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Research Report

The origin of pleasant sensations: Insight from direct electrical brain stimulation

Cécile Villard [a], *Zoé Dary* [b], *Jacques Léonard* [b], *Samuel Medina Villalon* [a,c], *Romain Carron* [d], *Julia Makhalova* [a,c], *Stanislas Lagarde* [a,c], *Christophe Lopez* [b] *and Fabrice Bartolomei* [a,c,*]

[a] *APHM, Timone Hospital, Epileptology Department, Marseille, France*
[b] *Aix Marseille University, CNRS, LNC, FR3C, Marseille, France*
[c] *Aix Marseille University, Inserm, INS, Inst Neurosci Syst, Marseille, France*
[d] *APHM, Timone Hospital, Functional Neurosurgery Department, Marseille, France*

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ABSTRACT

Research into the neuroanatomical basis of emotions has resulted in a plethora of studies over the last twenty years. However, studies about positive emotions and pleasant sensations remain rare and their anatomical-functional bases are less understood than that of negative emotions. Pleasant sensations can be evoked by electrical brain stimulations (EBS) during stereotactic electroencephalography (SEEG) performed for pre-surgical exploration in patients with drug-resistant epilepsy. We conducted a retrospective analysis of 10 106 EBS performed in 329 patients implanted with SEEG in our epileptology department. We found that 13 EBS in 9 different patients evoked pleasant sensations (.60% of all responses). By contrast we collected 111 emotional responses of negative valence (i.e., 5.13% of all responses). EBS evoking pleasant sensations were applied at 50 Hz with an average intensity of 1.4 ± .55 mA (range .5–2 mA). Pleasant sensations were reported by nine patients of which three patients presented responses to several EBS. We found a male predominance among the patients reporting pleasant sensations and a prominent role of the right cerebral hemisphere. Results show the preponderant role of the dorsal anterior insula and amygdala in the occurrence of pleasant sensations.

Abbreviations: EBS, direct electrical brain stimulation; SEEG, stereoelectroencephalography; AI, anterior insula.

* *Corresponding author*. Epileptology Department, Timone Hospital, 264 Rue Saint Pierre, 13005, Marseille.
E-mail addresses: cecile.villard18@gmail.com (C. Villard), zoe.dary@univ-amu.fr (Z. Dary), Jacques.leonard@univ-amu.fr (J. Léonard), Samuel.medina@ap-hm.fr (S. Medina Villalon), romain.carron@ap-hm.fr (R. Carron), julia.scholly@ap-hm.fr (J. Makhalova), stanislas.lagarde@ap-hm.fr (S. Lagarde), Christophe.Lopez@univ-amu.fr (C. Lopez), fabrice.bartolomei@ap-hm.fr (F. Bartolomei).

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1. Introduction

Emotions are a major part of our psychic life and brain function. They can be defined by the triad of: (1) affect (conscious experience), (2) motor and behavioral adaptation and, (3) autonomic nervous system response (Hamann, 2001; Lang, 1995). Emotions with positive valence have an important impact on quality of life and well-being. They can improve cognitive and social capacities by facilitating decision making, problem solving, social interaction and creativity (Ashby et al., 1999; Carpenter et al., 2013; Fredrickson, 2004; GROSS, 2002)). The genesis and regulation of positive emotions have been mainly studied using functional MRI with different tasks evoking pleasant sensations, including sensory experiences (Koelsch & Skouras, 2014), viewing of images of loved ones (Bartels & Zeki, 2000; Nitschke et al., 2004) or other images or films (Brassen et al., 2011; Garavan et al., 2001; Kim & Hamann, 2007), recollection or imagination of pleasant situations (Matsunaga et al., 2016; Pelletier et al., 2003; Zotev et al., 2011) or social relationships (Scharnowski et al., 2020). Despite some variability depending on the paradigm used, these studies highlighted the implication of ventral, "emotional" cortico-subcortical networks including the orbitofrontal cortex, the anterior cingulate cortex, the insula, the amygdala, as well as the caudate, the putamen, the globus pallidus and the brainstem.

