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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Several directions have been pursued toward the achievement of our research goals. We have continued to record the somatosensory responses in trained and untrained monkeys, looking for modulation related to both the state of arousal and to various aspects of the attention paradigm. Experiments have been conducted toward developing the techniques required to determine corticothalamic mechanisms responsible for this modulation. Some of the results reported here concerning the effects of arousal state on thalamic somatosensory processing are currently in press. The stereotaxic atlas developed for this study has been further enhanced to include a horizontal view of thalamic structures. HISTAT, the statistical program for intra- and inter- histogram analysis has been upgraded to include additional statistical comparisons. (A 10)			
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Modulation of Thalamic Somatosensory Neurons by Arousal and Attention.

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18 August 1988

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1. Scientific Goals

The primary goal of this study is to identify at the cellular level, those mechanisms involved in the modulation of thalamic somatosensory responses by arousal and attention. To this end the specific objectives are as follows:

- to record from neurons in the ventral posterior lateral thalamus of the awake, behaving monkey that respond to somatosensory stimuli applied to the body surface .
- to detect and quantify any changes in the sensory responsiveness of the above population of thalamic neurons during changes in the level of arousal or attention.
- to determine for units showing attention related changes in activity, whether these changes are 1) non-specific only related to generalized changes in attentional state or 2) are more closely correlated with specific somatosensory attention.
- to physiologically identify (when possible) whether these somatic VP neurons are cortical projection neurons using standard antidromic activation techniques.
- to compare physiological characteristics and anatomical location of the above neurons with those of other somatosensory units showing no behavioral state relationships.
- to determine to what extent the thalamic reticular nucleus may participate in the the behavioral state modulation of somatosensory responses in the ventral posterior thalamus.
- to identify possible cortical mechanisms involved in arousal or attention related somatosensory modulation in the VP thalamus.

The scientific goals of this study are essentially unchanged from those described in the original proposal. Some new techniques for the identification of mechanisms have been tested in pilot experiments to determine their feasibility for use in the awake monkey. These are discussed under the appropriate sections below.

2. Status of the Research

This report covers the course our research has followed and accomplishments made toward the successful completion of our project from August 1, 1987 to July 31, 1988.

Stereotaxic Atlas Preparation

While no new anatomical animals have been prepared during this time period, our current atlas database was enhanced and updated to include not only coronal sections, but also a horizontal view of the diencephalon. This added horizontal view is based on a polar coordinate system centered about the middle of the chronic recording chamber. The translation of coronal atlas coordinates into this plane has made it easier to accurately place recording electrodes within the ventral posterior thalamic nuclei. A sample section of the horizontal view - polar coordinate system is shown in figure 1.

As stated in a previous report, the African green monkey has proved to be an excellent choice for primate stereotaxic procedures. Actual, histologically confirmed coordinates from recording experiments have shown only slight variation from animal to animal, and from computed atlas coordinates.

Focal Cortical Suppression - Primate Model

During the current grant period we have conducted several experiments designed to implement a chronic primate model for assessing cortical controls on thalamic somatosensory responsiveness. This model is based on focal cortical suppression using MgSO_4 . Our previous experiments in the anesthetized and awake rat and more recently in anesthetized monkey, showed that MgSO_4 applied to the surface of the dura above S1 cortex suppresses the spontaneous as well as the activity evoked in cortex. This effect was quite focal in that it was restricted to the area of application. Concurrent with this reduction in cortical activity, we found that thalamocortical projection neurons to the suppressed area of cortex also exhibited a reduced responsiveness to somatic stimuli.

To test whether this technique could be used in the awake monkey, radioactive tracer and dye experiments were needed to determine the degree of spread of MgSO_4 when applied to S1 cortex. This was critical in the chronic monkey because the electrode passes directly through S1 on its path to the VP thalamus. We had to be sure that the applied compound did not diffuse down the electrode track, allowing a direct action on the thalamic recording site. In our earlier work in awake and anesthetized rat we used a

contralateral electrode approach, which avoided this problem. Differences in the gross anatomy in the monkey brain, however, make this situation unavoidable.

These experiments indicate that application of $MgSO_4$ in the region of the electrode track does not appear reach the VP thalamus in our awake monkey preparation. Other experiments, in monkeys prepared with a chronic catheter above S1 cortex, however, suggest that it will be impossible to restrict application of $MgSO_4$ to the area above S1 cortex in the chronic recording situation. The solution spreads quickly over the entire cortical surface when injected epidurally under the recording chamber above S1 cortex. Unless the latter problem can be corrected, this method not permit us to draw solid conclusions concerning the cortical mechanism(s) involved in thalamic response modulation using this method. We will continue to work toward a solution to this problem.

Development and Implementation of PETH and HISTAT

Previously we described some of the details of a unique computer program, PETH, which was developed for the special data acquisition needs of this project. The companion program to PETH, called HISTAT, was also briefly described at this time. This latter software has since been enhanced and extensively tested over the last year. It has proved to be an invaluable tool for testing for statistical differences in histograms computed by PETH under various behavioral conditions, especially when these differences are subtle.

