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Photic-Induced Sensitization: Acquisition of an Augmenting Spike-Wave Response in the Adult Rat Through Repeated Strobe Exposure

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Uhlrich, D. J., K. A. Manning, M. L. O'Laughlin, and W. W. Lytton. Photic-induced sensitization: acquisition of an augmenting spike-wave response in the adult rat through repeated strobe exposure. *J Neurophysiol* 94: 3925–3937, 2005; doi:10.1152/jn.00724.2005. It is well established that patterns of sensory input can affect neuroplastic changes during early development. The scope and consequences of experience-dependent plasticity in the adult are less well understood. We studied the possibility that repeated exposure to trains of stroboscopic stimuli could induce a sensitized and potentially aberrant response in ordinary individuals. Chronic electrocorticographic recording electrodes enabled measurement of responses in awake, freely moving animals. Normal adult rats, primarily Sprague-Dawley, were exposed to 20–40 strobe trains per day after a strobe-free adaptation period. The common response to strobe trains changed in 34/36 rats with development of a high-amplitude spike-wave response that emerged fully by the third day of photic exposure. Onset of this sensitized response was marked by short-term augmentation of response to successive strobe flashes. The waveform generalized across the brain, reflected characteristics of the visual stimulus, as well as an inherent 6- to 8-Hz pacing, and was suppressed with ethosuximide administration. Spike-wave episodes were self-limiting but could persist beyond the strobe period. Sensitization lasted 2–4 wk after last strobe exposure. The results indicate visual stimulation, by itself, can induce in adult rats an enduring sensitization of visual response with epileptiform characteristics. The results raise the question of the effects of such neuroplastic change on sensation and epileptiform events.

INTRODUCTION

Neurons modify their responses on the basis of sensory experience. Experience-dependent neuronal plasticity comprises many forms and is associated with long- and short-term changes at synaptic, cellular, and morphological levels. Plasticity is considered integral to brain capacity to adapt to the environment (Chuckowree et al. 2004; Destexhe and Marder 2004; Poncer 2003; Tsodyks and Gilbert 2004), but can also have mixed (Hodzic et al. 2004) or detrimental effects (Romanelli and Esposito 2004; Sah et al. 2003). We are only beginning to understand the changes induced by natural sensory stimuli and how the functions of whole circuits in active vertebrate brains may be altered by neuroplastic change.

Plasticity is present in the visual system, and long-term neuroplastic changes have been shown in the adult visual pathways (Castro-Alamancos and Calcagnotto 1999; Heynen and Bear 2001; Otsu et al. 1995; Salami et al. 1999). Plasticity is often associated with perceptual learning tasks (Tsodyks and Gilbert 2004), but sensory stimulation, itself, appears to alter visual responses outside of learning paradigms. A common finding is long-term response sensitization, that is, a persistent increase in responsiveness resulting from repeated visual stimulus presentation. Sensitization has been reported in human psychophysical studies (Seitz and Watanabe 2003; Watanabe et al. 2001) and in late components of the rat occipital–evoked potential (Dyer 1989). Clinical reports (Appleton et al. 2000; Gastaut et al. 1962; Harding and Jeavons 1994; Walter and Walter 1949) have also raised the possibility that repeated exposure to strobe stimuli may sensitize responses. Taken together, these results indicate that individuals may acquire a sensitized response through long-term plastic processes following repeated exposure to photic stimulation.

Stroboscopic stimulation was effective in previous basic science and clinical studies providing evidence of long-term change (e.g., Appleton et al. 2000; Dyer 1989; Gastaut et al. 1962; Harding and Jeavons 1994; Walter and Walter 1949). In addition, trains of electrical shocks to the thalamus or cortex produce a form of short-term neuroplasticity, the thalamocortical augmenting response (Bazhenov et al. 1998a,b; Castro-Alamancos and Connors 1996a–c; Dempsey and Morison 1943; Steriade and Timofeev 1997), which in some cases can lead to self-sustaining paroxysmal activity (Steriade et al. 1993). Thus we theorized that trains of intense photic stimulation might be efficacious in inducing neuroplastic change leading to photoparoxysmal activity.

To test this, we exposed ordinary laboratory rats to strobe trains and evaluated their response by means of electrocorticographic recording. Repeated photic exposure in this intact, mature vertebrate nervous system led to induction of a long-lasting sensitization of visual response that exhibited spike-wave morphology and generalized across the brain. We evaluated the acquisition and expression of this sensitized response.

METHODS

Subjects

Normal 200- to 500-g young adult commercially obtained (Harlan Sprague-Dawley) outbred rats were used. Experiments were conducted with 30 male Sprague-Dawley rats. Essential findings were confirmed additionally in two female Sprague-Dawley rats, two male Long-Evans rats (Blue Spruce), and two male Wistar Rats. All rats were in good health and exhibited normal behavior before testing with no history of epileptiform activity.

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The experimental protocol was approved by the University of Wisconsin Animal Care and Use Committee. Rats were maintained on a 12-h:12-h light/dark cycle in standard laboratory animal housing at the University of Wisconsin, with food and water ad libitum. Animals were tested experimentally in the morning, within 2–6 h after the lights turned on at 0600 hours.

Surgical procedures

Before surgery for implantation of chronic recording electrodes, animals were administered a combination of ketamine (60–90 mg/kg, ip) and xylazine (5–10 mg/kg, ip) to effect. Supplemental doses of ~25–33% of the original dose were readministered as necessary to maintain deep anesthesia throughout the surgical procedure, with xylazine supplements administered one-third as often as ketamine supplements. Rectal temperature was maintained throughout surgery at 37.5–38.0°C using a feedback-controlled heating blanket.

The deeply anesthetized rat was placed in a stereotaxic apparatus and prepared for aseptic surgery. Surgical instruments were wet sterilized. The dorsal surface of the head overlying the brain was shaved and bathed in povidone/iodine solution. The skull was exposed by a midline incision and retraction of overlying tissues. Craniotomies <1 mm diam enabled insertion of electrographic recording electrodes at four predetermined sites, bilaterally from occipital to frontal cortex (occipital 2.0 mm, 5.0 mm, 8.0 mm, frontal 11.0 mm anterior to lambda; ±2.0 mm lateral; Paxinos and Watson 1986). Craniotomies for ground and reference electrodes were placed over the cerebellum. We evaluated the suitability of this commonly used reference location (e.g., Meeren et al. 2002) in preliminary tests by recording from it against reference electrodes in muscle and contralateral cerebellum. There was no evidence of any visually related response from the electrode overlying cerebellum. At each craniotomy site, the uninsulated tip (0.5 mm) of a strand of 30-gauge stainless steel ultraminiature wire (Cooner) was bent at a right angle, placed flat on the dura, and held in place with miniature stainless steel or Teflon screws tapped into the skull through the craniotomy. Wires exiting the craniotomy fed into one end of a miniature connector (Ginder), and the assembly was secured to the skull with additional stainless steel screws and dental acrylic. Wound margins were closed (4-0 nylon) and treated with a broad-spectrum antibiotic ointment and 1% lidocaine. Animals were administered buprenorphine (0.05 mg/kg, sc) postoperatively.

Electrocorticographic recording

Signals arising from the miniature connectors on the rat skull fed into a multi-channel Grass EEG amplifier model 8–16 and band-pass filtered between 1 and 70 Hz. Stimulus presentation and digitized data collection were under computer control (Brainware, TDT). Signals were collected at 25,000 samples/s and computer analyzed typically with 1,000 samples/s (MATLAB and NeuroExplorer).

Experimental design

Experimentally naïve rats were introduced to the experimental environment, minus the strobe light, 1 wk after surgery. Rats were kept in their home cages at all times and preadapted to minimize the incidence of exploratory behavior during recording. Previous studies showed that driven thalamocortical oscillations, paroxysmal responses, and seizures in photosensitive individuals are affected by behavioral state and that exploratory movement or its EEG correlate, theta activity, are related inversely to response amplitude (Bigler 1977; Castro-Alamancos and Connors 1996b; Dyer 1989; Gastaut et al. 1962; Hishikawa et al. 1967). The 3-day adaptation period, with one session daily, allowed rats to become familiar with all aspects of the experiment before the introduction of strobe flashes, provided confirmation that electrodes were working properly, and enabled examination of electrographic recordings before introduction of the strobe stimulus. No rats exhibited spontaneous spike-wave responses or other seizure abnormalities during the adaptation period.

