NEURAL ACTIVITY ELICITED BY A COGNITIVE TASK CAN BE DETECTED IN SINGLE-TRIALS WITH SIMULTANEOUS INTRACEREBRAL EEG-FMRI RECORDINGS

Mani Saignavongs*
Lyon Neuroscience Research Center, INSERM U1028 / CNRS UMR 5292, Lyon, France; Epilepsy Institute IDEE, Lyon, France.

Carolina Ciumas*
Lyon Neuroscience Research Center, INSERM U1028 / CNRS UMR 5292, Lyon, France; Department of Clinical Neurosciences, Centre Hospitalo-Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; Epilepsy Institute IDEE, Lyon, France

Mathilde Petton
Lyon Neuroscience Research Center, INSERM U1028 / CNRS UMR 5292, Lyon, France.

Romain Bouet
Lyon Neuroscience Research Center, INSERM U1028 / CNRS UMR 5292, Lyon, France.

Sébastien Boulogne
Lyon Neuroscience Research Center, INSERM U1028 / CNRS UMR 5292, Lyon, France; Department of Functional Neurology and Epileptology, Hospices Civils de Lyon, France; Epilepsy Institute IDEE, Lyon, France.

Sylvain Rheims
Lyon Neuroscience Research Center, INSERM U1028 / CNRS UMR 5292, Lyon, France; Department of Functional Neurology and Epileptology, Hospices Civils de Lyon, France; Epilepsy Institute IDEE, Lyon, France.

David W. Carmichael
Developmental Imaging and Biophysics, UCL Institute of Child Health, University College London, UK.

Jean-Philippe Lachaux†
Lyon Neuroscience Research Center, INSERM U1028 / CNRS UMR 5292, Lyon, France. *jp.lachaux@inserm.fr*

Philippe Ryvlin†
Department of Clinical Neurosciences, Centre Hospitalo-Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; Epilepsy Institute IDEE, Lyon, France. Philippe.Ryvlin@chuv.ch

Running head: Task-induced HFA recorded with icEEG-fMRI

*These authors equally contributed to this work.
† Corresponding authors who equally contributed to this work. Address: Rue du Bugnon 46, CH-1011 Lausanne.

Recent studies have shown that it is feasible to record simultaneously intracerebral EEG and fMRI in patients with epilepsy. While it has mainly been used to explore the hemodynamic changes associated with epileptic spikes, this approach could also provide new insight into human cognition. However, the first step is to ensure that cognitive EEG components, that have lower amplitudes than epileptic spikes, can be appropriately detected under fMRI.

We compared the High Frequency Activities (HFA, 50-150 Hz) elicited by a reading task in icEEG-only and subsequent icEEG-fMRI in the same patients (n=3), implanted with depth electrodes.

Comparable responses were obtained, with 71% of the recording sites that responded during the icEEG-only session also responding during the icEEG-fMRI session. For all the remaining sites, nearby clusters (distant of 7 mm or less) also demonstrated significant HFA increase during the icEEG-fMRI session. Significant HFA increases were also observable at the single-trial level in icEEG-fMRI recordings.

Our results show that low-amplitude icEEG signal components such as cognitive-induced HFAs can be reliably recorded with simultaneous fMRI. This paves the way for the use of icEEG-fMRI to address various fundamental and clinical issues, notably the identification of the neural correlates of the BOLD signal.

Keywords: Intracranial EEG; simultaneous icEEG-fMRI; high frequency activity; gamma activity; data quality

1. Introduction

Over the last fifteen years, intra-cerebral EEG (icEEG) recordings of high frequency activities (HFAs) induced by cognitive tasks in epileptic patients have provided a new dynamic view of the human brain at work, compared to that derived from functional Magnetic Resonance Imaging (fMRI). Task-induced HFAs are typically recorded in the 50-150 Hz range and allow to investigate cognitive processing at a very high temporal resolution, albeit with a limited spatial sampling (estimated at about 1% of the human brain[1]). In contrast, fMRI allows to map the blood-oxygen-level dependent (BOLD) signal changes in response to a cognitive task over the entire brain but with a low temporal resolution. An emerging trend is to combine icEEG and fMRI in humans[2-4], if possible simultaneously, as previously done in animals[5, 6]. However, simultaneous acquisition of icEEG and fMRI data raises a number of safety, technical, and data quality issues that have been only recently addressed[7-9]. In particular, specific postprocessing is required to minimize the distortions of the magnetic field produced by the introduction of the EEG acquisition system in the MRI room and the gradient artefact caused by the MRI sequences on the EEG signal. So far, a few patients have undergone simultaneous icEEG-fMRI to either record epileptic spikes or high gamma activity during a finger tapping motor task, demonstrating that such simultaneous icEEG-fMRI recording was feasible[10-14]. Detection of cognitive HFAs remains challenging, however, due to the combination of low amplitude signal (generally inferior to 150µV) and a frequency range largely contaminated by MRI-related artefacts. To tackle this challenge, we recorded icEEG in three patients performing a simple language task twice, inside and outside the MR scan, and compared the detection of task-induced HFA in both experimental modalities.

