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Diversity of kindling of limbic seizures after lateral fluid percussion injury in the rat

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Abstract

Lateral fluid percussion injury (LFPI) in rats is used to model post-traumatic epilepsy (PTE), with spontaneous seizures occurring in up to 1/2 of the subjects. Using the kindling paradigm, we examined whether animals without detectable seizures had an altered seizure susceptibility. Male Sprague Dawley rats were subjected to LFPI. Seven-nine months later, spontaneous seizures were monitored for two weeks. Afterward, the animals underwent kindling of basolateral amygdala. For kindling outcomes, the animals were categorized based on the 95% confidence intervals of mean number trials to kindling (ie 3 consecutive stage 4-5 seizures). Spontaneous seizures were detected in 7 out of 24 rats. There was no correlation between the severity of LFPI and either baseline afterdischarge properties, or kindling rates. Six LFPI rats kindled at a rate comparable to those in sham-LFPI (n = 10) and in naïve (n = 7) subjects. Ten LFPI rats kindled faster and 8—slower than controls. None of slow-kindling rats had spontaneous seizures during the prekindling monitoring. During the same period, six fast-kindling and three normal-kindling rats had been seizure-free. Thus, kindling reveals a diversity to seizure susceptibility after LFPI beyond an overt seizure symptomatology, ranging from the increased susceptibility to the increased resistance.

KEYWORDS

epileptogenesis, post-traumatic epilepsy, traumatic brain injury

1 | INTRODUCTION

Lateral fluid percussion injury (LFPI) in rats is employed to model post-traumatic epilepsy (PTE).^{1,2} Documenting PTE has been mainly relying on video and EEG.³⁻⁵ A notable weakness of such approach is its binary nature: It assumes that LFPI is either epileptogenic or is largely inconsequential. Passive observation does not address alternative scenarios. For example, even when seizures are not detected (which is possible because of their low frequency⁴), the animals may

still have the increased seizure susceptibility. Conversely, LFPI may lead to the over-activation of endogenous compensatory mechanisms (as it has been suggested for epilepsy⁶⁻⁸), which effectively counteract the progression of PTE.

There have been few attempts to apply active interventions for probing the susceptibility to epilepsy after TBI. Acutely, the increased susceptibility to pentylenetetrazole (PTZ) convulsions was reported.^{9,10} Several chronic studies employed kindling paradigm. When started one day after TBI, both PTZ¹¹ and amygdala kindling¹² were accelerated