The neural underpinnings of pleasant conscious sensations have also been studied using direct electrical brain stimulation (EBS) in the context of pre-surgical evaluation of patients with drug-resistant epilepsy using electrocorticography or stereotactic electroencephalography (SEEG). Brain explorations through EBS in awake patients offer several advantages. SEEG has better temporal resolution than functional MRI (Mercier et al., 2022)and targeted EBS allows to establish a direct causal "stimulation–clinical event" relationship. However, only few studies showed that EBS can evoke emotional sensations, reproducing usual ictal symptoms or more rarely sensations not encountered during seizures. Penfield and his collaborators were among pioneers in describing experiential and emotional phenomena in response to EBS during per-operative stimulations in patients (Penfield & Jasper, 1954). More recent studies on the effects of EBS on emotion have provided a functional brain map of the cortical regions involved (Drane et al., 2021; Gordon et al., 1996). In particular, the amygdala has repeatedly been involved in triggering emotional responses, which were mainly perceived as negative (Bujarski et al., 2022; Inman et al., 2020; Lanteaume et al., 2007). Other brain regions have been shown to produce emotional affects, such as other medial temporal regions (rhinal and temporal pole cortices) (Bartolomei et al., 2004; Meletti et al., 2006; Smith et al., 2006a) and the insula (Bartolomei et al., 2019; Mazzola et al., 2019). However, studies on positive emotions triggered by EBS remain very sparse when compared to stimulation-based studies of brain areas involved in other cognitive and emotional functions (Drane et al., 2021) and we are lacking causal evidence of brain network implications in pleasant sensations.

The aim of the present study was to identify the brain areas underlying conscious perception of pleasant sensations using direct EBS in a large, unselected cohort of patients with epilepsy. For this purpose, we retrospectively analyzed the effects of all EBS performed during SEEG in our department over the past twenty years.

2. Materials and methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. *Patients*

The analysis of clinical responses to EBS was performed from a database established on EBS collected from 329 consecutive patients (167 females, 162 males; mean age: 24.9 ± 13.38 years) who underwent SEEG for pre-surgical evaluation of drug-resistant epilepsy between August 2000 and September 2020 in the Epileptology Unit–Clinical Neurophysiology Department of the Timone University Hospital in Marseille, France. The left cerebral hemisphere was explored in 254 patients (6.93 ± 4.44 electrodes per patient) and the right cerebral hemisphere was explored in 269 patients (7.14 ± 4.52 electrodes per patient).

This study was approved by the local ethics committee (the institutional review board of the Assistance Publique Hopitaux de Marseille, C3BHV2), and informed written consent was obtained from all patients. Three patients of the present series have been reported in two publications about ecstatic feelings during anterior insula stimulation (Bartolomei et al., 2019; Picard et al., 2013).

2.2. *SEEG*

SEEG was performed using intracerebral multi-contact electrodes (Dixi Medical or Alcis), which had 10, 15, or 18 contacts with a length of 2 mm, a diameter of .8 mm, and a spacing of 1.5 mm. Electrodes were placed stereotactically using the Talairach technique for older implantations, or with the aid of the ROSA™ robotic surgical assistant for implantations performed after 2016 (Contento et al., 2021). SEEG was recorded with a 128- or 256-channel Natus system depending on the year of recording, sampled at 256, 512, or 1024 Hz, and recorded on a hard drive (16 bits/sample) without digital filters. Two computer filters were applied during data acquisition: a high-pass filter (cutoff frequency = .16 Hz at 3 dB), and an anti-aliasing low-pass filter (cutoff frequency = 97 Hz for a 256 Hz sampling rate, 170 Hz for a 512 Hz sampling rate, 340 Hz for a 1024 Hz sampling rate). The implantation scheme of electrodes was determined in a multidisciplinary meeting in the presence of neurologists specialized in epileptology as well as neurosurgeons. Electrodes number and their implantation sites were established in relation to the suspected epileptogenic zone on the basis of clinical examination, semiology of usual seizures, morphological and functional

imaging data (cerebral MRI, PET scan), neuropsychological tests and scalp video-EEG recorded previously.

