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Review

Emergence of semiology in epileptic seizures ☆

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ABSTRACT

Semiology, the manifestation of epilepsy, is dependent upon electrical activity produced by epileptic seizures that are organized within existing neural pathways. Clinical signs evolve as the epileptic discharge spreads in both time and space. Studying the relation between these, of which the temporal component is at least as important as the spatial one, is possible using anatomo-electro-clinical correlations of stereoelectroencephalography (SEEG) data. The period of semiology production occurs with variable time lag after seizure onset and signs then emerge more or less rapidly depending on seizure type (temporal seizures generally propagating more slowly and frontal seizures more quickly). The subset of structures involved in semiological production, the "early spread network", is tightly linked to those constituting the epileptogenic zone. The level of complexity of semiological features varies according to the degree of involvement of the primary or associative cortex, with the former having a direct relation to peripheral sensory and motor systems with production of hallucinations (visual and auditory) or elementary sensorimotor signs. Depending on propagation pattern, these signs can occur in a "march" fashion as described by Jackson. On the other hand, seizures involving the associative cortex, having a less direct relation with the peripheral nervous system, and necessarily involving more widely distributed networks manifest with altered cognitive and/or behavioral signs whose neural substrate involves a network of cortical structures, as has been observed for normal cognitive processes. Other than the anatomical localization of these structures, the frequency of the discharge is a crucial determinant of semiological effect since a fast (gamma) discharge will tend to deactivate normal function, whereas a slower theta discharge can mimic physiological function. In terms of interaction between structures, the degree of synchronization plays a key role in clinical expression, as evidenced, for example, by studies of ictal fear-related behavior (decorrelation of activity between structures inducing "release" phenomena) and of déjà vu (increased synchronization). Studies of functional coupling within networks underlying complex ictal behavior indicate that the clinical semiology of a given seizure depends upon neither the anatomical origin of ictal discharge nor the target areas of its propagation alone but on the dynamic interaction between these. Careful mapping of the ictal network in its full spread offers essential information as to the localization of seizure onset, by deducing that a given network configuration could only be generated by a given area or group of areas.

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1. Introduction

Clinical semiology is the manifestation of epilepsy. Significant advances in the comprehension of the epileptic diseases, at least in seizure structure, were achieved long before the advent of electrophysiology and neuroscience, notably in the second part of the 19th century by Herpin [1], Gowers [2], and Jackson [3]. In this era, the only available approach to the investigation of epilepsy (apart from postmortem brain examination) was, of course, through direct observation of seizures, allowing the formulation of hypotheses regarding their pathophysiological basis that show remarkable accuracy in light of the modern understanding of epilepsy [3–7]. The ability to use this clinical information alone to categorize seizures and to form such hypotheses of underlying disordered brain function indicates that semiology is not an epiphenomenon but rather a hallmark of this peculiar disorder in the brain. Decades later, the advent of EEG recording led to a second major step in the advancement of seizure understanding, just as important as semiological observation but more readily quantifiable: the identification of an electrical marker of neuronal dysfunction. The resulting dialogue between these two identifiers of epilepsy, that is, clinical signs and

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pathological electrical activity, has remained at the center of clinical evaluation and, consequently, clinical research.

Among the pioneering concepts of John Hughlings Jackson, one of the most important is represented by his term "discharging lesion" to designate the brain functional process at the origin of seizures. Once the electrical counterpart of this process was discovered some 40 years later, it seemed legitimate to merge both clinical and electrical aspects of seizure expression into a single entity. The time markers of epilepsy rhythms, thus, became labeled according to a presumed binary relation between observable clinical features and measurable electrical activity. The first axiom has been that there are periods of time characterized by abnormal electrical activities without clinical manifestations, which define interictal activities [8]. The second axiom is that there is a dependency of clinical signs and symptoms on electrical activity.

The observed dependency of clinical semiology on electrical activity could have well been a simple coincidence or an epiphenomenon. Taking examples from other neurological conditions, the presence of a sensorimotor deficit in stroke or cognitive impairment in neurodegenerative disease is not necessarily due to the EEG slow waves that may be observed in these situations. However, in epileptic seizures, the causal relation between electrical abnormality and production of ictal signs is real. What has led to establishing the link between semiology and electrical discharge in epilepsy is certainly the observation that "auras" and full seizures could be induced by electrical stimulation of the cerebral cortex, with frequencies in the same range and likely time correlation of the two phenomena [9]. Intracerebral recordings allowed demonstration that abnormal electrical activity preceded the onset of a clinical manifestation [10,11]. Nevertheless, this precession alone did not ipso facto demonstrate linear causality. Again, Jackson, reasoning in terms of his hypothetical "discharging lesion" and unencumbered by the (as yet unknown) physical electrical discharge, had well anticipated the debate in envisaging how this discharge might remotely activate or inactivate the normal regions of the brain.