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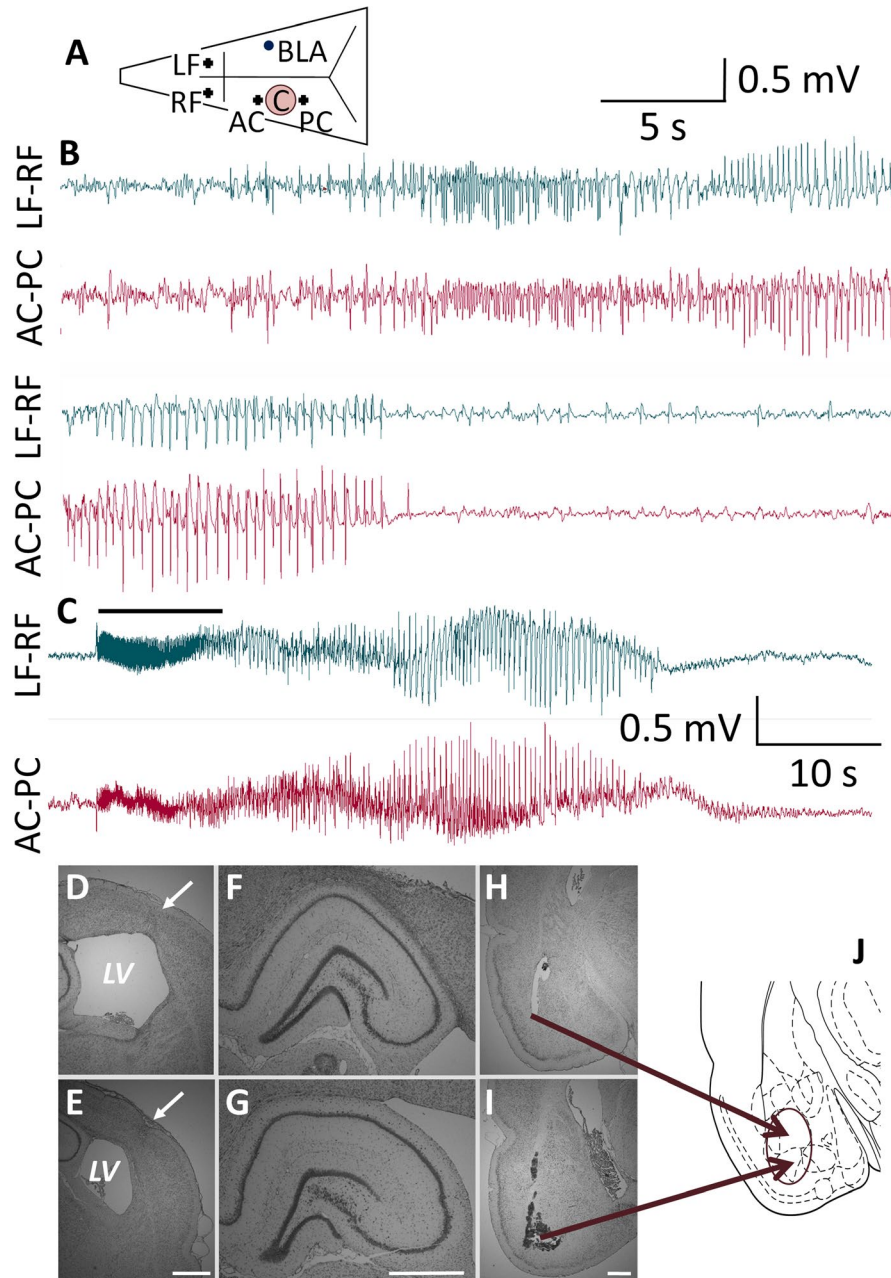


FIGURE 1 Craniotomy, EEG, and histology. A, Schematic representation of craniotomy and of electrode placement. C—Craniotomy window. Recording electrodes: left frontal cortex (LF); right frontal cortex (RF); cortex anterior to craniotomy window AC; cortex posterior craniotomy window (PC). Stimulating electrode: basolateral amygdala (BLA). B, A typical spontaneous seizure, recorded during 2-week monitoring prior to kindling, corresponding to stage 4-like behavioral seizure on Racine scale (rearing). The four consecutive lines show continuous recording. The seizure starts as focal seizure (apparently in the AC-PC), quickly becomes generalized, and resolves in the postictal depression. C, Kindling seizure in response to the stimulation of BLA, corresponding to the stage 4 behavioral seizure. Horizontal bar denotes stimulation artifact. (D, E) Area of impact is characterized by the thinning of cortical mantle (arrows), enlargement of lateral ventricle (LV), and scattered neuronal disorganization, which are all typical chronic features of LFPI.²³ Cortical layers remain largely preserved. (F, G) Hippocampi are slightly deformed, due to the enlargement of lateral ventricle; neuronal layers remain well preserved. (H, I) BLA is structurally intact. Stimulating electrode tracks appear in both panels. In H, the electrode ends in anterior BLA, in I—in ventral BLA. J, Camera Lucida image of the area, which includes BLA (outlined by the oval; -2.8 from Bregma). Arrows from H to J and I from to J point to the locations of the stimulating electrodes; H—anterior BLA; I—ventral BLA

after controlled cortical impact (CCI), but not after central fluid percussion.¹³ CCI did not modify perforant path kindling 10 weeks after the injury.¹⁴ No kindling studies in

conjunction with LFPI have been performed. To date, there is no conclusive evidence as to the effects of TBI on the propensity to kindling. Studies, involving different TBI paradigms,

times vis-à-vis trauma, and closer look at kindling parameters may be useful for clarifying the connection between PTE and kindling, and for establishing whether kindling may be helpful for studying the predisposition to PTE. We used kindling of basolateral amygdala (BLA)¹⁵ to examine the susceptibility to epilepsy during chronic post-LFPI period, when animals with epilepsy are identifiable.^{4,5}

