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On seizure semiology

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Key words: neural networks, epilepsy, behavior, semiology, seizure classification

Summary

The clinical expression of seizures represents the main symptomatic burden of epilepsy. Neural mechanisms of semiological production in epilepsy, especially for complex behaviors, remain poorly known. In a framework of epilepsy as a network rather than a focal disorder, we can think of semiology as being dynamically produced by a set of interconnected structures, in which specific rhythmic interactions, and not just anatomical localization, are likely to play an important part in clinical expression. This requires a paradigm shift in how we think about seizure organization, including from a presurgical evaluation perspective. Semiology is a key data source, albeit with significant methodological challenges for its use in research, including observer bias and choice of semiologic categories. Better understanding of semiologic categorization and pathophysiological correlates is relevant to seizure classification systems. Advances in knowledge of neural mechanisms as well as anatomic correlates of different semiological patterns could help improve knowledge of epilepsy networks and potentially contribute to therapeutic innovations.

Key words: neural networks, epilepsy, behavior, semiology, seizure classification

Introduction

The French word “sémiologie” (from the Greek *semeíon* meaning sign) was originally used as a general term in medicine from the 18th century onwards to express the symptoms and signs associated with disease, and became adopted in medical writings elsewhere in Europe throughout the 19th century¹. The term has come to be employed internationally in its English form particularly in the context of epilepsy, meaning the pattern of symptoms and signs produced during seizures.

To state the obvious, epileptic seizures are made manifest through their tangible semiological expression, which is the cardinal feature of epilepsy: “disease is only revealed by the symptoms it produces”². Success or failure of medical and surgical treatments of epilepsy are judged on their ability to suppress the clinical expression of seizures³. Seizure semiology was the original data source in the ancient study of epilepsy: descriptions of different patterns exist from as early as 2000B.C., including motor signs and their corporeal localization and lateralization, alteration of consciousness, somatosensory features and autonomic changes, and attempts to hypothesize the origins of these⁴. From the end of the 19th century into the 20th century, in refining knowledge of the cerebral basis of epilepsy, the value of semiological analysis was understood by many investigators: notable landmarks include the work of John Hughlings Jackson (correlation of seizure semiology with neuroanatomical findings including post-mortem investigation)⁵, Wilder Penfield (study of signs triggered by intraoperative cortical stimulation studies)⁶, Henri Gastaut (categorization of semiology and correlations with surface electroencephalography (EEG))⁷ and Jean Bancaud, in collaboration with Jean Talairach (anatomical electroclinical correlations of seizures recorded on stereoelectroencephalography (SEEG))^{8,9}. The work of Henri Gastaut

merits special mention, as amongst many other contributions his detailed observations and precise definition¹⁰ of semiological features and electroclinical correlations led to the first proposed classification of seizure types in the mid 1960's. Gastaut's emphasis on specific semiologic subtypes has remained a key component throughout subsequent revisions of the ILAE seizure classification until the present¹¹⁻¹³.

While seizure semiology is the tangible expression of epilepsy, and a key element in epilepsy diagnosis, classification and localization, it can paradoxically appear an elusive and somewhat challenging entry point to understanding seizure organization, especially where correlation between semiology and EEG is not evident. In epileptic seizures, congruence can be observed in terms of the grouping and the evolution of clinical signs: semiological expression does not occur haphazardly but follows a sequence that is related to the cerebral progression of the seizure discharge¹⁴, with the organization of semiological elements having been compared to "words in a meaningful sentence"¹⁵. We could also think of clinical seizure phenomenology as representing a specific behavioral architecture, with its own spatial and temporal dynamic¹⁶. On the other hand, while clearly linked to cerebral seizure activity, how exactly semiologic architecture maps onto cerebral dynamics remains elusive for many seizure patterns.

This article attempts to provide an overview of current understanding of semiology as a data source in epileptic seizures, with an emphasis on focal epilepsy, especially with regards to neural correlates. This is especially relevant in a context of presurgical evaluation, but also in terms of how semiology is used in classification systems, and more generally in a perspective of neuroscientific progress.

Semiology and seizure classification systems

Semiology is the core feature of seizure classification systems. Henri Gastaut's proposal for seizure classification¹⁷, the precursor to subsequent ILAE classification schemes, was based on a phenomenological approach, incorporating "site of origin, the extent of spread of the excessive neuronal discharge, and the consequent clinical symptomatology"⁷. Thus, from the outset clinical expression and EEG were analyzed together and assumed to be linked, indeed considered "inseparable" by Gastaut⁷, who effectively thus put forward a form of multiscale framework implying underlying pathophysiological mechanisms. His classification underlined the importance of precise diagnosis for individual patients in terms of prognosis and treatment, as well as the need to compare data internationally in a clinical research perspective. He emphasized the likely interplay of cortical and midline subcortical structures within anatomically connected systems with regards to both seizure organization and semiological production⁷. Indeed, he preferred the term "partial" to "focal" seizures, "in order to emphasize that the participating neural system may be distributed to a variable extent throughout a segment of the entire three-dimensional cerebral volume. It therefore cannot be represented geometrically as a locus, even less as a focus"⁷.

On the other hand, it was commented by Luders and colleagues that the ILAE seizure classification, developed as a direct result of Gastaut's work¹³, was not well adapted for use in a presurgical context, in which the zones of seizure onset, propagation and clinical expression required to be elucidated¹⁸. In this localizationist approach, anchored in a practical need to better identify and select candidates for epilepsy surgery, a specific semiological classification system¹⁹ was proposed by Luders and co-workers that aimed at addressing perceived limitations¹⁸ of the existing International League Against Epilepsy

(ILAE) classification scheme. Following progressive revisions of the ILAE seizure classification system up until the present¹², the issue of how best to represent semiological information within a seizure classification scheme remains energetically debated within the epileptology community²⁰.