2. Localizational reductionism

With technical advances in the field of imaging and the rapid development of epilepsy surgery to remove the cerebral lesion that has become visualizable by radiological means, emphasis has been increasingly placed on localization. Curiously, two trends have evolved in parallel. On the one hand, some papers have seriously questioned the capability and, therefore, the utility of clinical semiology as compared with morphological techniques in localizing the epileptogenic zone [12,13]. The presence of a radiological lesion is regarded as a heavily weighted piece of evidence in favor of the zone of seizure origin more or less independent of clinical seizure presentation [14,15], leading to less emphasis on detailed semiological analysis, especially in mesial temporal lobe epilepsies [15]. Indeed, the better prognosis in epilepsies treated by resection of MRI-visible lesions compared with those with no such lesion [16–19] and the apparent lack of ability to predict outcome based on seizure semiology [20] continue to influence selection of patients for presurgical evaluation. This has almost certainly led to potentially operable cases being excluded from intracranial exploration on the supposed basis of likely poor outcome [21]. On the other hand, enthusiasm for classification has induced an opportunist concept of "localization-related epilepsies", with inevitable confusions between seizures and epilepsies and between the epileptogenic zone (misunderstood as seizure-onset zone) and its clinical expression. The ILAE 1989 classification [22] is particularly informative from that perspective, providing a ready-to-use compendium of signs and symptoms supposed to support a lobar localization. Such a compendium was in fact drawn from the SEEG experience at that time [23], but in the interests of simplicity and practicality, contrived to constrain an evolving sequence of manifestations within anatomical lobar limits. It could be considered that, unfortunately, this commendable effort led to the opposite effect, being inaccurate and often misleading. Why do we imagine that the propagation of an epileptic discharge should respect "lobar" boundaries? Since anatomical systems are based on neural connections between structures rather than spatial proximity [24], it seems logical that the propagation of seizure discharges should occur within existing brain wiring patterns, albeit in a pathophysiological context.

3. Anatomo-electro-clinical correlations and the network concept

From the patient's point of view, semiology is the experience of their epilepsy. In order to understand what semiology represents in terms of its localization within brain structures, it is crucial not to neglect the time dimension of a seizure. Many studies have failed to demonstrate any significant localizing value for isolated signs or symptoms, taking either the lesion or the region of surgical resection as a point of reference [12]. On the other hand, attributing entire sequences of ictal signs to paroxysmal activity in the area of seizure onset [25] is also misleading. The anatomo-electro-clinical method proposed by Bancaud and Talairach [10,26], which was of course developed in the pre-imaging era, is robust whether or not a radiologically visible lesion is present [27]. Rather uniquely amongst means of intracranial recording, SEEG allows appreciation and documentation of temporo-spatial relations in seizure spread, including across distant structures. It is essential to remember here that there is a time lag of variable duration between electrical onset (usually in the form of rapid discharge) and the appearance of the first clinical sign; indeed this time lag (discharge preceding clinical onset) is considered an essential criterion for ensuring the accuracy of localization of the epileptogenic zone as measured by SEEG [10,28]. This is an especially important point given the substantial number of intracranial EEG studies devoted to analysis of discharge pattern at seizure onset (especially fast discharge, see [29] for review) compared with the much smaller number of reports of electro-clinical correlations as they occur during semiological expression of seizures. Time lag between electrical and clinical onset may vary from milliseconds to seconds, depending on the brain regions involved. The time window between clinical onset and full expression of clinical signs is also variable. This "period of installation", when symptoms and signs emerge slowly and progressively (for example in medial temporal seizures), or rather rapidly (for example in frontal seizures), is the critical time window for analysis in order to understand the relationship between clinical semiology and anatomical localization.

The fact that electrical activity at seizure onset cannot alone explain emergence of semiology is quite easy to understand. Functional neuroimaging has extensively documented the fact that any observable behavioral trait or any definable cognitive process is underlain by co-activation/deactivation of (often distant) cortical areas organized as a network [30]. It would indeed be odd if paroxysmal behavioral or cognitive dysfunction due to seizures did not share this basic principle. The relationship between semiology of a given seizure and the so-called "seizure onset zone" therefore cannot be other than complex, since this critically depends on the cortical system in which the seizure develops. The following paragraphs will discuss how seizure localization, propagation, type of discharge, and interaction between structures within the epileptogenic network influence semiological expression.

4. Hard-wired connections and localization

Let us look at the cerebral cortex and how it is organized. In terms of the primary sensory areas (somatosensory, auditory, visual, olfactory, gustatory), there are very few intermediate synapses between the peripheral receptors and the cortex. In other words there is a fairly simple and direct linear relation between clinical signs and seizure discharge arising from primary sensory cortex. Therefore, there is no apparent reason that hallucinations or illusions should not be localizing. This relation has been confirmed for the visual modality through intracranial stimulation and surgically treated case studies [11,31]; for example elementary hallucinations such as colored circles, twinkling stars or

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