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RESEARCH REPORT

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Intracerebral electrical stimulations of the temporal lobe: A stereoelectroencephalography study

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Abstract

The functional anatomy of the anteromesial portion of the temporal lobe and its involvement in epilepsy can be explored by means of intracerebral electrical stimulations. Here, we aimed to expand the knowledge of its physiological and pathophysiological symptoms by conducting the first large-sample systematic analysis of 1529 electrical stimulations of this anatomical region. We retrospectively analysed all clinical manifestations induced by intracerebral electrical stimulations in 173 patients with drug-resistant focal epilepsy with at least one electrode implanted in this area. We found that high-frequency stimulations were more likely to evoke electroclinical manifestations ($p < .0001$) and also provoked 'false positive' seizures. Multimodal symptoms were associated with EEG electrical modification (after discharge) ($p < .0001$). Visual symptoms were not associated with after discharge ($p = .0002$) and were mainly evoked by stimulation of the hippocampus ($p = .009$) and of the parahippocampal gyrus ($p = .0212$). 'False positive seizures' can be evoked by stimulation of the hippocampus, parahippocampal gyrus and amygdala, likely due to their intrinsic low epileptogenic threshold. Visual symptoms evoked in the hippocampus and parahippocampal gyrus, without EEG changes, are physiological symptoms and suggest involvement of these areas in the visual ventral stream. Our findings provide meaningful guidance in the interpretation of intracranial EEG studies of the temporal lobe.

KEYWORDS
clinical neurophysiology, epilepsy surgery, stereo-EEG, temporal lobe epilepsy, visual stream

List of Abbreviations: AD, after discharge; EEG, electroencephalogram; HF, high frequency; LF, low frequency; MRI, magnetic resonance imaging; RR, relative risk; SEEG, stereoelectroencephalography; VIF, variance inflation factor.

1 | INTRODUCTION

The surface of the temporal lobes constitutes approximately 17% of the human cerebral cortex (Mai et al., 2008). The anteromesial portion of the temporal lobe includes the hippocampus, the amygdala, the parahippocampal gyrus, the uncus and the temporal pole and is implicated in multiple cognitive, emotional, sensory and neuroendocrine functions (Lech & Suchan, 2013). Abnormalities of this region are associated with many neurological and psychiatric disorders (Ochoa-Escudero et al., 2015), proving the complexity of its functional anatomy. Mesial temporal lobe epilepsy is the most common form of refractory focal epilepsy, often associated with hippocampal sclerosis, and amenable to surgical treatment (Blumcke et al., 2017). Stereoelectroencephalography (SEEG) is currently the most accurate method available to define the association between clinical manifestations and their anatomo-functional substrate, either 'physiological' or 'pathological'. SEEG indeed enables to record the electrical cortical activity of the regions where the intracerebral electrodes are located. The electrical activity is 'physiological' when the cerebral region is not involved in disease processes, for example, the response of the occipital cortex during intermittent luminous stimulation, or is 'pathological' when the cerebral cortex is dysfunctional due to disease processes, such as in epilepsy. Abnormal electrical discharges on SEEG recording in epilepsy can correspond to specific clinical manifestations ('electroclinical manifestations') or can present without any clinical correlate (e.g., interictal spike waves in the hippocampus in mesial temporal lobe epilepsy). Previous SEEG studies have defined the semiology of temporal lobe seizures according to the localization of the epileptogenic zone across the different temporal substructures (Kahane & Bartolomei, 2010; Maillard et al., 2004).

Intracerebral electrical stimulations during SEEG, as part of the presurgical work-up, are an important tool to localize the epileptogenic zone and to explore functional anatomy. Eloquent areas have been extensively studied with electrical stimulations (Penfield & Jasper, 1954).

There is established evidence on the effectiveness of low-frequency (LF) and high-frequency (HF) intracerebral stimulations during SEEG (Balestrini et al., 2015; Munari et al., 1993) and on the correct interpretation of their clinical effects, particularly when they induce seizures (Cuello Oderiz et al., 2019; Trebuchon et al., 2020). The clinical manifestations evoked by electrical stimulations of the temporal lobe in people with epilepsy have been extensively described (Feindel & Penfield, 1954; Fish et al., 1993; Mullan & Penfield, 1959; Selimbeyoglu & Parvizi, 2010). Some studies have focused on specific clinical manifestation such as déjà vu or memory hallucinations (Bartolomei et al., 2004; Curot et al., 2018; Vignal et al., 2007). Other studies have drawn their attention to clinical manifestations evoked by stimulation of a specific temporal lobe structure, such as the amygdala (Meletti et al., 2006) or the temporal pole (Ostrowsky et al., 2002). To the best of our knowledge, no studies have extensively reported the whole spectrum of clinical manifestations evoked by electrical stimulations of the temporal lobe and looked for possible correlations with specific substructure, frequency of stimulation and presence or absence of EEG modifications.

The main aims of this study were (i) to investigate the functional organization of the anteromesial portion of the temporal lobe and to expand on the knowledge of the electroclinical correlations of seizures involving this anatomical region, by studying the association between evoked clinical manifestations, type and site of stimulation and EEG modifications, and (ii) to assess the effectiveness of electrical stimulations of the anteromesial portion of the temporal lobe in evoking clinical manifestations and guide their interpretation in physiological and pathological contexts.

2 | METHODS

2.1 | Patients

Between January 2010 and December 2014, 173 consecutive patients with refractory focal epilepsy underwent SEEG at the 'Claudio Munari' Epilepsy Surgery Centre, Niguarda Hospital, Milan (Italy). All the anatomical data were routinely coregistered in a unique space. The multimodal scenes were assembled with the software 3D Slicer (Fedorov et al., 2012) and were reviewed by two neurologists (IS and LT) and one neurosurgeon (FC) to assess the exact position of all recording contacts. Patients with at least one electrode implanted in the anteromesial portion of the temporal lobe were included in the study.

The hemispheric dominance for language was determined through functional MRI or electrical stimulations. Patients with any degree of intellectual disability or psychiatric disturbances were excluded as these conditions might affect the evoked subjective perceptual and behavioural phenomena.

The final analysis included 108 patients: 53 females and 55 males; median age was 28 years (interquartile range 24–33). All patients were fully informed of the aims of the SEEG recording and stimulation procedures, and provided informed consent. Research was conducted in accordance with the Declaration of Helsinki (1964). The study was approved by the local Ethics Committee.

2.2 | SEEG and electrical stimulations

The number of electrodes and the sites of implantation were tailored for each patient according to the hypothetical localization of the epileptogenic zone (Cardinale et al., 2019).

Fifty-three implantations were on the right side (49%), 42 on the left side (39%) and 13 bilaterally (12%). Some examples of SEEG implantation including the anteromesial portion of the temporal lobe are provided in Figure 1. The exact position of every recording/stimulating lead was assessed by means of SEEG Assistant software package (Arnulfo et al., 2015; Narizzano et al., 2017). The implantation technique was already detailed in previous publications (Cardinale et al., 2013, 2017).