2.3. Identifying contacts of interest

The electrode contacts which stimulation induced pleasant sensations were localized on the patient's MRI using a co-registration process based on the automatic SEEG electrode localization, segmentation and reconstruction GUI GARDEL (Medina Villalon et al., 2018) (freely available at https://meg.univ-amu.fr/wiki/GARDEL:presentation). First, a co-registration of the preoperative MRI on the post-implantation CT-scan including images of the electrodes was performed. Then, the co-registered MRI was segmented in order to extract the white matter, the grey matter and the cerebrospinal fluid. Following steps comprised automated localization of each electrode and the associated contacts and their labeling as belonging to the gray matter, white matter or the cerebrospinal fluid. Finally, the reconstruction and labeling of each contact was verified visually on MRI by expert clinicians. For older SEEG, where post-implantation CT scan was not available, electrodes were manually reconstructed from MRI post-implantation followed by automatic labeling and visual verification as previously mentioned.

2.4. Electrical brain stimulation

EBS were performed while patients were lying in bed and instructed to keep their eyes open and relax. A current-regulated neurostimulator designed for diagnostic purposes delivered EBS according to routine procedures used in our department and according to French guidelines on SEEG (Isnard et al., 2018). Square current pulses were applied between two adjacent contacts at 50 Hz, with a pulse duration of 1 ms and a train duration of 3–5 s. These parameters were used to avoid tissue damage (charge density per square pulse <55 mC/cm^2). The stimulus intensity was increased from .3 mA by .2 mA increments, until sensation or after-discharge was evoked, and up to a maximum of 3 mA. Due to the clinical purpose of EBS, a stimulation evoking a response was usually not repeated to assess the reproducibility of the response with the same stimulation parameters. However, for two patients the same electrode contacts where a positive sensation was evoked were stimulated twice at different intensities, showing reproducible responses (Table 1).

2.5. Data collection and assessment

Subjective reports and behavioral responses to cortical EBS in 329 epilepsy patients were recorded with video-SEEG. They were carefully analyzed and entered into an Excel database.

A total of 10 106 EBS using 50 Hz electrical stimulation (train duration: 3–5 s) were collected. After each stimulation, the patients were systematically asked to express the sensations and symptoms that may have been evoked by that stimulation. The effects on the EEG (after-discharge) as well as the clinical effects were routinely collected and systematically documented in dedicated notebooks, and the video-EEGs of positive responses were stored. For the present study, all the reported emotional responses of positive valence (feelings of happiness, well-being, joy, pleasant sensation of any intensity) were systematically retained and verified on the video-EEG by two expert clinicians (CV and FB). The patient's baseline emotional status was estimated from the video-EEG immediately preceding each selected stimulation and the patient's status regarding psychiatric co-morbidities was verified from the medical records. No analysis code was used in this study.

No part of the study procedures or analysis plans was preregistered prior to the research being conducted.

3. Results

3.1. Frequency and phenomenology of pleasant sensations evoked by EBS

Of the 10 106 EBS performed in our department between August 2000 and September 2020 in 329 patients, 2 165 evoked one or several responses or sensations, 1 286 during stimulation of the right cerebral hemisphere and 879 during stimulation of the left hemisphere. A pleasant sensation was reported during only 13 of these stimulations (i.e., .60% of all responses) in nine patients (i.e., 2.74% of the sample), making it a very rare experiential phenomenon evoked by EBS. By contrast, 111 emotional responses of negative valence (i.e., 5.13% of all responses) were observed in the same cohort of patients in 50 patients (i.e., 15.2% of the sample).

Among the nine patients (P1 to P9) who reported pleasant sensations, three (P4, P6 and P8) showed responses to several EBS (Table 1). Regarding the experienced phenomena, a pleasant sensation was reported by six patients, well-being by six patients, positive emotion or joy was reported by two patients and bliss by one patient. These positive sensations were accompanied by sensations of floating (three patients), warmth (one patient) or shivering (one patient). Of note, patient P5 presented a change in emotional valence of his semiology during the same stimulation, starting with a pleasant floating sensation and well-being followed by an unpleasant sensation of anxiety.

