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Long-term amygdala kindling in rats as a model for the study of interictal emotionality in temporal lobe epilepsy

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Abstract

Temporal lobe epileptics often experience profound interictal (i.e. between seizure) emotional disturbances, such as fear, anxiety, and depression. Although the presence of this interictal emotionality has been well documented, little progress has been made in identifying its precise nature and cause because it is not amenable to experimental analysis in clinical populations. Accordingly, there is much to gain by studying the fundamental nature and neural basis of interictal emotionality using animal models. Kindling is a widely studied animal model of temporal lobe epilepsy in which daily electrical stimulation of certain brain regions results in the gradual progression and intensification of limbic motor seizures. Several investigators have found that partial and short-term kindling produce robust changes in emotional behavior in both cats and rats. Recently, our laboratory has developed a new model to study interictal emotionality using long-term kindling in rats. These long-term kindled rats display profound changes in fearful and defensive behavior which last for at least two months after the final stimulation. We are now beginning to use this model to study the neural mechanisms underlying the development and expression of interictal emotionality.

Keywords: Kindling; Seizure; Temporal lobe epilepsy; Amygdala; Hippocampus; Dentate gyrus; Fear; Anxiety; Serotonin; Emotion; Defensive behavior

1. Overview

Epilepsy is a chronic disorder that is characterized by spontaneously recurring seizures. Of the many forms of epilepsy, temporal lobe epilepsy represents the biggest problem for modern medicine: It is the most prevalent form, comprising 55% of all cases in adults, and it is the most resistant to treatment [35]. Furthermore, up to 50% of temporal lobe epileptics experience profound interictal (i.e. between seizure) disturbances in emotional behavior [22]. However, little progress has been made in characterizing the fundamental nature and etiology of this interictal emotionality because of the difficulties inherent in the experimental study of epileptic populations. Accordingly, the use of an animal model for investigating the interictal emotionality associated with temporal lobe epilepsy is critical for furthering our understanding of this problem and developing effective treatments for it (see Ref. [34]). The focus of this paper is to review the current state of knowledge about temporal lobe epilepsy and interictal emotionality in temporal lobe epileptics, to describe recent findings from studies using rats and cats to study interictal emotionality, to present a new animal model that we have developed for this purpose, and to discuss our initial attempts to use this model to identify the neural mechanisms underlying the development and expression of interictal emotionality.

2. The nature of temporal lobe epilepsy

The symptoms of temporal lobe epilepsy have both fascinated and frustrated medical scientists for centuries. Laplante [81] has written about the complexity of temporal lobe seizures in great detail. She highlights several common features of these seizures: They are variable and unpredictable in their course; they are frequent; they are difficult to control; they are accompanied by a extreme emotions that can change within a single seizure or from seizure to seizure; and they sometimes leave patients with feelings of irritability long after the actual seizure has ceased.

Temporal lobe seizures are usually of the complex partial type. In this context, the word “partial” means that the seizure has a focal onset and does not spread through the entire brain, and the word “complex” means that consciousness is altered or lost. In 90% of patients, the first manifestation of a temporal lobe seizure is an aura [46]. Auras may take many forms: they may take the form of epigastric discomfort, sensory-motor problems that typically involve only the face and extremities, illusions or hallucinations,

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Table 1
Traits of the Bear–Fedio Inventory [13]

Emotionality
Elation, Euphoria
Sadness
Anger
Aggression
Altered sexual interest
Guilt
Hypermoralism
Obsessionalism
Circumstantiality
Sense of personal destiny
Hypergraphia
Religiosity
Philosophical interest
Dependence, passivity
Viscosity
Humorlessness, sobriety
Paranoia

dysphasia, dysmnesia (e.g. *deja vu*, *jamais vu*, or flashbacks), cognitive disturbances (e.g. forced thinking or dreamy states), or affective disturbances (e.g. euphoria, fear, or anger). After the aura, there is a period of semiconsciousness, which is often accompanied by behavioral arrest. During a period of behavioral arrest, the patient simply stops what she or he is doing and stares blankly ahead, often engaging in simple repetitive behaviors called automatisms. Common automatisms include repeated lip smacking, licking, chewing, swallowing, mimicking, gesturing, repeating nonsense phrases, tugging at pieces of hair, and doing and undoing buttons [127]. However, some temporal lobe seizures involve complex sequences of nearly normal behavior. In addition, temporal lobe seizures are sometimes accompanied by secondarily generalized convulsions. In such cases, the focal seizure discharge spreads throughout the brain, and the partial seizure develops into a generalized convulsion.

Temporal lobe seizures are particularly resistant to treatment [41]. In patients who experience complex partial seizures that develop into secondarily generalized seizures, anticonvulsant medication often controls the generalized convulsion but not the complex partial seizure [87]. The resistance of temporal lobe epilepsy to treatment may be related to its neuroanatomical basis [89]. Wieser [132,133] used depth electrodes to locate the epileptic foci of temporal lobe epileptics and found that two major subcortical structures of the temporal lobe, the hippocampus and amygdala, play the major role in seizure initiation—25% of the seizures in these patients appeared to originate in the hippocampus, 10% appeared to originate in the amygdala, and 65% appeared to originate in the hippocampus and amygdala simultaneously. Because the hippocampus and amygdala have particularly low seizure thresholds, seizure discharges that involve these structures may be particularly resistant to antiepileptic drugs.

In addition to the seizures themselves, up to half of all temporal lobe epileptics experience interictal emotional disturbances [35]. These emotional disturbances range from mild fear to pathological levels of anxiety and depression, or sometimes schizophrenic episodes (e.g. Refs. [11,13,21,35,50,52,64,99,100,115]). However, anxiety and depression are by far the most common disturbances experienced by temporal lobe epileptics. Gaining an understanding of the nature and cause of these emotional disturbances is important for at least two reasons. First, the interictal emotional disturbances associated with temporal lobe epilepsy are often more incapacitating and more difficult to control than the seizures themselves: They can disable epileptic patients to the point where they cannot work, sustain normal relationships, or otherwise function normally in society [35]. Second, the study of the interictal emotional disturbances associated with temporal lobe epilepsy may provide a basis for inferring the role of temporal lobe structures in psychological processes such as fear and defense, and for assessing how these processes can progress into pathological forms of anxiety and depression.

