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Research report

Effects of amygdala lesions on sleep in rhesus monkeys

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Abstract

The amygdala is important in processing emotion and in the acquisition and expression of fear and anxiety. It also appears to be involved in the regulation of sleep and wakefulness. The purpose of this study was to assess the effects of, fiber-sparing lesions of the amygdala on sleep in rhesus monkeys (*Macaca mulatta*). We recorded sleep from 18 age-matched male rhesus monkeys, 11 of which had previously received ibotenic acid lesions of the amygdala and seven of which were normal controls. Surface electrodes for sleep recording were attached and the subjects were seated in a restraint chair (to which they had been adapted) for the nocturnal sleep period. Despite adaptation, control animals had sleep patterns characterized by frequent arousals. Sleep was least disrupted in animals with large bilateral lesions of the amygdala. They had more sleep and a higher proportion of rapid-eye-movement (REM) sleep than did either animals with smaller lesions or control animals. Based on these results, it seems likely that, in the primate, the amygdala plays a role in sleep regulation and may be important in mediating the effects of emotions/stress on sleep. These findings may also be relevant to understanding sleep disturbances associated with psychopathology.

Theme: Neural basis of behavior

Topic: Biological rhythms and sleep

Keywords: Sleep; Non-human primate; Amygdala; Insomnia

1. Introduction

The amygdala is a critical part of the neural circuitry involved in mediating responses to fearful stimuli as well as to other stressful situations [13,14]. Located in the medial temporal lobe, the amygdala receives cortical and subcortical inputs, and projects to brainstem, hypothalamus, forebrain and cortical regions that are involved with the hormonal, autonomic and behavioral aspects of the stress response [5]. Studies in rodents and primates have demonstrated that the amygdala is important in the processing of emotion and in mediating the acquisition and expression of fear and anxiety [10,15,19,22]. Additionally, data from human functional neuroimaging studies and from individuals with amygdala destruction support the role of the human amygdala in the processing of negative emotions such as fear [2,3,25,26,28]. Recent research has shown that patients with stress-related psychopathology have altered amygdala function. For example, neuroimaging studies in patients with depression and some anxiety disorders indicate increased amygdala activity [1,16,17], suggesting that altered amygdala activity is involved in the pathophysiology of these disorders.

In addition to its role in emotion, the amygdala may be involved in modulating sleep and wakefulness. It is highly interconnected with a number of brain regions involved in sleep regulation, such as the basal forebrain, hypothalamus and brainstem [5]. Furthermore, there are reciprocal connections between the amygdala and brainstem areas involved in the regulation of waking and rapid-eye-movement (REM) sleep. These include the parabrachial region, dorsal raphe nuclei, pedunculopontine tegmentum (PPT) and laterodorsal tegmental nuclei.

Various studies have provided evidence suggesting that the amygdala may be involved in sleep regulation.

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Changes in neuronal firing patterns in the amygdala in cats and rats correlate with sleep and wakefulness [18,24,30,35]. Administration of pharmacological agents into the amygdala influences REM/non-REM (NREM) sleep patterns [11,12,32]. More recently, human neuroimaging studies using positron emission tomography (PET) have shown increased activation of the amygdala during REM sleep in comparison to waking or NREM sleep [23,27].

To the extent that cognitive and cortical processes modulate human sleep, studies in the rat and the cat cannot fully model human sleep. Non-human primates, on the other hand, provide a highly relevant model to examine mechanisms associated with cortical–subcortical regulation of sleep–waking behavior. Important similarities in sleep architecture exist between primates and humans [33]. Like humans, primates have a consolidated nocturnal sleep period, and may take naps during the day. Primates also have more extensive linkages between prefrontal cortical and amygdaloid regions than other mammals [5]; these are the neural connections that are likely to be involved in the modulation of emotion.

This study is a report of sleep in rhesus monkeys that had received selective, bilateral lesions of the amygdala and the sleep of age-matched controls. There have been no recordings of sleep in amygdalectomized monkeys, and few nocturnal sleep recordings of normal rhesus monkeys. For this reason it was impossible to predict the changes that might be seen in the amygdalectomized animals. It nevertheless seemed likely that any emotionally mediated sleep disruption (for example a 'first night effect') would be less pronounced in the experimental animals than in the controls.

2. Materials and Methods

2.1. Monkeys

Sleep was recorded in rhesus monkeys (*Macaca mulatta*) living in the colonies at the Wisconsin Regional Primate Research Center and Harlow Center for Biological Psychology. There were 18 animals: seven normal controls and 11 animals with selective bilateral lesions of the amygdala. All animals studied were males that were approximately 2–3 years old.