Rats were brought to the quiet recording room in their clear, plastic home cages. Low-level room lighting (<5 cd/m^2) was maintained (e.g., Gastaut et al. 1962; Hishikawa et al. 1967; Leroy and Roussel 1961). The home cage (length 0.5 m × height 0.21 m × width 0.27 m) was placed inside the recording chamber (0.55 × 0.4 × 0.4 m), lined on all sides with mirrors to ensure visual stimulation regardless of the position of the rat. Long, lightweight overhead wires connected the recording apparatus to the headmount. Rats were otherwise completely unrestrained.

After adaptation sessions, experimental sessions with strobe lights commenced. Each session began with 1 h of electrocorticographic (ECoG) recording without stroboscopic stimulation during which baseline data were collected. We then initiated trains of stroboscopic stimulation. Data were recorded continuously before, during, and after each train of strobe flashes, which we refer to as a "trial." Intertrial intervals during which no stimulation occurred ranged from 30 s to 1 min. Experimental sessions typically comprised 20–40 strobe trials, but extended ≤180 trials for experiments that used pharmacological manipulation or multiple strobe conditions. Experimental parameters were kept constant within experiments. Thus the strobe portion of the experiment ranged from 25 min to 1.5 h, with one session conducted per day.

Activity of the rat was monitored through video surveillance and direct observation. Most data were collected while rats were in a quiet waking state. Data collection was suspended during episodes of protracted, active movement or if rats closed their eyes to sleep.

Visual stimulation

Stroboscopic flash stimuli (10 μs) were generated with a standard Grass photostimulator (Model PS33). The stroboscope was positioned centrally over the recording chamber, with the front diffusing surface of the lamp level with the top of the recording chamber. An integrating photometer was used for luminance calibration; luminance of reflected light from the stroboscope flash within the animal cage measured 5.1 cd·s/m^2 (see Fig 12, x-axis). Variations in strobe intensity were accomplished by means of neutral density filters in front of the strobe; this eliminates confounding spectral changes in the strobe flash that occur if intensity is manipulated by varying current to the strobe (cf. Riggs 1965). The strobe light was triggered externally by the computer, enabling precise control of temporal stimulus frequency (1–30 Hz) and stimulus train duration (0.5–6 s). Preliminary results suggested large magnitude responses were elicited with 8-Hz stimulation, and the shortest strobe train at which response incidence and duration appeared maximized was 1–2 s (see *Response quantification*). Thus 1- to 2-s trains of 8-Hz stroboscopic stimulation were chosen as the standard stimulus in most experiments.

Response quantification

The emergent spike-wave response varied in both amplitude and duration. For quantification, response magnitude was calculated as the rectified and integrated ECoG voltage during the period of strobe stimulation.

RESULTS

Acquisition of a sensitized response

Repeated exposure to trains of strobe flashes led to a progressive change in the electrographic responses recorded over rat cortex. Figure 1 shows responses from occipital cortical electrodes in one rat on the first and third days of exposure to the photic stimulus. The rat displayed simple photic responses

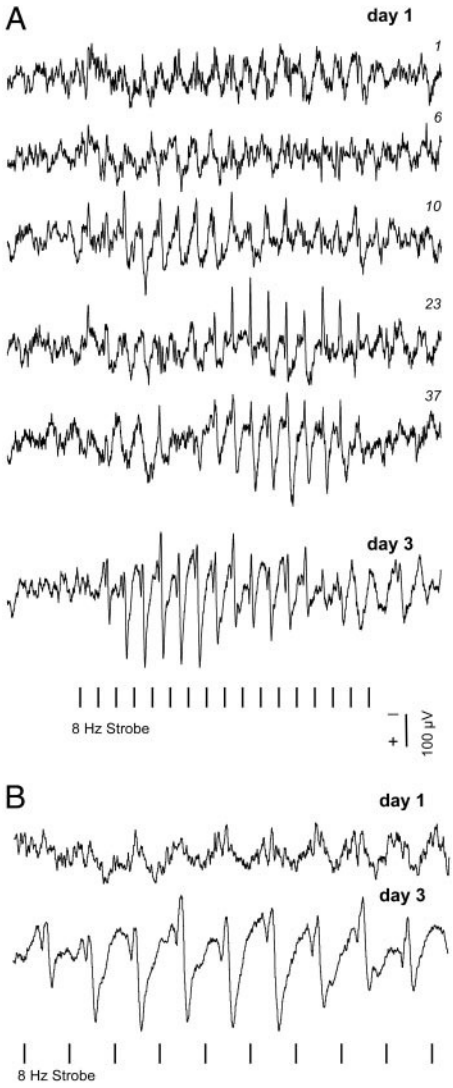

FIG. 1. Emergence of the sensitized response. Electrocorticographic (ECoG) records from occipital cortex of a naïve adult Sprague-Dawley rat on 1st and 3rd day of exposure to an 8-Hz train of stroboscopic stimulation (tick marks). *A*: representative individual records. Number on *right* indicates trial number. Note gradual inclusion of cycles of larger amplitude response. *B*: expanded records. Trial 1 on day 1, common photic response. Day 3 record, sensitized spike-wave response. Negative potentials plotted upward. Stimulus and recording conventions the same in subsequent figures unless specified otherwise.

during initial trials on day 1 (Fig. 1*A*, day 1, trial 1; Fig. 1*B*, day 1). These ranged from a weak, irregular periodic response to photic driving, characterized by rhythmic, low-to-moderate amplitude, occipitally recorded sinusoidal-shaped responses at the temporal frequency of the strobe. As strobing trials continued on day 1, however, the strobe-driven electrographic response exhibited cycles of increasingly higher amplitude and transient spikes (<50 ms width; Fig. 1*A*). By the end of day 1 (20–40 strobe trials) and on subsequent days, the waveform on growing number of trials assumed a spike-wave morphology (e.g., Fig. 1*B*, day 3). The spike-wave response was observed only in conjunction with strobing and did not occur spontaneously. Additional results showed that implantation of electrodes, by itself, did not produce sensitization. Six rats were implanted surgically, but exposure to the strobe regimen was delayed 3 days to 3.5 wk. Rats underwent the standard adaptation procedure followed by the strobe regimen. No sensitized responses were evident on initial strobe exposure, and all rats followed the standard time-course of sensitization on exposure to the strobe regimen.

In a sample of normal adult rats, 34 of 36 animals acquired the spike-wave response after photic exposure. This sample included 28 of 30 male Sprague-Dawley rats, two female Sprague-Dawley rats, two pigmented male (Blue Spruce) rats, and two male rats of another albino strain (Wistar).

CHARACTERISTICS OF THE SENSITIZED RESPONSE. The spike-wave response differed from the common photically driven response in its distinct spike-and-wave morphology and in amplitude (Figs. 2 and 3). Spike-wave responses were significantly larger in magnitude than the common photic responses observed on adjacent trials in the same sensitized rat (unpaired *t*-test with Welch correction, $P < 0.0001$). There was no apparent relation between the magnitude of the eventual spike-wave response and the photic response observed in initial trials of the experiment; rats that initially displayed a weak visual response could nevertheless develop a robust spike-wave response (Fig. 2).

