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FACULTE DE MEDECINE DE GRENOBLE

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N°

COMPARISON OF INDUCED GAMMA BAND RESPONSES TO ELECTRO-CORTICAL STIMULATION AND FUNCTIONAL MRI DURING A LANGUAGE TASK: ARE THEY REDUNDANT OR COMPLEMENTARY TO ASSESS COGNITIVE POST-OPERATIVE OUTCOME IN EPILEPSY SURGERY ?

Apport des activités cérébrales gamma comme méthode de cartographie fonctionnelle et marqueur du devenir cognitif dans le bilan pré-chirurgie de l'épilepsie.

Comparaison avec les stimulations électriques cérébrales et l'IRM fonctionnelle lors d'une tâche de langage.

THESE PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE  
DIPLOME D'ETAT

**CUISENIER Pauline**

*[Données à caractère personnel]*

THESE SOUTENUE PUBLIQUEMENT A LA FACULTE DE MEDECINE DE GRENOBLE\*

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# Abstract

**Rationale:** Like any brain surgery, epilepsy surgery can have various negative effects on cognition and behaviour. The best way to anticipate post-operative deficits is to test, before surgery, the 'functional integrity' of the brain. Different methods can be used for that purpose, including neuropsychological testing, functional neuroimaging (fMRI), and Electro-Cortical Stimulation (ECS). None of these approaches, however, has been proved accurate enough to reliably anticipate the risks of postoperative cognitive deficits.

**Study aims:** This last decade, intracranially recorded task-related Gamma Band Responses (GBR) has emerged as a putative biomarker of various cognitive processes. The present study aimed at comparing the GBR method with the classical fMRI and ECS procedures for localizing language functions, and at evaluating whether the removal of brain tissue exhibiting GBR might have significant consequences on language processing.

**Methods:** Fourteen epileptic patients who underwent stereotactic intracerebral EEG (SEEG) recordings and who were subsequently operated on were included in the study. SEEG signals were recorded while the patients performed a language task involving two different language processes: semantic and phonologic. Language-related GBR (50–150 Hz) were analysed at every recording site, and compared with the results of ECS-elicited clinical responses. These findings were also compared with the results of fMRI language assessment in a sub-group of 6 patients. Post-operative language outcome was evaluated in patients in whom at least one GBR+ site was resected versus those in whom no GBR+ site was resected.

**Results:** GBR predicted ECS language interference with a high specificity (92.4%) and negative predictive value (NPV, 95.5%), but with a low sensitivity (11.7%) and positive predictive value (PPV, 7.4%). Similar findings, although a little bit weaker, were found when comparing GBR and fMRI (specificity: 89.2%, NPV: 84.7%, sensitivity: 8.4%, PPV: 12.2%). Resections that included GBR+ sites, as compared with resections that spared GBR+ sites, did not show any significant language decline both in semantic and phonological conditions. Only a few patients, however, had a resection that included GBR+ sites (n=2 for semantic condition, n=2 for phonological condition).

**Conclusion:** GBR mapping appears as a useful tool for pre-surgical evaluation of language functions, complimentary to ECS, that might be used to build a preliminary functional map to reduce the duration of ECS sessions. Although preliminary, these findings emphasise the benefit of a multimodal screening for language features before epilepsy surgery.

**Keywords:** epilepsy surgery; stereo-electroencephalography; gamma band response; brain functional mapping; language

## 1. Introduction

Resective surgery is the only treatment able to suppress drug-resistant seizures in epileptic patients. This therapeutic surgery is possible only if the Epileptogenic Zone (EZ) is focal, clearly identified, and can be safely removed (Kahane & Landré, 2008 for a review of EZ definition). The identification of the EZ, and the evaluation of its functional integrity is a difficult process which requires intracranial EEG (iEEG) recordings in 25-50% of the cases. However, even when using such iEEG information, epilepsy surgery still fails in a substantial ratio of patient (Téllez-Zenteno, 2010), and post-operative cognitive/psychiatric deficits still exist in a significant number of the cases (Baxendale et al., 2006 ; Helmstaedter, 2004), especially for language processes (Sherman et al., 2011).

Language is a high-level and non-monolithic cognitive function supported by an extended network of brain regions and by several complex dynamic processes (Price, 2012) such as lexico-semantic, phonological and motor commands. Brain structures which support such processes are relatively well described in literature. For instance, the semantic network involves mainly the pars orbitalis and triangularis of the inferior frontal gyrus (Bookheimer, 2002) and the left mid and inferior temporal gyri (Binder et al., 2009), while the phonological network is mostly supported by the pars opercularis of the left inferior frontal gyrus (Vigneau et al., 2006) and the left posterior and superior temporal regions (Démonet et al., 1992). Nevertheless, an important inter-subjects variability exists on brain language representation and this variability is more important in epileptic patients (Baciu & Perrone-Bertolotti, 2015 for a review). Hence, pre-operative language mapping should delineate eloquent areas at the individual level.

Currently, many tools and methods are available for pre-surgical evaluation of cognitive and language processes, of which none has been proved accurate enough to reliably anticipate the risks of postoperative deficits. These exams include neuropsychological testing, functional neuroimaging, chemical inactivation (Wada test), and Electro-Cortical Stimulation (ECS).

ECS, as performed during iEEG, is classically considered as the ‘gold standard’ method for the identification of the cortical regions that have to be spared during surgery (David et al., 2010; Penfield & Jasper, 1954 ; Lesser et al., 1994 ;Ojemann et al., 1989). It is an invasive method, the clinical validity of which to assess post-operative outcome has been reported (Haglund et al., 1994; Hermann & Wyler, 1988). However, ECS mapping has several limitations: (i) ECS has a limited spatial sampling, since it can be applied only at the sites where the intracranial electrodes are implanted; (ii) ECS is a time-consuming method, that may occasionally lead to seizures (Lesser et al., 1984) and therefore limitates the repetition of ECS and subsequently reduces inter-subject reproducibility; (iii) ECS does not always trigger objective clinical signs, especially in associative cortices such as language areas; (iv) elicited signs can be subtle, especially in the language domain (e.g., a specific lexico-semantic deficit), and they may be therefore difficult to detect or interpret; (v) patient's subjective experience can be misleading, or may add difficulties for ECS interpretation; (v) it is currently not clear whether ECS trigger inhibition or activation of neuronal networks (David et al., 2010). For all these reasons, ECS may fail to reveal the functionality of a given brain region, revealing only the “tip of the iceberg” of functional cortical networks.

Functional Magnetic Resonance Imaging (fMRI), by comparison, is a non-invasive method which has an excellent spatial coverage and can be routinely used for brain mapping, notably language (Price, 2010), including pre-operative mapping in patients (Perrone-Bertolotti et al., 2012; Baciu et al., 2001 ; Baciu et al., 2005). Nevertheless, it has limitations in terms of temporal resolution, relationships to neural processing and statistical quantification. Functional activity assessed by fMRI depends on the statistical threshold used, which is most important during single brain mapping (Baciu et al., 2005 ; Baciu & Perrone-Bertolotti, 2015 for a review). Still, fMRI shows widely distributed networks that are mainly relevant to lateralize language processing before surgery, rather than to precisely delineate those of language areas that should be spared during surgery.

In order to overcome ECS and fMRI limitations, High Frequency Activities (HFAs > 40Hz) elicited by various cognitive tasks, as recorded in patients submitted to iEEG exploration, have been proposed as putative

biomarkers of cognitive processes, especially for language functions, (e.g.,Mainy et al., 2008; Vidal et al., 2011) HFAs induced by cognitive tasks were first described in animal studies which reported that primary visual cortex neurons fired jointly at 40Hz during a visual task (Gray, 1989). A more recent micro-electrodes recordings study in the human cortex showed that broadband HFAs (40Hz-150HZ) could reflect summed local population of neurone spiking and thus allowed the evaluation of direct neural activity (Manning et al., 2009). Two decades ago, two studies showed that cognitive information processing generated transient activities in a high frequency range between 40 and 150 Hz in motor ( Crone et al., 1998) and sensory ( Lachaux et al., 2000) cortices. These HFAs, called Gamma Band Responses (GBR), are currently considered as a proxy of population level spiking activity while patients perform a cognitive task. Since then, an increasing number of studies have reported GBR in specific brain regions related to the task performed (Lachaux et al., 2012). GBR are not visible in raw intracerebral iEEG traces, but are revealed by simple signal processing techniques involving time-frequency analysis (Jerbi et al., 2009). These studies have revealed the functional role of GBR in almost every sensory modality and its subserving cortical regions, as well as in various high-level cognitive processes such as visual selective attention (Ossandón et al., 2011), auditory perception (Bidet-Caulet et al., 2007), language processing (Perrone-Bertolotti, 2012;Mainy et al., 2008; Lachaux et al., 2007) and many others.