2 | METHODS

Male Sprague Dawley rats (Charles River, Wilmington, MA), 50 days old at the beginning of the study, were housed individually, at 12-hr normal light-dark cycle (Zeitgeber time [Z] 0 = 7:00), food and water ad libitum. The procedures were approved by the UCLA Animal Research Committee and by the Animal Care and Use Review Office of the US Army Medical Research and Materiel Command.

LFPI.^{4,5} Under isoflurane anesthesia and core temperature maintained at 37°C, a five-millimeter circular craniotomy was performed (center from Bregma: posterior 4.5 mm, left 3.0 mm, Figure 1A), a modified female Luer cap was fitted in, and fixed to the skull with dental acrylic. The animal was disconnected from anesthesia. Upon the recovery of the toe pinch, the rat was connected to the male Luer cap mounted on the fluid percussion device (Amscien, Richmond, VA), and a pressure pulse (target 2.0 atm) was delivered. The duration of apnea, the recovery of toe pinch, and righting reflexes were recorded, and the wound was closed. Sham subjects underwent the same procedures, save for the pressure pulse. One day later, neuromotor score was measured (forelimb contraflexion, hindlimb flexion, lateral pulsion, the ability to stand on the angled board); the maximal score is 28, with points deducted for each failure.¹⁶

Electrode implantation. Seven-nine months later, 24 LFPI, 10 sham-LFPI, and 7 age-matched naïve rats were implanted with four recording skull electrodes and a stimulating electrode in the right BLA (P1, Roanoke, VA; Figure 1A).¹⁷

EEG and video monitoring started one week after surgery and continued for up to 26 days (first 14 days—recording of spontaneous seizures only, and the remaining days—during kindling). The rat was connected to the MP150/EEG100C acquisition system (Biopac, Santa Barbara, CA) by means of a low-torque swivel (P1). Signals were sampled at 250 Hz, through 35Hz low-pass and 1 Hz high-pass filters. Electrographic seizures were reviewed using AcqKnowledge 4.1 software (Biopac). An electrographic seizure was defined as high-amplitude rhythmic discharges that represents a new pattern of activity (repetitive spikes, spike-and-wave discharges, and slow waves) that lasted ≥ 10 sec, showed evolution in pattern, frequency or field, and culminated in postictal depression¹⁸ (an example is in Figure 1B). Behavior was video-recorded; seizures were analyzed off-line by adopting the Racine scale.¹⁹

Kindling^{20–22} started after the 2-week monitoring. Stimulating electrode was connected to the DS8000 stimulator/DSL100 isolating unit (WPI, Sarasota, FL). Afterdischarge threshold (ADT) and afterdischarge duration (ADD) were determined by applying stimuli (10 seconds train, 20 Hz, 1 ms square wave monophasic pulse) to BLA every 15 min, starting at 100 μ A, with 25 μ A increments. Kindling was induced by applying stimuli at ADT, twice daily, around Z2:00 and Z10:00, upon the verification of the absence of spontaneous seizures during at least three preceding hours. Behavioral seizures were quantified using Racine scale¹⁹ and confirmed by EEG (Figure 1C). The animal was considered kindled once it developed stage 4–5 seizures in response to three consecutive stimulations. After 24 stimulations, or once the animal was kindled (whichever occurred first), stimulations were discontinued. For those animals, which failed to kindle after 24 stimulations, in order to make data amenable to statistical analysis, the number of stimulations was conjectured so as to project their minimal number, which would have been required to kindle. Therefore, while the maximal number of actual stimulations was 24, the highest projected number was 27. A detailed explanation is in Supplemental Material.