Figures 2 and 3 enable further comparison of the common photically driven response and the spike-wave response, and two notable features associated with initiation of the spike-wave response are observed. First, the latter response to successive strobe flashes builds in amplitude at the onset of each spike-wave episode, typically peaking by the fourth spike-wave discharge in an episode (Figs. 2, *1, 2,* and *3* and *inset,* and

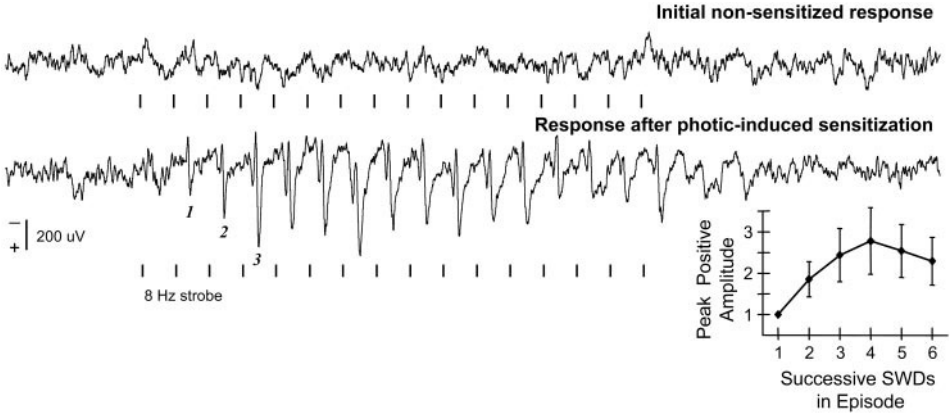

FIG. 2. Response to stroboscopic stimulation, pre- and postsensitization. Single occipital ECoG responses to strobe stimulation (tick marks). Initial poor visual response (*top*) and later spike-wave response in the same rat (*bottom*). *1, 2,* and *3*: spike-wave discharges at the start of an episode build in amplitude with successive flashes. *Inset*: augmentation in response from the start of a spike-wave episode. Data averaged from 5 rats and normalized relative to amplitude of the positive peak on the 1st spike-wave discharge (SWD). Error bars, ±SE.

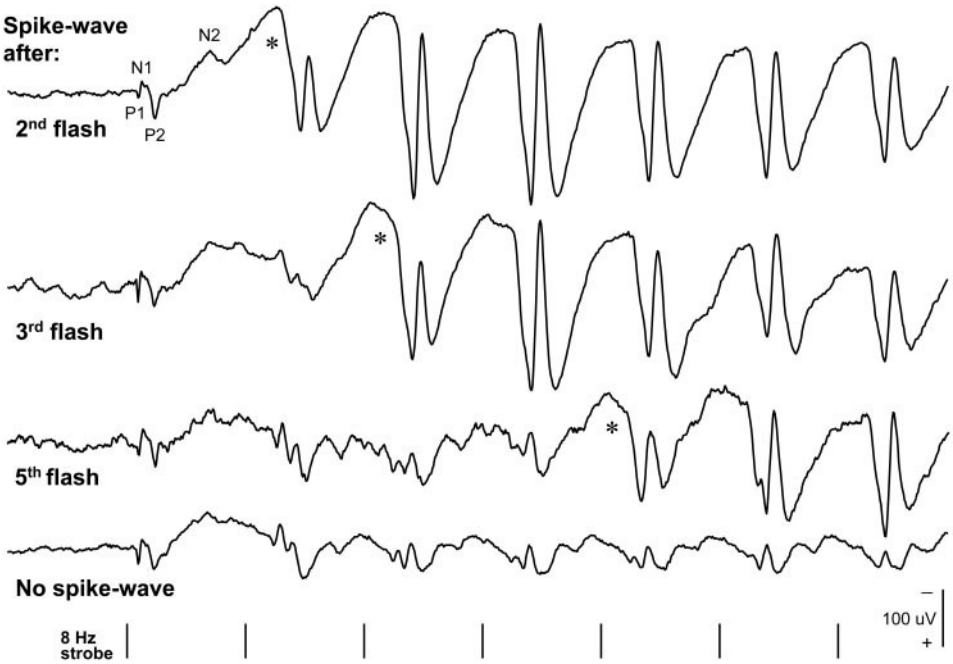

FIG. 3. Averaged, expanded ECoG responses of varied latency to spike wave response. Averages of trials in which the spike-wave response occurred after the 2nd, 3rd, or 5th strobe or never appeared (n = 12, 8, 5, and 19, respectively). *Large negative potential at onset of sensitized response. P1, P2, N1, and N2 refer to surface positive and negative components of the conventional evoked cortical potential evident in all 4 traces. From 1 sensitized rat in 1 session.

3). This response augmentation is observable in 90/100 randomly selected records from 10 rats and is seen in individual records and averaged ECoG recordings. Expanded, averaged recordings reveal the earliest response to the first strobe in all cases is similar, the small polyphasic waveforms of the commonly described early components of the flash-evoked visual potential (Fig. 3, *N1, P1, N2,* and *P2*). The response to the ongoing stimulus continues as either the periodic photically driven response (Fig. 3, no spike wave) or develops into a high-amplitude spike-wave episode after some interval (Fig. 3, 2nd , 3rd, and 5th strobe flash). Second, a large negative ECoG potential (asterisks) marks the onset of a spike-wave episode, regardless of spike-wave response latency. The negative potential seems to be the point of deviation between the spike-wave response and the common photically driven response, with no such potential observed in the latter (Fig. 3).

Termination of a spike-wave episode is characterized by a diminution of spike-wave amplitude of variable time-course that could occur rapidly across a few spike-wave discharges or over a more protracted period.

EPILEPTIFORM NATURE OF THE SENSITIZED RESPONSE. Throughout the course of the sensitization experiments, behavioral alterations were not evident in animals during spike-wave episodes. There was no clear pattern of blinking or synchronized movement. No motor convulsions were observed. Although it seemed at times that there were behavioral pauses during a response, this was not observed consistently and was difficult to evaluate given the brief duration of the episodes and the usually calm state of the animal during recording.

While the sensitized response lacked a behavioral correlate, it displayed a number of electrographic epileptiform characteristics. In addition to the spike-wave morphology, the response generalized across cerebral cortex in every rat. Electrographic electrodes arrayed from occipital to frontal cortex recorded synchronized large amplitude spike-waveforms (Fig. 4). The response tended to be occipitally dominant, with the spike-waveform often appearing first in the occipital leads and secondarily in the other leads, but this varied across rats and across trials within the same rat. In addition to generalization, the response exhibited persistence beyond the end of the strobe period (see below).

A final epileptiform characteristic of the sensitized response is suppression after administration of ethosuximide, a multichannel blocker effective in treatment of absence seizures (Crunelli and Leresche 2002) (Fig. 5). Ethosuximide dosage (100 mg/kg, ip) was the same as that used therapeutically in models of generalized absence seizures in rodents (Snead 1992) and had no gross effect on animal behavior during recording. Strobe-response data were collected before and 30–60 min after administration of ethosuximide in three rats

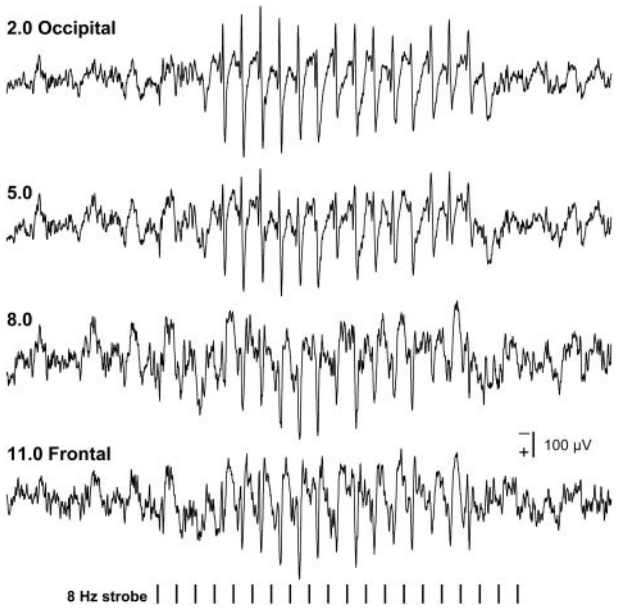

FIG. 4. Spike-wave response generalizes. Simultaneous individual recordings from ECoG electrodes at 3-mm intervals across rat cortex. Numbers on *left* indicate position relative to lambda.