Brain mapping using GBR evaluation offers many advantages. It provides an exquisite anatomical, functional and temporal specificity, and GBR can be compared with an estimate of the intensity of any given neuronal population's engagement in a specific task processing (Lachaux et al., 2000). Thus, it can distinguish neural activity increases and decreases, i.e., activations and deactivations, which is interesting in terms of cognition as cognitive processes, mainly attention, are mediated not only by distributed cerebral activations, but also by concurrent suppressions (Ossandón et al., 2011). Moreover, this method offers high signal-to-noise ratio and low sensitivity to artifacts that are not offered by surface EEG, for instance. As GBR are elicited during cognitive tasks, high level processes, namely those supported by associative cortices, can be explored in each subject depending on specific tasks availability. Furthermore, functional

networks revealed by GBR assessment have been proven to be complementary to those revealed by fMRI activation studies (Lachaux et al., 2007; Conner et al., 2011).

GBR studies in the language domain has been showed as a reliable method (Llorens et al., 2011), that combines a high temporal and spatial resolution with a low sensitivity to artifacts. It provides highly specific results which depend on the functions that are tested, and allows the study of specific language processes, including their neural mechanisms and time courses. This has been showed, as an example, for word recognition (Mainy et al., 2008), sentence comprehension, reading (Perrone-Bertolotti, 2012), and naming (Crone et al., 2001). Therefore, GBR recording during cognitive tasks seems to be an efficient method to perform brain mapping and, more specifically, to perform language mapping. Nevertheless, few studies have compared this method with the classical methods (ECS and fMRI) used to perform pre-surgical functional mapping (Sinai et al., 2005), and only a few have evaluated the value of GBR assessment to predict post-operative cognitive outcome (Towle et al., 2008).

The present study aimed at evaluating the clinical relevance of induced GBR as a functional mapping method for pre-operative assessment of cognitive functions before epilepsy surgery. Attention was focused on language-induced GBR, since language is one of the most frequently impaired functions following epilepsy surgery. Also, language is classically mapped, in our clinical environment, by ECS and fMRI, allowing direct comparison of results of the three methods. We firstly evaluated the reliability of the GBR as compared with ECS and fMRI. In a second step, we evaluated the value of GBR to predict post-operative language outcome.

## 2. Materials and Methods

### 2.1 Patients selection and characteristics

Fourteen patients were included in this study, based on the following inclusion criteria: (i) aged over 12 years, native French speakers; (ii) having undergone SEEG recordings with stereotactically implanted multilead depth electrodes at the Epilepsy Department of Grenoble University Hospital (France); (iii) in whom the cognitive brain mapping assessment, as performed during SEEG procedure (ISD-SEEG project, DRCI Grenoble, 2009), included at least a language task allowing the assessment of behavioural performance and related gamma band responses; (iv) who were subsequently operated, after the SEEG study, between January 1, 2013 and July 1, 2016.

The 14 patients (6 men, 8 women, mean age: 30 years) were all suffering from drug-resistant partial epilepsy. The operability of this epilepsy could not be decided on the basis of a non-invasive screening including scalp-video-EEG monitoring, and neuropsychological tests. See Figure 2 for experimental paradigm. A summary of the patients' characteristics is given in Table 1.

P	Age	Gender	VIQ/PIQ	HL	HDL	EZ location	MRI	Resection	Pathology	E outcome
1	38	F	NA	R	L	L temp	NL	L Temporo-basal	FCD	Engel IV
2	23	F	99/76	L	L	L temp	NL	L- Cingulo-parietal	NS	Engel I
3	23	F	79/76	R	L	R front	MG	R-Fronto-opercular	FCD	Engel III
4	20	F	102/92	R	L	L temp	HS	L-Temporo-mesial	HS	Engel I
5	37	M	100/115	R	L	L front	NL	L-Frontal-polar and orbital	FCD	Engel I
6	13	F	90/105	R	L	R front	NL	L-Prefrontal	FCD	Engel I
7	15	F	NA	R	L	R temp	NL	R-Temporo insulo-opercular	FCD + HS	Engel IV
8	23	F	96/60	L	L	L pariet	NL	L- Mesio parietal	NS	Engel III
9	59	M	112/104	R	L	L temp	NL	L-Fronto-basal	NS	Engel I
10	29	M	131/116	R	L	R front	DNET	R- Fronto orbital and anterior insula	DNET	Engel I
11	28	M	106/112	R	L	R front	POG	R- Pre motor frontal	ODG	Engel I
12	41	M	98/106	R	L	L front	FCD	L-Frontal superior	FCD	Engel I
13	27	F	104/90	R	L	L front	NL	L-Frontal superior	NS	Engel I
14	48	M	112/106	L	R	R temp	NL	R-Temporo-mesial	FCD	Engel I

**Table 1.** Patients' (P) characteristics: Age, Gender, Pre-operative neuropsychological scores on Verbal and nonverbal performances (VIQ/PIQ; Handedness lateralization as assessed by Edinburgh Handedness inventory (HL)(Oldfield, 1971); Hemispheric dominance for Language (HDL) as assessed by fMRI; epilepsy characteristic (epileptic zone -EZ- location and MRI findings); anatomical resection location (Resection); pathology, seizure outcome (Engel et al., 1996). Abbreviations: NA: not available; L: Left handed R: Right handed; NL: Non Lesional; MG: Micropolygyria; FCD: Focal Cortical Dysplasia; HS: Hippocampal sclerosis; DNET: Dysembryoplastic neuroepithelial tumour; POG: post-operative gliosis; NS: Nonspecific; ODG: Oligodendrolioma.

## 2.2 Electrode implantation and localization

The number and placement of intracerebral electrodes was defined according to the prior hypothesis regarding the localization of the epileptogenic tissue, based on seizure semiology and on the results of the non-invasive investigations. A total number of 199 semi-rigid, multi-lead electrodes were stereotactically implanted in the 14 patients (mean: 12-18/patient), which allowed a good coverage of mesial and lateral brain structures as well as deep-seated areas (e.g., insula). Every SEEG electrode had a diameter of 0.8mm and comprised 8 to 18 contact leads 2mm wide and 1.5mm apart, depending on the target structure

(DIXI Medical, Besançon, France). Every electrode contact was identified on a post-implantation MRI. The MNI (Montreal Neurological Institute) coordinates for every electrode contact were extracted using SPM (<http://www.fil.ion.ucl.ac.uk/spm/>).

### 2.3 Stereotactic intracerebral EEG (SEEG) recordings

Intracranial recordings were conducted using a video-SEEG monitoring system (Micromed®, Treviso, Italy), which allowed the simultaneous recording from up to 128 depth-EEG electrode sites. Data was bandpass filtered online from 0.1 to 20Hz and sampled at 512 Hz in all patients. At the time of acquisition, data was recorded using a reference electrode located in the white matter, and each electrode trace was subsequently re-referenced with respect to its direct neighbour (bipolar derivations). This bipolar montage has a number of advantages over common referencing. Notably, it helps eliminate signal artifacts common to adjacent electrode contacts and allows an accurate focal recording. The spatial resolution achieved by bipolar SEEG recordings was in the order of 3mm (Jerbi et al., 2009); (Lachaux et al., 2003). The localization of epileptogenic brain tissue was based on the visual analysis of interictal and ictal SEEG activity.

### 2.4 Electrical cortical stimulations (ECS)

As part of our routine procedure, ECS were performed during the SEEG monitoring, during sessions that lasted 1-3 hours. The aim was to reproduce part or the totality of the ictal clinical symptomatology, and to localize functionally eloquent areas that had to be spared during surgery. Bipolar ES were performed using a constant current rectangular pulse generator, and applied at 1 Hz (pulse width: 1 msec; ES duration: 40 sec) and 50 Hz (pulse width: 1 ms; ES duration: 5 sec) between contiguous contacts at various levels of the electrode axis, with stepwise increasing intensities ranging from 0,2 to 3 mA and until clinical subjective or objective responses or after-discharges were obtained. ECS were performed after checking that the electrode site to be stimulated exhibited its baseline activity. Patients were asked to perform different simple

tasks, depending on the stimulated region. More specifically, for language assessment, patients were asked to perform several speech tasks audibly including counting, naming pictures or listing series of words. ECS were performed immediately after every speech task onset. ECS findings were classified by the examiner (neurologist) into different categories (motor, sensitive, sensory, vegetative, language, emotional, etc...) and documented in the patients' files.

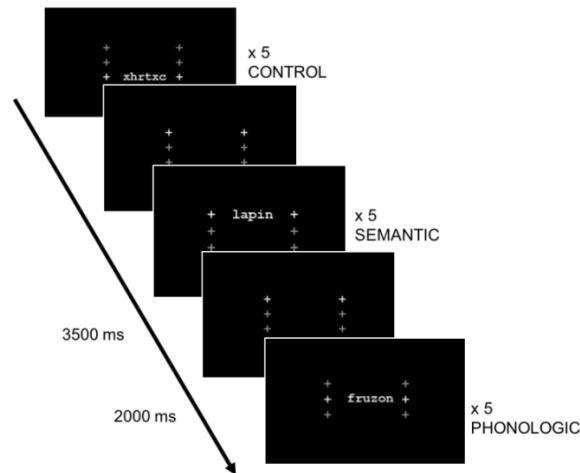
## 2.5 Functional mapping using task-related gamma-band responses (GBR)

During the SEEG procedure, patients were asked to participate to an experimental protocol screening various cognitive processes (ISD and SEEG project, DRCI Grenoble, 2009) to extract task-related GBR. This experimental protocol was approved by the local Ethical Committee (CPP Sud-Est V n° 09-CHUG-12), and all participants provided their written informed consent before entering the project.

