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## **Exploring Post Rehabilitation Plasticity with Intra-cerebral Recordings on Anomic Profiles**

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## Abstract

**Background:** Patients with drug-resistant epilepsy involving the language network often exhibit anomia profiles in daily life due to difficulties with lexical selection processes. There is very little evidence available regarding the effects of language rehabilitation in this population.

**Objective(s):** We aim to induce brain plasticity combined with improvements in behavioral performance through language therapy in patients with epilepsy.

**Methods:** We implemented a therapy focused on phonological and semantic features of infrequent words over three treatment sessions, each targeting a specific semantic category. Intracranial signals were recorded in 10 patients during baseline and post-therapy picture-naming sessions. Response time and percentage of correct responses during naming tests were collected. Time-frequency analyses were conducted on intracranial signals, and comparisons were made between baseline and post-therapy conditions for each patient.

**Results:** Half of the patients demonstrated improved naming skills following the treatment. We observed significantly different recruitment of frontotemporal areas in the left hemisphere (including “Broca's Area”) post-therapy in patients that improved naming skills. Specifically, we found significantly different high-gamma activity in the posterior left inferior frontal gyrus 500 ms after stimulus onset in patients with improved naming skills vs non-improved naming skills. This effect was not observed in the right hemisphere.

**Conclusions:** These findings suggest that enhanced performance following language therapy is associated with modifications in posterior left IFG activations during latencies closely tied to the lexical selection process.

*Keywords:* Anomia profile; intracranial EEG; rehabilitation; epilepsy;

## Introduction

Patients with drug-resistant epilepsy may exhibit impairments in language production alongside their pathology. Individuals with temporal lobe epilepsy (TLE) localized in the dominant hemisphere for language are particularly susceptible to experiencing language difficulties during the interictal state. These patients often demonstrate an anomia profile characterized by relatively intact semantic processing but difficulties in accessing lexical and phonological information (Trebuchon-Da Fonseca *et al.*, 2009; P. Campo *et al.*, 2013; Bartha-doering and Trinka, 2014; Miozzo and Hamberger, 2015). This deficit is occasionally accompanied by verbal memory deficits (Trebuchon-Da Fonseca *et al.*, 2009; P. Campo *et al.*, 2013). Factors such as the duration of epilepsy, seizure frequency, antiepileptic drug, history of temporal lobe surgeries, presence of brain lesions, and potential interictal epileptiform discharges have been identified as significantly impacting naming ability (Dodrill and Ojemann, 2007; Trimmel *et al.*, 2021; Caciagli *et al.*, 2023). Surgical resections performed to control seizures increase these language deficits in a sizeable number of cases (Ives-Deliperi and Butler, 2012). Connectome analysis have demonstrated that naming proficiency in TLE patients is linked to the involvement of subnetworks involved in semantic memory and lexical retrieval, rather than being dependent solely on discrete brain regions (Munsell *et al.*, 2019).

Because patients with cognitive impairments encounter difficulties in daily life, rehabilitation effectiveness is a significant concern. Mazur-Mosiewicz *et al.* conducted a systematic review of cognitive rehabilitation programs offered to patients experiencing cognitive disorders after surgery. Evidence from the literature suggests that post-surgical rehabilitation can be effective in some cognitive domains such as memory (Joplin *et al.*, 2018). However, the rehabilitation of language or word-finding difficulties in LTLE patients has been understudied, and various authors emphasized the necessity for systematic evaluation in this population (Mazur-Mosiewicz *et al.*, 2015; Sabadell, Trébuchon and Alario, 2024).

The impact of language therapy on behavior and neural activity has been extensively explored in the vascular aphasic population. Most studies utilized fMRI measurements, focusing on patients with an anomic profile, closely related to language production deficits observed in our target population. These investigations revealed that the alterations in brain area recruitment post-therapy vary with therapy type (Kiran and Thompson, 2019). Brain area involvement is rationalized under the dual-stream model, encompassing the ventral stream (Inferior Temporal Sulcus, ITS; Middle Temporal Gyrus, MTG; and Superior Temporal Gyrus, STG) and the

dorsal stream (Inferior Frontal Gyrus, IFG; anterior insula; and premotor area) (Del Gaizo *et al.*, 2017). Therapies employing phonological exercises, particularly phonological cueing, showed a link to bilateral activation of dorsal pathways (Nardo *et al.*, 2017). Interventions focusing on phonological and semantic exercises were associated with left ventral activation of brain regions (Bonilha *et al.*, 2016). The engagement of areas adjacent to the classical language network might relate to using additional cognitive functions, such as executive functions, to enhance language skills (Fridriksson *et al.*, 2022).

The research utilizing EEG or MEG is less abundant and yields diverse outcomes. A common theme in these studies is the correlation between therapy effectiveness and its intensity. The success of rehabilitation is gauged using various metrics, such as latency and amplitude changes in ERP/Fs (N400, P300) and modifications in sleep slow waves. Multimodal therapies, which include, for instance, phonological and semantic exercises, have demonstrated varied results (Cornelissen *et al.*, 2003a; Breier *et al.*, 2010; Wilson *et al.*, 2012; Sarasso *et al.*, 2014). There is a tendency to observe changes in signal modification in the left hemisphere post-therapy (Breier *et al.*, 2010; Wilson *et al.*, 2012), particularly in the frontal area (Sarasso *et al.*, 2014).