2.2. Amygdala lesions

Due to the large variability in skull and brain size in nonhuman primates, attempts to produce stereotactic lesions in monkeys with no guidance other than standard atlases are subject to substantial inaccuracy. The method for producing amygdala lesions was developed in collaboration with Dr David Amaral (University of California, Davis). This is a multi-step process and is briefly summarized. All surgical procedures were performed under strict aseptic conditions and anesthesia.

Landmarks were established by stereotactically implanting two 3-mm glass beads filled with a 3% solution of copper sulfate (which is hyperintense in T1-weighted MRI images) into shallow indentations in the skull. The beads were placed 11 mm lateral to the midline coordinate (AP +9, 15 mm from the interaural line), approximately at the mid-anteroposterior level of the amygdala, and fastened in place with dental acrylic.

After at least 3 days of recovery following bead implantation, the animal was brought to the MRI center. Under anesthesia (ketamine, 15 mg/kg), the monkey was placed in a MRI-compatible stereotactic apparatus (Crist Instruments, Damascus, MD) that was positioned in the head coil. Using a 1.5 Tesla GE Signa scanner, the brain was initially imaged in the coronal plane to verify symmetric alignment to the stereotactic apparatus and the scanner. The animal was then scanned in the sagittal plane to show the relationship of the bead to each coronal slice. Lastly, for the coronal scan, a three dimensional fast spoiled gradient pulse sequence (3D/FSPGR/20) was employed using the following parameters: a repetition rate (TR) of 11.5, a fractional echo time (TE) of 2.2/F, one echo (EC), a receiver bandwidth of 15.6 kHz, an inversion time of (TI) of 400, and a 20×15 field of view (FOV). Using 256×224/4 excitations (NEX), 60 contiguous 1-mm coronal brain images were created.

Measurements were made by overlaying and centering on the midline a 1.0-mm matrix onto the coronal MRIs. The mediolateral and anteroposterior location of the amygdala in relation to the bead and the dorsoventral relation of the amygdala from the cortical surface were determined. These measurements were used to plan the stereotactic coordinates of the ibotenic acid injections used to create the lesion.

Animals were returned to the surgical suite for the last part of the procedure. Prophylactic doses of antibiotics were given just before surgery. After anesthesia was established, the skull was exposed, and an appropriate opening made above the intended lesion site as determined from the MRI procedure. To confirm the measurements obtained from the MRI, an insulated tungsten microelectrode was first lowered along the trajectory of the proposed lesion. Single unit recordings were made at several levels defining characteristic zones such as the cortical surface, the cell-rich zones of the amygdala, and the ventral surface of the brain. These were compared with the MRI images to determine more accurately the proper dorsoventral position for the lesion.

Lesions were produced bilaterally using the excitotoxin ibotenic acid (Biosearch Technologies, San Rafael, CA) mixed with 10 μl of phosphate-buffered saline. Between 16 and 23 injections per side of 1 μl each were given to each amygdala in a 2-mm^3 injection matrix defined from the magnetic resonance images [4].

2.3. Sleep recording

Sleep recordings took place at a mean of 10.7±4.9 (S.D.) months after lesion surgeries. Sleep was recorded using surface electrodes. To protect the surface electrodes, animals were recorded while in a primate restraining chair. To habituate the animals to the recording conditions, they were placed in the chair daily for at least 1 week prior to sleep recording. These adaptation sessions took place during the daytime for increasing periods each day (up to 8 h).

Each monkey's sleep was recorded for one night. On the afternoon before recording, monkeys were manually restrained for application of electroencephalogram (EEG), electrocardiogram (ECG) and electro-oculogram (EOG) electrodes. Monkeys were placed in the restraining chair immediately afterwards (at approximately 17:00 h), at which time EKG and electromyogram (EMG) electrodes were affixed. Recording began at about 17:45 h and lights were turned off at 18:00 h. A dim red light was left on during the recording period and monkeys were monitored continuously using a video camera. Several monkeys were videotaped throughout. Lights were turned on at 06:00 h the next morning and recording ended at about 06:15 h. The electrodes were removed and the animals were returned to their home cages.