Each stimulation consisted of monophasic rectangular electrical stimuli of alternating polarity (IRES 600 CH electrical stimulator, Micromed or OSIRIS NeuroStimulator, Inomed) between two adjacent contacts (bipolar stimulation). The electrical bipolar stimulations were carried out at LF (1 Hz, pulse width 1–3 ms, 15–30 s, 0.2–5 mA) and HF (50 Hz, pulse width 1 ms, 5 s, 0.2–5 mA).

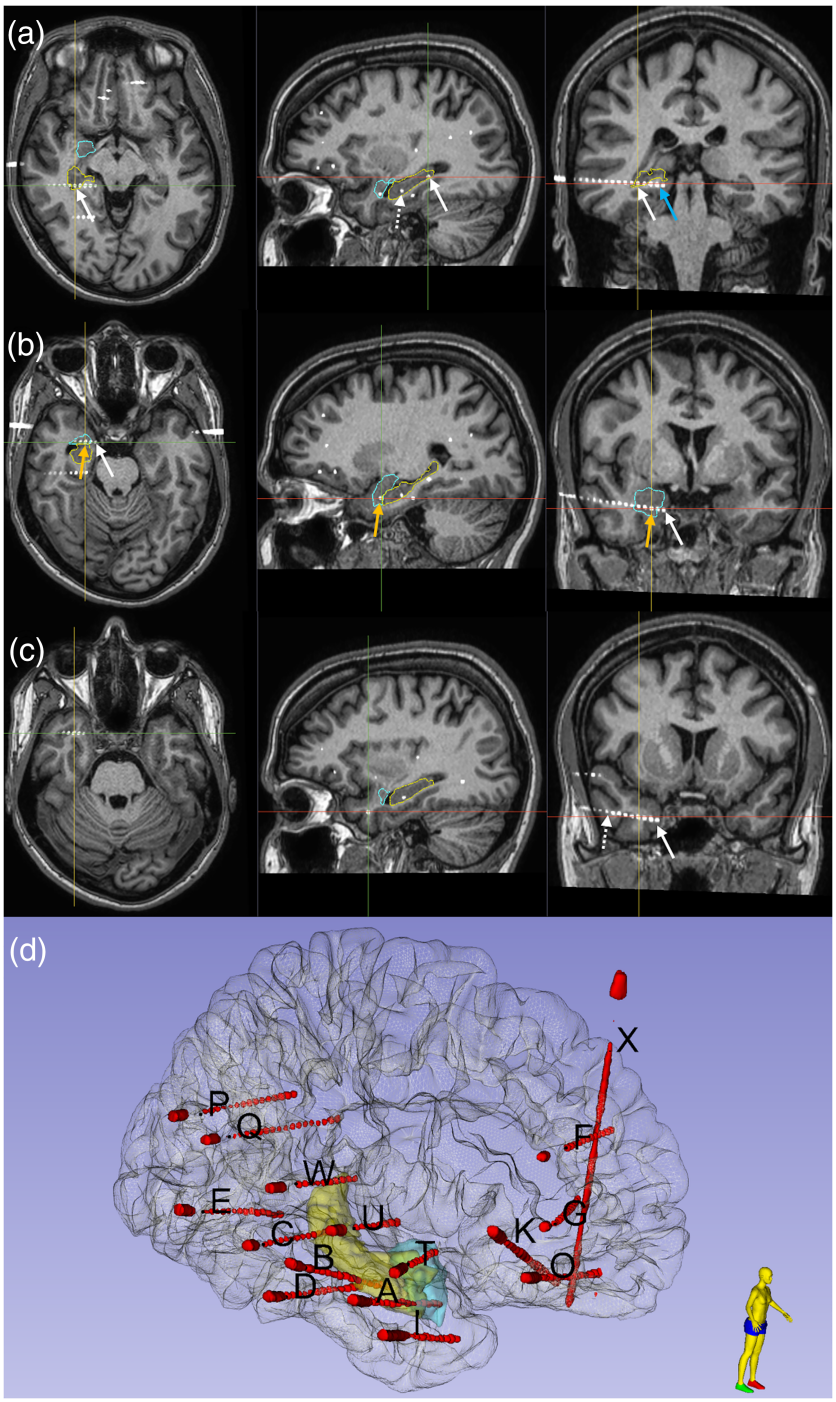


FIGURE 1 Stereoelectroencephalography (SEEG) implantation involving mostly the right frontotemporal region. Light blue and yellow colours define the amygdala and the hippocampus structure, respectively, according to automatic Freesurfer segmentation. (a) Multiplanar reconstruction showing recording contacts in the anterior (white dotted arrow) and posterior (white continuous arrow) hippocampus and in the posterior parahippocampal gyrus (blue arrow). (b) Multiplanar reconstruction showing recording contacts in the amygdala (yellow arrow) and in the uncus (white arrow). (c) Multiplanar reconstruction showing recording contacts in the mesial (continuous white arrow) and lateral (dotted white arrow) temporal pole. (d) Overview of the SEEG implantation, including the trajectory of the implanted electrodes (in red), the amygdala and hippocampus structures (in light blue and yellow, respectively) and the pial surface (transparent model)

After placement of the intracerebral electrodes, patients underwent prolonged video-SEEG monitoring. Electrical stimulations were performed in order to functionally map brain structures and reproduce ictal manifestations.

For the purpose of this analysis, we excluded electrical stimulations performed within structural lesions visible on the MRI or revealed by neuropathological examination in the operated patients, and also electrical stimulations performed at contact pairs located in white matter tracts.

During the stimulation session, patients were asked to sit upright on their beds and made to feel comfortable and relaxed. They were asked to report any symptoms or changes that were immediately investigated by the clinician with further questions to obtain a detailed characterization of the subjective clinical symptoms. All the evoked subjective and objective evoked signs and symptoms were recorded. During the procedure, the patients were not aware of when, where or whether stimulation was applied.

2.3 | Data collection and variable definition

Effects of the electrical stimulations of the sites of interest were reviewed on the video-SEEG records by three different neurologists (RM, LT and IS). All the stimulations evoking a clinical manifestation were considered as effective, except for those inducing symptoms throughout the propagation of the stimulus to extra-cerebral areas (e.g., meningeal pain or scalp paresthesia) which were considered as non-effective.

We included in the analysis the following demographic and clinical variables: gender, age at seizure onset, age at SEEG, duration of epilepsy, presence of sleep-related seizures, frequency of seizures, presence of clusters of seizures and generalized seizures at the time of SEEG.

The anatomical structures considered were hippocampus, parahippocampal gyrus, amygdala, uncus, mesial temporal pole and lateral temporal pole. They were segmented by means of Freesurfer Software Package (Figure 1) (Fischl et al., 2002).

Stimulation parameters included frequency (LF or HF), intensity, duration and side (left/right and language dominant/non-dominant).