Increasing evidence suggests that therapies may induced a reorganization in the left hemisphere activation. However, the link between rehabilitation type and plasticity remains unaddressed in the context of focal epilepsy. Recently, a group of experts proposed a new paradigm through which individual treatments can be systematically characterized in terms of targets, ingredients, and mechanisms of action (Fridriksson *et al.*, 2022). Based on their recommendations, rehabilitation in epilepsy should target naming abilities by stimulating both phonological and semantic processes through a multimodal approach, employing repetitive and intensive training.

The reorganization of brain activity in the context of TLE could manifest either as a shift in language dominance from the left hemisphere to the right hemisphere, or as a relocation of language processing from temporal regions to frontal regions (Tzourio-Mazoyer *et al.*, 2017). Furthermore, studies have shown that the reorganization of the neural language network away from the seizure onset zone correlates with improved language abilities post-surgery (M Perrone-bertolotti *et al.*, 2012). Frontal regions involved in language network in particular posterior part of IFG are typically preserved in surgeries for drug-resistant epilepsy, it is relevant to investigate whether there is any electrophysiological plasticity in this area following rehabilitation. Due to the inconsistent anatomical definition of Broca's area (Tremblay and

Dick, 2016) and the heterogeneous functional involvement of this region in either the 'language network' or the domain-general network (Fedorenko and Blank, 2020), we have chosen to define Broca's area in the present study as the posterior IFG, including the posterior part of the pars triangularis and the pars opercularis (Amunts *et al.*, 2010).

This study aims to explore the effects of naming rehabilitation on epileptic patients exhibiting anomia. A novel feature of our approach is that the therapy and its appraisal were conducted during the presurgical invasive evaluation. Specifically, we assessed how three therapy sessions may influence naming performance and neural activity, recorded via intracranial stereo-electroencephalography (SEEG) in several region involving in naming processing such as posterior IFG, MTG, STG, left baso-temporal area. In our research, we opted to employ the same picture naming task for both behavioral and neural evaluations. We anticipated that in post-therapy sessions, patients' performance would improve alongside corresponding changes in brain activity, compared to the baseline condition.

## Methods

### *Patients*

We included ten drug-refractory epileptic patients (7 females) during their pre-surgical investigation. Patients underwent intracranial video-SEEG recording following complete or partial withdrawal of antiepileptic drugs during a period that could range between 4 to 10 days, to record the patient's seizures. The strategy of electrode positioning was established in each patient based on hypotheses concerning the localization of the epileptogenic zone (EZ), to define the subsequent cortectomy. The clinical procedure for the localization of EZ included the visual and quantitative analysis of electro-clinical correlations recorded in video-SEEG. The patients were included in the study because they presented cognitive complaints concerning word retrieval in daily life during neuropsychological assessment. Details of clinical data are summarized in Table I. All patients were native speakers of French. For the current study, the patients were bedside tested collaterally to the diagnostic procedures performed during presurgical investigations. All patients signed an informed consent form prior to participation. This study was approved by the institutional Review Board of the French Institute of Health (IRB00003888).

### *Experimental design*

The experimental design was shaped by the constraint of SEEG recording durations. Patients performed two (pre-therapy) picture naming blocks included in the functional cartography. The therapy protocol then consisted of three sessions, one per day. After each training session, patients did one post-treatment picture-naming block (Figure 1). The total duration of the procedure was four days.

### *Materials*

#### *Therapy*

As encouraged by Fridriksson et al. (Fridriksson *et al.*, 2022), we describe our language rehabilitation program according to the treatment specification system: target, active ingredients, and possible mechanisms of action of the treatment. The rehabilitation target was anomia. To select active ingredients, we drew on theoretical considerations from the fields of neuropsychology, cognitive neuroscience, and re-adaptation sciences. We reviewed the literature on anomia rehabilitation, primarily conducted with stroke patients, but also successfully applied in the context of other pathologies such as primary progressive aphasia (Pagnoni *et al.*, 2021) and most recently epilepsy (Sabadell, Trébuchon and Alario, 2024). The ingredients were selected from a cognitive perspective while considering patients' frequent memory problems.

Finally, for the mechanisms of action, we largely adhered to Kiran and Thompson's hypothesis about brain plasticity driving language recovery after stroke (Kiran and Thompson, 2019). They identified general principles and factors to be incorporated into language rehabilitation. The first two principles encourage the treatment of impaired—rather than preserved—language processes, to promote underlying recovery mechanisms. The third principle highlights the need to reinforce patients' motivation and attention. Other principles call for repetition and intensity. Finally, task complexity is thought to promote learning and generalization. Given current cognitive accounts for word-finding difficulties in LTLE patients, combining semantic and phonological tasks seemed the most relevant approach for our purposes. During the procedure, items that shared semantic features were grouped to induce a contextual priming (Kiran and Thompson, 2003; Boyle, 2017). In addition, the semantic complexity (operationalized in terms of atypicality in the category) was controlled to improve generalization effects to other words (Kiran and Thompson, 2003; Gilmore *et al.*, 2020). In a recent pilot study, we demonstrated the

effectiveness of this rehabilitation program for trained items and observed encouraging results for untrained items (Sabadell, Trébuchon and Alario, 2024).

### *Therapy procedure*

The procedure was the same for each therapy session; it was divided into ten steps (Figure 1B). For each item, the written and spoken name was provided to the patient who then performed different tasks: read, copy, delayed copy, spell, recall, reverse spell, analyze phonologically, recall a personal memory, answer semantic yes / no questions, gesture (if relevant), and recall. If a step was not successfully completed, the experimenter went back to the previous step. Before the end of the session, the experimenter grouped all trained items and asked the patient to alternatively name and repeat them. Each therapy session lasted 45 minutes and was dedicated to tens items from a given semantic category (mammals, objects, or fruits and vegetables).