Neural networks versus epileptic focus: relevance to semiological analysis

Concept of epileptogenic networks

When thinking about semiology and its relation to cerebral organization, the concept of the network basis of epilepsy is fundamentally different from the epileptic focus model.

It has been progressively accepted by clinicians that there is much evidence in favor of epilepsy being a network disorder²¹⁻²³; this idea is decades old, having been formally explored using mathematical²⁴ and animal models²⁵ of epilepsy from the 1970's onwards. In a clinical context, Susan Spencer and collaborators, based on observations from depth electrode recordings and subdural grids in the 1980's and 1990's, highlighted the concept of the epilepsy network, considering this to be a "functionally and anatomically connected, bilaterally represented, set of cortical and subcortical brain structures and regions in which activity in any one part affects activity in all the others"²¹. Spencer linked semiological output to this network organization, pointing out that "the *network as a whole* is responsible for the *clinical* and electrographic phenomena that we associate with human seizures"²¹.

However, many years prior to this, the concept of network organization of seizures and its expression via specific semiological patterns had already begun to be investigated by Jean

Bancaud²⁶ based on his observations with Jean Talairach and coworkers from the early 1960's onwards, using SEEG for presurgical epilepsy evaluation⁹. Bancaud and Talairach observed that seizure activity may be recorded simultaneously or near-simultaneously in distant (yet connected) structures; and that initial organization of the seizure could be more or less separate from a cerebral lesion, if present^{9, 27, 28}. This framework derived from SEEG observations distinguished *lesional zone* (interictal slow activity), *irritative zone* (interictal spikes) and *epileptogenic zone* (initial organization of the seizure), which were linked and could overlap to a variable degree^{9, 23, 28}. A key concept of the SEEG method was "anatomical electroclinical correlation", comparing semiology as it evolved with the characteristics of the signal in different anatomical locations, not only considering seizure onset but also the period of early spread of the discharge^{9, 28, 29}. With the advent of digital EEG, quantification of SEEG signal allowed mathematical analysis of signals in different anatomical structures across time. SEEG studies particularly employing novel, non-linear signal analyses from the late 1990's onwards^{30, 31} permitted the formal demonstration of specific neural networks in the genesis and propagation of seizures³². Notably, rather than "epilepsy network", the more specific term "epileptogenic network" has been proposed based on study of underlying pathophysiologic processes using brain biomarkers of epileptogenicity^{23, 33}. SEEG studies of different seizure types and semiological patterns have highlighted the importance of *temporal* aspects of seizure organization, that is, concerning discharge frequency, lag and synchrony between signal in different structures (Table 1), as well as *spatial* (anatomical) aspects (Table 2). These studies, especially those utilizing signal analysis methods in relation to the period of clinical expression of the seizure, have suggested some putative mechanisms of semiological production.

Concept of symptomatogenic zone

In contrast to this epileptogenic network view, which was the hallmark of the French SEEG school, the domain of correlating semiology with intracranial EEG data was subsequently developed by Luders and collaborators³⁴⁻³⁶ as well as other groups³⁷⁻⁴⁰ using a different investigative method, recording from the brain using subdural grids and/or mesial temporal depth electrodes. A system of “zones” was expounded by Luders and coworkers²⁷ that included representation of how semiological output was linked to cerebral seizure organization. However, it is important to note that the origin of the “zones” model can in fact be traced back to Bancaud as described above, who had initiated this novel framework decades earlier. Luders defined *symptomatogenic zone* as “the area of cortex that, when activated by an epileptiform discharge, produces the ictal symptoms”; the definition of *epileptogenic zone* by this school was considered pragmatically as the minimum amount of cortex that must be resected to render the patient seizure-free²⁷. These constructs were strongly influenced by data from direct cortical stimulation studies and their clinical correlates⁴¹, as well as study of cases becoming seizure-free following epilepsy surgery. This approach therefore tended to employ a “focus” model of epilepsy, albeit one that recognized the variable spatial extent of seizure onset as well as an anatomical separation between epileptogenic zone and symptomatogenic zone. In this framework, the relation between structures involved in seizure onset and those involved in semiological production was essentially conceptualized as a linear and mechanistic process occurring within the spatial domain and the symptomatogenic zone model did not attempt to address issues of pathophysiological mechanisms other than inferring local functional anatomical correlations.

The fundamental difference between Luders' focal definition of the EZ, and that proposed previously by the SEEG school- which represented initial seizure organization within a set of connected structures, as well as more complex mechanisms involved in producing clinical signs- was indeed acknowledged by Luders and co-workers²⁷. Some of these differences in focal versus network epilepsy models can be directly attributed to choice of recording method and the view thus afforded of seizure organization with regards to clinical expression²⁸.

Network or focus model for investigating neural correlates of semiology?

There is a somewhat contradictory and ambiguous relation between the epileptogenic network model and the epileptic focus model in clinical practice, both probably representing different aspects of reality (perhaps akin to the co-existence of wave and particle theories of light). The conceptual and scientific appeal of epilepsy networks notwithstanding, the idea of an "epileptic focus" can seem logical, intuitive and even necessary as a working model for clinicians. The focal epilepsy model seems to fit with the observed success of focal surgical resection in many cases, initiated by the earliest epilepsy surgical resections in the 19th century⁴² and reinforced following the development of widespread epilepsy surgery programs based on high surgical success rates in mesial temporal epilepsies⁴³. Indeed, it has been commented that, in an epilepsy surgical framework, "thinking of networks then seems impractical, because resection is ultimately focal"⁴⁴. However, this ambiguity may become increasingly important to resolve if progress is to be made in understanding and treating epilepsy. This seems an important goal in the light of increasing numbers of complex, often extra-temporal cases being evaluated for epilepsy presurgical evaluation⁴⁵ and the

significant proportion of patients with “focal” pharmaco-resistant epilepsy who are not cured by surgery⁴⁶.