The effective electrical stimulations were classified according to the presence or absence of electrical modification on the EEG, defined as after discharge (AD). We considered as AD 'any rhythmic activity on the EEG that was different from the pre-stimulation activity, starting during or immediately after the stimulation, with no time interval from the end of the stimulation, and lasting at least one second' (Fish et al., 1993) (Figure 2). The responses to effective stimulations were classified as usual if similar to the typical ictal symptomatology recognized by the patient and/or by the habitual witnesses of the seizures or unusual if never experienced by the patient before (Table 1). The responses were further categorized as subjective if only perceived and reported by the patient or objective when clinical signs were obvious to the clinician performing the stimulation. Clinical responses

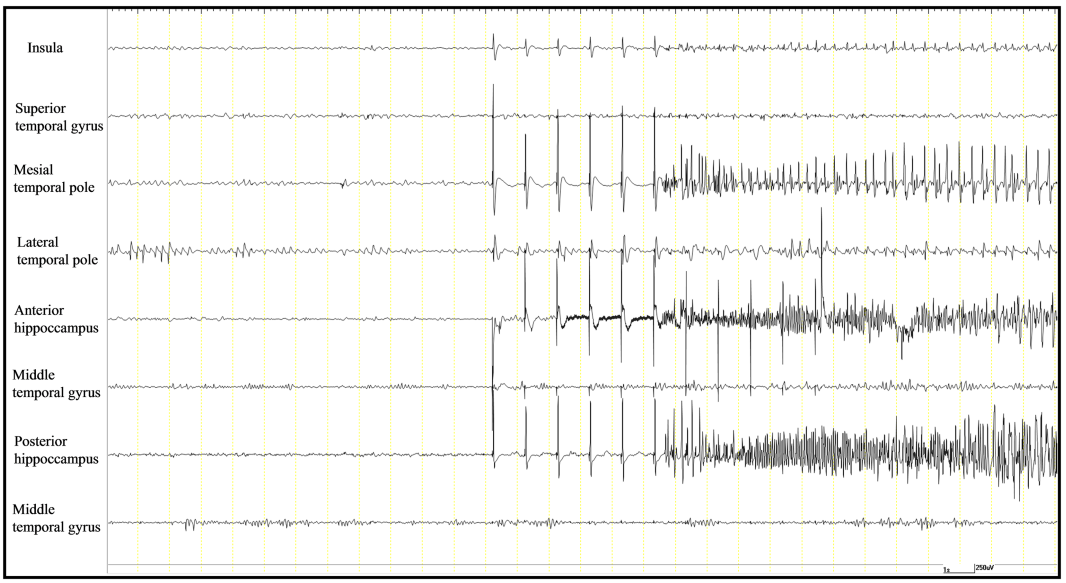


FIGURE 2 Example of after discharge (AD) during low-frequency stimulation of the anterior hippocampus. At the end of the sixth stimulus an AD appears, involving the whole hippocampus and the mesial temporal pole, starting with recruiting spike activity

TABLE 1 Glossary including the main definitions used for symptom classification in the study

Glossary
A *usual symptom* is a clinical manifestation that resembles the usual ictal symptomatology and is recognized by the patient and/or the habitual witnesses of the seizures.
An *unusual symptom* is a clinical manifestation that is not recognized by the patient and/or the habitual witnesses of the seizures as it is different from the patient's usual seizure semiology.
An *after discharge* (AD) is 'any rhythmic activity on the EEG that is different from the pre-stimulation activity, starting during or immediately after the stimulation, with no time interval from the end of the stimulation, and lasting at least one second' (Fish et al., 1993).
An *electroclinical symptom* is a symptom associated with AD. Epileptic seizures include one or more electroclinical symptoms.
A *'false positive' seizure* is an unusual symptom associated with AD.

were also labelled as unimodal when characterized by only one symptom or multimodal when including multiple symptoms. Finally, we divided the symptoms according to semiology: somatosensory symptom, visual illusion/hallucination, auditory illusion/hallucination, olfactory hallucination, psychic phenomenon (e.g., fear and déjà vu), visceral sensation (e.g., nausea and epigastric sensation), neurovegetative symptom, unclassified response (e.g., feeling of confusion and vague symptoms), loss of contact, motor symptom, automatisms (oroalimentary and gestural) and language disturbances.

2.4 | Statistical analysis

After normal distribution of data was verified with the Shapiro–Wilk test, Kruskal–Wallis rank sum test or *t* test was used for univariate analysis of numerical variables, as appropriate. After accurately reviewing the actual position of the electrodes and considering the cyto-architectonics of the different regions of interest, the lateral temporal pole was considered as the reference category for multivariate analyses, being the only one outside the paralimbic structures (Mesulam, 1998).

Chi-square or Fisher's two-tailed exact test was used for univariate analysis of categorical (binomial or multinomial) variables, as appropriate. For multivariate analysis, mixed-effects logistic regression models (with Wald test) were fitted to assess which explanatory variables were associated to different outcome variables. The patient was considered as random effect. The considered outcome variables were AD (yes/no), usual symptom (yes/no), modality (unimodal/multimodal) and each semiological category (yes/no).

Manual selection of potential explanatory variables was guided by the results of univariate analysis and was performed by fitting a number of preliminary models. The univariate analysis was undertaken before the multivariate one, as a sort of advanced inspection of data. For every model, all the potential regressors were listed in order of increasing *p*-value (obtained during univariate analysis). All regressors with $p < .2$ were then added to the model, one by one, looking carefully at the outputs. Only variables that were significant in at least one contrast and that did not induce biases to the model (e.g., multicollinearity, outliers and leverage) were included in the model. Variance inflation factor (VIF) was accepted if < 4. All results are detailed in the Supplementary tables.

Presence of AD, intensity and type of stimulation were included as explanatory variables in all logistic regression models with a semiological category as outcome variable. When there were less than 50 events of interests (e.g., olfactory hallucination), no multivariate analyses were performed. Furthermore, multivariate analysis was not performed for unclassified responses considering the lack of specificity and the high heterogeneity of this clinical manifestation. In case of high collinearity, the more clinically relevant variables were maintained in the final best model. Statistical significance was set at *p*-value $< .05$. Relative risk (RR) was computed for categorical variables with the technique described by Zhang and Yu (1998). The statistical analysis was performed with R 3.5.1 Statistical Package.

3 | RESULTS

Demographic and clinical data of the included subjects are summarized in Table 2.

Ten patients had MRI abnormalities in the temporal lobe (9%). The epileptogenic zone defined by SEEG included the temporal lobe in 78 patients (70.4%). Of the included 108 patients, 74 (69%) underwent surgical treatment (details are shown in Table S1).

A total of 1529 electrical stimulations were included in the analysis: 1065 LF and 464 HF. A clinical response was evoked by 149 of the 1065 (14%) LF stimulations and by 221 of 464 (47.6%) HF stimulations ($p < .001$). Therefore, the effective stimulations were 370, of which 272 (73.5%) were associated with AD, 143 (38.6%) evoked multimodal responses, 202 (54.6%) determined usual symptoms and 306 (82.7%) caused exclusively subjective symptoms.

TABLE 2 Demographic and clinical data of our cohort

Variable		Number of patients = 108
Gender	Female, *n* (%)	53 (49)
	Male, *n* (%)	55 (51)
Neurological examination	Abnormal, *n* (%)	23 (21)
	Normal, *n* (%)	85 (79)
Language hemispheric dominance	Left, *n* (%)	102 (94)
	Right, *n* (%)	6 (6)
Onset (years), mean (standard deviation)		10.9 (9.1)
Duration (years), mean (standard deviation)		16.6 (9.3)
Age at SEEG (years), mean (standard deviation)		27.5 (10.3)
Side of SEEG	Right, *n* (%)	53 (49)
	Left, *n* (%)	42 (39)
	Bilateral, *n* (%)	13 (12)
Side of EZ	Right, *n* (%)	60 (55)
	Left, *n* (%)	45 (42)
	Bilateral, *n* (%)	3 (3)

Abbreviations: EZ, epileptogenic zone; SEEG, stereoelectroencephalography.