Unit Recording in the Awake, Behaving Monkey

Problems

Since the last year end report several problems arose as mentioned in our earlier Forecast - research progress report for this period. Two animals implanted for unit recording developed chronic systemic infections which our Laboratory Animal Medicine staff were unable to check completely. It is presumed that the the infection was introduced at the time of insertion of a recording electrode. This has slowed progress in recording from these animals.

In addition, on several occasions, another animal developed motor seizures following the removal of the recording microelectrode from the thalamus. This animal's condition returned to normal within a 24 hours. Thus far it has not be determined whether this was due to an irritative process caused by the presence of the microelectrode or an electrode induced infarct. In either case, this situation has slowed the recording process in this subject.

Since the development of the infection problems in the above mentioned animals, some technical modifications have been made to the recording system, which more closely approximates the situation in our squirrel monkey experiments. We are now employing a closed sealed system using a silicone rubber diaphragm in the bottom of the recording chamber. It was hoped that this would reduce the likelihood of such infections developing in any future recording subjects. While this currently appears to be working as planned, only time will tell if this has provided a solution to this problem.

Current Status:

A total of 4 animals were chronically implanted during this past year, 2 untrained and 2 behaviorally trained monkeys. In that time, the responses of 24 somatosensory neurons were recorded in the untrained animals were studied for changes related to the state of arousal. As with our previous work in the squirrel monkey, we find that about 50% of all somatically responsive neurons in VP thalamus show some form of modulation correlated with the level of arousal the animal. This modulation appears to be independent of stimulus modality, and can appear as both facilitation or inhibition of response for a specific behavioral state. The data from this aspect of the project was presented at the AFOSR review held in San Antonio in December 1987. This work is also now in press in Brain Research Bulletin.

Unit recording also in progress in the trained subjects mentioned above. During this reporting period only twelve of all units recorded could be adequately studied during this year within the constraints of the behavioral paradigm. Although data analysis is in its early stages at this time, it seems clear that thalamic neuronal excitability is markedly effected by several factors within the behavioral task. An example of changes in the spontaneous discharge of one VP unit during different behavioral states is shown in the interspike interval histograms (ISIH) of figure 2. The top panel shows the ISIH computed for spontaneous activity of a VP somatosensory neuron during the quiet alert state, just prior to the presentation of a behavioral trial. The bottom panel shows the ISIH for the same unit during a visual attention trial during while the monkey is actively pulling the response lever.

In these animals as well as in the naive animals, some units have also been studied for changes in discharge after the administration of various drugs (namely, morphine, valium, naloxone and halothane). These drugs affect the behavioral state of the animal, and we have looked for possible corresponding changes in thalamic responsiveness. The use of such drugs may prove to be a

valuable tool for determining possible underlying neurochemical mechanisms in thalamic somatosensory modulation.

Technical and Methodological Developments

Additional refinements have been made to the chronic recording technique which have led to better, more stable recordings. As we continue to use this method we have found it necessary to further modify the system to increase its utility and ease of use. Chronic unit recording is still a slow, tedious process and our methods will be a continual ongoing evolution.

The development of a computerized data base for the descriptive information as to unit response properties is still in evolution. A new version is currently under development since it was necessary to change to different vendor's database management software. Furthermore the underlying data structure is still being modified as we learn more about the response properties of the cells from which we are recording.

In an earlier report, I stated that we were abandoning the development of a fine wire electrode array for stimulation in the midbrain spinal lemniscus, and were returning to the use of twisted pair electrodes. New progress in this area has allowed us to reliably use this fine wire technique for electrical stimulation of deep brain structures.

We have continued our investigation into the use of chronic microinjection of an excitatory neurotransmitter or possibly a local anesthetic (tetracaine) into the thalamic reticular nucleus (TRN). This would provide a more "physiological" means of controlling activity if TRN in an effort to elucidate its role in VP modulation during behavior. This entire process has not been as successful as hoped and has taken longer than expected to implement. As stated earlier, our chronic recording chamber leaves little or no room for the placement of the catheter, without interfering with the operation of some other part of the system. In addition, prior to this study, we had no experience with this type of procedure. We are therefore proceeding with additional pilot experiments to development of these methods for use in this work.

3. Publications

Journal Articles

Casey, K.L. and Morrow, T.J.: (1988) Supraspinal nocifensive responses of cats: spinal cord pathways, monoamines and modulation. *J. Comp. Neurol.* (in press).

Sorkin, L.S., Morrow, T.J. and Casey, K.L.: (1988) Physiological Identification of afferent fibers and postsynaptic sensory neurons in the spinal cord of the intact, awake cat. *Exptl. Neurol.* 99: 412-427.