Cup electrodes (Rochester Electro-medical) were attached to left and right frontal (F3, F4), and occipital (O1, O2) areas for recording EEG according to the international 10/20 system. The restraining chair interfered with normal placement of reference electrodes and with the placement of the electrodes for recording EMG. Reference electrodes were placed at left and right parietal (P3 and P4). EMG electrodes were placed on the surface of the leg overlying the anterior tibialis muscle. Biopotential electrodes (Rochester Electro-medical) were also attached lateral to the outer canthus of each eye for recording EOG. Electrodes were attached to shaved skin after cleaning and abrasion with Omni-Prep (Boulder, CO). A drop of conductive gel was added and electrodes were glued to the skin for additional physical stability. Electrocardiogram (EKG) was monitored using surface silver/silver chloride electrodes ('S'Offsett' Medi-Trace, Buffalo, NY) attached to the shaved chest and left flank.

All EEG electrodes were recorded with reference to one of the parietal electrodes, the other parietal electrode served as a backup. All physiological parameters were amplified, digitized at 200 Hz and displayed and stored using the Sandman system (Nellcor-Puritan-Bennet Mellville, Ottawa, ON). All signals were filtered for 60 Hz line noise. EEG was filtered with a band pass of 0.1–100 Hz. All electrode impedances were less than 10 kΩ.

Each channel was calibrated using 25 and 50 μV sine waves before each subject was recorded. Recording of the physiological variables began about 15 min before lights-out and continued for about 15 min after lights-on in the morning. A technician monitored the signal quality throughout the recording session. If signals deteriorated, then the technician either fixed the problem with the electrode, or switched to the backup reference electrode.

Since sleep EEG in rhesus monkeys resembles human sleep EEG, human sleep staging criteria were used [29]. Two experienced scorers, blind to the experimental condition of the animals staged sleep records. Each 30-s epoch was classified as wake, stage 1, stage 2, slow-wave sleep (SWS), REM sleep or movement time. Stagers staged each record independently, which resulted in >95% agreement between stagers for each animal. For epochs in which stagers disagreed, the epoch was reviewed and a consensus stage assigned.

Data from epochs excluded from staging because of artifact (generally <1% of epochs) were also excluded from all subsequent analyses. The following parameters were calculated for each night: total sleep time (TST), sleep stage minutes and percentages of total sleep time, sleep efficiency (SE), and REM sleep latency (time from stage 2 onset to REM sleep onset).

2.4. Sacrifice and histology

Experimental animals were humanely euthanized using methods of euthanasia consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. An overdose of pentobarbital was given intravenously and they were perfused with heparinized phosphate-buffered saline (PBS) and 4% paraformaldeyde. The brains were removed and histologically processed. The brain slab containing the volume of interest were cryoprotected in 2% DMSO (dimethyl sulfoxide) and 20% glycerol for12–18 h, encased in a gelatin matrix after hardening in 10% buffered formalin, and then freeze-sectioned at 40 microns. Every sixth section (240 μm) was collected in standard phosphate-buffered 10% formalin and mounted on 2×3-inch glass slides, air dried and stained for Nissl substance with thionine.

To determine the extent of the lesions, the brain sections were matched to six coronal templates through the amygdala. The templates were used to define the extent of the lesion by drawing the left and right amygdala lesion on them. Drawings of the lesion were compared to template drawings of an intact amygdala using imaging (PhotoShop v.3.0, Adobe Inc.) by individuals unaware of the behavioral results. The number of pixels that defined the lesion was divided by the total pixels representing the amygdala. This comparison was done for each of the coronal sections to determine the percent of the amygdala that was lesioned.

Sleep efficiency (SE), total sleep time (TST), sleep latency, Stage 1, Stage 2, slow-wave sleep (SWS) and REM sleep percentages (St1%, St2%, SWS% and REM%), as well as REM latency (REML) were computed

Table 1
Data from experimental subjects

Group	Subject ID	Plot label	Extent of lesion		Sleep			Stage percentages of sleep time				REM latency (min)
			Overall	Left/right	Efficiency (%)	Time (h)	Latency (min)	Stage 1	Stage 2	SWS	REM	
'Large' lesions	AT41	A	95.1%	97.8%/92.5%	77.8	8.8	6.0	7.1	42.2	15.6	13.2	45.5
	AT16	B	86.1%	78.3%/93.9%	85.9	11.2	15.0	9.3	61.3	10.7	6.3	162.5
	AS86	C	73.7%	61.5%/86.0%	81.6	10.6	10.0	4.8	36.9	26.4	14.1	43.5
	AT67	D	73.3%	64.3%/82.2%	65.1	7.8	46.0	2.8	50.8	8.7	3.5	422.0
	AS82	E	72.0%	49.7%/94.3%	70.7	8.8	53.0	10.8	47.6	11.0	5.1	351.5
	AT59	F	67.0%	60.3%/73.8%	70.9	8.5	34.0	3.8	52.6	8.4	9.8	65.0
'Small' lesions	95037	G	54.8%	91.5%/18.0%	52.7	6.3	149.0	4.7	47.4	7.2	0.0	
	AT52	H	46.0%	66.1%/25.9%	65.2	8.2	119.0	12.9	39.4	12.3	6.6	249.5
	AT56	I	41.2%	0.0%/82.3%	58.1	7.4	61.0	8.3	42.0	6.2	4.0	12.5
	AT55	J	36.3%	2.6%/69.9%	33.5	4.0	199.0	6.4	40.7	2.3	2.8	435.5
	AT09	K	6.6%	1.6%/11.6%	55.6	7.2	1.0	5.7	28.0	17.4	5.5	250.0