According to the semiological classification, we obtained 146 visceral sensations (0.09% of the total stimulations performed), 93 unclassified responses (0.06%), 81 psychic phenomena (0.05%), 64 neurovegetative symptoms (0.04%), 61 visual illusion/hallucinations (0.04%), 38 automatisms (0.02%), 37 episodes of loss of contact (0.02%), 37 somatosensory symptoms (0.02%), 27 motor symptoms (0.02%), 15 auditory illusion/hallucinations (0.01%), 14 language disturbances (0.01%), and two olfactory hallucinations (0.001%).

3.1 | Frequencies and univariate analyses

3.1.1 | Hippocampus

Of 578 stimulations, 171 were effective (30%). The most common symptom evoked was visceral sensation (79/171, 46% of effective stimulations) which was associated with AD in 69/79 (87%) stimulations. Other effective stimulations resulted in unclassified responses (41/171, 24%), psychic phenomena (37/171, 22%) and neurovegetative symptoms (32/171, 19%), which were associated with AD in most cases (38/41, 93%, 33/37, 89% and 26/32, 81%, respectively). Visual symptoms were evoked by 35/171 (20%) of the effective stimulations, and these were associated with AD in 17/35 (49%) (see Section 3.3). Objective symptoms were evoked by 25/171 (15%) of the effective stimulations, were always linked with AD and included automatisms, loss of contact and motor symptoms.

3.1.2 | Parahippocampal gyrus

Of 232 stimulations, 56 were effective (24%). The most common evoked symptom was visceral sensations (21/56, 37.5%) which were associated with AD in 17/21 (81%). Visual symptoms were evoked by 15/56 (27%) of the effective stimulations, and 6/15 (40%) were linked with AD (see Section 3.3). Unclassified responses, psychic phenomena and neurovegetative symptoms were evoked by 14/56 (25%), 13/56 (23%) and 11/56 (20%), respectively, of the effective stimulations, and the majority was associated with AD (13/14, 93%, 10/13, 77% and 11/11, 100%, respectively). Objective symptoms were evoked by 5/56 (9%) of the effective stimulations and were always linked with AD.

3.1.3 | Amygdala

Of the 144 stimulations, 43 were effective (30%). The most common evoked symptom was visceral sensations (23/43, 53%) which were associated with AD in 20/23 (87%). Neurovegetative symptoms, psychic phenomena and unclassified responses were evoked by 12/43 (28%), 11/43 (26%) and 8/43 (19%), respectively, of the effective stimulations, and the majority was linked with AD (11/12, 92%, 8/11, 73% and 6/8, 75%) respectively). Other subjective symptoms were rare, such as visual symptoms in 3/43 (7%). Objective symptoms were evoked by the 12/43 (28%) of the effective stimulations and were always linked with AD.

3.1.4 | Uncus

Of the 51 stimulations, 12 were effective (24%). The most common evoked symptom was unclassified responses (5/12, 42%) and was associated with AD in the 4/5 (80%). Somatosensory symptoms were evoked by 4/12 (33%) and were always linked with AD. Psychic phenomena, visceral sensation and neurovegetative

symptoms were evoked by 3/12 (25%), 3/12 (25%) and 2/12 (17%), respectively, of the effective stimulations, and the majority was linked with AD (3/3, 100%, 3/3, 100% and 1/2, 50%). Other subjective symptoms were rare. Objective symptoms were evoked by 5/12 (24%) of the effective stimulations and were always linked with AD.

3.1.5 | Mesial temporal pole

Of 182 stimulations, 32 were effective (18%). The most common evoked symptoms were psychic phenomena and visceral sensations (11/32, 34% and 10/32, 31%, respectively), and they were associated with AD in the majority of cases (8/11, 82% and 7/10, 70%, respectively). Unclassified responses and visual symptoms were evoked by 5/32 (16%) and 4/32 (12.5%), respectively, of the effective stimulations, and the majority was linked with AD (5/5, 100% and 3/4, 75%). Other subjective symptoms were rare. Objective symptoms were evoked by the 5/32 (16%) of the effective stimulations and were always linked with AD.

3.1.6 | Lateral temporal pole

Of 342 stimulations, 56 were effective (16%). The most common evoked symptom was unclassified responses (20/56, 36%) which were associated with AD in 14/20 (70%). Both auditory symptoms and visceral sensations were evoked by 10/56 (18%) of the effective stimulations and were linked with AD in 8/10 (80%) and 7/10 (70%), respectively. Neurovegetative symptoms were evoked by 5/56 (9%) of the effective stimulations and were linked with AD in 4/5 (80%). Psychic phenomena and somatosensory symptoms were evoked in 6/56 (11%) and 5/56 (9%), respectively, of the effective stimulations and were linked with AD in 2/6 (33%) and 2/5 (40%). Other subjective symptoms were rare. Objective symptoms were evoked by 12/56 (21%) of the effective stimulations and were always linked with AD; the most common was language disturbance (7/12, 75%).

The results of univariate analyses are reported in Tables S2–S16. All the clinical responses obtained in each substructure are summarized in Figure 3, grouped by the presence/absence of AD.

3.2 | Multivariate analyses

The results of multivariate analyses are detailed in Table 3.

In every model, at least two explanatory variables resulted as significantly associated with the outcome variable. We summarize the main findings below.

3.2.1 | After discharge

The chance of evoking AD was lower with LF stimulations and was higher when hippocampus, parahippocampal gyrus and amygdala were stimulated in comparison with the lateral temporal pole (reference category).

3.2.2 | Unimodal versus multimodal responses

The probability of evoking multimodal responses was higher when AD occurs and when hippocampus, parahippocampal gyrus, uncus and amygdala were stimulated.

3.2.3 | Usual versus unusual responses

The chance of evoking symptoms recognized as usual by the patient was higher using LF stimulations and when AD occurred, whereas it was lower when the stimulation was performed in the language-dominant hemisphere and when the patient suffered mostly from sleep-related seizures.