2. Materials and Methods

2.1. *Patients*

The three patients suffered from focal intractable epilepsy and were implanted with 9 (Patient 1) or 15 (Patient 2 and 3) depth semi-rigid electrodes as part of their presurgical evaluation. Electrodes locations were chosen on the basis of clinical considerations only, and therefore varied across patients (**Figure 1**). Patients 1 and 3 were implanted only in the left hemisphere while patient 2 had 13 electrodes in the right hemisphere and two electrodes in the left hemisphere. All patients were right-handed and native French speakers, with left hemispheric dominance for language. This study was reviewed and approved by the local ethical committee, with written informed consent obtained from each patient.

Antiepileptic drugs' overall dosage on recording day as compared to usual dosage, delay between icEEG-only and combined icEEG-fMRI acquisitions, and lapsed time since last seizure for both acquisition sessions are given in **Table 1**. All experiments took place at least 24 hours after the last seizure.

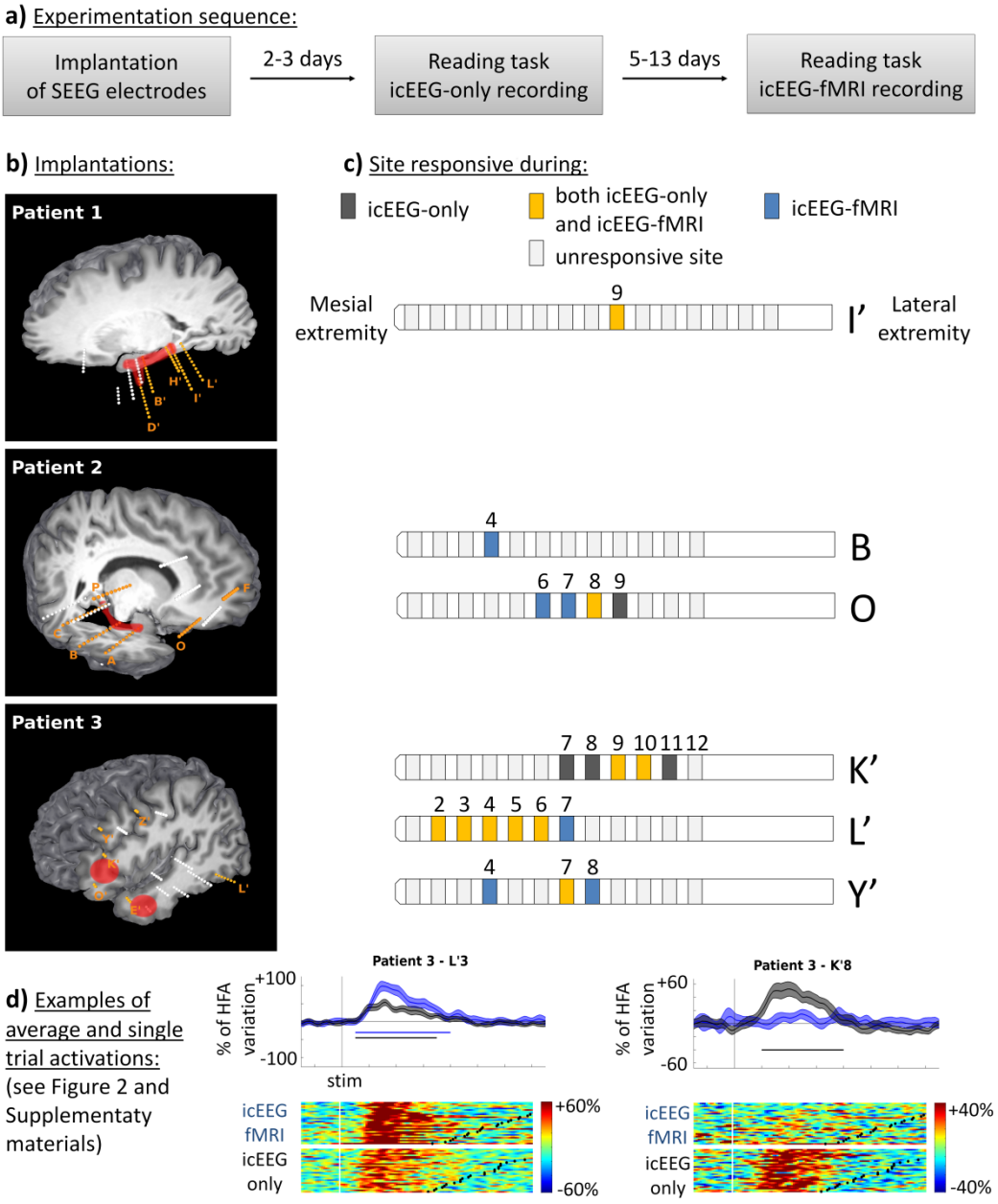

Figure 1. Experiment summary. a) Experiment sequence; b) implantation scheme for each patient. In orange, electrodes selected for the icEEG-fMRI acquisition, either because they displayed reading-induced HFAs during the icEEG-only recording session or epileptic spikes; c) Illustration of sites recorded both in icEEG-only and icEEG-fMRI that presented task-induced HFA increases during either one or both recording sessions; d) Examples of averaged (top charts) and single-trial (down charts) responses. For detailed figure of activation, see Figure 2.