Pertovaara, A., Belczynski, C.R., Morrow, T.J. and Casey, K.L.: (1988) The effect of systemic cocaine on spinal nociceptive reflex activity in the rat. *Brain Res.*, 438: 286-290.

*** Morrow, T.J. and Casey, K.L.: (1988) Modulation of the spontaneous and evoked discharges of ventral posterior thalamic neurons during shifts in arousal. (*Brain Res. Bull.*, in press).

Lin, Y., Morrow, T.J., Kiritsy-Roy, J.A., Terry, L.C. and Casey, K.L.: (1988) Cocaine: A supraspinal, dopamine mediated, non-opiate analgesic. (*Brain Res.*, in press)

Abstracts

Casey, K.L., Butler, J., Lewis, K.G. and Morrow, T.J.: Evidence that the distribution of polymodal nociceptors does not determine both thermal and mechanical thresholds of human glabrous and hairy skin. *Neuroscience Abstracts*, Vol 13, 1987.

Belczynski, C.B., Pertovaara, A., Morrow, T.J. and Casey, K.L.: Cocaine: Neurophysiological effects on bulboreticular projection neurons. *Neuroscience Abstracts*, Vol 13, 1987.

Lin, Y., Morrow, T.J. and Casey, K.L.: Cocaine: Mechanisms of CNS analgesic action in the rat. *Neuroscience Abstracts*, Vol 13, 1987.

Pertovaara, A., Belczynski, C.R., Morrow, T.J. and Casey, K.L.:
Cocaine: Neurophysiological evidence on central analgesic
mechanisms. Abstract and presentation, XIX Nordic
Congress of Physiology and Pharmacology, Univ. of Oslo,
Blindern, Norway, 1988.

*** Reprint enclosed.

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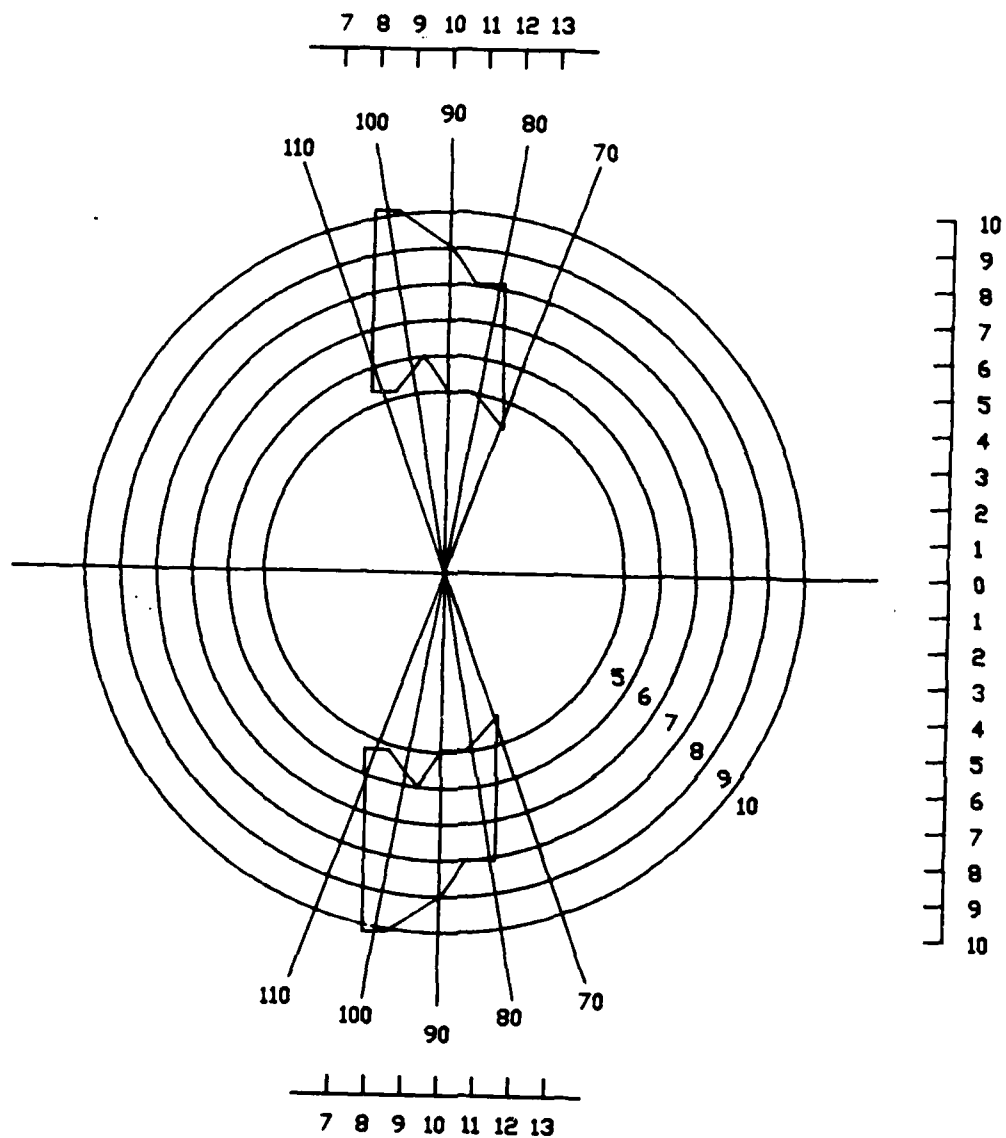
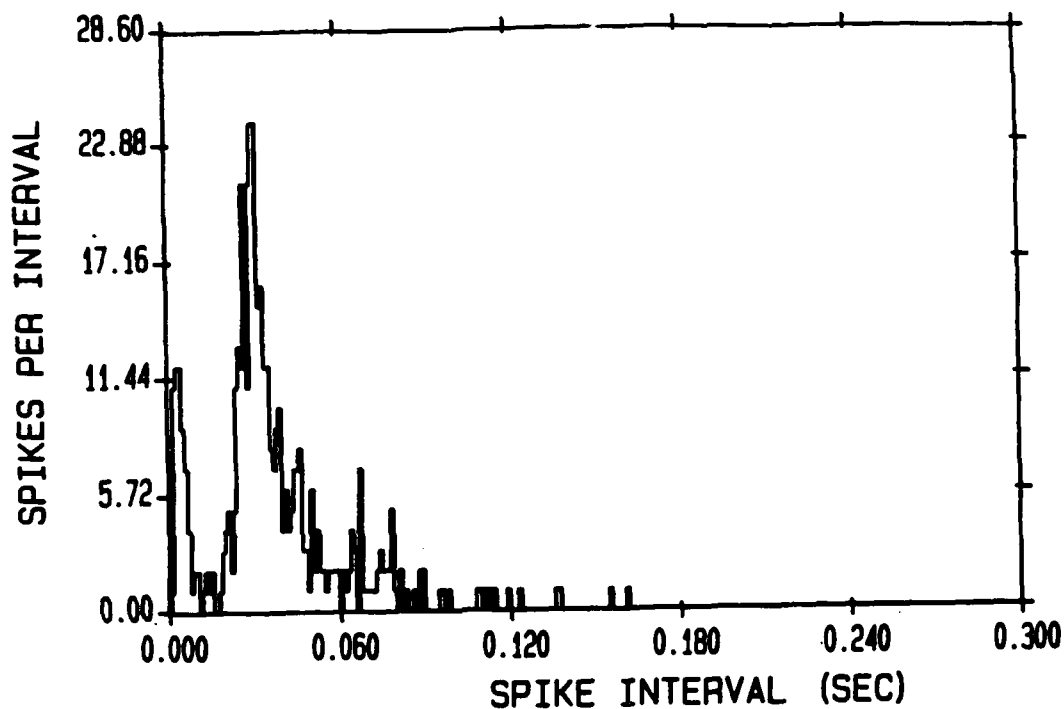