for each recording session. Sleep latency was the length of time from lights-out to the beginning of the first 300 s of consecutive sleep. REML was the time from sleep onset to the first epoch of a sustained (90 s) REM sleep bout. These data, together with the histological data, are presented in Table 1. The experimental animals were divided into groups based on lesion size. The large lesion group included all animals with lesions larger than the mean lesion size (59.28%, $n=6$) and the small lesion group included all animals with lesions below the mean size ($n=5$). All statistical testing was performed using SPSS (SPSS-WIN v.10.01, SPSS Inc., Chicago, IL). Each sleep variable was compared among the groups (ANOVA – General Linear Model). Post hoc comparisons (Tukey HSD) between groups were made for variables which met criterion for significance ($\alpha=0.05$). In addition regressions on lesion size were performed for variables on which lesion size appeared to have an effect.

3. Results

3.1. Histology

Histological analysis of the brains of the 11 animals with lesions showed variability in the size and extent of the lesions (Table 1). The mean reduction in total amygdala volume was 59%: two of the lesions were greater than 85%, four were between 60 and 85%, four were between 35 and 60% and one lesion (AT09) reduced overall amygdala volume by only 7%. All subjects in the large lesion (above the mean) group had a lesion of at least 50% on each side, whereas each subject in the small lesion (below the mean) group had at least one side on which the lesion was less than 30%. Photomicrographs of a representative lesioned and a non-lesioned amygdala are shown in Fig. 1.

3.2. Sleep patterns

In general, the sleep of the control animals was fragmented by frequent arousals. These disruptions are characteristic of stress-induced effects and observation of videotapes of the control animals sleeping in the primate restraining chair revealed repeated head drop followed by awakening. This suggests that even though the animals were 'habituated' to the chair restraint during wakefulness, their disrupted sleep patterns reflected the stress associated with sleeping in the restraining chair.

Sleep parameters for the individual experimental animals are shown in Table 1. As a rule, larger lesions were associated with 'better' sleep. As might be expected from a single night of recording, many of the parameters showed relatively high variability. The summary statistics of sleep variables for each of the lesion size groups and for the control subjects are presented in Table 2. Statistical comparison of the sleep variables among these groups (ANOVA) revealed significant group differences for sleep efficiency and TST and a near significant difference for REM% ($P=0.086$). Post hoc testing (Tukey HSD) indicated that, for both TST and sleep efficiency, the large lesion group was different from the other two groups, which were not significantly different from each other.

To further elucidate the relationship between lesion size and sleep we performed regression analyses between lesion size and selected sleep variables including those that had significant or near-significant differences between large lesions and other groups (Fig. 2). The entire group of 11 lesioned animals was used for these analyses. Total sleep time and sleep efficiency were significantly and positively correlated with extent of lesions, whereas there was a trend for a correlation between lesion size and REM sleep percentage.

One subject, AT09, had a minimal lesion (less than 7%) and the values of its sleep variables were very near the midpoint of the controls (see Tables 1 and 2); it thus might

