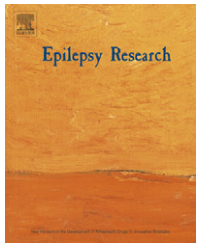
Epilepsy Research (2007) **73**, 85—97

journal homepage: www.elsevier.com/locate/epilepsyres



Temporal sequence of ictal discharges propagation in the corticolimbic basal ganglia system during amygdala kindled seizures in freely moving rats

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Received 17 March 2006; received in revised form 16 August 2006; accepted 29 August 2006
Available online 16 October 2006

KEYWORDS
Hippocampus;
Substantia nigra pars reticulata;
Epilepsy;
Rats;
Synchronization;
Single unit recording

Summary We used a multiple channel, single unit recording technique to investigate the neural activity in different corticolimbic and basal ganglia regions in freely moving rats before and during generalized amygdala kindled seizures. Neural activity was recorded simultaneously in the sensorimotor cortex (Ctx), hippocampus, amygdala, substantia nigra pars reticulata (SNr) and the subthalamic nucleus (STN). We observed massive synchronized activity among neurons of different brain regions during seizure episodes. Neurons in the kindled amygdala led other regions in synchronized firing, revealed by time lags of neurons in other regions in crosscorrelogram analysis. While there was no obvious time lag between Ctx and SNr, the STN and hippocampus did lag behind the Ctx and SNr in correlated firing. Activity in the amygdala and SNr contralateral to the kindling stimulation site lagged behind their ipsilateral counterparts. However, no time lag was found between the kindling and contralateral sides of Ctx, hippocampus and STN. Our data confirm that the amygdala is an epileptic focus that emits ictal discharges to other brain regions. The observed temporal pattern indicates that ictal discharges from the amygdala arrive first at Ctx and SNr, and then spread to the hippocampus and STN. The simultaneous activation of both sides of the Ctx suggests that the neocortex participates in kindled seizures as a unisonant entity to provoke the clonic motor seizures. Early activation of the SNr (before the STN and hippocampus) points to an important role of the SNr in amygdala kindled seizures and supports the view that different SNr manipulations may be effective ways to control seizures.

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doi:10.1016/j.eplepsyres.2006.08.008

Introduction

Kindling is a widely used animal model to study basic mechanisms underlying epileptic seizures. Kindled seizures initiated in limbic structures share several characteristics of temporal lobe epilepsy (TLE), the most common and intractable form of human epilepsy (Engel, 1996). Elucidating how epileptiform activity is initiated and how it propagates is essential for our understanding of epileptogenic processes and the state of epilepsy.

Lesion studies have implicated various brain structures in the expression of kindled seizures, such as the prefrontal and orbital cortices, the stria terminalis, the hippocampus, brain stem and basal ganglia structures (McIntyre, 1975; Corcoran et al., 1975; Engel and Katzman, 1977; Racine et al., 1988).

The amygdala and hippocampus are believed to be key structures involved in TLE. Indeed epileptiform paroxysms in both structures were found in patients with complex partial seizures and many of these patients remained seizure-free for years following selective amygdala/hippocampectomies or temporal lobectomy (Feindel and Rasmussen, 1991; Degado-Escueta and Walsh, 1985; Quesney, 1986). Accordingly, manipulations of the amygdala and hippocampus have served as useful experimental models for epilepsy research, including kindling, kainic acid and tetanus toxin models (Racine, 1978; Bertram, 1997; Tremblay et al., 1983; Bragin et al., 1999; Hawkins and Mellanby, 1987).

The basal ganglia have been hypothesized to be involved in the transition from limbic to generalized motor seizures (McNamara et al., 1986). Most studies have focused on the substantia nigra pars reticulata (SNr), the output nucleus of the basal ganglia system. Gale and Iadarola (1980) first described the existence of nigral control of an epilepsy system. SNr activation is thought to inhibit a ''dorsal midbrain anticonvulsant zone'' and thereby to facilitate seizure occurrence (Redgrave et al., 1992a,b). Other basal ganglia structures, either directly or indirectly connected to the SNr, may also be involved in the modulation of seizures. For example, microinjection of GABA antagonists into the striatum has been shown to protect against amygdala-kindling seizures in the rat (Cavalheiro et al., 1987). A number of studies have recently focused on the role of the subthalamic nucleus (STN) in epileptic seizures. Injection of GABA agonists into the STN significantly reduced motor seizures, probably due to decreased excitatory input to the SNr (Veliskova et al., 1996; Deransart et al., 1998). And, finally, the frontal cortex is believed to be the route seizures taken from subcortical limbic structures to the brainstem and spinal cord, where the convulsive components are manifested (Corcoran et al., 1975; Kelly et al., 1999; McIntyre and Gilby, 2005).

A critical question concerning the pathophysiology of epileptic seizures is how the ictal discharges propagate within epileptic networks. In the present study, taking advantage of the high temporal and spatial resolution of single unit recording, we sought to determine the sequence of propagation of ictal discharges within the corticolimbic basal ganglia network in amygdala kindled rats.

Materials and methods

Animals

Fifteen adult male Sprague—Dawley rats weighing 350—400 g at the time of surgery were used in this study. Animals were housed individually under a reversed dark—light cycle (lights off from 7:00 to 19:00) for 7 days before surgery. Animals were treated in accordance with the U.S. Public Health Service Guide for the Care and Use of Laboratory Animals and the experimental protocol was approved by the Animal Care and Use Committee of Wake Forest University School of Medicine.

Surgery

Rats were anesthetized with ketamine (100 mg/kg, i.m.) and xylazine (10 mg/kg, i.m.). Two types of microwire arrays were used. For single unit recording only, six arrays of eight stainless steel Teflon-insulated microwires (50 μm diameter, Biographics Inc. Winston-Salem, NC), soldered onto connecting pins on a headstage, were stereotaxically lowered bilaterally into the motor cortex (Ctx), SNr and either CA1 region of the dorsal hippocampus or STN. For simultaneous recording and stimulation, two arrays of 10 microwires were used; the additional two microwires (same as recording microwires) were used to deliver kindling stimulation. These arrays were implanted in the basal lateral amygdale (Fig. 1). Coordinates for these regions were obtained from the atlas of Paxinos (1986) as follows: 1.0 mm anterior to the bregma (A), 2.8 mm lateral to the midline (L), 1.7 mm ventral to the dorsal surface of the brain (V) for the Ctx; −2.8 mm (A), 4.5 mm (L) and 7.5 mm (V) for the basolateral amygdala; −3 mm (A), 1.5 mm (L) and 2.2—2.5 mm (V) for the CA1 region of dorsal hippocampus; −3.8 mm (A), 2.5 mm (L) and 7.3 mm (V) for the STN; −5.4 mm (A), 2.0 mm (L) and 7.8 mm (V) for the SNr. Since only four sites could be targeted, the Ctx, amygdala and SNr were recorded in every rat. For the fourth target, either the hippocampus or STN was selected. Due to this limitation there are no simultaneous recordings of hippocampal and STN neurons. The headstage was secured onto the rat's cranium with dental cement using six anchoring screws (1 mm diameter) surrounding the surgery area. Animals received ampicillin (60,000 U, i.m.) before surgery to prevent infection. Animals were housed individually and allowed to recover from surgery for at least 14 days before being subjected to the experiment.