3.2.4 | Visual illusions/hallucinations

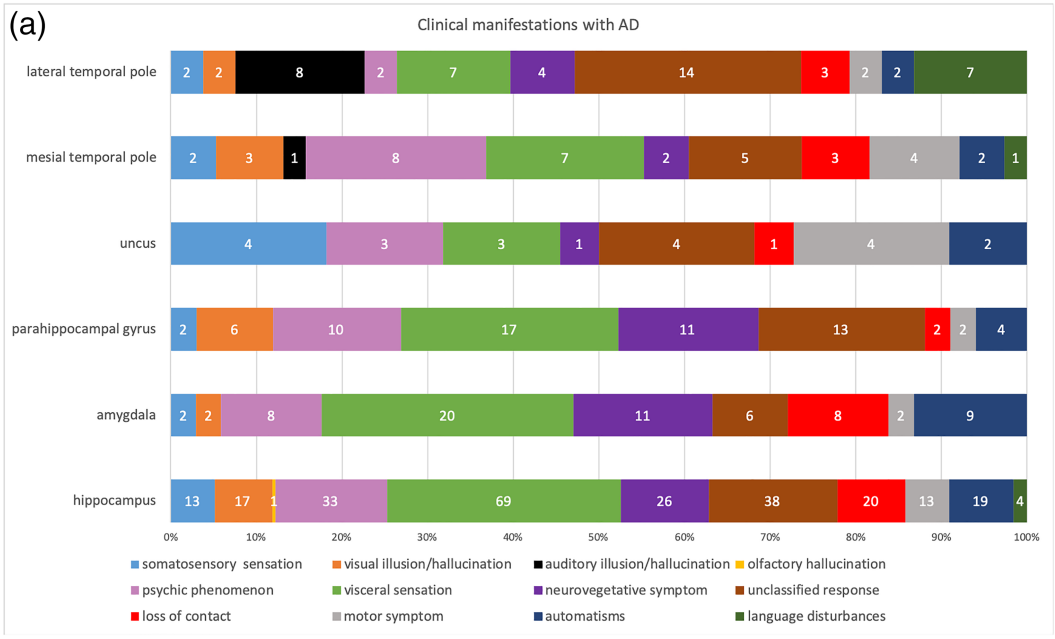
The probability of evoking visual illusions/hallucinations was lower when AD occurred and when LF stimulation was used. The possibility to induce these symptoms was higher when hippocampus and parahippocampal gyrus were stimulated or when the intensity of the stimulation was increased.

3.2.5 | Visceral sensations

The possibility to evoke a visceral sensation was higher when AD occurred and when hippocampus, parahippocampal gyrus and amygdala were stimulated.

3.2.6 | Neurovegetative symptom

The probability of evoking neurovegetative symptom was higher when AD occurred and when amygdala was stimulated.



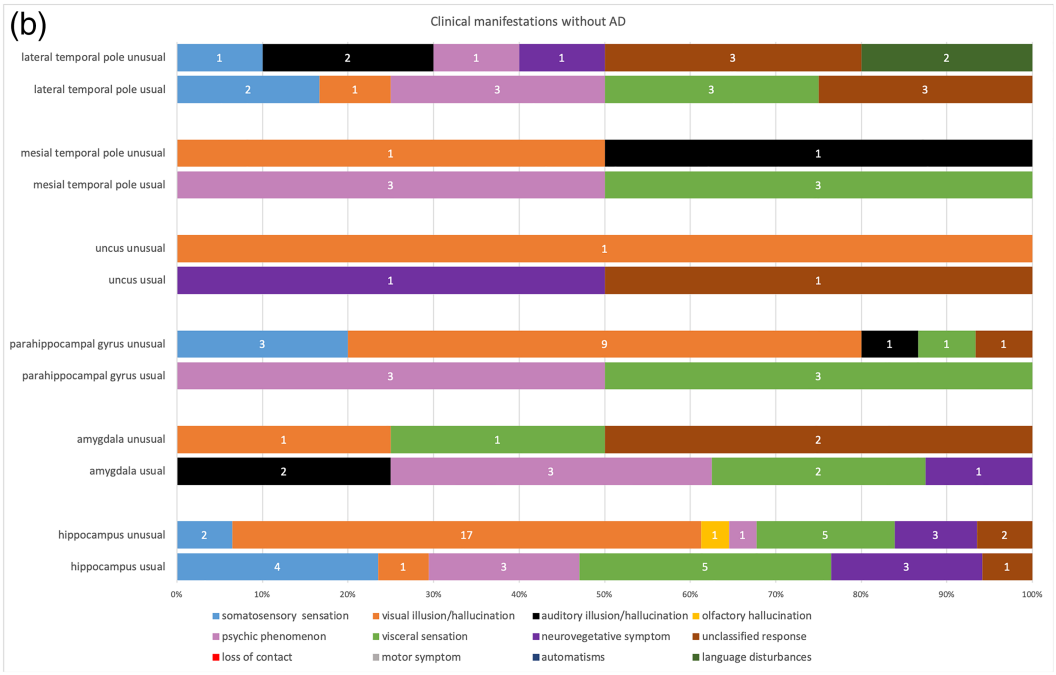


FIGURE 3 Summary of all the effective clinical responses obtained in each substructure, grouped by (a) presence or (b) absence of after discharge (AD)

3.2.7 | Psychic phenomenon

The chance to elicit a psychic phenomenon was higher when hippocampus, amygdala and mesial temporal pole were stimulated.

The occurrence of AD was significantly associated to all the considered outcome variables (only for the outcome of psychic phenomena there was a trend towards significance instead of a 'true significance'). In other words, the occurrence of AD facilitated multimodal responses, recognized by the patient as usual and was associated with the occurrence of visceral, neurovegetative or psychic phenomena. Conversely, it was less probable to have visual manifestations when AD occurred.

The use of LF stimulations significantly reduced the probability of AD occurrence and of evoking visual

