address: hagiwara-kyu@umin.ac.jp (K. Hagiwara).

http://dx.doi.org/10.1016/j.clinph.2017.01.022

segregation of insular seizures with respect to those originating from other brain regions. To date, clinico-electrophysiological features of the insular lobe epilepsy have not been fully established. Previous reports consist of classic case description and interpretation of clinical data set (Dobesberger et al., 2008; Isnard et al., 2000, 2004; Montavont et al., 2015; Nguyen et al., 2009; Ryvlin et al., 2006; von Lehe et al., 2009). Seizure propagation and related semiologies of the insular lobe epilepsy have not been linked by objective indices.

In principle, identification of seizure focus largely relies on interpretation of clinical presentation, which proved useful in epilepsies of frontal (Bonini et al., 2014), temporal (Dupont et al., 2015; Marks and Laxer, 1998), parietal (Francione et al., 2015), and occipital (Appel et al., 2015) lobe origins. Recently, however, exploration with SEEG enabled identification of the insular origin of seizures in patients with various extra-insular semiologies, mimicking temporal (Isnard et al., 2004; Nguyen et al., 2009; Ostrowsky et al., 2000), frontal (Dobesberger et al., 2008; Nguyen et al., 2009; Ryvlin et al., 2006), and parietal (Montavont et al., 2015; Nguyen et al., 2009) lobe epilepsies. These evidences suggest a potential risk for diagnostic error when relying on clinical presentation especially in MRI-negative focal epilepsies.

However, understanding the association between an insular-origin seizure and a clinical presentation of frontal epilepsy is not straightforward. The involvement of mesial frontal cortex during propagation of insular seizures has been suggested by several studies based on electro-clinical analysis of intra-cerebral recordings (Dobesberger et al., 2008; Dylgjeri et al., 2014; Nguyen et al., 2009; Proserpio et al., 2011; Ryvlin et al., 2006). However the recording of cortico-cortical evoked potentials (CCEPs) failed to demonstrate direct functional connections between the insula and mesial frontal cortex (Almashaikhi et al., 2014); furthermore the strength and directionality of functional coupling between these two regions have not been quantified during insular seizures. In the current study, we analyzed ictal SEEG in five patients with insular onset seizures presenting with elementary motor/hypermotor seizures in three, and with an insular semiology in two. We aimed at assessing the functional coupling pattern during seizures propagation associated with a frontal presentation and at understanding the reason for the semiological difference between these two types of seizures.

2. Methods

2.1. Patients

Five insular lobe epilepsy patients were analyzed in this study (Table 1). These patients met the following criteria: (1) their ictal onset zones were localized to the insula by clinical interpretation of SEEG based on low-voltage fast discharge (LVFD); (2) Regions explored by SEEG included the insula as well as the mesial frontal/cingulate regions; (3) Radiofrequency-thermocoagulation (Catenoix et al., 2008; Guénot et al., 2004) targeted at the insula achieved more than 50% reduction of seizure frequency. The five patients represented 21.7% of twenty-three patients diagnosed with insular lobe epilepsy in our department over the 2000–2015 period, of whom six patients presented seizures with a predominant frontal lobe semiology. The first three patients (the patients 1–3) represented each different type of frontal semiology in this population.

Patient 1 was a 17-year-old male with age of epilepsy onset at 9. His ictal semiology consisted of initial right-sided paresthesia sparing the face and trunk, and tonic contraction in the right leg and later also in the right arm, accompanied by elevation and abduction of the right arm. The seizures occurred several times a day and mostly during sleep. Scalp EEG showed bilateral diffuse supra-sylvian theta activity at the end of seizures. While there was no abnormality on MRI, FDG-PET demonstrated hypometabolism in the peri-sylvian region, and inter-ictal MEG also pointed to a peri-sylvian origin of seizure. Ictal SEEG disclosed LVFD in the middle and posterior short gyri (MSG and PSG) of the left insula. He remained free of seizure for 9 months after thermo-coagulation.

Patient 2 was an 18-year-old male with epilepsy onset at 5. He presented axial-dominant, almost symmetric tonic contraction preceded by an auditory hallucination (a very brief mechanical sound, as "sound of a hammer stroke" above his head) several times a day. His scalp EEG during seizures revealed a diffuse depression followed by bilateral fronto-central rhythmic theta activity, which was slightly lateralized to the right. His MRI did not show any abnormality. On the contrary, ictal SPECT demonstrated hyperperfusion in the right posterior insula. Ictal SEEG revealed LVFD in the anterior and posterior long gyri (ALG and PLG) of the right insula. Direct cortical stimulation of the PLG reproduced the full sequence of his seizures. Thermo-coagulation resulted in a 1.5-month seizure freedom and in an 80% reduction in seizures frequency afterward.

Patient 3 was a 24-year-old female with epilepsy onset at 5. Fear and hyperkinesia were the prominent features of her seizures. Her hyperkinesia was initially expressed as proximal-stereotypy (rocking) of the pelvis. Then she became progressively agitated with frightened facial and verbal expressions, and eventually she ambulated. Ictal scalp EEG showed a right frontal theta activity after the onset of hyperkinesia. Brain MRI was negative, and MEG was also not informative because of lack of inter-ictal spike. However, FDG-PET showed right insular hypometabolism. Ictal SEEG demonstrated LVFD in the anterior short gyrus (ASG) of the right insula. Thermo-coagulation resulted in one-month seizure freedom. Her seizure reappeared gradually but the frequency was decreased from several a day to a few per month.

Patient 4 was a 49-year-old female who started having seizures at age 39. She reported during her seizures a sensation of strangulation, a metallic taste in the mouth, and a cold sensation in both thighs. Her seizure occurred multiple times a day. Although ictal scalp EEG did not disclose any abnormalities at seizure onset (only right or left temporal slow activity was suspected at the end of seizures), her MRI showed a slight cortical thickening with T2-enhanced signal in the right insula. FDG-PET as well as ictal SPECT also indicated a focal region of functional abnormality in the right infero-posterior insula. Her ictal SEEG revealed LVFD in the right insula, most predominantly in the PLG and insular central sulcus. Only the cold sensation was reported 2–3 times a week after thermo-coagulation.

Patient 5 was a 22-year-old male who started having painful seizures of the whole left side of the body, sparing the head, 8 months before admission. Although his ictal scalp EEG did not indicate origin of seizures, his brain MRI suggested a cortical dysplasia in the posterior insula. His Ictal SEEG demonstrated LVFD in the ALG of the right insula. Stimulation using the insular contact reproduced his painful sensation. Thermo-coagulation led to a 2-year seizure freedom. The detailed electro-clinical data in this patient have been already published (Isnard et al., 2011).

2.2. SEEG data acquisition

The intracerebral recordings were performed with the orthogonally-oriented implantation method in Talairach space. Each single electrode placement was guided by pre-surgical video-scalp EEG and other non-invasive investigations. Clinical surveillance and interpretation of SEEG traces were conducted on a video-EEG monitoring system (Micromed, Italy). All signals were sampled at a frequency of 256 Hz and were analyzed in a bipolar