3. Interictal emotionality in temporal lobe epileptics

Recognition of the association between epilepsy and abnormal interictal behavior has a long history. In the middle ages, epileptics were rejected as menaces to society and were often incarcerated or executed [15,68]. In the late 19th century, pioneers of modern psychiatry began to discuss the role of epilepsy as an important cause of mental pathology [35]. At about the same time, anecdotal reports relating temporal lobe seizures in particular to psychopathology started to be published. For example, Hughlings Jackson [67] was the first to suggest that focal seizures produced greater mental pathology than did generalized convulsions. Later, Gibbs, Gibbs, and Fuster [51] reported that patients with focal temporal lobe seizures in particular had a much higher incidence of "psychopathology" than did other epileptics.

In 1975, based on their own clinical observations, Waxman and Geschwind [130] characterized an interictal behavioral syndrome that they believed was associated with temporal lobe seizures (i.e. the "epileptic personality"). This syndrome comprised deepened emotions, circumstantiality, hyperreligiosity, hyposexuality, and hypergraphia. Waxman and Geschwind [130] stressed that although the behavior of temporal lobe epileptics is different, it is not qualitatively abnormal; they believed that temporal lobe epileptics were merely prone to overengage in the normal behaviors of non-epileptic individuals.

Experimental efforts to measure the emotionality associated with temporal lobe epilepsy have taken two forms. By far the most frequent approach has been to assess behavioral changes with conventional psychiatric tests such as the Minnesota Multiphasic Personality Inventory

(MMPI). Unfortunately, the findings of studies that have taken this approach have been equivocal (see Ref. [39]). One problem with this approach is that it is based on the a priori assumption that altered emotions in temporal lobe epileptics fit traditional psychiatric diagnostic categories [35]. A second problem is that some of the test items reflect the experience of the seizures per se, rather than interictal emotional changes [39]. Thus, the MMPI may not adequately assess the nature of interictal emotional problems in epileptic patients.

The second approach to measuring the behavioral changes associated with temporal lobe epilepsy has used the Bear–Fedio Inventory (see Table 1). Motivated by the inappropriateness of the MMPI for the task, Bear and Fedio [13] constructed this inventory for the expressed purpose of characterizing interictal changes in behavior. The Bear–Fedio Inventory assesses 18 behavioral traits; each of the 18 was either included in Waxman and Geschwind's [130] clinical description of the temporal lobe epileptic personality or described in previous anecdotal reports. In their initial validation study, Bear and Fedio [13] administered their inventory to a group of temporal lobe epileptics, a group of neuromuscular-disorder patients, and a group of normal control subjects. All of the subjects were asked to rate themselves by responding "true" or "false" to five questions related to each trait. The temporal lobe epileptics scored significantly higher on each of the 18 traits than did the subjects in both of the other groups; in contrast, the neuromuscular-disorder patients scored significantly higher than the normal controls on only 3 of the 18 traits.

Is there a single underlying psychological change that is the basis of all 18 of the behavioral changes documented by the Bear–Fedio Inventory? In their paper, Bear and Fedio [13] suggested that the behavioral traits result from an attachment of enhanced affective significance to previously neutral stimuli, events, or concepts. Bear [12] later suggested that this attachment could be the result of repeated seizure activity in limbic structures such as the amygdala, which links sensory association cortices with drive-controlling centers within the hypothalamus. According to Bear, the sensory–limbic hyperconnection produced by repeated seizures could lead to the association of experience with heightened emotion in temporal lobe epileptics. This hypothesis is intuitively appealing because it is consistent with the large literature implicating the amygdala in the mediation of emotional behavior (e.g. Refs. [31,78,83,112]) and the processing of complex stimuli (e.g. Ref. [82]), and with the recent finding that hyperexcitability (i.e. long-term potentiation) of certain amygdala pathways is necessary for the expression of interictal defensive behavior in cats [4] (and Adamec and Young, this volume).

There have been several attempts to replicate the original findings of Bear and Fedio [13], with mixed degrees of success. Clear behavioral differences have been observed between epileptic patients and normal controls. Brant, Seidman, and Kohl [23] found that a mixed epilepsy group (i.e. temporal lobe and primary generalized seizures) scored higher than normal controls on 5 of the 18 traits (i.e. circumstantiality, humorlessness, viscosity, sadness, and dependence), and Rodin and Smaltz [110] found that a mixed group of epileptics scored significantly higher than normal controls on 18 of the 18 traits. However, the differences are not so clear when temporal lobe epileptics are compared to other psychiatric inpatients or to patients with a generalized seizure disorder. Bear, Levin, Blumer, Chethan, and Ryder [14] found that temporal lobe epileptics scored significantly higher on seven traits (i.e. viscosity, circumstantiality, religiosity, philosophical interest, humorlessness, paranoia, and hypermoralism) compared to psychiatric patients. However, Rodin and Smaltz [110] found that a mixed epilepsy group scored lower on all 18 traits compared to psychiatric inpatients and Mungas [95] found no significant trait differences between a group of temporal lobe epileptics with a diagnosed psychiatric illness and a group of nonepileptic psychiatric controls. Finally, Hermann and Reil [64] compared temporal lobe epileptics to epileptics with primary generalized seizures and found significantly higher scores in the temporal lobe epileptics on only 4 of the 18 traits (i.e. sense of personal destiny, dependence, paranoia, and philosophical interest).

The Bear–Fedio Inventory has been criticized, largely because it does not reliably differentiate between temporal lobe epileptics and other neurological or psychiatric patients, (e.g. Ref. [2,35,39]) and because the original Bear-Fedio validation study [13] involved both small samples (i.e. $ns = 12$) and a sample of temporal lobe epileptics who were particularly prone to psychiatric problems. However, despite these problems, studies using the Bear–Fedio Inventory have confirmed that temporal lobe epileptics do differ from healthy control subjects in their behavioral traits and that the difference is primarily in emotional types of behavior—even though there is no general consensus on the exact nature of these emotional differences. Particularly problematic is the widely-held belief that increased emotionality in temporal lobe epileptics makes them prone to outbursts of aggression (see Refs. [21,47]). This belief persists despite a paucity of empirical support [53] and its adverse social repercussions for temporal lobe epileptics.