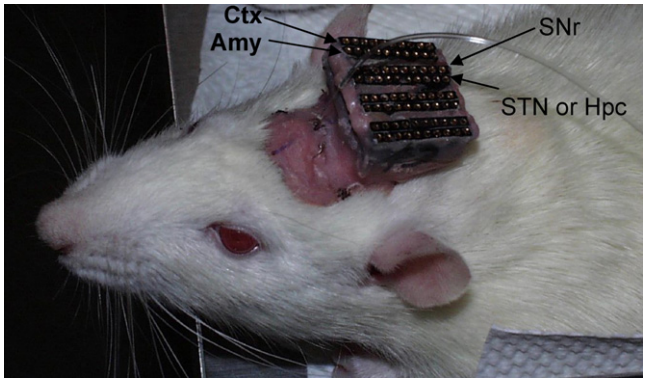

Figure 1 Photograph showing the configuration of electrode arrays. Eight electrodes arrays were implanted into the Ctx, Amy, SNr, STN or Hpc bilaterally. Arrows indicted the arrays implanted in different regions in the right side of the brain, same arrangement was made in the left side of the brain.

Experimental procedures

Kindling stimulation was delivered daily into one amygdala (eight right side and seven left side) using a 1 s stimulation train at 60 Hz, 1 ms pulse width, at 100—300 μA. Rats were placed in a chamber with dim light. Rats were more active and performed better during the dark cycle in operant tasks. Stimulation was initiated when the rat was at rest, usually about 10 min into the experimental session. Daily kindling gradually induced progressive symptoms of seizures as classified by Racine (1972). Initially head bobbing and jaw movement were observed, followed by facial clonus, rearing, forelimb clonus and finally stage 5 kindled convulsive seizures were apparent with 1—2 weeks of kindling. Animal behaviors were recorded with a digital video camera that was synchronized with a data acquisition system with 30-ms time resolution (Magnet, Biographic Inc. Winston-Salem, NC).

Extracellular recording of the four selected brain areas were performed by connecting a head stage plug with unity gain preamplifiers and a lightweight cable between a motor-assisted commutator and the implanted microwire assembly. The commutator was free to turn as necessary, permitting unrestricted movement of the rat. Neuro-electric signals were passed from the headset assemblies to programmable amplifiers, filters (0.5 and 5 kHz) and a multichannel spike-sorting device (Plexon Inc., Dallas, TX). Valid spikes (signal to noise ratio >3) were selected using amplitude and duration thresholds. And waveforms were recorded during experimental sessions.

As many as 62 neurons from the Ctx, amygdala, SNr and the STN or hippocampus were monitored simultaneously from 64 microelectrodes. Spike activity before and during amygdala kindled seizures was recorded (1 kHz sample rate) and monitored with Magnet data acquisition software (Biographics Inc.). Spike train activity was analyzed offline with the PC-based programs Stranger (Biographics Inc.) and Nex (Plexon Inc.).

Data analysis

Cross-correlation analysis was performed to reveal the temporal sequence of synchronized firing (Chang et al., 2000). Cross-correlation histograms were created with the Nex program. One neuron was selected as the reference neuron and all other neurons recorded within that same session were defined as partner neurons for the cross-correlation analysis. The time of occurrence of spikes from the reference neuron was set at 0 s and the partner neuron's firing 0.2—0.5 s before and after each reference neuron's spike was plotted using a 1-ms bin size. The spikes appearing on the plus side of the time scale represent the firing of a partner neuron after the reference neuron, and the spikes on the minus side of the time scale represent the partner neuron's firing before the reference neuron. The significance level of the cross-correlograms was tested using 99% confidence level in the Nex program. The numeric results were then exported to *Matlab* as a matrix, peaks above the 99% confidence level were detected by Matlab and the distance (called peak latency) between the peak and 0 point were calculated in *Matlab* for each significant pair of the cross-correlation. Each calculated 0 point to peak distance was transformed to a time lag value using the following formula:

$$\text{time lag} = \text{peak latency} \times \text{bin size}.$$

Depending on the duration of the seizure episode, a 60—398 s period immediately following kindling stimulation was selected for cross-correlogram analysis. This period covered the whole seizure episode including all stages of that particular seizure. In some cases, the early stage of a seizure lasted for a very short period of time (<5 s), which prevented us from analyzing different stages of seizures due to an insufficient number of spikes. Thus, the data described below can be thought of as representing the total expression of a fully generalized stage 5 seizures. Student's *t*-test was used to compare the time lags between brain regions. In all cases, $p < 0.05$ was considered significant.

Histology

At the conclusion of the final experimental session, each animal was subjected to the same anesthesia as in surgery. A positive current of 10—20 μA was passed through selected microwires for 10—20 s to deposit iron ions. Animals were then sacrificed and perfused intracardially with a 4% paraformaldehyde solution. Coronal sections (45 μm thick) were cut through the Ctx, hippocampus, amygdala, STN and SNr and mounted on glass slides. Incubation of the mounted sections in a solution containing 5% potassium ferricyanide/10% HCl revealed the iron deposits (recording sites) in the form of blue dots. Boundaries of the four brain areas were assessed with reference to the rat brain atlas of Paxinos (1986).

Results

Histology and data selection

The data from all kindling and recording sites were confirmed to be located in the desired structures (Fig. 2). The cross-correlograms were taken from fully kindled rats, which had previously experienced no less than stage 5 seizures. The average kindling rate to the first stage 5 seizure was 8.9 ± 2.1 stimulations.

Synchronization of neural activity during amygdala kindled seizures

Pairwise cross-correlograms were created for all sets of simultaneously recorded neurons. A total of 8216 pairs of cross-correlograms from 485 recorded neurons (146 Ctx, 114 basolateral amygdala, 31 STN, 83 hippocampus and 111 SNr neurons) were analyzed in kindled rats expressing stage 5 seizures. Depending on the duration of seizure episode, periods of 60—398 s (186 ± 29 s) immediately following the kindling stimulus were selected to be analyzed. These periods covered all stages of kindled seizures in each case. A matched period before the kindling stimulation in the same session was selected as the control period. Example of single neural activity before and during kindled seizures is shown in Fig. 3. Fig. 4 demonstrates crosscorrelogram of pairs of neurons in different brain regions before and during kindled seizures. Synchronized activity between different neurons was rarely found before the kindling stimulation (Fig. 4A and C). However, amygdala stimulation in the kindled rats triggered immediate seizures with massive synchronized activity (Fig. 4B and D), as well as behavioral seizures, beginning with jaw movements, followed by nodding of the head and ultimately stage 5 clonic motor convulsions. Table 1 shows the percentage of significantly cross-correlated pairs of neurons between different and within the same brain regions. The degree of synchronization within the same structure, in terms of percentage of significantly correlated pairs of neurons, surprisingly was lowest in the kindled focus, the amygdala (27%), and highest in the cerebral cortex (64%).