Table 1. Clinical parameters

Age & sex

	Patient 1	*Patient 2*	*Patient 3*
	38y, F	28y, M	21y, M

Elapsed time between icEEG-only and icEEG-fMRI sessions

	Patient 1	*Patient 2*	*Patient 3*
	5 days	12 days	13 days

Antiepileptic drugs' overall dosage on recording day as compared to usual dosage

	Patient 1	*Patient 2*	*Patient 3*
icEEG-only	62%	100%	75%
icEEG-fMRI	100%	25%	50%

2.2. *Electrodes*

We used platinium/iridium MRI compatible icEEG electrodes (Dixi, Besançon, France) with a diameter of 0.8 mm and five to 15 equally spaced contact leads along the linear shaft (the exact number depending on the target brain structure). Electrodes were secured at the skull with dedicated screws that ensure lack of electrodes' displacement during the entire icEEG procedure. The contact leads were 2mm wide and 1.5mm apart. Their location was visually identified by a neurologist on the patient's post-implantation MRI that displays electrodes-related artefacts.

2.3. *Task*

We used a reading task similar to the design proposed in a previous study by our group combining non-simultaneous fMRI and icEEG [3]. Patients performed an animacy decision on foveally presented words (5 to 6-letters long French words: "is it a living entity?"). Stimuli were displayed on a screen (Presentation®, Neurobehavioral Systems, Inc. www.neurobs.com) during 2000 ms, using white letter strings on a black background, with inter-stimulus interval of 3500 ms. Thirty trials were presented, grouped in six blocks of five trials for a total duration of about seven minutes. In each trial, patients were instructed to give their answer by pressing a button on a joystick with the right (yes) or left (no) thumb. No training session was needed prior to acquisitions, due to the simplicity of the task.

2.4. *icEEG-only acquisition*

Patients performed the task within the first days of their icEEG long term monitoring. Data were acquired in the patients' room with the 256-channel video-EEG monitoring system used for clinical monitoring (SD LTM Express, Micromed, Treviso, Italy), with the following settings: sampling rate 2048Hz, high-pass filter 0.18Hz, low-pass filter 220Hz, resolution 0.0976µV.

2.5. *Combined icEEG-fMRI acquisition*

During the second week of implantation, patients performed the task a second time in the MR scanner. For this second session, icEEG was recorded with a 64 channels MR-compatible amplifier system (Brain Products, Munich, Germany) and associated software (Brain Vision Recorder). Five (patient 1) or six (patients 2 and 3) electrodes were selected for the combined icEEG-fMRI acquisition, including the leads showing reading-triggered HFAs during the icEEG-only recordings. According to the more limited number of recording channels of the MR-compatible system (N=64) as compared to that used in the epilepsy monitoring unit (N=256), we made a selection of the electrodes and leads displaying either reading-induced HFAs during the icEEG-only session, or epileptic spikes. The acquisition system was synchronized to the scanner's internal clock (10MHz) and received a trigger from the scanner at the start of each volume

acquisition (R128 marker). The sampling rate was set to 5000Hz, the resolution to 0.5µV and the acquisition filters to 0.016Hz (high-pass) and 250Hz (low-pass).

MRI acquisitions were performed on a Siemens Sonata 1.5 T scanner (Siemens, Erlangen, Germany) associated with a CP 1-channel head coil. Echo-planar imaging (EPI-FID) sequences were used for functional MRI. Acquisition parameters were the following: 64 × 64 matrix, TE = 50 ms, TR = 2500 ms, FOV (in-plane) = 220 mm, flip angle = 90°, 29 slices, 0.4 mm gap between, slice thickness = 3 mm, voxel size = 3.4 mm × 3.4 mm × 3.0 mm. We acquired two runs in each patient, for a total duration of 13 minutes. The same sequences as those previously tested by our group for safety[9], were used in the current study, with similar SAR (average 0.013W/kg).

2.6. *icEEG preprocessing & analysis*

Preprocessing for icEEG data consisted in the removal of MR gradient artefact and was performed using the MR scanner artefact correction built in Brain Vision Analyzer 2.0.4 (Brain Products, Munich, Germany). This correction was previously described[15]. Gradient artefacts were detected using the triggers sent by the fMRI scanner at the start of each volume acquisition (R128 marker). Artefacts were averaged over 21 (patients 1 and 3) or 7 (patient 2) sliding intervals (i.e. one scanned volume), depending on raw signal quality, to provide a template that was then subtracted from the artefacted signals on all channels.

HFA extraction was then performed in Matlab (The MathWorks, inc) following our previously described procedure[16]. Each electrode trace was referenced to its direct neighbor by bipolar derivation. The whole icEEG signal was then bandpass filtered in successive 10-Hz-wide frequency bands, from 50Hz to 150Hz (i.e. covering the classic "high-gamma" range). The envelope for each frequency band was then computed using a standard Hilbert transform. The envelope signal that was obtained was divided by its mean across the entire recording session and multiplied by 100, so that instantaneous envelope values were expressed as a percentage of the mean. Finally, the envelope signals obtained for each frequency band were averaged together to provide one single time-series across the entire session. The same procedure was applied to icEEG data in the icEEG-only session.

2.7. *Statistical analysis*

Behavioral data

We compared behavioral data during icEEG-only versus icEEG-fMRI sessions using R statistical package. We used the paired Wilcoxon signed rank test with continuity correction to test eventual significant difference between reaction times, and the McNemar's Chi-squared Test for error rates.