Aside from confirming that a significant proportion of temporal lobe epileptic patients do suffer from interictal emotional disturbances, there has been little progress to date in identifying the fundamental nature of the disturbances, the factors that influence their development and expression, and their neural basis. This lack of progress can be attributed to problems inherent in the experimental study of epileptic patients. First, many patients who experience temporal lobe seizures also experience other types of seizures, making it difficult to select a homogeneous group of "pure" temporal lobe epileptics for study [39]. Second, most studies of interictal emotionality in temporal lobe epileptics are fraught with methodological problems. For

example, in many cases, the control subjects are epileptics with generalized seizures that likely invade limbic regions, and in almost all cases, behavior is examined at only one moment in time instead of repeatedly from onset through the course of the epilepsy [35]. Third, it is often difficult to document important factors such as seizure frequency and origin and to ascertain whether certain interictal symptoms are due to some undetected ictal events [43]. Fourth, the interictal emotional disturbances associated with temporal lobe epilepsy per se can be affected by anticonvulsant medication: Some anticonvulsant drugs have side effects that can cloud the interictal emotionality [42] and some anticonvulsant drugs have effects that can exacerbate the interictal emotionality [49]. Fifth, the experience of suffering from a disorder that is both traumatic and unpredictable, and the emotional impact of the social stigma that is attached to it produces psychosocial problems that can influence the expression of interictal emotionality [42]. And finally, the diffuseness and variability of the structural and functional brain pathology in temporal lobe epileptics [9,32,53] makes it difficult to link the interictal emotionality with changes in particular brain structures. Consequently, the availability of a useful animal model of interictal changes in emotional behavior would greatly facilitate the study of the interictal emotional disturbances associated with temporal lobe epilepsy. To that end, the kindling model of temporal lobe epilepsy has proven to be very useful—it is described in the next Section.

4. The kindling model of temporal lobe epilepsy

Periodic administration of initially subconvulsive stimulations to certain brain structures results in the development and progressive intensification of elicited motor seizures—this phenomenon has been termed *kindling* [54]. Kindling is the most widely studied model of temporal lobe epilepsy. It can be induced by a variety of different convulsive agents, delivered either diffusely or focally to particular brain loci. For example, it has been induced by electrical or chemical stimulation of the pyriform cortex, amygdala, entorhinal cortex, ventral hippocampus, olfactory bulb, septum, caudate, and anterior neocortex in such species as frogs, mice, gerbils, rats, rabbits, cats, dogs, rhesus monkeys, and baboons [93,107]. It has also been induced by repeated acoustic stimulations in sound-susceptible rats [65]. However, despite the variety of agents, structures, and species that can be kindled, it has been most frequently studied in rats subjected to daily electrical stimulations of the amygdala.

At first, electrical stimulation of the amygdala at an intensity sufficient to evoke afterdischarges (i.e. to evoke epileptic spiking in the EEG record that outlasts the stimulation) elicits little or no behavioral response. Then, with each subsequent stimulation, the afterdischarges at the site of stimulation last longer and generalize further from the site of stimulation, and motor seizures begin to accompany them. After about 15 periodic stimulations, rats respond reliably to each stimulation with a generalized clonic convulsion, which is characterized in sequence by jaw clonus, head clonus, forelimb clonus, rearing, and falling [92,106] and has a duration of about 40 s [70,103]. Once an animal has been kindled (i.e. once it displays three consecutive generalized convulsive seizures), it will continue to respond to each stimulation with a generalized convulsion even after a stimulation-free period lasting several months [54]. However, it is important to note that kindling is a progressive disorder that is far from complete once three consecutive generalized convulsions have been elicited: if the program of stimulations is continued, the severity of the motor seizures increases (i.e. multiple fits of rearing and falling, running fits, and tonic motor seizures develop), interictal epileptic spikes begin to punctuate the EEG records, and after about 250 stimulations, motor seizures begin to recur spontaneously [101,126].

Kindled convulsions are usually rated in terms of the following convulsion classes, originally described by Racine [106]: Class 1, facial clonus; Class 2, head nodding; Class 3, contralateral forelimb clonus; Class 4, forelimb clonus and rearing; Class 5, forelimb clonus, rearing, and falling. Because kindled convulsions increase in severity in animals that receive an extended number of stimulations, Pinel and Rovner [103] have expanded Racine's [106] original scale to include 3 additional classes: Class 6: a class 5 with multiple falling episodes; Class 7: running fits; Class 8: any of the preceding symptoms with periods of tonus.

Several lines of evidence support the view that rats kindled by amygdala stimulation are valid models of human complex partial seizures with secondary generalization. First, drug effects on kindled convulsions in rats are predictive of drug effects on complex partial seizures in humans [86,108]. Second, rats subjected to large numbers of kindling stimulations (i.e. 150 stimulations) display neuronal loss [26] and mossy fibre sprouting [120,128] in a pattern that is similar to the neuropathological changes characteristic of the human disorder (e.g. Ref. [121]) (although some criticize the kindling model on the basis that the neuronal loss is not evident at the time that the animal first becomes "kindled"). And third, extensive kindling (e.g. 250 stimulations in rats) ultimately results in the recurrence of spontaneous motor seizures, which is the defining feature of clinical epilepsy [101,126]. Kindling is particularly useful for studying the progression of epilepsy and its behavioral consequences because animals can be studied at particular stages in the kindling process, up to and including the emergence of spontaneous motor seizures. Moreover, kindling provides a high degree of experimental control over key parameters, such as where in the brain the seizures are elicited, when they are elicited, and how many of them are elicited. Accordingly, several investigators interested in the interictal emotional disturbances associated with temporal lobe epilepsy have studied the changes in

interictal emotional behavior that accompany various stages of kindling in rats or cats (see Ref. [2,34]).

5. Behavioral effects of kindling

Kindling is the most commonly used animal model for the study of interictal emotionality, and the effects of kindling on emotional behavior are the primary focus of this paper. However, it is important to note that kainic acid-induced seizures have also been used to investigate interictal emotionality [58]. In this model, cats are given unilateral injections of kainic acid directly into the dorsal hippocampus. This produces a period of status epilepticus that lasts up to 72 h after the injection. After the status epilepticus, the cats recover and begin to exhibit periodic spontaneous seizures, consisting of EEG activity in the amygdala but few motor convulsions. In between the seizures, the cats often display an extreme defensive reaction when handled. Interestingly, administration of the anticonvulsant drugs carbamazepine or valproate attenuates the seizures but exacerbates the defensive reactions [57]. This work has recently been thoroughly reviewed elsewhere (Refs. [2,34,44]).