When thinking about how to analyze neural correlates of seizure semiology, what is the optimal conceptual framework and methodological approach? The genesis of complex semiological patterns (e.g. gestural motor behaviors, altered consciousness, emotional signs and so on) cannot be directly attributed to electrical alterations limited to a restricted volume of cortex: by definition, the emergence of such patterns requires larger scale distributed networks to be brought into play, even if such a process may nevertheless be *triggered* from discharge arising within a restricted volume of cortex, according to connectivity of the epileptogenic network. It would seem impossible to adequately explain neural correlates of this type of clinical expression by the “symptomatogenic zone” model, without taking into account the role of distributed cortico-subcortical circuits; epileptogenic network-based analyses thus appear better suited to investigating these.

Seizure semiology as a dynamic data source

The semiological expression of each epileptic seizure represents a set of complex interactions between the brain (electrical discharge), body (paroxysmal physical and/or mental symptoms and signs) and the environment (effect of specific time, circumstances and interactions with people and/or objects during the seizure). This multi-level and dynamic interaction, which brings with it significant methodological challenges for analyzing semiology, could evoke the idea of “embodiment”, a concept posited in the cognitive neurosciences⁴⁷. Each seizure is a newly occurring event, prone to be influenced by the patient’s state and environmental conditions, and yet as seizures repeat over time, a certain

core stability of semiological expression is typically observed both within and between patients (the latter being the basis of seizure classification systems). This reproducible “choreography”, which lends itself to phenomenological study, indicates that a particular configuration of neural circuitry is being brought into play each time, which may be reinforced by seizure repetition through a process of neuroplasticity²⁸ albeit with degrees of variability related to the dynamic nature of the system. Semiology does not arise from an isolated structure but from a system defined and constrained by its connectivity, in which pathophysiological activity tends to be organized in a structured and reproducible way across seizures^{28, 48}.

Considering epilepsy to be a disorder of brain networks, in which a seizure may be seen as an expression of a dynamical system^{23, 49}, seizure semiology also reflects a dynamic process operating on a different scale, characterized by both spatial and temporal aspects within the cognitive and behavioral domains^{16, 50} (Figure 1). Attempts to understand correlations between brain activity and clinical signs during seizures must therefore take into account information collected across multiple scales^{51, 52}: behavioral features, anatomical spread of seizure discharge and temporal organization of electrical changes (e.g., discharge frequency and synchrony between structures). Scientific study of neural correlates of semiology thus ideally requires a method allowing meaningful comparison of recorded spontaneous seizure semiology with concomitant spatiotemporal evaluation of neural activity, employing appropriate categorization of semiological features and optimal measurement of the onset and spread of seizure discharge. The biggest challenges in this context include not only issues of cerebral sampling and network analysis, but also how best to observe, describe and quantify semiological features.

Figure 1

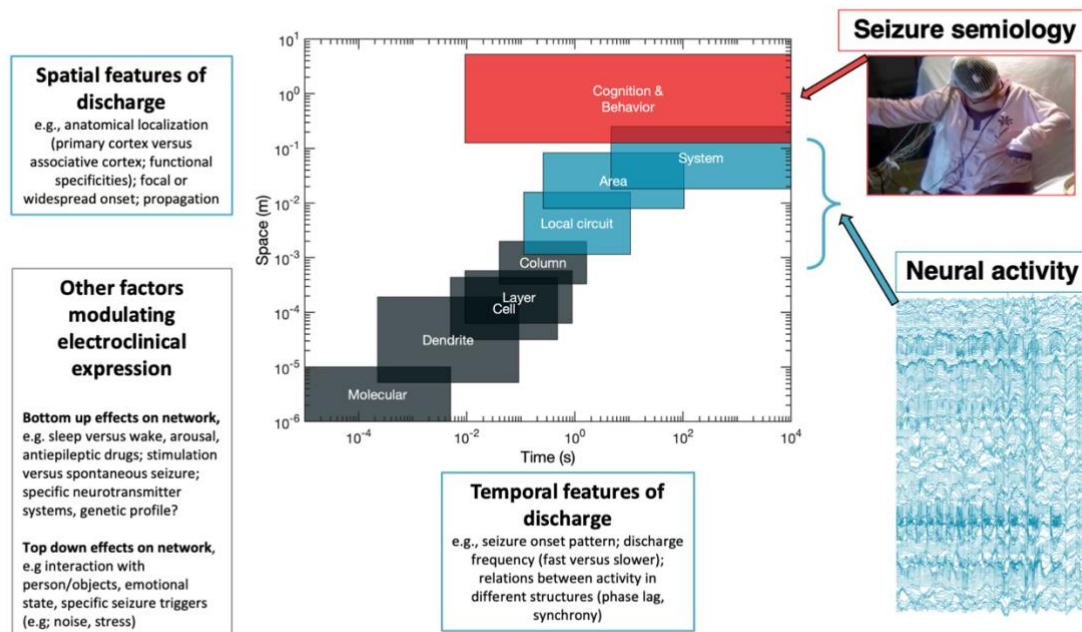


Figure 1. Use of a multi-scale framework to think about spatial and temporal features in epileptic seizure expression. The center panel illustrates temporal and spatial scales of organization in the nervous system (adapted from Lytton et al⁵²). Both semiological expression and cerebral epileptic activity can be mapped onto this spatiotemporal framework. Semiology involves the higher level dimension shared by cognition and behavior, whereas cerebral electrical discharge involves the local circuit, area, and system levels. Apart from spatiotemporal features of the seizure discharge, other factors influencing electroclinical expression can be bottom-up (driven by neuronal changes) or top-down (driven by environmental factors).