Multi-trial analysis

For both recording sessions, the neural responses induced by the language task were identified by comparing pre- (-300 to -15 ms) and post-stimulus HFA signals on fourteen 200 ms post-stimulus windows between 0 and 1500 ms (50% overlap; Wilcoxon signed rank test with Bonferroni correction for multiple comparisons, $p>0.01$). A site was considered responsive if HFA was significantly different from baseline in at least one time-window. We first identified the global response across the entire session, by computing this statistic over all trials. For Patient 2, two trials of the icEEG-fMRI session were heavily contaminated by artefacts despite gradient correction and had to be discarded from the statistical analysis. Thus, the total number of available trials was 28 for patient 2 and 30 for the two other patients.

Single-trial analysis

A subsequent single-trial analysis was performed for sites that were responsive during icEEG-only and/or icEEG-fMRI. The aim of that analysis was to compare the proportion of trials with significant HFA responses, at the single trial level, in the two modalities (to test the ability of icEEG-fMRI recordings to reveal HFA responses at the single trial level, relative to icEEG-only). For each responsive site, the analysis focused on the 200 ms time-window with the highest HFA response (as determined from the average over all trials), and compared – in each individual trial separately – HFA values during that window and during the baseline (Wilcoxon signed rank test, $p < 0.01$) to provide a binary criterion of responsiveness for that particular trial (responsive or not). In short, a trial was said to be "responsive" if HFA values during a 200 ms window centered in the response-peak were significantly higher than HFA values measured in an equivalent window before the stimulus. Proportions of responsive trials in

icEEG-only and icEEG-fMRI modalities were then compared using a paired Wilcoxon signed-rank test (one pair of values per channel).

3. Results

3.1. *Behavior*

None of the patients reported any discomfort or unpleasant sensation during the entire experiment, including the icEEG-fMRI recording sessions.

Patients 1 and 2 responded faster during the second session, by an average of 338ms, which might be due to a greater familiarity with the task when performed a second time. However, error rates were not significantly different between the two sessions. Behavioral data for both recording sessions are provided in **Table 2**.

3.2. *General observation*

A total of 166 cortical sites were recorded both in icEEG-only and icEEG-fMRI in the three patients (53 in patient 1, 56 in patient 2, and 57 in patient 3). In the following sections, we consider only sites recorded in the two sessions, thus excluding those solely recorded in icEEG-only. Only two sites (in patient 3) that presented a significant response to the task during icEEG-only were not recorded in icEEG-fMRI because of setup limitations, as explained in the Material & Methods section.

Sites with an HFA increase during the language task were mostly distributed in the language network (left inferior frontal sulcus and posterior part of the middle temporal gyrus) including basal temporal "reading" areas (i.e. Word Form Area). In addition, we found HFA increases in the left superior frontal sulcus (patient 3), in the right orbital gyrus (patient 2), and in the right hippocampus during patient 2 second session only (**Table 3** and **Figure 1**).

3.3. *Multi-trial analysis*

We first compared multi-trial responses across sessions (i.e. the average effect of the language task, over all the trials) and found that 14 sites displayed a significant HFA increase after stimulus presentation during icEEG-only (1, 2 and 11 sites in patients 1, 2 and 3 respectively), and 16 sites during icEEG-fMRI (1, 4, and 11 sites in patients 1, 2 and 3 respectively) (see **Figure 2, A** for an example). Importantly, all but two sites with significant HFA increases during icEEG-fMRI were either the same (10/16) or adjacent to (4/16) sites responsive in the icEEG-only session (that is, at most 7 mm away on the same electrode, see **Figure 1**). One site (Y'4, Patient 3) was not immediately adjacent but only 8,5 mm away from an active cluster (same anatomical structure, i.e. superior frontal sulcus). The only site which was active in the icEEG-fMRI session and distant from all regions activated in the icEEG-only session was located in the right hippocampus of patient 2.

Table 2. Behavioral data

Mean error rates

	Patient 1	*Patient 2*	*Patient 3*
icEEG-only	16.7%	16.7%	43.3%
icEEG-fMRI	3.3%	6.7%	36.7%

Mean reaction times (ms)

	Patient 1	*Patient 2*	*Patient 3*
icEEG-only	1003.1	1359.4	1246.9
icEEG-fMRI	784.8	902.2	1300.3
	*p=0.0003	*p=0.0052	

Table 3. Leads showing significant averaged reading-induced HFA increase during icEEG-only and icEEG-fMRI acquisitions. Suggested role for reading, in some cases extrapolated from surrounding regions, is taken from Ref. [26]

icEEG-only	icEEG-fMRI	Location	Side	Suggested role
Patient 1				
I'9	I'9	*Middle temporal gyrus, posterior part*	Left	Semantic processing
Patient 2				
	B4	*Hippocampus*	Right	unknown
	O6	*Orbital gyrus*	Right	
	O7	*Orbital gyrus*	Right	unknown
O8	O8	*Orbital gyrus*	Right	
O9		*Orbital gyrus*	Right	
Patient 3				
K'7		*Inferior frontal sulcus*	Left	
K'8		*Inferior frontal sulcus*	Left	
K'9	K'9	*Inferior frontal sulcus*	Left	Grapho-phonological conversion
K'10	K'10	*Inferior frontal sulcus*	Left	
K'11		*Inferior frontal sulcus*	Left	
L'2	L'2	*Temporo-basal gyrus*	Left	
L'3	L'3	*Temporo-basal gyrus*	Left	
L'4	L'4	*Temporo-basal gyrus*	Left	Prelexical and early phonological processes
L'5	L'5	*Temporo-basal gyrus*	Left	
L'6	L'6	*Temporo-basal gyrus*	Left	
	L'7	*Temporo-basal gyrus*	Left	
	Y'4	*Superior frontal sulcus*	Left	
Y'7	Y'7	*Superior frontal sulcus*	Left	Nonspecific attention
	Y'8	*Superior frontal sulcus*	Left	

