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Fluency tasks generate *beta-gamma* activity in language-related cortical areas of patients during stereo-EEG monitoring

Chiara Pastori [a], Stefano Francione [b], Federica Pelle [b], Marco de Curtis [a], Vadym Gnatkovsky [a,*]

[a] Unit of Epileptology and Experimental Neurophysiology, Fondazione Istituto Neurologico Carlo Besta, Milano, Italy
[b] Claudio Munari Epilepsy Surgery Center, Ospedale Niguarda, Milano, Italy

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ABSTRACT

A quantitative method was developed to map cortical areas responsive to cognitive tasks during intracerebral stereo-EEG recording sessions in drug-resistant patients candidate for epilepsy surgery. Frequency power changes were evaluated with a computer-assisted analysis in 7 patients during phonemic fluency tasks. All patients were right-handed and were explored with depth electrodes in the dominant frontal lobe. We demonstrate that fluency tasks enhance *beta-gamma* frequencies and reduce background activities in language network regions of the dominant hemisphere. Non-reproducible changes were observed in other explored brain areas during cognitive tests execution.

1. Introduction

Patients with drug-resistant focal epilepsies are potential candidates for epilepsy surgery designed to obtain seizure relief with minimal side effects. Non-invasive evaluation based on clinical, neuroimaging, scalp EEG and neuropsychological data are utilized to select candidates for surgery and to predict post-surgical prognosis in terms of epileptological and cognitive outcome. In a subpopulation of patients with extra-temporal (Hosking, 2003; Janszky, Jokeit, Schulz, Hoppe, & Ebner, 2000; Jeha et al., 2007; Jehi, O'Dwyer, Najm, Alexopoulos, & Bingaman, 2009) or temporal-plus (Barba, Barbati, Minotti, Hoffmann, & Kahane, 2007) focal epilepsies, intracranial EEG recordings are needed to accurately identify the epileptogenic zone (EZ). In these cases, the identification of eloquent cortical areas and their relationship with the EZ is crucial to minimize post-surgical cognitive deficits (Engel et al., 2003). Eloquent areas are usually identified with either functional MRI or intracranial electrical stimulations during EEG recordings (Cossu et al., 2005; Kahane et al., 1993; Kojima et al., 2012; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). Cognitive functions and networks can be also investigated by electrophysiological techniques that study averaged stereotyped EEG response to a repeated stimulus (event-related potentials), or by their magnetic counterparts (event-related field) during magnetoencephalography (Frye, Rezaie, & Papanicolaou, 2009).

We developed a quantitative method to map cortical areas responsive to the performance of cognitive tasks during stereo-EEG (SEEG) recording sessions. We analysed frequency modifications in SEEG traces during the whole cognitive task running time with respect to the baseline conditions. To validate our method we utilized phonemic fluency task (phoFT) that is considered to be processed by the dominant frontal lobe (Alvarez & Emory, 2006; Robinson, Shallice, Bozzali, & Cipolotti, 2012). Preliminary data were presented in the abstract form (Pastori et al., 2012).

2. Materials and methods

Seven right-handed, Italian-native patients that suffered from drug-resistant focal epilepsy were selected at *Claudio Munari* Epilepsy Surgery Center (clinical data in Table 1). All patients underwent invasive SEEG exploration in the dominant frontal and fronto-temporal lobes. SEEG recordings were performed for strictly diagnostic purposes with intracerebral electrodes (DIXI Medical, France: 5–18 contacts each, length 2 mm, 1.5 mm apart, diameter 0.8 mm) implanted following the stereotactic method (Cossu et al., 2005; Munari et al., 1994; Talairach & Szikla, 1980; Talairach et al., 1974). SEEG signals from 13 to 17 implanted electrodes with a maximum number of 192 recording channels were sampled at 1 kHz with a Neurofax EEG-1100 system (Nihon Koh-

* Corresponding author at: Unit of Epileptology and Experimental Neurophysiology, Fondazione Istituto Neurologico Carlo Besta, via Celoria 11, 20133 Milan, Italy.

E-mail address: gnatkovsky@istituto-besta.it (V. Gnatkovsky).

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Table 1
Clinical and imaging data.

Patient	Age at 1st seizure (y)	Age at SEEG (y)	Seizure rate	Years of active epilepsy	Pre-surgical RM
1	6	42	Weekly	36	Negative
2	22	34	Several/day	12	Post traumatic anterior frontal lesion
3	4	25	Several/day	21	Negative
4	14	37	Several/day	23	Suspected frontal dysplasia
5	3	27	Monthly	24	Negative
6	16	26	Several/week	10	Post surgical cavity (cavernoma)
7	4	18	Several/day	14	Negative

den, Tokyo, Japan), with HPF at 0.016 Hz and LPF at 300 Hz. Data were digitized with 16-bit resolution. Weighted average of two contacts recorded from the white matter was used as the reference signal.