What can SEEG tell us about the neural correlates of semiology?

Stereoelectroencephalography, because of its multilobar sampling, including medial and lateral structures and sometimes also subcortical structures, has contributed important data on neural correlates of semiology that cannot be achieved using other intracranial recording techniques that share its millisecond temporal resolution. The detailed analysis of semiology as it unfolds during the whole course of the seizure with reference to sequential signal changes (anatomical electroclinical correlation) has traditionally been the foundation of the SEEG method⁹ and the remainder of the article will discuss SEEG data. As such, the emphasis here is on semiology in the context of focal seizures, since SEEG data has primarily come from patients undergoing presurgical evaluation for intractable focal epilepsies. There is a bidirectional relation between SEEG exploration and semiological analysis: at the individual patient level, semiology critically informs implantation strategy and is an essential component of clinical SEEG interpretation; and on the other hand, SEEG data amassed over many cases and over time informs us about neural correlates of semiology through studying electroclinical patterns that are recognizably similar across patients. Ideally each aspect should contribute to advancing the other, since better recognition of semiological patterns and their correlates should hopefully lead to refinement of implantation strategies for future patients. A main caveat here is evidently the intrinsic sampling limitations of the method with the risk of missing important information from unexplored regions¹⁴, both cortical and subcortical. Another important issue is that SEEG methodology is highly dependent on hypotheses of epilepsy organization, which strongly influence implantation strategy: erroneous hypotheses can lead to misleading or unhelpful results, if key structures are not optimally sampled.

As knowledge and also technical capacity evolve, both within individual teams and in the wider epileptological community, implantation strategies tend to adapt over time to take this into account. A case in point is the demonstration of the role of the insula in various seizure types⁵³, its stimulation mapping features⁵⁴ and, more recently, descriptions of larger series of insular seizures with electroclinical correlations across insular subregions^{55, 56} including in terms of their connective⁵⁷ architecture. These are aspects that were unknown in the early decades of SEEG use since the insula tended to be not often explored partly because of vascular constraints. Because certain electroclinical features suggesting different insular subregions are now recognized, as well as technical improvements including vascular imaging, the indications for implanting this region have therefore changed, thus continuing to add to available electroclinical data. More generally, mean number of SEEG electrodes implanted per case has tended to increase across time, related to evolving indications for exploration and technical advances⁵⁸.

Investigation of semiological patterns and their correlates using SEEG has followed 2 main approaches: (1) grouping patients with a similar semiological picture or a common semiological feature and looking at cerebral correlates of seizures including temporal features of discharge (Table 1); (2) grouping patients with similar anatomical organization of the epileptogenic zone (EZ) or seizures arising from a particular brain system and looking at clinical correlates (Table 2). Single case reports can also be of interest because of specific features that can be analyzed within a single patient.

Taken together, these studies have 2 main goals: improving knowledge of *anatomical correlates* (with direct clinical implications for future patients); and shedding light on possible *neural mechanisms* underlying semiological production (which improves neuroscientific

understanding of epilepsy). The latter objective has benefited from signal analysis studies (Table 2), especially using connectivity measures that assess codependency of signal between connected structures; see ref.²³ for review. The present review focusses mainly on data from spontaneous seizures, but useful information on possible mechanisms of semiology has also been gathered from SEEG stimulation studies including signal analysis^{59, 60}.

Semiological hierarchy with respect to cortical localization

Cases in which seizure semiology is highly specific for certain spatially restricted cortical regions often involve elementary signs (such as somesthetic, visual or auditory aura, or focal clonic jerks) arising in relation to seizure activity within primary cortex. In such cases, habitual semiology can often also be reproduced by local direct cortical stimulation and indeed these were the types of presentation leading to the very early cases of epilepsy surgery⁴². In focal primary motor cortex seizures, clinical expression of elementary motor signs appears to depend on ictal discharge frequency as well as anatomic localization⁶¹. Some more complex signs arising from non-primary cortex can also be highly specific for anatomical location and can also often be readily reproduced by cortical stimulation (e.g. déjà vu arising from networks involving mesial temporal structures, especially entorhinal cortex⁵⁹). In frontal lobe, stimulation of different regions of cingulate cortex has been shown to produce complex motor behaviors and emotional signs (especially laughter)^{62 63}.

On the other hand, the majority of more complex semiological patterns involving for example gestural or hyperkinetic motor behavior, emotional change and/or altered consciousness tend to involve associative cortex, usually associated with seizure propagation within more extensive networks and more complex seizure dynamics⁵⁰. It is recognized that subcortical

mechanisms must play a role in clinical expression of many forms of focal seizure^{7, 64-68}. While subcortical structures are much less often sampled than cortical structures, growing interest has led to increasing EEG data in a clinical context from structures including the thalamus, putamen and caudate nucleus^{69, 70}. SEEG studies of synchrony during seizures have confirmed a link between degree of thalamic involvement and degree of alteration of consciousness, for example (see Table 1)⁷¹. Recent work has highlighted the potential role of basal ganglia within a strictly topographically organized framework according to cortical localization of seizures and cortico-subcortical connectivity⁷⁰.

Current concepts of brain function are based on the principle that each part of the brain has a different set of specializations and that the specializations of a brain region depend on its connections⁷². Regions of primary and unimodal cortex have sparse connectivity between them, in contrast to multimodal and transmodal regions of cortex, which are densely connected to allow binding of distributed information⁷². Following on from this distinction between unimodal and multimodal cortex, a spatial hierarchy of semiology with regards to cortical involvement of seizure organization could be posited, in which more elementary signs with highly specific relation to cortical localization are likely to involve unimodal cortex; whereas more complex signs or constellations of signs, which are relatively non-specific for individual cortical regions (e.g. hyperkinetic motor behavior⁷³) or which may depend on widespread cortical involvement (e.g. altered consciousness^{66, 71}) would be related to dynamic effects involving higher-level, multi-modal or transmodal cortex and their cortical and subcortical connections.