TABLE 3 Results of multivariate analyses

Variable	Category	Ref cat	Coeff	SE	OR	95% CIor		RR	95% CIrr		*p* value
Outcome variable: After discharge (category of interest: yes; reference category: no)											
Type of stimulation	LF	HF	−2.03	0.42	0.13	0.06	0.30	0.37	0.19	0.62	<.0001*
Intensity (mA)			−0.16	0.12	0.86	0.68	1.08				.1877
Site	Hippocampus	Lateral pole	1.71	0.49	5.50	2.12	14.29	1.23	1.14	1.27	.0005*
	Parahi. gyrus		1.19	0.56	3.29	1.10	9.84	1.31	1.03	1.44	.0328*
	Uncus		1.64	0.97	5.16	0.77	34.61	1.25	0.93	1.32	.0908^
	Amygdala		1.93	0.64	6.92	1.99	24.07	1.22	1.12	1.25	.0024*
	Mesial pole		1.03	0.61	2.81	0.85	9.27	1.17	0.96	1.24	.0887^
Outcome variable: Modality of response (category of interest: multimodal; reference category: unimodal)											
AD	Yes	No	2.13	0.41	8.40	3.79	18.60	1.88	1.64	2.01	<.0001*
Type of stimulation	LF	HF	0.53	0.37	1.69	0.82	3.48	1.31	0.89	1.71	.1523
Intensity (mA)			0.01	0.12	1.00	0.80	1.26				.9907
Site	Hippocampus	Lateral pole	1.20	0.49	3.32	1.27	8.68	1.64	1.14	1.98	.0144*
	Parahi. gyrus		1.23	0.58	3.41	1.09	10.65	1.76	1.05	2.24	.0349*
	Uncus		2.02	0.89	7.50	1.31	42.88	1.57	1.11	1.70	.0235*
	Amygdala		1.74	0.64	5.70	1.63	19.93	1.73	1.25	1.94	.0064*
	Mesial pole		0.13	0.61	1.13	0.34	3.75	1.10	0.41	2.22	.8375
Generalized seizures	Yes	No	−0.65	0.37	0.52	0.25	1.08	0.61	0.33	1.05	.0787^
Outcome variable: Usual (category of interest: yes; reference category: no)											
AD	Yes	No	2.39	0.50	10.93	4.08	29.30	1.59	1.45	1.66	<.0001*
Type of stimulation	LF	HF	1.48	0.49	4.41	1.69	11.49	1.46	1.20	1.60	.0024*
Intensity (mA)			−0.01	0.14	0.99	0.75	1.31				.9477
Language-dominant hemisphere	Yes	No	−1.27	0.49	0.28	0.11	0.74	0.40	0.17	0.83	.01*
Sleep-related seizures	Yes	No	−2.01	0.76	0.13	0.03	0.60	0.19	0.05	0.70	.0084*
Outcome variable: Visual illusion/hallucination (category of interest: yes; reference category: no)											
AD	Yes	No	−2.00	0.53	0.14	0.05	0.39	0.15	0.05	0.41	.0002*
Type of stimulation	LF	HF	−1.25	0.62	0.29	0.08	0.97	0.34	0.11	0.98	.0448*
Intensity (mA)			0.57	0.19	1.76	1.22	2.55				.0028*
Site	Hippocampus	Lateral pole	2.06	0.79	7.84	1.67	36.77	3.31	1.47	4.51	.009*
	Parahi. gyrus		2.01	0.87	7.49	1.35	41.49	2.72	1.23	3.48	.0212*
	Uncus		0.98	1.51	2.68	0.14	51.55	2.36	0.15	10.22	.5143
	Amygdala		0.56	1.06	1.74	0.22	13.93	1.66	0.23	7.31	.6006
	Mesial pole		1.34	0.97	3.83	0.58	25.44	2.80	0.61	6.09	.1639
Outcome variable: Visceral sensation (category of interest: yes; reference category: no)											
AD	Yes	No	1.33	0.41	3.78	1.70	8.41	1.68	1.29	1.94	.0011*
Type of stimulation	LF	HF	0.40	0.42	1.49	0.66	3.38	1.24	0.77	1.69	.3393
Intensity (mA)			−0.13	0.13	0.88	0.68	1.13				.3072
Site	Hippocampus	Lateral pole	1.68	0.54	5.39	1.87	15.49	1.79	1.34	2.02	.0018*
	Parahi. gyrus		1.48	0.63	4.40	1.27	15.19	1.92	1.15	2.38	.0192*
	Uncus		0.38	1.03	1.47	0.19	11.08	1.31	0.24	3.15	.7105
	Amygdala		2.12	0.68	8.36	2.21	31.66	1.71	1.35	1.84	.0018*

(Continues)

TABLE 3 (Continued)

Variable	Category	Ref cat	Coeff	SE	OR	95% CIor		RR	95% CIrr		p value
	Mesial pole		0.89	0.65	2.45	0.69	8.73	1.69	0.76	2.57	.1682
Outcome variable: Neurovegetative symptom (category of interest: yes; reference category: no)											
AD	Yes	No	0.94	0.46	2.56	1.05	6.25	1.95	1.04	3.05	.0391*
Type of stimulation	LF	HF	−0.21	0.44	0.81	0.34	1.91	0.84	0.38	1.68	.6333
Intensity (mA)			−0.02	0.14	0.98	0.74	1.28				.8709
Site	Hippocampus	Lateral pole	0.90	0.59	2.45	0.77	7.81	1.92	0.81	3.41	.1287
	Parahi. gyrus		1.16	0.67	3.19	0.85	11.94	2.22	0.88	3.74	.0842^
	Uncus		0.80	1.05	2.23	0.29	17.44	1.85	0.33	4.60	.4441
	Amygdala		1.62	0.69	5.05	1.30	19.69	2.37	1.20	3.16	.0195*
	Mesial pole		−0.69	0.92	0.50	0.08	3.06	0.52	0.09	2.72	.4557
Outcome variable: Psychic phenomenon (category of interest: yes; reference category: no)											
AD	Yes	No	1.08	0.66	2.96	0.81	10.74	2.01	0.85	3.22	.0995^
Type of stimulation	LF	HF	−0.18	0.73	0.84	0.20	3.46	0.86	0.24	2.40	.8040
Intensity (mA)			−0.07	0.24	0.93	0.58	1.48				.7626
Site	Hippocampus	Lateral pole	2.32	0.95	10.16	1.59	64.92	3.37	1.41	4.31	.0143*
	Parahi. gyrus		2.03	1.06	7.59	0.94	61.18	3.02	0.95	4.12	.0569^
	Uncus		0.03	2.11	1.03	0.02	64.62	1.02	0.02	3.82	.9876
	Amygdala		2.41	1.17	11.13	1.12	110.44	3.06	1.09	3.75	.0396*
	Mesial pole		2.10	1.01	8.13	1.12	59.18	2.37	1.07	2.85	.0386*

Abbreviations: AD, after discharge; CI, confidence interval; Coeff, regression coefficient; HF, high-frequency stimulation; LF, low-frequency stimulation; OR, odds ratio; Parahi., parahippocampal; Ref cat, reference category; RR, relative risk; SE, standard error.

*Statistically significant ($p < .05$).

^Trend towards significance ($.1 < p < .05$).

illusions/hallucinations, whereas it increased the chance of evoking symptoms recognized as usual by the patient.

Higher stimulation intensities independently predicted a higher chance of evoking visual illusions/hallucinations.

The site of stimulation was an independent predictor of the outcome in all fitted models but the one with usual/unusual symptoms as dependent variable. Overall, the reference category (lateral part of the temporal pole) responded differently compared with the mesial temporal structures in the vast majority of performed contrasts. The stimulation of the lateral temporal pole resulted in a lesser chance of AD occurrence, multimodal response, visual illusions/hallucinations, visceral sensations, neurovegetative symptoms and psychic phenomena (the numerous contrasts are detailed in Tables S2–S16).

Loss of consciousness, somatosensory sensations, motor responses, auditory hallucinations, language disturbances and olfactory hallucinations were elicited 37, 37, 27, 15, 14 and two times, respectively. Because such symptoms occurred rarely, we could not fit any multivariate regression models according to Agresti (2007).

3.3 | Physiological symptoms

Fifty-seven stimulations evoked clinical manifestations without electrical modification and which were not part of the ictal semiology (Figure 3b). Below, we describe them by anatomical substructures.

3.3.1 | Hippocampus

The most common symptoms were visual ($n = 17$), mainly simple visual hallucinations such as flash, bright or black dots, without other associated symptoms except for one instance when it was associated with a 'strange sensation in both arms'. We also obtained five visceral sensations such as nausea and epigastric sensation, one of these was associated with tachycardia, one other with 'strange sensation on one arm' and the others were isolated. We also recorded isolated neurovegetative symptoms ('heat sensation on the chest') ($n = 2$), olfactory hallucination ('smell of solvent') ($n = 1$) and an isolated feeling of anxiety ($n = 1$). Also

undefined symptoms such as confusion were reported ($n = 2$).

3.3.2 | Parahippocampus

The most common symptoms were visual ($n = 9$), either simple visual hallucinations, as in the hippocampus, or illusions such as 'seeing shadows or blurred vision'. We also obtained somatosensory symptoms localized in the arms or in the mouth ($n = 3$), associated with nausea in one case, a 'muffled' sensation and an undefined sensation ('discomfort in the head') ($n = 1$).

