Deciphering the Great Mimicker

Mapping the Insula With Stereo-Electroencephalography: The Emergence of Semiology in Insula Lobe Seizures

Singh R, Principe A, Tadel F, et al. *Ann Neurol.* 2020;88(3):477-488. PMID: 32542728. doi:10.1002/ana.25817

Objective: Insula epilepsy is rare and can be evaluated effectively by stereotactic intracerebral electroencephalography. Many previous studies of insulo-opercular seizures have been unable to separate insular and opercular onset. With adequate sampling of the insula, this study shows this is possible. Methods: We analyzed intrainsular dynamics and extrainsular propagation in 12 patients with "pure" insula epilepsy (n = 9) or insular and only deepest opercular involvement (n = 3) at seizure onset. Review of semiology defined clinical groups, agglomerative cluster, and principal component analysis of semiological features were performed. Quantitative epileptogenicity and intrainsular and extrainsular propagation were computed via time frequency analysis and epileptogenicity mapping. Results: Seizure-onset patterns were heterogeneous; the seizure-onset zone was focal. Seizure-onset and first ictal change within insula functional subdivision correlated with aura and reflex component. No paninsular spread occurred; contralateral insular spread was very early. While the discharge was intrainsular, clinical signs were related to aura or vegetative signs. Extrainsular propagation was early and related to the emergence of the majority of clinical signs. Cluster analysis found an anterior, intermediate, and posterior insula seizure-onset group. 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. Interpretation: Aura is vital to identifying seizure onset and relates to insula functional subdivision. Seizures are heterogenous; extrainsular propagation occurs early, accounting for most of the semiology. With adequate sampling, "pure" insula epilepsy can be identified and focal curative resection is possible.

Commentary

I have long thought of insula seizures as being the equivalent of the tertiary syphilis of the epilepsy world. You know, they are rarely seen but always show up on board examination questions, case presentations of challenging patients at the national society meetings, and in the differential diagnosis whenever surgical hypotheses are discussed at epilepsy surgery conference. Seizures originating in or around the insula have a well-deserved reputation of being mimickers of seizures that originate from other parts of the brain.[1] This likely stems from the fact that the insula has extensive connectivity with the temporal lobe, frontal lobe, and parietal lobe[2,3] as well as its homotopic contralateral cortex. Indeed, corticocortical evoked potentials triggered by electrical stimulation have shown propagation times between the contralateral insulas as low as 8 milliseconds, suggesting possible monosynaptic connections through the corpus callosum.[4] This robust and extensive connectivity to other brain regions is thought to underlie why some seizures with clinical semiologies commonly associated with frontal

lobe epilepsy or mesial temporal lobe epilepsy actually originate in the insula. The pioneering work of Isnard and colleagues[5] at the turn of the century first highlighted certain symptoms and signs such as perioral paresthesias and laryngeal constriction which suggested a higher likelihood of insular seizures. Since then, our knowledge of this focal epilepsy has progressed slowly, mainly due to its relative rarity and the difficulty in accessing this region for in-depth study.

The work of Singh et al[6] adds to the existing literature by presenting a careful clinico-electrophysiologic-anatomic study of one of the largest case series of "pure" insula lobe seizures. This is a single-center retrospective study reviewing almost 30 years of data on patients with drug-resistant focal epilepsy undergoing surgical evaluation. Of the 552 patients in their database, 12 patients with insular onset or deep opercular onset seizures were identified (2.2%). Only patients who had intracranial stereo electroencephalography (EEG) recordings were studied. Over 150 clinical seizures recorded by stereo EEG were analyzed clinically and 1 to 3 seizures