For the purpose of the present study, attention was focused on one these cognitive tasks, namely a behavioural language task (abbrev. LEC1) that involved two different language processes (visual input), phonology and semantic, and three different experimental conditions (phonological, semantic and visual control). During the phonological condition, patients were asked to judge whether or not a presented pseudo-word was composed of two syllables (e.g., scrount; fruzon). During the semantic condition, participants were instructed to perform a semantic categorisation on words. They also were instructed to judge whether a presented word was a living being (e.g., dog or dove) or not (e.g., table or car). In the visual control condition, patients were asked to judge whether a randomly arranged consonants string had capital or lower case letters (e.g., XTVNXD or xbxnbd). In all conditions, patients were instructed to answer as rapidly and accurately as possible. The three conditions (semantic, phonological and control) were presented randomly in a block dressing of 5 consecutive trials per condition. A total of 60 stimuli per condition was presented. Stimuli were presented in a fixed 2 s duration with an interstimulus interval of 3.5 s (see Figure 1). Visual stimulation was delivered using Presentation stimulus delivery software (Neurobehavioral systems Inc.) and was displayed on a 19-inch computer screen located 60cm away from

the subject. Participants were instructed to respond by pressing a key with the index finger of their left hand for a yes response and of their right hand for a no response. Responses were recorded in order to assess behavioural performances in terms of response exactitude (accuracy) and rapidity (reaction times).

Patients performed this task twice: during the pre-operative assessment conjointly with the iEEG recordings in order to obtain both behavioural performances and language-related GBR and then after surgery to evaluate behavioural performances only (see Figure 2). All participants went through a short training session with different items from those presented during the pre- and post-operative evaluation. Furthermore, to reduce a possible learning effect induced by task repetition, stimuli used during the pre- and post-operative evaluations were different.



**Figure 1.** Language task paradigm. Example of arrays for control, semantic and phonologic conditions. Every condition stimuli were presented during 2000 ms and after 3500 ms. The semantic stimuli were presented on the top, phonologic stimuli in the middle and visual control stimuli on the bottom of the screen. The patient was instructed and trained to perform every condition in a block of 5 consecutive trials.

## 2.6 Functional mapping using functional MRI (fMRI) for language

Among our group of 14 patients, all underwent a fMRI scan prior to surgery in order to lateralize language functions, either before or after the SEEG study. Nevertheless, only 6 of them had available fMRI data (P1, 2, 4, 7, 13, 14). These six language fMRI were performed at the Grenoble University Hospital (Grenoble, France) in a whole-body 3T Philips scanner (Achieva 3.0T TX Philips–Philips Medical systems, Best, NL) with an 8-channel head coil. For functional scans, the manufacturer-provided gradient-echo/T2\*-weighted

EPI method was used. Forty-one adjacent axial slices parallel to the bicommissural plane were acquired in sequential mode. Slice thickness was 4 mm. The in-plane voxel size was  $4 \times 4$  mm ( $256 \times 256 \times 168$  mm field of view acquired with a  $64 \times 64$  pixels data matrix). For the two functional runs, the main sequence parameters were: TR = 3 s, TE = 35 ms, and flip angle =  $90^\circ$ . Finally, a T1-weighted high-resolution three-dimensional anatomical volume was acquired, by using a T1 TFE sequence (field of view =  $256 \times 256 \times 160$  mm; resolution:  $1 \times 1 \times 1$  mm; acquisition matrix:  $256 \times 256$  pixels).

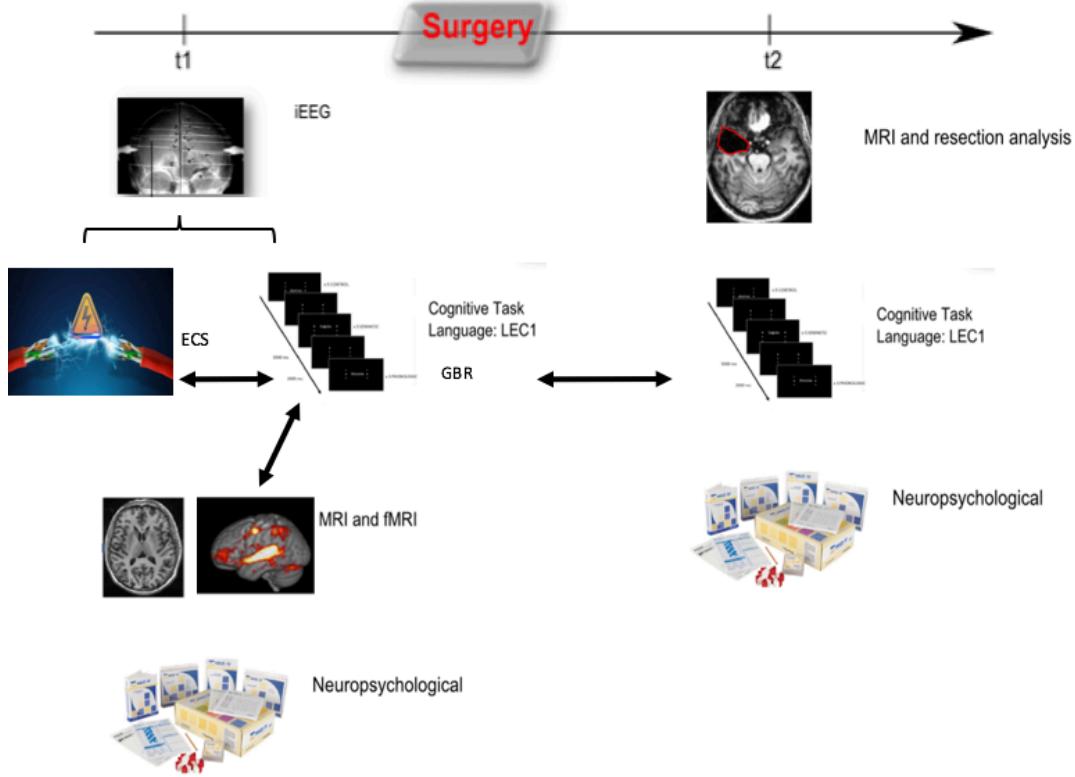
One task composed of two identical sessions was carried out during MRI acquisition. The two sessions were block design-alternating task periods consisting of a pseudorandomized presentation of auditory stimuli and baseline periods (rest). Auditory stimuli were names (e.g., ball). A total of 24 stimuli were presented in four blocks per fMRI sessions. Patients were instructed to mentally perform a sentence including the word that they have just heard. Auditory stimuli were presented via the Presentation stimulus delivery software (Neurobehavioral systems Inc.).

## 2.7 Surgery and post-operative follow-up

Surgery was performed according to SEEG results (Table 1). It concerned the dominant hemisphere for language in 10 patients, and consisted in frontal (n=7), temporal (n=3), parietal (n=2) and multilobar (n=2) resections. The extent of the resection was assessed on a 3D-T1 post-operative MRI usually performed 3 months after surgery. Volume of resection (in  $\text{mm}^3$ ) was computed through voxels number into the resected area and MRI acquisition characteristics. The volume of the resection was not computed for Patient 9 since he presented a post-traumatic subdural haemorrhage 3 months after surgery which underestimated the extent of resection on the post-operative MRI.

Patients were usually followed up at three months, six months, and then once a year. Final post-operative outcome in terms of seizure was evaluated at the last follow-up visit, according to Engel's Classification (Engel et al., 1996) 10 patients became seizure-free (Engel's class I) after surgery, 2 were improved and 2 did not show any seizure frequency changes.

## 2.8 Data analysis



**Figure 2.** Schematic illustration of the experimental design. Left: pre-operative assessment (time 1 -t1-) including iEEG evaluation including electro-cortical stimulation (ECS) and gamma band activity screening (GBR) through behavioural language task (LEC1), neuropsychological, anatomical (MRI) and functional MRI (fMRI). Right: post-operative assessment (time 2 -t2-) including LEC1, neuropsychological assessment and anatomical MRI (resection characteristics). Arrows represent the different comparison computed in the study.

### 2.8.1 ECS analysis

The clinical effect of ECS delivered over sites were retrospectively reviewed from patient's video-SEEG files. Only speech disturbances, labelled as absent, incorrect or delayed responses or paraphasia, were taken into account. Other elicited clinical signs were not considered in this work. Thus, stimulated sites were binary classified into sites which showed language symptoms (ECS+) and those which did not (ECS-). As bipolar ECS were performed between two contiguous sites, each electrode was counted separately to allow comparison with GBR mapping. Any site that was common to two tested pairs, was regarded as ECS+ only

when it exhibited positive response in both paired stimulations that included the site. If the site was tested only in a single pair, it was labelled the same as the including pair.