FIGURE 1.

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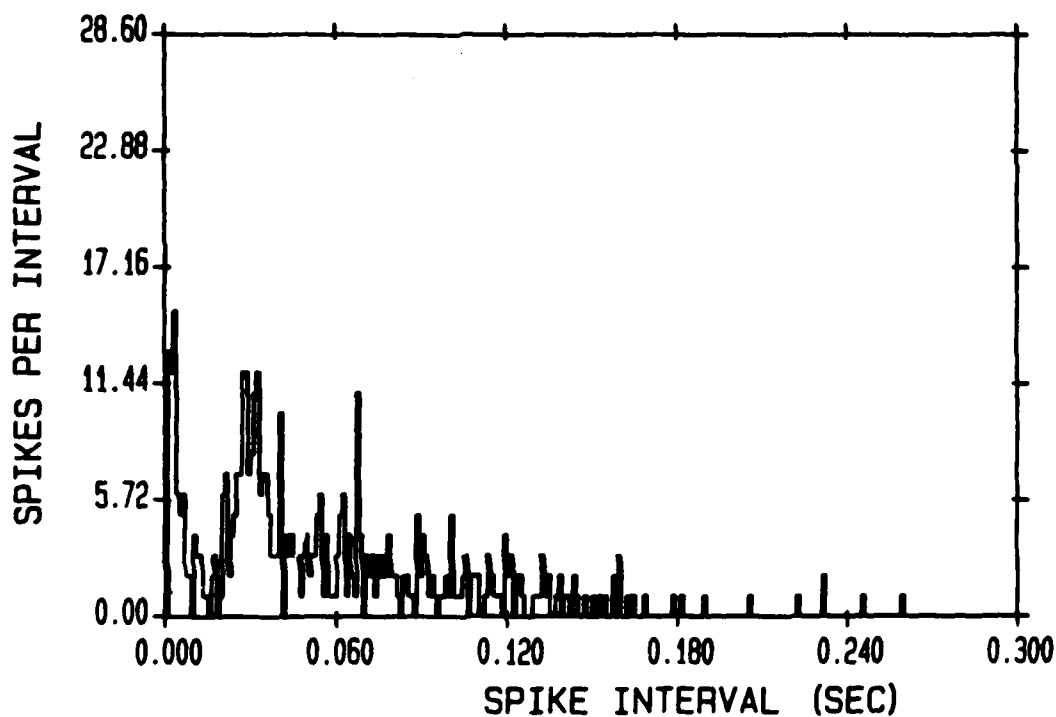


FIGURE 2.