representing the most typical for each subject were further studied with agglomerative hierarchal cluster analysis and principal component analysis. The seizures from a subset of patients (66%) were also studied with time frequency analysis and epileptogenicity mapping using Brainstorm software. Results showed that 9 patients (75% of cohort) had seizure onset only in the insula, while 3 had both an insular and deep opercular onset. Seizure onset was very focal and the electrographic patterns were stereotyped for each individual but heterogeneous across the cohort. Beta sharp discharges >15 Hz was the most common initial ictal change followed by low-voltage fast activity (LVFA) preceded by slow-wave direct current shift or high-amplitude polyspikes followed by LVFA. The initial propagation was usually intrainsular to an adjacent insular gyrus. In addition, spread of ictal EEG changes to the contralateral homologous insular area was early (mean = 32 milliseconds) and often *preceded* spread to ipsilateral structures outside of the insula. Electroclinical analysis indicated that the majority of clinically obvious behavioral changes occurred *after* extrainsular propagation. Agglomerative cluster analysis differentiated clinical symptoms/signs between anterior and posterior insula onset seizures by virtue of 6 principal components: early hypermotor signs, early recovery, lack of aura for anterior insula onset seizures, early dystonia, early tonic motor features, and sensorimotor aura for seizures originating from posterior insula. Seven patients in this cohort underwent resective surgery and 85% achieved an Engel 1 outcome.

The main strength of this article is the detailed correlation of clinical symptoms and signs with anatomic location within the insula. Many earlier studies on "insular" seizures did not specifically differentiate between insular and opercular region or "perisylvian" onset seizures. Singh et al used a mean of 4.4 electrodes in covering just the insular cortex, thereby providing much greater spatial coverage than in most previous studies. This allowed the authors to sample both anterior and posterior divisions of the insula and cover all 4 functional areas (cognitive, social–emotional, chemical sensory, and sensorimotor). For point of reference, most surgical epilepsy teams use 2 to 3 stereo EEG electrodes to record from the insula if the surgical hypothesis suggests a strong likelihood of an insulo-opercular epileptogenic region.

The main takeaway point of this careful and detailed clinicoanatomic study is that a good understanding of the patient's initial aura symptoms is essential to localizing the seizure-onset zone. Data from the recordings of spontaneous seizures as well as direct electrical stimulation correlated specific patient symptoms with activation of specific insular functional subdivisions. While this finding is neither surprising nor unexpected because of our understanding of functional neuroanatomy, it nevertheless is heartening to have our assumptions elegantly validated. The practical implication of this finding is that we should redouble our efforts in the clinics to perform a very careful and detailed history of seizure semiology. I am fond of telling my trainees that at least 80% of the time in performing an epilepsy evaluation should be devoted to history taking and that the aura

portion of the history provides us important clues of the seizure-onset zone. It is commonplace for patients to report 2 or 3 different aura symptoms. What this study highlights is the importance of the clinician developing an accurate temporal sequence of the evolving symptom complex if one is to have any chance of recognizing and correctly localizing an insula epileptogenic zone. For example, focusing on a description of hypermotor activity and tonic motor signs while overlooking (or failing to elicit) a stereotyped brief auditory hallucination is likely to lead to an incorrect surgical hypothesis and misguided surgical planning. As Singh et al nicely demonstrated, seizure propagation out of the insular focus occurs early and it is the activation of functionally connected extrainsular brain regions that results in most of the clinical semiology.

Ultimately, this article provides a roadmap for accurately diagnosing and treating seizures originating from the insula. Because insula lobe epilepsy may mimic seizures from temporal lobe, frontal lobe, or sensorimotor cortex, it is essential to obtain a careful history of auras with special attention to initial symptoms. If an insular epileptogenic zone is suspected, extensive sampling of the insula with stereo EEG is advised as intrainsular or paninsular spread is uncommon while extrainsular propagation and/or spread to contralateral insula is rapid and typical. Contrary to older notions that surgery of insular cortex has high complication rates and should be avoided, the data from Singh et al support recent work[7] showing that surgery resecting or ablating certain insula subdivisions is associated with good outcomes. While the Great Mimicker will always challenge and test our clinical abilities, this article has given us added understanding and approaches to help decipher the mysteries of insular epilepsy.

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