

Embrasement = kindling

Définition

L'embrasement résulte de la stimulation répétée (électrique ou chimique) d'une structure cérébrale (le plus souvent amygdale ou hippocampe). On provoque ainsi des crises épileptiques électrocliniques d'abord partielles puis progressivement généralisées.

Modèle d'épilepsie partielle secondairement généralisée

Modèle d'épilepsie temporale

Pathologie synaptique

The kindling effect

“The phenomenon of kindling in epilepsy was first discovered by accident by researcher Graham Goddard in 1967. Goddard was studying the learning process in rats, and part of his studies included electrical stimulation of the rats' brains at a very low intensity, too low to cause any type of convulsing. What he found was that after a couple of weeks of this treatment, the rats did experience convulsions when the stimulation was applied.”

The kindling effect

Kindling

Using the analogy of a small fire being used to start a large one, a progressively increasing, neural response that leads to a profound change in behaviour.

Kindling Effect

The 'Kindling Effect' refers to how epileptic seizures are thought to occur. The idea of seizure kindling is that large scale seizures can be triggered by small but repeated stimulation events

Embrasement = kindling

Découverte du phénomène

G. Goddard

Nature (1967)

Experimental Neurology (1969)

The kindling effect

- A model of epileptogenesis
- A model of cerebral plasticity
- A model of learning and memory

The kindling effect

- Is it a universal phenomenon ?
- May we kindle all the brain structures ? If not which ones are susceptible to the KE?
- Phylogenesis of the KE?

Embracement = kindling

Etudes chez l'animal

Amphibien

Rat

Chat

Singe

Homme ?

Embrasement = kindling

Structures stimulées

Amygdale

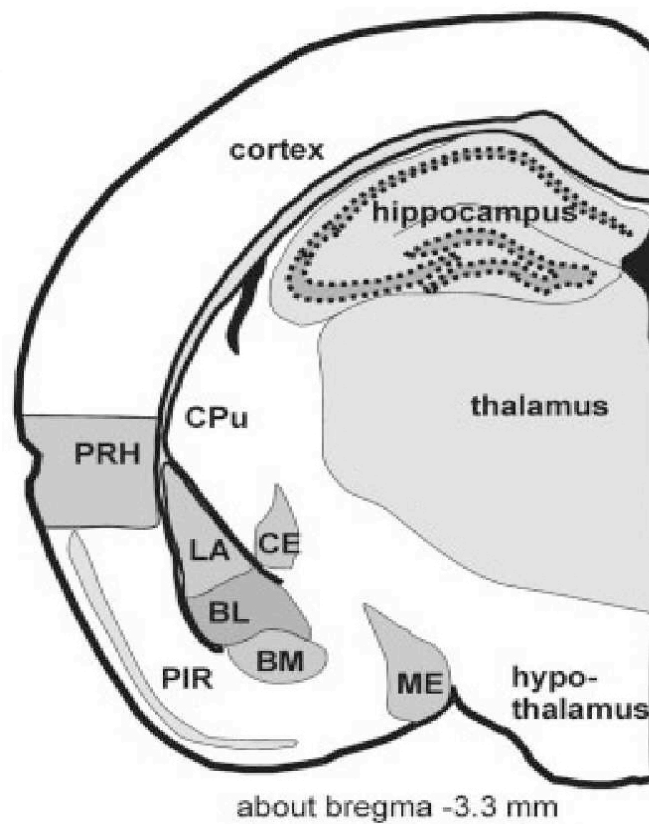
Hippocampe

Septum

Cortex

Implantation stéréotaxique d'une électrode de stimulation bipolaire dans ces structures

Embracement = kindling



Embrasement = kindling

Paramètres optimaux

Stimulation électrique ou chimique initialement subconvulsivante

Intervalle entre les stimulations

Embrasement = kindling

Effet de la stimulation

Induction d'une post-décharge dont la durée, la fréquence et l'amplitude des pointes dépendent de la structure stimulée

Induction concomitante d'une crise clinique dont la symptomatologie initiale est fonction de la structure stimulée

Embrasement = kindling

Codification de la réponse: Racine 1972

Mesure du seuil épileptogène (seuil de post-décharge):
l'intensité de stimulation dépend de la structure stimulée

Stades (correspondant au développement)
comportementaux (1 à 5)

Nombre de stimulations nécessaires pour passer d'un stade
à l'autre

Mesure de la durée des post-décharges

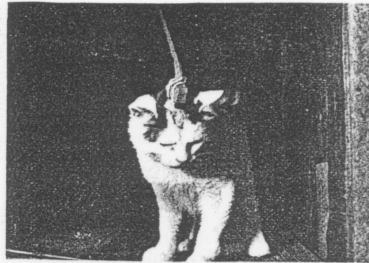
The kindling effect

Kindling stages (Racine 1972)

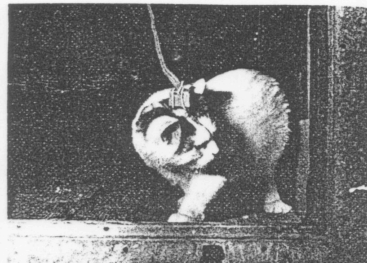
- 1 ear and facial twitching**
- 2 mouth and facial jerks**
- 3 myoclonic jerks of the forelimbs**
- 4 rearing**
- 5 falling (generalized tonic clonic seizures)**

1. Stage 0: no response
2. Stage 1: ear and facial twitching
3. Stage 2: convulsive waves through the body
4. Stage 3: myoclonic jerks, rearing
5. Stage 4: turn-over onto side position
6. Stage 5: turn-over onto back position, generalized tonic-clonic seizures.

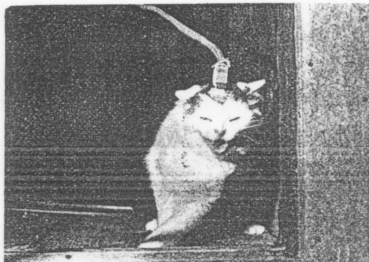
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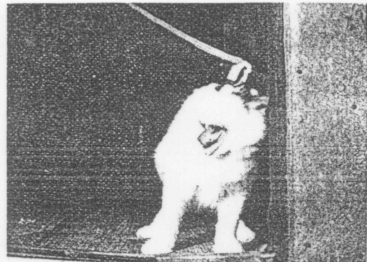
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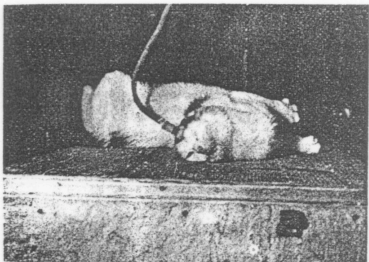
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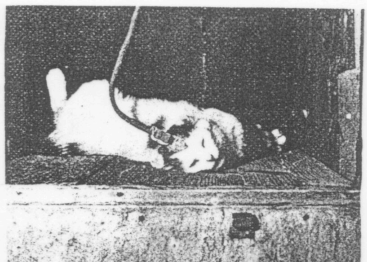
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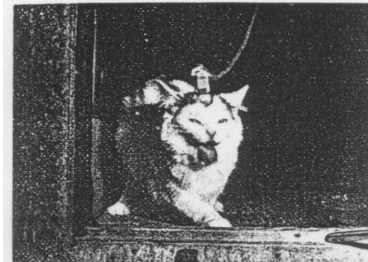
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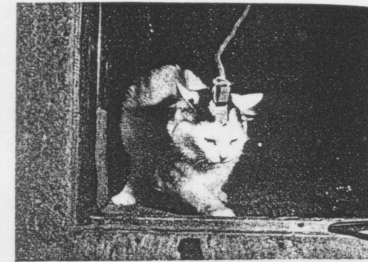
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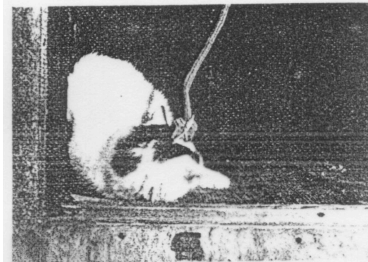
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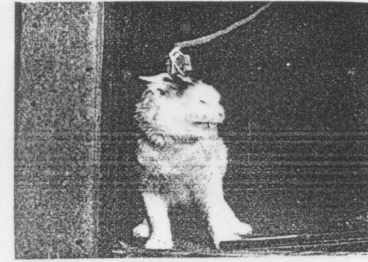
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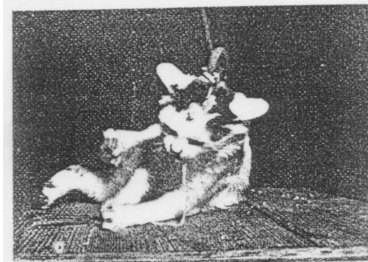
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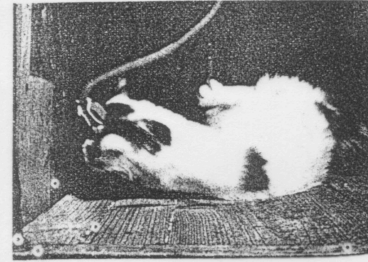
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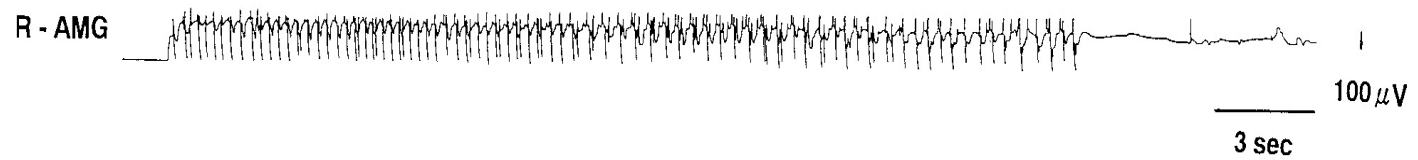
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Embracement = kindling

Post-décharge



The kindling effect

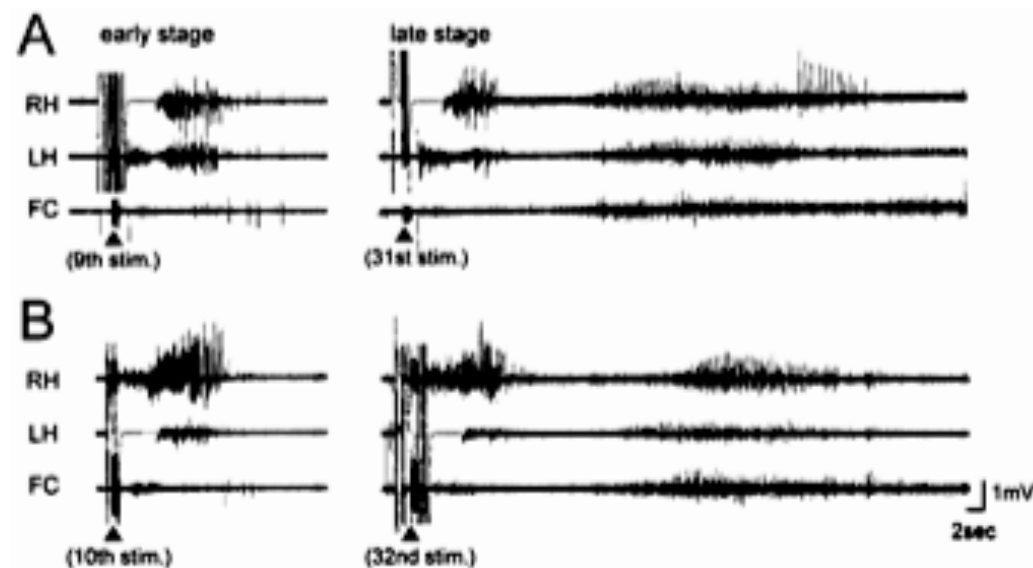
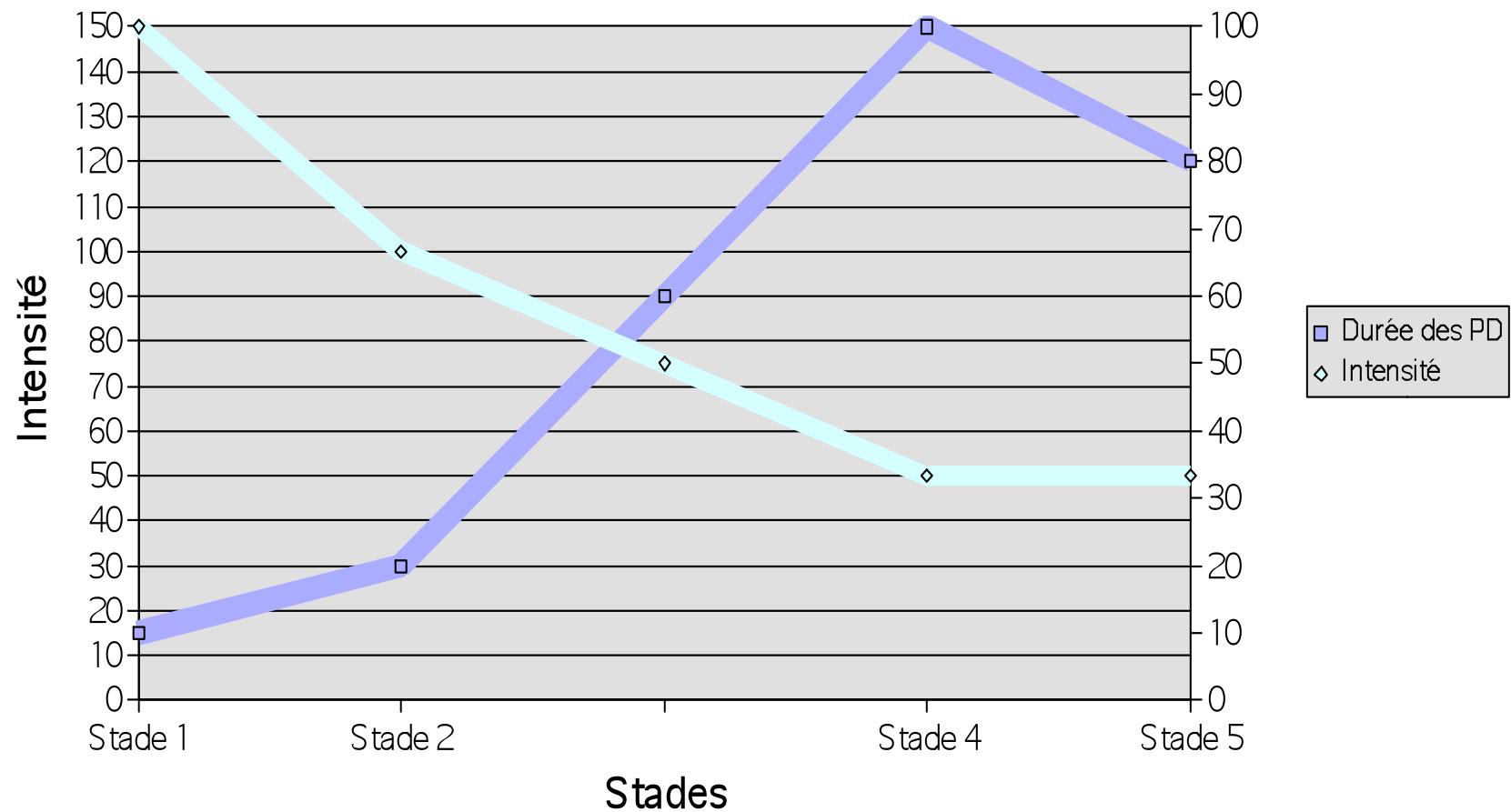