MANUSCRIPT #2973

TITLE: Modulation of the spontaneous and evoked discharges of ventral posterior thalamic neurons during shifts in arousal.

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Running Head/Short Title: Arousal related modulation of thalamus.

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ABSTRACT

MORROW, T.J. AND K.L. CASEY. Modulation of the spontaneous and evoked discharges of ventral posterior thalamic neurons during shifts in arousal. **BRAIN RES BULL** The responses of 154 ventral posterior thalamic neurons to a variety of somatic stimuli and to electrical stimulation of the midbrain spinal lemniscus were recorded in the awake squirrel monkey during varying states of arousal. Many VP (42/93) neurons showed changes in somatosensory responsiveness which correlated with shifts in arousal. Arousal related modulation (ARM) of somatic responses were not selective for any specific stimulus modality. Most cells (N=36) responded maximally during quiet waking with responses significantly reduced during drowsiness or periods of waking movement. Other neurons (N=5) responded maximally during drowsiness, and gave decreased responses as the level of arousal increased. Similar changes were seen for neurons driven by spinal lemniscal (SL) stimulation. All changes in evoked responses were independent of prestimulus background discharge frequency. At least one site of ARM takes place at the level of the VP thalamus.

KEYWORDS-INDEX TERMS:

Thalamus, Arousal, Somatosensory modulation, Single unit recording, behavioral neurophysiology, awake monkey.

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INTRODUCTION

Our sensory systems are continually bombarded by inputs from which we select information as a basis for action. Perception of a sensory stimulus can be altered during shifts of attention, vigilance or arousal. It is therefore reasonable to hypothesize that certain properties of the response of a neuron to a specific sensory stimulus should covary with changes in an animal's behavioral state. Accordingly, the somatosensory responses of ventral posterior (VP) thalamic neurons would be expected to vary with the level of arousal in unanesthetized, behaving animals.

With few exceptions, most studies of the somatosensory properties of thalamic neurons have been done in anesthetized animals. This work has suggested that most neurons in the ventral posterior part of the thalamus possess what have come to be designated as "lemniscal properties". These cells have well defined receptive fields, typically respond to only one stimulus quality or modality (i.e. hair movement), and exhibit response characteristics that remain unchanged (10,16). In addition, Poggio and Mountcastle (17) showed that such neurons possess certain static properties that are unchanged by general anesthesia.

Several studies have demonstrated that some neurons in the primary somatosensory pathway are functionally modulated during behavioral state. Steriade and Deschenes (19) described the development of rhythmic bursting in resting spontaneous discharges and tonically increased firing of VP neurons during brain-activated behavioral states. Other studies (15) described significant enhancement of both spontaneous and evoked multiple unit activity in specific and nonspecific thalamic nuclei when cats increased their state of arousal. Single unit recordings from the ventral posterior lateral nucleus of awake cats (1) and ventral posterior medial nucleus of awake monkeys (6) also showed changes in the spontaneous discharge of these neurons associated with shifts between waking and sleep. Single unit techniques, however, have been less successful in demonstrating arousal relationships in somatically evoked activity in VP. Hayward (6) and Baker (1) were unable to show any apparent arousal-related changes in the discharges evoked by somatic stimuli, and only qualitative descriptions of unit responses to

somatic stimuli were attempted in these studies.

The present study was designed to explore the effects of changes in the level of arousal on the unitary discharges of neurons in the ventral posterior thalamus of unanesthetized, partially restrained monkeys. The recent development, in our laboratory, of an array of calibrated, mechanical somatic stimulation devices, specialized computer data acquisition hardware and software, and a real-time EEG synchronization detector has made it possible to detect and quantify subtle changes in the excitability of single somatosensory neurons during changes in behavioral state.