Although a wide range of behavioral changes have been observed in temporal lobe epileptics, it is the changes in fear and anxiety-like behavior that have been most often modeled in laboratory animals using the kindling model. There are three primary reasons for this: Hyperemotionality is thought to underlie the majority of behavioral problems experienced by temporal lobe epileptics [12]; fear and anxiety are among the most prominent emotional problems reported in temporal lobe epileptics [39]; and there are numerous behavioral paradigms available for modeling human fear and anxiety in animals.

Adamec was the first to document the effects of kindling on interictal emotional behavior [1]. Adamec found that partial kindling (i.e. kindling that produces afterdischarges but no generalized convulsions) of the amygdala or ventral hippocampus in cats results in behavioral changes that appear to be independent of convulsions or interictal spiking for their maintenance [2]. After partial kindling, the cats displayed increased defensive responses when they were exposed to rats, mice, and conspecific threat vocalizations [1] or when they received electrical stimulations of the ventromedial hypothalamus [116]. These behavioral changes may dissipate over time, lasting from several weeks to as long as the animals are kept (four months) [2], and they can be blocked by low doses of flumazenil, a benzodiazepine receptor antagonist [3]. Interestingly, flumazenil normally has no anxiolytic effects on cat behavior; its anxiolytic effects appear only after partial kindling. This suggests that kindling may produce functional changes to benzodiazepine receptors.

More recently, two groups reported the effects of partial amygdala kindling on emotional behavior in rats. Helfer, Deransart, Marescaux, and Depaulis [60] found that partial amygdala kindling decreased the percentage of open-arm exploration in an elevated plus maze. In addition, Rosen, Hamerman, Sitcoske, Glowa, and Schulkin [111] found that partial amygdala kindling, but not partial hippocampal kindling, exaggerated conditioned fear-potentiated startle.

Since the seminal experiments of Adamec, most investigators interested in the interictal emotional disturbances associated with temporal lobe epilepsy have studied the changes in emotional behavior that accompany short-term amygdala kindling (see Ref. [2]). Short-term kindling refers to a protocol in which animals receive enough stimulations to induce three consecutive generalized convulsions, usually between 15 and 25 in the case of amygdalar stimulations in rats. The subjects are tested at least 24 h after the final kindling stimulation, in order to ensure that any apparent behavioral differences are interictal and not due to postictal electrical activity. Using this protocol, amygdala kindling in squirrel monkeys has been shown to cause increases in defensiveness and social withdrawal [85]; in cats, it has been shown to decrease the threshold to electrically elicit defensive hissing and growling [66] and in rats, it has been shown to decrease exploratory behavior [6,60,97], decrease open-arm exploration on an elevated plus maze [2,5,60,97] decrease the latency to muricide in spontaneous mouse-killers [91], increase immobility in a social interaction test [60], increase corticotrophin releasing-factor-induced defensive fighting [135], and increase stress-induced stomach ulcers [61].

The alterations in interictal emotional behavior produced by short-term amygdala kindling appear to be specifically related to changes in fear or anxiety-like behavior. They do not depend on a general increase or decrease in motoric activity [6,60]. Furthermore, no differences have been found between short-term amygdala-kindled rats and control rats on tests of depression, such as the sucrose-preference or the forced swimming tests [60], or on tests of spatial memory, such as the Morris water maze [97] or radial arm maze [84]. Note that amygdala kindling can result in transient acquisition deficits in the Morris water maze, but only in animals that have received extended kindling stimulations (i.e. 300 stimulations) [25].

Taken together, the studies of partial and short-term kindling in cats and rats have provided important data regarding the effects of repeated seizures on emotional behavior. The advantage of studies of partial kindling is that they assess behavioral changes at a stage in kindling before afterdischarges have become generalized. However, because the animals in these studies are only partially kindled, their findings may not directly relate to temporal lobe epilepsy. In addition, although the results of studies of short-term amygdala kindling have documented a wide range of changes in emotional behavior, they have not been consistent with respect to the precise nature of the emotional changes produced by kindling. For example, the effects of short-term kindling in rats have been inconsistent

with respect to behavior on the elevated plus maze—left basolateral-amygdala kindling has been associated with both anxiolytic [6] and anxiogenic [97] effects. Accordingly, the development of a new kindling model employing animals that relate more closely to the chronic epileptic state is an important step for confirming and extending the findings from studies of partial and short-term kindling.

6. Long-term amygdala kindling as a model for studying interictal emotionality

My colleagues (i.e. John Pinel and Dallas Treit) and I have developed an animal model of interictal emotionality using long-term (i.e. 100 stimulations) amygdala kindling in rats (see Refs. [77,102]). We chose to study long-term, as opposed to short-term, kindled rats because kindling is a progressive disorder that is far from complete once a few consecutive generalized convulsions have been elicited. This suggested to us that long-term kindling might produce some changes in interictal emotional behavior that are not apparent after partial kindling and some changes that are larger and more reliable than those that are apparent after short-term kindling. We selected 100 stimulations as our standard treatment for two main reasons. First, we wanted to study animals that were as close to the "epileptic state" as possible. Our experience with long-term kindling suggested that 100 stimulations would be enough to guarantee that all subjects were well kindled, but not so well kindled that they would be displaying spontaneous seizures, which would confound the behavioral testing. Second, Pinel and Treit had success in one previous experiment investigating the effect of 99 kindling stimulations on emotional behavior in rats. In their experiment, rats that received 99 stimulations of the amygdala, hippocampus, or caudate nucleus were compared for their defensive reaction to a pencil tap on the back and their resistance to being captured. The amygdala- and hippocampal-kindled rats displayed a substantial defensive response to tail tap and a greater resistance to capture than did the caudate-kindled rats [104]. Thus, we had reason to believe that 100 stimulations would produce significant changes in emotional behavior.

We have conducted a series of studies on the effect of long-term kindling on emotional behavior. Each of these studies is dealt with separately in the following Sections.