How might gradations between these more complex expressions of semiology and the spatial hierarchy of their neural correlates be demonstrated? This would require approaches taking

into account sufficient numbers of cases, with adequate semiological categorization and optimally sampled brain regions at seizure onset and during emergence of semiology (early spread). In reality, such approaches are always limited by clinical factors, since the minimal cerebral (SEEG) exploration for individual patients is performed based on clinical need, limiting spatial sampling within and across subjects; in addition, complex semiologies are heterogeneous and achieving series with sufficient data can be challenging. However even without signal analysis, SEEG data has shown correlation between clusters of semiological signs and co-involved brain structures in frontal epilepsy, indicating that behavioral signs and in particular motor behaviors are organized along a rostrocaudal gradient according to their complexity⁷⁴, in keeping with current thinking on frontal lobe functional and anatomical hierarchy⁷⁵. This type of observation confirms the interest of pursuing this line of semiological analysis even when clinical patterns are complex and brain sampling necessarily limited, since semiological output seems to be tightly linked to early cortical seizure activity despite large scale cortical and subcortical networks likely being involved^{28, 76}. On the other hand, analyzing seizure onset alone rather than incorporating anatomical structures involved in early spread does not appear to correlate as well with semiological subgroups, at least in frontal seizures⁷⁷.

Putative mechanisms of semiological production

How might seizure activity interact with brain networks to produce clinical effects? Seizures may produce both abnormal inhibition and abnormal activation of involved regions and their connected structures⁶⁵. Attempting to untangle the possible mechanisms of how the seizure discharge determines clinical expression is difficult, all the more so since neural mechanisms of even physiological expressions of complex brain functions remain incompletely

understood, for example motor behavior⁷⁸, emotion⁷⁹ and consciousness⁸⁰. Looking at expression of other neurological conditions such as movement disorders⁶⁸ and parasomnias⁸¹ may help to illuminate this question. For example, stereotypies (abnormally repetitive behaviors) have been increasingly well characterized in terms of their anatomical and neurobiological substrates, involving cortico-striatal circuits that deal with learning of sequences⁸². Many seizures contain repetitive movements (and indeed the whole seizure/semiological architecture could be seen as being reinforced by repetition over time), so the stereotypies model could be an interesting one for studying these mechanisms in epilepsy⁸³.

How has SEEG analysis informed us about possible mechanisms of semiological production? A main line of research has investigated not only spatial (anatomic structures involved) but also temporal features of electrical seizure organization using signal analysis. This could be thought of as not only looking at where the network is, but how it reverberates.

Several possible mechanisms have been suggested for seizure patterns beyond the simplest clinical expressions of unimodal cortex. These are still under investigation, and it should be noted that current evidence is stronger for some patterns than others (based on numbers of cases analyzed, use of a control situation, etc. (Table 1)).

1. The concept of binding has previously been proposed as a putative mechanism for some forms of semiological production^{50, 84}, that is, functional coupling at specific (physiological-range) frequencies between connected structures, leading to a certain clinical output according to the function of the thus-activated anatomical network. This mechanism has been suggested by SEEG studies of neural correlates of dreamy state⁸⁵, ictal humming⁸⁶ and oroalimentary automatisms⁸⁷, which are characterized by

correlations in specific frequency bands across co-involved structures during semiological production.

2. In seizures with altered consciousness, the degree of cortical +/- thalamic synchrony appears to correlate with degree of clinical expression, with excessive synchrony being associated with greater impairment of consciousness, across different lobar seizure localizations^{71, 88, 89}.
3. In seizures with hyperkinetic motor behavior involving an emotional character (explosive onset of fear/defense behavior), sudden transient decorrelation between prefrontal cortex and amygdala at onset of clinical signs was demonstrated⁹⁰. This disruption of functional connections could then result in the disruption of emotional regulation leading to the release of altered behaviour.
4. Finally, in seizures with rhythmic movements, coupling between frequency bands may reflect a temporal assembly of neural structures acting as an oscillator (rhythmic pattern generator)⁹¹. This is exemplified by an analysis of prefrontal seizures with rhythmic body rocking, in which phase lag coupling was demonstrated between gamma band activity within the epileptogenic zone and propagation regions, and the delta-band rocking frequency (quantified using video analysis)⁷⁶.

These last two mechanisms could fit with and refine Tassinari's proposal of the presence of central pattern generators that would "generate rhythmic movements and express species-specific innate emotions"^{92, 93}. Such central pattern generators are generally presumed to be subcortical, and possibly common to both some forms of epilepsy and some parasomnias⁹⁴. However, rather than being brought into play via a non-specific top-down effect of loss of inhibition, SEEG data suggest that these would depend on interaction between cortical

activity and subcortical circuits in a topographically organized way^{70, 83}. This means that cortical electrophysiological signatures are likely to be detectable even for those seizures in which clinical expression is strongly linked to subcortical components of the specific cortico-subcortical network, as may be the case for example for ictal rocking behaviors⁹¹ and emotional expression such as defense behaviors⁹⁰ and ictal aggression⁹⁵.

Additional indirect evidence in favor of specific complex motor and/or emotional patterns being encoded within predominantly subcortical circuits comes from SEEG stimulation studies, in which complex semiology can be triggered with extremely short latency following train stimulation, especially in frontal seizures, with habitual semiology occurring before the cortical discharge emerges, contrary to the observed time course in the same patients' spontaneous seizures⁹⁶.