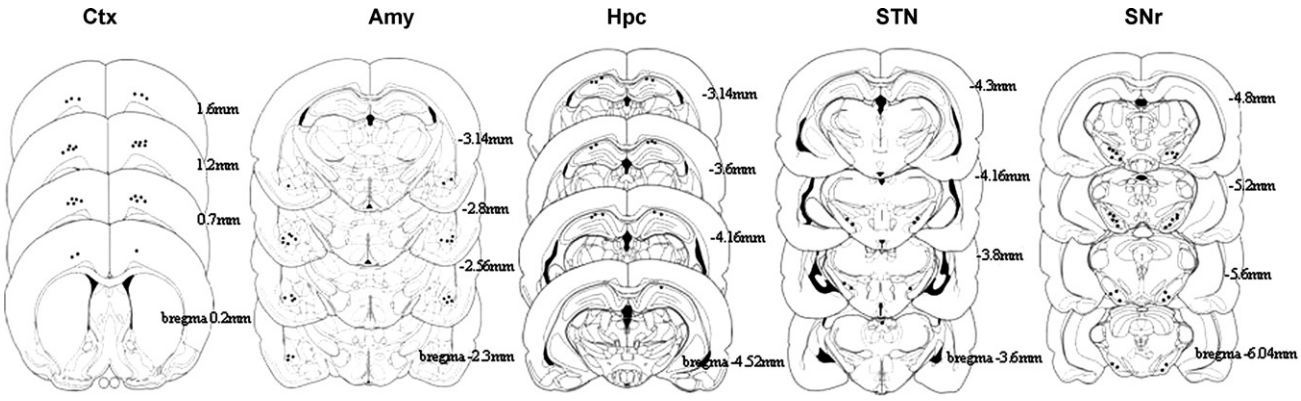

Figure 2 Histological localization of recording electrodes in the Ctx, Amy, Hpc, STN and SNr.

Spread of ictal discharges in the ipsilateral side of corticolimbic basal ganglia system

Temporal relationship between amygdala kindling site and other brain regions

Detailed analysis of time lag in the cross-correlogram provides the sequence of spread of ictal discharges within the mesocortical and basal ganglia system. Activity in the amygdala kindled site led activity in all of the other regions in the cross-correlation analysis. The time lag from the amygdala spikes ranged from 14 ms in the Ctx to 30 ms in the STN (Fig. 5A). Fig. 6 shows the distribution of synchronized peaks of different brain regions in relation to spikes within the amygdala kindled site. Peaks of neurons in the hippocampus and the STN never preceded the zero point set for the amygdala reference spikes in the cross-correlogram. That is, STN and hippocampal neurons consistently fired on the 'plus side' of amygdala neurons. This finding indicates that the amygdala generally led the STN and hippocampus in synchronized firing. In the SNr and Ctx, there were a few peaks of

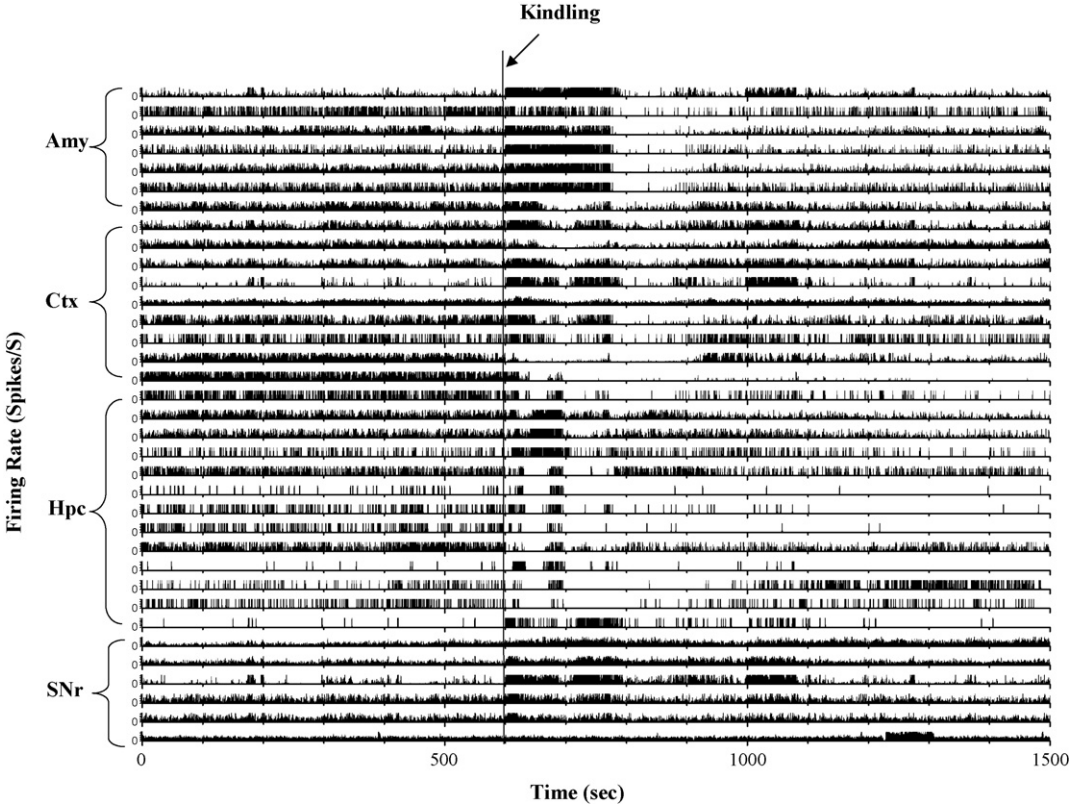

Figure 3 Example of single unit activity recorded simultaneously from the amygdala (Amy), cortex (Ctx), hippocampus (Hpc) and substantia nigra pars reticulata (SNr) during kindled seizures. Kindling stimulation was delivered at 600 s as indicated by arrow. Notice a variety of neural responses took place immediately following kindling stimulation. Rate meter was plotted using two times of local mean as maximum firing rate.