6.1. Effect of 100 stimulations on emotional behavior

Our first experiment was a replication of Pinel et al.'s [104] original finding (see Ref. [77] for a complete description of our experimental methods). We tested the effect of 100 amygdala kindling stimulations on the rats' resistance to capture from an unfamiliar open field. Rats had a bipolar stimulating electrode implanted into the left basolateral amygdala. After a post surgical recovery period of about seven days, some of the rats received convulsive stimulations (1 s, 60 Hz, 400 μA) three times per day, five days per week and some received sham stimulations. A sham stimulation consisted of attaching the stimulation lead to a rat's electrode but not passing any current through it. The resistance to capture testing was conducted in the following manner. One day after the final stimulation, each rat was placed by itself into an unfamiliar open field for 5 min. After the 5 min, each rat was forcefully picked up from above by an experimenter who was wearing a large leather glove. The rat's resistance to being picked up was scored according to the following 7-point scale: 0 = does not resist being picked up, 1 = vocalizes or shies away from hand, 2 = shies away from hand and vocalizes, 3 = runs away from hand, 4 = runs away and vocalizes, 5 = bites or attempts to bite and 6 = launches a jump attack at the experimenter's hand. The kindled rats were substantially more resistant to capture than the sham-stimulated rats [77]. In fact, the effect was so large that there was virtually no overlap in the scores of the kindled and the scores of the sham-stimulated rats.

6.2. Effect of different numbers of stimulations

Next, we compared the emotional behavior of kindled rats that had received different numbers of stimulations. We also added open-field exploration and elevated-plus-maze exploration to the battery of tests used to assess emotional behavior in the rats. Rats received 20, 60, or 100 left basolateral amygdala or sham stimulations and were tested for their emotional behavior a couple of days after the final stimulation. We found that rats that received 20 amygdala stimulations displayed significant increases in thigmotaxia in an unfamiliar open field, but no other changes in emotional behavior; rats that received 60 amygdala stimulations displayed significant decreases in open-field activity, increases in resistance to capture, and increases in open-arm activity on an elevated plus maze; and rats that received 100 amygdala stimulations displayed all of these changes plus significant increases in attempts to escape from the elevated plus maze by jumping off the open arms [77]. These results demonstrated that the number and magnitude of changes in emotional behavior after amygdala kindling are directly proportional to the number of stimulations the rats receive.

6.3. Fundamental nature of kindling-induced emotionality

Are the changes in emotional behavior observed in kindled rats defensive or aggressive in nature? (see Ref. [75]). This distinction has great clinical and theoretical significance. There has long been a belief that temporal lobe epileptics are prone to outbursts of aggression, despite the fact that little empirical evidence exists to support this claim [47]. Alternatively, it has been suggested that the emotional outbursts are fundamentally defensive in nature [53]. If interictal emotionality is fundamentally defensive, it is important that corroborative evidence be gathered so that it can serve as a basis for reducing the psychosocial problems associated with labeling epileptic patients as

aggressive. Such evidence is also critical for guiding the research on the neural mechanisms underlying interictal emotionality: There are important differences between aggressive and defensive behaviors—each serves a different function, has a different topography, occurs in different situations, and is mediated by different neural circuits, (e.g. Refs. [8,17]).

As in our previous experiments, rats first received 100 amygdala or sham stimulations. A couple of days after the final stimulation, the rats were tested in a resident-intruder paradigm. This paradigm was utilized because sequences of aggressive and defensive behaviors that commonly occur in the interaction between the resident and intruder rat are readily discriminable, (e.g. Refs. [18,19]). During the 10-min test, each kindled and sham-stimulated rat was tested as an intruder; the residents were naive weight- and age-matched rats. The kindled rats displayed more active defensive behaviors such as defensive upright postures and defensive attacks and fewer aggressive behaviors such as lateral displays and biting than did the sham-stimulated rats. The next day, the rats were tested for their resistance to capture from both their home cages and an unfamiliar open field. The amygdala-kindled rats displayed extreme levels of resistance to capture from an unfamiliar open field, but virtually no resistance to capture from their home cages or from an open field that was familiar to them [75]. The sham-stimulated rats were not resistant to capture in any of the testing conditions. Unfamiliarity decreases aggression and increases defense [17]. Thus, the results of this experiment suggest that kindling-induced emotional behavior is primarily defensive in nature.

6.4. Persistence of kindling-induced emotionality

We have also addressed the critical question of how long the emotional behavior persists once the kindling stimulations cease. Knowledge of the longevity of the emotional behavior is important for forming hypotheses about the type of neural mechanism that is mediating it: If the emotionality rapidly declines once the seizures are curtailed, it suggests that the emotionality may be an after-effect of the seizures per se; alternatively, if the emotionality persists, it suggests that the emotionality may be a manifestation of the epileptic state. We tested rats for their resistance to capture from an unfamiliar open field either 1 day, 1 week, 1 month, or 2 months after the last of 100 amygdala or sham stimulations. The kindled rats tested 1 day after the final stimulation were substantially more resistant to capture than the sham-stimulated rats. Although this effect dissipated somewhat over time, the rats tested 2 months after the final stimulation were still significantly more resistant to capture than the sham-stimulated rats [76]. In addition, although the resistance to capture declined monotonically in the first month after the final stimulation, there was no difference in the resistance to capture of kindled rats tested one month and two months after the final stimulation. This is an important finding because it demonstrates that the effects of kindling on fearful behavior are long lasting, if not permanent. This suggests that interictal emotionality occurs as a result of long-lasting neural changes accompanying the epileptic state.

6.5. Effect of kindling different brain sites

Finally, we investigated whether the effects of kindling on emotional behavior are specific to amygdala kindling. Rats received 100 kindling or sham stimulations of the basolateral amygdala, ventral hippocampus, or caudate nucleus. We found that both long-term amygdala kindling and long-term hippocampal kindling produced significant increases in emotional behavior, but long-term caudate kindling did not [74]. In addition, the increases in emotional behavior were greater after amygdala kindling than after hippocampal kindling. The results of this experiment are significant for two reasons. First, they suggest that the effect of kindling on emotional behavior may be limited to kindling of limbic structures. Second, they show that the activation of neural circuits involving the amygdala and hippocampus are important for the expression of kindling-induced emotional behavior.