METHODS

Surgery

Five adult male squirrel monkeys were initially tranquilized with ketamine HCl (10mg/kg, im) and intubated with a pediatric endotracheal tube. Animals were then deeply anesthetized using halothane in combination with nitrous oxide (60%) and oxygen (40%). The level of halothane was adjusted (0.5 to 1.0%) as needed during surgery to suppress all somatic reflexes. Under aseptic conditions, subjects were prepared for unit recording by making a 10mm diameter craniotomy above the stereotaxic coordinates calculated for the exploration of the ventral posterior (VP) thalamus. A microdrive chamber (12) was positioned above the craniotomy and a stainless steel reference electrode inserted at the lateral edge of the skull opening, 2 to 3mm into the underlying parietal cortex. Bipolar stainless steel stimulating electrodes, with a 2mm tip separation, were implanted bilaterally under stereotaxic control into each spinal lemniscus (SL), which is comprised of the combined trajectories of the medial lemniscal and spinothalamic pathways at the midbrain level. All electrode leads were routed to an electrical connector situated on the skull, posterior to the microdrive. All electrodes, the microdrive assembly and connector were fixed to the skull using four stainless steel skull screws and dental acrylic cement. Two of these skull screws served as EEG electrodes and another as system ground. Postoperative care included administration of subcutaneous fluids to maintain hydration and routine use of systemic

antibiotics (penicillin, im, 45,000 units/kg/day for 10 days).

Recording and Arousal State Determination

Subjects were allowed to recover for at least two weeks before unit recording was attempted. Each monkey was adapted to tolerate up to three hours of partial restraint in a primate chair. Based on previous work (4,6), the level of arousal was divided into three categories: 1) Waking with movement (WM), where the animal is moving and low voltage fast activity dominated the EEG; 2) Quiet waking (QW), where the monkey is not moving and the EEG is desynchronized as in WM; and 3) Drowsy (D), where the EEG shows primarily high voltage, slow activity and the animal is not moving. Two parameters were continually monitored on a chart recorder and by computer to define each arousal state during single unit recording. The amplified output of a vibration sensor (weighted phonograph cartridge) attached to a flexible wand on the back of the primate chair reliably triggered output from a voltage level detector whenever the monkey produced visible movements of a body part the size of a hand or foot. Similarly, a laboratory constructed EEG synchronization detector (13) was used to register the presence of high voltage ($> 50 \mu V$), synchronized slow EEG activity, occurring within a frequency range of 6 - 17 Hz. This device indicated the presence of synchronized EEG activity. The outputs of both EEG and movement detection circuits were monitored on separate channels of a chart recorder and led into a laboratory minicomputer along with standard pulses triggered by the discharge of single neurons (see below).

During experimental sessions, extracellular single unit activity was recorded while slowly advancing an Epoxylite[™] insulated stainless steel microelectrode (5-10 Megohms impedance at 100 Hz) into the somatosensory thalamus through a silicone rubber seal located at the bottom of the microdrive. The experimenter tested each unit for responses to somatic or SL stimulation as the electrode was advanced. Only well isolated action potentials (average amplitude: $586 \mu V \pm 287 \mu V$ s.d.; range: 200 - 2000 μV ; signal/noise ratio $\geq 2/1$) were used to trigger pulses from a window discriminator (Frederich Haer Co.) with an output to a laboratory

minicomputer (Data General S-140) for construction of peristimulus time histograms (PSTH). These same trigger pulses were fed into: (1) a frequency to voltage converter with analog output to the chart recorder, (2) a second channel of the oscilloscope, (3) a audio monitor, and (4) a digital counter. These monitoring devices were all used in combination to maintain the accuracy and reliability of action potential discrimination throughout each recording session.

SL stimuli were bipolar, square wave pulses (100 - 1000 μ A; 0.1 msec duration) delivered through the midbrain electrodes at 1 to 2 Hz. For unit testing, stimulus intensities were 2x threshold, typically placing them in 100-300 μ A range. We have found no evidence that low frequency SL stimulation, even at intensities of 1mA, had any effect on spontaneous behaviors or the pattern of EEG activity.

Somatic stimuli consisted of controlled air puffs (.2msec duration,) for the selective hair stimulation, calibrated von Frey hairs (14 to 58 g) for skin stimulation, manual muscle palpation and joint manipulation. Tactile stimulation over wide areas of the body surface and SL stimulation at 1-2 Hz were used to search for inactive neurons. During quantitative testing, somatic stimuli were always delivered in the center of the identified receptive field.

Data Analysis

After a unit was isolated, a detailed evaluation of the receptive field and stimulus-response characteristics was undertaken for each cell. Somatic receptive fields were mapped and adequate stimulus determined. In addition, the rate and pattern of any spontaneous discharge was noted. Quantitative testing was then begun to determine whether the somatic or SL responsiveness of the neuron was altered during shifts in the state of arousal. All data were acquired and stored by computer using a specially developed software program, PETH. The use of this software was critical to the success of this project, since an animal's level of arousal changes frequently during the course of testing a single neuronal response to a given stimulus. The algorithm employed, acquired all data in such a way as to not only maintain the real-time relationship of the unit's discharge with other relevant events, but also detect spontaneous changes in the state of arousal.