## 2.8.2 Language-related GBR

To compute high-frequency activity amplitudes between 50 Hz and 150 Hz during Lec1 task, we applied a classical procedure performed in our team (see for instances Ossandon et al., 2011; Perrone-Bertolotti et al., 2014; and Vidal et al., 2011 for a review) and including the following processing steps: first, we bandpass filtered iEEG signals in multiple successive 10 Hz-wide frequency bands (e.g. 8–10 bands as [50–60 Hz], [60–70 Hz], etc.) using a zero phase shift non causal finite impulse filter with 0.5 Hz roll-off. Next, for each bandpass filtered signal we computed the envelope using a standard Hilbert Transform. The obtained envelope is down sampled to a sampling rate of 64Hz (i.e., one-time sample every 15,625ms). For each frequency interval, the time-varying amplitude was divided by its mean across the entire recording period of the experiment and multiplied by 100. This yields instantaneous amplitude envelope values as percentage-of-the-mean. Finally, the envelope signals computed for each consecutive band were averaged to provide one single time series (the GBR) across the entire recording session. The obtained envelopes had a sampling rate of 64 Hz. We also performed single trials GBR maps for each electrode contact. These single-trial maps were screened visually one-by-one. Hence, we determined electrodes sites which showed statistically significant GBR, labelled as GBR+, and those which did not show any statistically significant GBR, labelled as GBR-. Gamma band deactivations were not taken into account in this study.

The visual method used in this work was previously evaluated by two independent observers of our team: inter-rater agreement on detecting gamma activation was estimated on 17 666 single-trial maps using a Cohen's kappa coefficient, which showed a substantial agreement (Cuisenier et al., 2016).

## 2.8.3 Language-fMRI BOLD responses

Data analysis was based on the general linear model (Friston et al., 1999) in SPM12 (Welcome Department

of Imaging Neuroscience, London, UK) implemented in MATLAB (MathworksInc., Sherborn, MA, USA). Each condition, language and rest, was modelled using a canonical hemodynamic function model. Data analysis started with the spatial pre-processing steps. The T1-weighted anatomical volume was co-registered to mean images created by the realignment procedure and was normalized to the MNI space using a trilinear interpolation. The anatomical normalization parameters were subsequently used for the normalization of functional volumes. Finally, to be able to compare fMRI results with the SEEG data, each functional volume was smoothed by a 3-mm FWHM Gaussian kernel. Time-series for each voxel were high-pass filtered (1/128 Hz cut-off) to remove low frequency noise and signal drift. Pre-processed data were then statistically processed and included into one design matrix including both sessions. Movement parameters derived from the realignment corrections (3 translations and 3 rotations) were also included in the design matrix as additional factors using ART toolbox for Matlab available on the Web at [https://www.nitrc.org/projects/artifact\\_detect/](https://www.nitrc.org/projects/artifact_detect/). The block presentation allowed us to analyse data performing average response for all items, task vs control. Statistical parametric maps were generated from linear contrasts between the HRF parameter estimates for the different experimental conditions. Whole brain statistical analyses were first performed at an individual level in order to evaluate the language effect ( $K = 5$ ;  $p$  value < .001 uncorrected,  $T = 3.55$ ). Statistical analyses were subsequently performed at a group level (one sample t-test,  $k=5$ ,  $p < .001$  uncorrected;  $T=3.55$ ). Finally, in order to compare fMRI results with GBR maps, we performed Region of Interest (ROI) analysis on fMRI data. We defined a sphere-type 3mm-radius ROI on each electrode contact from their MNI coordinates using SPM. We extracted the BOLD signal change for each of the ROI per patients. According to the statistical significance of the signal change on each site ( $p < .001$ ,  $T = 3.55$ ), we classified sites into two labels : fMRI + or fMRI -.

## 2.8.4 Functional data fusion

Visualization and fusion of data was assessed using a home-made software (IntrAnat Electrodes, GIN INSERM U1216, Grenoble) available on the WEB at <https://f-tract.eu/index.php/softwares/>. This software

allows co-registration (using ANTs or SPM12) of the different imaging modalities (pre-implantation anatomical 3DT1 MRI, per-implantation 3DT1 MRI, post-operative 3DT1 MRI, fMRI) and visualization of respective surgery, electrode implantation and functional maps. 3-D modelized intracerebral electrodes were inserted on post-implantation MRI using IntrAnat Electrodes®. Cortex parcellation was achieved with Mars Atlas® (Brainvisa toolbox, UMR 7289, Marseille (Auzias et al., 2016)). Through this procedure, each electrode site was labelled according to i) its parcel in MarsAtlas, ii) its MNI (Montreal Neurological Institute) coordinates iii) its relation with resection mask (computed by subtracting post-operative 3D-T1 brain segmentation from the pre-implantation one) iv) fMRI ROI results v) clinical responses to ECS vi) language-related GBR. This allowed comparison between ECS, GBR and fMRI maps, as well as comparison of ECS and GBR maps with the extent of the resection.

## 2.8.5 Comparison between GBR, ECS and fMRI maps

As ECS is classically considered as the gold standard for localization of language, only anatomical sites where ECS were applied were taken into account.

GBR were first compared to ECS results, according to the methodology proposed by Sinai et al (2005). We thus determined the i) sensitivity, ii) specificity, and iii) positive and negative predictive values (PPV and NPV) of GBR maps in relation to ECS maps. GBR sensitivity was defined by the percentage of electrode sites that were positive for both methods (GBR+ and ECS+) among all ECS+ sites. GBR specificity was calculated as the percentage of electrode sites that were negative for both methods (GBR- and ECS-) among all ECS- sites. The PPV was defined by the probability that a GBR+ site showed language interference after ECS (ECS+) and was calculated as the percentage of sites that were both GBR+ and ECS+ among all GBR+ sites. Finally, the NPV was defined by the probability that a GBR- site did not exhibit any language interference by ECS (ECS-) and was computed as the percentage of sites that were both GBR- and ECS- among all GBR- sites.

Then, GBR were compared with fMRI in the 6 patients in whom fMRI data was available. The sensitivity, specificity, PPV and NPV were determined according to the same methodology as described above.

Finally, to test the relation or agreement between GBR and the other two functional mapping methods (i.e., ECS and fMRI), a tetrachoric correlation ( $rt$ ) was performed (see for instance Divgi, 1979). The  $rt$  allowed the evaluation of the correlation on binary data, thus the  $rt$  coefficient ( $\rho^*$ ) showed the strength of the relationship or association between ratings for two raters (i.e., a "0" indicates no agreement and a "1" represents a perfect agreement between the measures). Thus, tetrachoric correlation coefficients ( $\rho^*$ ) were computed.

## 2.8.6 Effect of surgery

Pre and post-operative behavioural performances during LEC1, in both phonological and semantic conditions, were compared using an analysis of variance (ANOVA) in terms of accuracy (percentage of correct responses) and reaction times (in ms).

Whether language post-operative outcome was related to the extent of the resection was evaluated using a Bravais-Pearson correlation ( $r$ ) between the *Delta performance* (difference between pre- minus post-operative behavioural performances) and the volume of resection (in  $\text{mm}^3$ ).