6.6. Summary of long-term kindling

Taken together, the results of our initial experiments suggest that long-term kindling is a powerful model for the study of the interictal fear and anxiety associated with temporal lobe epilepsy. Long-term kindling produces large and robust changes in emotional behavior: Kindled rats freeze in an unfamiliar open field, resist being captured from an unfamiliar open field, attempt escape from an unfamiliar elevated plus maze, and engage in active defensive behavior in a resident-intruder paradigm. These defensive reactions increase dramatically as the rats receive more stimulations and persist for at least two months following the final stimulation. They are also greater in amygdala- and hippocampal-kindled rats than in caudate-kindled rats. On the basis of these findings, we have begun to use the long-term kindling model to study the neural mechanisms that underlie the development and expression of interictal fear and anxiety.

7. Receptor regulation in long-term kindled rats

The precise neural mechanisms underlying kindling-induced interictal emotionality remain largely unknown. The emotionality does not appear to be directly related to interictal spiking [60], recent generalized seizure activity [2], or structural lesions within the hippocampus [58]. However, several hypotheses have been put forth based on the results of recent experiments: lasting hyperexcitability of amygdala neurons [2,34]; activation of a defense pathway between the amygdala and the periaqueductal gray

Table 2
Receptor changes in long-term amygdala-kindled rats(5-HT, serotonin; BZ, benzodiazepine; and GR, glucocorticoid receptor; ↑, indicates regions in which kindled rats were significantly higher than sham-stimulated rats; ↓, indicates regions in which kindled rats were significantly lower than sham-stimulated rats; –, indicates regions in which there were no significant differences between kindled and sham-stimulated rats)

Receptor	Dentate Gyrus	CA1	Amygdala	Cortex
Serotonergic				
5-HT_{1A} receptor	↑	–	–	–
5-HT_{1A} mRNA	↑	–	–	–
5-HT_2 receptor	–	–	–	↑
5-HT Transporter	–	–	–	–
GABAergic				
$GABA_A$ receptor	↑	–	–	–
BZ receptor	↑	–	↓	–
Glutamatergic				
AMPA receptor	↓	–	–	–
NMDA receptor	↓	↓	–	↓
Glucocorticoid				
GR mRNA	↓	↓	–	—

[4,34,60]; functional modification of the benzodiazepine binding site on the $GABA_A$ receptor complex [3]; overproduction of the neuropeptide corticotropin releasing-hormone [135]; and withdrawal from the effects of opioid peptides that are released during seizure activity [44]. These hypotheses were well presented in a recent review by Depaulis et al. [34]; therefore, they will not be discussed in detail in this paper.

Using the observations from our behavioral studies of long-term kindled rats as a guide, we have recently begun to use receptor autoradiography and in situ hybridization to identify changes in receptor binding and mRNA expression that may underlie the development of kindling-induced emotionality. A summary of our initial findings is presented in Table 2.

We first focused on potential changes in serotonin (5-HT) receptor subtypes. There is a large literature implicating serotonin in the mediation of emotional behavior [40,56]. Serotonergic neurotransmission is complex: It consists of a system of pre and postsynaptic events involving at least 14 receptor subtypes [10]. Of the 5-HT receptor subtypes, 5-HT_{1A} and 5-HT_{2A} receptors have been most commonly linked to emotional behavior [33,94]. Two previous studies had found that short-term kindling increases 5-HT_{1A} receptor binding selectively in the dentate gyrus [24,30]. Neither of these experiments assessed emotional behavior in the kindled rats. We have extended these findings by showing that the increased 5-HT_{1A} receptor binding in the dentate gyrus may be related to the development of kindling-induced emotionality [71,72]. In this experiment, rats received 20, 60, or 100 amygdala or sham stimulations. One day after the final stimulation, they were tested for their resistance to capture from an unfamiliar open field. Two days after the behavioral testing, the animals were sacrificed and changes in 5-HT transporter binding, 5-HT_{1A} and 5-HT_{2A} receptor binding, and 5-HT_{1A} mRNA expression in several brain regions were quantified. As we have observed previously, the resistance to capture of the kindled rats increased dramatically as they received more stimulations. There were no significant differences between kindled and sham-stimulated rats in binding to the 5-HT transporter in any of the brain regions quantified. However, 5-HT_2 receptor binding in the parietal cortex increased significantly as the rats received more kindling stimulations. In addition, 5-HT_{1A} receptor binding and mRNA expression in the granule cell layer of the dentate gyrus increased dramatically with greater numbers of stimulations (i.e. the 100 amygdala stimulation rats had 100% more binding than did the sham-stimulated rats). No significant changes in 5-HT_{1A} receptors were observed in the amygdala, CA1, CA3, pyriform cortex, entorhinal cortex, or dorsal/median raphe.

The results of this experiment are notable for several reasons. First, the lack of changes to 5-HT transporter binding suggests that the level of extracellular 5-HT was not altered by kindling. This is consistent with Kokaia et al [79], who reported that short-term kindling had no effect on extracellular 5-HT concentrations within the hippocampus. Second, the increases in 5-HT_{1A} receptor binding and mRNA in the kindled rats were significantly correlated to resistance to capture (Spearman $r = 0.57$ for receptor binding and $r = 0.53$ for mRNA). In fact, there is a remarkable degree of similarity between the development and expression of emotional behavior in kindled rats and the changes in 5-HT_{1A} receptors in the dentate gyrus. Both increase with almost an identical slope with increasing numbers of stimulations. In addition, both dissipate somewhat during the month following the final stimulation, but they still remain above control levels [24]. Taken together, these results suggest that increased 5-HT_{1A} receptor binding and mRNA expression in the dentate gyrus may be associated with increased emotional behavior in long-term kindled rats.