The PETH system is schematically illustrated in figure 1. The time of occurrence of all critical events, including each unit discharge, SL or somatic stimulus, and the presence of movement and EEG synchronization are computed and stored. The data are then dynamically sorted and grouped off-line so that neural responses to all stimuli presented during a specific arousal state can be separately analyzed and unit excitability determined. In addition to compiling peristimulus time histograms, this program computes the mean pre- and post-stimulus spikes /stimulus, spike frequencies, pre-post differences and their associated standard deviations. These data provide measures of response change and variability, so that statistical comparisons can be made between all stimulus and arousal conditions.

Histology

At the end of the final recording session, the subjects were deeply anesthetized with pentobarbital sodium (50 mg/kg) and transcardially perfused with saline, followed by a solution of 10% formalin. Serial 50-100 micra coronal sections through the diencephalon and midbrain were cut in the anterior-posterior and vertical stereotaxic planes and stained with cresyl violet. Electrode tracks and stimulation sites were reconstructed from projected images of the stained sections. Identification of unit recording sites was based on electrolytic lesions made at two or more points along each track by passing 30 uA anodal d.c. current (20 sec) through the microelectrode.

RESULTS

One hundred and fifty-four somatically responsive units were recorded in the lateral thalamus, including the ventral posterior lateral (VPL), medial (VPM), inferior (VPI), ventral lateral (VL) and thalamic reticular (RT) nuclei. Neurons in VL (N=9) and RT (N=6) were included in our sample because they responded to somatic stimuli, were located immediately adjacent to VPL and could be studied for changes during different states of arousal. Of the total, 93 could be tested for changes in responsiveness as the monkey's level of arousal shifted among the waking with movement, quiet waking and drowsy states. Fifty-four somatically activated cells

were also reliably driven by SL stimulation, 35 of which were also tested for arousal related modulation.

We found that approximately 45% of all somatically driven VP neurons tested (42/93), exhibited changes in their somatosensory responsiveness which correlated with shifts in the state of arousal. Similarly, 15 of the 35 (43%) neurons tested showed arousal related modulation of their responses to SL stimulation. Consistent with earlier reports, we also found that the spontaneous activity of many VP neurons varied with the level of arousal. Table 1 summarizes the response properties of the single units recorded in this study.

The majority of units exhibiting arousal related modulation of evoked activity fell primarily into two groups. The first and most predominant group (N=36) consisted of units that fired maximally to somatic stimuli presented during the quiet waking (QW) state. These neurons showed decreased responsiveness during periods of either decreased (D) or increased (WM) arousal. The second and less prevalent group (N=5) was composed of neurons that responded best during the drowsy state, and exhibited progressively lower responses as the level of arousal increased from D to QW to WM. One neuron, not included in either group above, discharged maximally during WM and with decreased responsiveness during the QW and D states.

Figure 2 illustrates the response of a typical neuron from the largest group above. Here we see the discharges of a cell to repetitive hair movements produced by an air puff stimulus applied to a contralateral receptive field on the hand. As shown in both PSTH records and chart recordings, this neuron responds maximally to stimuli presented during the awake state (QW), when the EEG was desynchronized and there were no obvious movements. When the EEG became more synchronized as the monkey became drowsy, somatic responsiveness was markedly reduced or even eliminated. It is important to note that background activity, seen in the pre-stimulus period, was unchanged during the time of reduced somatic responsiveness. This finding that the spontaneous discharge did not change or when changed, did not follow direction of change(s) seen in the evoked responses was typical for many arousal modulated somatosensory

neurons.

The effect of arousal state on the short latency responses elicited by SL stimulation of this same somatically activated neurons is also shown in figure 2. During repetitive stimulation of SL (1Hz) while the monkey was in the quiet waking state, most unit discharges occurred within a narrow 1 msec wide post-stimulus latency band, 3-4 msec after the stimulus. During drowsiness, the overall responses to the same SL stimulus were reduced and the discharges became more dispersed, occurring over the broader 2-4 msec post-stimulus period. Although not shown in figure 2, as the responses to SL stimulation decreased with lower levels of arousal, the spontaneous interstimulus activity of the cell was unchanged during shifts in arousal.

In contrast to the neuronal responses just described, second group of cells exhibited evoked responses which were facilitated during drowsiness and depressed as the level of arousal increased to waking with movement. Figure 3 illustrates this type of arousal related response modulation. As in the previous example, the neuron was driven by repetitive movement of hairs within the receptive field on the contralateral limb. The histograms presented here show a depression of both the somatic and SL responses as the monkey's behavioral state changed from drowsy to quiet waking to waking with movement. Again, it is important to note that the interstimulus or pre-stimulus background did not follow the same trend as did the evoked response. For this unit, the spontaneous discharge in fact increased slightly with increasing arousal while at the same time the somatic and SL responses were diminished.

It was not possible to test for arousal related changes in response to both somatic and SL stimulation for all units. However, in the 35 cases where this was possible, 34% of the units (12/35) showed similar arousal related effects for both stimulus types whenever response modulation could be demonstrated for either stimulus alone. Only 3 neurons exhibited modulation of the response to peripheral somatic stimulation exclusively. No units showed arousal related modulation of the SL responses alone.