The reproducibility of the responses was not systematically assessed because EBS was delivered only for clinical. However, for patient P2 two EBS of the same electrode contacts (CC2–3) successively at 1.6 and 2 mA evoked the same feeling of well-being; for patient P6, two stimulations of the same bipolar contacts (OF1–2) successively at 1.3 and 1.6 mA, evoked the same pleasant sensation (Table 1). In conclusion, in two patients where the same electrode contacts were stimulates twice, the responses were reproducible.

3.2. Patients' characteristics

We found a male predominance among the patients reporting pleasant sensations (one 1 female, eight 8 males; sex ratio: .13), although the sex ratio was close to 1 in the whole cohort (167 females, 162 males; sex ratio: 1.03). This is in contrast with the female predominance for emotional responses of negative valence in the same cohort of patients (31 females, 19 males; sex ratio: 1.63). There was a significant effect of sex on the valence of the emotional response evoked by EBS

Table 1 – Table showing the features of the patients who had pleasant sensations during electrical 50 Hz (3–5 s) brain stimulations.

Patient (sex)	Age (years)	Subjective seizure semiology	MRI	Epileptogenic zone	Electrodes nb (right/left)	Stimulation site	Intensity (mA)	Induced clinical response	After-discharge
P1 (M)	31	Chest tightness	Left amygdala& hippocampus hypersignal	Undetermined (no seizures recorded)	17 (15/2)	Left AI	2.0	Pleasant warm sensation in the body, well-being	no
P2 (M)	35	Well-being, euphoria, floating	Right temporal FCD	Right temporal lateral	17 (14/3)	Right ACC	1.6 & 2.0	Feeling of well-being	no
P3 (M)	41	Visual illusion, well-being	Normal	Right mesial temporal	10 (10/0)	Right amygdala	.5	Pleasant sensation	no
P4 (M)	24	Well-being, numbness of the left hemibody, auditory illusion	Normal	Right temporal mesio-lateral	10 (10/0)	Right TP	1.0	Feeling of well-being	no
						Right amygdala	.5	Feeling of well-being	yes
P5 (M)	18	Well-being, reminiscence of memory, auditory illusion, déjà-vu	Left mesial temporal hypersignal	Left mesial temporal and insula	11 (0/11)	Left AI	2.0	Pleasant floating, well-being followed by anxiety and lipothymia	yes
P6 (F)	23	Pleasant epigastric sensation, floating, space distortion, auditory hallucination	Normal	Right mesial temporal and insula	10 (10/0)	Right AI	1.3 & 1.6	Pleasant floating, well-being, pleasant shivering	no
						Right amygdala	1.0	Pleasant epigastric sensation	yes
P7 (M)	24	Modification of temperature perception	Left temporal Ganglioglioma	Left mesial temporal	12 (1/11)	Left amygdala	1.0	Joy, pleasant sensation	yes
P8 (M)	45	Well-being, bliss, floating, pleasant sensation, chest tingling	Normal	Right mesial temporal	16 (13/3)	Left AI	2.0	Bliss	yes
						Right AI	2.0	Positive emotion, well-being	yes
						Right amygdala	1.0	Positive emotion, well-being	yes
P9 (M)	40	Positive emotion, bliss, tachycardia	Right fronto-opercular lesion	Right prefrontal	12 (11/1)	Right AI	1.6	Pleasant sensation, floating	no

Abbreviations; AI: anterior insula; ACC: anterior cingulate gyrus; TP: temporal pole; FCD: focal cortical dysplasia.

($\chi 2 = 7.96$; $P = .005$). The mean age of these patients reporting pleasant sensations was 31.2 ± 9.5 years.