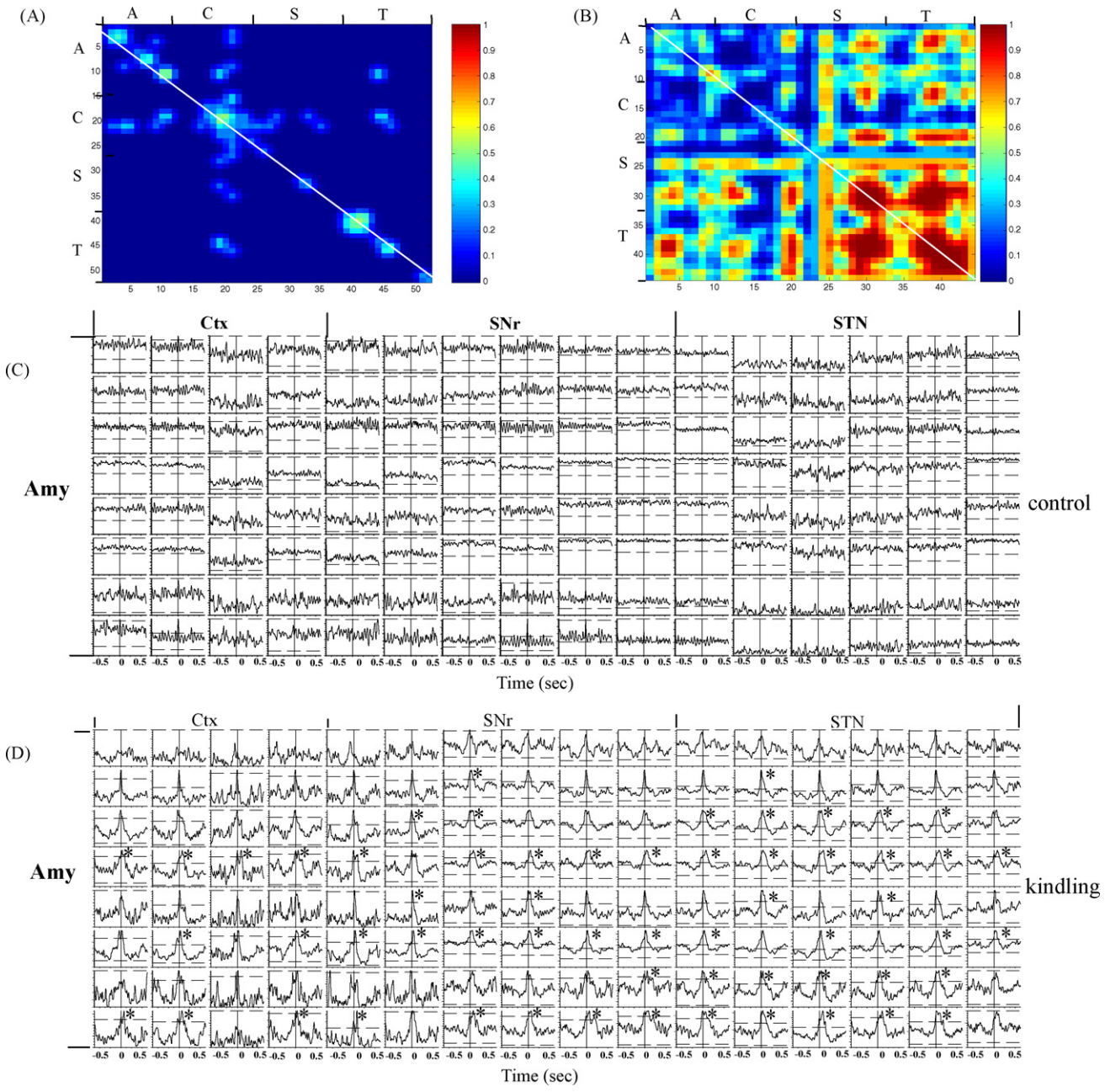

Figure 4 Synchronized activity between simultaneously recorded neurons from the Amy, Ctx, STN and SNr before and during amygdala kindled seizures. (A) Color coded significant cross-correlation level (99% confidence level shown as red) between neurons in different brain regions before amygdala kindling. Note that there was negligible cross-correlation between different neurons. (B) During amygdala kindled seizures, massively synchronized firing appeared between neurons within the same and across different brain regions. The white diagonal line represents autocorrelation. (C) Cross-correlogram analysis of synchronized activity between the neurons in the amygdala kindling site and other regions before amygdala kindling. Note that there was no obvious cross-correlation between the neurons. (D) During amygdala kindled seizure, however, massive synchronization took place between neurons as demonstrated by peaks above 99% confidence lines. Many of the cross-correlations revealed a time lag of synchronized activity peaks. Note that most of the synchronized peaks lay on the plus side of cross-correlogram plot, indicating a delay following spikes in the amygdala kindling site (indicated by asterisk '*'). A, amygdala; C, cortex; S, SNr; T, STN).

correlated firing that appeared before the amygdala spikes (on the minus side), however, most of peaks occurred after the amygdala spikes, indicating a leading position of amygdala cells in synchronized firing through the entire seizure epoch.

Temporal relationship between basal ganglia structures

Two basal ganglia sites, the STN and SNr, were examined in the present study. These two sites have been implicated in seizure control (Gale and Iadarola, 1980; Depaulis et al., 1994; Veliskova et al., 1996). The STN sends a major gluta-

Table 1 Percent of cross-correlated pairs between neurons in different brain regions

	ak	ck	hk	sk	tk	an	cn	hn	sn	tn
ak	*27.5*	24.3	15.8	43.7	45.3	18.8	23.2	8.5	41.8	20.0
ck		*64.3*	22.5	46.3	37.0	28.9	50.5	9.6	38.9	17.3
hk			*39.9*	44.0	[a]	18.0	27.3	21.5	19.7	[a]
sk				*40.0*	46.9	21.9	35.8	27.6	34.3	37.3
tk					*56.1*	14.3	34.7	[a]	50.0	36.1
an						*32.5*	21.9	9.7	24.6	14.3
cn							*51.8*	10.9	29.3	38.5
hn								*30.4*	10.9	[a]
sn									*44.7*	27.0
tn										*50.0*

Ak, amygdala kindling side; ck, cortex kindling side; hk, hippocampus kindling side; sk, SNr kindling side; tk, STN kindling side; an, amygdala non-kindling side; cn, cortex non-kindling side; hn, hippocampus non-kindling side; sn, SNr non-kindling side; tn, STN non-kindling side.

[a] Data not available since STN and Hpc were not recorded simultaneously.

matergic projection to the SNr, by which it regulates basal ganglia output. Unexpectedly, we found that the STN usually lagged the SNr in synchronized firing during kindled seizures. Fig. 7A demonstrates cross-correlogram plot using SNr spike as a reference event in one representative rat before and during amygdala kindled seizures. No synchronized firing was observed before amygdala kindling when the rat was behaving normally (left panel). All of these neurons exhibited synchronized firing during amygdala kindled seizures (right panel). Most of STN synchronized spikes appeared after SNr spikes (on the plus side). Fig. 7B shows the distribution of time lags of all cross-correlated pairs between the SNr and STN. As can be seen, most of the synchronized spikes of the STN laid on the plus side of the plot, indicating a time lag behind SNr spikes. The mean time lag of STN spikes was 8.2 ± 2.6 ms ($p < 0.01$, Student's *t*-test, STN lagged behind SNr spikes, Fig. 5B).

Temporal relationship between basal ganglia and cortex

No obvious time lag was found between the SNr and Ctx. As demonstrated in Fig. 8A, the correlated peaks were evenly distributed around the 0 s point in the cross-correlation plot with a mean time lag of 1.4 ± 1.5 ms ($p > 0.05$ Student's *t*-test, Fig. 5B). The STN neurons, on the other hand, consistently lagged Ctx neurons with a mean delay of 10.6 ± 2.6 ms ($p < 0.01$, Student's *t*-test, Figs. 5B and 8B).

Temporal relationship between hippocampus and cerebral cortex/basal ganglia

Fig. 9A shows the distribution of synchronized hippocampal spikes in relation to cortical neurons during amygdala kindled seizures. Many correlated spikes in the hippocampus occurred 10 ms after cortical spikes in the cross-correlogram plot. Few hippocampal peaks appeared before cortical spikes, and the biggest hippocampal peak appeared at 10 ms. Overall, hippocampal cells lagged cortical cells in synchronized firing with a mean time lag of 7.1 ± 2.0 ms (Fig.5B, significant difference from 0 ms, Student's *t*-test $p < 0.01$).

Hippocampal cells also lagged SNr cells in synchronized firing. Fig. 9B shows the distribution of synchronized hippocampal spikes around SNr spikes. Most of the hippocampal spikes occurred on the plus side of SNr spikes with mean time lag of 11.6 ± 1.9 ms ($p < 0.01$, Student's *t*-test, Fig. 5B).