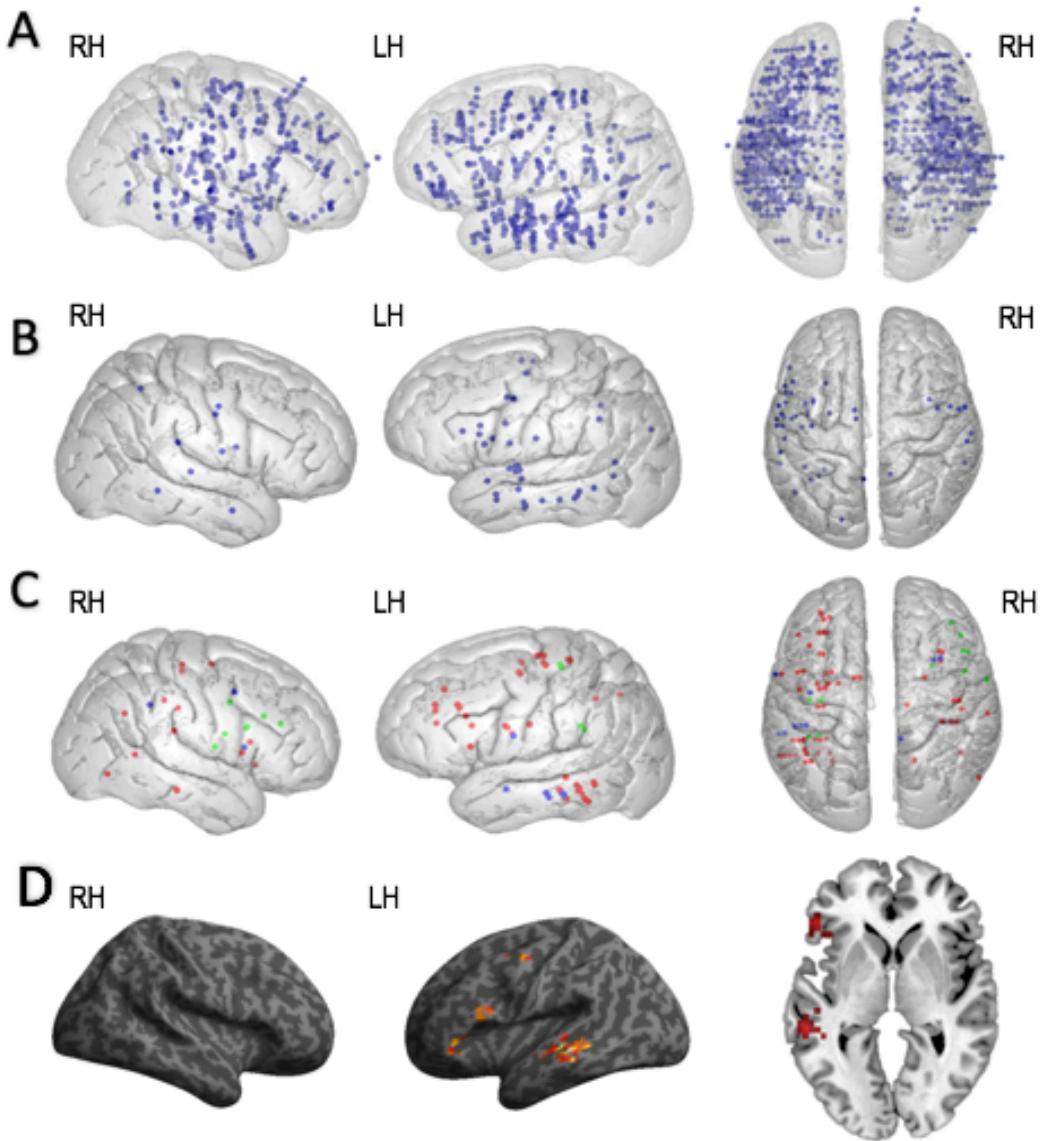
Finally, to evaluate the prognostic value of removing brain regions displaying significant language-related GBR, we compared the *Delta performance*, for each experimental condition, between patients in whom at least one GBR + site was resected with the group of patients in whom none of the GBR+ site was resected (called control group). This comparison was performed using a Crawford and Howell's modified t-test (Crawford et al., 1998), with a significance level set at  $p < 0.05$ . A similar analysis was performed to compare post-operative language outcome of patients in whom at least one ECS+ site was resected with the group of patients in which no ECS+ site was resected. As the language task performed during ECS was a picture naming, close to the semantic condition of LEC1, only the performances obtained during the semantic condition were used to perform this latter comparison.

### 3. Results

#### 3.1. Functional Maps

Among all 14 patients, 979 electrodes sites were explored through ECS and GBR (662 left, 317 right; mean: 70 sites/patient) and were thus considered in this study. This represented 58% of the total number of intracranial sites. The other 42% of intracranial sites (n=715; 360 left, 355 right) provided information only for GBR but were not stimulated, so that they were excluded from the analysis.

All patients exhibited GBR during the LEC1 task regardless of the experimental condition, at 81 of the 979 relevant sites (8%; mean: 6 GBR+ sites/patient). Twenty-five (30%) of the 81 GBR+ sites showed a selective activation for the semantic condition (n=12) or the phonological condition (n=13). ECS showed language interference in 9/14 patients at 51 of the 979 investigated sites (5 %, mean: 4 ECS+ sites/patient). BOLD signal changes were observed in all the 6 patients in whom language fMRI data was available: 59 of the 393 explored sites (as only sites where ECS were applied were considered) showed significant BOLD signal changes (15%, mean: 10 sites/patient). Figure 3 illustrates the cortical distribution of all investigated sites and sites that were positive for each method (ECS+, GBRs and fMRI+ sites).



**Figure 3** : Spatial distributions of the investigated sites, and positive responses during each method from all 14 patients (P1-14) in common coordinates. Distributions are presented on axial and lateral views of MNI brain template. **A.** All electrode sites studied, where both ECS and GBR were performed (n=979) **B.** sites where ECS interfered with language. **C.** Electrode sites with significant GBR during Lec1. Different colours of the sites indicate the two different language processes: semantic (blue) and phonology (green). Red areas indicate sites which exhibited GBR in both conditions. **D.** Results from fMRI group analysis: Activated regions during the speech production task displayed on a 3D anatomical template and a 2D axial slice.  $k=5$ ,  $p < .001$  uncorrected;  $T=3.55$ ,  $n=6$ . See Figure 6 in appendix for more details. LH: Left hemisphere, RH: Right hemisphere.

### 3.2. Comparison between GBR and ECS

Six of the 979 relevant sites were GBR+ECS+ and 857 GBR-ECS- as shown in Table 2. GBR+ECS+ sites were all located on the left (and language dominant) hemisphere. Specifically, they were localised in the

superior parietal, dorsolateral somatosensory, medial visual, dorsomedial premotor and dorsomedial motor cortices. These sites showed GBR during LEC1 in both semantic and phonological conditions, except for one site located in the medial superior parietal cortex that showed GBR for the semantic condition only (see Table 3 and Figure 4 in Appendix for details).

	ECS+	ECS -	Total
GBR +	6	75	81
GBR -	40	858	898
Total	46	933	979

**Table 2:** Electrode sites distribution depending on ECS and GBR results.

Patient	Site	x	y	z	Label	GBR results
4	C'11	-59	-35	-13.3	LSPC	Sem + Phono -
8	C'8	-31	-46	43	LSdl	Sem + Phono +
8	F'6	-37	-56	-7	LSPC	Sem + Phono +
9	D'5	-41	-47	-13	LVCm	Sem + Phono +
12	L'6	-23	1	50	LPMdm	Sem + Phono +
13	M'1	4	3	53	LMdm	Sem + Phono +

**Table 3:** GBR+ and ECS+ sites. Including the name of the site (site), MNI coordinates (x, y, z) and the anatomical label (Label). Results of GBR analyses for the two experimental conditions are presented. Abbreviations: LSPC: Left Superior Parietal Cortex; LSdl: Left Dorsolateral Somatosensory Cortex; LVCm: Left Medial Visual Cortex; LPMdm: Left Dorsomedial Premotor Cortex; LMdm: Dorsomedial Motor Cortex; Sem: semantic task; Phono: phonological task.

Sensitivity and specificity of GBR for language mapping relative to ECS were respectively 11.7% and 92.4%, with a PPV and NPV of 7.4% and 95.5%, respectively.

### 3.3. Comparison of GBR maps with fMRI activations

Only 6 patients had available data from a fMRI for language mapping, in whom a total of 393 sites were stimulated and were thus considered in this study. Five of these 393 sites were GBR+fMRI+ and 298 were GBR-fMRI- (see

Table 4), and none were positive for the three methods (GBR+fMRI+ECS+). GBR+fMRI+ sites were all located on the left hemisphere, except one which was located on the right mid temporal gyrus (See

Table 5 and Figure 5 in Appendix for details).

	fMRI+	fMRI -	Total
GBR +	5	36	41
GBR -	54	298	352
Total	59	334	393

**Table 4:** Electrode sites distribution depending on fMRI and GBR results.

Patient	Site	X	Y	Z	Location	GBR results
1	G'9	-55	-50	-15	L SPC	Sem + Phono +
4	Q'1	-38	24	15	L VCm	Sem + Phono +
4	X'5	-31	20	0	L VCm	Sem + Phono +
7	D3	44	-52	5	R MTC	Sem + Phono +
13	X'5	-28	19	-1	L ICC	Sem + Phono +

**Table 5:** MNI coordinates for the GBR+ IRMf+ sites. x, y, and z refer to the MNI coordinates of the sites, in millimetres. L SPC: Left Superior Parietal Cortex; L VCm: Left Medial Visual Cortex; R MTC: Right Middle Temporal Cortex; L ICC: Left Isthmus Cingulate Cortex.

Sensitivity and specificity of GBR for language mapping relative to fMRI were respectively 8.4% and 89.2%, with a PPV and NPV of 12.2% and 84.7%, respectively.

### 3.4. Correlation between functional mapping methods

The tetrachoric correlation showed low correlation between GBR and fMRI, and between GBR and ECS as well, both for semantic and phonological conditions (see Table 6 for correlations values). The best correlation - although low - was observed between GBR and ECS for the semantic condition ( $\rho^* = -.343$ ).

Language condition	GBR - ECS			GBR - fMRI		
	Phonological	Semantic	Phonological and Semantic	Phonological	Semantic	Phonological and Semantic
$\rho^*$	-.285	-.343	-.217	-.053	.025	.104

**Table 6 :** Correlation between GBR and both ECS and fMRI results for the sub-group of patients who performed fMRI exploration.

### 3.5. Effects of surgery

Behavioural performances were considered as impaired post-surgery when they showed, as compared with pre-operative data, a statistically significant decrease of accuracy and/or statistically increase of reaction time. By opposition, Behavioural performances were defined as improved when they showed, as compared with pre-operative data, a statistically significant better accuracy and/or statistically shorter reaction time.

#### 3.5.1. Effects of surgery on behavioural performances

Seven patients showed language changes in the semantic domain after surgery (see Table 7 and Table 8 in appendix for statistical details): 2 patients exhibited a significant impairment, one for reaction times (P11) and one for both accuracy and reaction times (P5), while 5 patients demonstrated a significant improvement, 3 in terms of accuracy (P7, P8 and P14) and 2 for reaction times. Behavioural comparison revealed no change in the other patients.