FIG. 4. Typical examples of after-discharge evoked by right (A) and left hippocampal stimulation (B) at early (ninth and 10th stimulation) and late stages (31st and 32nd stimulation). The abbreviations used are the same as in Fig. 1.

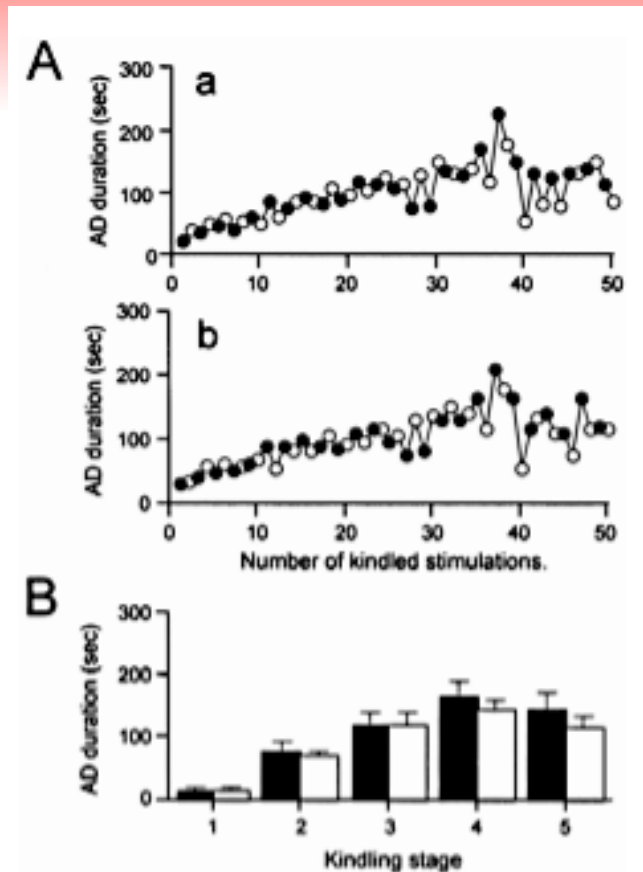
Progression of kindling through repeated hippocampal stimulations

Embrasement = kindling

Développement



The kindling effect



Progression of kindling through repeated hippocampal stimulations

Embrasement = kindling

Propagation des post-décharges

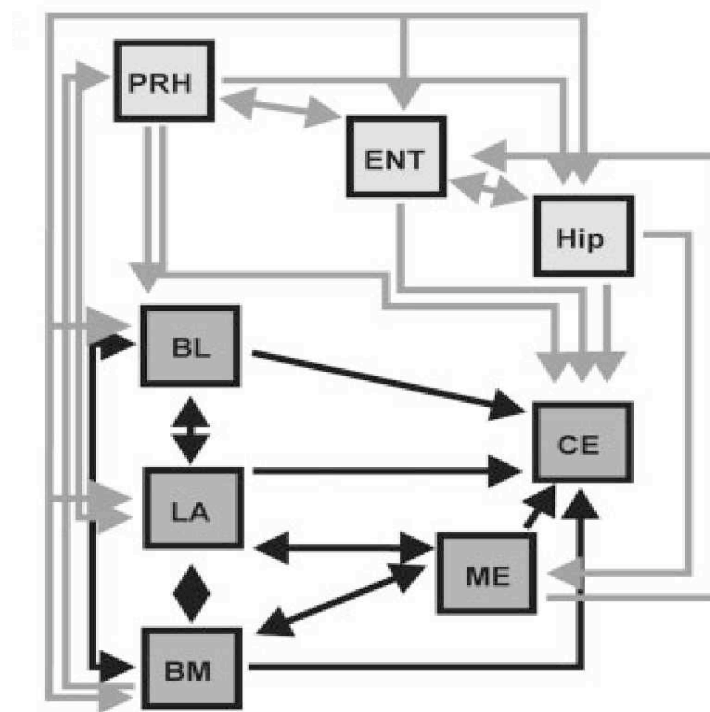
D 'abord localisées, les décharges se propagent à d'autres structures

amygdale -> hippocampe -> cortex

Strucuture stimulée vers la structure controlatérale
homologue

Apparition de décharges intercritiques

Embracement = kindling

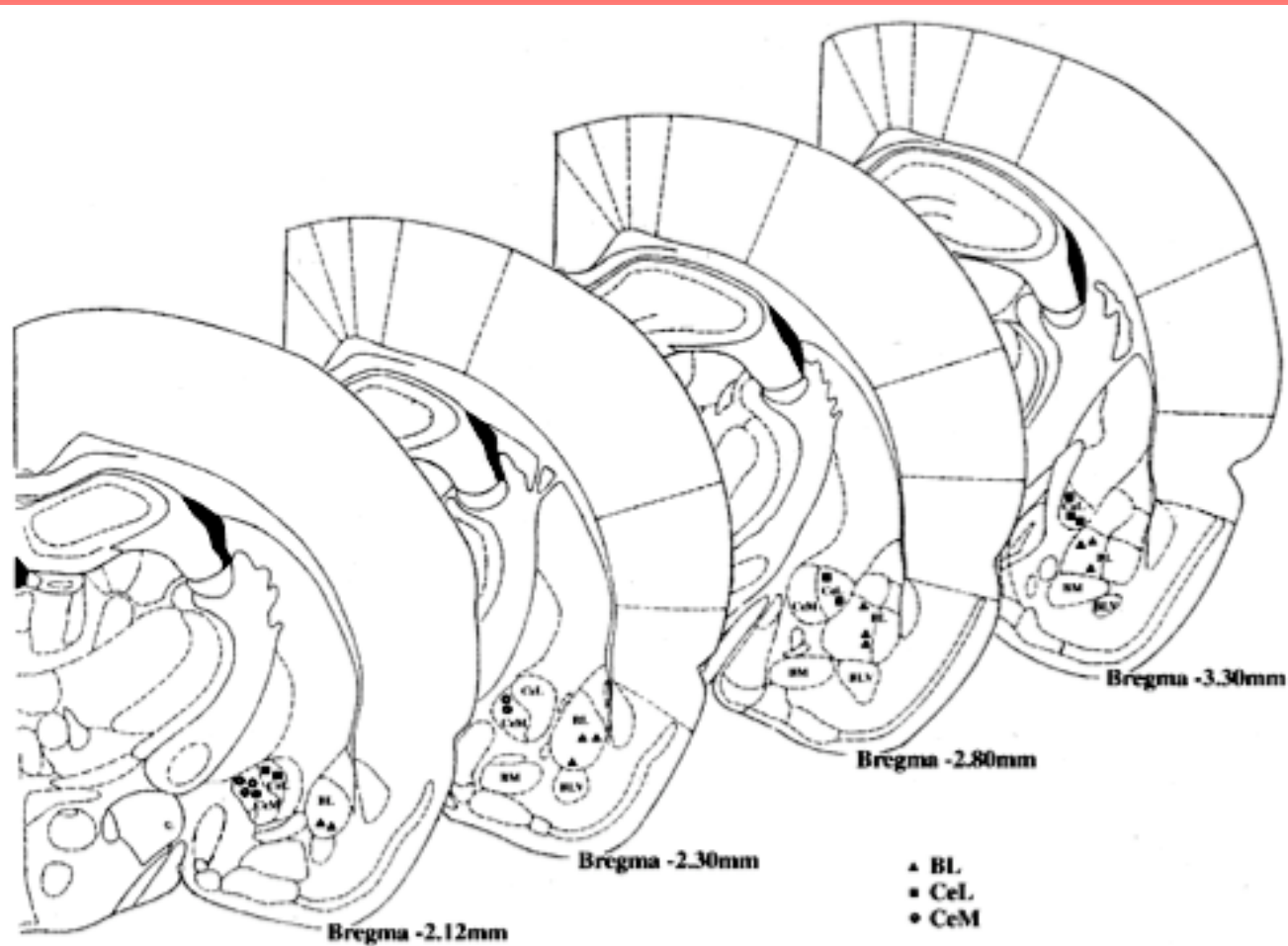


The kindling effect



Inter Ictal discharges in hippocampal kindled rats

The kindling effect



Kindling of the amygdala

Specific amygdaloid nuclei are involved in suppression or propagation of epileptiform activity during transition stage between oral automatisms and generalized clonic seizures

Martina Sitcoske O'Shea^{a,b,*}, Jeffrey B. Rosen^c, Robert M. Post^a, Susan R.B. Weiss^a

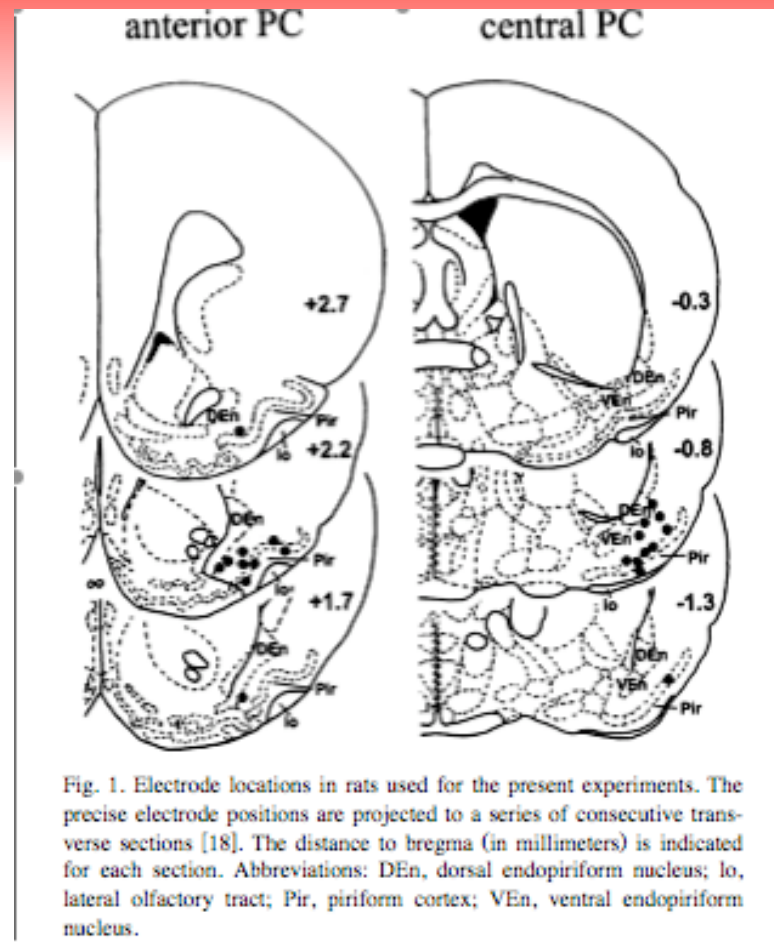
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The kindling effect



Development of kindling and spontaneous seizures after massed stimulation of different loci in the rat piriform cortex