Histology was performed to verify the placing of stimulating electrode, and to evaluate gross integrity of LFPI- and epilepsy-relevant brain sites.²³ Histological appearance was assessed in coronal 4% paraformaldehyde-fixed, 40 micron-thick cresyl violet-stained sections.

Data were analyzed using Prism 6 software (GraphPad, San Diego, CA). Samples that failed D'Agostino and Pearson normality test were analyzed using Kruskal-Wallis (KW), Mann-Whitney (MW), and Spearman correlation. Normally distributed samples were analyzed using one-way ANOVA. Animals were categorized vis-à-vis susceptibility to kindling based on the 95% confidence interval (CI) of mean number of stimulations required reach the kindling state.

3 | RESULTS

LFPI data are in Table 1, row 1 (“All rats”).

Spontaneous seizures. During the 2-week recording, 7 out of 24 post-LFPI subjects displayed seizures, all analogous to the Racine stages 4–5 (Figure 2B). Electrographically (Figure 1B), all seizures corresponded to stage 4–5. No correlation between any of the parameters of LFPI and seizure counts were noticed ($P > 0.1$, Spearman). Individual seizure duration varied between 20 seconds and 115 seconds both in the group and for the same animal; we found no correlation between seizure duration and LFPI severity ($P > 0.1$, Spearman). No seizures were detected in sham rats.

Afterdischarge properties were similar between post-LFPI and control rats (ADT/ADD Mean \pm SD: LFPI 421 \pm 56 μ A/25 \pm 9.6 seconds; Sham 385 \pm 63 μ A/23 \pm 12.5 seconds;

TABLE 1 Parameters of lateral fluid percussion injury and afterdischarge properties in LFPI rats

Category vis-à-vis 95% CI	LFPI parameters					Afterdischarge properties	
	Impact, atm	Apnea, seconds	Toe pinch, seconds	Righting, min	Neuro-score	Afterdischarge threshold, μ A	Afterdischarge duration, seconds
1. All rats, n = 24 (4/13/27)	1.9 \pm 0.12	42 \pm 13	245 \pm 37	13.6 \pm 2.7	15.9 \pm 3.1	421 \pm 56	25 \pm 9.6
2. Within 95% CI, n = 6 (12/14.5/18)	1.9 \pm 0.08	42 \pm 14	244 \pm 33	13.0 \pm 3.5	16.0 \pm 2.4	408 \pm 56	20 \pm 5.5
3. Below 95% CI, n = 10 (4/6.5/9)	1.9 \pm 0.13	41 \pm 7	238 \pm 18	13.5 \pm 1.4	16.6 \pm 2.4	418 \pm 62	24 \pm 8.4
4. Above 96% CI, n = 8 (21/26/27)	1.9 \pm 0.14	47 \pm 19	257 \pm 54	14.3 \pm 3.5	15.3 \pm 4.5	434 \pm 52	33 \pm 10

Note: Parameters of LFPI, ADT, and ADD are presented as Mean \pm SD. Kindling rate is shown as minimal/median/maximal number of stimulations required to reach the kindling state. No significant differences were observed for any of the parameters, when comparing the animals of different subgroups (one-way ANOVA, $P > 0.01$).

naïve $436 \pm 72 \mu\text{A}/24.2 \pm 9.8$ seconds; $P > .1$, one-way ANOVA). No correlation was observed between the LFPI parameters and either ADT, or ADD ($P > 0.1$, Spearman).

Kindling: all rats (Figure 2A; Table S1). Rats of the LFPI group (n = 24) kindled after 4-27 stimulations (95% CI 11.08-18.26). All five rats, which failed to kindle, presented with 1-2 stage 4-5 seizures during the course of the stimulations (Table S1). All sham (n = 10; 95% CI 15.42-17.18) and naïve subjects (n = 7; 95% CI 14.84-18.02) kindled after 14-19 stimulations. There were no differences for the number of stimulations required to kindle among the animals of LFPI and control groups, whether the latter were counted separately (LFPI vs. Sham vs. Naïve, KW = 1.57, $P = 0.46$) or pooled (LFPI vs. Sham + Naïve, MW $P = 0.2$). Individual seizure duration varied between 25 and 90 seconds both in the group and for the same animal; we found no correlation between seizure duration and LFPI severity ($P > 0.1$, Spearman).

