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# Is iEEG-based cognitive neuroscience research clinically relevant? Examination of three “neuromemes”

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## Abstract

Much progress has been made in the field of cognitive neuroscience thanks to intracerebral EEG (iEEG) research, largely due to the possibility of directly recording brain activity with unsurpassed spatial and temporal precision while patients perform cognitive tasks. However, do these patients gain anything from the time and effort they devote to this endeavour? In this chapter, we focus on three neuromemes, the “eloquent cortex”, “localisationism” and the “nociferous cortex” to provide possible answers to this question. We discuss the value of these neuromemes and show that clinical care of epilepsy and iEEG-based cognitive neuroscience are consubstantial in the sense that iEEG during epilepsy assessment provides an understanding of physiological processes of the healthy brain; but also, that cognitive iEEG research in epileptic patients has a direct impact on semiology and curative neurosurgery. Last, we highlight how recent cognitive iEEG research provides insights into interictal complaints and could improve identification of the epileptogenic zone.

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## Introduction

Concept neurons and the famous Jennifer Aniston cell [1–3], memories induced by direct electrical brain stimulation (EBS) as if a neurostimulator could replace a madeleine [4]... Neuroscience based on intracerebral EEG (iEEG) led to fundamental scientific discoveries that are widely popularised. Some of them became mainstream and culturally shared. Compared to scalp EEG or functional MRI, iEEG is recorded with unsurpassed spatial and temporal precision. Such an approach has been used in a large number of cognitive studies that take advantage of iEEG to investigate the electrophysiological correlates of cognition in humans (for recent reviews, see [5–8]). Although there is no doubt that iEEG research has significantly contributed to cognitive neuroscience, it would only be fair to ask the opposite. Has iEEG-based cognitive neuroscience contributed to the clinical workup of epileptic patients and their welfare? After all, many patients have contributed time to cognitive iEEG studies with the sincere hope it would help other patients like them in the future.

In this chapter, we will focus on three aspects that are commonplace concepts used every day by clinicians, electrophysiologists and neurosurgeons with epileptic patients in their care: the “eloquent cortex” [9], “localisationism” [10] and the “nociferous cortex” [11]. We suggest that these concepts are in fact “neuromemes”, exchangeable cognitive units that spread easily from one individual to another and which can be maintained throughout time [12, 13]. Memes gather ideas, behaviours or styles, with a common goal to easily replicate within a group. Some of these memes directly concern the epilepsy pathology as analysed recently by Baxendale [14]. Neuromyths have been the focus of other authors such as Devinsky [15] who commented on three: “*epilepsy is a static disorder with minimal morbidity and mortality; epileptogenic tissue impairs only the functions of the seizure focus; and the anterior temporal lobes contain areas of non-functional, “silent” cortex.*” Hence, the medical culture, like any other culture, is rich with easily replicated and sustainable concepts and theories, i.e., “neuromemes”. Although the term “neuromyths” has infiltrated the neuroscience community [16–18], “neuromemes” seems to be a more appropriate term in the context of this chapter because neuromemes are not systematically wrong or lack rationality.

However, one characteristic of a neuromeme is that it is loosely defined. It is this malleability that makes it so useful. It can be used in many situations and can be adapted

to the needs, circumstances or even the epoch. However, this represents a paradox since medicine usually relies on the efficiency of precisely defined concepts. This suggests that there is a high risk of such neuromemes causing a bias or polluting clinical practice.

In this chapter, we will show that intracranial explorations have played an important role in the genesis of neuromemes. However, we will also show that as a result of the progress made in the field, neuromemes can now be examined and refined for the benefit of patients.

## **1. iEEG research: a cocoon for neuromemes**

Paradoxically, while iEEG has been the historical nest for the creation or enrichment of some neuromemes, and neuromyths for that matter, it can also simultaneously play a significant role in confirming or invalidating them. First, we will review each of our selected neuromemes, which are closely related to Penfield's work either in terms of their origin or significant promotion.