There are several pieces of evidence that support this conclusion. For example, there is evidence that the dentate gyrus is important for the expression of contextual fear [55,88]. This is important because the context of the situation is critical for the expression of fear in kindled rats—they only display high levels of fear when exposed to unfamiliar situations [75]. There is also evidence that infusion of 5-HT_{1A} agonists into the dentate gyrus, but not the raphe nuclei, produces anxiogenic effects in the elevated plus maze [48]. Finally, there is evidence that animals with similar behavioral characteristics to those of long-term kindled rats also display dramatic increases in 5-HT_{1A} receptors in the dentate gyrus. Korte et al. [80] recently showed that wild house mice that prefer active defensive responses in a resident intruder paradigm have increased 5-HT_{1A} receptor binding and mRNA expression in the dentate gyrus, but not the dorsal or median raphe nuclei. Korte et al. [80] suggest that high levels of 5-HT_{1A} receptors in the dentate gyrus produce active coping responses (i.e. active avoidance,

Table 3
Comparison of interictal affective symptoms observed in human temporal lobe epilepsy and in various stages of kindling (TL.E., temporal lobe epilepsy; P.K., partial kindling; ST.K., short-term kindling, LT.K., long-term kindling; ?, indicates symptoms that have not yet been studied in kindled rats)

Symptom	Human TLE	PK	STK	LTK
Depression	Yes	?	No	?
Pain	Yes	?	?	?
Insomnia or Sleep Disturbance	Yes	?	Yes	?
Fear	Yes	Yes	Yes	Yes
Anxiety	Yes	Yes	Yes	Yes
Aggression	Rare	No	No	No
Mania	Rare	?	?	?
Euphoria	Yes	?	Maybe (reward)	?

defensive burying, escape, defensive attacks) in animals whereas low levels of 5-HT_{1A} receptors produce passive coping responses (i.e. freezing, withdrawal, helplessness) in animals. This hypothesis is consistent with reports that chronic stress paradigms, which produce passive coping responses in rats and mice, are associated with low levels of 5-HT_{1A} receptors in the dentate gyrus [16,129].

The changes in 5-HT_{1A} receptors in the dentate gyrus that we have observed are a promising starting point for developing more comprehensive hypotheses that will encompass the whole range of neural changes that are certainly involved in producing the complex emotionality associated with temporal lobe epilepsy. On a broader scale, the pattern of receptor changes (see Table 3) that we have observed in long-term kindled rats suggests that an imbalance of inhibitory and excitatory receptors may be important. For example, we have found that benzodiazepine (BZ) receptor binding is significantly increased in the dentate gyrus of long-term kindled rats—an effect that is also significantly correlated to increases in resistance to capture [73]. In contrast, we have found that NMDA and AMPA receptor binding is significantly decreased in the dentate gyrus of long-term kindled rats [89,90]. Although we do not yet know if these latter effects are correlated to the increased emotional behavior, the pattern that is emerging here is that increases in inhibitory receptors and decreases in excitatory receptors in the dentate gyrus are associated with the expression of interictal emotionality. The consequence of this imbalance for neural activity is unknown, but one possibility is that it results in an increase in inhibition. This idea is supported by the finding that increased defensive behavior after partial kindling in cats is associated with increased recurrent inhibition in the ventral hippocampus [7]. Furthermore, it is consistent with an increasing popular hypothesis from the clinical literature that interictal emotionality arises as a by-product of the inhibitory processes that build up to protect against the future occurrence of seizures [20,45]. Indeed, interictal emotionality often becomes worse in patients whose seizures have been well-controlled with antiepileptic medication [114]. This observation is paralleled in animal studies: Administration of anticonvulsant drugs exacerbates the interictal defensiveness observed in spontaneously epileptic cats [57], whereas administration of a BZ receptor antagonist (i.e. flumazenil) decreases the interictal defensiveness observed in partially kindled cats [3].

Another interesting avenue of investigation that has received very little attention is the involvement of stress mechanisms in interictal emotionality. Stress activates the hypothalamic–pituitary–adrenal (HPA) axis, culminating in increased release of hypothalamic corticotropin releasing-hormone (CRH), pituitary adrenocorticotropic hormone (ACTH), and adrenal corticosteroids (CORT). There is indirect evidence linking HPA axis activation with temporal lobe epilepsy. For example, limbic seizures dramatically elevate circulating CORT in both humans and laboratory animals [122,105]. These CORT levels may reverse to lower than basal levels in between seizures [5]. Interestingly, CORT has a strong influence over the expression of 5-HT_{1A}, $GABA_A$ and NMDA receptors in the hippocampus—receptors which all appear to be changed in long-term kindled rats [131,98,28]. In addition, kindling produces substantial changes in CORT and CRH receptors in hippocampal regions. For example, we have preliminary evidence that glucocorticoid (GR) receptor mRNA is decreased in the dentate gyrus and CA1 region of long-term kindled rats [69]. This has previously been reported in short-term kindled rats [29]. There is also evidence that short-term kindling increases CRH mRNA specifically in the dentate gyrus [117]. This is particularly interesting given that CRH is an important regulator of anxiety-like behavior [59]. Thus, an important topic for future research is investigating whether CORT and CRH have any direct role in mediating the interictal emotionality observed in kindled animals.

8. Relevance of long-term kindling to human temporal lobe epilepsy

The symptoms and etiology of the interictal emotional disturbances associated with temporal lobe epilepsy are diverse. For example, many temporal lobe epileptics experience fear as a prominent ictal and interictal symptom [52,62] and have significant atrophy of the amygdala [27]; however, many do not. In addition, many temporal lobe epileptics experience emotional disturbances almost continuously, but some experience them intermittently [35].

There are several factors that may account for the diversity of the interictal emotionality associated with temporal lobe epilepsy. First, each patient's environment is likely to have an important impact on the frequency of interictal emotionality: Patients who experience more psychosocial and interpersonal problems are more likely to experience interictal problems [123]. Second, the nature of interictal disturbances may depend on the cerebral hemisphere in which the epileptic focus is located [6,36]. Third, patients with temporal lobe epilepsy may also have structural lesions (i.e. hippocampal or amygdala sclerosis) that may alter their ability to process and attach affective tone to certain types of information [45]. And finally, in addition to the seizure disorder itself, patients may experience alterations in their emotional behavior as a result of pharmacological treatment. These alterations may arise from the common side effects of the medication or from some uncommon effects that potentiate the interictal behavioral disturbances [125].