Five out of nine patients had abnormal brain MRI. The epileptogenic zone was mainly located in the right hemisphere (six patients). The epileptogenic zone defined by SEEG included the mesial temporal regions in six patients. The epileptogenic zone was limited to these regions in three cases, extended to the temporal lateral in one case, and extended to the insula in two cases. The epileptogenic zone was temporal lateral in one case, prefrontal in one and remained undetermined in another case. Of note, seven out of nine patients also reported pleasant sensations during their usual seizures. However, no one patient had a history of mood disorder or any other psychiatric comorbidity.

3.3. *EBS characteristics and anatomical location*

EBS evoking pleasant sensations were applied at 50 Hz with an average intensity of 1.4 ± .55 mA (range .5–2 mA). Among the twelve EBS that induced positive emotional responses in 9 participants, seven induced an after-discharge. Electrode contacts where a pleasant sensation could be evoked were mostly located in the anterior insula (AI, a total of six stimulation; right AI: n = 3, left AI: n = 3) and in the amygdala (five stimulation; right amygdala: n = 4, left amygdala: n = 1) (Fig. 1). One stimulation of the right anterior cingulate cortex and another of the right temporal pole also induced a feeling of well-being (Table 1). Overall, most EBS that evoked pleasant sensations were applied to the right cerebral hemisphere (n = 9), whereas only four were applied to the left hemisphere. In two patients (P4 and P8), the same sensation could be elicited from two different brain structures, i.e., a feeling of well-being by EBS in the right temporal pole and the amygdala (P4) and a positive emotion and well-being by EBS in the right AI and the amygdala (P8). Interestingly, patient P8 also reported bliss induced by the simulation of the left AI. All but one of the positive stimulations were performed outside the MRI-visible lesion. In two patients, the stimulation site was located outside the epileptogenic zone (anterior cingulate and anterior insula).

4. Discussion

To our knowledge, our study is the first to focus specifically on the generation of pleasant sensations, in the broad meaning of the term, from a large collection of EBS obtained during SEEG recordings (10 106 stimulations in 329 patients). We found that pleasant sensations were exceptional events during EBS, much rarer than negative sensations, as we observed only 13 positives sensations (.55%, versus 5.13% for negative feelings). This is possibly a particularity of the mammalian brain, which is more likely to generate negative emotions for rapid adaptive reactions favoring survival of species, e.g. when facing a danger (Phan et al., 2002). Another explanation lies in the largely subcortical and brainstem location of reward networks (Liu et al., 2011; Wise, 2002) when compared to the focus of EBS on cortical structures during SEEG for presurgical evaluation of epilepsy (*see limitations*).

4.1. *Amygdala and anterior insula: two core regions for pleasant sensations*

Our results identified two brain regions more frequently involved in pleasant sensations: the anterior insula (AI) and the amygdala. The AI is the source of heterogeneous clinical manifestations when it is involved in seizure or stimulated electrically as it can evoke gustatory, olfactory, auditory, somatosensitive, vestibular, viscerosensitive, visceromotor, experiential or emotional sensations (Mazzola et al., 2006, 2014, 2017, 2019). Functional neuroimaging highlighted the role played by the insula in the integration of information from our environment and the genesis of adapted emotions, showing the notable role of the AI (Kurth et al., 2010). Our data