3.4. *Single trial responses*

For electrodes responsive to the task (HFA-wise), the HFA response was also apparent and statistically significant at the single-trial level in both icEEG-only and icEEG-fMRI recordings (example in **Figure 2, B**), with a proportion of "responsive" single trials per site ranging between 33.3% and 96.7% (icEEG-only) and between 39.3% and 100% (icEEG-fMRI). For sites responsive in both icEEG-only and icEEG-fMRI, the proportion of responsive trials was significantly higher in the icEEG-fMRI condition, ($p=0.04$, see **Figure 3**).

3.5. *Other frequency bands*

While the present study focused on HFA for reasons explained in the introduction, we applied the same analysis to theta [4-7Hz], alpha [8-12Hz] and beta [13-25Hz] frequency bands. Yet, responses were scarce: the stimulus presentation
triggered changes in alpha activity in few sites with similar trends in icEEG-only and icEEG-fMRI but these changes were significant at only one site (**Figure 4A**). In the theta band, two channels showed significant decreases but in only one acquisition session (patient 3: L'3 during icEEG-fMRI and L'6 during icEEG-only). In the beta band, we found significant task-induced decreases at 3 recording sites (patient 1: lead H'6; patient 3: L'3 and L'4) but only for the icEEG-fMRI session (**Figure 4B, 4C and 4D**). In all the mentioned sites, the shape of the theta or beta band response during both sessions mirrored each other although one failed to reach significance.

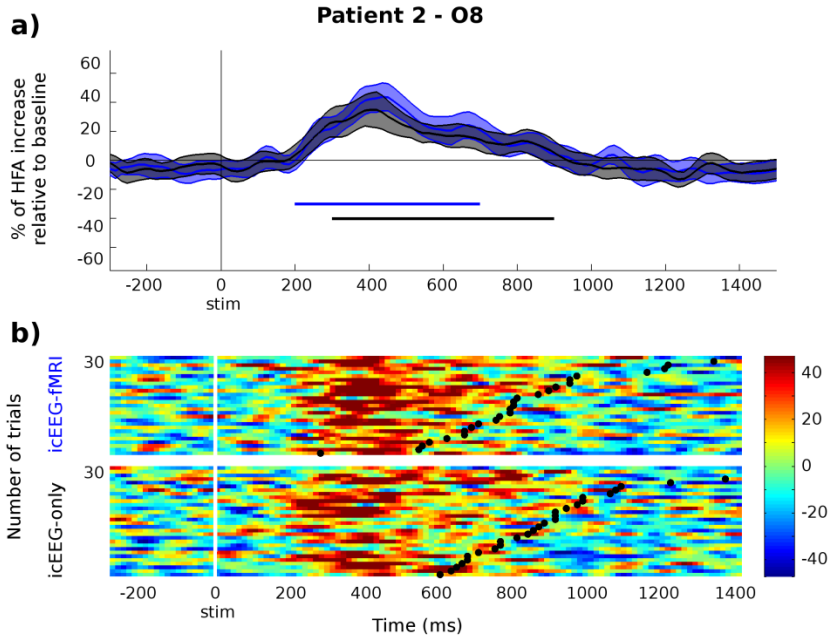

Figure 2. Example of averaged (A) and single trial (B) task-induced HFA increase. (A) Averaged task-induced HFA increase and its confidence intervals at 95% obtained during icEEG-only (black) and icEEG-fMRI (blue) recordings at site 'O8' of Patient 2. Horizontal black and blue lines indicate time-windows significantly different from baseline, for icEEG-only and icEEG-fMRI respectively ($p < 0.01$). (B) Task-induced HFA increases at the single trial level for the same patient and recording site. Each line corresponds to one trial. All trials are sorted by reaction times, with black dots indicating the response latency. The color scale indicates the percentage of HFA variation compared to the baseline, at each time point (from +40% to -40%).

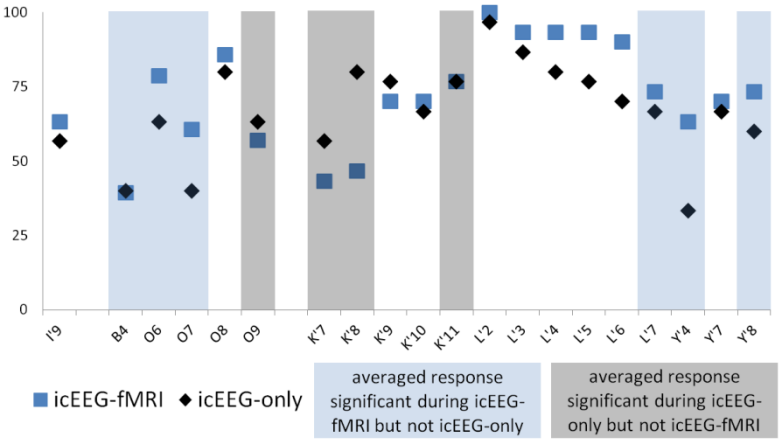

Figure 3. Proportions of single trials with a significant response (HFA increase), compared across sessions. For all sites where the task induced a change in HFA, in either session, the plot shows the % of trials with a significant deviation of HFA relative to prestimulus baseline, in icEEG-only (black diamonds) or icEEG-fMRI (blue squares). Overall, for sites responsive in both sessions, the amount of significant single trials was higher in the icEEG-fMRI session (paired Wilcoxon signed rank test comparing blue squares versus black diamond values, $p = 0.02$).