3.3.3 | Amygdala

Here, we evoked undefined symptoms ('feeling strange') ($n = 2$), nausea ($n = 1$) and a simple visual hallucination ($n = 1$).

3.3.4 | Uncus

We obtained a visual illusion ('tremoulous vision') ($n = 1$).

3.3.5 | Mesial temporal pole

Here, we obtained a simple visual hallucination ('flashing light and blurred vision') ($n = 1$) and a simple auditory hallucination ('hearing something undefined').

3.3.6 | Lateral temporal pole

We evoked undefined sensations (strangeness, sensation of breathlessness) ($n = 3$), language disturbances ('awkward speech') ($n = 2$), somatosensory sensations on the head ($n = 2$) and auditory illusions ('feeling his/her voice strange') ($n = 2$).

4 | DISCUSSION

In the present study, we provide an overview of all clinical manifestations evoked by LF and HF cortical electrical stimulations of the anteromesial portion of the temporal lobe. LF stimulations were significantly less effective than HF ones in evoking clinical manifestations, this being in line with previously reported data (Balestrini et al., 2015;Cuello Oderiz et al., 2019 ; Munari et al., 1993).

Previous studies exploring functional anatomy using electrical stimulations included in the analysis only clinical manifestations without AD (Balestrini et al., 2015; Caruana et al., 2018; Mazzola et al., 2009; Mulak et al., 2008). We chose to include also symptoms associated with AD for comprehensiveness and to distinguish physiological and pathological symptoms evoked by electrical stimulation of the same area.

In our study, as shown by the multivariate analyses, LF stimulations were more likely to evoke clinical manifestations without AD compared with HF stimulations, confirming their role in studying human physiology especially in primary cortical areas (Balestrini et al., 2015; Chauvel et al., 1996). Furthermore, LF stimulation is a useful tool to study cortico-cortical evoked potentials that can shed light on pathological and physiological connectivity (Keller et al., 2014). HF stimulations were more likely to evoke electroclinical manifestations (Cuello Oderiz et al., 2019; Munari et al., 1993) probably because they involve a wider cortical area that includes epileptogenic networks; they can provide useful information for the definition of the epileptogenic zone.

The stimulation of the hippocampus, parahippocampal gyrus and amygdala, compared with the stimulation of the lateral temporal pole, was more likely to elicit AD and electroclinical manifestations. There has been much debate on the role of the hippocampus in the genesis of temporal lobe epilepsy considering the loss of inhibitory circuits as the possible 'primum movens' (Swanson, 1995). A predominant pathogenetic role of other anatomical structures such as the amygdala and parahippocampal gyrus has also been suggested (Wennberg et al., 2002). In patients with temporal lobe epilepsy, it is quite obvious that electrical stimulation of the hippocampus evokes an electroclinical manifestation, but in our study different types of epilepsy were included, not necessarily involving the temporal lobe. The low epileptogenic threshold of these areas can be explained by their intrinsic high epileptogenicity or by the fact that the underlying epilepsy condition (not necessarily localized to the temporal lobe) may increase their sensitivity to electrical stimulation (Peng & Bonaguidi, 2018).

One of the aims of cortical stimulations during SEEG is to reproduce the usual ictal semiology. The occurrence of AD and LF stimulations were independent factors predicting usual ictal semiology. The occurrence of AD likely mimics ictal spreading of the seizure, thus explaining why elicited symptoms are more frequently recognized as usual by the patient. Therefore, seizures induced by cortical stimulation can reliably identify the epileptogenic zone as spontaneous seizures do (Cuello

Oderiz et al., 2019). LF stimulations were more prone to evoke usual seizures than HF stimulations, suggesting that the cortical area involved in LF stimulations is a reliable reproduction of the 'real' epileptogenic zone, not exceeding its limits. On the other hand, HF stimulations can provoke unusual symptoms, i.e., 'false positive' seizures, most likely because HF stimulations are able to engage a wider cortical area including the epileptogenic network and inducing seizures even outside the epileptogenic zone. In some patients, stimulation of the hippocampus, parahippocampal gyrus and amygdala evoked unusual symptoms associated with AD that can be considered as 'false positive' seizures, as these areas are very sensitive to stimulation despite not being involved in the epileptogenic zone, as mentioned above. On a clinical basis, it becomes therefore crucial to distinguish the characteristics of the seizures that the patient usually experiences from the 'false positive' manifestations, that are never experienced before and likely to be induced only in the context of the stimulations. In our study, usual and unusual seizures were generally distinguished by the patient, especially in case of subjective symptoms, and this should guide the neurologist in the recognition of 'false positive' symptoms.

The multivariate analysis showed that the probability to evoke multimodal symptoms is associated with the presence of AD, suggesting the stimulation of a network involving different connected anatomical areas. The AD may involve multiple near and distant cortical areas, inducing more heterogeneous clinical manifestations by exploiting the already present epileptogenic network. In fact, some clinical manifestations recorded in our study, for example, somatomotor symptoms and oroalimentary automatisms, suggest the spreading of the AD beyond the temporal lobe (Bossi et al., 1984; Munari et al., 1985). Furthermore, the study of neuronal networks in temporal lobe epilepsy suggests the presence of a widespread network including both medial temporal structures and distant cerebral areas (Bartolomei et al., 2001). Multimodal clinical manifestations were evoked mainly by the stimulation of the hippocampus, parahippocampal gyrus, uncus and amygdala compared with the stimulation of the lateral temporal pole, probably because these structures are closely connected to each other and to a complex network that can evoke many different and complex symptoms likely resulting from the large amount of connections of the limbic circuit (Catani et al., 2013). Studies investigating the connectivity of the temporal lobe structures also with other distant cortical areas might shed light on the pathophysiology of complex multimodal clinical manifestations (Bartolomei et al., 2019; Fox et al., 2020).

The majority of clinical manifestations were exclusively subjective symptoms (82.7%), in agreement with the hypothesis that the temporal lobe is involved mostly in subjective processes (Lech & Suchan, 2013).

The visceral sensations were the most common symptoms evoked by stimulation of the anteromesial part of the temporal lobe. The multivariate analysis indicated that they were associated with AD and with the stimulation of the hippocampus, parahippocampal gyrus and amygdala. These symptoms, particularly 'rising epigastric sensation', are commonly associated with temporal lobe epilepsy and usually they point to a mesial involvement (Maillard et al., 2004). The association with AD suggests that these symptoms are usually caused by stimulation of an epileptogenic network and can be explained by the limbic component of the network or by the involvement of the insula in the AD (Isnard et al., 2000). Hippocampus, parahippocampal gyrus and amygdala are probably part of a network that, when stimulated, can elicit a visceral sensation (Mulak et al., 2008).