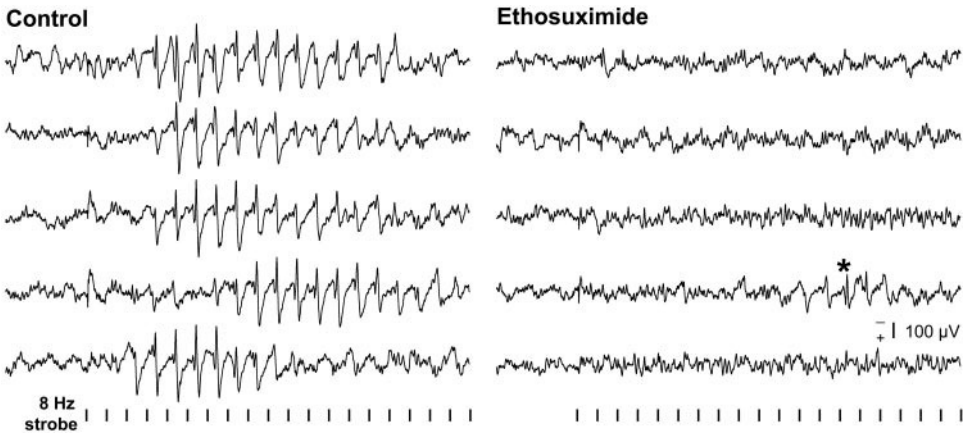

FIG. 5. Ethosuximide suppresses expression of the sensitized response. ECoG responses from a sensitized rat before (Control, *left*) and 30–60 min after drug administration (Ethosuximide, *right*). Every 3rd trial shown. *Spike-wave responses are brief, of low-amplitude, and rarely observed with ethosuximide.

that had fully acquired the sensitized response. The percentage of trials in which spike-wave responses occurred dropped substantially, from 73 to 13%, after ethosuximide treatment. The infrequent spike-wave responses that persisted in the ethosuximide condition (Fig. 5, *) were observed only with longer duration strobe trains (2 s) and were smaller in amplitude than control responses in the same rats. The duration and latency to response were also affected. Average duration of spike-wave response with ethosuximide was significantly shorter than control duration in the same rats (ethosuximide, 6.5 spike-wave discharges per episode vs. control, 10.3 spike-wave discharges; paired *t*-test, $P < 0.004$). Average latency to spike-wave response with ethosuximide was significantly longer than control latency (ethosuximide, 9.5 strobe flashes vs. control, 5.0 strobe flashes to 1st spike-wave discharge; paired *t*-test, $P < 0.002$). Injections of vehicle solution alone had no effect on spike-wave parameters (paired *t*-test, all $P > 0.05$).

TIME-COURSE OF ACQUISITION OF THE SENSITIZED RESPONSE. None of the rats exhibited the spike-wave response on first exposure to the strobe stimulus. Rather, the sensitized response emerged over successive days of exposure, with increases in amplitude, duration, and frequency of occurrence of the spike-wave response. Electrographic response magnitude increased in all rats over the course of trials on day 1 (Figs. 1, 6*A*, and 7). To use an objective measure of an emerging response, recordings from every trial were incorporated into the averaged data, regardless of whether or not a spike-wave response was present. The occurrence of trials with common photic responses, averaged with trials with sizeable spike-wave response, created variability that contributed to the size of the error bars in Fig. 6*A*.

Spike-wave magnitude increased over the course of stimulation on days 1 and 2 (Fig. 7). Average response magnitude in the first 10 trials versus the last 10 trials was significantly different on day 1 (paired *t*-test, $P < 0.0001$) and day 2 (paired *t*-test, $P < 0.002$). By day 3, spike-wave response began high in amplitude and remained elevated across trials. No significant change in magnitude was observed between early versus late trials on day 3 or day 4 (paired *t*-test, $P > 0.05$). Overall, significant differences were observed in the data collected over the first 3 days of strobe exposure (repeated-measures ANOVA, $P < 0.0001$; Fig. 7), with substantial change occurring between day 1 and day 2 (Tukey-Kramer post-test, $P < 0.01$) and between day 2 and day 3 (Tukey-Kramer post-test, $P < 0.001$), and no significant change between day 3 and day 4 (Tukey-Kramer post-test, $P > 0.05$). Regression analysis provides support for a progressive change in magnitude of response across successive trials during this period: day 1 ($r = 0.834$, $P < 0.0001$); day 2 ($r = 0.560$, $P < 0.01$); day 3 ($r = 0.494$, $P < 0.05$); and day 4 ($r = -0.005$, $P > 0.5$). Thus by the end of day 3, the response appeared fully acquired. Two rats were tested daily for 4 wk with no marked change in response magnitude or incidence on subsequent days.

The time-course of acquisition of the sensitized response was similar when the data were quantified alternatively by counting the number of spike-wave discharges or by calculating the spectral power of the response at 8 Hz. Thus rats with 3 or more successive days of strobe regimen exposure were defined as having fully developed spike-wave responses. Further inspection indicated the increase in overall response magnitude during acquisition reflected a change in incidence and number of individual spike-wave discharges in an episode

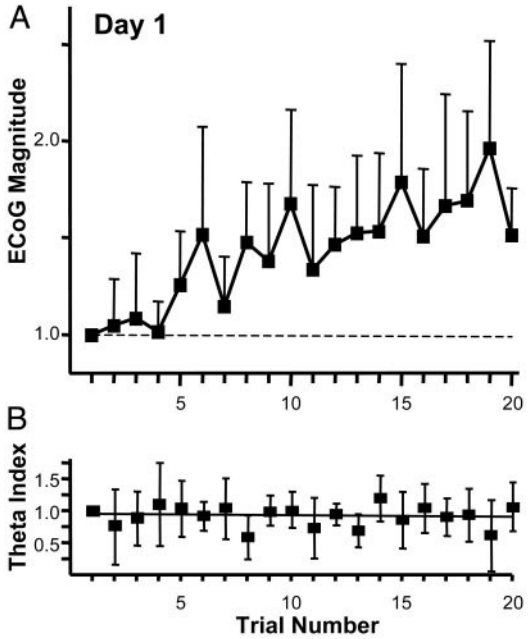

FIG. 6. *A*: time-course of acquisition of sensitization. ECoG magnitude in response to 8-Hz strobe stimulation averaged in 6 rats and plotted across trials for day 1. Data normalized relative to the 1st trial on day 1 (value of 1.0, dashed line). Includes data from all trials. Error bars: ±SE. *B*: theta values for corresponding day 1 trials. Theta index, an indicator of behavioral activity level measured just before strobe onset, is unchanged with sensitization. Best fit regression line. Error bars: ±SE.

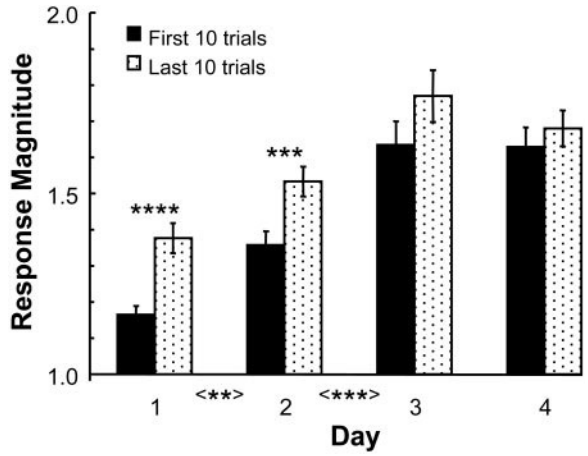

FIG. 7. Change in ECoG response magnitude on days 1–4 of testing. Averaged data from 6 rats; 8-Hz strobe stimulation. Error bars: ±SE. *Degree of statistical significance between bar pairs (above) and between test days (below).

(duration) combined with increased amplitude of spike-wave discharges making up an episode.

Previous study of paroxysmal visual responses or driven oscillations showed suppression of response with exploratory behavior (Bigler 1977; Castro-Alamancos and Connors 1996b,c). Our observations indicated a similar decline in incidence of the sensitized response when animals were exploring actively. The current protocol was designed to minimize and control for such state-dependent factors (cf. Dyer 1989). However, it remained possible that the observed electrocorticographic change corresponded to change in behavioral state. To test for this, we used a theta index measure of activity level in electrical recordings for quantification of the incidence of exploring-type behavior (cf. Bland 1986; O'Keefe and Recce 1993; Skaggs et al. 1996). The theta index was defined as the percentage of power in the 5- to 9-Hz band of the spectral composition of the prestrobe portion of the ECoG on each trial.