### *Picture naming*

We used colored pictures in a picture naming task to quantify behavioral and neurophysiological modifications following language therapy. The pictures were selected from the MultiPic database (Duñabeitia *et al.*, 2017). We excluded repeated words. We collected words' features in the Lexique database (New *et al.*, 2004). We created five different lists, each comprising 100 items. These items were matched across blocks for several relevant parameters: visual complexity, percentage of modal name, oral and written French lemma frequency, number of phonemes, number of phonological neighbors, semantic categories and number of syllables (van Casteren and Davis, 2007). The items to be trained in the therapy procedure were selected within the list of 500 words created for the naming tasks, with the inclusion criteria of being of low frequency (*i.e.* below an arbitrary threshold of 4 occurrences per million) and belonging to specific semantic categories.

### *Naming procedure*

We implemented the task on E-prime 2.0 (Psychology Software Tools, Pittsburgh, PA). Patients were tested bedside at least two hours after a seizure, while they were comfortably seated in their hospital room. The pictures were presented on a laptop screen (size 12x8'') placed on a table. The laptop was connected to the clinical SEEG/video acquisition system Natus. The video recordings were not used in this research. One marker was written on the SEEG recording at the moment when the picture was presented. Each trial started with a fixation cross, presented



for 1,000 ms, followed by the experimental picture. The experimenter proceeded to the subsequent trial manually. The 100 trials composing each block were presented in a random order. Patients were instructed to name each picture aloud, as soon as possible without time or accuracy constraints. Patients received no feedback during this naming task to ensure that any learning effect could be linked to the prehabilitation procedure. The audio responses were recorded for offline scoring.

#### *Analysis of behavioral performance*

Due to diversity of patient etiology and of electrode localization, we chose a multiple cases approach in which the data of each of the 10 patients were analyzed independently of one another.

#### *Pre-processing*

The responses to each trial of the picture naming task were analyzed offline using CheckVocal (Protopapas, 2007) to accurately measure the Response Time (RT in ms) and assess the quality of the response. We considered a response correct if the patient provided the target word within a 12 second time delay. The types of errors were classified as described in Table 1S. We excluded trained items from behavioral analyses (13 items across the three posttherapy blocks).

#### *Statistical analyses*

Pre-therapy and post-therapy performance were contrasted with a bootstrap procedure. We computed single-case bootstrap estimates of the confidence interval (CI) around the mean performance at baseline (blocks 1 and 2; algorithm by (DiCiccio, science and 1996), implemented in the R package `boot` version 1.3-30), separately for response time (RT) and percentage of correct responses (%CR). The performance measure at each post-therapy block (blocks 3, 4, or 5) was then compared to this 95% confidence interval and declared significantly different from baseline whenever it lied outside the CI. For the group analysis, the same procedure was used, now with the whole dataset. The resampling procedures preserved the hierarchical (patient and session) structure of the data. In other words, the sampling with replacement was conducted within each patient x session cell of the design.

## *Analysis of neural activity*

### *Signal processing*

Intracerebral EEG signals were recorded using intracerebral multiple contact electrodes (10 to 15 contacts, length: 2mm, diameter: 0.8mm, 1.5mm apart edge to edge) implanted according to Talairach's stereotactic method. Neurophysiological signals were recorded continuously using a 256-channel Natus system, sampling at 512 Hz, with a low-frequency filter setting of 0.1 Hz.

The signals were extracted from the Natus software and preprocessed in Brainstorm (Tadel *et al.*, 2011). We excluded trials on which the behavioral response was classified as incorrect. In addition, epochs containing epileptic spikes were removed by visual inspection, as were contacts with flat and noisy recorded activity. The signals were epoched in two different ways. First, epochs were extracted from 1 s before to 2 s after the onset of each picture stimulus; these were used in "stimulus-locked" analysis. Second, epochs were extracted from 1s before to 0.5s after each verbal response onset; these were used in "response-locked" analysis.

We focus our analysis on high-gamma activity, which has been linked to cognitive processing (Lachaux *et al.*, 2012). We processed the data using MIA (Dubarry *et al.*, 2022). Time-frequency power was computed on consecutive 10-Hz bands between 80 and 150 Hz using a 7-cycle Morlet wavelet transform on bipolar montage of contacts. To compensate for the 1/f distribution of power across the spectrum, a baseline correction was applied to each trial at each 10-Hz band by computing a z-score relative to activity during the baseline from 600 ms to 50 ms before picture onset. Then, high-gamma activity was averaged across trials for each couple of contacts. Pairs of contacts of interest were selected if they recorded high gamma activity during the naming task, while inactivated sites were excluded.

All patients underwent a structural preoperative MRI scan and an intraoperative computed topography scan as part of the clinical routine. An expert neurologist labeled each pair of contacts according to the brain atlas by observing the fused CT-MRI images (Mai, Paxinos and Voss, 2008). Thanks to the 3DViewer extension from Gardel software, all contact sites of each patient can be visualized into a 3D representation (Medina Villalon *et al.*, 2018).

### *Statistical analyses*

As for verbal performance, the statistical analyses contrasted pre-therapy blocks 1 and 2, grouped, with post-therapy outcome blocks, we chose to average high-gamma activity recorded in a couple of contacts of interest during blocks 1 and 2, *i.e.* baseline condition, and high-gamma

activity recorded in a couple of contacts during blocks 4 and 5, *i.e.* posttherapy condition. For each pair of adjacent contact, we computed paired Student t-tests at each time sample. Thus, we obtain a time-course of t-values corresponding to moments when signals significantly differ between conditions with  $p < .001$  (Figure2).