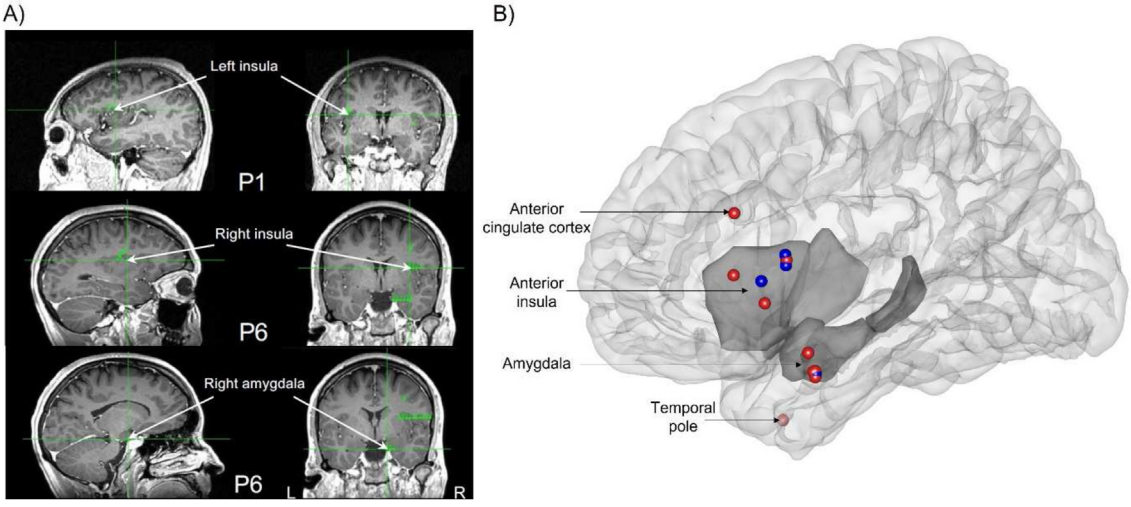

Fig. 1 – A) Example of localization and projection on patient's MRI of stimulated contacts inducing positive emotional sensations in some patients (GARDEL software. B) EBS sites are summarized by projection on the right hemisphere of the 3D mesh of the MNI normalized brain appended with meshes of amygdala and insula for better visualization. Colours indicate the lateralization these sites (blue = left side, red = right side).

are congruent with previous EBS studies showing the involvement of AI in pleasant emotions and particularly ecstatic sensations (Bartolomei et al., 2019; Nencha et al., 2022a; Ostrowsky et al., 2000). Gschwind and Picard (2016), in a meta-analysis of ecstatic aura, defined ecstatic sensations as the association of "intense positive emotion (bliss)", "improved physical well-being", "increased self-awareness or increased perception of the external world (clarity)". According to a recent neurocognitive theory, the brain would operate on a prediction model (Clark, 2013), comparing real internal and external stimuli with reference theoretical patterns. The insula would be the key structure for processing the internal states of the body through interoceptive signals. Disruption of the predictive role of AI has been proposed as an explanation of the ecstatic auras (Picard et al., 2021). Recently a feeling of time dilation with a sense of pleasant eternity has been reported during AI stimulation (Sheikh et al., 2022).

The role of amygdala in generating negative emotions, especially fear, is well known both from animal and human studies (Davis & Whalen, 2001; LeDoux, 2003). However, the amygdala has also been involved in brain circuits related to happiness and pleasant sensations (Garavan et al., 2001; Hamann & Mao, 2002; Lanteaume et al., 2007; Sabatinelli et al., 2011). Animal studies showed that amygdala neurons respond to conditioning stimuli that have been associated with either appetitive or aversive outcomes (reviewed in Fernando et al., 2013). The activation of the amygdala in response to pleasant stimuli is suggested by human fMRI studies, notably when observing a pleasant image, face, word or scene (Garavan et al., 2001; Hamann & Mao, 2002; Sabatinelli et al., 2011), or during mental imagery of pleasant situations (Costa et al., 2010). On the other hand, only few publications reported pleasant sensations during EBS in the amygdala (see (Guillory & Bujarski, 2014) for review). Lanteaume et al. (2007) reported sensations of "joy" or "happiness" during left amygdala stimulation in a minority of patients, as most EBS resulted in negative sensations. This study quantified subjective responses using a basic emotion scale (Izard scale). A more recent study found that only one out of 150 amygdala stimulation resulted in a subjective feeling of joy (Inman et al., 2020).