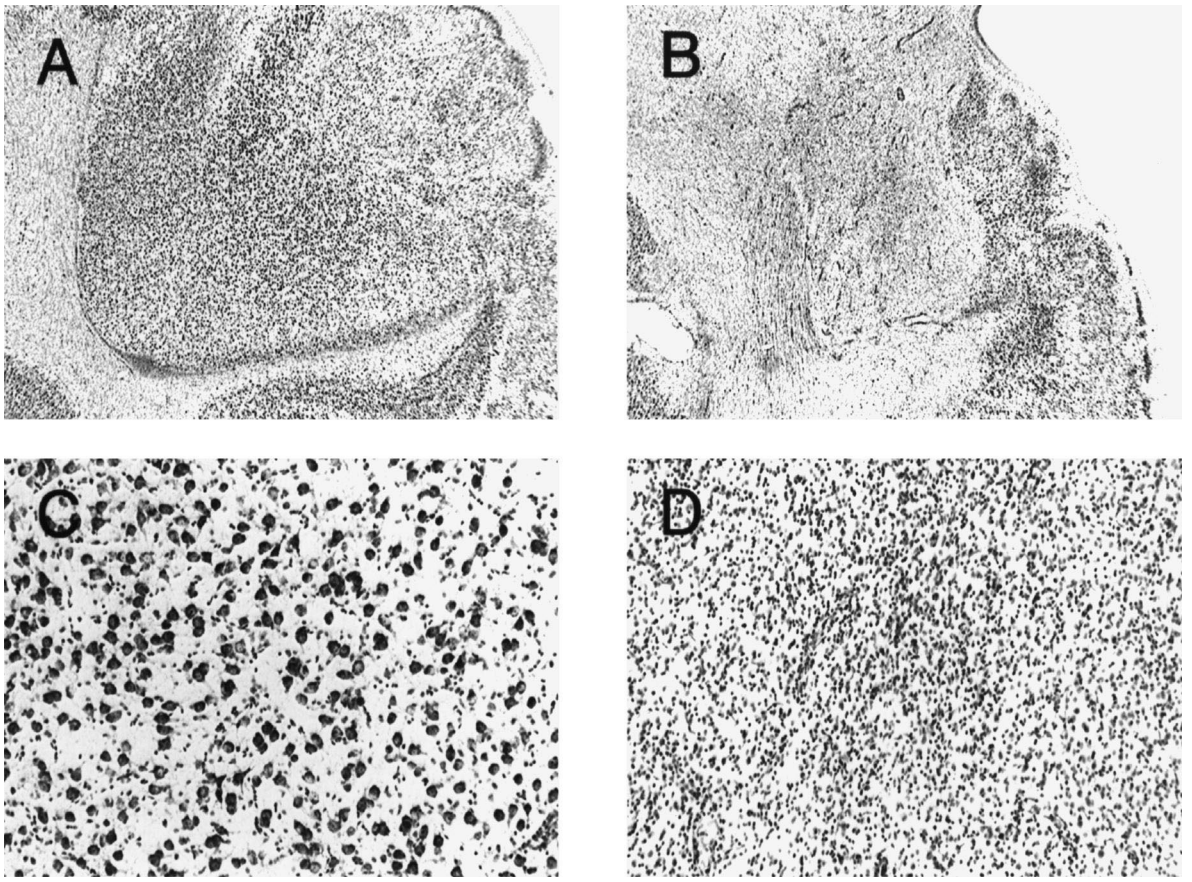

Fig. 1. Sections through the left amygdala of (A) animal AT56 showing a non-lesioned amygdala, and (B) animal AT16 showing a large amygdala lesion. Higher power views demonstrate neuronal loss and gliosis in animal AT16 (D) vs. animal AT56 (C).

be regarded as qualitatively different from the other lesioned animals. To determine how this possible outlier might have changed the results, the analyses were repeated with AT09 excluded. Eliminating this subject increased the correlations and steepened the slopes. In the original analysis the correlation between SE and lesion extent was 0.73 and sleep efficiency increased by 0.43% for every percent lesion size; excluding AT09, $r=0.83$ and each percent in lesion size changed sleep efficiency by 0.65%. For TST, the correlation increased from 0.63 to 0.73 and the slope changed from 0.048 to 0.077 h (2.9–4.6 min) of sleep/percent lesion. REM% was affected similarly, changing from the observed $r=0.47$ to $r=0.59$; the slope of REM%/lesion% changed from 0.08 to 0.14. When AT09 was defined as an outlier the relationship between lesion size and REM% was significant (one-tailed). Removing AT09 from the analysis produced the most dramatic change in the relationship between lesion size and sleep latency. There was no significant relationship between these variables when all subjects were analyzed.

Table 2
Sleep parameters[a]

	Control ($n=7$)	Small lesion ($n=5$)	Large lesion ($n=6$)
Sleep efficiency (%)*	55.3±12.4	53.0±11.8	75.3±7.8
Total sleep time (h)*	6.8±1.6	6.6±1.6	9.3±1.3
Sleep latency (min)	90.3±146.4	105.8±77.0	27.3±19.8
Stage 1 (%)	9.0±5.5	7.6±3.2	6.4±3.2
Stage 2 (%)	43.8±10.2	39.5±7.1	48.6±8.5
Slow wave sleep (%)	9.0±5.6	9.1±5.9	13.5±6.8
REM (%)[§]	5.1±3.3	3.8±2.6	8.7±4.4
REM latency (min)	189.7±145.9	236.9±173.3	181.7±166.3

[a] Sleep variables in groups with small and large lesions of the amygdalae, presented as mean±standard deviation. Animals with large lesions were significantly different (*$P<0.05$) from animals with small lesions as well as from control animals. [§] indicates a trend ($P=0.086$).