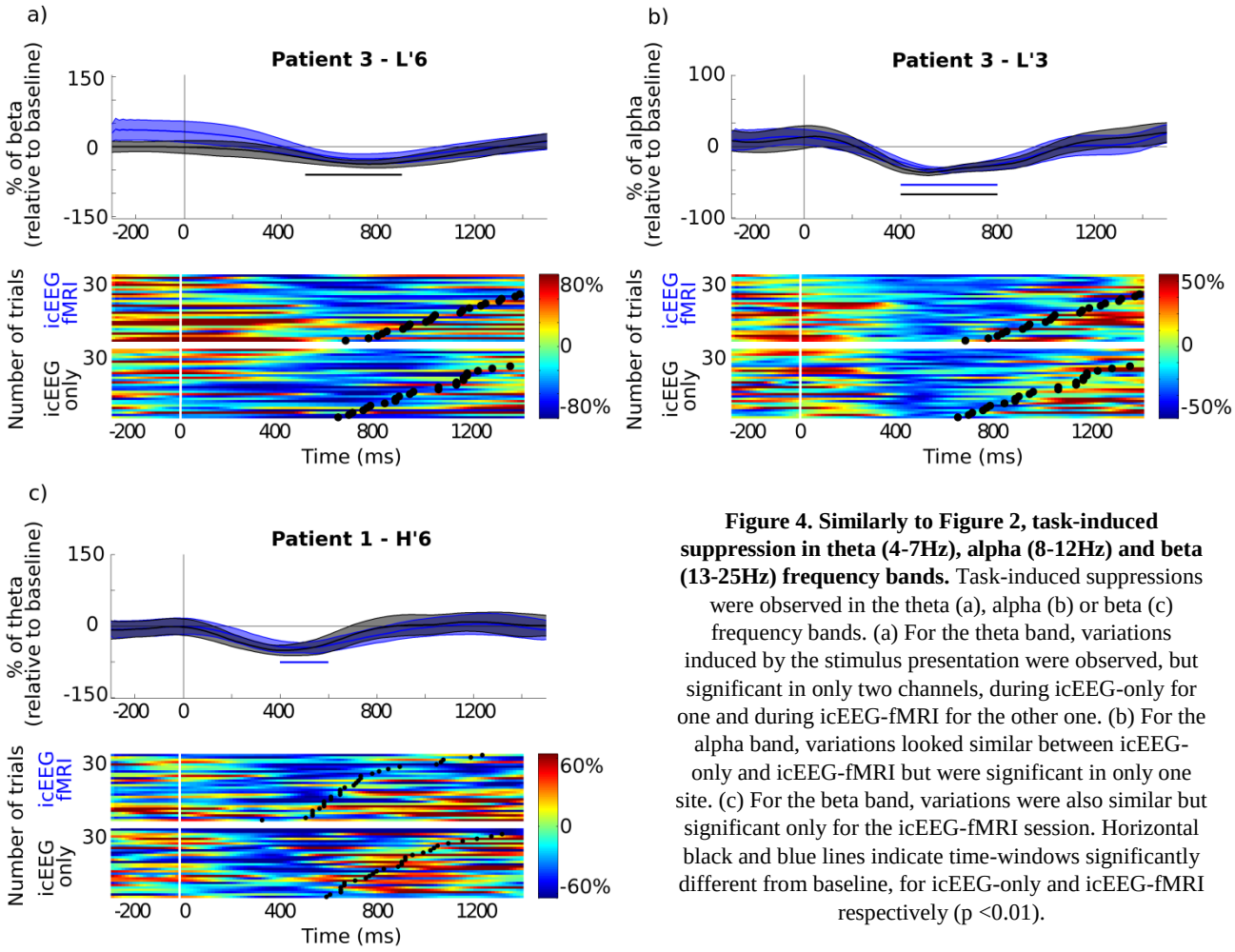

Figure 4. Similarly to Figure 2, task-induced suppression in theta (4-7Hz), alpha (8-12Hz) and beta (13-25Hz) frequency bands. Task-induced suppressions were observed in the theta (a), alpha (b) or beta (c) frequency bands. (a) For the theta band, variations induced by the stimulus presentation were observed, but significant in only two channels, during icEEG-only for one and during icEEG-fMRI for the other one. (b) For the alpha band, variations looked similar between icEEG-only and icEEG-fMRI but were significant in only one site. (c) For the beta band, variations were also similar but significant only for the icEEG-fMRI session. Horizontal black and blue lines indicate time-windows significantly different from baseline, for icEEG-only and icEEG-fMRI respectively ($p < 0.01$).