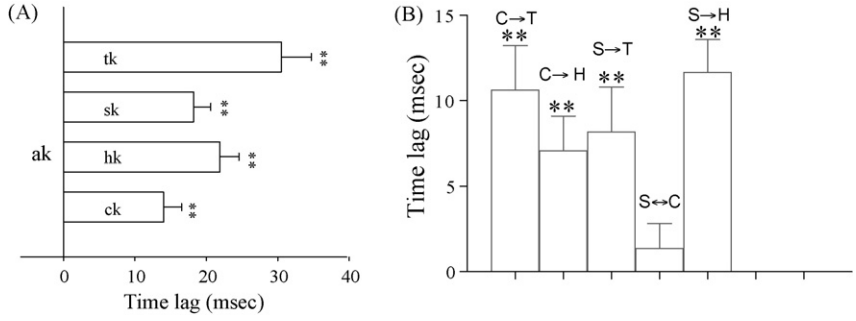

Figure 5 Time lags between the amygdala kindling site and other regions in the kindling side of the brain during amygdala kindled seizures. (A) Amygdala neurons led cortical, hippocampal, SNr and STN neurons in synchronized firing, ranging from 14 ± 2.5 ms for cortical neurons to 30.5 ± 4.2 ms for STN neurons. (B) Time lags between the neurons of different regions in the kindling side. A, amygdala; C, cortex; H, hippocampus; S, SNr; T, STN. The arrow indicates the direction of the temporal sequence (Student's *t*-test, $^{**}p < 0.01$ vs. reference spike).

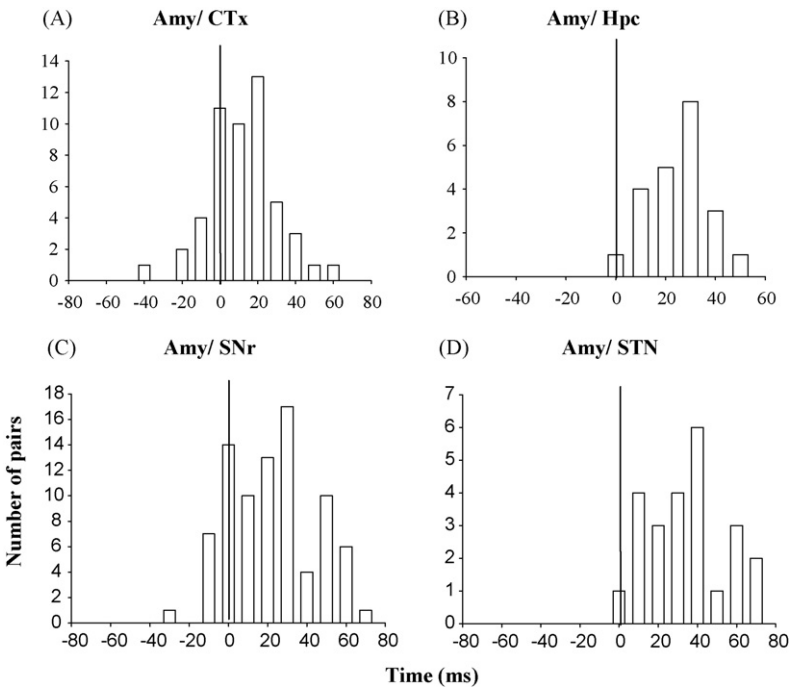

Figure 6 Distribution of synchronized activity peaks between neurons in the amygdala kindling site and other regions ipsilateral to the kindled site. The numbers of neuron pairs (ordinate) that exhibited different time lags (abscissa) are shown. Note that most of correlation peaks in the Ctx and SNr and all of the peaks in the hippocampus and STN occurred in the plus side of the plots, following amygdala spikes, indicating that amygdala neurons led the other regions in synchronized firing.

Spread of ictal discharges between ipsilateral and contralateral regions

As ictal discharges spread globally and caused massive synchronization among widespread brain regions in both hemispheres, the temporal sequence of synchronized activity between the analogous regions in different sides of the brain can provide additional information about the organization of epileptic network underpinning amygdala kindled seizures. Cross-correlogram analysis revealed that the contralateral amygdala lagged the kindled amygdala in synchronized firing during seizures (Fig. 10A). The mean lag time between the ipsilateral and contralateral amygdala was about 10 ms ($p < 0.05$, Student's *t*-test, Fig. 10A and F). A similar time lag, ~8 ms, existed between the ipsilateral and contralateral SNr ($p < 0.01$, Student's *t*-test, Fig. 10B and F). For the Ctx, hippocampus and STN, synchronized spikes in the contralateral side were evenly distributed around ipsilateral spikes with time lags less than 2 ms, which were not significantly different from the 0 s reference point (Fig. 10C—F). Thus, our data indicate that there is simultaneous synchronized firing between the ipsilateral and contralateral sides of these regions during the majority of the period encompassing the totality of the amygdala kindled seizures.

Synchronized activity within the same brain region during amygdala kindled seizures

Cross-correlogram analysis of neurons co-localized within the same regions during amygdala kindled seizures showed no significant time lags. Fig. 11A depicts the time lags of synchronized activity within the five recording regions. The time lags ranged from 0.2 ms in the contralateral SNr to 3.3 ms in the contralateral hippocampus. None of them differed significantly from the 0 point when the reference neurons fired.

The schematic plot depicted in Fig. 12 shows the temporal relationship within the corticolimbic and basal ganglia systems during amygdala kindled seizures. The ictal spikes clearly originated in the amygdala kindling site and spread to other regions of the system. In the ipsilateral side, they reached Ctx and SNr first. The ictal discharges then further traveled to the STN and hippocampus. During most of the seizure period, synchronized spikes fired simultaneously between ipsilateral and contralateral cortex, hippocampus and STN. Meanwhile synchronized firing in the amygdala and SNr *contralateral* to the kindling site did lag spikes in the homotopic structures on the kindled side.

Discussion

Of great interest in epileptic research is the temporal sequence of ictal discharge propagation during epileptic seizures (Faingold, 2004; Morimoto et al., 2004; Blumenfeld, 2005). 2-Deoxyglucose uptake and Fos-like immunoreactivity have been employed to measure the activity of different structures related to seizure expressions. The early stages of seizures are likely to involve the amygdala and amygdalo-hippocampal regions in both status and amygdala kindling induced seizures. Activity spreads to other brain regions, including basal ganglia, thalamic nuclei, neocortex as the seizure progress into later stages of general-