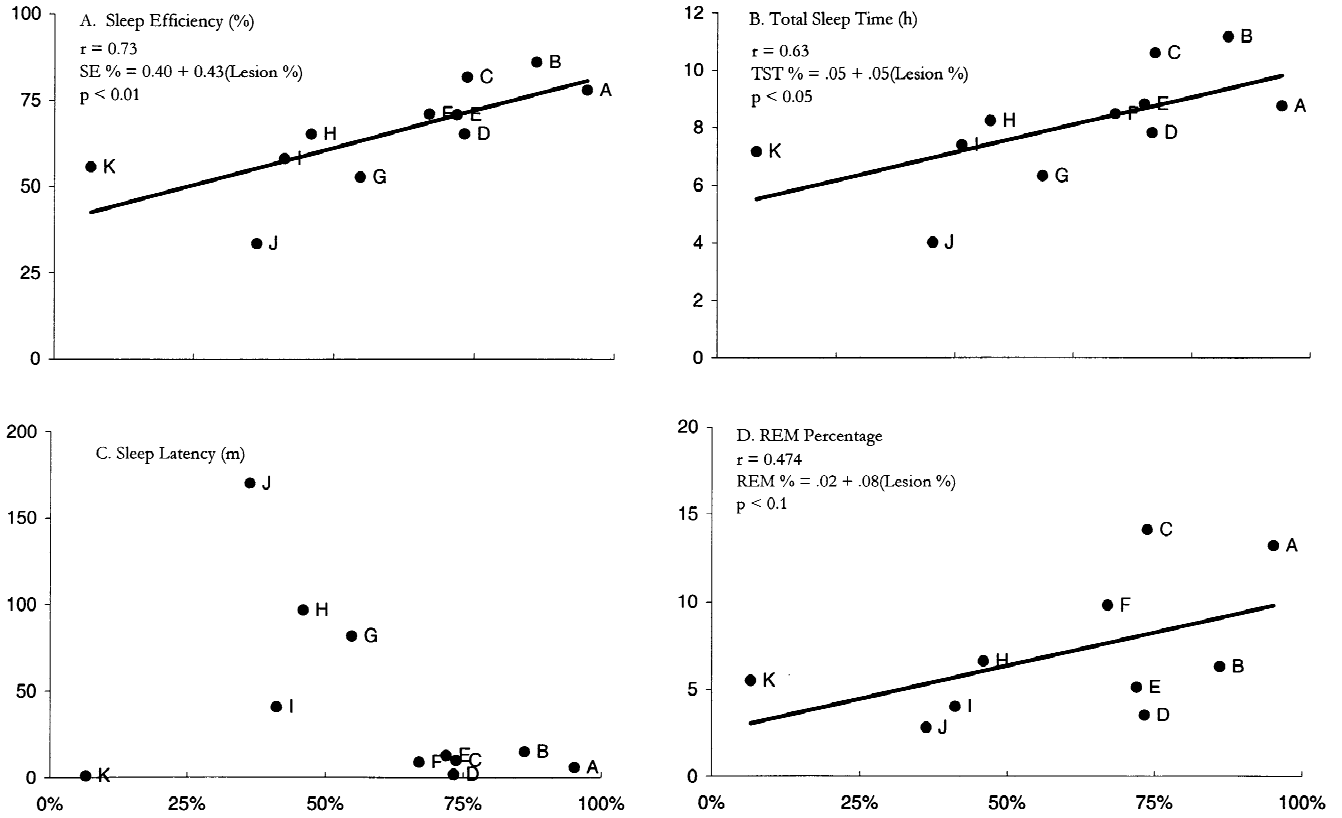

Fig. 2. Hypnograms from animals with bilateral lesions of the amygdala (Subject AT41), a unilateral lesion of the amygdala (Subject AT56), and a normal control (Subject AT23). Time in 30-s epochs is indicated on the *x*-axis.

Excluding AT09 led to a highly significant ($r=0.81$, $P=0.005$) linear relationship. Inspection of Fig. 2 suggests that this relationship could also be interpreted as a difference between large and small lesions, a plateau, or even a curvilinear relationship.