### **The eloquent cortex**

The concept of the “eloquent cortex” did not originate with Penfield, but is derived from his work. In fact, Drake was very likely the first to use the term “eloquent” after a series of lectures by Penfield in the sixties in a paper on the surgical treatment of arteriovenous malformation [9, 19, 20]. One literal definition of “eloquent” that can be found in the dictionary is “*clearly expressing or indicating something*”. In the epilepsy literature, it is defined as the “*cortex related reproducibly to a given function.*” [21]. “*Cortical stimulation allows the most precise localization of eloquent cortex*” [22] or “*Fast-ripples near the resection and in distant pathologic areas could have changed the resection in 8 patients without harming functionally eloquent areas*” [23] are just two of the countless occurrences of the term “eloquent” (see [19]). In the current scientific literature, particularly in the context of preoperative functional mapping, the term “silent cortex” appeared in opposition to the parts of the cortex that were *not* “eloquent”, which is consistent with previous ideas concerning brain equipotentiality [15].

However, in 1993, Fried questioned the myth of the eloquent cortex and highlighted the danger of such terminology “*which replaces the neurological reality it sets out to simplify*” [9]. In 2005, Devinsky tried to dismiss the myth of the silent cortex based on the example of temporal lobe surgery: “*Because the normal brain does not contain*

*functionless, "silent" areas, the procedure can have negative as well as positive cognitive or behavioural consequences*" [15]. This is obviously an important issue for patients undergoing neurosurgery.

### **Localisationism**

According to the localisationist theory, the brain is conceived as a mosaic of relatively independent functional regions, i.e., each part of the brain is associated with a particular function, in keeping with the seminal suggestions by Franz Gall in the early 19th century. This view appeared to be supported by later discoveries, for example, of Broca's area and the motor and sensitive homunculus proposed by Penfield.

Let us take the example of Penfield's interpretative cortex [24]. The experiential phenomena that Penfield reported were always produced by electrical stimulations applied to a large area of the temporal neocortex, which included the superior, lateral and inferomedial temporal lobes [25]. He named this area the interpretative cortex since, contrary to the pericentral and visual regions that he also studied, only stimulation here led to flashbacks of past experiences or to interpretative illusions of the present situation [25, 26]. His surgical exploration technique restricted his application of electrical stimulation to only the surface of the temporal cortex. Despite a few attempts at deep stimulation, he only exceptionally observed such responses by stimulations of the temporal uncus, and never by stimulations of the hippocampus. However, the subsequent history of intracranial EEG research clearly demonstrated that the interpretative cortex was not by any means the only region that induces experiential memory phenomena when stimulated and that the memory network extends far beyond [18, 27]. This implies that cognitive functions depend on networks of brain areas [28], the complexity of which is probably only barely understood at present [29] (see also Chapters 37 and 39).

While no clinician will deny that complex cognitive functions are subtended by distributed networks [30, 31], daily clinical thinking remains contaminated by the localizationist approach, from which the idea of the "eloquent cortex" is derived [15]. This impacts the quality of patient care because it oversimplifies neurosurgery planning and in particular its consequences.

### **The nociferous cortex**

This is perhaps the least identifiable of the three neuromemes we selected. In 1954, Penfield and Jasper suggested the concept of a "nociferous cortex" to describe the

notion that the epileptic focus, now more appropriately defined as the epileptogenic zone, may be deleterious for widespread areas beyond the epileptogenic zone and may disrupt normal processes [32] (see also Chapter 5). The “nociferous cortex” in epilepsy refers to the fact that local brain damage can have remote consequences, a secular concept, which could date back to the time of Brown Sequard in the middle of the 19th century [33, 34]. It is, for example, closely related to the concept of diaschisis described by Von Monakow [35, 36]. The distributed effects of focal lesions on brain dynamics, such as diaschisis, compensation or transneuronal degeneration, are nowadays widely supported by the study of brain connectomics and are applicable to a wide range of diseases [29, 33, 37].

