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INVITED COMMENTARY

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Commentary on Schotte et al. "Development of temporal lobe epilepsy during maintenance electroconvulsive therapy: A case of human kindling?"

Solomon L. Moshé[1,2] | **Aristea S. Galanopoulou**[1]

[1]Saul R. Korey Department of Neurology, Isabelle Rapin Division of Child Neurology, Dominick P. Purpura Department of Neuroscience, Laboratory of Developmental Epilepsy, Albert Einstein College of Medicine, Einstein/Montefiore Epilepsy Center, Montefiore Medical Center, Bronx, New York

[2]Department of Pediatrics, Albert Einstein College of Medicine, Einstein/Montefiore Epilepsy Center, Montefiore Medical Center, Bronx, New York

Correspondence
Solomon L. Moshé and Aristea S. Galanopoulou, Albert Einstein College of Medicine, Bronx, NY.
Emails: Solomon.moshe@einstein.yu.edu; aristea.galanopoulou@einstein.yu.edu

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Kindling is a phenomenon whereby repeated subthreshold stimulations for inducing a particular initial behavior eventually produce that behavior, and with further stimulations additional behaviors are observed.[1] It is a model of learning, memory, and epileptogenesis/epilepsy; the latter is because the measured behavior is most often a seizure that becomes progressively more severe. For example, in kindling of the limbic structures in adult rodents, the Racine scale is used.[2] These seizures are initially focal and then become bilateral clonic[3–5] and eventually tonic (Table 1).[2] In experimental studies, kindling can be induced by a variety of electrical or chemical stimuli.[3,4,6–16] Another form of kindling is the progressive intensification of bilateral (probably generalized) seizures triggered by repeated administration of chemoconvulsants such as flurothyl with associated decrease in the latencies of the onset of the convulsions.[17] In almost all the studies, the data suggest that focal seizures eventually become bilateral or the bilateral seizures become more severe. There

is only one observation that with repeated audiogenic stimulation in one strain of rats (genetically epilepsy prone rats [GEPR-3]), after a series of bilateral seizures (which are presumed to be of brainstem origin), focal electroencephalography (EEG) discharges appeared in the amygdala with seizure types reminiscent of the Racine stages 1-3.[18,19]

The notion that kindling may occur in human epilepsies has been proposed and debated since the first description of the phenomenon by Graham Goddard in 1967.[1] There are several excellent reviews on the topic describing the pros and cons of the available studies,[5,20] and the evidence is at best scant. This may be due, in part, to the greater number of stimulations needed to elicit kindling, the higher the animal is on the phylogenetic scale.[5]

Schotte et al[21] presented a 67-year-old right-handed woman with no family history of epilepsy or febrile seizures, who had been receiving electroconvulsive therapy (ECT) sessions for medically refractory bipolar disease. She received weekly bilateral temporal ECT for 9 years before being switched to right temporal ECT (weekly initially; then reduced to every other week), due to concerns of cognitive deterioration. In parallel, she had been receiving valproate, among other medications, for management of her bipolar disorder. After 17 years and 800 sessions of bilateral or unilateral ECT, and after reducing the sessions from weekly to every other week, she started manifesting epileptic seizures consisting of hyperventilation, tachycardia, impaired awareness, oral and left hand automatisms, and postictal aphasia. Her video-EEG monitoring captured left more than right temporal epileptic discharges and ictal seizure patterns with bilateral onset, although lateralizing electroclinical signs were suggested (reported as starting at or rapidly propagating to the left temporal, although electrographic onset remains unclear). Subtraction ictal SPECT (single-photon emission computed tomography) coregistered with MRI (SISCOM) showed left hyperperfusion, and interictal fluorodeoxyglucose positron emission tomography (FDG-PET) with anatomy-corrected asymmetry index analysis showed bilateral but greater on the left hemisphere hypometabolism. No obvious association between the timing of ECT sessions and her seizures was observed.

The authors propose that this presentation may be a form of ECT kindling of the development of temporal lobe epilepsy (TLE) in humans. In this case, this will resemble the studies in the GEPR-3 audiogenic-prone rats and one would have to assume that the ECT seizures are of brainstem origin. Prior reports of epilepsy diagnosed after many episodes of ECT included focal or bilateral onset seizures, while epileptic activity after bitemporal ECT or ipsilateral temporal onset seizures have been reported after unilateral ECT[22,23] and often subside after ECT discontinuation. However, as was the case in the patient described by Schotte et al, ECT discontinuation may not always be possible due to the severity of depression.