Theta band analysis confirmed that variation in active exploring was controlled during acquisition of sensitization (Fig. 6*B*). Linear regression analysis revealed no relation between theta index and trial number ($r = 0.149$, $P > 0.1$). Thus while day 1 yielded significant change in the magnitude of the strobe-driven response (Fig. 6*A*), the day 1 theta index curve was unchanged across trials (Fig. 6*B*). Additional regression analyses of prestrobe activity similarly revealed no relation between the changes observed across trials and comparable measure in other ranges of frequencies (1–5, 10–20, 20–100, 40–100, and 40–70 Hz; all $P > 0.1$)

TIME-COURSE OF RETENTION OF THE SENSITIZED RESPONSE. The sensitized spike-wave response, once acquired, persisted across subsequent test days. To evaluate retention over time, we tested rats after gaps in exposure to the daily strobe regimen. Figure 8 shows average response magnitude as a function of days (note log scale) elapsed since rats with fully acquired spike-wave responses were last exposed to the strobe regimen. We limited quantification to four trials in a rat's daily session, which was sufficient to quantify the ECoG magnitude while minimizing the effects of strobe exposure on reacquisition of sensitization (cf. Fig. 6*A*). Sensitization, as indicated by response magnitude, remained high in test sessions 0–2 wk after previous testing. However, longer duration periods without strobe exposure resulted in a drop in response magnitude to levels observed in naïve rats on their first day of strobe exposure (Fig. 8, naïve). The sensitized response seems to be retained about 2 wk and returned to baseline levels by 4 wk.

Stimulus–response characteristics

To better understand the factors that underlie expression of the sensitized response, characteristics of the strobe stimulus were varied to examine stimulus–response relations in sensitized rats.

EFFECT OF STIMULUS FREQUENCY. To determine the effect of the temporal frequency of the visual stimulus on response expression, sensitized rats ($n = 7$) were tested with a range of strobe frequencies (1–30 Hz). As shown (Fig. 9), the amplitude and appearance of the sensitized responses varied with strobe frequency. The initial response to the 1-Hz stimulus has the appearance of a flash-evoked potential with enhanced late components (i.e., flash-evoked after discharge; Bigler 1977). Increases in stimulus frequency led generally to more regular expression of the spike-wave response. When ECoG magnitude was quantified and plotted as a function of frequency of stroboscopic stimulation, the greatest magnitude responses were observed at 4–8 Hz, with a consistent peak at 8 Hz (Fig. 10). A secondary peak occurred near 16 Hz, and a diminution in response was observed at frequencies between the primary and secondary peaks and at the lowest and highest frequencies tested. While 8 Hz was the standard strobe frequency for sensitizing rats, 3-Hz stimulation was used in three rats to test the effect of sensitizing with a different stimulus frequency. There was no difference in the frequency response curve for rats sensitized through exposure to 8-Hz strobe trains or to 3-Hz strobe trains (paired *t*-test, $P > 0.25$). Data from both sets of rats were combined in Fig. 10.

Examination of the power spectra of the spike-wave responses (Fig. 11) suggested factors that contributed to the energy in the sensitized response. First, the frequency of stroboscopic stimulation was associated with a peak in the power spectrum at that particular frequency. Second, harmonic frequencies of the stimulation rate yielded observable peaks. Finally, every tested frequency yielded a peak in energy in the vicinity of 6–8 Hz. When the primary frequency or a harmonic or subharmonic frequency fell in the vicinity of 6–8 Hz, this

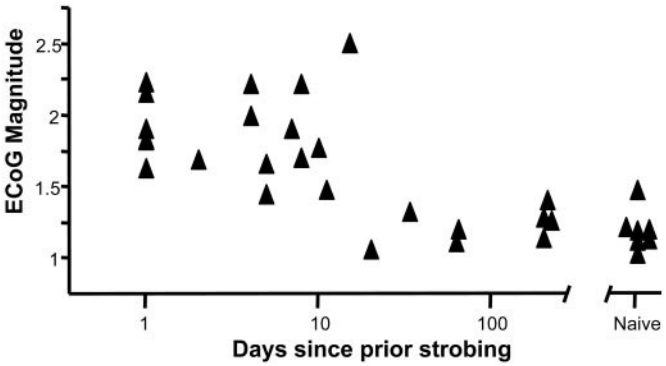

FIG. 8. Retention of sensitization. ECoG magnitude on strobe exposure after a hiatus of the indicated number of days in sensitized rats and naïve rats on initial exposure. Data normalized to magnitude of baseline ECoG during the 1-s period before strobe onset.

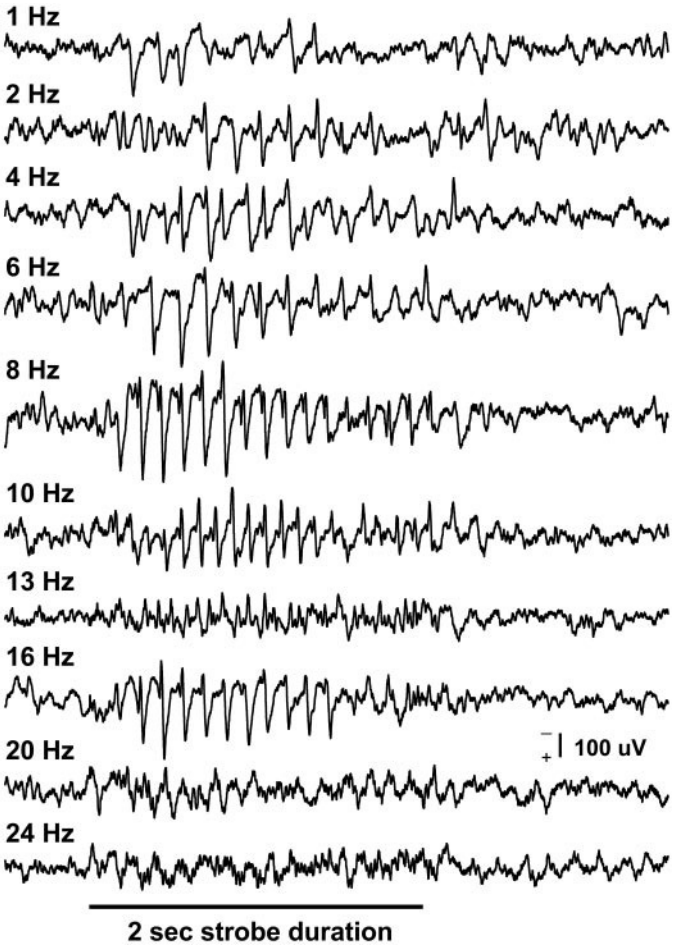

FIG. 9. Character of the sensitized response varies with temporal frequency of strobe stimulation. Individual responses to 2-s strobe trains of 1–24 Hz from 1 sensitized rat.

resulted in a marked boost in power in this spectral region and likely contributed to the particular efficacy of these stimulus frequencies. The result suggests the presence of an inherent resonance in the neural circuitry at 6–8 Hz.

EFFECT OF STIMULUS INTENSITY. To examine the effect of stimulus intensity on response expression, sensitized rats ($n = 4$) were tested with 8-Hz strobe flashes that ranged from dim to full intensity (Fig. 12). Higher intensity stimuli were associated

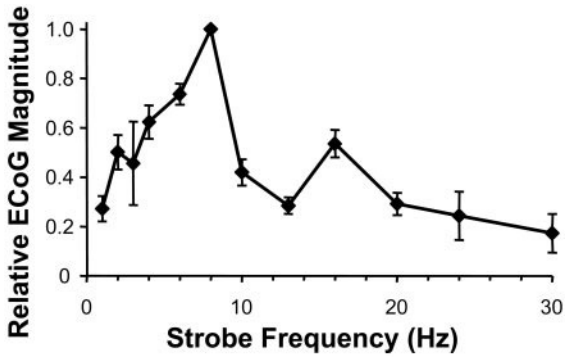

FIG. 10. Effect of strobe frequency on response magnitude. ECoG magnitude vs. frequency of strobe stimulation averaged for 7 sensitized rats. Within-rat data were normalized with respect to their no-strobe response with peak responses assigned a value of 1.0. Error bars, ±SE.