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Accepted 16 November 1999

Kindling of the piriform cortex

Embrasement = kindling

Permanence du phénomène

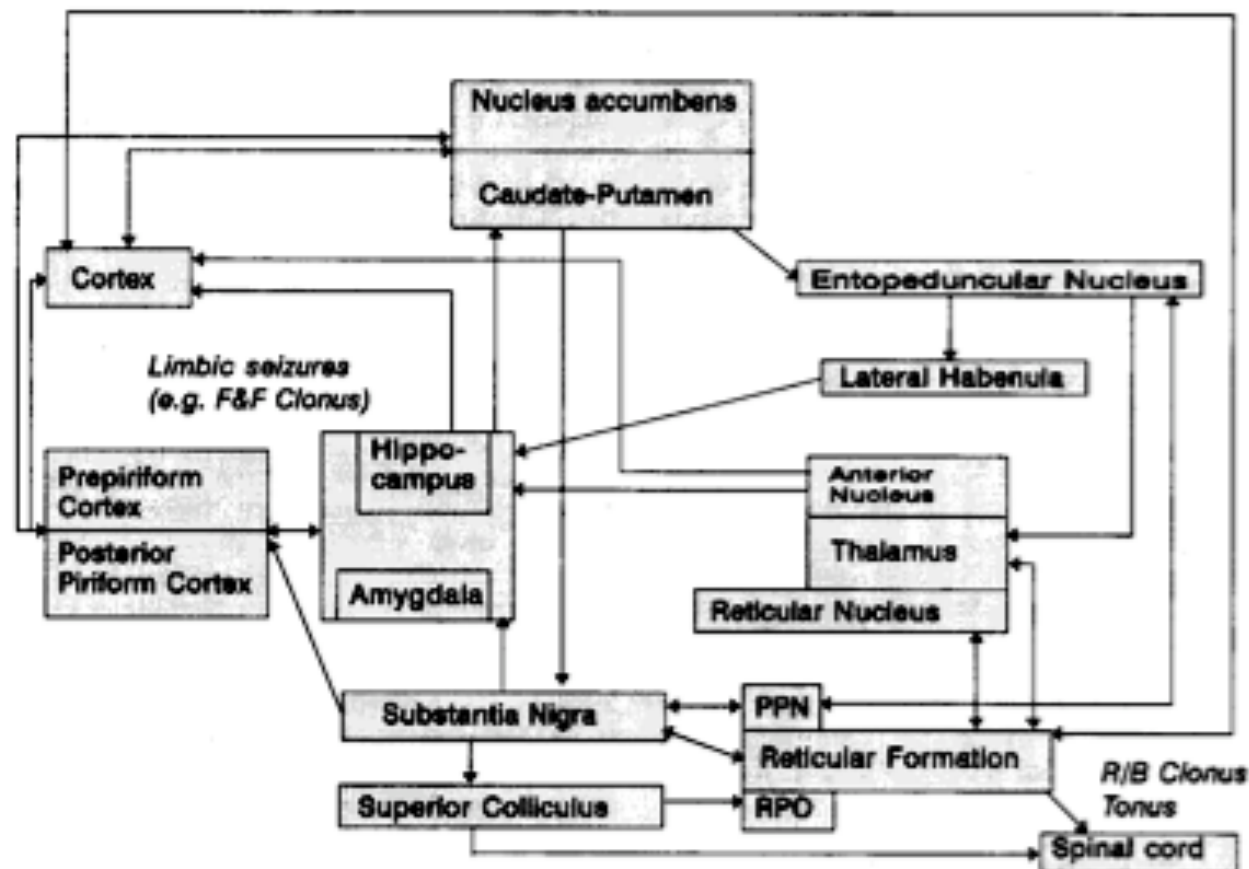
Une fois obtenu, l'embrasement se maintient

Toute nouvelle stimulation entraîne une crise partielle
secondairement généralisée récapitulant tous les stades

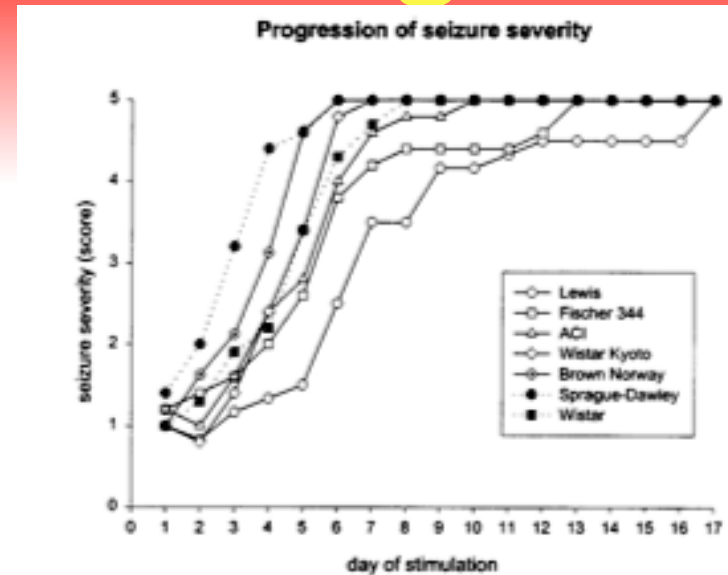
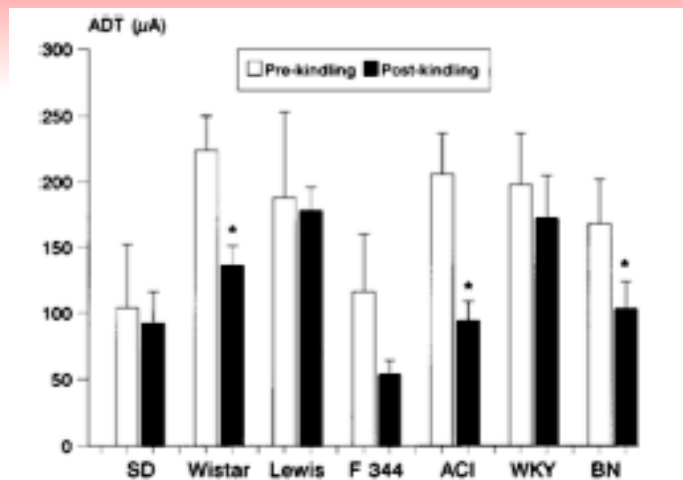
The kindling effect

- **Positive
transfert**
- **Negative
transfert**

The kindling effect



The kindling effect

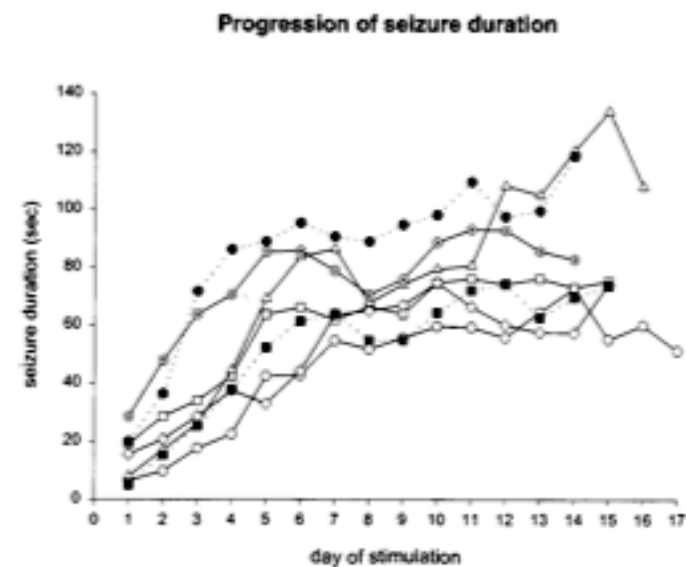


Differences in Kindling Development in Seven Outbred and Inbred Rat Strains

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Received February 23, 1998; accepted September 4, 1998



The kindling effect

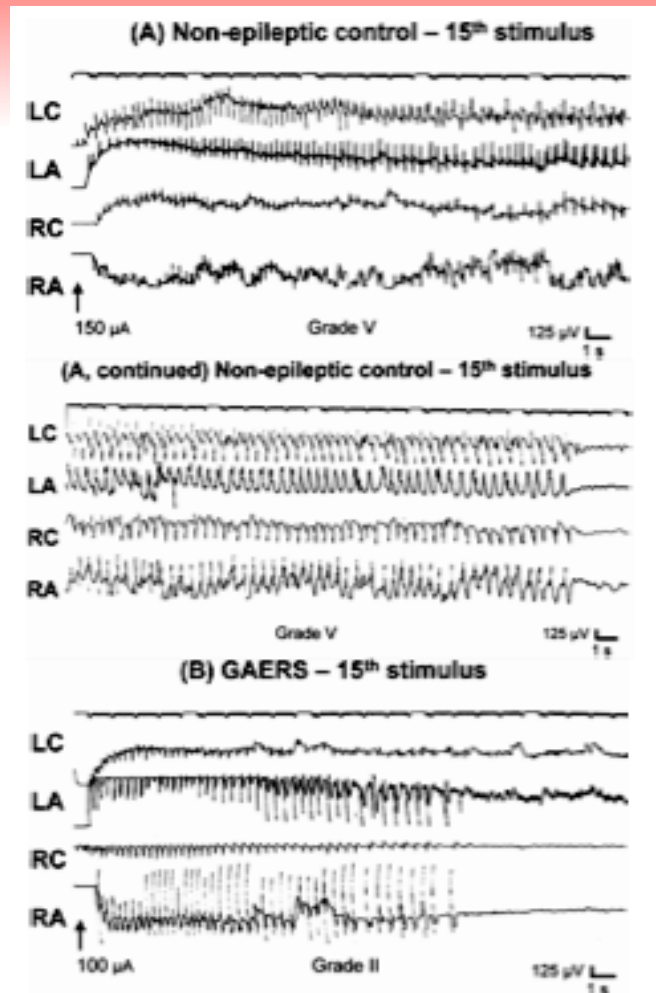


FIG. 3. EEG recordings of non-epileptic Wistar control rat (A) and genetic absence epileptic rats from Strasbourg (GAERS) (B). LC, left cortex; LA, left amygdala; RC, right cortex; RA, right amygdala.

Resistance to Propagation of Amygdaloid Kindling Seizures in Rats with Genetic Absence Epilepsy

*Esat Eşkazan, †Filiz Yılmaz Onat, †Rezzan Aker, and *Gülşay Öner

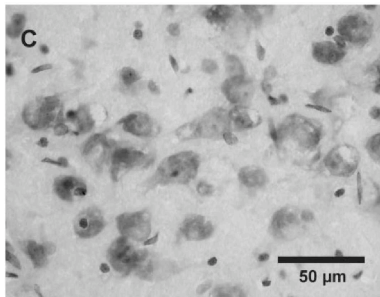
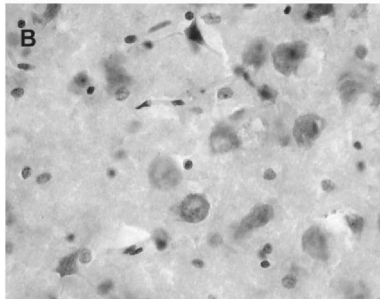
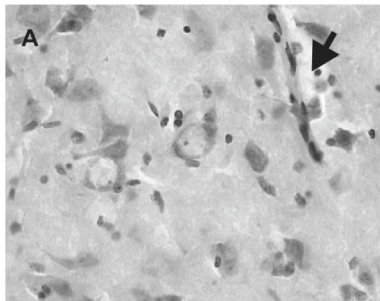
Departments of Pharmacology and Clinical Pharmacology, *Istanbul University, Cerrahpaşa Medical School, and †Marmara University School of Medicine, Istanbul, Turkey

The kindling effect

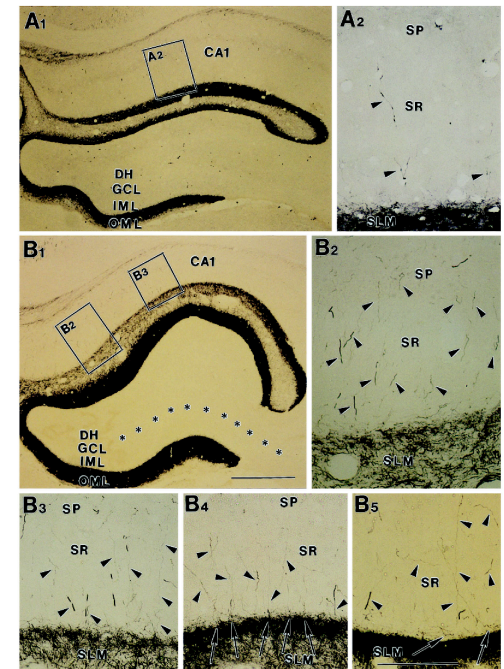


Embrasement = kindling

Lésions neuronales ?
Bourgeonnement ?