Our study also shows that the anterior cingulate gyrus and the temporal pole may also contribute to pleasant sensations. These observations are consistent with some data from EBS of the temporal pole. Analyzing the semiological aspects of temporal pole stimulation, Ostrowsky et al. (2000) reported a sensation of happiness in 4 out of 150 temporal pole stimulation. Meletti et al. (2006) also described a pleasant and relaxing sensation during EBS in the temporal pole. Similarly, experiments involving recollection of positive autobiographical memories and positive emotions revealed the activation of hippocampus and temporo-polar regions (Markowitsch et al., 2003; Zotev et al., 2011)Concerning the anterior cingulate gyrus, in his work on the lateralization of affect, Smith et al. (2006a) described an euphoric sensation after its stimulation. Some functional imaging studies highlighted also the role of the anterior cingulate gyrus in the emotional mechanisms of happiness. Studies reported that when participants were asked to recall and attempt to re-experience and re-enact intense personal emotional episodes, there was an activation of the right insula, right somatosensory cortex, bilateral anterior cingulate cortex and right posterior cingulate cortex (Damasio et al., 2000; Suardi, Sotgiu, Costa, Cauda, & Rusconi, 2016).

While our study highlights the predominant role in the conscious expression of positive affect of the AI and amygdala, these structures are likely embedded in a network of neural structures and probably do not act in isolation. There is evidence that direct high-frequency EBS activates a network of regions depending on the stimulation site and the effect produced (Bartolomei et al., 2019; Perrone-Bertolotti et al., 2020). As such, a recent study on a manic state induced by EBS of the right lateral prefrontal cortex demonstrated significant increase of functional coupling between the right hemispheric limbic nodes, the temporal pole and the claustrum (Scholly et al., 2022). There is evidence that the genesis of emotions requires the interaction between several brain networks, widely distributed, although none of them seems to be specific to the "emotion function" (Morawetz et al., 2020; Pessoa, 2018). Among these networks, the "salience network", which has been widely studied, would be involved in a larger scale network leading to the generation of emotions. The salience network involves, among others, connections between the anterior cingulate gyrus, the AI, the amygdala and the hypothalamus (Kober et al., 2008; Lindquist, Satpute, Wager, Weber, & Barrett, 2016; Pessoa, 2018). The relative contribution of each of these regions in positive emotion networks remains to be determined.

A network of brain areas underpinning the experience of positive emotions and pleasant sensations could explain why, in two patients, stimulating different structures evoked the same sensations, with for patient P4, stimulation of the right amygdala and temporal pole evoking a feeling of well-being and for patient P8, stimulation of the right amygdala and AI evoking a feeling of well-being and positive emotion. The dense bidirectional connections between the anterior ventral part of the insula and the amygdala (Jakab et al., 2012; Mesulam & Mufson, 1982) and between the AI and the anterior cingulate gyrus (Ghaziri et al., 2017) can account for similar sensations evoked by EBS in distant areas within the same functional network.

4.2. *Effect of hemispheric laterality and sex*

Our study revealed a right-sided predominance of pleasant sensations. A right-side predominance of negative emotional valence induction for right side stimulations has been reported in previous EBS studies (review in (Guillory & Bujarski, 2014)). A left lateralization of positive emotion during amygdala stimulation has been previously suggested (Lanteaume et al., 2007). This apparent contradiction could be linked to the underrepresentation in the previous studies of the anterior insula stimulation which is the prominent site in our experience for pleasant evoked sensations. Smith et al. (2006b) also reported dysphoric responses primarily during right stimulation, but no lateralization for pleasant emotional responses. No clear lateralization effect was found as a function of emotional valence in amygdala activation in a large neuroimaging meta-analysis (Baas et al., 2004).

There was a predominance of pleasant sensations in men in our study. No previous study using EBS has reported such a

predominance of positive emotions, which could be related to the small number of patients in most EBS studies when compared to the large sample investigated here. However, regarding negative emotions Meletti et al. (2006) reported that the feeling of fear occurred significantly more in women than in men.

Data in the literature on gender differences in emotion are often inconsistent (Brody & Hall, 2000; Wester et al., 2002). There is evidence, primarily from self-report data, that women experience emotions with greater intensity than men (Whittle et al., 2011). Women have been found to be more reactive to emotional stimuli, and particularly to unpleasant, threatening, or traumatic stimuli. Research has also suggested that gender differences in self-report are greater for negative emotions such as fear and jealousy, and some neuroimaging studies support greater brain activation in women for negative stimuli (review in (Whittle et al., 2011)). There is also evidence that males may be physiologically more reactive to certain pleasurable stimuli, particularly erotic ones (Allen et al., 2007). A study reported that males exhibited greater activity than females in the frontal lobe and amygdala during exposure to photo stimuli with positive valence (Wrase et al., 2003).