3.6. *Post hoc analysis*

In order to explore the potential causes of the discrepancies between multi-trial responses in icEEG-only and icEEG-fMRI, we looked at the variability inherent to the task by comparing the responses elicited by the first 50% versus the last 50% trials. We performed the same statistical analysis as for the icEEG-only/icEEG-fMRI comparison. All of the channels that presented an activation during the first 50% trials were also activated during the 50% latest trials. However, three additional channels were active during the last 50% trials (I'9 in Patient 1, L'7 and Z'2 in Patient 3).

4. Discussion

In recent years, the study of High-Frequency Activity (HFA, >50 Hz) in icEEG signals became a popular approach to study the dynamic networks supporting human cognition, complementary to the more global but also more static fMRI studies. Our primary aim was to assess the possibility of detecting HFA induced by a cognitive task in icEEG signals, while simultaneously recording fMRI activity, to pave the way for a fruitful combination of the two approaches. We show that this is the case, even at the single-trial level, and argue that this is an important new step in the field of simultaneous icEEG-fMRI, following previous evidence that icEEG-fMRI can recover high-amplitude signals such as epileptic spikes[10, 13, 14]. While most EEG-fMRI and icEEG-fMRI studies use a 70Hz low-pass filter to the (ic)EEG signal, we demonstrate the possibility to explore icEEG high frequency components up to 150Hz.

4.1. *icEEG-fMRI acquisition issues*

Surprisingly, the detection of task-induced HFA during fMRI required neither specific hardware nor specific

preprocessing algorithm – beyond what is commonly used for simultaneous scalp EEG-fMRI. As described in the Material and Methods section, however, particular care was taken to 1) shorten the length of the electrical wires and ribbon cables, as the recorded signal is no longer affected by MR artefacts once converted into an optical signal at the output of the amplifiers; 2) minimize the area of the loops formed by the electrodes wires by twisting them together, hence reducing the electromotive force induced by the magnetic currents; 3) reduce the movements of the whole EEG setup caused by the scanner vibration by using weighting sandbags and adhesive tape. In addition, we were eager to maximize the patient's comfort, especially around the head, which is particularly sensitive in icEEG-fMRI recordings. Indeed, pleats in the head bandage can rapidly cause annoying sensations at the back of the head when the patient lies horizontally, and movements of the patient in the magnetic field generate additional artefacts. We prevented this by placing a cushion under the patient's head. Also, we carried our experiments on 1.5T scanner, first because we performed a safety testing of the EEG equipment in our 1.5T scanner, and second – it is supposed to induce less artefacts in the images due to MR compatible/conditional material introduced in the MR field at 1.5T than at 3T. However, recent studies in the simultaneous recordings indicate plausible results for 3T simultaneous recordings [7, 17].

4.2. *Differences between icEEG-only and icEEG-fMRI results*

The increases of HFA induced by the task in icEEG were largely similar, in all patients, whether fMRI was conjointly recorded or not. However, for about half of the recording sites that responded significantly to the task, it was not the same lead that demonstrated a significant response in both the icEEG-only and the icEEG-fMRI sessions, but rather nearby leads from the same electrode (<7mm from each other), located in the same anatomical structure. This difference could reflect physiological changes in the way a given cortical region generates HFA in response to our language task, as a function of various environmental or internal factors, including the impact of task-repetition, and/or change in patient's strategy, motivation and attention, level of fatigue or even reduction of antiepileptic medication (see **Table 2**). This possibility is supported by the finding that similar response's disparity was observed when comparing the first to the second half of trials during the icEEG-only session. Conversely, the repetition of the language task, with a unique presentation of each item during each session, appears unlikely to induce a significant priming effect that would modulate the gamma response (see Ref. [18] for review). Finally, one cannot rule out the role of different EEG acquisition system between the two sessions.

Preferably, it would have been optimal to perform both recording sessions with the same EEG system. Unfortunately, this proved to be incompatible with other requirements: 1) our protocol requires that patients are tested twice on different days, first in icEEG only, then in icEEG-fMRI, 2) the icEEG-only equipment is not MRI compatible, 3) repeating a third session using the icEEG-fMRI equipment outside the scanner, immediately before or after the icEEG-fMRI session, was also considered inappropriate (patient tired or bored of tasks, risk of response changes due to immediate repetition). We acknowledge that difference in the recording equipment's used for the icEEG-only and icEEG-fMRI sessions might be responsible for the slight variability in the HFAs obtained during these two sessions, but wish to emphasize that our main findings point to a high level of reproducibility of task-induced recorded HFAs despite differences in equipment. As such, our data offer more potential for other research groups that look forward using simultaneous icEEG-fMRI to study cognition, since most are likely to face the same issues of using two different recording systems in their epilepsy monitoring unit and MRI scanner.

Our study demonstrates that one can detect neural activation supporting a cognitive-task execution at the single trial level, just as well with icEEG-fMRI as with icEEG alone. This might be our most important observation, as trial-by-trial analysis of HFA has become essential to understand the exact functional role of a given brain region with icEEG and the formation of the large-scale cortical networks subtending cognition. Indeed, HFA "time x trials" matrices, sorted by reaction times as shown in this study, reveal whether neurons react only transiently to the stimulus or to the motor response, or whether they are actually active throughout the task. Such timing information, at the single-trial level, discriminates between very different functional interpretations. HFA responses can also be related, both in amplitude and latency, with reaction time and accuracy, to evaluate their impact on behavior[16]. Further,

the time fluctuations of HFA during the response, in single-trials, can be correlated across brain regions to measure functional connectivity[19]. Finally, the possibility to associate and compare HFA responses with BOLD fluctuations largely depends on the ability to observe those responses in single-trials. In short, the ability to detect HFA responses while recording fMRI at the same time would have been strongly undermined if it came at the cost of detecting HFA in single-trials.