Ces phénomènes existent mais leurs expressions sont modérées

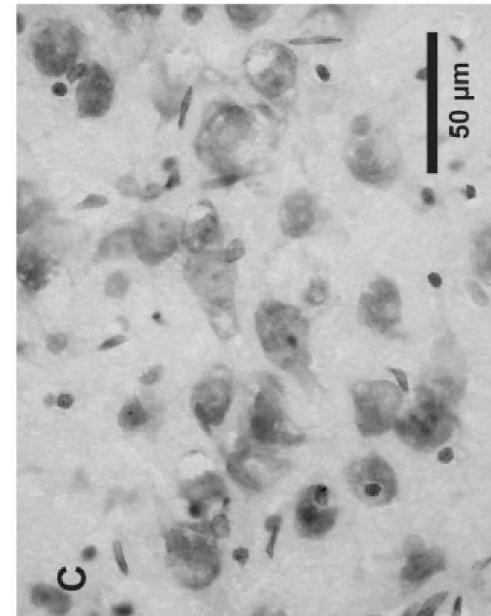
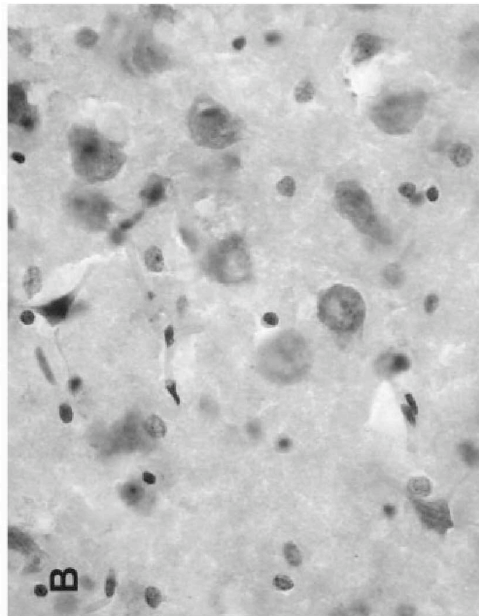
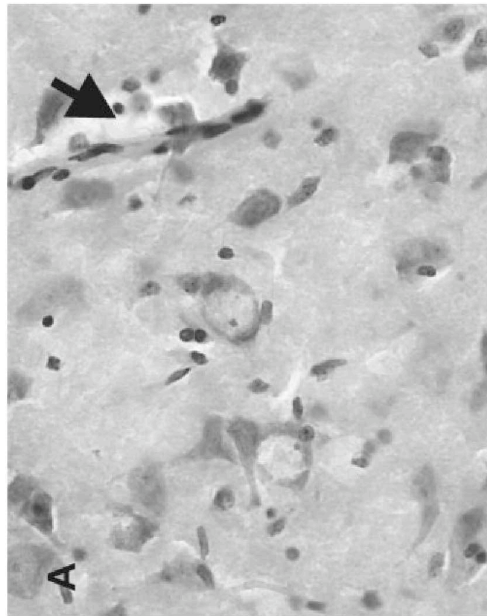


Embrasement = kindling

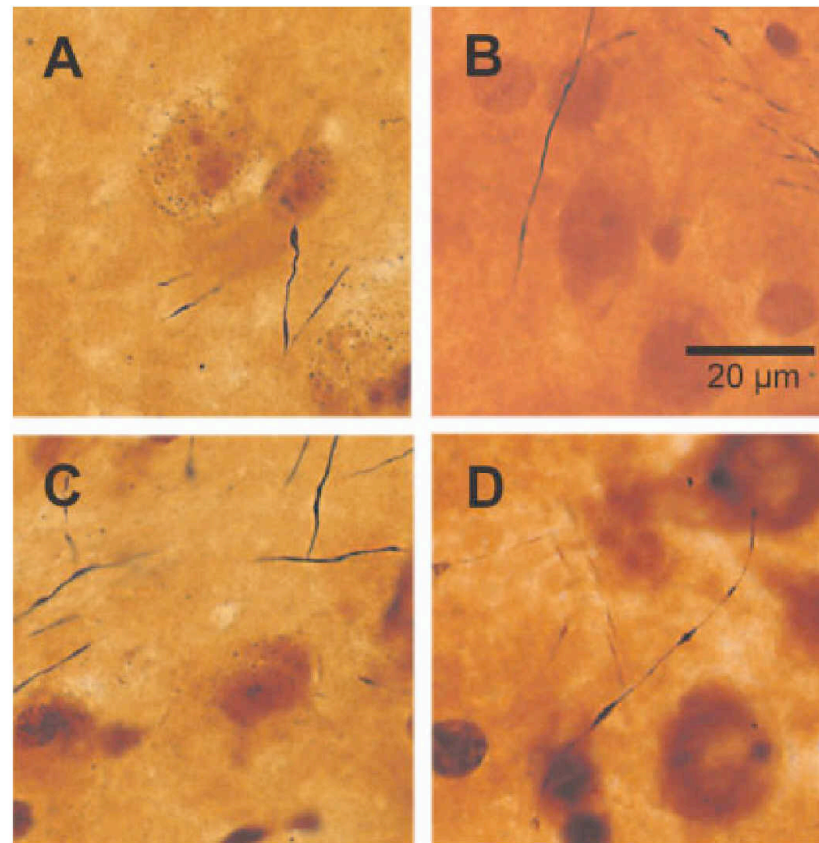
Lésions neuronales ?

**Le processus d'embrasement provoque
une « réduction » du nombre de neurones et
« une augmentation » de la densité des fragments axonaux lésés
non seulement dans la structure stimulée mais aussi dans
les structures connectées**