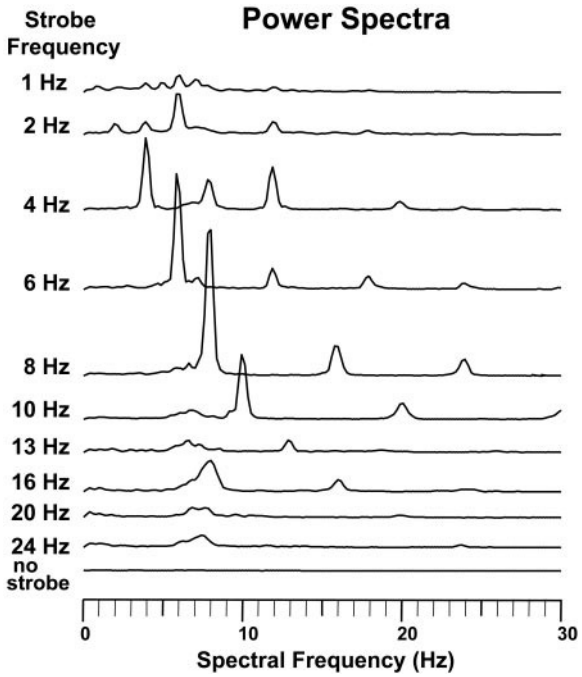

FIG. 11. Power spectra of sensitized responses with varied temporal frequency of photic stimulation. Spectral responses ($n = 18$/strobe frequency) averaged from 1 rat. Response in the absence of strobe stimulation (no strobe) exhibits peaks in power at frequencies <10 Hz but looks flat at this magnification.

significantly with a higher proportion of trials with spike-wave response ($r = 0.783$, $P = 0.0002$), longer duration of spike-wave responses ($r = 0.445$, $P < 0.0001$), increased magnitude of the spike-wave response ($r = 0.574$, $P < 0.0001$), and a significant decrease in response latency ($r = -0.603$, $P < 0.0001$). Thus characteristics of the sensitized response varied systematically with strobe intensity.

A bimodal distribution of spike-wave and common photic responses was observed across strobe intensities. While both types of response increased in magnitude with strobe intensity, the greater magnitude responses consistently showed spike-wave morphology (filled symbols) and the lower magnitude responses common photic responses (open symbols). The two groups are separated by a gap between the clusters (brackets) or, at the weakest strobe intensity, by responses of indeterminate form (half-filled symbols). Thus the majority of responses were distinguishable on both a morphological basis and by means of magnitude measures. The results suggest a capacity to switch between two distinct response states: the common photically driven response and the sensitized spike-wave response.

EFFECT OF STIMULUS DURATION. The incidence of occurrence of a spike-wave response was affected little by the duration of the strobe train. A spike-wave response occurred in sensitized rats on 70–80% of trials for virtually every length strobe train (from 4 to 50 strobe flashes per train). Spike-wave incidence (31% of trials) was reduced only when single strobe flashes presented at 1 Hz were used, consistent with the latency results below, because most spike-wave episodes triggered by the fourth strobe flash.

While the incidence of spike-wave episodes remained relatively invariant, the actual duration of a spike-wave episode

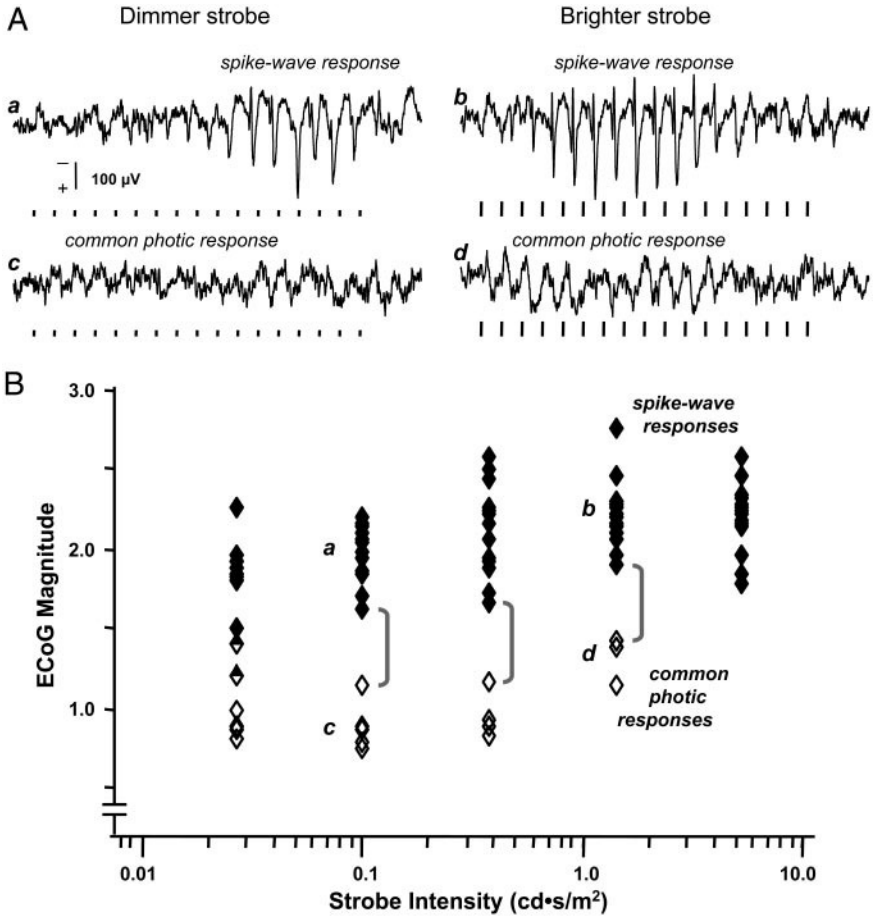

FIG. 12. Effect of strobe intensity. *A*: individual ECoG responses to moderately dim (*a* and *c*) or moderately bright (*b* and *d*) strobe flashes. *a* and *b*: spike-wave responses. *c* and *d*: common photic responses. *B*: bimodal distribution of response magnitude with change in flash intensity from dim (*left*) to full intensity (*right*). Filled diamonds, spike-wave responses; open diamonds, common photic responses; brackets, gap between the 2 types of responses; half-filled diamonds, ambiguous responses. *a*–*d*: corresponding records in *A*, all with 8-Hz strobe stimulation. Representative data from 1 of 4 sensitized rats.

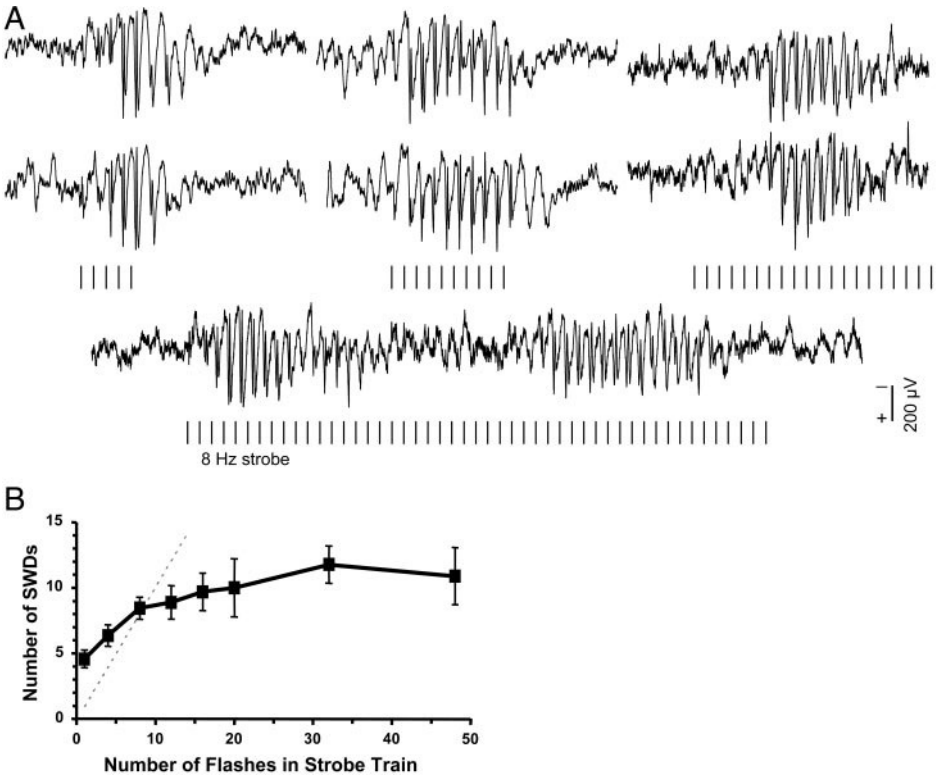

FIG. 13. Effect of strobe train duration on response duration. *A*: ECoG records. *Top 2 rows*: typical responses to strobe trains of 3 durations (tick marks). *Bottom row*: response to a prolonged 6-s strobe train. *B*: relation between length of strobe train (number of flashes in strobe train) and response duration [number of spike-wave discharges (SWDs)] shows a plateau in response duration. Data from the 1st spike-wave episode of a strobe train. Dashed line indicates 1:1 correspondence between a strobe flash and a SWD; points above line indicate more SWDs than flashes, and points below the line indicate fewer SWDs than flashes. Error bars: ±SE.