Further studies are needed to better define the effects of these two factors in the genesis of pleasant sensations.

4.3. *Limitations of the study*

The first limitation of our study is its retrospective nature. Responses were systematically collected, but subjective reports may not have been exhaustive. Patients may have described their symptoms in a simplified way because of difficulties in expressing their feelings (Cirignotta et al., 1980). Moreover, how to perceive and express these sensations may depend on education, culture, information given to the patients, context of occurrence, the patients ability to introspection, their vocabulary and therefore vary between patients but also within the same patient (Williams, 1956). To overcome these difficulties, quantification by self-administered questionnaires (Lanteaume et al., 2007) is interesting but was not carried out in the majority of patients in the study. Prospective studies using standardized questionnaires will be particularly useful, especially if coupled with objective measures of the autonomic response, such as the electrodermal response (Inman et al., 2020; Lanteaume et al., 2007).

The second limitation is related to the spatial sampling of SEEG as it has been estimated that about 10 000 electrode contacts would be necessary to explore the brain volume covered by functional MRI (Lachaux et al., 2003). This limitation is partially counterbalanced by the large cohort of patients included and the large number of EBS considered in our analysis (the highest in the literature to date) that allow a large spatial sampling. In addition, the included patients cover a large temporal period with variations in the number of implanted electrodes and implanted sites. Insular implantations with orthogonal and especially oblique electrodes became more common from 2010 in our center. We can also note that, for feasibility and safety reasons, some regions cannot be explored, in particular the brainstem whose role in emotional processing is important (Venkatraman et al., 2017).

Third, SEEG was performed in patients with epilepsy, and seven of them reported positive sensations belonging to the subjective symptoms of their usual seizures. Moreover, the stimulated sites were part of the epileptogenic zone in 8 out of 13 cases. Indeed, the organization of brain networks and the excitability of the brain of patients with epilepsy may be different from a non-epileptic subject. Nevertheless, direct brain stimulation in the history of neuroscience has allowed progress in the knowledge of the role of certain regions in subjective phenomena generated by the human brain, such as psychosensory or emotional phenomena (reviewed (Trébuchon & Chauvel, 2016). Moreover, these phenomena can be obtained outside the usual clinical semiology of the patients (patients P1 and P7 in the present study) (Nencha et al., 2022b).

5. Conclusions

This study is the largest to date collecting positive emotional responses evoked by EBS. This study confirms that these are rare manifestations and mainly evoked by the stimulation of the amygdala or/and the anterior insula.

CRediT author statement

Cecile Villard: Investigation (data collection and analysis), writing original draft; Zoé Dary: Investigation (data collection and analysis), reviewing and editing draft; Jacques Léonard: Investigation (data collection); Samuel Medina Villalon: Data curation, Software development, visualization/data presentation; Romain Carron: investigation, reviewing and editing draft; Julia Makhalova: investigation, reviewing and editing draft; Stanislas Lagarde: investigation, reviewing and editing draft; Christophe Lopez: Conceptualization, Methodology, reviewing and editing, funding acquisition; Fabrice Bartolomei: Conceptualization, Methodology, supervision of the study, funding acquisition.

Data availability

Coregistration process (MRI/CT scan with electrode) is based on the automatic SEEG electrode localization, segmentation and reconstruction GUI GARDEL freely available at https://meg.univ-amu.fr/wiki/GARDEL:presentation. The participant data cannot be placed in an open archive because it is not permitted under the study's institutional review board of the Assistance Publique Hopitaux de Marseille due to the sensitive nature of patients' data. Qualified researchers wishing to access the data should contact the corresponding author (FB). Data may be shared after a data sharing agreement has been signed and approved by the institutional review board of the Assistance Publique Hopitaux de Marseille.

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