Methodological challenges of investigating semiology

If progress is to be made in investigating neural correlates of semiology, it is important to be aware of certain methodological considerations (Table 3). Semiology as a data source is complex and difficult to work with for various reasons. The majority of semiological information in clinical practice of course comes in narrative form, notoriously prone to inaccuracies compared to recorded seizures⁹⁷. When dealing with recorded seizures, there are various considerations concerning quality of data, including technical conditions, adequate ictal examination⁹⁸ and ability of individual expert observers to perceive key signs⁹⁹ or patterns, especially for seizure types involving complex motor behavior¹⁰⁰.

A main methodological challenge relates to description and interpretation of semiological signs, and especially choice of category. This is important for accurate description and for

meaningful comparison across series. Terms such as “hyperkinetic” and “automatism” can be useful in some circumstances but despite having been formally defined¹⁰¹, may prove to be unhelpful or even misleading due to lack of precision and consensus as to their meaning. One issue is in conflating an individual semiological feature with the description of the overall seizure, for example the term “hyperkinetic seizure”: while this category is included in the current ILAE classification¹², it does not correspond to any known localization, etiology or pathophysiological correlation. Ideally a useful semiological category should be helpful clinically, with good inter-observer and intra-observer reliability and should refer to a cohesive pattern or group of signs whose occurrence might be linked pathophysiologically. A goal for clinical research approaches and for future classification systems would be to incorporate such semiological features as knowledge progresses.

Future research directions

There is much potential for further study of semiology and its neural correlates. Epilepsy is a privileged model for studying the brain-behavior relation, given ready means of analyzing semiology with concomitant (causal) brain activity using video-EEG or SEEG; this is in contrast to non-epileptic seizure disorders¹⁰² and psychiatric disorders more generally¹⁰³. Electroclinical data can be complemented with other sources including functional imaging studies in the ictal^{104, 105} and/or interictal period⁶⁷. An advantage of using functional imaging is its whole-brain approach, which can be used in a complementary way to other data, relevant for example to better understanding the role of basal ganglia and other subcortical structures in epilepsy and potentially in semiology production¹⁰⁴⁻¹⁰⁶. In fact

“interictal semiology” (e.g. psychiatric^{107, 108} and cognitive¹⁰⁹ symptoms) could be an interesting line of study, the neural correlates of which may prove to be related to epilepsy organization¹⁰⁸ and even ictal semiology¹⁰⁷. Mapping approaches using intracerebral data to study cortical correlates of cognition and emotion could also help to advance knowledge of the neural correlates of higher brain functions¹¹⁰.

For future advances in semiological analysis, harnessing technological advances in quantifying semiology via video analysis seems of interest¹¹¹, for example facial expression¹¹² and body/limb movements^{91, 113}. These methods require expert supervision and/or specific technical capacities and are not yet widely used but may become more available if they prove effective. Refining current use of autonomic recording during seizures (e.g. electrocardiographic analysis, respiration, electrodermal response), possibly including use of wearable devices¹¹⁴, could also be informative. Modelization approaches are of interest since they can potentially overcome the problem of spatial sampling⁴⁹; such models would benefit from being able to incorporate semiological data, but present approaches do not yet include these because of the challenges of sufficiently simplifying and quantifying complex behavioral data.

Analyzing larger case series seems important for achieving higher power in demonstrating differences between different semiological subtypes and their brain correlates, bearing in mind that most semiological series in the SEEG literature to date report on around 20-50 subjects, often less. Beyond encouraging more multi-center collaboration, potential use of larger scale international databases, adapted to a multi-scale approach¹¹⁵ could be of future interest. For this to occur, various practical issues would need to be resolved, including how to protect patient confidentiality. In addition, analyzing large amounts of video data is

onerous and would ideally be supplemented by some automated approaches if this becomes more reliable.

Evolving concepts and therapeutic implications

An important element for making progress in elucidating neural correlates of semiology may be evolution of current concepts. As discussed earlier, the network model of epilepsy appears better suited than the focus model to understanding relations between electrical seizure organization and clinical expression. Since thinking about epilepsy in terms of network theory represents a paradigm shift, it may be useful to reconsider how we use some current language. An example is the term “symptomatogenic zone”, used by many clinicians in a presurgical context, which in fact proves not to be compatible with the network model of seizures and semiology: we can recall that the term was defined by Luders and collaborators as “the *area of cortex* that, when *activated* by an epileptiform discharge, produces the ictal symptoms”²⁷. This appears imprecise in the light of the data discussed earlier, because not only *spatial* but also *temporal* features of discharge affect clinical expression; and not only *cortical* but also *subcortical* structures likely shape clinical expression. In addition, for some semiologic features (such as altered consciousness), the mechanism appears not to be *activation* but rather dysfunction or inhibition of cortical networks.

Semiology can teach us much more about epilepsy, and about the brain, than we currently know. Using behavioral data to drive research and improve understanding of the brain-behavior relationship may be pivotal in achieving neuroscientific progress more generally¹¹⁶. Better knowledge of the significance of semiologic substrates may help advance therapeutic

strategies especially from a neurosurgical point of view: understanding an individual patient's seizures as events that emerge from a dysfunctional brain network could allow multi-modal personalized treatment plans aimed at "taking the seizure network offline"¹¹⁷, encompassing tailored neuromodulation methods in some⁷⁰, as well as physical disruption of key nodes in the network¹¹⁸ by resection or laser therapy for example where indicated. Future therapeutic approaches may even be directly driven by semiology in some cases, targeting specific disabling symptoms such as altered consciousness¹¹⁹.