Hypnograms from the animal with the most extensive lesion (AT41), an animal with a small lesion (AT56), which was the also most clearly unilateral, and a randomly selected control (N) are shown in Fig. 3. The hypnograms illustrate the findings that animals with large lesions showed better sleep continuity than controls or animals with smaller lesions.

4. Discussion

The results suggest that large, bilateral lesions of the amygdala produce substantial effects on sleep in monkeys sleeping in a primate restraining chair. Observation of the animals' behavior as well as the EEG sleep data suggest that the sleep of the control animals was affected by the stress of the recording condition. In contrast, animals with extensive amygdala lesions showed more consolidated sleep, with greater sleep efficiency, increased total sleep and increased REM sleep percentage in comparison to normal controls or monkeys with smaller lesions.

The amygdala is a complex structure and is composed of several nuclei [5]. Recent studies have investigated the neuroanatomical connections between these nuclei as well as their functional roles. Most of the information entering the amygdala arrives via afferents to the lateral nucleus. In the rat, most of the amygdaloid outflow mediating simple behavioral, autonomic, and endocrine responses associated with fear emanates from the central nucleus [22]. The central nucleus is also connected to areas involved in sleep and wakefulness; both afferent and efferent projections have been demonstrated between the central nucleus and the parabrachial region and the dorsal raphe nuclei [5]. Because of its strategic connections, it is possible that the central nucleus is primarily responsible for mediating the sleep disruption noted in the control animals. Alternatively, effects on sleep may be mediated by several subnuclei within the amygdala, which would also explain the association between lesion size and changes in sleep parameters. Studies of animals with selective, bilateral lesions of the central nucleus as well as other subnuclei will be needed to identify the specific regions within the amygdala involved in sleep regulation.

Our observations may be explained by primary effects of the amygdala on sleep and/or by mitigation of the possibly disturbing effects of sleeping in a restraining chair. Thus these results may in part be secondary to

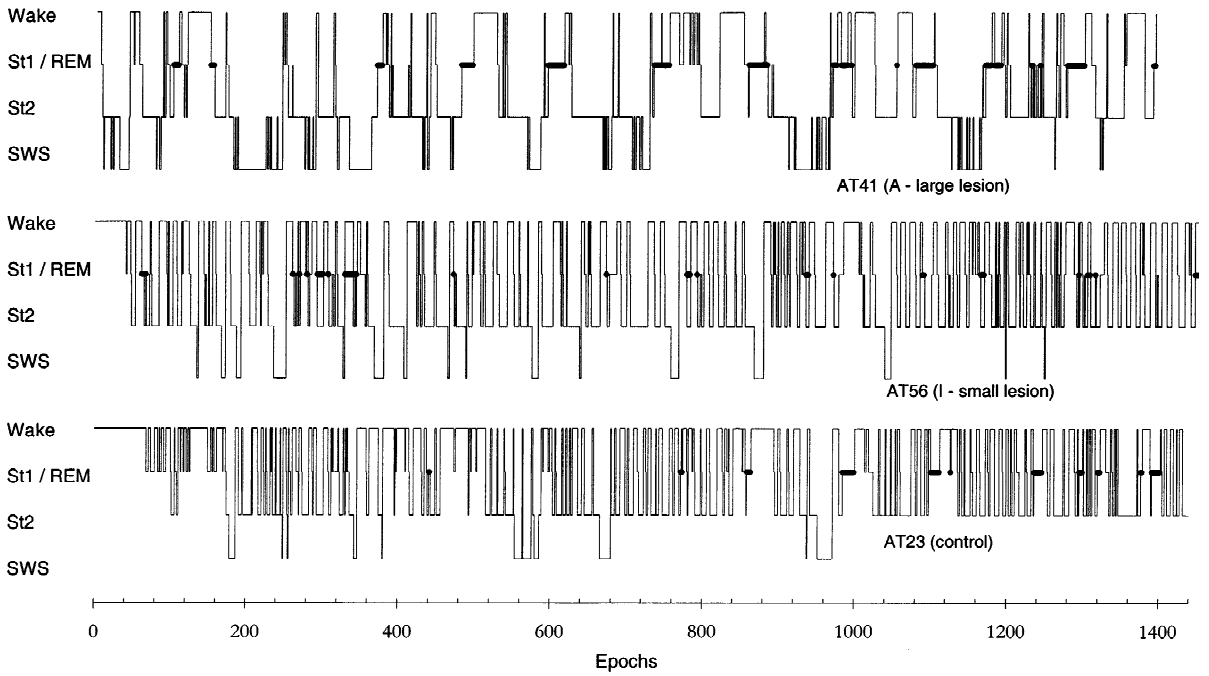

Fig. 3. The above graphs plot sleep variables against the size of the amygdala lesion. Probabilities and *r* values are from the corresponding Pearson correlation. Equation is from linear regression of sleep variable on lesion size.