## Results

### *Behavioral performance*

Behavioral results before and after therapy are presented in Table 2 A & B. We observed a significant improvement in both speed (RT) and accuracy of naming (%CR) post-therapy in five patients (P1, P2, P3, P4, and P6), and an improvement in naming accuracy (%CR) alone in one patient (P5). These patients are classified as 'good responders.' However, the pattern is not entirely consistent across all patients, particularly for the remaining four patients (P7 to P10). All patients exhibited similar language errors, particularly semantic paraphasia and omissions, as described in Table 2S (supplementary materials).

In the group analysis, Response Times in post-therapy sessions lied within the bootstrapped confidence interval; in contrast, Correct Response rates lied outside of this confidence interval. In other words, the group overall was not faster after performance, but it was more accurate. This average increase in accuracy overlooks the large inter-patient variability we observed.

### *Electrophysiological activity*

Figure 2 presents the detailed electrophysiological results for one patient (P1), while Figures 3 and 4 summarize the electrophysiological results across all patients. Due to clinical constraints, not all patients underwent the same exploration, and since the temporo-frontal areas were not investigated in P10, we decided to exclude this patient from the electrophysiological analyses. However, the left posterior IFG was sampled in all nine remaining patients.

### *Stimulus-locked activities*

We found significant differences in high-gamma activity ( $p \leq .001$ ) between baseline and post-therapy conditions for patients who showed improvements in both %CR and RT during post-therapy blocks (P1, P2, P3, and P6) in the posterior left IFG between 400 and 1000 ms. Additionally, no significant differences were found in patients with posterior right IFG exploration (P2 and P6). No such changes were observed in other patients, despite all being

sampled in this region. The time course of high-gamma activity and the specific time points of significant differences are detailed for each area in the Supplementary Material.

In addition, our analyses time-locked to stimulus presentation revealed three other brain areas in the left hemisphere (Figure 3) that were engaged during picture-naming tasks, showing significant differences between baseline and post-therapy conditions: the Basal Temporal Area (BTA), Middle Temporal Gyrus (MTG), and Postcentral Gyrus (PCG). Two additional areas, the Primary Auditory Cortex (PAC) and the hippocampi in both hemispheres, also showed significantly different activations between conditions (Figure 4)

#### *Response-locked activities*

Time-locked to response onset, we recorded significant modifications in high-gamma activity in the left MTG (Figure 3) and in the bilateral PAC and hippocampi (Figure 4).

## Discussion

Patients with drug-resistant epilepsy that disorganizes the language network are likely to display an anomia profile with verbal memory impairments between seizures; these deficits may increase after surgery (Bartha-doering and Trinka, 2014; Busch *et al.*, 2016). Our study is the first to assess behavioral and neural changes induced by a language therapy in this population. Furthermore, we assessed brain activity using SEEG recordings during the intracerebral presurgical evaluation. In four patients, we observed improvements in behavioral performance following therapy, which were associated with electrophysiological modifications in “Broca's area” (left posterior IFG).

### *Behavioral changes*

First of all, behavioral assessments show that all patients presented the same kind of language errors, especially semantic paraphasia and omissions that have been previously reported (Trebuchon-Da Fonseca *et al.*, 2009; Minkina *et al.*, 2013; Bartha-doering and Trinka, 2014). Accuracy (% Correct Responses) is typically used in the literature to compare behavioral performance before and after therapy. We observed heterogeneous accuracy patterns across patients (Table 2). To provide a more comprehensive description of the behavioral patterns, we also assessed response times (RT). Notably, five patients demonstrated significantly faster post-therapy RTs naming times and significant improvement of accuracy. As depicted in Table 2 the improvement of %CR is not always combined with shorter RT and *vice-versa*. However, increasing %CR along with shorter RT does not reflect the same behavioral strategy than increasing %CR along with longer RT. We can assume that behavioral compensatory mechanisms would be different. For these reasons, we believe it is important to add RT measurements more systematically in further studies. The RT variable has been neglected for quite some time (Crerar, 2004; Conroy, Sage and Lambon Ralph, 2009), despite its potential significance. Although there is considerable interest in analyzing naming speed in anomic patients, the rehabilitation effects on this aspect present several methodological challenges. The interindividual variability of the success of therapy is already documented (Wisernburn and Mahoney, 2009)

Effects reported in the literature are mainly focused on trained items. In our study, we excluded trained items from our data set, thus, we analyzed therapy effects on unexposed words. Additionally, considering the decrease in naming speed with practice (Levelt, 1999) it remains

unclear whether the effects on untrained items results from the intervention or merely from task repetition (Basso *et al.*, 2013). In our study, we exclusively collected RT data for untrained items across five distinct blocks that had never been named previously, thereby eliminating the risk of re-test effects. We can attribute modifications of behavioral performance to generalization effect to other categories. In the literature, the effect size of semantic therapy seems to be relatively small but larger than for other therapy types (Wisenburn and Mahoney, 2009). In general, most of the gains after language therapy are reported for exposed/trained words (Wisenburn and Mahoney, 2009). Generalization is the targeted effect of a therapy because it is the sign that training of some items from some semantic categories has an extended impact to other categories. In our study, the behavioral performance we recorded demonstrated a generalization effect, meaning they extended to untrained words a result that is often difficult to measure consistently (Mayer *et al.*, 2024). We hypothesize that this generalization effect occurred because post-therapy assessments were conducted *immediately* after the therapy. Generalization effects may have been facilitated by several ingredients of our therapy, including the utilization of a semantic task, the incorporation of an orthographic model, the high frequency of repetitions within each session, and the frequency of sessions within the same week (SZE *et al.*, 2021).