was related in part to strobe train duration (Fig. 13). For shorter strobe trains, the number of spike-wave discharges rose with increases in the number of flashes in the train (Fig. 13*A*, *left* vs. *middle column*). However, further increases in the strobe train length yielded limited increase in duration of the spike-wave episode (Fig. 13*A*, *middle* vs. *right column*), despite presentation of a strobe frequency (8 Hz) that elicits the strongest response. The longest strobe trains were instead associated with the appearance of multiple, discrete spike-wave episodes (e.g., Fig. 13*A*, *bottom*). Quantified data show the spike-wave episode usually exceeded the period of stimulation for the shortest strobe trains (these data points lie above the dashed line in Fig. 13*B* that indicates correspondence between number of flashes and spike-wave responses). However, for longer strobe trains, the response plateaus maximally around 10–12 spike-wave discharges in length, regardless of the number of flashes per strobe train.

The duration of a spike-wave response also depended on its latency of response. This is shown by evaluating responses to a 16-strobe train (Fig. 14). Despite the occasional occurrence of a single flash evoking a spike-wave response, the majority of responses were triggered by the second through fifth strobe flash in a train. Moreover, shorter latency responses lasted longer than longer latency responses ($r = -0.653$, $P < 0.0001$). The dashed line in Fig. 14 corresponds to the end of the 16-strobe train (i.e., the longer the response latency, the closer the end of the strobe train), and points above the dashed line indicate responses with a spike-wave after-discharge. When present, the spike-wave afterdischarge was two to three cycles long, regardless of response latency. Thus while more spike-wave responses were initiated earlier in a strobe train, those longest in response latency (i.e., initiated closer to termination of the strobe train) were disproportionately more likely to show an afterdischarge.

The results indicate three factors in the control of the duration of a spike-wave response. First, the response requires stroboscopic stimulation; the end of the strobe train is associated with the end of a response. Second, the response is self-limiting and terminates before completion of strobe trains longer than ~10 flashes. Third, the response exhibits a limited, but persistent self-sustained character, persisting up to three cycles after termination of the strobe.

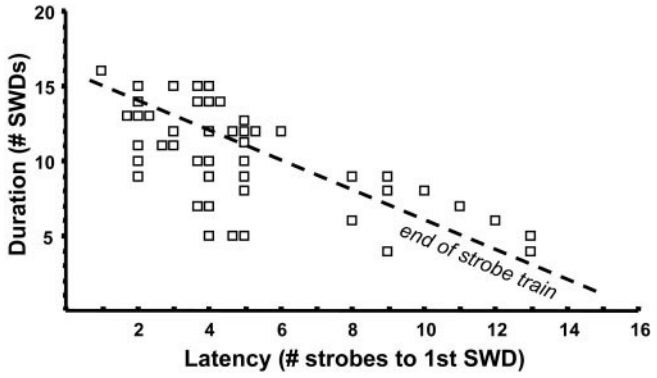

FIG. 14. Relation between response duration (number of individual SWDs) and response latency (number of strobe flashes preceding 1st SWD). Data from 1 sensitized rat. The longer the latency to respond, the briefer the spike-wave response duration. Strobe train stimulus, 2 s at 8 Hz. Dashed line indicates end of strobe train (i.e., latency + duration = 16 cycles).

DISCUSSION

These results provide evidence of acquired, long-lasting response sensitization induced in ordinary adult rats over the course of days through repeated photic stimulation. The sensitized response increased in magnitude and developed spike-wave morphology that generalized across cortex and persisted for weeks.

The sensitized response exhibited both stimulus-dependent and stimulus-independent features. Longer and more intense visual stimuli were associated with larger, more frequent, and more rapidly triggered spike-wave responses within selected ranges of strobe parameters, and spectral response characteristics reflected the frequency of the photic stimulation. However, the spike-wave response also exhibited characteristics unrelated to the triggering stimulus. Spectral analysis revealed an underlying 6- to 8-Hz rhythm, regardless of the frequency of photic stimulation. The response also exhibited persistence after termination of strobing and yet was ultimately self-limiting in duration regardless of ongoing photic stimulation. Many features of the sensitized response are consistent with properties of the visual thalamocortical pathways. This neural circuitry provides the primary ascending pathway for vision and at the same time is implicated strongly in the generation of the normal oscillations of sleep and pathological spike-wave oscillations of certain generalized epilepsies (Destexhe and Sejnowski 2001; Destexhe et al. 1993, 1999; Sherman and Guillery 2001).

The finding of an inherent 6- to 8-Hz rhythm is consistent with the natural pacing of the rat thalamocortical circuitry, which resonates optimally at 5–10 Hz, even during spike-wave seizures (Destexhe and Sejnowski 2001). This results from hyperpolarization-mediated pacing dominated by $GABA_A$ receptors and contrasts with the lower-frequency spike-wave oscillations in primates and cats paced by longer-lasting $GABA_B$-mediated hyperpolarization (Destexhe and Sejnowski 2001; Pinault et al. 1998; Steriade and Contreras 1995; von Krosigk et al. 1993). The observed decline in response at 10 and 13 Hz likely reflects short interflash intervals so that the response to a flash is opposed by deep hyperpolarization from the preceding flash.

The spike-wave response showed both persistence and self-limitation. The response can continue up to three spike-wave cycles after termination of the strobe train, yet, even in the presence of an ongoing strobe stimulus, it ceases after a maximal duration of 10–15 cycles. The visual stimulus plus an inherent self-sustaining mechanism appear to drive the response, while a self-limiting mechanism that may build up over the course of an oscillatory episode terminates the response. Thus qualities of persistence and self-limitation were not mutually exclusive. These results support and extend observations (Jayakar and Chiappa 1990; So et al. 1993) that time of delivery or triggering by a photic stimulus help determine whether a photoparoxysmal response terminates before the end of photic stimulation or persists beyond stimulus termination. Spike-wave episodes that start near termination of the strobe train in the present experiments were more likely to persist beyond strobe termination.

Sensitization reflects long- and short-term change

Our data suggest both long-term and short-term neuroplastic changes occur in thalamocortical circuitry in the adult brain as a consequence of repeated strobe stimulation. First, the sensitized response exhibits long-term plasticity, building up over days and with retention for weeks after the last stimulus exposure. The previously reported flash-evoked afterdischarge (FEAD) that follows the rat visual-evoked occipital response to a single pulse also has some epileptiform features, can evolve over days with extended exposure (Bigler 1977; King et al. 1980), and involves long-term response sensitization (Dyer 1989). This experiment examined responses to trains of strobe stimuli, rather than to isolated flashes, and further showed response retention and generalization. However, the spike-wave responses in this study likely reflect an interaction between afterdischarge processes and the primary visual responses to subsequent strobes in a train, and a similar sensitization process may underlie both the FEAD results and these findings.

The present response features are consistent with long-term potentiation (LTP). LTP occurs in adult thalamo-cortical, cortico-cortical, and cortico-thalamic synapses (e.g., Aizenman et al. 1996; Castro-Alamancos and Calcagnotto 1999; Heynen and Bear 2001). Potentiation at one or more of these synapses could transform circuit dynamics to support the robust, synchronized oscillation of the sensitized spike-wave response. Furthermore, the time scale for retention of the spike-wave response, several weeks, corresponds well to that for maintenance of forms of LTP (Abraham 2003; Malenka and Bear 2004). Thus while other mechanisms may be involved, these results are consistent with features of LTP.