Kindling: stratification vis-à-vis 95% CI (Figure 2A). Comparison of rats for which number of stimulations were within 95% CI (LFPI n = 6, sham n = 3, naïve n = 5) found no differences among the three subgroups, whether sham and naïve rats were counted separately (LFPI vs. Sham vs. Naïve KW = 4.12, $P = 0.13$), or pooled (LFPI vs. sham + naïve MW $P = 0.07$). Comparison of rats for which number of stimulations were below the lower 95% CI (LFPI n = 10; sham n = 3; naïve n = 1) showed that LFPI rats kindled significantly faster than controls (sham + naïve, MW $P = 0.001$). Comparison of rats for which the number of stimulations was above the upper 95% CI (LFPI n = 8; sham n = 4; naïve n = 1) showed that LFPI rats kindled significantly slower than controls (sham + naïve, MW $P = 0.002$). Afterdischarge parameters had no effects on kindling (stimulations to kindling ADT $r = 0.15$; ADD $r = 0.34$ $P > 0.1$). LFPI parameters and afterdischarge properties were similar among the animals of the three subgroups (Table 1, rows 2-4).

Spontaneous seizures vs. kindling. (Figure 2B) There was significant correlation between the number of spontaneous

seizures during the prekindling monitoring and the number of stimulations required to kindle ($r = -0.41$, $P = 0.049$). All 8 slow-kindling rats had been seizure-free. Out of 10 fast-kindling rats, 6 had been seizure-free. Among the 6 rats within 95% CI, 3 had been seizure-free. Rats that showed no seizures during prekindling monitoring, remained seizure-free during kindling. Among seven rats with seizures detected before kindling, three developed 1-2 spontaneous seizures during kindling; seizures appeared between Z17:00 and Z01:00.

Histology. The area adjacent to LFPI was characterized by the thinning of cortical mantle, enlargement of lateral ventricle and signs of cellular disorganization (Figure 1D,E), all typical of LFPI.²³ Hippocampi were slightly deformed due to the lateral ventricle enlargement, but neuronal cell layers remained largely preserved (Figure 1F,G). Stimulating electrodes were located in BLA, within the boundaries of its anterior and ventral subareas (Figure 1H-J). No visible differences were observed among the rats with different susceptibility to kindling, in terms of the extent of injury, gross anatomical appearance, and BLA locations.

4 | DISCUSSION

During chronic post-LFPI period, there was a diversity in the susceptibility of individual rats to kindling: 25% of the animals kindled similar to, 42% kindled faster, and 33% kindled slower than controls. All slow-kindling animals had been spontaneous seizure-free, while 40% of fast-kindling animals had shown spontaneous seizures. Thus, kindling allows revealing two-tail differences in seizure susceptibility beyond an overt seizure symptomatology. While histological studies were limited, the observed variations in kindling were unlikely due to gross histopathological differences or locations of stimulating electrodes. Slow-kindling rats did not lose the ability to develop stage 4-5 seizures, suggesting that ictogenic networks were preserved. Preservation of intact afterdischarge properties