In epilepsy, the “nociferous concept” was updated about 25 years ago thanks to cognitive psychology. Hermann and Seidenberg demonstrated executive disorders in temporal lobe epilepsy, whereas executive functions are thought to depend primarily on the prefrontal lobes [38]. In 2014, Coan et al. revealed decreased grey matter in extratemporal regions in patients suffering from temporal lobe epilepsy [39]. The influence of such ideas is now growing in the field of epilepsy as a result of a series of recent intracranial EEG-based neuroscience studies that demonstrate the remote influence of epileptic activities on brain functions [40–43]. Unlike the “localisationism” and “eloquent cortex” neuromemes, the meme of the nociferous cortex holds up only if networks are considered [44]. This may be the reason why it is the only one of the three selected neuromemes that appears to have some validity. It is likely that in the future, the strong interest in network neuroscience will contribute to improving the cognitive status of epileptic patients, particularly following neurosurgery.

## **2. Dispelling the myth of the eloquent vs the silent cortex**

Many years after Drake (1963), Spetzler and Martin (1986) defined the eloquent cortex as “*areas that speak to readily identifiable neurological function*” and, “*if injured, result in a disabling neurologic deficit*” [19, 45].

At first glance, the etymological choice of “eloquent” to name the primary cortices that induce obvious and easily reproducible symptoms after EBS appears sound. EBS can trigger oral and written language symptoms [46–49], motor [50–52] or sensory manifestations [53], during either awake surgery [54, 55] or intracerebral explorations [56–58].

Moreover, there seems to be “silent” areas that do not respond to electrical brain stimulation: for instance, the posterior cingulate cortex where EBS never induces memory or other symptoms, whereas stimulation of surrounding areas can easily trigger motor, vestibular and visual symptoms[18, 59]. A similar phenomenon can be observed in the orbitofrontal cortex, a ghost area, almost absent from the EBS literature [56]. Therefore, “silent” and “eloquent” do not appear to be inappropriate terminology.

Unfortunately, the term “eloquent” has since been extensively used and deviated from the original (literal) definition [19]. In neurosurgery, it is now a synonym of “which should be preserved” and the silent cortex is that which can be easily resected without visible or disabling deficit. In that respect, numerous articles and reviews have suggested that EBS is a good functional mapping method to determine the “eloquent cortex” before epilepsy surgery (e.g., [60, 61]). The premise is that if resecting the eloquent cortex is avoided there is a reasonable likelihood that the patient will not suffer from cognitive deficits following neurosurgery. Despite the rise of functional imaging, EBS is still considered the gold standard for mapping “functional areas” and predicting functional deficits. However, there are several conceptual difficulties with this approach.

(1) How can the limits of eloquent and silent brain areas be defined? This question is particularly relevant since a series of studies demonstrated that EBS effects are dependent on the parameters [62–66], that EBS effects may not be reproducible despite using the same parameters [18], that optimal parameters are not known [67] and that the understanding of the physiological mechanisms underlying EBS is limited [68]. Should EBS be accompanied by afterdischarges [69], or should they remain under the threshold for induction [70, 71]?

(2) The term “silent cortex” is still inappropriately used for areas where no obvious symptoms were elicited during functional mapping, while their resection may lead to deficits after surgery. For example, who is able to predict spatial and navigation deficits [72] or de novo psychiatric symptoms [73, 74] that occur after right anterior and medial temporal lobectomy guided by EBS? Do we know what type of postoperative cognitive decline to expect and how this can be adequately assessed? At present there are too few studies regarding memory, social cognition and psychiatric consequences of right anterior temporal lobe surgery to conclude that this is a silent cortical area, if such a

notion is even possible. The situation is just as unclear for other regions such as the cingulate or the prefrontal cortex.

(3) What is the value of the “eloquent cortex” when the patient is no longer eloquent? Not all patients can report their symptoms, due to either ictal amnesia or aphasia, especially in temporal lobe epilepsy [75].