The weakness of the behavioral results, specifically the lack of significant group improvement in accuracy, can be explained by the experimental design of our study. Our study was focused on short-term effects through the administration of three sessions that lasted 45 minutes each (for a total of 135 minutes). These constraints were imposed by the clinical setting in which the therapy took place. Indeed, patients included were involved in presurgical investigations for localizing the EZ; they were admitted for a period that lasted from 4 to 10 days. It is possible that some patients needed more time for training to present positive effects, given that a better recovery is associated to 8.8 hours of therapy per week for 11.2 weeks in treatment in poststroke aphasia (Bhogal, Teasell and Speechley, 2003). It also has been demonstrated that the intensity of the therapy is an essential component of its efficiency (Jacquemot, Dupoux and Robotham, 2012; Kiran and Thompson, 2019). A higher dosage and a higher number of repetitions of items have been associated with the short-term effects of therapy (SZE *et al.*, 2021).

In addition, the location of the EZ may be a factor linked to the benefit of the therapy. P1, P4, and P5 are all patients with temporal lobe epilepsy; in contrast there is a higher proportion of frontal lobe epilepsy patient in individuals with more various behavioral evolutions after therapy. Neural networks involved in language deficits and those that can be engaged in

plasticity induced by the therapy are potentially different between these patients. Furthermore, it has been shown that the location of the EZ is a factor involved in reorganizing language representation in the brain (Marcela Perrone-bertolotti *et al.*, 2012; Baciú and Perrone-Bertolotti, 2015) .

### *Electrophysiological changes*

Intracranial recordings give the opportunity to investigate brain activity with an optimal signal-to-noise ratio in contrast to other neuroimaging techniques. The major inconvenience is the limited spatial sampling guided by clinical assumptions. Thus, SEEG allows us to make time-frequency analyses in high frequencies (high-gamma) known to be closely linked to cognitive processing (Lachaux *et al.*, 2012). In parallel to behavioral changes, electrophysiological analyses show modifications of high gamma activity elicited by the naming task in the posterior IFG (“Broca’s area”) in the left hemisphere.

We found significant differences in high-gamma activity in the left posterior IFG/ “Broca's area” before and after therapy only in the four patients who showed improvements in their naming skills. No significant differences were observed in patients where the right IFG was sampled and engaged during the task. These results suggest that the effectiveness of rehabilitation may be linked to changes in the recruitment of the left posterior IFG.

Neural changes following a language therapy reported in the case of post stroke aphasia show two main kinds of neuroplasticity: the engagement of left perilesional areas and/or the recruitment of homologous contralateral regions. Some studies about patients with vascular aphasia have demonstrated that gains in naming ability following early intensive therapy are correlated with increased activation of the posterior left IFG/ “Broca’s Area” (Mattioli *et al.*, 2014; Crosson *et al.*, 2019). The main implication of the left hemisphere in language treatment effects is in line with EEG and MEG studies of neural plasticity induced by language therapy (Cornelissen *et al.*, 2003a; Meinzer *et al.*, 2004; Wilson *et al.*, 2012; MacGregor *et al.*, 2014; Sarasso *et al.*, 2014; Singh *et al.*, 2018). Cornelissen *et al.* observed training-specific effects in the left inferior parietal cortex, close to the impaired areas, without changes in the right hemisphere after therapy (Cornelissen *et al.*, 2003a). Mohr and collaborators measured MMNm changes after Intensive Language Action Therapy (ILAT). They found a therapy-related increase of MMNm amplitudes over the left language-dominant hemisphere approximately 200

ms after words could first be recognized in meaningful words in contrast to pseudowords (Mohr *et al.*, 2016). They proposed that left fronto-temporal topography of the pre-post MMNm change may reflect better functionality of lexical semantic networks, which may be the basis for the observed improvement of language processing. Singh *et al.* (2018) observed that ERPs source analysis post rehabilitation revealed that the ability to recruit left frontal areas within a 300–550 ms time window after stimulus onset contributed to correct responses (Singh *et al.*, 2018).

In the context of brain tumors, functional reorganization appears to follow a hierarchical sequence, initially engaging peri- and intralesional areas and subsequently involving regions in the opposite hemisphere for compensation (Nieberlein *et al.*, 2023). Interestingly, the region most frequently reported to exhibit plasticity, whether perilesional or contralateral, is Broca's area (Gunal *et al.*, 2018; Nieberlein *et al.*, 2023). Closer to the population studied here, a case study of a patient with temporal lobe epilepsy shows that phonological tasks activated the left IFG and the right MTG with impaired behavioral performances before surgery. After surgery, phonological tasks activated left IFG and left temporal regions, with behavioral performance revealing average scores. The authors concluded that the right hemisphere is less efficient than the left for phonological processing (Marcela Perrone-bertolotti *et al.*, 2012). However, we must be cautious with our asymmetric result of brain plasticity given the clinical implantation schemas; the left hemisphere is more sampled than the right in our patients (35 recorded sites in the left *versus* 28 in the right hemisphere in all patients).