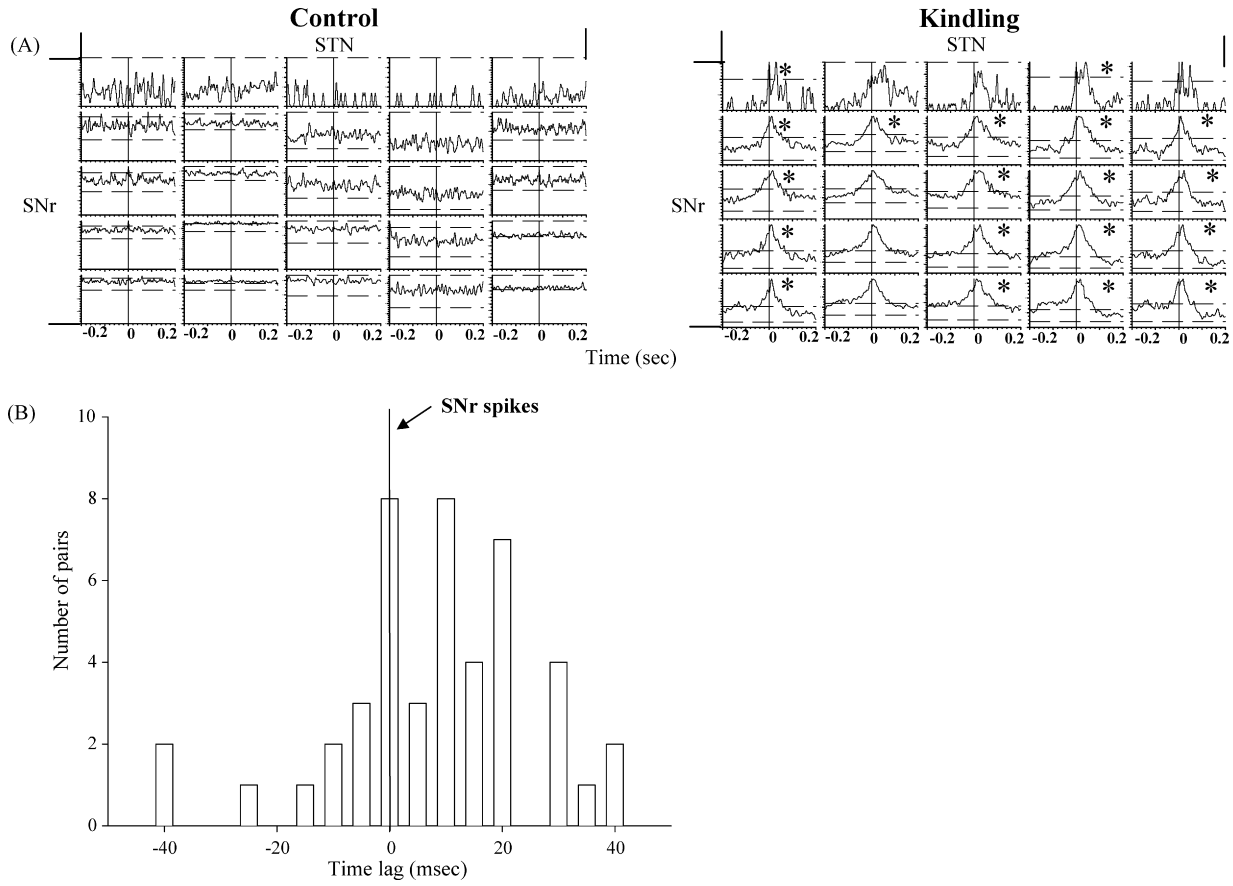

Figure 7 Temporal relationship between STN and SNr neurons during amygdala kindled seizures. (A) Cross-correlogram plots from selected STN and SNr neurons in the kindling side before (left panel) and during amygdala kindled seizures (right panel). SNr neurons were used as reference neurons. Synchronization occurred in these neurons only during amygdala kindled seizure (displayed in the right panel). Most STN neurons lagged behind SNr neurons in synchronized firing (marked by asterisk '*'). (B) Distribution of time lags between synchronized firing of STN and SNr neurons (SNr neurons were reference neurons). Most of the STN spike peaks followed SNr spikes with time lags up to 40 ms.

ized motor seizures (Engel et al., 1978; Clark et al., 1991; McIntyre et al., 1991; White and Price, 1993a,b; Handforth and Ackermann, 1995; Veliskova et al., 2005). Owing to their low temporal resolution (in the order of minutes), these methods can only measure brain activities involved in certain stage of seizures, it cannot detect the propagation of discharge within epileptic networks during the ictal state. The major advantages of single unit recording are the high temporal (ms range) and spatial (mm range) resolutions. When large scale, multiple region recording is employed, as

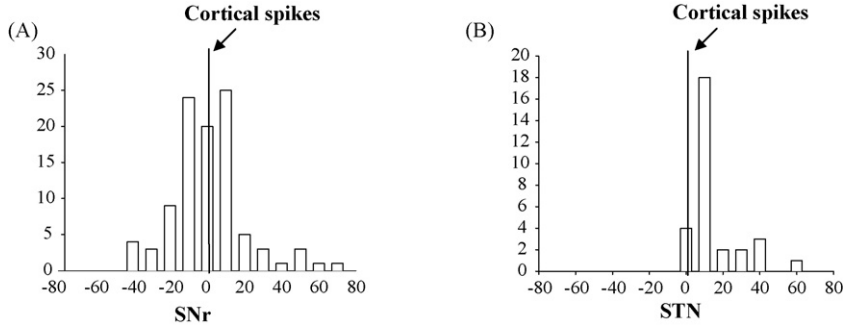

Figure 8 Temporal relationship of correlated firing between Ctx and basal ganglia neurons in the kindling side during amygdala kindled seizures. (A) Distribution of correlated spikes between cortical and SNr neurons using cortical neurons as a reference. Synchronized SNr spikes were distributed evenly around the cortical spikes at the 0 s reference point with an average time lag of -1.4 ± 1.5 ms. (B) Distribution of correlated spikes between cortical and STN neurons. All correlated STN spikes were located on the plus side of the time lag with a peak at 10 ms.

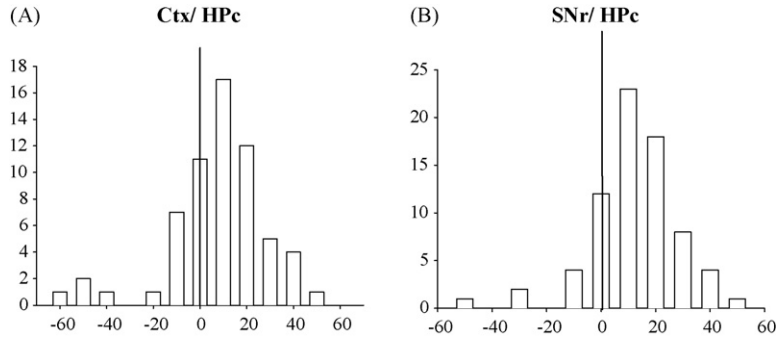

Figure 9 Temporal relationship of correlated spikes between hippocampal and cortical\nigral neurons in the kindling side during amygdala kindled seizures. (A) Distribution of correlated spikes of hippocampal neurons in relation to cortical neurons. The majority of correlated spikes of hippocampal neurons were on the plus side of the plot with a mean time lag of 4.8 ± 3.3 ms. (B) Distribution of correlated spikes of hippocampal neurons in relation to SNr neurons. Most of correlation spikes of hippocampus were on the plus side of plot, with the mean lag time being 11.6 ± 1.9 ms.

in this study, the temporal sequence of propagation of ictal discharges within the epileptic network can be determined precisely.