(4) Are “non-eloquent” and “silent” synonymous? Does “not responding to EBS” really mean constantly and reliably silent areas? Aren’t “silent” areas just “shy” areas? Patients are not always assisted to verbalise subjective experiences through specific appropriate questions, especially when the temporal lobes are explored. In case of neuropsychological disturbances, such experiences are only revealed if an appropriate cognitive task is performed at the time of stimulation [69, 76]. Coleshill et al. [71] for example, were able to demonstrate material-specific recognition memory deficits in some patients by combining unilateral electrical stimulations in the hippocampus synchronised with the presentation of verbal or visual stimuli. To date, no such routine is standardised and EBS still cannot replace the Wada test. The aim of the Wada test is to assess the hemispheric lateralization of speech or memory during preoperative evaluation of refractory epilepsy in order to avoid a risk of sequela. It consists of an intracarotid injection of an anaesthetic drug (barbiturate or propofol), which transiently inhibits the ipsilateral cerebral hemisphere in order to assess the activity of the contralateral one [77].

This also implies that theoretically, different tasks must be carried out for a single stimulation of a given region in order to test the role of this region in different functions and to determine with certainty whether the errors observed in the tests are indeed related to the EBS (and not to the preoperative cognitive state of the patient). For instance, the procedures to evaluate language are not standardised and each centre uses its own battery of tests (image naming, reading, spontaneous speech, repetition, auditory comprehension, etc.). Usually, only one of these tasks is performed for the sake of time, which strongly limits the understanding of the links between the stimulated area and its precise function in language.

(5) Cognitive functions are supported by large-scale networks. All cognitive processes are due to the emergence of a distributed, specific, transient, and synchronous neural assembly characterised by the level of synchrony of its components [30]. There is

dense interregional connectivity, which makes each brain region part of an extensive network [29, 37]. These large-scale brain networks consist of nodes that share many of the same connections, sometimes reciprocally [31, 78]. There is now evidence that EBS does not only have a local effect at the EBS site but also long-range effects. Intracranial implantations are governed by hypotheses about the epileptogenic network [79, 80] and sample only a fraction of the brain. Functional and physiological processes are not considered in the surgical plan. For instance, language investigation would theoretically require bilateral implantation and should cover a large fronto-temporo-parietal surface [81], which is generally not the case, for an accurate mapping of the patient's specific language network. Indeed, about 40% of patients show a decline in image naming after left temporal lobe neurosurgery [82], whereas the preservation of regions essential for naming, for example by limiting the posterior ventral extent of the resection, could help preventing such outcome. EBS effects propagate far away from the electrode [83], with the capacity to inhibit distant cortical regions through afferents connections [84]. In addition, networks can only be activated by some of their hubs and not by all regions involved in the network [85–87]. This is the case for memory. The rhinal cortex seems to be the “gatekeeper” of memory networks [88], the site where EBS most frequently induces memories. There are also “closed doors” to neuromodulation, such as the posterior cingulate region, where EBS never induces memory phenomenon [18], even though it is a region that is known to play a role in memory. Hubs are defined as “nodes occupying a central position in the overall organization of a network”, having a key role in information integration, making them “points of vulnerability that are susceptible to disconnection and dysfunction in brain disorders” [89]. However, hubs should not be conceived of as an updated and more timely formulation of the concept of “eloquent cortex”. The properties of a network cannot be limited to its hubs and the use of this term should be restricted to the context of the definition above to avoid to go back to poorly defined terminology.

In conclusion, there are alternatives to EBS such as using ERPs [90, 91] or high-frequency activity induced by specific cognitive tasks [92, 93]. Some authors have suggested that these approaches could be a means of reducing the duration of the EBS procedure, which would be more efficient and at the same time more comfortable for the patient and save time for the clinician. They could also be a complement to EBS to preselect the sites to stimulate [94].

While EBS is probably one of the major sources of the misleading “eloquent” vs “silent” cortices concepts, an analysis of the limits of EBS demonstrates that the term “eloquent” should be avoided in clinical practice. New ways of thinking about the possible postoperative deficits can be imagined. iEEG-based cognitive neuroscience suggests that standard, multimodal, cognitive procedures should be performed that are tailored to each location and if possible standardised among centres, to better assess the predictive value of EBS in postoperative deficits. A collective effort to this end, guided by recent progress in the methods and concepts developed recently in the framework of iEEG-based cognitive neuroscience, would clearly benefit epileptic patients.