The left posterior IFG activity significantly increased around 500 ms after stimulus onset. According to various models, at that timing the left posterior IFG is involved in the end of lexical selection and the beginning of syllabification and the preparation of the articulation of the word in subjects without language impairments (Indefrey and Levelt, 2004; discussed by Laganaro, 2016; Munding, Dubarry and Alario, 2016). The temporal dynamics of processing stages might be different in patients who present language production deficits with an offset of stages linked to longer RT. In addition to the role of the left posterior IFG in linguistic features of word production, our results do not exclude a potential impact of neuroplasticity in this area on executive functions. It has been demonstrated that the left IFG, among other regions, is involved in inhibitory control over motor responses (Swick, Ashley and Turken, 2008). In addition, a study on Parkinson's disease patients showed that linguistic and executive function processes interact in the left posterior IFG, during word production tasks involving selection



with cortical asymmetries between patients with left- *versus* right-sided Parkinson's disease (Di Tella *et al.*, 2018; MacPherson *et al.*, 2019).

In addition to left IFG activity changes, we found early increased high-gamma activity in the left BTA, which has been previously linked to the lexical selection process (Llorens *et al.*, 2016; Munding, Dubarry and Alario, 2016; Dubarry *et al.*, 2017). Such modification of the activity in this area, along with better performance mainly measured in naming speed, may reflect better and faster lexical selection after the language therapy.

We recorded MTG activities at later latencies than those documented in the literature; it is usually recruited from 200 to 400 ms after picture onset whereas in our data its activity begins from 600 to 1,500 ms. The MTG is known to be part of the ventral stream and is engaged in the combination of information provided by different temporal areas. Thus, it has the potential to monitor the response through an internal loop (Hickok and Poeppel, 2007). Finally, the left PCG engagement was significantly different before and after therapy from 600 to 1,500 ms post-stimulus onset, suggesting a possible effect on motor preparation of the response induced by therapy protocol. Around 600 ms, this area may also be engaged in phonological processing (Cornelissen *et al.*, 2003b). Electrophysiological changes recorded in hippocampi and PAC are likely to be linked to duration of RT. It has been demonstrated that the latency of hippocampal high-gamma activity predicts naming latency (Hamamé *et al.*, 2014); however, our data do not allow us to link modifications of activity in this area to an effect of the therapy. In the same way, PAC activity is significantly different between conditions at latencies close to the RT. It has been reported that the two STGs are involved in the external loop of self-monitoring (Indefrey and Levelt, 2004). These changes may be more related to the moment of word production than to the effect of the rehabilitation.

We also find minor changes in the right hemisphere. The involvement of a widespread inter-hemispheric network after language therapy has been demonstrated in similar studies, depending on the language task performed by patients (Pulvermüller *et al.*, 2005; Meinzer *et al.*, 2008). Studies interested in the investigation of abnormal electrophysiological markers in aphasic patients have demonstrated shifts between right and left hemisphere in a specific time-window, suggesting an effect on a particular encoding process (Laganaro *et al.*, 2008). In addition, the authors proposed that variability in right hemisphere activations in different recovery stages indicates changes occurring between hemispheres during recovery. In addition,

the right hemisphere activation may be linked to the hemispheric complementarily properties and more generally the idea of a dynamic continuum of involvement of both hemispheres in language production (and language processing) (Lindell, 2006; Tzourio-Mazoyer *et al.*, 2017).

This study is the first to investigate the neural modifications related to language therapy in epileptic patients using the SEEG exploration method. The small number of patients involved limits the strength of the conclusions that can be drawn from the study. Also, the inherent variability in etiology, EZ localization, lesions and behavioral profiles across the participants warranted all the behavioral and electrophysiological data to be analyzed at the individual participant level. The explicit attempt to account for and detail the inherent variability across the patients (*i.e.* multiple cases approach) is a clear strength of this study (Jacquemot, Dupoux and Robotham, 2012).

More generally, the results of this study support the promotion of Enhanced Recovery After Surgery (ERAS) protocols. Several reviews report specific protocols proven to optimize the pre-, peri-, and postoperative care of patients undergoing surgery. ERAS protocols now exist for several neurosurgical procedures and populations (Greisman *et al.*, 2022; Liu *et al.*, 2022) but have not been established in the epilepsy surgery literature. The idea of prehabilitation to improve cognitive reserve can help patients cope with post-surgery cognitive decline (Mazur-Mosiewicz *et al.*, 2015; Baxendale, 2020). To date, few data are available in this field. Two studies report the benefits of prehabilitation before surgery. One study showed improved memory performance supported by the right hemisphere, thus reducing the risk of the surgical procedure (Verentzioti *et al.*, 2017). Another case study (n=3) reported a rehabilitation of twenty proper names before surgery and showed the preservation of some progress on trained items post-surgery (Kendall *et al.*, 2016). According to these authors, it is possible to shift critical functions for naming (*i.e.*, from left temporal lobe neural networks) to language networks distributed in the left hemisphere through multimodal training involving dimensions supported by other networks (*e.g.*, semantic, phonological, orthographic, and articulatory dimensions).

Finally, the link between improved naming performance parallel to brain activity changes provide an argument for using specific neuromodulation procedures in targeted regions to improve cognitive performance before surgery, particularly for low-grade gliomas (Barcia *et al.*, 2012; Rivera-Rivera *et al.*, 2017). This procedure has also been used in the context of

epilepsy surgery. In the reported case, six days of stimulation were sufficient to induce the neuroplasticity needed to extend the surgical procedure (Serrano-Castro *et al.*, 2020).

Boccuni *et al.* (2024) reported a case in which a patient underwent 20 days of non-invasive inhibitory rTMS and tDCS stimulation over the language network, coupled with intensive cognitive training before brain tumor surgery (Boccuni *et al.*, 2024). Prehabilitation resulted in increasing the distance between the tumor and the eloquent language network. Furthermore, enhanced functional connectivity within the language circuit was observed. This positive result confirmed the feasibility of a larger trial (Boccuni *et al.*, 2023).