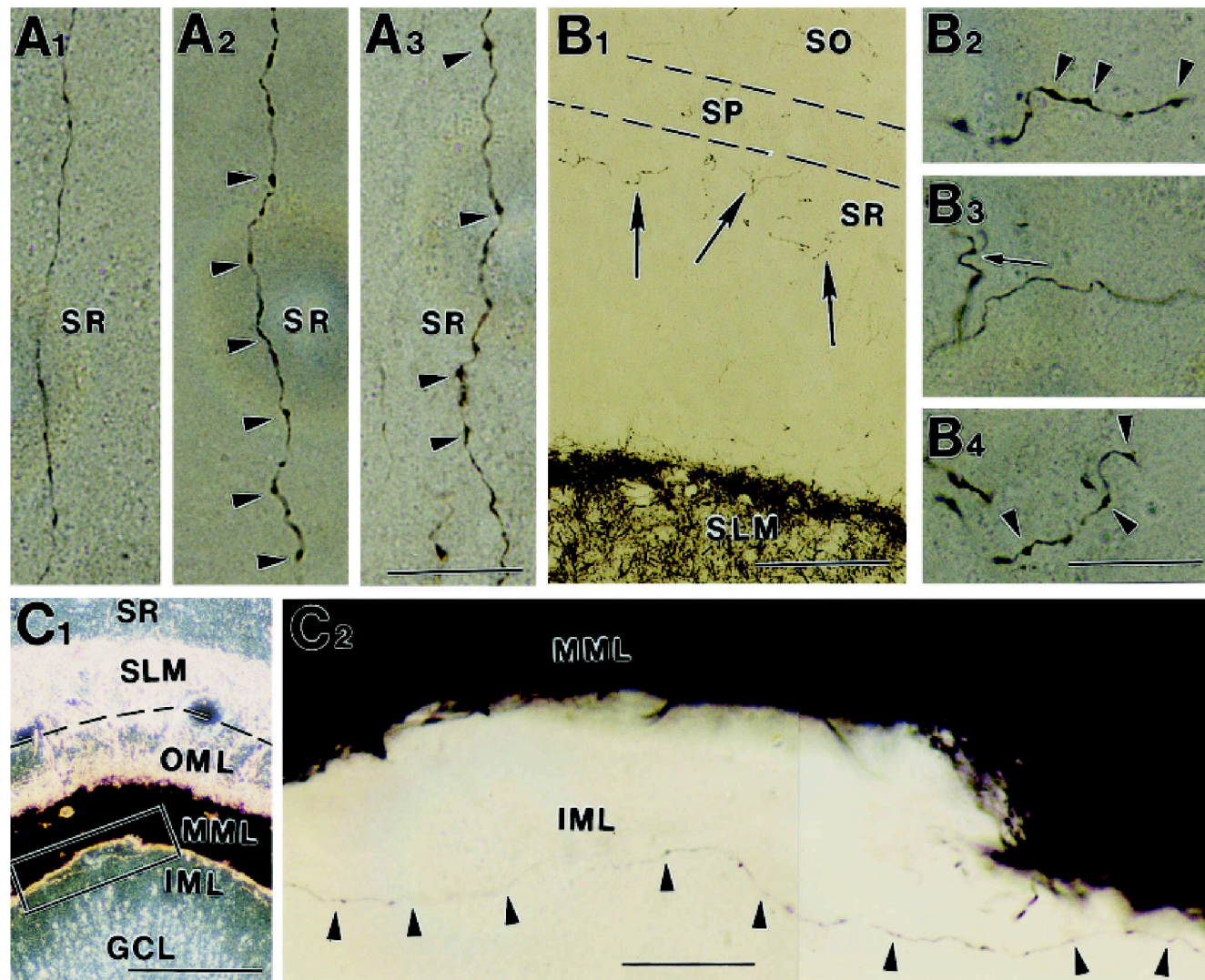
Embracement = kindling



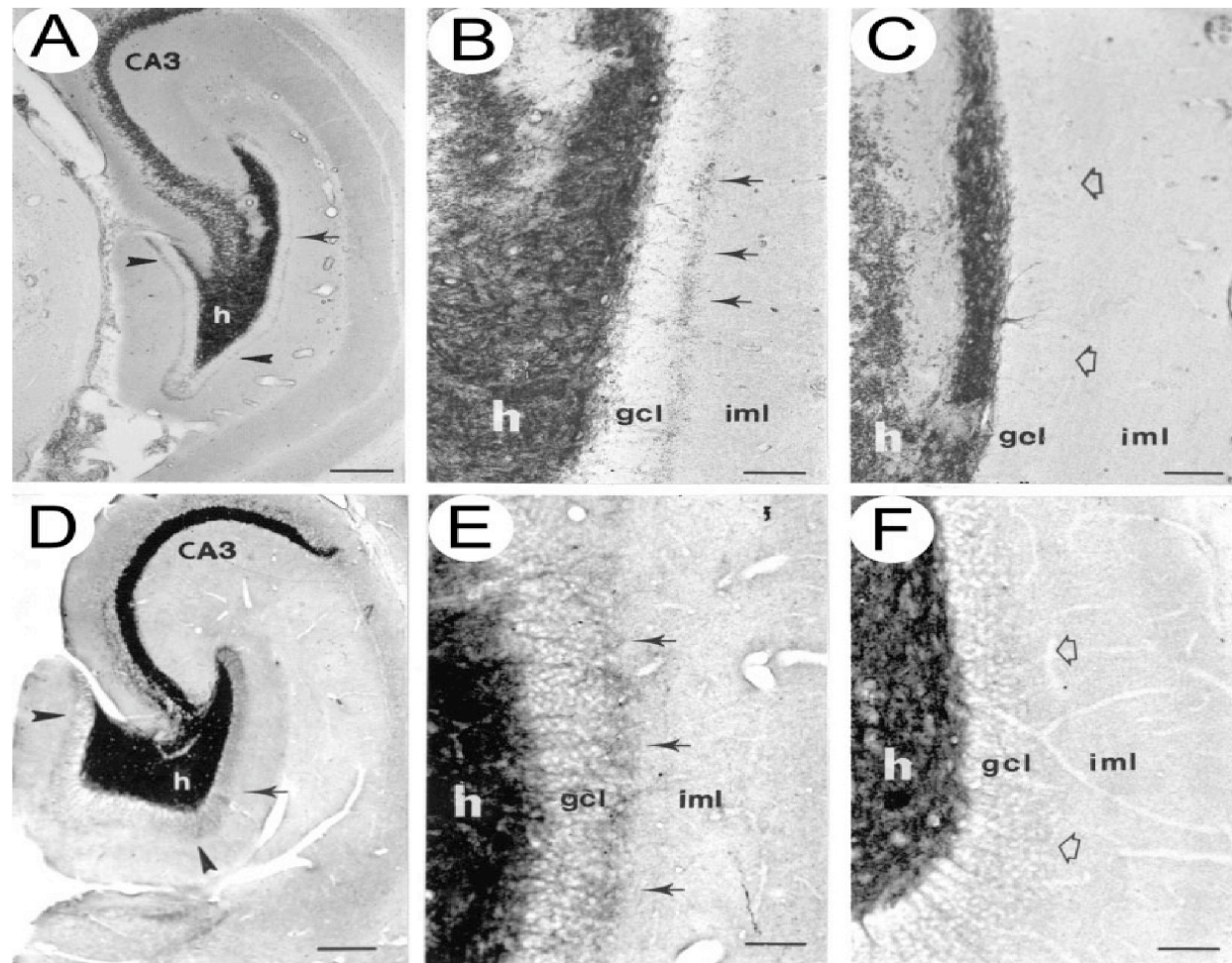
Embracement = kindling



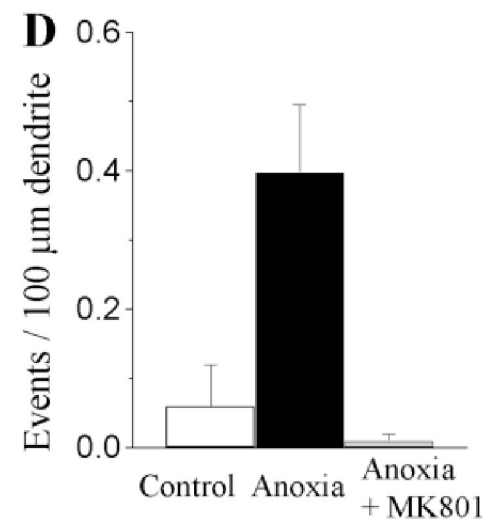
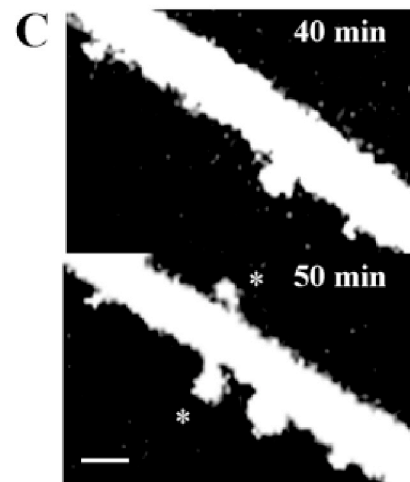
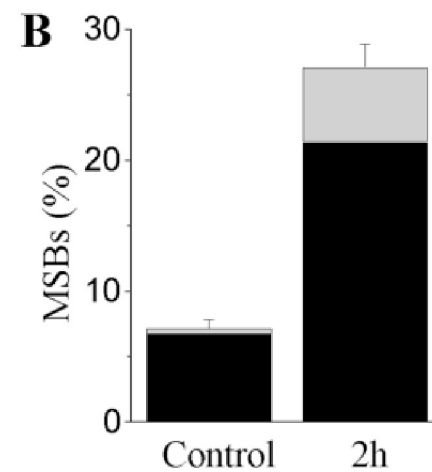
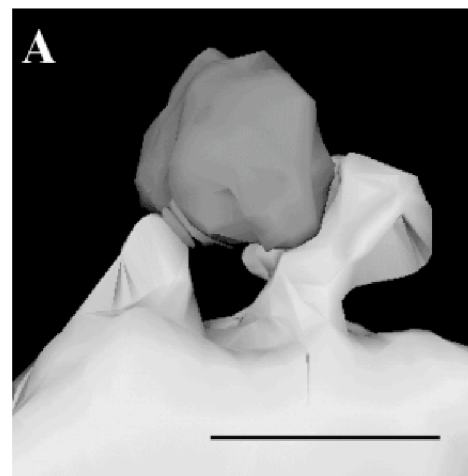
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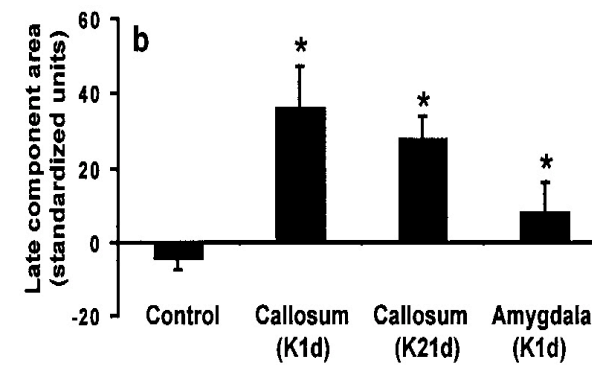
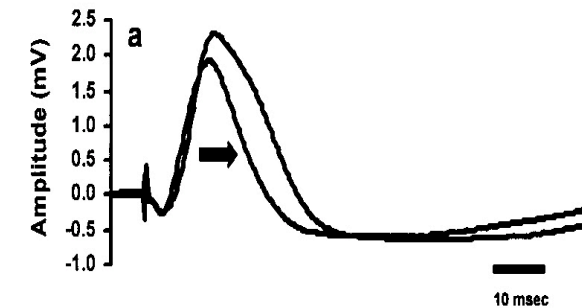
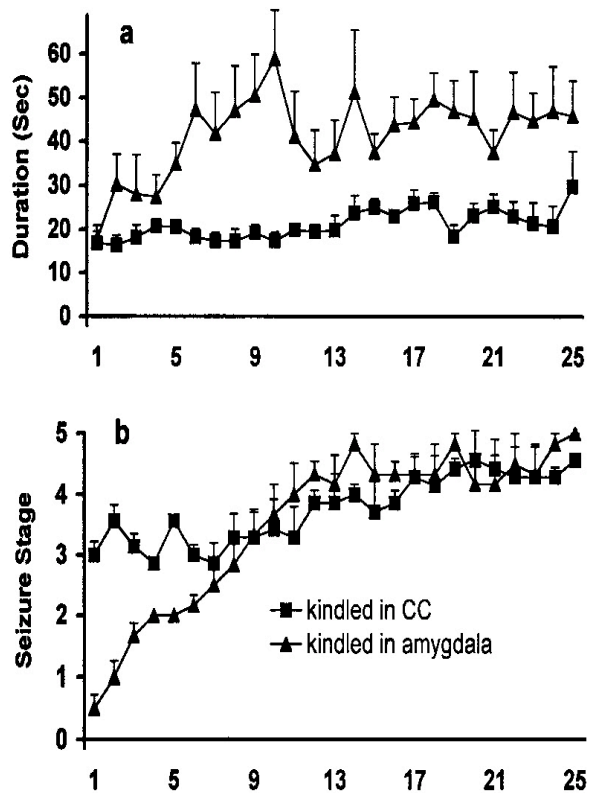
Embracement = kindling



Embrasement = réorganisation synaptique



Embracement = réorganisation synaptique



Embrasement = réorganisation synaptique

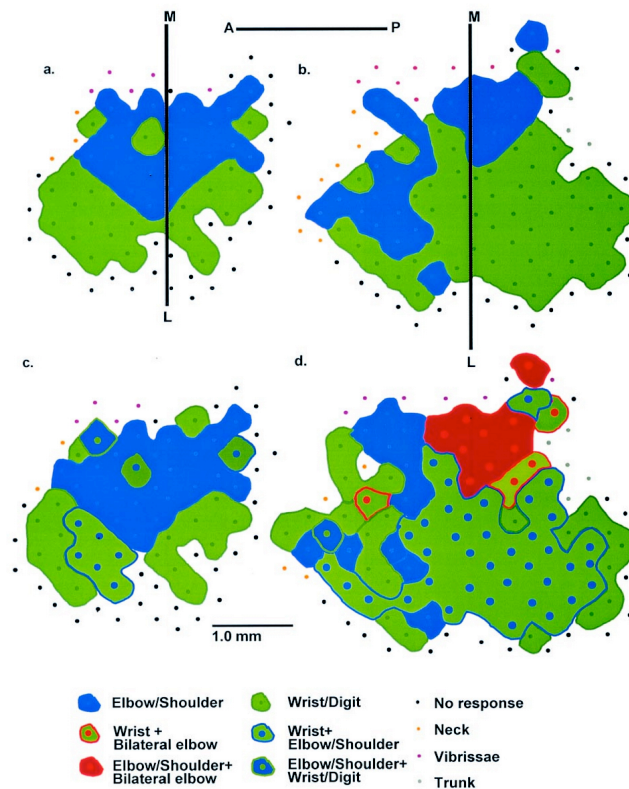
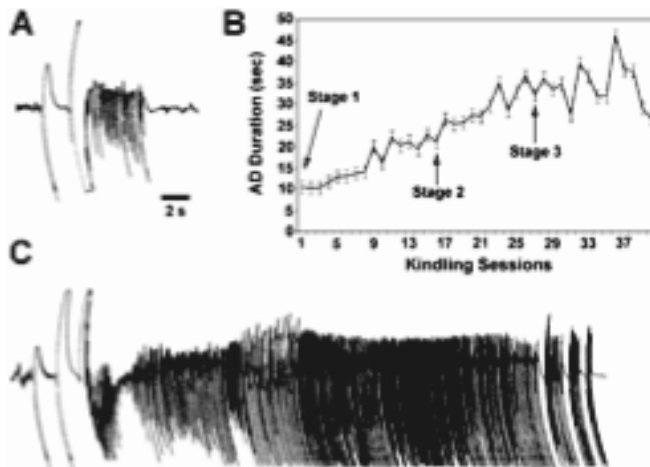


Figure 3. Threshold and suprathreshold forelimb motor representations. Color-coded representation of the mapping of the rat caudal forelimb area for the (a) threshold map of an implanted control rat (no. 9), (b) threshold map of a callosal-kindled rat (no. 13) that displayed kindling-induced potentiation, (c) the suprathreshold map of the same implanted control rat and (d) the suprathreshold map of the same callosal-kindled rat that displayed kindling-induced potentiation. The stimulating microelectrode was repeatedly lowered 1500 μ m into the left hemisphere motor cortex, and stimulation was applied (up to 60 μ A) until movement was elicited. External map boundaries were always defined as electrode penetrations that failed to elicit movement or non-caudal forelimb area movements. A-P refer to the direction of the anterior-posterior axis. M-L refers to the direction of the medial-lateral axis and also defines the coronal plane in which the stimulating electrode was situated (+1.0 mm anterior of bregma).

The kindling effect

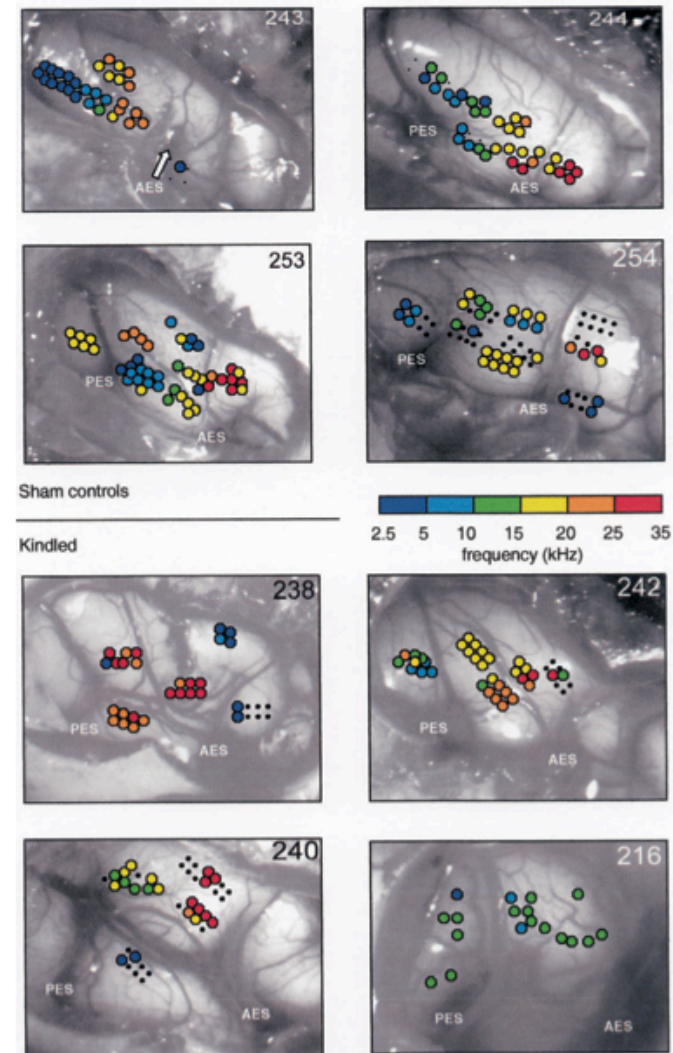
Kindling Changes Burst Firing, Neural Synchrony and Tonotopic Organization of Cat Primary Auditory Cortex



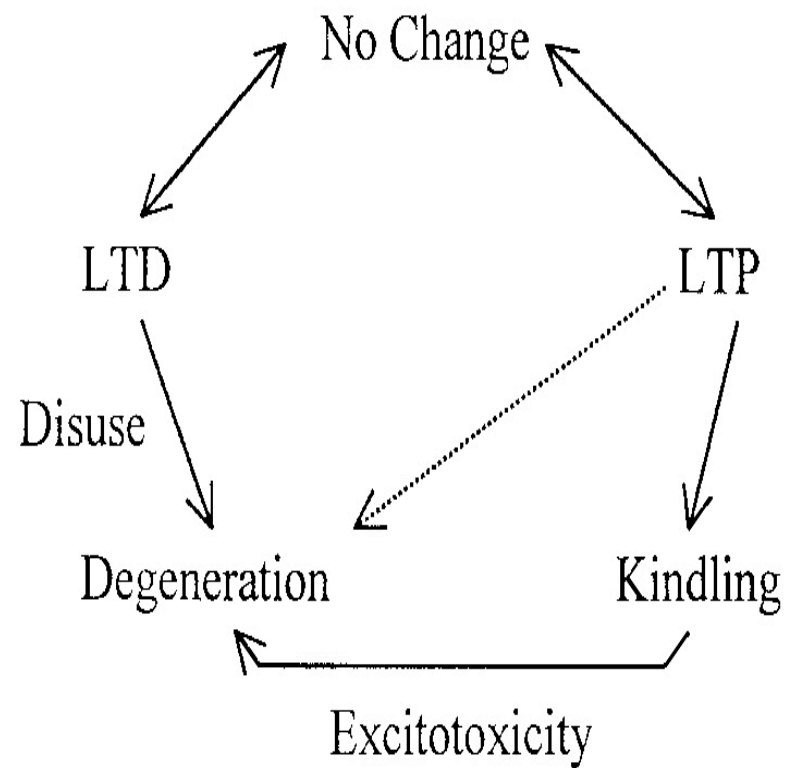
Kindling Changes Burst Firing, Neural Synchrony and Tonotopic Organization of Cat Primary Auditory Cortex

Pamela A. Valentine^{1,2}, G. Campbell Teskey¹ and Jos J. Eggermont^{1,2}

¹Behavioural Neuroscience Research Group, Department of Psychology, University of Calgary, Calgary, Alberta, Canada and ²Department of Physiology and Biophysics, Neuroscience Research Group, University of Calgary, Calgary, Alberta, Canada



Embracement = pathologie synaptique



?

Embrasement: physiopathologie

Implications des différents systèmes de neurotransmetteurs

Embrasement: physiopathologie

Système gabaergique

« altération » de l'inhibition GABAergique

perte des interneurones inhibiteurs ?