The sensitized response also exhibits short-term enhancement of response over a shorter time scale at the start of a spike-wave episode. The progressive build-up in response to successive flashes early in the strobe train resembles the thalamocortical augmenting response, a rapidly growing enhancement in cortical evoked responses to repetitive electrical stimulation of the thalamus first described by Dempsey and Morison (1943); also see Bazhenov et al. 1998a,b; Castro-Alamancos and Connors 1996a,b,c; Morison and Dempsey 1943; Steriade and Timofeev 1997). The augmenting response is proposed to be involved in the generation of sleep spindles and pathological thalamocortical oscillations. The augmenting response is triggered optimally with 8- to 15-Hz electrical stimulation (Dempsey and Morison 1943) and observed during periods of awake immobility and abolished with states of movement and arousal (Castro-Alamancos and Connors 1996b; Steriade et al. 1969), all of which bears similarity to these results.

The finding that we can induce an augmenting response with visual stimulation is novel; prior studies of thalamocortical augmenting responses failed to produce the response with electrical stimulation peripheral to thalamus (Bazhenov et al. 1998a; Castro-Alamancos and Connors 1996b; Ferster and Lindström 1985). One key difference between those experiments and the present may be choice of stimuli. Natural visual stimulation may be more effective at driving an augmenting response than electrical stimulation of an afferent pathway (e.g., optic tract). In addition, acquisition of a sensitized state may also be relevant. We did not observe augmentation of response in initial trials in naïve animals and also did not observe a fully developed spike-wave response. Only after acquisition of sensitization was an augmenting response observed. Thus the visually-driven augmenting response appears to be a property of the circuit that has undergone induction of the sensitized state.

Similar mechanisms are likely to underlie ECoG response augmentation at onset of a spike-wave episode and the thalamocortical augmenting responses elicited with electrical stimulation (e.g., Bazhenov et al. 1998a,b; Castro-Alamancos and Connors 1996c; Destexhe and Sejnowski 2001; Steriade et al. 1998), in which a key factor is the rebound spike burst in thalamic and cortical neurons from a hyperpolarization that follows an excitatory drive from the stimulus. With appropriate interflash intervals, the rebound burst and excitatory response to a subsequent stimulus coincide, leading to response augmentation. While other explanations exist, a negative potential recorded at the dural surface can reflect a current source in deep cortical layers, so the negative potential that precedes the first spike-wave discharge in this experiment would be consistent with the proposal that hyperpolarization is critically involved in onset of the spike-wave wave episode. Repeated visual stimulation in these experiments or repetitive thalamic stimulation (Steriade et al. 1998) both appear efficacious in producing strong augmenting responses in combination with intact reciprocal pathways between thalamus and cortex. Augmentation is reported at intrathalamic, corticocortical, and corticothalamic connections (Granseth 2004; Granseth and Lindstrom 2004; Houweling et al. 2002; Steriade and Timofeev 1997; Timofeev and Steriade 1998; Timofeev et al. 2002). Augmentive change at any of these sites may potentially contribute to the generation of a sensitized response.

Broader implications

These results are not specific to a particular type of rat. Both sexes and three standard strains of rat acquired the spike-wave response. Prior studies suggest that comparable photic-induced responses may occur in the normal primate brain. These include a strobe-induced, state-dependent spike-wave response (termed "spike and hump") in macaque monkey (Walker et al. 1944) and the proposal that human subjects with no prior evidence of epileptiform activity can show paroxysmal responses after extended stroboscopic stimulation (Brandt et al. 1961). These findings appear distinct from genetic models of photoparoxysmal response and seizure, which can display dissimilar anatomic and electrocorticographic features and need not require sensitization (e.g., Naquet et al. 1995).

The sensitized responses observed in these normal rats share electrographic characteristics with photoparoxysmal responses in humans (e.g., Chatrian et al. 1983; Jayakar and Chiappa 1990; Noachtar et al. 1999; Reilly and Peters 1973). While exhibiting characteristics of photic driving because it is propelled by and reflects the strobe stimulus, the rat response develops additional features not seen in photic driving. Reilly and Peters (1973) described in humans a high-amplitude, visually entrained photoparoxysmal response unlinked to epilepsy that they termed "stimulus-dependent," but this was localized occipitally. Instead, the rat response exhibits electrographic features of the human type 4 photoparoxysmal response, defined as a spike or poly-spike-and-slow-wave re-

sponse to photic stimulation that generalizes across the brain (Doose and Waltz 1993).

While we did not observe a behavioral correlate to the acquired response, it presents epileptiform electrographic characteristics of photo-triggered synchronization. Its persistence after termination of the strobe stimulation is consistent with a prolonged photoparoxysmal categorization (Reilly and Peters 1973), which is highly correlated with epilepsy in human subjects. Because of this correlation, one might infer that the photoparoxysmal response resulted from abnormal expression in an epileptic brain. In this study, however, the spike-wave response was acquired in normal rats and thus may reflect a normal, albeit extremely sensitized, response. Alternatively, repetitive exposure to intense visual stimuli may induce pathological overexpression of learning-based plasticity processes, resulting in anomalous neural activity that yields the spike-wave response.

Photic-induced sensitization may have greatest impact on individuals with epilepsy. Concern persists that exposure to repetitive photic stimulation from video games, television, and other entertainment-related venues may not only trigger abnormal corticographic responses in vulnerable individuals but may contribute in some manner to development of a vulnerability to triggerability (Appleton et al. 2000; Gastaut et al. 1962; Harding and Jeavons 1994; Singh et al. 2001; Walter and Walter 1949). This raises the question whether neuroplastic changes such as those underlying the present acquisition of sensitization, with heightened propensity for generalized synchrony, could exacerbate expression of photo-triggered seizures in patients with a genetic propensity toward photo-triggered epilepsy. Gastaut et al. (1962) previously raised concern that extended television viewing could "progressively increase brain excitability to such an extent that, after a few hours, stimuli that are otherwise without effect, become at last epileptogenic." Acquisition of the sensitized state in the normal subject could yield benign photoparoxysmal responses, but acquisition of the sensitized state in a seizure-prone subject could lower the threshold for photo-triggered and perhaps primary-generalized seizures. Thus sensitization could, in essence, serve as a mild form of photic kindling or visual priming. Support for this arises from the observation that electrical kindling of the lateral geniculate nucleus in cats administered the convulsant, Metrazol, reduces the threshold for photo-triggered seizures (Wada et al. 1986). Additional support arises from a twin study in which a teenager with frequent exposure to stroboscopic stimulation exhibits far greater photosensitivity than his less photically exposed monozygotic brother (de Haan et al. 2005).

Sensitization through photic exposure appears transitory in our preparation, with rat responses returning to normal after a few weeks once exposure has ceased. Transient sensitivity may be a factor in patients reported to have photo-triggered seizures that were unconfirmed on later clinical examination (e.g., Graf et al. 1994; Ishiguro et al. 2004). These results suggest acquired sensitization could have dissipated in the delay before patients were tested. These results also may provide insight into the shown benefits of abstinence in treating video game epilepsy (De Marco and Ghersini 1985; Graf et al. 1994; Maeda et al. 1990 provide additional references). Abstinence from game-playing and other provocative stimuli may remove patients not only from potential visual triggers of seizure, but also from visual stimuli that contribute to acquisition or maintenance of a sensitized state.

The ordinary neural response to the strobe stimulus has been clearly altered in these experiments. The results provide an example of experience-dependent long-term neuronal plasticity. In the adult visual system, long-term plasticity is associated commonly with perceptual learning (Tsodyks and Gilbert 2004). The strobe stimulation in these experiments could cause either an overexpression of learning-related synaptic plasticity or could bring into play other mechanisms, possibly protective, that modify synaptic strengths. In either case, such synaptic alterations are likely to impact sensory processing and may affect perception. Human patients with photosensitive epilepsy exhibit potentiated visual responses (Hishikawa et al. 1967) and altered visual perception, notably in measures of contrast gain (Porciatti et al. 2000; Wilkins et al. 2004), and the altering effects of repeated peripheral stimulation on somatosensory cellular responses, receptive field size, and perception are well recognized (Klein et al. 2004; Recanzone et al. 1990). Thus the neuroplastic changes observed in this study may have perceptual consequences as well.

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GRANTS

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