Because of the diversity of interictal emotionality and the numerous factors that can affect its course, and because kindled rats appear to model only certain aspects of temporal lobe epilepsy and the interictal emotional disturbances experienced by temporal lobe epileptics, caution must be exercised in directly applying the results of studies of kindling to the human epileptic condition. Nevertheless, there are several points worthy of discussion. For example, the results from our studies of long-term kindled rats suggest that seizure number may account for some of the diversity in interictal emotionality. Indeed, seizure number is a major predictor of emotional problems in epileptics who experience generalized tonic–clonic convulsions [38]; personality disorders are found more frequently the earlier the seizures start and if the seizures are generalized [113,124]; behavioral alterations may be intensified in some patients during periods of increased seizure frequency [63]; and greater degrees of neuropsychological impairment are associated with the onset of seizures at an early age, a large total number of seizures, and a long history of seizures [37]. To our knowledge, the relationship between seizure number and the onset of interictal emotionality has not been systematically studied in a selective population of temporal lobe epileptics. However, in a study of 114 epileptic patients, most suffering from complex partial seizures, Adamec [2] found that the degree of interictal emotionality varied with the frequency and intensity of aura experiences. The emotionality was manifested as an increase in intensity as well as a lability of emotional responses. Because auras are thought to originate from focal epileptic limbic system discharges, Adamec's data suggest that greater numbers of limbic seizures precipitate greater changes in emotion. These findings confirm our conclusion that the number of seizures is a critical variable for the expression of interictal emotionality and suggest that long-term kindling may be a particularly useful way to model the fear and anxiety experienced by temporal lobe epileptics.

Our finding that long-term kindling of both the amygdala and the hippocampus produces high levels of emotionality in rats is consistent with findings from the clinical literature. Depth recording studies in human epileptics suggest that the anxiety and fear are associated with amygdala and hippocampal discharges [96]. In addition, patients who received a series of periodic amygdala or hippocampal stimulations eventually displayed extreme stimulus-bound emotional behaviors, such as fear or rage; these emotions occurred suddenly and without any relation to the motive state of the patient just prior to the stimulations [118]. And finally, the Kluver–Bucy syndrome, which results largely from damage to the amygdala in monkeys [134], is characterized by changes in emotional behavior that are opposite to those observed in temporal lobe epileptics. Thus, there is a convergence of evidence implicating both the amygdala and hippocampus in the generation of interictal emotionality in human epileptics, to which the results of from our studies of long-term kindled rats can be added.

Finally, our finding that kindling-induced emotionality is defensive rather than aggressive in nature has important practical implications. For decades, it has been assumed that epileptic patients were prone to outbursts of aggression, despite the paucity of relevant empirical evidence. Indeed, the few adequately designed studies that have attempted to document a relation between temporal lobe epilepsy and aggression have been largely unsuccessful; for example, Riley and Neidermayer [109] found that temporal lobe epileptics are not particularly predisposed to acts of violence, recurrent aggressive behavior, or outbursts of anger that were serious enough to warrant neuropsychiatric evaluation. Although the prevalence of aggression is somewhat higher in people with temporal lobe epilepsy than in the general population, it is not higher than that found in people suffering from other forms of epilepsy or other chronic illnesses [119]. Thus, the finding that the emotional outbursts are fundamentally defensive may help to change the common assumption that temporal lobe epileptics are particularly aggressive.

9. Conclusions and future directions

Temporal lobe epilepsy is clearly a problematic disorder. It is characterized by seizures that are complex and difficult to treat. It is also often accompanied by severe interictal emotional disturbances that can be more troublesome for patients than the seizures themselves. This paper has described the clinical literature on this topic, summarized the animal literature using the partial- and short-term kindling models, and introduced a new model using long-term kindling that has promise for identifying the specific nature and neural mechanisms underlying interictal emotionality. Our initial experiments using the long-term kindling model had three purposes: to establish the potential of long-term amygdala kindling as an animal model of the interictal emotionality associated with temporal lobe epilepsy, to

identify some of the major variables that influence the expression of interictal emotionality, and to characterize its fundamental nature. These purposes have been accomplished. First, we have established the potential of long-term kindling by demonstrating large, reliable, and systematic increases in emotional behavior that are similar in major respects to those reported in temporal lobe epileptics. Second, we have identified the number of seizures, the site of stimulation, the testing environment, and the time since the last seizure as factors influencing the expression of interictal emotionality—these variables may account for some of the diversity of interictal emotionality in human temporal lobe epileptics. And third, we have shown that the fundamental interictal emotional change is an increase in defensiveness rather than an increase in aggression.

How does long-term kindling compare to other models that can be used to study interictal emotionality? There are many animal models of temporal lobe epilepsy. None of these models is ideal, but many of them are appropriate depending on the specific question that is being studied. Our emphasis is in trying to investigate factors influencing the changes in emotional behavior that relate to the epileptic state. In theory, a model of spontaneously occurring seizures would be most appropriate for this work. However, in practice, this type of model is of limited use because the occurrence of spontaneous seizures complicates the behavioral testing. Moreover, these models afford little experimental control over important variables, such as when, where, and how many seizures the animals experience. Consequently, long-term kindling is a more appropriate model for our work. Long-term kindled animals experience a large number of elicited seizures, and the protocol provides for a high degree of experimental control. However, long-term kindling is not always the most appropriate model to use. Studies of partial and short-term kindling are also important, especially for studying brain changes concomitant with the onset of hyperexcitability, and how those changes may produce early manifestations of interictal emotionality. And, despite the fact that models of spontaneously occurring seizures have certain limitations, studies using these models are important to identify similarities and differences between behavioral changes produced by elicited vs. spontaneous seizures. The convergence of information from studies using all these models will lead to discoveries of substantial clinical and scientific relevance.

In conclusion, most investigators interested in the kindling model study it to learn about kindled seizures themselves or synaptic plasticity in general. As a result, studies of kindling-induced interictal emotional behavior are relatively small in number, and many questions remain to guide future research on this topic. Table 3 depicts a comparison between affective symptomatology in human temporal lobe epilepsy and the various stages of kindling. It is clear that kindling produces many changes in behavior that are similar to those observed in temporal lobe epileptics. However, there are many more symptoms that have not yet been studied using the kindling model. From our perspective, several questions are particularly pertinent for future study. First, does long-term kindling produce changes in behavior that model other aspects of interictal behavioral change, such as pain, depression, and sleep disturbances? Second, how do the receptor changes in the dentate gyrus that we have observed in long-term kindled rats influence the functionality of the amygdala and periaqueductal gray, two brain regions closely involved in the manifestation of defensive behavior? Do drugs acting at these receptor sites have promise as therapeutic treatments for interictal emotionality? Third, how are the neural mechanisms underlying interictal emotionality related to changes in the HPA axis and stress neuropeptides? We are presently using long-term kindling as a framework from which to study these questions.

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