### **3. Eliminating the implicit dogma of “localisationism”**

Although clinicians may still, often implicitly or unconsciously, use localisationism to interpret brain-behaviour relationships, it is undeniable that modern neuroscience has considerably modified clinical thinking by introducing the idea that it is probable that networks are the underpinning of the cognitive or behavioural symptoms that occur during seizures.

#### **EBS in the areas of epileptogenic networks**

One major contribution of iEEG-based cognitive science is the improvement in knowledge about seizure semiology, initiated by scalp EEG [95]. This was achieved through analysis of the sequence of symptoms that occur at the onset of seizures, that coincided temporally with the iEEG recorded in the different brain areas that were sampled[96]. Semiology is one of the keys to clinical reasoning in epilepsy and to the nosology and syndromic classification of epilepsy [97]. Semiology is the basis for building hypotheses on the epileptogenic network. It significantly influences the strategy of electrode implantation in patients who will benefit from an invasive pre-surgical assessment. It may also drive tailored neuromodulation treatments in the future as has recently been suggested [98, 99].

A part of the diagnostic arsenal in epileptology is video-EEG, especially during phase 2 (intracranial EEG recording), and it has simply revolutionised the understanding of seizure semiology. The primary contribution of intracranial EEG to the understanding of semiology is related to the possibility of simultaneously recording iEEG and analysing symptomatology on video during seizures and then analysing the networks underlying

each symptom through the correlation of the symptoms to the distribution of the concomitant ictal discharge on EEG. The *symptomatogenic zone* (“*the area of cortex that, when activated by an epileptiform discharge, produces the ictal symptom*”) should be dissociated from the *epileptogenic zone* [21] (see also Chapter 2).

Clinical symptoms have also been studied beyond a simple visual analysis of the regions concerned by the propagation of the epileptic discharge. This is particularly true of cognitive symptoms, for which a panel of spectral or network analyses have been proposed. For instance, coherence analyses (see Chapter 36) during ictal humming demonstrated the activation of a network involving the superior temporal and inferior frontal gyrus [100]. Faced with such results, any clinician who observes early ictal humming in the seizure semiology will pay specific attention to these brain areas when analysing an MRI in order to identify any structural abnormality or will want to target these two areas during the presurgical workup. Fear is another example. Fear networks identified by coherence analyses during seizures [101, 102] revealed the synchronisation of the amygdala, ventral medial PFC, cingulate and dorsomedial prefrontal cortex during fear [103]. Electrode implantations, as well as structural brain MRI to identify possible lesions, could therefore be driven by such results and target these regions in patients who are frightened while having a seizure.

Such a paradigm becomes particularly important to understand the semiology of brain areas for which EBS does not or rarely induces symptoms. By improving knowledge of the semiology of seizures, iEEG-based cognitive neuroscience can certainly play a role in the electrode implantation strategy.

### **EBS in “healthy areas”**

The contribution of intracranial EEG goes beyond simply understanding the sequence of symptoms that occurs during seizures. In reality, the direct benefit for a patient who agrees to participate in a cognitive protocol during his or her own intracranial exploration is not obvious and most of the time is not measurable. Nevertheless, the data acquired during each of these procedures improve clinicians' knowledge of the brain networks that underly normal cognition (see also Chapter 6), which incidentally influences their ability to draw anatomical-functional conclusions from the seizure semiology. The possibility to identify the “normal” networks that underly specific cognitive functions through the study of functional or effective coupling

(i.e., using coherence or other measures) or cortico-cortical evoked potential (CCEP; [104, 105]; see also Chapter 39) improves the overall knowledge of clinicians. Long-term collaboration between clinicians and cognitive neuroscience researchers, and other neuroscience methods such as functional MRI constantly, if only gradually, increase the quality of interpretation of the symptoms reported by patients or observed during seizures [106].

In sum, the age-old tension between segregation and integration in the field of neuroscience also pervades the field of epilepsy. However, results clearly show that the network paradigm is a more accurate description of how the brain works and is also more nuanced (see also Chapters 37 and 39). It opens the way to other critical questions for patients, such as how these networks reorganise in the context of the pathology or how brain plasticity can be preserved or promoted after neurosurgery. The network approach is fully embedded in the notion of the “nociferous cortex” as will be seen in the next section.