Seven patients showed language changes in the phonological condition after surgery (see Table 7 and Table 11 in appendix for statistical details): 2 patients (P5, P14) had a significant impairment of behavioural in terms of accuracy, while 5 patients were improved, 4 (P6, P7, P8, P11) in terms of accuracy and one (P13) in terms of reaction times.

No correlation was found between the *Delta Performance* (difference between pre- and post-operative behavioural performances) and the extent of the resections for both semantic and phonological conditions (see details in Table 10 in appendix).

P	Lec1					Speech evaluation DO 80 Pre/post	Resection		S/A (Months)		
	Semantic		Phonological				GBR+R	Vlm			
	RT	Acc	RT	Acc							
1	ns	ns	ns	ns		77/49	Y	591	30		
2	ns	ns	ns	ns		80/78	N	1256	30		
3	ns	ns	ns	ns		74/77	N	8988	25		
4	ns	ns	ns	ns		79/NA	N	24379	19		
5	--	--	++	--		NA/NA	N	24141	15		
6	++	ns	++	++		NA/NA	N	23118	15		
7	ns	++	++	++		NA/NA	N	33221	18		
8	ns	++	++	++		77/NA	N	5413	5		
9	ns	ns	ns	ns		78/NA	N	NR	3		
10	ns	ns	++	ns		80/NA	Y	40623	3		
11	--	ns	++	++		NA/NA	N	5025	4		
12	ns	ns	ns	ns		75/78	N	6576	4		
13	++	ns	++	ns		80/80	Y	6603	28		
14	ns	++	ns	--		80/80	N	47210	24		

**Table 7 :** Functional outcome of surgery and resection features: statistical significance of the behavioural outcome of patients as assessed by LEC1 (including semantic and phonological condition), pre- and post-operative denomination score (DO80) assessed by speech therapist, resection details (relationship with GBR and volume in mm<sup>3</sup>) and time between surgery and post-operative assessment (S/A). Abbreviation: RT: Reaction Time; Acc: Accuracy; ++: indicates a significant improvement in behavioural performances after surgery; --: indicates a significant decrement in performances after surgery; ns: no statistical difference between before and after surgery; GBR+R: indicates the resection of an GBR+ site or no; Y: yes, N: no; Vlm: volume.

### 3.5.2. Effect of GBR resection on behavioural performances

Two patients underwent a resection including at least one GBR+ site during the semantic condition (P1 and P13). P1 did not demonstrate any significant change after surgery, and its Delta performance did not statistically differ from the Delta performance of the control group (i.e., without GBR+ sites resected). P13 significantly improved after surgery for reaction times, but its Delta performance did not show any statistical difference with the Delta performance of the control group (see Table 8 in appendix)

Two patients underwent a resection including at least one GBR+ site during the phonological condition (P10 and P13). Both exhibited a significant post-operative improvement for reaction times but not for accuracy.

The Delta performance of these 2 patients was not statistically different from the Delta performance of the control group (See Table 9 in Appendix).

By comparison, 4 patients had a resection upon ECS+ sites (P4, P6, P12, P13), of whom 3 (P4, P12, P13) showed a significant decrease of accuracy after surgery as compared to the control group, and one (P6) showed a significant improvement of both accuracy and reaction times as compared to the control group (see Table 8 in appendix for statistical details).

## 4. Discussion

The aim of this study was to assess whether task-related GBR might be used to anticipate cognitive deficits after surgery, and whether they might complement the classical methods for language mapping, namely ECS and fMRI. Indeed, GBR have been described as a putative biomarker of cognitive functions for almost 20 years (Lachaux et al., 2012) but their clinical relevance in predicting post-operative language outcome has never been formally assessed. To do so, we choose a language task that have the advantage to be compared with other modalities (ECS, fMRI) and provide quantitative features of behavioural performances to evaluate possible changes after surgery. The main results of the study, as well as its methodological limitations, are described in the followings sections.

### ***GBR mapping may help to choose the sites that have to be stimulated***

Our results, though preliminary and extracted from a small cohort of patients, suggest first that GBR assessment can be a realistic complementary tool to ECS as part of iEEG recordings. Language-related GBR predicted ECS language interference with a high specificity (92.4%) and NPV (95.5%), meaning that if language tasks did not induce GBR on a cortical site, the likelihood of language impairment by stimulating the same site was very low. This highlights the possibility to first perform a functional map with GBR before starting the ECS procedure, and therefore save time and avoid stimulating sites that are *a priori* not relevant. These results compare favourably with the only two other studies having evaluated GBR and ECS during naming (n=13, Sinai et al. 2005) and word repetition (n=12, Towle et al. 2008) tasks, and which showed a specificity of 78% and 63%, respectively. These two studies, however, reported a much higher sensitivity (38% and 57%, respectively) than the one we found in our series (11.7%, with a PPV of 7.4%), a finding which can be related to the differences between the iEEG methods used. Sinai et al. (2005) and Towle et al. (2008) performed ECS and recorded GBR through subdural grids, that offered a broad coverage of neocortical areas. Compared with grids, SEEG electrodes provide narrower neocortical coverage resulting in a restricted mapped of cortical regions, which is particularly true for language areas.

Also, ECS using SEEG electrodes is very focal, since stimulation is applied bipolarly between contacts that are only distant from 2.5mm (center to center). Still, the current intensity used for functional mapping with grids is usually much higher (up to 15mA) than with SEEG electrodes (up to 3-4 mA), a difference which is related to the fact that subdural electrodes record the cortical surface while SEEG electrodes are intra-cortical. Previous studies suggested that ECS effects depend on several factors, such as the intensity of stimulation (Kahane & Dubeau, 2014; Trébuchon & Chauvel, 2016). Hence, it remains uncertain whether the ECS intensity applied in our study (ranging from 0,2 to 3mA) was sufficient enough to show obvious language disturbances. In any cases, there do not exist any studies having evaluated the 'optimal' ECS parameters to perform cognitive mapping.

### ***GBR, ECS and fMRI do not reveal similar functional maps***

Our results indicate that GBR and ECS were weakly correlated ( $R = - .22$ ), suggesting a lack of concordance between GBR and ECS maps. A potential explanation for this result is related to the method itself. Indeed, ECS is a technique that disrupts functions (and therefore reveals key structures for a given cognitive process), while GBR is an activation method (which thus reveals the whole cortical network subserving a cognitive process). Still, subtle language dysfunctions triggered by ECS can be easily missed, leading to an underestimation of functional tissue. Consequently, language regions revealed by GBR are broader than - and partly overlap with - those defined with ECS (Brown et al., 2008). This is in line with the results of the present study, which showed that 81 GBR+ sites were identified, as compared with only 51 ECS+ sites. Furthermore, ECS may produce effects that are distant from the stimulated area, as the current may spread through axons or fibres to distant sites (Lesser et al., 1984; Blume, Jones, & Pathak, 2004). Indeed, current density models have showed that focal current application similar to ECS can interfere not only with cell body activity but also with axons transmission, thus influencing distant areas (Ranck, 1975).

Our results also indicated that GBR and fMRI were even less correlated than GBR and ECS. This was an unexpected result, because previous studies have showed that GBR and BOLD signal assessed with fMRI demonstrated significant functional relationships (Lachaux et al., 2007)There exists, however, several

methodological limitations that might explain these findings, including first the small number of patients assessed throughout both methods (n=6). Also, we deliberately choose small-sized (3mm-radius) ROI to compute comparisons between BOLD and GBR, this choice being motivated by the spatial resolution achieved by depth electrodes (3mm). In previous studies comparing GBR and BOLD activity (Conner et al., 2011; Esposito et al., 2013; Conner et al., 2011), greater ROI sizes were used (10mm) that guaranteed stronger correlation but reduced accuracy. Still, the restricted number of relevant cortical sites (i.e. only those sites where ECS were applied) represented another limitation, and a better relationship between GBR and BOLD signal might have been obtained if consideration had been given to all implanted sites. A final limitation, detailed below, is related to the difference between the language tasks used during fMRI (speech production) and SEEG (visual presentation of single words for language comprehension).

### ***Are GBR maps more accurate than ECS or fMRI maps?***

The language system involves several linguistic processes and in clinical settings it may be important to discriminate and precisely localise these processes (see, for instance, Perrone-Bertolotti et al., 2012). Our results pinpointed one site among GBR+ECS+ sites, which illustrates nicely the capacity of GBR to specify language processing: C'11 (P 4) located in the medial superior parietal cortex. Indeed, this electrode site exhibited specific GBR induced only during the semantic condition, while ECS triggered a non-specific aphasia. This is in line with intracranial studies which established that GBR provided a powerful means to detect task-specific activations (Crone et al., 2001; Towle et al., 2008). Language mapping through ECS is based only on disruption of language and provides only rough "yes" or "no" responses. Stimulation therefore may appear as a less specific and as a less subtle mapping tool than GBR. Moreover, the slow time course of haemodynamic imaging technique (fMRI) makes it difficult to distinguish different linguistic processes (Towle et al., 2008). As neural activity during language occurs on a millisecond time scale, it appears to be better explored by intracranial EEG signal analysis than using fMRI.