Amygdala kindling is a desirable model to study the spread of ictal discharges for several reasons. Firstly, the amygdala is one of the most epileptogenic regions in the brain and kindled seizures can be readily developed and triggered with intra-amygdala stimulation. Secondly, the epileptic focus (amygdala) is clearly known to the investigators and can be used as a control for validating analysis proce-

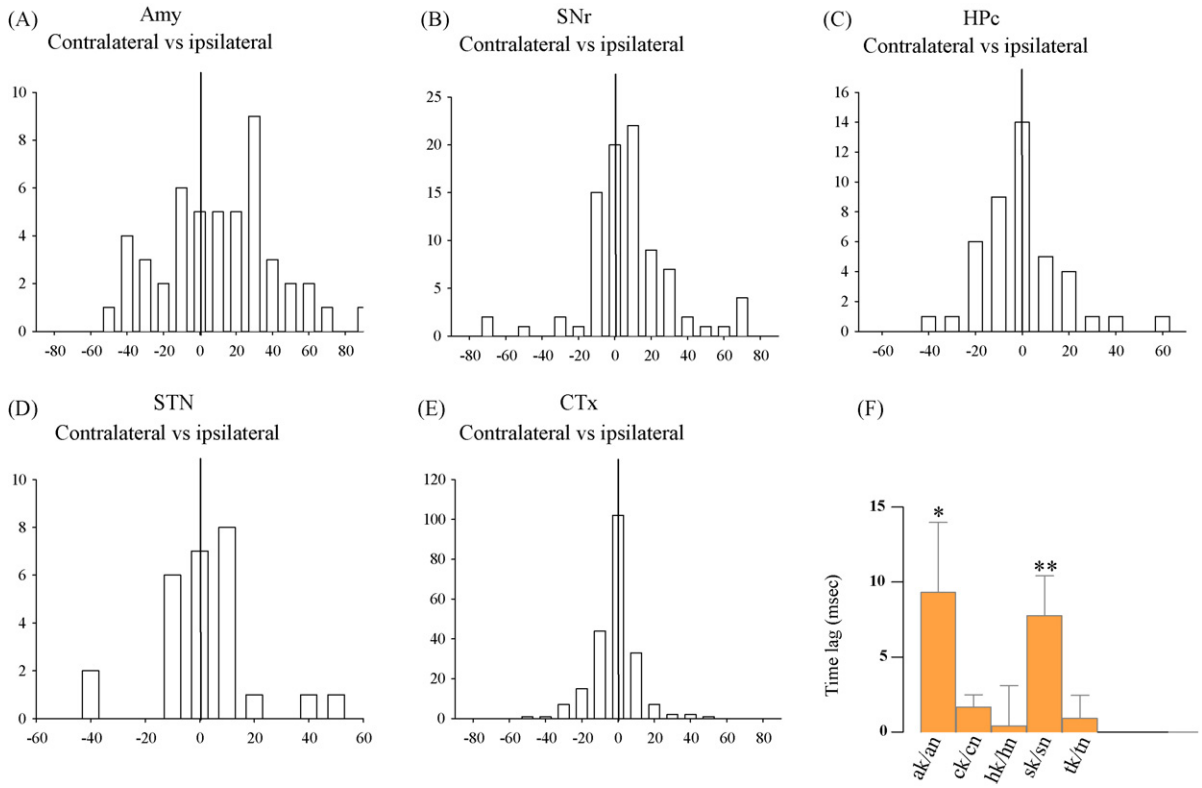

Figure 10 Temporal relationship of correlated spikes between the same region ipsilateral and contralateral to the kindling site. (A) Distribution of correlation spikes in the amygdala contralateral to the kindling site. The contralateral amygdala neuronal spikes occurred with a 9.7 ± 4.7 ms delay following the spikes of neurons within the kindled amygdala. (B) Distribution of correlation spikes of contralateral SNr in relation to SNr ipsilateral to the kindling site. Contralateral SNr neurons fired with a delay of 7.8 ± 2.6 ms relative to SNr neurons ipsilateral to the kindling site. (C—E) Distributions of correlation spikes of neurons in the Ctx (C), hippocampus (D) and STN (E) contralateral to the kindling, relative to neurons in the same structures ipsilateral to the kindling. No time lag was found between the opposite sides in these structures. (F) Summary of time lag data between contralateral and ipsilateral sides of the same regions. A significant time lag was found in the amygdala and SNr regions only ($^{*}p < 0.05$, $^{**}p < 0.01$, Student's t-test).

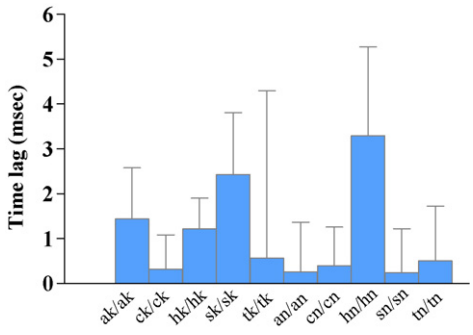

Figure 11 Time lags between synchronized activity of neurons within the same recording region during amygdala kindled seizures. No significant difference between the time lag and reference spikes (at 0 s point) was found in any of the recording regions.

dures. Thirdly, widespread propagation of ictal discharges into different brain regions allows us to study the broad neural network associated the triggered epileptic seizures. And last but not least, this model is relevant to one of the most common clinically observed and intractable forms epilepsy, TLE (Sato et al., 1990; Coulter et al., 2002; Loscher, 2002).

One of the most interesting findings of this study is the early activation of the SNr by the ictal discharges originating from the amygdala. It was unexpected that the SNr would be activated even earlier than the hippocampus, which has

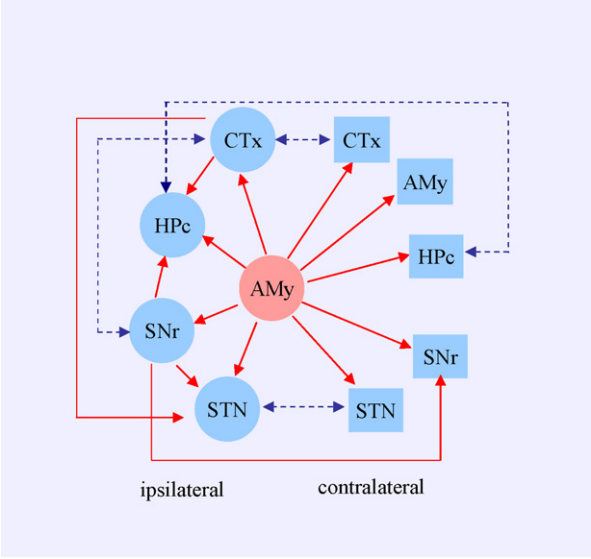

Figure 12 Schematic summary of ictal discharge propagation within the corticolimbic basal ganglia system. Kindling initiates ictal discharges in the amygdala kindling site. Synchronized activity is sequentially propagated to other corticolimbic basal ganglia regions; it reaches the cortical and SNr regions first and than propagates to the hippocampus and STN. Simultaneous spikes were detected between ipsilateral and contralateral cortex, STN and SNr while a time lag occured between spikes in the ipsilateral and contralateral amygdala and SNr neurons. The solid line indicates the existence of a time lag in the direction of the arrow. The dashed line indicates the simultaneous activation of synchronized firing.

reciprocal connections with the amygdala (Amaral et al., 1992; van Groen and Wyss, 1990; Pikkarainen et al., 1999; Braak et al., 1996), and than the STN, which sends a glutamatergic projection to the SNr (Hamani et al., 2004). The anatomic substrate for such early SNr activation is likely to be a direct projection from the amygdala to the SNr (Bunney and Aghajanian, 1976), which could provide orthodromic activation of SNr cells. Early activation of the SNr supports the idea that it might play an important role in seizure control. As a basal ganglia output site, the SNr regulates epileptic seizures through three pathways, the nigrothalamic pathway connecting to the cerebral cortex (Alexander et al., 1990), the nigrotectal pathway regulating the ''dorsal midbrain anticonvulsant zone'' (Redgrave et al., 1992a,b) and the pedunculopontine pathways projected to the pons and spinal cord (Depaulis et al., 1994; Mena-Segovia et al., 2004; Nolte et al., 2006). Several lines of evidence have indicated the SNr plays a key role in mediating epileptic seizures. (1) Endogenous GABA concentrations were decreased in amygdala kindled seizures (Loscher and Schwark, 1987). (2) Microinjection of GABA and its agonists into the SNr blocked the seizure induced by chemical stimulation (Iadarola and Gale, 1981; Zhang et al., 1989), kindling (Loscher et al., 1987; McNamara et al., 1984), electroshock (Mirski et al., 1986), audiogenic stimulation (Gonzalez and Hettinger, 1984) and genetic manipulations (Depaulis et al., 1988). (3) Deep brain stimulation (DBS) of the SNr, presumably via local inhibition, can block amygdala kindled (Morimoto and Goddard, 1987; Shi et al., 2006) and drug induced seizures (Velisek et al., 2002). These findings suggest that the SNr is strategically located in a pivotal position such that it can regulate the propagation of ictal discharges during amygdala kindled seizures (Moshe and Garant, 1996).