#### **4. Updating and validating the “nociferous cortex” concept**

The concept that a pathological area can impact remote healthy areas is not necessarily intuitive. However, it fits perfectly with the view that the brain relies on dynamic network activity. A series of recent studies contributed to renewed interest in this concept. For example, it was shown that interictal epileptic discharges can alter large-scale networks beyond the epileptogenic zone [40, 107], either by pathological coupling (e.g. spikes pathologically coupled to the spindles involved in memory consolidation [42, 43] or by remote inhibition of healthy tissue (e.g. fast-ripples, a local phenomenon, that inhibits distant neurons outside the epileptogenic zone [108]. With regards to the nociferous cortex, combining the study of interictal epileptic activities and cognitive tasks is clinically relevant in different ways.

##### **An impact on antiseizure medicine**

The nociferous concept can help clinicians to determine how to adjust an antiseizure medicine, not only in terms of seizure persistence but also in relation to residual interictal cognitive complaints. More than 50% of patients with epilepsy complain that their memory moderately or severely limits their daily life [109]. In a recent study, we showed that approximately 75% of a large population of patients with

temporal lobe epilepsy with initial *subjective* memory complaints had *objective* memory impairment after 3 weeks, regardless of whether they had a brain lesion, the type of lesion or how they responded to antiseizure medicine [110]. Such results suggest that there are other factors that explain cognitive alterations in epileptic patients, the best candidate being interictal epileptic discharges (IED). Some iEEG studies have provided convincing evidence that IED can disrupt cognitive processes, particularly those involved in memory [40, 111] (see Chapter 5). Beyond correlational results, it is suggested that IED disrupt memory processes because they occur at key moments (encoding and recall, [112], retrieval and maintenance, [107]), most notably because they directly disrupt the physiological interactions between neocortical (spindles) and hippocampal oscillations (ripples) necessary for memory consolidation. IEDs lead to pathological coupling with spindles [42] or they interfere with hippocampal physiological ripples during encoding and recall [41]. Such studies are almost impossible to conduct with scalp EEG or functional MRI. This clearly reinforces the importance of treating certain epileptic patients who are apparently free of seizures but who have a persistent interictal cognitive complaint probably due to IED [113].

### **A fingerprint of the EZ/non-EZ?**

Recent studies have led to a renewed interest in cognitive tasks as markers of the EZ. To be succinct, the question is whether examination of the iEEG recorded during cognitive tasks can inform clinicians about the EZ or the epileptogenic network. A few studies suggest that seizure onset regions are dysfunctional at baseline and are functionally disconnected from the other functional network hubs [114, 115]. IED (interictal epileptic spikes, interictal high frequency oscillations) during cognitive processes [107, 116–118] or coherence analyses during cognitive paradigms [119], or even resting state analyses may reveal these fingerprints. IEDs that occur in the areas where a seizure starts do not impact cognitive scores, whereas IEDs recorded contralateral to the SOZ or bilaterally doubled the risk of errors on a short-term memory task where letters within a sequence had to be recognized a few seconds after encoding [107]. A network synchronized in the theta-band activated during episodic memory was not found in the electrodes that belong to the seizure-onset zone [119]. The seizure onset and non-seizure onset zones may also show different electrophysical patterns during interictal cognitive tasks [118]. Increased relative entropic differences between the SOZ

and non-SOZ were observed during a verbal memory task while the number of IEDs decreased during the task only in the non-SOZ, suggesting that iEEG recordings coupled with cognitive tasks might be able to unmask interictal fingerprint patterns specific to the EZ [118]. Similarly, cognitive tasks may induce a differential “reactivity” of interictal epileptic activities within or outside the EZ: for instance, an oddball task induced a significant decrease relative to high frequency oscillation rates, in particular ripples (see also Chapter 33), within the epileptic, but not in the non-epileptic hippocampus [116, 117]. Transient suppression of ripples in the seconds following the stimuli presentation was also only observed in the non-epileptic hippocampus.