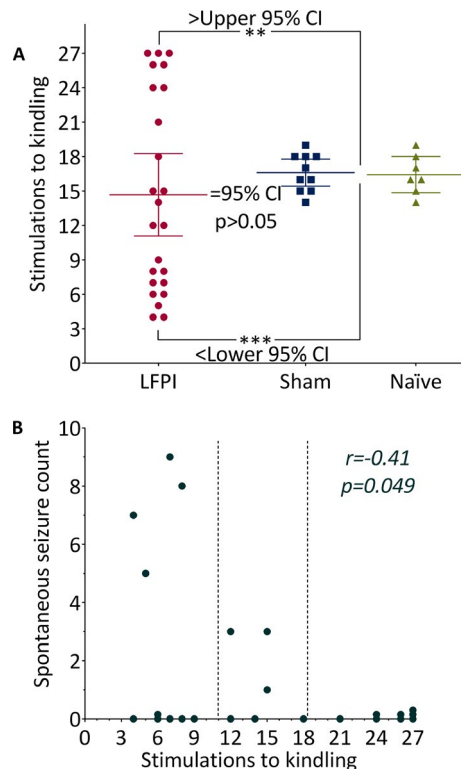


FIGURE 2 Kindling and spontaneous seizures after LFPI. A, Kindling 7–9 months after LFPI. Scatter plot shows number of trials needed reach the kindling state (ie 3 consecutive stage 4–5 seizures). Mean, upper, and lower limits of 95% CI are indicated by the horizontal lines. Statistical comparisons of trials to kindling were performed across 95% CI limits among LFPI ($n = 24$) and control (10 sham and 6 naïve) rats. Comparisons are shown for the data pooled for sham and naïve rats. Within the 95% CI limits, LFPI and control (ie sham + naïve) rats kindled at statistically similar rate. Below the lower 95% CI limit, LFPI rats kindled significantly faster, and above the upper 95% CI limit significantly slower than controls. $**P < 0.01$; $***P < 0.001$, Mann-Whitney test (LFPI vs. Sham + Naïve). B, Correlation between kindling rate and spontaneous seizure count in the LFPI subjects. Dashed vertical lines denote 95% CI limits. Statistics—Spearman correlation. The correlation was statistically significant, with those rats, which had more seizures before kindling, requiring fewer trials to reach kindling state (hence negative correlation coefficient)

after LFPI implied that ambient neuronal excitability was not altered. In short, the differences were specific for the kindling progression.

Several studies explored kindling in conjunction with TBI. When started one day after CCI, kindling was uniformly accelerated.^{11,12} While the findings were instructive, it is difficult to judge on their long-term significance. Inflammation, edema, and acute injury shortly after CCI^{11,24} likely enhance seizure susceptibility, leading to lower afterdischarge threshold and faster kindling. At the same time, adaptive plasticity might not have emerged yet. Whether or not these early changes contribute to PTE is questionable. Firstly, they are far removed from spontaneous seizures, which first occur 10 weeks after CCI.²⁴

Secondly, while the facilitation of kindling shortly after CCI is uniform, the incidence of spontaneous seizures during the remote period is 42%.²⁴ Therefore, early facilitation of kindling is a poor prognosticator of PTE. Beretta et al,¹⁴ studied perforant path kindling 10 weeks after CCI, but the description was scant. The authors noted that CCI had no bearing on the number of stimulations required to kindle and on the duration of seizures. While this study and ours used different TBI paradigms and stimulation sites, they were conceptually close in that both used kindling during remote post-TBI period. In fact, data from¹⁴ and ours may be not that different, as we also found no effects of LFPI on kindling when the rats were analyzed as a group with no regard for the stratification. Beretta et al did not elaborate on individual rats, only noting that “some animals kindled faster than others”,¹⁴ and it is possible that detailed analysis could have revealed the diversity in kindling rates.

Increased seizure susceptibility during chronic post-LFPI period was reported in the acute PTZ test.^{9,10} We found no changes in afterdischarge properties, but PTZ and afterdischarge probe different aspects of brain excitability (ie propensity to primary generalized²⁵ vs. focal limbic seizures). Since post-LFPI seizures are complex partial,^{4,5} the use of afterdischarge test may be more appropriate than PTZ.

Further studies to explain the diversity of kindling after LFPI, and its association with PTE, should include histological and imaging analyses, prolonged and multiarray electrographic monitoring, and the identification of possible endophenotypes.^{26,27}

In conclusion, this is the first report, which examined the relationship between LFPI, PTE, and amygdala kindling, to reveal the diversity of seizure susceptibility beyond an overt seizure symptomatology, ranging from the increased susceptibility to the increased resistance. The former may help in identifying epilepsy-susceptible rats (even those in which spontaneous seizures were not detected); the latter may reflect the engagement of endogenous antiepileptic mechanisms and may have therapy implications.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest. 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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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