However, there is an alternative hypothesis that should be considered. The 800 ECT seizures recorded prior to clinical seizure onset could have produced hippocampal injury, and the observed seizures may be a reflection of this injury. The observed cognitive deterioration, reported before the onset of clinical seizures, is supportive evidence. It is also possible that this injury may have been exacerbated by the focal delivery of ECT via a right temporal lobe electrode. This hypothesis could be considered in the interpretation of the data. Of interest, although bilateral temporal pathologies were observed, the interictal pathology (FDG-PET) as well as the lateralizing signs on the ictal SISCOM and electroclinical manifestations showed a preponderance of left temporal pathology, that is, contralateral to the right temporal ECT sessions. If ECT is indeed implicated in the development of TLE in this patient, whether directly by kindling or indirectly as a result of the ensuing temporal lobe pathology, what are the mechanisms responsible for the greater pathology and epileptogenesis at a contralateral focus? Paradoxical lateralizing signs (eg, postictal expressive and receptive aphasia with or without right gaze deviation and right-sided motor signs)

TABLE 1 Stages of amygdala-induced kindled seizures in adult rats

Stage	Sign
0	Behavioral arrest
1	Chewing
2	Chewing and head nodding
3	Chewing, head nodding, and contralateral forelimb clonus
4	The above plus bilateral forelimb clonus with rearing
5	The above plus loss of balance
6	The above plus wild running, jumping, and rolling
7	The above plus tonic posturing
8	Spontaneous seizures

Modified from Racine 1972, Pinel & Rovner 1978, and Moshé and Ludwig 1983.[2,4,5]

have been reported very rarely after right unilateral ECTs of right-handed patients, either immediately after the ECT or postrecovery ("*tardive seizures*").[24,25] These have been postulated to reflect "stunning" of eloquent regions after ECT seizure generalization, although it is also likely that underlying predisposing conditions or coadministered drugs may render some patients more vulnerable to manifesting persisting or reactivated seizure foci, contralateral to the ECT. Certainly, the frequency of these paradoxical associations is too low to confirm causality. Furthermore, pre-ECT data on neuroimaging or video-EEG monitoring to determine preexisting pathologies at the contralateral site are missing. The chronic concomitant use of valproate or benzodiazepines for the treatment of psychiatric disorders in some of these patients,[21,25] may have masked or delayed the onset of the clinical manifestations of prior epilepsy.

On the contrary, could the unilateral ECT have protected the ipsilateral temporal lobe from injury or propensity to manifest or sustain ictal activity?[21,24,25] Electroconvulsive seizures result in a period of postictal refractoriness to seizures or epileptic activity[26,27] that may contribute to apparent antiseizure effects. Bilateral ECT has been used to stop superrefractory status epilepticus,[28–30] although most studies have been retrospective or case reports, thus warranting further confirmation with prospective studies before recommending its use. Unknowns and possible confounders include the ECT effects on blood-brain barrier permeability and its potential effects on seizure activity or the brain penetration of coadministered drugs (including antiseizure drugs), vascular and cerebral blood flow changes after ECT, direct effects of (unilateral or bilateral) ECT on seizure propensity, comorbidities, and the reciprocal influences of the concomitant brain pathologies due to psychiatric and other comorbidities. Additional factors potentially controlling outcomes are the impact of ECT electrode placement and stimulation protocol on the function of and connectivity patterns within a network that has already been altered by the comorbid conditions and individual factors that may modify the effects of all these interactions.

We commend the authors for reviving these interesting and clinically important questions through their "*concept and hypothesis*" manuscript prompted by their case report. Despite certain, and often unavoidable, practical limitations, inherent to everyday clinical practice, that prevent definitive conclusions, the implications for future systematic research in this area are important. To date the evidence that kindling occurs in humans is still at best questioned. Time will tell.

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DISCLOSURE

The authors have no conflicts of interest with regard to this manuscript. SLM discloses that he is serving as Associate Editor of *Neurobiology of Disease* and is on the editorial boards of *Brain and Development*, *Pediatric Neurology*, and *Physiological Research*. He receives from Elsevier an annual compensation for his work as Associate Editor on *Neurobiology of Disease* and royalties from 2 books that he coedited. He received a consultant fee from UCB for participation in a Data Safety Monitoring Board. He has also received an honorarium for participation in advisory board meetings of Mallinckrodt and UCB, but there are no conflicts of interest with regard to the contents of this manuscript. ASG discloses that she is co-Editor in Chief of *Epilepsia Open* and has received royalties from Elsevier for book publications. She has also received an honorarium for participation in advisory board meetings of Mallinckrodt and Eisai, but there is no conflict of interest with regard to the contents of this manuscript. 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.

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