### ***Brain resection does not necessarily mean loss of function***

In the present study, the assumption was made that the extent of resections could affect cognitive/language post-operative outcome as there is evidence now from different sources that more restrictive tailored or selective resections have better cognitive outcomes (Helmstaedter, 2004; Clusmann et al., 2002; Pauli, et al., 1999). Our results were not consistent with this assumption and we even showed that 5 of the 14 patients exhibited post-operative language improvements in the phonological domain well as in the semantic domain. These results, in line with the current literature which shows that cognitive improvement after epilepsy surgery can be observed in up to 30% of patients (Helmstaedter, 2004), underlines the benefit of epilepsy surgery not only in terms of rendering the patient seizure-free, but also in terms of neuropsychological and behavioural abilities. Improving behavioural performance suggest that the suppression of epileptic activity allows efficient cerebral reorganisation and functional restoration.

We also hypothesized that surgical resection would be associated with language decline if the resection included a region activated (GBR+) during the language tasks. This was not confirmed by our results, probably due to the limited number of patient, and above all of patient with GBR+ sites resection (n=2 for phonological and n=2 for semantic condition). Furthermore, it seems likely that the small number of GBR+ sites resected (which represented only 5% of the GBR sites in each patient) was insufficiently important to provoke any deficit. Still, task-related GBR, as fMRI activation, reveals large networks involved in a given function, but not necessary critical for the task performance (Lachaux et al., 2012; Crone et al., 2006).

### ***Methodological concerns***

Using a unique set of tools combining both behavioural performances, electrophysiological findings and functional data, our study demonstrates the feasibility of language mapping through GBR during SEEG recording and the assessment of pre- and post-operative behavioural performances as an objective measure of cognitive outcomes. Some limitations, however, must be acknowledged, including: (i) the small sample of our patients population, that did not allow for statistical analyses at group level; consequently,

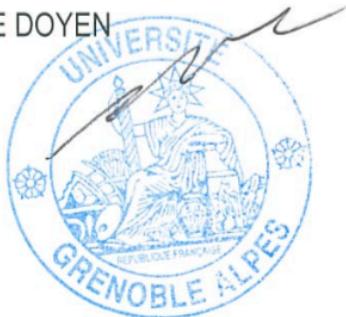
and even if we adopted a validated statistical method in clinical practice and in single-case research (Crawford et al., 1998), our results should be considered preliminary and further studies with larger population are needed; (ii) the differences in tasks used across the three methods evaluated (LEC1 during iEEG recordings, picture naming during ECS, and overt speech production during fMRI), that may explain the weak concordance that we found between the methods; cerebral regions involved in every task may differ, since different linguistic processes are used to trigger the response (see for a review (Baciu & Perrone-Bertolotti, 2015; Perrone-Bertolotti & Baciu, 2016); studies using a common task should be encouraged in the future to better evaluate relationship between GBR and other functional mapping techniques; (iii) the very small number of patients with available a fMRI examination, the realization of which was decided on the basis of clinical needs. Despite these limitations, our study can be viewed as a proof of concept.

# Conclusion

This study is the first, to our knowledge, to have assessed post epilepsy surgery language outcomes through functional data obtained from a behavioural task combined with iEEG recordings, and compared with ECS and fMRI data. It mainly shows that GBR elicited by a controlled language task may predict ECS language interference with a strong specificity, but with a weak sensitivity. This therefore suggests to use GBR mapping as a preliminary tool to adapt ECS sessions. The ability of GBR mapping to detect specific linguistic processes could make it also a useful complement to ECS that can be thus applied during specific tasks accordingly. The present study, however, must be considered as a proof of concept and deserves further studies.

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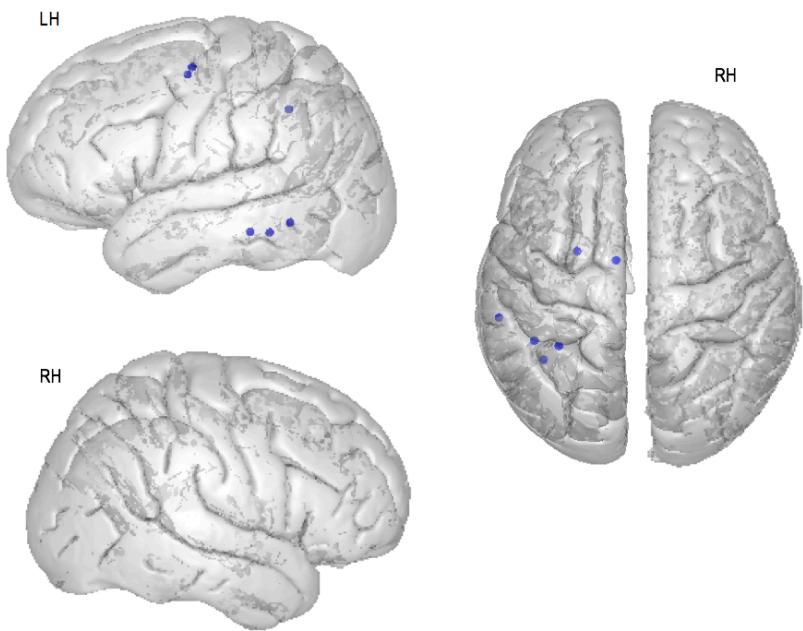


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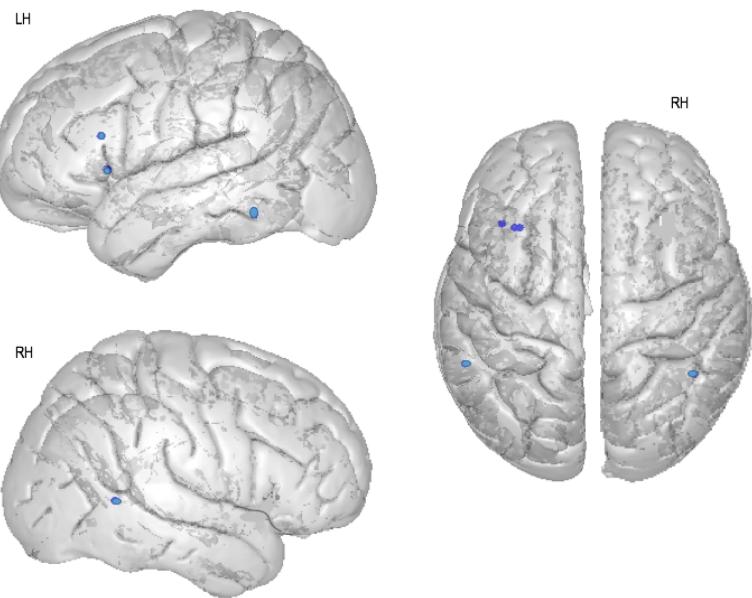
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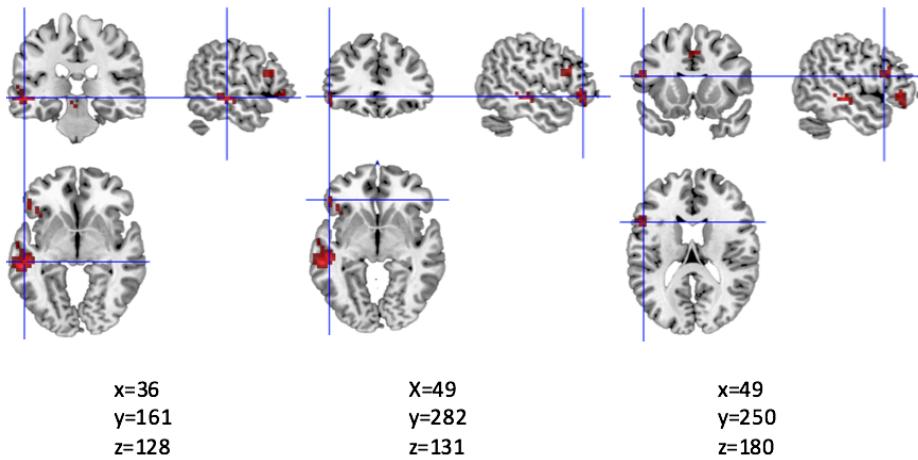
## Appendix



**Figure 4 :** Spatial distributions of the GBR+ and ECS+ sites from all 14 patients (P1-14) in common coordinates. Distributions are presented on axial and lateral views of MNI brain template. These six GBR+ECS+ sites are all located on the left (and language dominant) hemisphere.



**Figure 5 :** Spatial distributions of the GBR+ and fMRI + sites from all 6 patients with available fMRI data in common coordinates. Distributions are presented on axial and lateral views of MNI brain template.



**Figure 6** Brain activation during the speech production task projected onto 2D slices. For each activated site, MNI coordinates are showed. MNI, Montreal Neurological Institute.