The emerging evidence regarding prehabilitation is based primarily on isolated case studies. Although the target and type of stimulation have been well-documented, the type of procedure and the training target are rarely specified or are under-described. We hope that the results of the present study will help advance such preoperative care for patients undergoing surgery.

We must note that the limit of our investigation lies in the sampling of SEEG (stereo-electroencephalography), which does not permit comprehensive coverage of the entire neocortical surface as is possible with awake surgery. We did not show a specific effect in all the regions described involved in naming with direct electrical stimulation (Rofes *et al.*, 2024).

In conclusion, we found improved naming performance parallel to brain activity changes in patients with drug-resistant epilepsy after short-term language therapy administered during pre-surgical SEEG exploration. We observed a main effect of neuroplasticity in the left IFG/Broca Area, which is not included in the possible resection of the anterior part of the left temporal lobe proposed to patients with temporal lobe epilepsy. This could imply that the network involved in the success of the therapy should be preserved after surgery. Given that 34% of patients show decline of naming abilities after left temporal lobe resection, further studies including measurement of long-term language therapy effects should be interesting (Mazur-Mosiewicz *et al.*, 2015; Sabadell, Trébuchon and Alario, 2024).

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## Figures Captions

**Table1:** patients’ demographics and clinical information. NA non available data, TOT tip of the tongue, verbal fluency: number of word in 2 min

### **Table2A&B: Behavioral results in the picture naming tests**

**Table 2A:** Behavioral results in the picture naming tests (responses times RT).

Performance is reported as mean response times (RT) for each picture naming block and each patient. 95% bootstrap confidence intervals were computed within patient around the mean of baseline performance (blocks 1 and 2) to assess each post-therapy block (blocks 3, 4, or 5).

Significant differences are marked in bold; italics is for degraded performance after therapy.

Inf CI: 95% inferior confidence interval; Sup CI: 95% superior confidence interval; NA: not available

**Table 2B:** Behavioral results in the picture naming tests (% correct reponses).

Performance is reported as percentage of correct responses (% CR) for each picture naming block and each patient. 95% bootstrap confidence intervals were computed within patient

around the mean of baseline performance (blocks 1 and 2) to assess each post-therapy block (blocks 3, 4, or 5). Significant differences are marked in bold. Inf CI: 95% inferior confidence interval; Sup CI: 95% superior confidence interval; NA: not available.

### **Figure 1:**

#### **Experimental design and therapy procedure**

**A Experimental design:** Each picture-naming block is represented by an arrow, with red arrows indicating pre-therapy blocks and blue arrows for post-therapy blocks. Five naming blocks, each consisting of 100 trials, were completed over four days. The items in the five blocks were matched across several relevant parameters: visual complexity, percentage of modal name usage, oral and written French lemma frequency, number of phonemes, number of phonological neighbors, semantic categories, and number of syllables.

#### **B. Therapy procedure:**

The procedure was the same for each therapy session; it was divided into ten steps. For each item, the written and spoken name was provided to the patient who then performed different tasks: read, copy, delayed copy, spell, recall, reverse spell, analyze phonologically, recall a personal memory, answer semantic yes / no questions, gesture (if relevant), and recall. If a step was not successfully completed, the experimenter went back to the previous step (dotted arrow). Before the end of the session, the experimenter grouped all trained items and asked the patient to alternatively name and repeat them. Each therapy session lasted 45 minutes and was dedicated to items from a given semantic category (mammals, objects, or fruits and vegetables).

### **Figure 2:**

#### **Representation of electrophysiological processing for one contact located in the left IFG/Broca's Area of P1**

##### **A. Details of HGF recorded in the IFG before and after therapy, time-locked to stimulus presentation.**

Results of HGF analysis from P1 processed with the MIA pipeline (Dubarry et al, 2022). The colors represent the corrected t-values (bootstrap correction). We observed high-gamma activity recorded from one contact exploring the left IFG. Note that the high-gamma frequencies (orange) are sustained in blocks 3, 4, and 5 post-therapy.

B. In the 3D view, all the electrodes are shown, and the red dot corresponds to the contact recorded in A.

C. The time course of the HGF is extracted and summarized over time. Blocks 1 and 2 form the baseline condition, shown in red, while blocks 4 and 5 represent the post-therapy condition, shown in blue. The blue bar corresponds to the temporal window in which significant differences were observed.

### Figure 3

#### **Summary and schematic representation of high-gamma changes in patients over time in BTA, MTG, IFG, PCG:**

Each square represents the outcome for one patient. Since not all patients have the same implantation sites or recorded HGF, we present the results as follows: black square = region not sampled in this patient; gray square = recorded region with no significant HGF compared to baseline; orange square = significant HGF recorded during the naming task; red square = significant HGF differences between pre- and post-therapy (as shown in Figure 2).

**A:** Results of the stimulus-locked analysis during the naming task are presented. The left and right hemispheres are represented at the top and bottom, respectively.

We highlight our main result in the IFG in yellow. This region was sampled in all patients, and in 5 patients, we found HGF during the naming task. For 4 of them (P1, P2, P3, and P6), we observed significant differences between pre- and post-therapy. Note that for two of these patients, we recorded from the contralateral IFG and found no changes in HGF on the right side.

On the left side, we also found HGF in the left BTA and later in the left MTG.

Note that the significantly different activity in the right BTA of P9 is challenging to interpret because he presents an atypical hemispheric representation of language (with right specialization).

**B:** The results of the response-locked analysis are presented, focusing only on the MTG.

All individual results are available in the supplementary materials.