**Modification des propriétés membranaires des
interneurones ?**

**diminution de l'activation des interneurones
inhibiteurs?**

Embrasement: physiopathologie

- **Altération des Récepteurs GABA_A**
- **Modification de la modulation des récepteurs (NMDA, Zn⁺⁺)**
- **Diminution de la libération du GABA ou modification de sa régulation présynaptique**
- **Modification de la recapture du GABA**
- **Rôle des récepteurs GABA_B**

Embrassement: physiopathologie

Système sérotoninergique

5HT1A -
5HT2 & 5HT3 +

Embracement = kindling

Agoniste 5 HT4

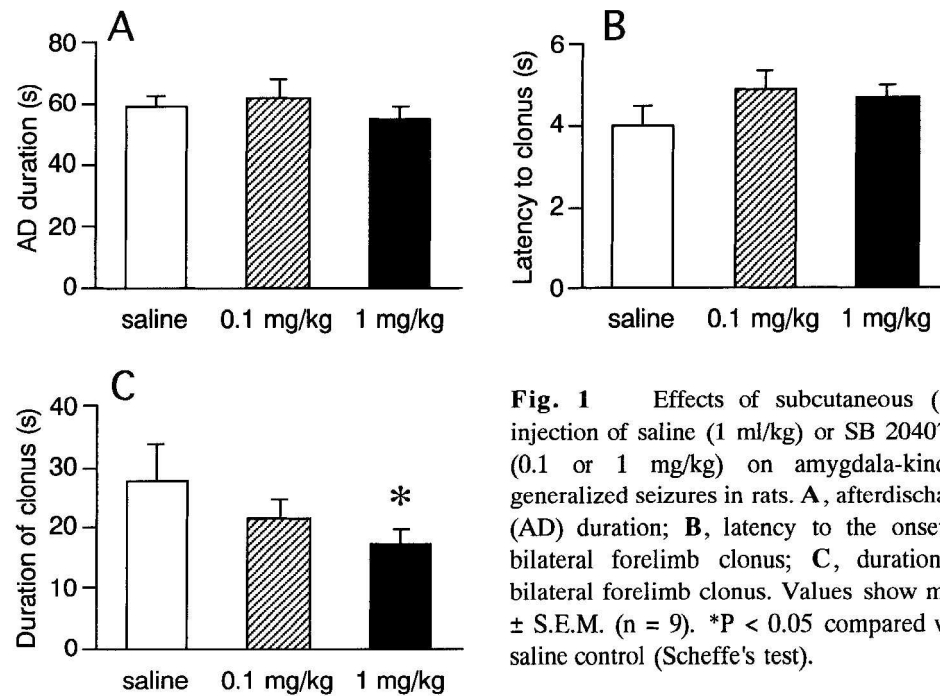


Fig. 1 Effects of subcutaneous (s.c.) injection of saline (1 ml/kg) or SB 204070A (0.1 or 1 mg/kg) on amygdala-kindled generalized seizures in rats. **A**, afterdischarge (AD) duration; **B**, latency to the onset of bilateral forelimb clonus; **C**, duration of bilateral forelimb clonus. Values show mean $\pm$ S.E.M. (n = 9). *P < 0.05 compared with saline control (Scheffe's test).

Embrasement: physiopathologie

Système cholinergique

Embracement: physiopathologie

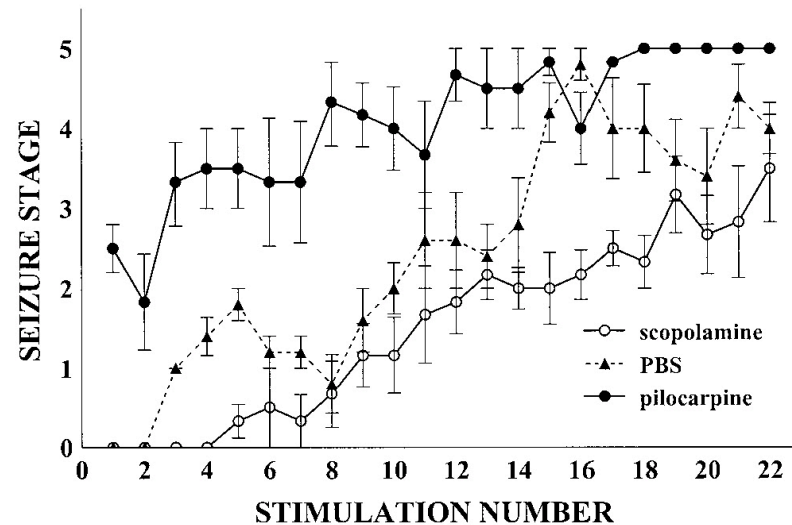


Fig. 1. Behavioral progression of seizure activity. Treatment with pilocarpine accelerates the behavioral progression of kindling, whereas treatment with scopolamine retards the progression of kindling. Values represent mean seizure stage $\pm$ SEM for pilocarpine-kindled ($n = 6$), PBS-kindled ($n = 5$), and scopolamine-kindled ($n = 6$) rats.

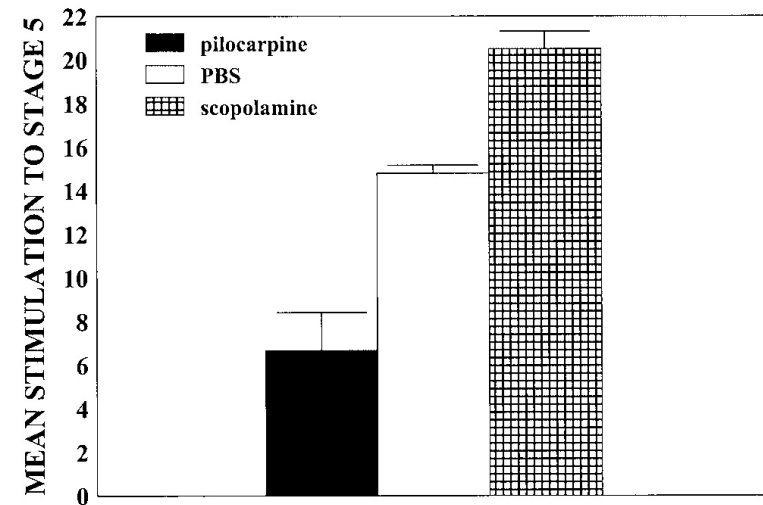
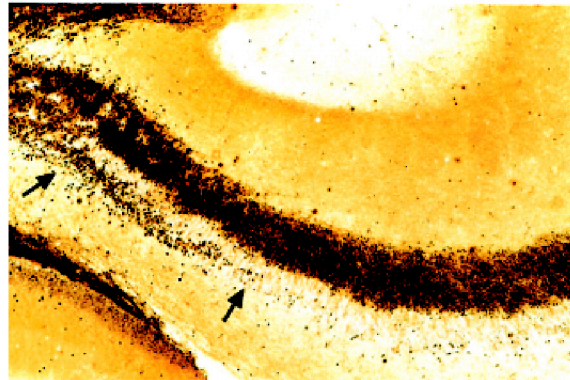


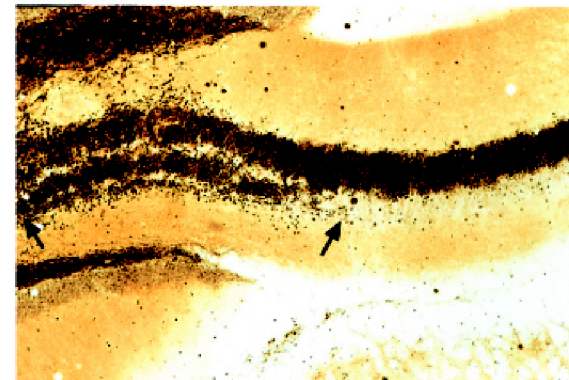
Fig. 2. Mean number of seizures to reach a stage 5 seizure. The pilocarpine group ($n = 6$) required approximately 64% fewer stimulations to reach a stage 5 seizure compared to the PBS group ($n = 5$) and approximately 74% fewer stimulations compared to the scopolamine group ($n = 6$) ($P < 0.001$). The PBS group required approximately 27% fewer stimulations to reach a stage 5 seizure compared to the scopolamine group ($P < 0.001$). Values represent mean number of stimulations $\pm$ SEM to reach a stage 5 seizure.

Embracement = kindling

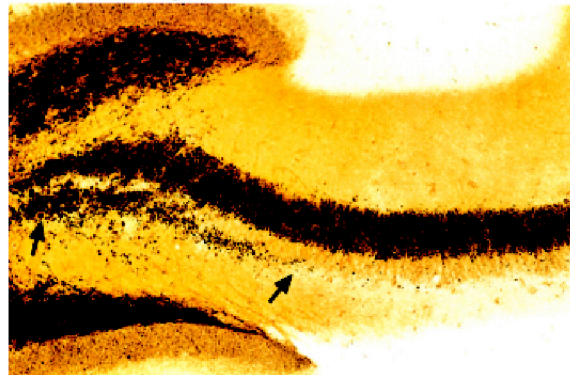
PBS Control



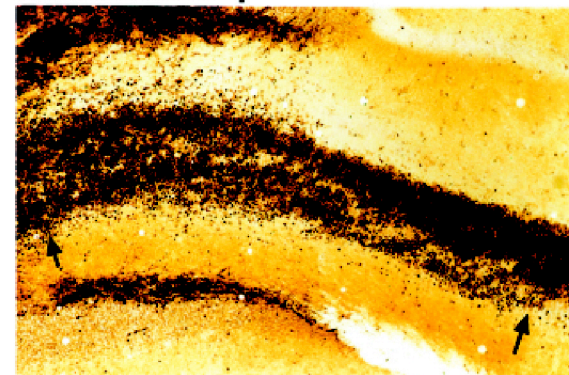
PBS Kindled



Scopolamine Kindled



Pilocarpine Kindled



Embrasement: physiopathologie

Système glutamatergique

Embrasement: physiopathologie

Récepteurs NMDA

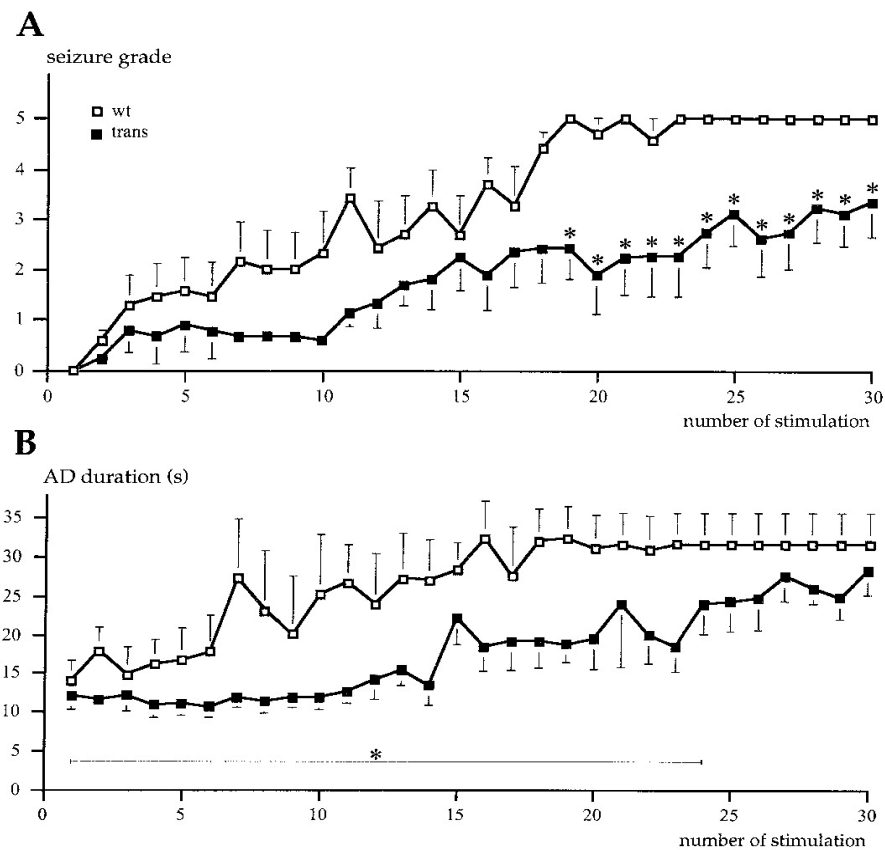


FIG. 1. Kindling development. Mean seizure grade (A) and duration of afterdischarge (B) in wild-type (wt) and transgenic (trans) mice in response to daily amygdala kindling stimuli. * $P < 0.05$, Mann-Whitney- U -test (A) or repeated analysis of variance (B).