In fact, the rate of statistically significant single trials was higher during icEEG-fMRI than during icEEG-only sessions, a counterintuitive finding given the more challenging recording environment and greater surrounding noise associated with icEEG-fMRI. We do not yet have explanation for these observations, but can speculate that the icEEG-fMRI setting, with the patient head still within the MRI bore, fostered enhanced attention as compared to the patient's room where icEEG-only recordings where performed.

4.3. *Perspectives*

This study paves the way for future icEEG-fMRI studies, investigating both the fine local neural dynamics of human cognition (icEEG) and its global organization (fMRI), in relation to behavior and at the single-trial level. The feasibility to record neural activity at that level in icEEG signals during simultaneous fMRI acquisition also offers novel opportunities to investigate the neurovascular coupling underlying physiological and pathological neuronal processes in human.

From physiological perspective, the possibility to record icEEG signals up to 150Hz in humans in fMRI can shed new light on the relationship between neural and BOLD responses. Animal studies have demonstrated that the BOLD signal is well correlated with all frequency bands in the LFP (see Ref. [20] for a review), especially with frequencies in the gamma range[5, 6], but this relationship must still be tested in humans, in a large variety of brain regions and cognitive tasks. To that aim, one previous study from our group combined non-simultaneous icEEG and fMRI in the same patients to show that increases of HFA (50-150Hz) induced by a reading task similar to that used in this study partially co-localized with BOLD activation clusters elicited by the same task[3]. A strong correlation between HFA in the 50-150Hz frequency range and the BOLD signal was also shown by others using a word pair association learning paradigm[4]. Another study using a spatial navigation task reported a positive correlation between BOLD and theta activity (4-8Hz) in para-hippocampal areas, but not in other regions[2]. Yet, in all these studies, fMRI and icEEG were acquired in distinct sessions a few days apart. While our findings in three patients suggest that one can extrapolate from the HFA recorded during a icEEG-only session prior to fMRI to those that would occurred during fMRI, this might not necessarily apply to cognitive functions that would be more sensitive to environmental factors than the reading task used in this study. Furthermore, interpretation of the BOLD response would be refined by incorporating precise single-trial level activities that clearly varied between sessions in our patients.

It has been demonstrated that cognitively induced alpha and theta variations can be correlated to the BOLD signal at the single trial level in simultaneous EEG-fMRI[21]. Yet, the latter study failed to record gamma oscillations on the scalp, possibly because such oscillations are of too low-amplitude to be detectable in the noisy MRI environment. Our results show that simultaneous icEEG-fMRI enables to overcome this issue and might allow to extend the correlation between single trial task-induced EEG and BOLD signal changes into higher frequencies.

In the only study that recorded simultaneous icEEG-fMRI in a patient performing a task (finger tapping task), the maximum positive correlation between BOLD signal and LFP was found in the sensorimotor cortex at 91Hz, with negative correlation in the beta band[12]. While these observations are consistent with other reports[2, 4], they should be confirmed with different tasks of various cognitive levels, and extended to other brain regions.

The possibility to record high-frequency neural activity in icEEG-fMRI could have important clinical applications in the field of epilepsy surgery. It might help better understand the HFA and BOLD signatures of brain regions playing an essential role in a given cognitive function, and distinguish the latter from regions activated during the task but which resection will not result in a significant cognitive deficit. To date, neither icEEG recorded HFAs nor fMRI studied separately have proved capable to provide data ensuring such distinction. Separating physiological from epileptic HFAs also appears challenging, and a prerequisite for the clinical use of HFAs to either map eloquent cortex or the epileptogenic zone. Epileptic HFAs have been described as ripples (80-250Hz) or fast ripples (250-500Hz), and

shown to co-localize with the epileptogenic zone even more specifically than epileptic spikes[22-24]. As icEEG can only detect fast oscillations where electrodes have been placed, it would be extremely beneficial to identify an unambiguous trace of ripples/fast ripples in the BOLD signal, which could be used to localize the EZ from whole-brain fMRI (and thus, guide the selection of icEEG target sites). We used a hardware setting preventing observation of the fast-ripples, but a previous study has reported high frequency activities up to 600Hz in combined scalp EEG-fMRI[25]. We can hope that shortly, studies of ripples and fast-ripples in icEEG-fMRI will provide important information about the location and spatial extend of the EZ.

However, all the above perspectives not only depend on the ability to reliably detect HFA during icEEG-fMRI, as reported herein, but also on the capacity to detect relevant BOLD signal despite the artefacts generated by intracerebral electrodes. This issue is particularly important for correlating physiological HFA and BOLD responses at the same site, given the void of MRI signal observed at the site of the recording leads. fMRI data from the three patients reported in this study are currently being processed to address this issue, but preliminary findings suggest that relevant BOLD activation can indeed be generated at the immediate vicinity of HFA-recording leads.

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