Key points

- Neural mechanisms of semiology are poorly known, especially for complex ictal behaviors
- Network approaches are better suited than the focus model to investigating neural correlates of semiology
- In a network context, specific rhythmic interactions of activity between structures and not just anatomic localization appear important
- Methodological challenges of investigating semiology are significant, including observer bias and categorization
- Better knowledge of neural substrates of semiology could help lead to therapeutic advances aimed at network modification

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Conflicts of interest

None of the authors has any interests to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Legends to tables

Table 1. Examples of studies examining semiology in conjunction with signal analysis of SEEG (temporal aspects of seizure organization)

Table 2. Examples of SEEG electroclinical studies examining semiology in conjunction with sublobar organization (anatomic correlates)

Table 3. Methodological challenges of using semiology as a data source in clinical research

Table 1. Examples of studies examining semiology in conjunction with signal analysis of SEEG (temporal aspects of seizure organization)

Table updated from ref.¹⁶

Authors	Year	Semiological pattern	Epilepsy localization	Number of subjects	Main anatomical structures	Control group	Signal analysis of SEEG during period of semiological expression
Bartolomei et al. ⁸⁶	2002	Humming	Temporal lobe	3	Superior temporal gyrus (STG), prefrontal cortex	No	Rhythmic discharge over STG (6Hz or 15Hz). Increased coherence between STG and prefrontal cortex
Bartolomei et al. ⁹⁰	2005	Fear behavior	Prefrontal cortex	3	Ventromesial orbitofrontal cortex, anterior cingulate, amygdala (limbic system)	No	Sudden loss of synchrony between orbitofrontal cortex and amygdala at seizure onset/clinical onset
Arthuis et al. ⁷¹	2009	Impaired consciousness	Temporal lobe	12	Temporal structures, parietal lobe, thalamus	Compared at group level according to degree of altered consciousness	Excessive synchrony (h2), i.e. functional coupling, between temporal and extra-temporal structures, notably parietal cortex and thalamus in seizures with marked alteration of consciousness
Lambert et al. ⁸⁸	2012	Impaired consciousness	Parietal lobe	10	Superior and inferior parietal lobules, precuneus, parietal operculum, supplementary motor area	Compared at group level according to degree of altered consciousness	Increased synchrony was associated with progressively greater degrees of altered responsiveness at subgroup level. A statistically significant nonlinear relationship was found between

							h2 values and degree of alteration of consciousness, suggesting a threshold effect. Cf Arthuis et al, 2009 ⁷¹ .
Bonini et al ⁸⁹	2016	Impaired consciousness	Frontal lobe	24	Internal and external prefrontal cortex, premotor cortex, parietal cortex	Compared at group level according to degree of altered consciousness	At subgroup level, seizures characterized by marked altered consciousness were associated with highest levels of synchrony. Significant correlation was found between consciousness scores and correlation values (h2) of the prefrontal and the parietal region but not with the premotor cortex. Cf Arthuis et al, 2009 ⁷¹ and Lambert et al ⁸⁸ .
Hagiwara et al ¹²⁰	2017	Motor signs	Insula	5	Insula, premotor and prefrontal cortex	Seizures with/without "frontal semiology" were compared	Non-linear regression analysis was applied to insular seizures with/without frontal presentation The three patients with frontal semiology showed strong couplings with the mesial frontal as well as cingulate regions, including the medial orbitofrontal cortex, pre-SMA/SMA, and the anterior to posterior cingulate. The two patients with the insular semiology only showed couplings between the insula and cingulate regions.
Bartolomei et al. ⁹⁵	2017	Ictal aggression	Temporal lobe	1	Bilateral temporal and frontal structures	No	Aggression occurred in the last part of the seizure, during which period functional connectivity study (h ² estimation of

							interdependencies) showed bilateral massive hypersynchronization between frontal and temporal regions
Aupy et al ⁸⁷ .	2018	Oro-alimentary automatisms (OAA)	Temporal lobe	15	Medial basal temporal lobe, opercular cortex	2/15 patients had seizures compared with and without OAA	Increased coherence occurred between medio-basal temporal structures and insulo-opercular cortex prior to onset of rhythmic chewing movements
Roux et al ¹²¹	2019	Ictal coughing	Temporal lobe	1	Mesial temporal structures	No	Functional connectivity study (h ² estimation of interdependencies) showed that during coughing, a network of cortical and subcortical regions was involved, particularly the perisylvian cortices and the caudate nucleus.
Zalta et al ⁷⁶	2020	Antero-posterior rocking	Frontal lobe	1	Prefrontal cortex	Compared with non-rocking seizures in same patient	Delta range rhythmic body rocking was associated with cortical delta oscillatory activity and phase-coupled high-gamma energy

Table 2: Examples of SEEG electroclinical studies examining semiology in conjunction with sublobar organization (anatomic correlates)

Table updated from ref.¹⁶

Authors	Year	Brain region involved in seizure organization	N° of subjects	N° of seizures	Main findings
Maillard et al. ¹²²	2004	Temporal lobe	55	187	Subgroups defined by clinical and SEEG features: mesial type (initial epigastric sensation and delayed appearance of oro-alimentary and gestural automatisms as well as later (if any) altered consciousness); lateral type (early auditory illusions or hallucinations, earlier altered consciousness, more frequent generalization); mesial-lateral type (initial epigastric sensation and early altered contact, long seizure duration). This study built on observations from SEEG signal analysis work ³¹ .
Bartolomei et al. ¹²³	2011	Parietal lobe	17	34	Neural network patterns with respect to seizure semiology, ¹²³ applying the previously developed Epileptogenicity Index (EI) ¹²⁴ to quantify fast discharge at seizure onset. Seizures predominantly arising from superior parietal lobule were often associated with vestibular symptoms, whereas hyperkinetic motor behavior was associated with inferior parietal involvement.
Bonini , McGonigal et al. ⁷⁴	2014	Frontal lobe	54	374	Using automated cluster analysis of clinical signs and of brain areas involved in seizure onset and early propagation, correlation was seen along a rostro-caudal gradient from frontal pole to precentral cortex. Four groups of patients were described, proceeding from central cortex and moving rostrally: Group 1 (elementary motor signs, no gestural motor behavior); Group 2 (association of elementary motor signs and gestural motor behavior, often with mainly proximal tonic signs and facial contraction; Group 3 (no