P	Response Time							Accuracy							GBR+ R	ECS- R
	Pre op <sup>1</sup>		Post op <sup>1</sup>		Delta <sup>2</sup>	P-value*	P value*	P value <sup>Ψ</sup>	Pre op <sup>1</sup>	Post op <sup>1</sup>	Delta	P- value*	P value*	P value <sup>Ψ</sup>		
1	1149	374,4	1133	317,4	16	>0,99	0,48		93,3	91,7	1,6	0,99	0,41		x	
2	903,4	266,7	950,5	310,3	-47,1	0,099			76,7	90	-13,3	0,06				
3	1060	356,4	1093	420,6	-33	0,75			81,7	85	-3,3	>0,999				
4	1131	413	1119	389,9	12	>0,99	0,46		86,7	81,2	5,5	0,92		<0,000001		x
5	1124	364,7	1550	490,1	-426	<0,0001			86,4	45	41,4			<0,0001		
6	1659	572	1196	443,3	463	<0,0001	0,021		70	78,3	-8,3	0,90		<0,000001		x
7	1353	541,9	1146	386,5	207	0,17			80	86,7	-6,7	0,0007				
8	1224	550,9	1232	339,8	-8	0,99			38,3	100	-61,7			<0,0001		
9	1065	330,3	962	224,4	103	0,38			93,3	95	-1,7	0,99				
10	958	457,2	822,7	185,9	135,3	0,065			88,3	95	-6,7	0,39				
11	794,5	218,2	991,3	392,7	-196,8	0,019			99	91,7	7,3	0,69				
12	1178	269,9	1095	314,1	83	0,70	0,33		95	93,3	1,7	0,99		0,012		x
13	1106	1113	864	369	242,6	<0,0001	0,19	0,12	91,6	98,3	6,7	0,17	0,46	<0,000001	x	x
14	1398	867	1223	1159	175	0,052			81,6	96,6	15	0,008				

**Table 8:** Semantic task results from all 14 patients in pre and post-operative. 1 Mean and Standard deviation, <sup>2</sup> difference between preoperative features (mean) minus post-operative features (mean),\* 2x2 ANOVA,• Crawford and Howell's modified t-test for patient with GBR+ site resected,Ψ Crawford and Howell's modified t-test for patient with ECS+ site resected; †P9 Vlm non available ( see 2.7 for details).

P	Response Time					Accuracy					GBR+ R	ECS+ R
	Pre op <sup>1</sup>	Post op <sup>1</sup>	Delta <sup>2</sup>	P-value*	P value•	Pre op <sup>1</sup>	Post op <sup>1</sup>	Delta	P-value*	P value•		
1	1936 402,2	1746 573	190	0,10		93	91,6	1,4	0,87			
2	989 360,3	964 300,5	25	0,99		95	91,7	3,3	0,98			
3	1569 458,6	1420 396,1	149	0,28		83,3	95	-11,7	>0,99			
4	1548 403,6	1419 489,6	129	0,48		91,7	95	-3,3	0,98		x	
5	1942 413	1434 417,6	508	<0,0001		46,7	40	6,7	<0,0001			
6	2084 669,8	1534 471,4	550	<0,0001		46,7	75	-28,3	0,005		x	
7	1356 622,5	1002 344,3	354	<0,001		85	98,3	-13,3	<0,001			
8	1910 732,9	1103 358,6	807	<0,0001		3,3	95	-91,7	<0,0001			
9	1107 281,7	1198 401,6	-91	0,52		100	98,3	1,7	0,99			
10	1032 228	854 191,5	178	0,004	0,36	98,3	100	-1,7	0,99	0,32	x	
11	1378 456,4	1097 360,9	281	<0,0001		51,7	96,7	-45	<0,0001			
12	1316 476,2	1207 386,1	109	0,41		93,3	90	3,3	0,96		x	
13	1243 1044	898 471	345	<0,0001	0,39	93,3	98,3	-5	0,17	0,25	x	x
14	1518 441	1419 915	98,75	0,29		91,6	75	16,6	0,04			

**Table 9:** Phonological task results from all 14 patients in pre and post-operative. <sup>1</sup> Mean and Standard deviation, <sup>2</sup> difference between preoperative features (mean) minus post-operative features (mean),\* 2x2 ANOVA,• Crawford and Howell's modified t-test for patient with GBR+ site resected, †P9 Vlm non available (see 2.7 for details).

Condition	Response Time	Accuracy
<b>Semantic</b>		
R	0,27	0,304
p value	0,36	0,31
<b>Phonological</b>		
R	-0,07	0,34
p value	0,59	0,13

**Table 10 :** Correlation between the extend of the resection and behavioural performances in the semantic and phonological tasks in terms of response time and accuracy. R = Pearson correlation coefficient value

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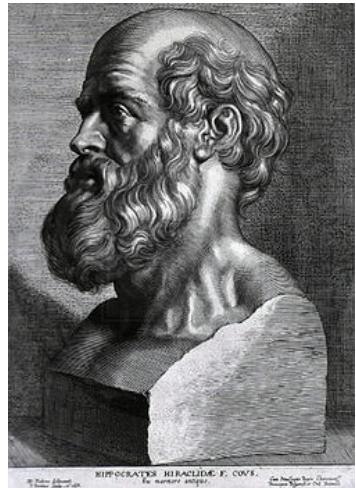
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## SERMENT D'HIPPOCRATE

*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,*

*Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*

# Résumé

**Contexte :** La chirurgie de l'épilepsie offre aux patients épileptiques pharmaco-résistants l'opportunité d'être libérés de leurs crises. Elle les expose néanmoins à un risque de déficits cognitifs post-opératoires, notamment à des troubles du langage. L'anticipation de ces déficits nécessite la réalisation d'une cartographie cérébrale pré-opératoire afin de localiser les régions cérébrales fonctionnelles à préserver durant la chirurgie. Il existe actuellement plusieurs méthodes de cartographie fonctionnelle cérébrale dont l'IRM fonctionnelle (IRMF) et les stimulations corticales électriques (SCE) réalisées au cours d'une exploration électroencéphalographique invasive par électrodes intracérébrales (Stéréo-EEG, SEEG). Les SCE constituent actuellement le « gold standard » en terme de cartographie fonctionnelle. Néanmoins, cette technique, comme l'IRMF, présente des limites.

**Objectifs :** Depuis une quinzaine d'années, l'étude des activités cérébrales haute fréquence dans la bande gamma (ou *gamma band responses*, GBRs) connaît un véritable essor. Ces activités constituent un marqueur robuste de l'activité neuronale pouvant être utilisé comme outil « localisateur » des régions corticales fonctionnelles. Les GBRs apparaissent ainsi comme une alternative aux autres méthodes de cartographie fonctionnelle. Cette étude vise à comparer l'analyse des GBRs, comme outil localisateur des régions qui sous-tendent le langage, avec les SCE et l'IRMF. Elle vise également à évaluer la capacité des GBRs à prédire le devenir cognitif post-chirurgical en déterminant si la résection d'une région ayant présenté des GBRs est à l'origine de plus de déficits post-opératoires que si ces régions sont préservées.

**Méthodes :** Quatorze patients épileptiques ayant bénéficié d'une exploration SEEG et subi une cortectomie au CHU de Grenoble ont été sélectionnés. Le signal EEG intracrânien était enregistré durant la réalisation d'une tâche informatisée de langage (Lec1) incluant deux conditions langagières (sémantique et phonologique). Des GBRs langage induites (50–150 Hz) ont été recherchées au niveau de chaque site exploré et comparées aux résultats obtenus lors des SCE. De plus, l'analyse des GBRs était comparée aux données de l'IRMF dans un sous-groupe de 6 patients ayant bénéficié d'une cartographie pré-opératoire du langage par IRMF. Une évaluation post-opératoire par Lec1 était réalisée. Ainsi le devenir post-opératoire du langage des patients ayant subi une résection comportant un site ayant GBRs + était comparé à celui des patients dont les sites GBR+ étaient épargnés (groupe contrôle).

**Résultats :** Les GBRs langage-induites ont prédit les résultats des SCE avec une forte spécificité (92.4%) et une forte valeur prédictive négative (VPN, 95.5%) mais une faible sensibilité (11.7%) et une faible valeur prédictive positive (VPP, 7.4%). Les résultats étaient similaires lors de la comparaison avec l'IRMF (spécificité : 89.2%, VPN : 84.7%, sensibilité : 8.4%, VPP : 12.2%). Les avantages des GBRs ont été soulignés, notamment leurs capacités à préciser le processus cognitif impliqué, spécifiquement linguistique. Les performances post-opératoires en langage des patients ayant subi une résection comportant un site ayant GBRs + n'étaient pas significativement différentes de celles du groupe contrôle. Seul un faible effectif de patients ont subi une résection comportant un site GBRs+ ( $n=2$  en condition sémantique et  $n=2$  en condition phonologique).

**Conclusion :** Nos résultats confirment la faisabilité des GBRs induites lors d'une tâche comportementale dans le bilan pré-chirurgical de l'épilepsie pharmaco-résistante. Les GBRs complètent les données obtenues en SCE et IRMF et guident la réalisation des SCE. L'intérêt d'une cartographie pré-chirurgicale multimodale est ainsi souligné.

**Mots-clés :** Chirurgie de l'épilepsie ; Stéréo-électroencéphalographie ; Activités gamma ; cartographie fonctionnelle ; Langage ;