changes in emotional responsivity. Although earlier studies in several primate species suggested that sleep is not significantly disrupted when animals are chair-adapted [7,8], observation of the videotapes of our animals indicated that the animals were reacting to the chair, even after 4 days of adaptation. For example, both experimental and control animals experienced frequent, brief arousals that appeared to occur in response to neck muscle relaxation and head drop. In fact, total sleep time and sleep efficiency were lower in control subjects than values reported for unrestrained macaques by other investigators [9,21,34]. This was also true of subjects with small lesions. Consistent with our observations, other investigators have also found that sleep recorded in a restraining chair is more fragmented than sleep recorded by telemetry in normal, unrestrained animals (D. Rye, personal communication).

Other testing on this same group of lesioned animals suggests that the lesions limited negative emotional responses. For example, lesioned animals showed significantly reduced acute fear responses post-lesion (Kalin et al., submitted). If this decrease in negative emotional responsivity bears on the quality of sleep, then sleep disturbance produced by acute emotional factors would be limited among subjects with larger lesions, whereas animals with more intact amygdala tissue would be free to express the full range of emotional effects on sleep. The correlations observed between lesion size and sleep parameters, as well as the variability observed in the controls, support such an interpretation.

The amygdala lesions might also have had a primary effect on arousal level. Early studies by Kluver and Bucy in monkeys demonstrated that the removal of large portions of the temporal lobes results in ‘tameness’ [20]. In our study, however, monkeys receiving fiber-sparing selective amygdala lesions and did not show ‘tameness’ or other dramatic features associated with the Kluver–Bucy syndrome (Kalin, unpublished data). From other behavioral tests, no overall effects on activity levels or alertness were found in the operated animals. These observations tend to argue against the possibility that the observed sleep changes were caused by a global change in arousal level.

A number of findings have suggested a role for the amygdala in regulating REM sleep. Recent microinjection studies in rats have shown that serotonin administration into the amygdala during REM sleep resulted in shortened REM episodes; administration during NREM sleep did not prevent entrance into REM sleep [31,32]. REM sleep was stimulated by injection of the cholinergic agonist carbachol into the central CeA but not the basolateral nucleus in cats [11]. Although the inhibitory effects of monoaminergic agents and stimulatory effects of cholinergic agents on REM sleep have been well documented for brainstem sites, such effects have not been explored in other brain regions.

We found that monkeys with more extensive lesions of the amygdala showed increased REM sleep percentage of total sleep. Since REM sleep expression is normally preceded by some undisturbed NREM sleep, the observed changes in REM sleep in the animals with larger lesions could have been related to improved sleep continuity rather than to specific regulatory influences of the amygdala on REM sleep. On the other hand, since REM sleep is exquisitely sensitive to both environmental and emotional

disturbance, primary abnormalities in REM sleep, REM sleep latency or NREM–REM sleep cycles could have been masked by the increased variability produced by the recording conditions. REM sleep latency was highly variable in all groups. REM sleep amounts were also low and probably below normal in all groups. Questions regarding the effects of amygdala lesions on REM sleep expression will need to be addressed in studies of unrestrained animals.

These studies suggest that the primate amygdala plays a role in mediating stress-induced insomnia. The amygdala is a complex structure, and the current study does not allow us to speculate on the function of selective subnuclei in relation to sleep. Further work aimed at understanding the respective roles of these nuclei will be important for understanding the mechanisms by which the amygdala influences sleep and wakefulness.

Defining a role for the primate amygdala in sleep regulation could have major relevance to understanding insomnia and the sleep abnormalities associated with acute stress exposure. Furthermore, virtually all psychiatric disorders studied to date are associated with disturbances of sleep continuity, including prolonged latency to sleep onset, decreased sleep efficiency and reduction in total sleep time (reviewed in Ref. [6]). Not surprisingly, anxiety is the psychiatric symptom most highly correlated with insomnia and psychiatric illnesses. The mechanisms underlying sleep abnormalities in insomnia and neuropsychiatric disorders are largely unknown. Results of more extensive studies in amygdalectomized primates may allow us to determine whether the amygdala is a likely candidate for mediating the sleep changes associated with psychiatric illnesses or caused by acutely stressful situations.

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