This approach, although promising, is still in its infancy and is dominated by verbal [40, 118] or visual [120] memory tasks, attentional tasks [116, 117] or short-term memory tasks [107]. Long-term memory tasks, especially episodic, are rare [119]). It is currently mostly relevant for EZ located in the left, dominant hemisphere, whereas only a few results are available for the right hemisphere. What is most notable is that there are still discrepancies and incongruences concerning the influence of cognitive tasks on epileptic activities according to the brain area. Results even appear to differ significantly within the same study [116, 117]. However, the study of IED during cognitive tasks could be of value to optimise presurgical assessment by distinguishing EZ and non-EZ structures, completing the information derived from the examination of spontaneous seizures.

Although the concept of the nociferous cortex is somewhat outdated and rarely used, it conveys the important, yet often overlooked idea that epileptic networks may impact healthy networks and brain areas. It may help to explain some of the cognitive deficits exhibited by patients beyond simply relating them to the EZ or lesions. It might also help to provide a more nuanced and complete pattern of the electrophysiological alterations in a given patient.

## **5. Conclusion**

Epilepsy and cognition are intricately intertwined in several ways. While epilepsy is related to basic dysfunctions of neural assemblies, its expression is often in the form of cognitive, affective or behavioural symptoms. In addition, epileptic patients often suffer from cognitive deficits. Last but not least, an important goal in patient management is

preventing an impact on cognition by antiseizure medicine or neurosurgery. The variety of types of epilepsy also makes this specific brain disease particularly abundant in terms of cognitive symptoms and profiles (see also Chapter 3), unlike other brain diseases which usually have more stereotyped cognitive profiles.

To return to the question raised in this chapter: has iEEG-based cognitive neuroscience contributed to the clinical workup of epileptic patients and their welfare? We think this is undoubtedly so. It guides the localisation of the epileptogenic network through a thorough analysis of the symptoms and subsequently often helps to clarify the type of epilepsy. It obviously guides intracerebral electrode planning and neurosurgery. It is also an important factor in improving the understanding of the cognitive deficits that patients experience. Directly and indirectly, iEEG studies have significantly contributed to improvements in these areas. *Table 1* provides an overview of the contribution of iEEG cognitive research to epilepsy management.

Cognitive iEEG research helps to question some neuromemes that, although widely disseminated in the field of epilepsy, appear inadequate or limiting, for example, the “eloquent cortex” and “localisationism”, especially since clinicians may be unaware of their influence. Given the highly detailed cognitive paradigms currently available, these loosely defined concepts should be refined. However, this can only be done through a collective effort of clinicians and researchers across many epilepsy centres, because the task is tremendous, requires agreement and guidelines, and probably the inclusion or large groups of patients to be able to update these concepts. In contrast, the “nociferous” neuromeme appears to fit more naturally into clinical practice as we have seen, with current trends of trying to assess the impact of the epilepsy network on the global functioning of the brain. Conversely, iEEG can reveal that what appears at first sight to be nociferous can also turn out to be functional and integrated with cognitive networks, as recently described for heterotopia with similar electrophysiological responses to the healthy cortex during an attentional task [121]. In any event, identifying neuromemes in epilepsy could be highly useful as many people in the field are unaware of them and therefore do not question the validity of some of the concepts they use every day.

In general, cognitive iEEG has helped to decrease the stigmatisation of patients. For example, an often-overlooked importance of iEEG is that it is continuously recorded for several days or even weeks. Therefore, it can be correlated with the fleeting, highly

subjective phenomena that sometimes occur during seizures but which are impossible to replicate using experiments in the lab. As such, iEEG is unsurpassed. For example, converging iEEG data demonstrate a pivotal involvement of the hippocampus and rhinal cortex in experiential memory phenomena such as “déjà-vu”, which has helped to discard the interpretation of déjà-vu as an unconscious fantasy or being related to a past-life experience [122, 123]. Only intracranial EEG can capture the semiological diversity of such subjective phenomena such as déjà-rêvé [124], or the degree of consciousness alterations [125], while improving our understanding of their neural correlates.