Embracement = kindling

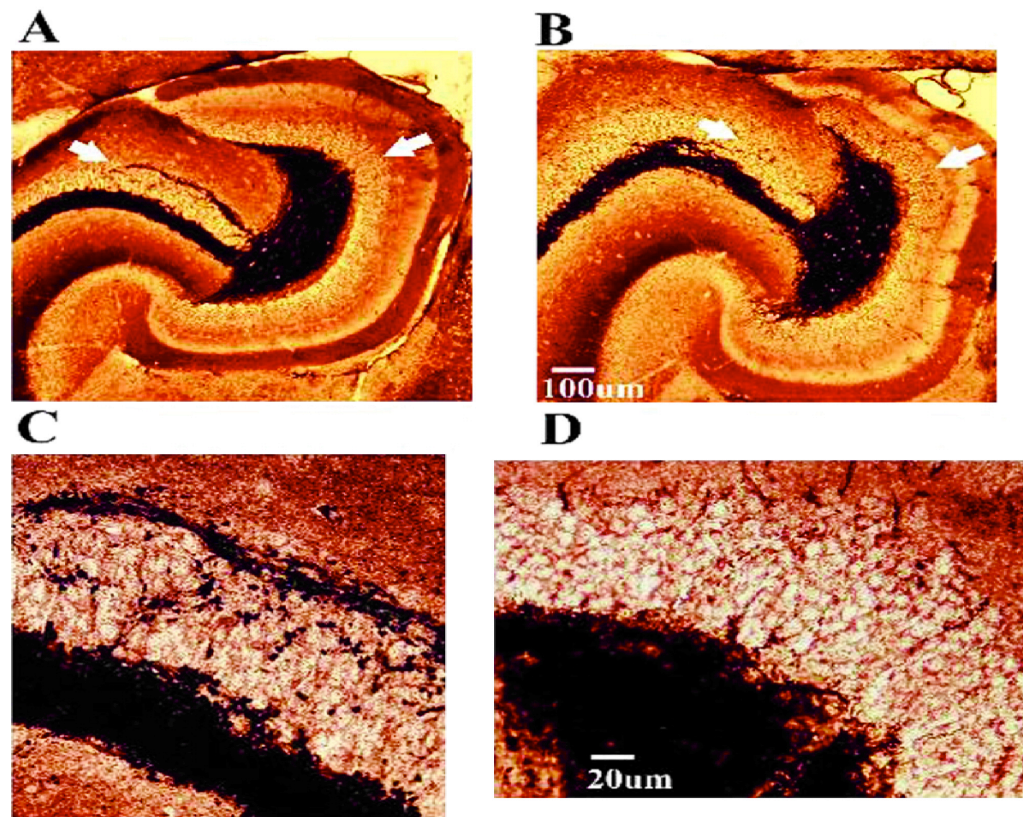


FIGURE 2. Digital images of (A) knockout and (B) wild-type mouse hippocampus following Timm staining. Scale bar in B applies to both A and B. Note easily seen enhancements in level of Timm staining in knockout mouse hippocampus, especially within the stratum oriens. Arrows indicate stratum oriens and inner molecular layer.

C: Higher magnification of stratum oriens shown in A. D: Higher magnification of inner molecular layer shown in A. Scale bar in D applies to both C and D. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

Embrasement: physiopathologie

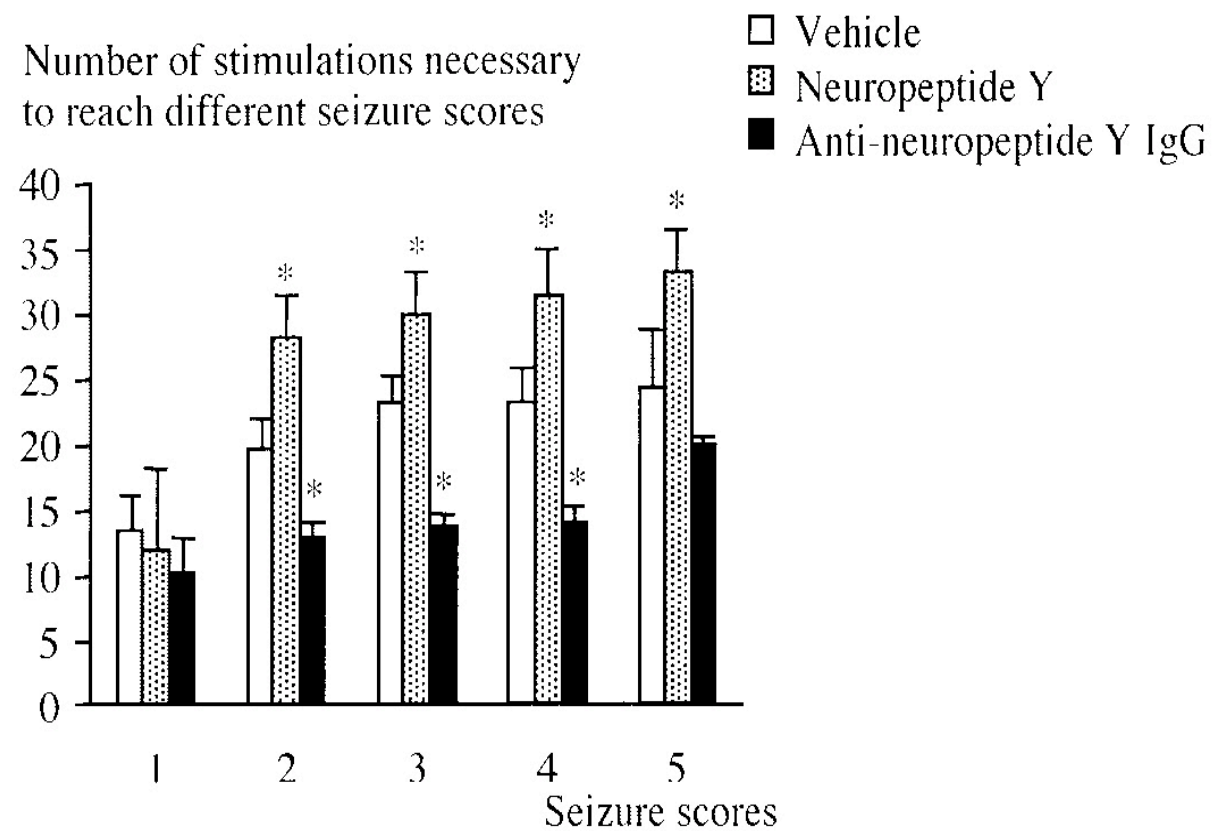
Neurotrophines

BDNF

**anticorps anti trkB (récepteur du BDNF) empêche
l'embrasement**

Injection de BDNF retarde l'embrasement

Embracement: physiopathologie



Embrasement: physiopathologie

Systeme adénosinergique

Récepteurs A1 -

L'embrasement altère l'efficacité de ce système

diminution de la densité des récepteurs A1

diminution de la dépression des PPSE

diminution de la libération d'adénosine

Embrasement: physiopathologie

Systeme histaminergique

Embracement: physiopathologie

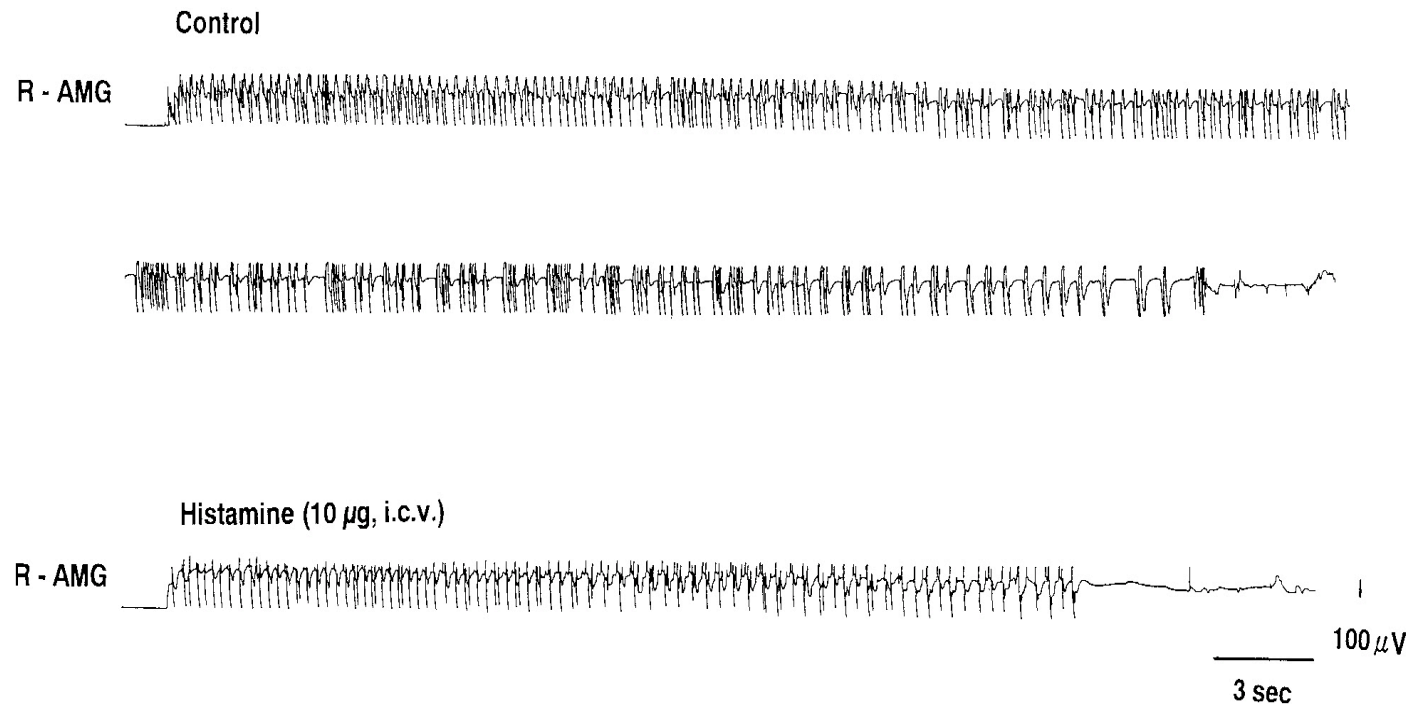
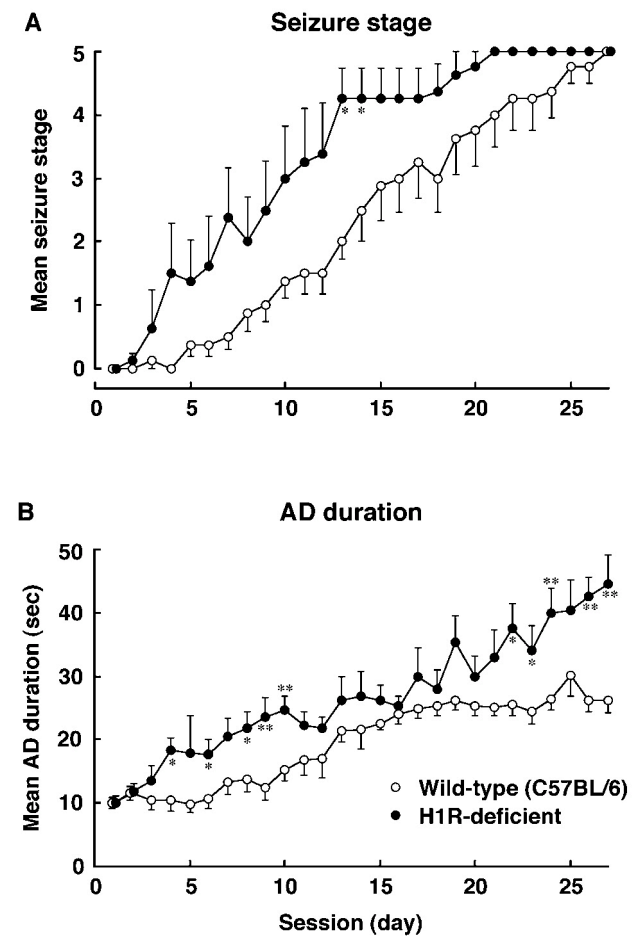
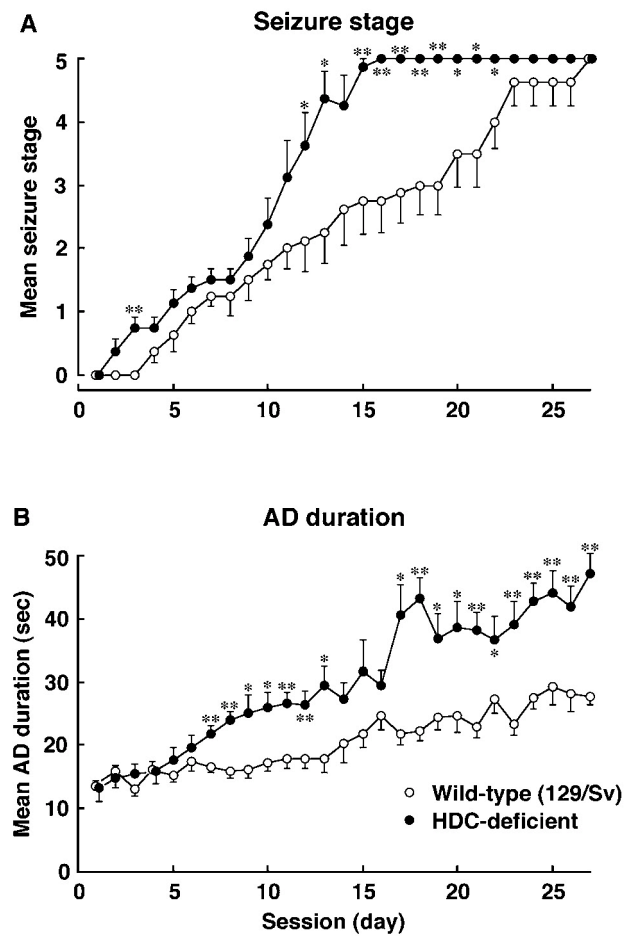


FIG. 1. Representative example for the effects of histamine on amygdaloid-kindled seizures in rats. Control: Twenty minutes after saline (5 μl , i.c.v.) injection, the right amygdala was stimulated electrically (150 μA), and seizure stage and afterdischarge (AD) duration were measured. Histamine (10 μg /5 μl , i.c.v.) was injected, and 20 min after injection, the amygdala was stimulated electrically (150 μA), and seizure stage and AD duration were measured.