The cortical position (referred Brodmann areas; Brodmann, 1912; Talairach & Tournoux, 1988) and trajectory of the implanted electrodes was post-operatively determined by CT (post-implantation) image fusion on pre-implantation magnetic resonance scans (1.5-tesla ACS-NT unit; Philips Medical Systems, Brest, The Netherland) customized according to electro-clinical information (Cardinale et al., 2013; Colombo et al., 2003). Neuropsychological testing was performed during SEEG recordings. After the identification of EZ, 6 out of 7 patients were operated with a surgical excision and one patient was submitted to stereotactic thermo-coagulation procedure (Guénot et al., 2004). EZ and seizure outcome follow up are illustrated in Table 2. All patients have been operated-on/coagulated, independently from the results of the present study, on the basis of our customary protocol. Notably, functional aspects have been evaluated by means of standard electrical stimulation protocols (Cossu et al., 2005)

Phonemic fluency task (phoFT) was utilized to analyse language frontal networks (Costafreda et al., 2006; Price, 2010) during SEEG recording. Patients had to list as many words as possible from three phonemic categories (words starting with letters F, L and P for adults). Each fluency test performed according to defined protocols (Bottini et al., 1996; Scarpa et al., 2002) lasted 60 s. Retrospective analysis was approved by the Ethical Committee of Niguarda Hospital (ID 939-2.12.2013). By utilizing a custom-developed software (Elpho-SEEG www.elpho.it; Gnatkovsky et al., 2011), we compared frequencies content of monopolar SEEG pattern during phoFT against two control conditions: quiet waking (QW, i.e. patient awake in bed, minimal movements of arms, free movements of eyes, no verbalization) and during a test designed to evaluate non-frontal visual-spatial skills (Benton Judgment Line Orientation Test – BJLOT; Benton, Varney, & Hamsher, 1992).

We calculated averaged frequency power over 3-min recordings obtained in each SEEG channel during phoFT, QW and BJLOT. Fast Fourier transform (FFT) was calculated in these three different conditions for each channel on one-second sliding windows, with 0.2 s consecutive window overlapped (Fig. 1A). Color intensity plots was calculated to evaluate each frequency band (Fig. 1A). Power spectrum averages were used to attenuate the influence of transitory interictal events. Frequency power integrals (vertical graphs on the right of each panel in Fig. 1B) during phoFT (left panels in Fig. 1B) and control conditions (QW and BJLOT; middle panel in Fig. 1B) were calculated and normalized (20–40 Hz frequency analysis illustrated in Fig. 1B). The difference between the frequency power integrals during QW (or BJLOT) and phoFT were calculated (right-most panel in Fig. 1B). Negative and positive values represented decreases and increases in frequency power integral during phoFT in comparison to control states. For statistical analysis Mann-Whitney test were used.

3. Results

Modifications of SEEG signals induced by performance of phoFT with respect to control conditions (QW and BJLOT) were analysed in 7 patients during pre-surgical evaluation. We analysed frequency changes in the range between 1 and 250 Hz for all contacts of each patient. To identify specific frequency changes, we analysed spectral pattern of the cortical activation during phoFT in respect to QW recorded in Broca's area (primary language region, BA 44 in Pt 1; red spot in Fig. 2A and upper traces in B). Frequency pattern changes in this area were compared with those observed in a region not involved in language network (anterior middle frontal gyrus, BA 10 in Pt 1; blue spot in Fig. 2A). The most specific pattern of frequency changes associated with phoFT was an increase in the range of *beta-gamma* (20–40 Hz) activity in language areas, as illustrated for Patient 1 by the shaded area in the upper right panel of Fig. 2B and by the red spot in Fig. 2C, corresponding to BA 44. No specific changes were observed in areas not involved in language networks (BA 10, blue spot and other gray dots in Fig. 2C) during phoFT task in comparison to both the resting state (QW) and BJLOT. A decrease in the frequencies slower than 20 Hz was more generally distributed among all recorded contacts (Fig. 2B and C). No specific increases of frequencies were observed in the range between 40 and 250 Hz (see spectrogram Fig. 2B, left panels). SEEG signals recorded in Broca areas (red dot) showed a significant increase of frequencies 20–40 Hz in comparison to both control condition patterns (QW and BJLOT in Fig. 2C).

Table 2
Stereo-EEG exploration, EZ location and epileptological follow up.

Pt.	Exploration topography (electrodes)	Location of EZ	Seizure outcome (Engel, Van Ness, Rasmussen, & Ojemann, 1993)		
			6 m	1 y	2 y
1	L fronto-temporal (15 el)	L fronto-temporal	IIa	IIa	IIa
2	L fronto-temporal (14 el) R frontal (3 el)	L frontal (mesial + lateral)	Ia	Id	Id
3	L fronto-temporal (13 el)	L temporal	Ia	Ia	Id
4	L frontal (14 el)	L frontal dorsal	Ia	Ia	Ia
5	L fronto-temporal (15el)	L temporal	Ia	Ia	Id
6	L fronto-centro-temporal (13 el)	L fronto-temporal	Ia	IIIa	IV
7	L fronto-centro-parietal (9 el) + R centro-parietal (4 el)	R frontal anterior	Ia	Ia	Ia

Abbreviations: L = left; R = right.