**Figure 4 Summary and schematic representation of high-gamma changes in patients in Hippocampus and Primary auditory cortex (PAC).**

Each square represents the outcome for one patient. Since not all patients have the same implantation sites or recorded HGF, we present the results as follows: black square = region not sampled in this patient; gray square = recorded region with no significant HGF compared to baseline; orange square = significant HGF recorded during the naming task; red square = significant HGF differences between pre- and post-therapy

The Primary Auditory Cortex (PAC) and the hippocampi in both hemispheres showed significantly different activations between pre and post therapy conditions in the stimulus locked activities and responses locked activities mainly in “good responders” patients (P1 to P6). These results are less left-lateralized and can be explain by the improvement in response time.

## Tables

### Table 1

Patient	Gender	Age	Handness	Education	First seizure	Seizure frequency	MRI	Hemispheric localization of EZ	Topography of EZ	Language organisation	Cognitive Complain	Naming	Fluency
P1	F	24	R	2	10	1	Negative	L	temporal	Typical	TOT++	A	7
P2	F	17	R	1	6	0,5	Negative	L	NA	Typical	TOT, Slowness	N	10
P3	F	34	R	3	12	3	Left DENT	L	temporal	Typical	TOT++	N	13
P4	F	34	R	3	21	3	Negative	Right	temporal	Typical			
P5	M	34	R	2	4	10	Negative	Bi	temporal	Atypical B	TOT++	A	16
P6	F	38	R	3	35	10	Negative	Bi	frontal	Atypical B	verbal memory, TOT, tiredness	N	19
P7	M	56	R	1	36	1	Post Stroke lesion TPJ	L	temporal	Atypical B	TOT (semantic and phonologic)	A	NA
P8	F	47	R	1	12	3	Temporal lobe atrophy	L	frontal	Typical	TOT	A	NA
P9	M	22	R	2	2,5	3	LTA post ganglioma	L	temporal	Atypical R	TOT, Slowness	A	12
P10	M	46	R	2	Birth day	3-4 per day	FCD Type II right cingulum post	L	frontal	Typical	working memory, phonological errors (syllabes inversion)	N	22

### Table 2

Patient	Before therapy					After therapy		
	Block 1	Block 2	Baseline mean	Inf CI	Sup CI	Block 3	Block 4	Block 5
N items	100	100				96	100	91
P1	3208	3775	3471	3154	3861	<b>2720 *</b>	<b>2573 *</b>	<b>2872 *</b>
P2	1372	1040	1205	1106	1338	<b>1085 *</b>	<b>1043 *</b>	<b>916 *</b>
P3	1352	1444	1399	1322	1494	1427	1463	<b>1312 *</b>
P4	2819	2948	2885	2611	3228	3293	2791	<b>2513 *</b>
P5	1569	1732	1649	1494	1900	1723	1803	1397
P6	1478	1332	1400	1325	1506	1571	<b>1267 *</b>	NA

P7	3183	2516	2823	2560	3135	<b>2455 *</b>	2810	<b>2502 *</b>
P8	2629	2051	2327	2068	2731	<b>1998 *</b>	2688	2645
P9	1568	2136	1871	1729	2060	<b>2618 *</b>	<b>2662 *</b>	<b>2112 *</b>
P10	1447	1425	1436	1352	1554	1486	1406	<b>1580 *</b>
Group	2062	2040	2051	1930	2123	2038	2050	1983

Tableau 2A: Behavioral results in the picture naming tests (responses times RT).

Performance is reported as mean response times (RT) for each picture naming block and each patient.

95% bootstrap confidence intervals were computed within patient around the mean of baseline performance (blocks 1 and 2) to assess each post-therapy block (blocks 3, 4, or 5). Significant differences are marked in bold; italics is for degraded performance after therapy. Inf CI: 95% inferior confidence interval; Sup CI: 95% superior confidence interval; NA: not available

Patient	Before therapy					After therapy		
	Block 1	Block 2	Baseline mean	Inf CI	Sup CI	Block 3	Block 4	Block 5
N items	100	100				96	100	91
P01	81	70	75.5	69.0	80.5	<b>82.3 *</b>	<b>87.0 *</b>	<b>83.5 *</b>
P02	82	83	82.5	76.0	86.5	85.4	<b>88.0 *</b>	81.3
P03	78	80	79.0	72.9	84.5	80.2	<b>87.0 *</b>	83.5
P04	55	57	56.0	48.5	62.5	<b>63.5</b>	62.2	<b>69.2 *</b>
P05	61	59	60.0	51.5	66.5	64.6	<b>71.0 *</b>	<b>67 *</b>
P06	66	77	71.5	64.5	77.0	<b>77.1 *</b>	71.0	NA
P07	64	75	69.5	62.5	75.5	68.8	72.0	73.6
P08	52	57	54.5	47.0	60.5	53.1	55.0	58.2
P09	58	66	62.0	54.5	68.0	61.5	61.0	61.5
P10	90	86	88.0	82.5	92.0	90.6	88.0	85.7
Group	68.7	71.0	69.8	67.1	71.2	<b>72.7 *</b>	<b>74.2 *</b>	<b>73.7 *</b>

Table 2B: Behavioral results in the picture naming tests (% correct reponses).

Performance is reported as percentage of correct responses (% CR) for each picture naming block and each patient. 95% bootstrap confidence intervals were computed within patient around the mean of baseline performance (blocks 1 and 2) to assess each post-therapy block (blocks 3, 4, or 5). Significant differences are marked in bold. Inf CI: 95% inferior confidence interval; Sup CI: 95% superior confidence interval; NA: not available.