Embracement: physiopathologie



Embracement: physiopathologie

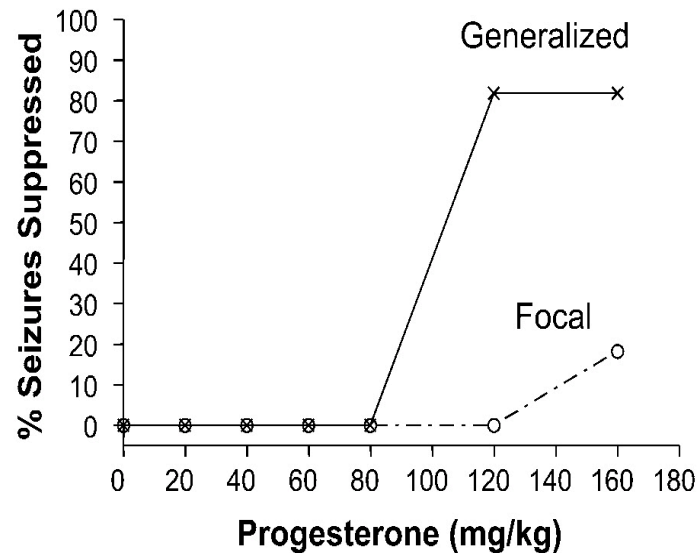


FIG. 2. A graph of the dose-response curve for the suppression of amygdala kindled seizures by progesterone (N = 11). Progesterone (varying doses) was injected s.c., and the kindling stimulus was administered 15 min later. Only one dose was administered to a subject on any given test day. None of the subjects showed sedation at this postinjection interval.

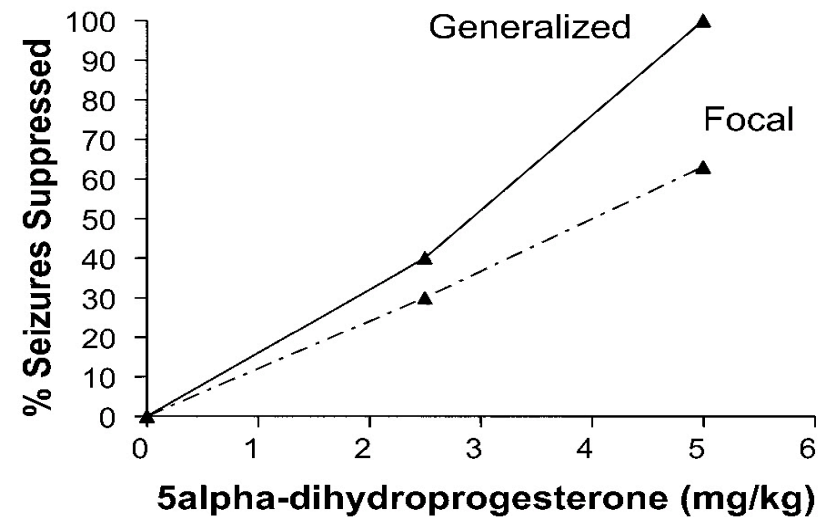


FIG. 4. A graph of the dose-response curve for the suppression of amygdala kindled seizures by 5α-dihydroprogesterone (N = 10). 5α-dihydroprogesterone (varying doses) was injected s.c., and the kindling stimulus was administered 15 min later. Only one dose was administered to a subject on any given test day. None of the subjects showed sedation at this postinjection interval (15 min after injection) or at any subsequent interval up to 3 h (longest interval tested).

Embrasement = kindling

Pertinence du modèle

Modèle d'épileptogénèse

**Données physiopathologiques sont similaires
à celles observées
dans l'ELT chez l'homme**

Mais peu (ou pas) de crises spontanées

Embracement = kindling

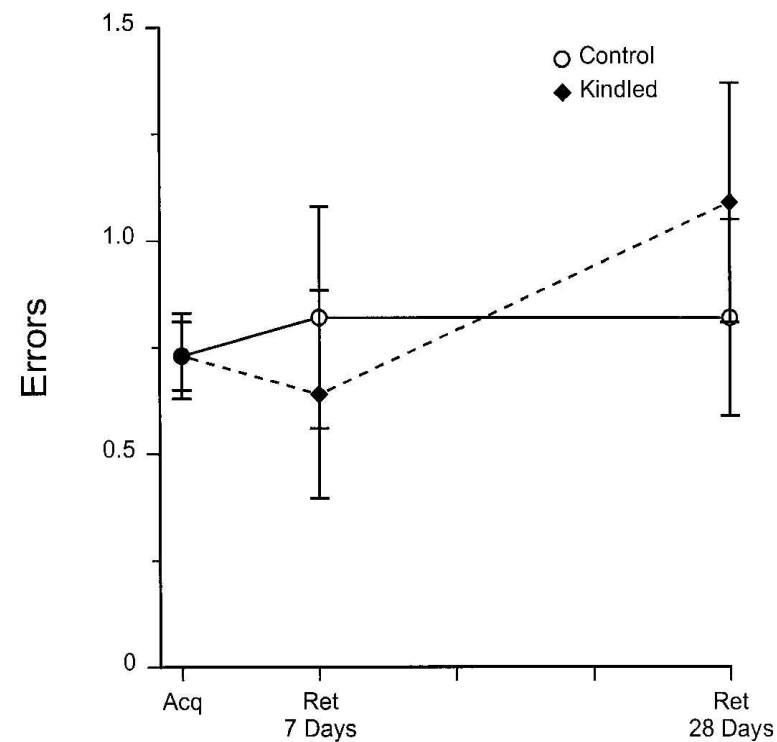


FIGURE 8. Total number of errors on last five OD trials of object discrimination acquisition and on five OD trials at 7 and 28 days retention.

Embrasement = kindling

Intérêt du modèle

Molécules antiépileptiques

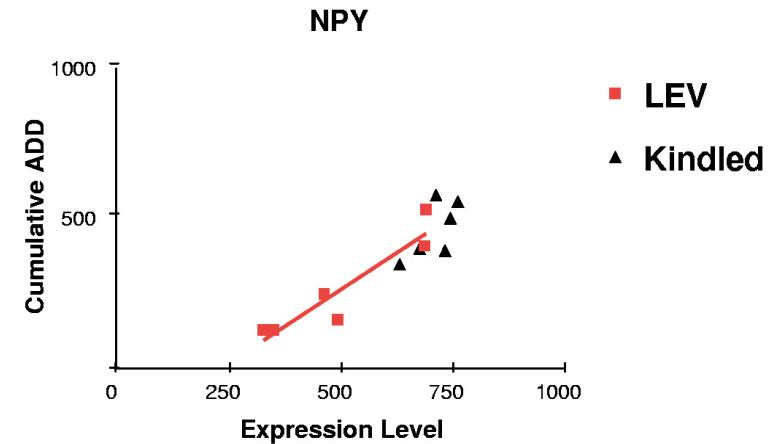
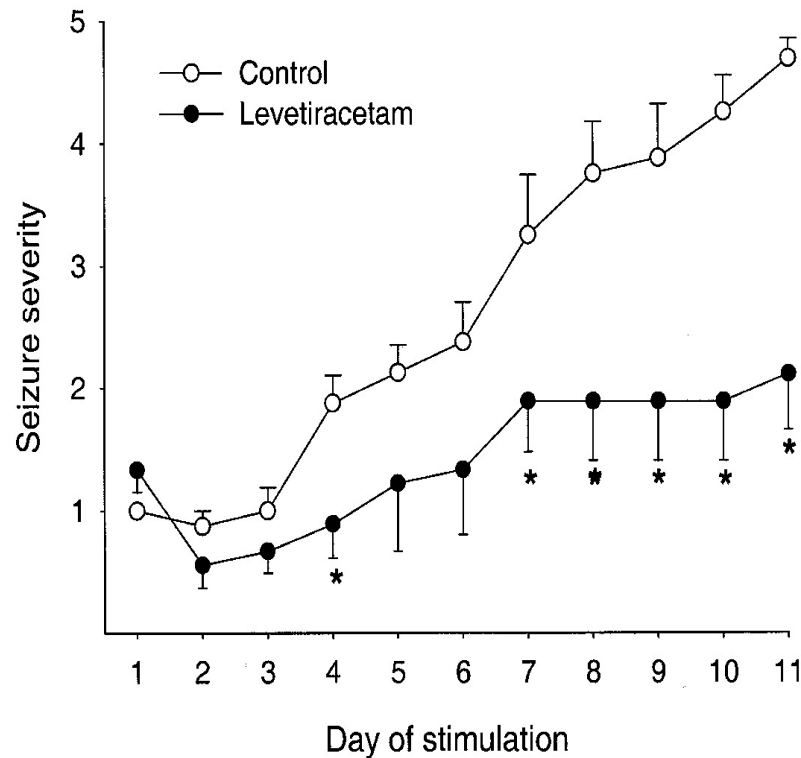
Effet antiépileptique

Effet anticonvulsivant

**Validation de nouveaux
traitements**

**Effet des stimulations à basse fréquence
sur le développement de l'embrasement**

Embracement = kindling



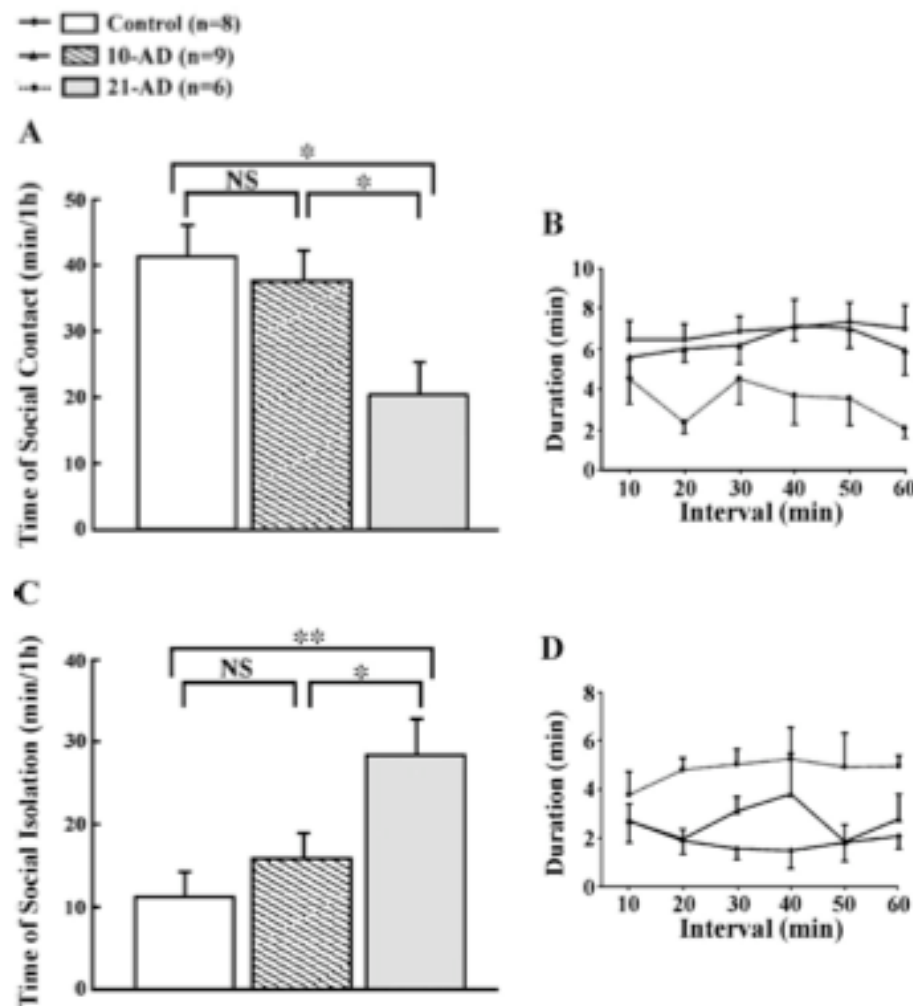
	Correlation Coefficient
Seizure Score	0.83
Cummulative ADD	0.93
Seizure Duration	0.60

FIG. 4. Linear regression analysis of NPY expression and kindling measurements in either the kindled group ($n=6$) or the LEV-treated kindled group ($n=6$). NPY expression level measured by the Affymetrix arrays correlates significantly to cumulative ADD measurements, with a correlation coefficient of 0.93 ($P < 0.0001$, $r^2 = 0.8565$). NPY expression level also correlates with seizure severity and seizure duration, and the correlation coefficients are 0.83 ($P = 0.0008$, $r^2 = 0.6904$) and 0.60 ($P = 0.0381$, $r^2 = 0.3632$), respectively. Linear regression was performed using the GraphPAD Prism[®] software.

The kindling effect

Schizophrenia-like behavioral changes after partial hippocampal kindling

Jingyi Ma*, L. Stan Leung



The kindling effect

Dr. Robert M. Post

- ... initial periods of cycling may begin with an environmental stressor, but if the cycles continue or occur unchecked, the brain becomes kindled or sensitized - pathways inside the central nervous system are reinforced so to speak - and future episodes of depression, hypomania, or mania will occur by themselves (independently of an outside stimulus), with greater and greater frequency.

The kindling machine