It has been reported that anterior and posterior parts of the SNr were differentially involved in seizure control (Moshe et al., 1994). Recent study by Veliskova et al. (2005) found that the SNr posterior was activated during pre-clonic period of flurothyl induced generalized seizures while the anterior part of SNr was not involved till pre-tonic clonic seizure. During the ictal state, both sites increased their activities. Anticonvulsant effect of deep brain stimulation was found only in the anterior part of SNr during flurothyl induced seizures (Velisek et al., 2002). Our recent study demonstrated antiepileptogenic effects of DBS of the anterior part of SNr in the amygdala kindling model (Shi et al., 2006). Based on these observations, electrodes were implanted in the anterior part of the SNr in the present study (Fig. 2).

The hippocampus is a key structure involved in TLE. In spite of the existence of abundant reciprocal connections between the hippocampus and amygdala (Amaral et al., 1992; van Groen and Wyss, 1990; Pikkarainen et al., 1999), we found that the ictal discharges reached the hippocampus later than the Ctx and SNr. The delayed activation of hippocampal neurons does not necessarily indicate that cortical or SNr activity drives hippocampal synchronized firing. The delay may be a result of the trisynaptic circuit and dentate filtering within the hippocampal complex (Coulter, 2000), whereby the signals traveling from the amygdala and entorhinal cortex to the dentate gyrus, and from there to the CA3 and CA1 regions, experience delays at each step (Anderson et al., 1971;

Swanson et al., 1978). On the other hand, tightly coupled synchronization between both sides of the hippocampus was found in the present study. This finding of bilateral hippocampal synchronization was consistent with previous research in which a similar finding was obtained during the clonic stage of amygdala kindled seizures (Pijn et al., 1991), and suggests that there is inter-hippocampal synchronized oscillation during kindled seizures. This may explain why the kindling of one hippocampus kindles in parallel the contralateral hippocampus (McIntyre and Edson, 1987).

In spite of the important role of the hippocampus in TLE, hippocampal inactivation had only a limited effect on retardation of amygdala kindling (Tanaka et al., 1991) or no effect at all (Racine et al., 1988). Furthermore, Sato et al. (1990) proposed that the hippocampus and amygdala might act as a mutually antagonistic circuit during seizure expression. The constant lag of hippocampus firing behind not only the amygdala kindling site, but also the Ctx and SNr, together with the smaller percent of neuron pairs with synchronized firing between the amygdala kindling site and the hippocampus (Table 1), supports the notion that the hippocampus may not be a critical structure in mediating amygdala kindled seizures. The hippocampus also appears not to be involved during the spontaneous convulsive seizures that occur days to weeks following exposure to pilocarpine induced status epileptics (Harvey and Sloviter, 2005).

It is clear, however, that the cerebral cortex is an important structure mediating amygdala kindling, especially during stage 5 convulsive seizures. Cortical regions send abundant projections to the hippocampus, STN and amygdala and are essential for the manifestation of motor seizures (Braak et al., 1996; McDonald, 1998; Hamani et al., 2004). Kelly et al. (1999) used cortical spread depression, a reversible lesion method to inactivate frontal motor cortex, and found that it could block the convulsive expression of amygdala kindled seizures. The authors emphasized that the cortex mediates a crucial role in clonic motor seizures by transferring the ictal discharges to the brain stem and spinal cord. Early activation of the cerebral cortex during synchronized firing supports the view that the cerebral cortex plays an important role in amygdala kindled seizures. The reciprocal connections between the cerebral cortex and amygdala (Mascagni et al., 1993; McDonald and Mascagni, 1996; McDonald et al., 1996) provide anatomic substrates for such synchronized activity. The lack of a time lag between the two cortical hemispheres may reflect a global activation of cortical circuits during the majority of the clonic motor seizures.

The STN is a pivotal structure in the basal ganglia system, which receives abundant cortical and pallidal inputs, and projects to basal ganglia output nuclei, such as the globus pallidus internal and the SNr. In addition, it also sends projections to the pedunculopontine nucleus and other brain stem structures. The STN thus is positioned to play a critical role in motor and other functions (Hamani et al., 2004). Paz et al. (2005) reported a synchronized, rhythmic burst of STN activity that was associated with cortical EEG spike and wave discharges in genetic absence epileptic rats. The authors suggested that such discharges may convey signals to the basal ganglia output nuclei and contribute to the thalamocortical spike and wave discharges.

Several recent studies have tried to use DBS in the STN to reduce epileptic seizures in both animal models and epilepsy patients (Bingaman et al., 2000; Chabardes et al., 2002; Dinner et al., 2002; Shon et al., 2004; Usui et al., 2005). The effect of DBS of the STN is presumably to induce local inhibition in the STN, which in turn reduces excitatory input to the SNr. Thus, the conceptual framework of both Paz's study and the DBS experiments is based on the activity of STN-SNr projections. However, our results demonstrated unexpectedly that the STN lags behind the SNr in synchronized firing during generalized amygdala kindled seizures. Again, time lag *per se* does not necessarily indicate a drive-follow relationship between pairs of neurons; it is possible that both cells follow the same driving signal, in this case ictal discharge from the amygdala via different pathways. It is possible that ictal discharge may pass through the cortex before reaching the STN, the possibility was supported by the fact that the STN lagged behind the Ctx in synchronized firing. A recent study by Sharott et al. (2005) revealed similar SNr to STN signal transfer directions during a period with 1 Hz slow wave cortical activity, whereas the direction was reversed during 15 Hz high frequency oscillations. A low frequency oscillation (around 2 Hz) was found during stage 5 amygdala kindled seizures in our study (Woodward et al., 2003), suggesting that there may be a common mechanism underlying SNr-STN signal transfer direction in both studies.

In summary, the present study provides a detailed account of the temporal sequence of propagation of ictal discharges during amygdala kindled seizures. The observed early activation of the cerebral cortex and SNr highlights the important role of these structures in generalized amygdala kindled seizures. Similar analyses can be used to explore possible different pathways subserving other types of epileptic seizures, and help us to further understand the mechanisms of epilepsy and to design new therapeutic strategies.

Acknowledgements

This study was supported by NIH grants NS-43441 and NS 40628, TW-006144 to JYC and NS-19608 to DJW, National Natural Science Foundation of China (30170307, 30370461) to FL.

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