					elementary motor signs, gestural motor behavior often with a distal expression, which could have an integrated appearance); Group 4 (no elementary motor signs; gestural motor behavior that occurred in a context of emotional expression, most often fearful, with an integrated appearance).
Marchi et al. ¹²⁵	2016	Occipital lobe	29	194	Used the EI ¹²⁴ quantification method. Widespread organization of the EZ was typical, with temporal and/or parietal cortex quite commonly being involved (“occipital-plus epilepsy”). Altered conscious level was more common when onset involved widespread posterior neocortex; automatic motor behavior and/or verbal automatisms more often seen with occipito-temporal organization.
Wang et al. ⁵⁷	2020	Insulo-opercular cortex	37	310	Used automated cluster analysis of clinical signs and of brain areas, based on a novel methodology of brain parcellation including connectivity parameters (Brainnetome). Four main semiologic subgroups of insulo-opercular seizures were identified, organized along an anteroventral to posterodorsal axis. Semiology, particularly sensory symptoms but also motor signs, significantly correlated with insulo-opercular subregion localization.
Singh et al. ⁵⁵	2020	Insula	12	25	Review of semiology defined clinical groups, agglomerative cluster and principal component analysis of semiological features was performed in twelve patients with "pure" insula epilepsy (n=9) or insular and only deepest opercular involvement (n=3) Quantitative epileptogenicity, intra-insular and extra-insular propagation were computed via time frequency analysis and epileptogenicity mapping. The largest principal component separated anterior insula manifestations including early hypermotor signs, early recovery and no aura from posterior insula features of early dystonia, early tonic motor features and sensorimotor aura.
Peltola et al. ⁵⁶	2020	Insula	11	79	Only pure insular epilepsies were selected. Epileptogenicity index was used to define seizure onset zone and seizure discharge type was assessed. Hyperkinetic signs, speech modifications, and viscerosensory symptoms were related to an anterior insular seizure-

					onset zone. Pain, asymmetric tonic, focal clonic, and tonic symptoms were more frequent in patients with a posterior insular seizure onset.
Machado et al. ⁷⁷	2020	Prefrontal cortex	31	51	Investigation of dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DMPFC), ventromedial prefrontal cortex (VMPFC), and orbitofrontal cortex (OFC). The seizure onset zone (SOZ) was determined from one or two seizures in each patient, using the epileptogenicity index (EI) method. Note that this methodology differed from that of Bonini et al. ⁷⁴ , as early spread was not considered. Optimal clustering was 4 subgroups of prefrontal seizures: a “pure DLPF” group, a “pure VMPF” group, a “pure OFC” group, and a “global prefrontal” group. No significant difference was found in the distribution of ictal signs between the different groups.

Table 3. Methodological challenges of using semiology as a data source in clinical research

Methodological issues	Challenges	Examples of main issues
Semiological analysis	Recording conditions	<ul style="list-style-type: none"> • Insufficient ictal testing (consciousness, language) • Patient covered by bedsheet or off camera • Poor lighting; low camera resolution
	Observer bias	<ul style="list-style-type: none"> • Seizures with emotional behavior, especially facial expression (may be more difficult to perceive other signs) • “Unnatural” patterns of motor semiology may be more difficult to observe and describe • Seizure semiology that is difficult to perceive, because of few signs or because of multiple signs evolving very rapidly • Well-known signs versus rarely seen signs or patterns of unknown significance • Observer’s level of experience and expertise • Inter-observer agreement
	Description of semiology	<ul style="list-style-type: none"> • Seizures with a complex and/or idiosyncratic appearance • Signs of which the significance remains unknown (risk of under-reporting) • Ambiguity of some current terms, e.g. “automatism”, “hyperkinetic seizure” • Non-specificity of some current categories in terms of localization

		<ul style="list-style-type: none"> • How to quantify semiology? E.g. intensity of emotional signs, degree of alteration of consciousness
	Numbers of data	<ul style="list-style-type: none"> • Individual patient: compare seizures with and without a specific sign? • Small versus large case series • Should a control group be used?
SEEG data	Spatial sampling limitations	<ul style="list-style-type: none"> • Cerebral sampling completely dependent on preimplantation hypotheses • Paradigm of the “missing electrode” • Some regions are technically difficult to explore (e.g. vascular constraints) • Subcortical structures are relatively little explored • Level of experience and knowledge influences implantation strategy
	Period of analysis of SEEG	<ul style="list-style-type: none"> • Choice of optimal time period? • Seizure onset, early spread? What duration? • Should period of analysis depend on signal, on semiology, or both? • How many seizures to ensure reproducibility of pattern?
	Signal analysis	<ul style="list-style-type: none"> • Choice of method? • Quantification of fast versus slow activity at seizure onset • Connectivity measures (H2) • Phase lag coupling • Coherence

Conceptual issues	Neural network versus focal/symptomatogenic zone model	<ul style="list-style-type: none">• Methodology of investigating mechanisms and anatomic substrates will be shaped by conceptual model• Concepts of seizure localization and semiological expression very influenced by level of expertise and experience in individual teams (inter-center variability)
	Mainly cortical versus cortico-subcortical view	

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