The neurovegetative symptoms were associated with AD and with stimulation of the amygdala. Meletti et al. (2006) reported the possibility to evoke emotions (especially fear) with electrical stimulation of the anteromesial portion of the temporal lobe, particularly the amygdala. Sensations of anxiety and fear are generally linked with a constellation of autonomic, visceral and neurovegetative symptoms, confirming the connection of the amygdala with the hypothalamus and the brainstem (Critchley & Harrison, 2013). Lanteaume et al. (2007) reported changes in skin conductance as a consequence of emotional changes after electrical stimulation of the amygdala, whereas Inman et al. (2018) recorded autonomic changes due to amygdala stimulation without concurrent emotional responses. The factors determining the link between autonomic and emotional responses after amygdala stimulation require further investigation and could also be related to the presence or absence of AD. In our cohort, the number of amygdala stimulations was relatively small, preventing an accurate analysis of the clinical data. Furthermore, we cannot determine the possible involvement of the subcortical structures, never explored during SEEG recordings.

Psychic symptoms were mainly evoked by the stimulation of the hippocampus, amygdala and mesial temporal pole. Psychic symptoms encompassed sensations such as anxiety, fear, déjà vu and 'dreamy state'. The hippocampus, particularly the ventral portion, is involved in the regulation of emotions (Bannerman et al., 2004) and also in the generation of symptoms related with anxiety (Canteras et al., 2009), often with a neurovegetative component. We found 10 psychic responses in our series including 'déjà vu', 'dreamy state'

or 'déjà-rêvé' evoked by stimulation of the hippocampus and the mesial temporal pole, in keeping with previous studies (Bartolomei et al., 2004; Curot et al., 2018; Vignal et al., 2007) and confirming the role of these structures in the recall of memories. Also, the visual component of the 'dreamy state' suggests the role of these regions in the integration of vision and memory and further supports the hippocampus involvement in the visual ventral stream. In our series, we identified four stimulations in the hippocampus or temporal pole that evoked visual illusion/hallucination associated with psychic phenomenon (such as anxiety or fear) confirming the close link between vision and complex psychic phenomena during stimulation of the anteromesial portion of the temporal, beyond memory. Stimulation of the amygdala may evoke both positive and negative emotions (Inman et al., 2018; Meletti et al., 2006). Stimulation of the temporal pole may also provoke psychic phenomena as well as viscero-sensory, autonomic and viscero-motor phenomena (Ostrowsky et al., 2002). Psychic symptoms evoked in the temporal pole suggest a possible integration of psychic functions and multisensory perception. We postulate that the mesial portion of the temporal pole, more than the lateral portion, also plays an important role in the genesis of psychic manifestations, in addition to amygdala and hippocampus. However, the functional anatomy of the temporal pole and its connectivity remains extremely complex and not fully understood (Olson et al., 2007).

As the intracranial electrode implantation was tailored to explore the epileptogenic zone in patients with drug-resistant epilepsy undergoing presurgical assessment, the number of symptoms that we interpreted as 'physiological' was inevitably very small (15.4.% of all effective stimulations). On the other hand, we believe that the criteria we used to define physiological symptoms, i.e. excluding any symptoms associated with any even minimal changes on the EEG and which were recognized by the patients as part of their habitual seizures, minimized the chance of error in the interpretation of the evoked symptoms. The most relevant physiological findings were the predominant visual symptoms evoked in the hippocampus and parahippocampus, which were mainly simple visual hallucinations (Figure 3b). The occurrence of AD was associated with a lower probability of visual illusions/hallucinations. According to previous studies (Balestrini et al., 2015; Caruana et al., 2018; Mazzola et al., 2009; Mulak et al., 2008), a clinical symptom evoked by cortical stimulation without AD can be considered as a reliable reproduction of the normal physiology of the stimulated area. Visual illusion/hallucinations were evoked mainly by HF stimulations and higher intensities. As a matter of fact, HF stimulations are more frequently used than LF stimulations in functional mapping as they are considered the most effective in evoking clinical manifestations (Trébuchon & Chauvel, 2016). Furthermore, increased stimulation intensity is obviously correlated with increasing clinical effects (Trébuchon & Chauvel, 2016) and in this case was associated with visual symptoms. Visual illusions/hallucinations were evoked mainly by the stimulation of hippocampus and parahippocampal gyrus. The hallucinations were usually uncoloured spots in the visual field (either lateralized or not) but in some cases were also complex, such as pictures. Limited data exist on the involvement of the hippocampus in the ventral stream of vision. Previous studies have suggested the hippocampus involvement in encoding visual processes and recollection-based memory (Miyamoto et al., 2014; Orban et al., 2014). To better understand the role of the hippocampus in the visual ventral stream of vision in humans, it would be important to conduct a study on a larger sample, along with further characterization of the evoked visual symptoms (for instance, illusion vs. hallucination, localization in the visual field and coloured vs. not coloured) and of the stimulation site (i.e., anterior vs. posterior hippocampus). The parahippocampal gyrus is also part of the ventral stream and is involved in different visual-cognitive functions. It plays an important role in the distinction of similar objects that can be easily confounded (Kivisaari et al., 2012), in the recognition of places and in spatial navigation (Epstein, 2008). Simple visual phenomena after hippocampus stimulation could also be due to stimulation of visual tract fibres instead of hippocampus itself. However, we included only contacts that were clearly located in the hippocampus and not in the optic radiations. For most patients, we also have visual evoked potentials and MRI tractography data that confirm the distance between the stimulated contacts and the optic radiations. To clarify this aspect, we provided an example in Figure S1.

There are some limitations in this study that need to be acknowledged. The contacts of each implanted electrode explore a small cerebral area, and each stimulation lasts for a short time providing limited sampling in terms of spatial and temporal resolution. Most implantations were unilateral and explored different anatomical structures in each patient. Most evoked clinical manifestations were subjective and dependent on the collaboration and cognitive function of the patients; we cannot still guarantee their entire reliability. Because the clinically driven topographical strategy of implantation usually does not include sampling from subcortical structures (e.g., basal ganglia), it was not possible to evaluate the involvement of such regions. Also, the criteria we used to classify the evoked symptoms were arbitrary and may have not allowed to capture the complexity of some responses.

On the other hand, we present the first large-sample systematic analysis of stimulations of the mesial portion of the temporal lobe, addressing both anatomo-functional and epilepsy-related aspects. Electrical stimulation of the anteromesial temporal lobe is a useful tool for functional mapping and for defining the epileptogenic zone but is associated with a considerable risk of 'false positive' seizures. Our findings suggest involvement of the anteromesial temporal structures in the visual ventral stream and provide further understanding of temporal lobe epilepsy-related symptoms.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Valeria Mariani conceptualized the study, curated the data, conducted the investigation and prepared the original draft of the manuscript. Simona Balestrini curated the data, conducted the formal analysis and reviewed and edited the manuscript. Francesca Gozzo curated the data and conducted the investigation. Veronica Pelliccia curated the data and conducted the investigation. Roberto Mai curated the data and conducted the investigation. Stefano Francione curated the data and conducted the investigation. Ivana Sartori curated the data and conducted the investigation. Francesco Cardinale conceptualized the study, curated the data, conducted the investigation, designed the methodology, conducted the formal analysis and reviewed and edited the manuscript. Laura Tassi conceptualized the study, conducted the investigation, designed the methodology, reviewed and edited the manuscript and supervised the study.

CONSENT TO PARTICIPATE

All patients were fully informed of the aims of the SEEG recording and stimulation procedures and provided informed consent to participate to the study.

CONSENT FOR PUBLICATION

All patients provided informed consent to publish their data for research purposes.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon reasonable request from the corresponding author SB.

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