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**Table: Aspects of patients' epilepsy impacted by iEEG cognitive neuroscience. CCEP: cortico-cortical evoked potential; ERP: evoked related potential; EZ: epileptogenic zone; IED: interictal epileptic discharge.**

Aspect	Clinical benefits	Consequence for patients	Example of iEEG methods
<i>Semiology</i>	More detailed understanding of symptoms, refinement of symptoms	<ul style="list-style-type: none"> <li>• More accurate classification of syndromes</li> <li>• Improved epilepsy diagnostic</li> <li>• Better knowledge of daily consequences of seizures</li> <li>• Less stigmatisation</li> </ul>	<ul style="list-style-type: none"> <li>• Verbatim analyses (e.g., diversity of experiential phenomena)</li> <li>• Video analyses</li> <li>• Behavioural scales (e.g., graduation of consciousness)</li> <li>• Anatomical and functional correlations (concomitant video &amp; iEEG)</li> </ul>
	Identification of the networks that underly specific symptoms	<ul style="list-style-type: none"> <li>• Help to focus the MRI analysis on specific areas, help to identify lesions with low visibility</li> <li>• Identification of targets for intracranial implantation, more relevant sample of intracranial recordings</li> <li>• Distinction between symptomatogenic vs epileptogenic zone</li> <li>• Choice of tailored neuromodulation treatments (in the future)</li> </ul>	<ul style="list-style-type: none"> <li>• iEEG visual analyses</li> <li>• Network analyses during symptoms</li> </ul>
<i>Presurgical assessment</i>	Functional mapping	<ul style="list-style-type: none"> <li>• Identification of functional / dysfunctional brain areas, not necessarily mapping the EZ</li> <li>• Information about the consequences of the neurosurgery,</li> <li>• Prediction of deficit(s)</li> <li>• Clearer information to patients</li> <li>• Guiding the boundaries of the surgical resection</li> </ul>	<ul style="list-style-type: none"> <li>• EBS that induces symptom</li> <li>• EBS during cognitive tasks, causal stimulation</li> <li>• High gamma activity activated by cognitive task</li> <li>• ERP to specific cognitive tasks</li> <li>• CCEPs (functional tractography)</li> </ul>

	Epileptogenic network mapping	<ul style="list-style-type: none"> <li>• More relevant EZ identification, theoretically better post-surgical outcome</li> </ul>	<ul style="list-style-type: none"> <li>• Interictal epileptic activity reactivity (e.g., ripple, fast-ripple, IEDs) during cognitive tasks</li> <li>• Fingerprints during resting state or cognitive tasks</li> </ul>
<i>Interictal cognitive complaint</i>	Impact of IED on cognition	<ul style="list-style-type: none"> <li>• Complementary tool for indication of antiseizure medicine</li> <li>• Curing cognitive deficits (interictal cognitive complaints) by adjusting treatment, when patients seem seizure free</li> </ul>	<ul style="list-style-type: none"> <li>• Correlation between IED rates and cognitive processes or performance</li> <li>• Correlation between IED rate during sleep and performance</li> <li>• Interferences of IED with cognitive processes and physiological oscillations</li> </ul>
<i>General knowledge about the brain</i>	Brain activity in healthy areas during cognitive tasks	<ul style="list-style-type: none"> <li>• Better identification and information of the possible postoperative deficits</li> <li>• Better identification and information of the consequences of epileptic activities on cognition</li> <li>• Questioning neuromemes</li> </ul>	<ul style="list-style-type: none"> <li>• Cognitive task proposed to patients during ECoG/SEEG/awake craniotomy</li> </ul>
		<ul style="list-style-type: none"> <li>• Extrapolation to other brain diseases</li> </ul>	<ul style="list-style-type: none"> <li>• Therapeutic neuromodulation (e.g. memory modulation in Alzheimer's disease, etc.)</li> </ul>
		<ul style="list-style-type: none"> <li>• Valuation of the patient who becomes a participant in understanding his own pathology and who contributes to neuroscience research</li> </ul>	