Only one neuron could be adequately tested for changes in the size of its receptive field

(RF) as a function of the state of arousal. Arousal related modulation of both the relative magnitude of its discharge to a somatic stimulus and the size of its receptive field was found for this neuron. This cell had a large receptive field that included a 14 cm x 0.6 cm (8.4 cm²) area on the tail during quiet waking (QW), and showed a reduction in field area to approximately 0.3 cm² when the monkey became drowsy (D).

The response properties of all somatic units tested are summarized in Table 1. The data presented here shows that the likelihood for occurrence of arousal-related response modulation in a given VP somatosensory neuron cannot be predicted on the basis of whether it receives input from the cutaneous or deep structures ($\chi^2 = 0.4396$). No differences in ARM were found across all response properties, regardless the particular adequate stimulus (hair, cutaneous, muscle, etc.).

DISCUSSION

Early studies examining the physiology of VP thalamus described the majority of VP neurons as having discharge properties that remained static and unchanged with changes in behavioral state, including general anesthesia (16). However, we have shown that a large proportion of somatically driven ventral posterior thalamic neurons possess discharge characteristics that would classify them as markedly dynamic and varying with behavioral state. These VP neurons showed changes in their spontaneous and evoked responses that are correlated with changes in the level of arousal as defined by objective electroencephalographic and behavioral criteria. Of those cells that showed arousal related modulation, most responded maximally to a somatic or SL stimulus when the monkey was in the quiet waking state. A smaller population of neurons showed a complementary type of arousal related modulation in that they responded best when the state of arousal was at its' lowest and increased responsiveness as arousal increased.

These data are in contrast with the findings of Baker (1) and Hayward (6) who were unable to demonstrate any effect of arousal on the evoked discharges of single neurons in the VP of awake cat and monkey, respectively. It is not clear why such findings were missed in these

studies, because the response modulation which we saw in many units was sufficiently robust to be seen even in the chart record output of our ratemeter. One possible reason for this discrepancy might be interstimulus variability of somatic stimuli when testing unit responses during the different arousal states.

It is also possible that the differences seen in these studies could relate to the specific behavioral states present during which testing was performed. The investigations of both Baker and Hayward focused on the changes occurring sleep and waking, rather than on the stages of arousal preceding sleep. It is possible that there can be no direct comparison of their findings and those of this study, because our monkeys did not sleep. It may be that the neuronal sensory responsiveness during sleep is more like that during quiet waking than in the drowsy state. Such a hypothesis in fact gains support from the work of Favale et al.(5), who showed that evoked potentials recorded in the cat fluctuated during the sleep-waking cycle with greater amplitude during sleep than during waking.

Our data provides evidence that the size of the somatic receptive field of a neuron can also vary as a function of arousal. While only one such neuron was found in this study, this may be due to the technical difficulty involved in accurately measuring changes in small receptive fields in the awake animal. Only cells with large receptive fields could be adequately tested for such changes. It is possible that many of the units showing ARM in the relative magnitude of their somatically evoked discharge, also had changes in receptive field size, which were undetected. Slight changes in response latency might also be missed.

The data presented here suggests that at least one site for the modulation of VP responses is at this thalamic level. SL stimulation bypasses spinal and dorsal column inputs and evokes short latency responses in VP neurons that involve only one or two synaptic relays. The activation of descending modulatory or collateral pathways does not influence our results because the short response latencies do not allow enough time for such long conduction delays. Arousal related modulation for SL responses must therefore occur within or very near the ventral posterior

thalamus. Additional sites for arousal related modulation of VP thalamus can not be ruled out. While most VP neurons showed ARM for responses elicited by both peripheral and SL stimulation, three units failed to exhibit modulation of both stimuli and showed exclusive modulation of the responses to somatic stimuli. This suggests other possible pathways or mechanisms in addition to direct thalamic action on VP neurons.

Other evidence suggests that arousal related response modulation is input specific and not the result of an overall change in the postsynaptic excitability of a VP thalamic neuron. If changes had occurred in the overall excitability of a neuron, then similar changes would be expected in both the evoked and spontaneous activity of the cell. Most VP neurons, however, showed no change or an opposite change in spontaneous activity relative to those changes obtained during the ARM of somatic and SL elicited discharges. This data therefore suggests an input specific modulation at the thalamic level, possibly by action on the distal portion of the dendrites of VP neurons. The role of local circuit interneurons within VP can also not be ruled out. Presynaptic inhibitory mechanisms involving axo-axonal contacts are unlikely because the anatomical basis for such inhibition is lacking in the primate thalamus (14).

The sensory responses of thalamic neurons could also be directly influenced by the activity of cortical, diencephalic or brainstem extralemniscal neurons that project to the somatosensory thalamic nuclei. The anatomical basis for direct corticothalamic control has been demonstrated (8,9). Recently, we described corticofugal influences on the responses of ventrobasal (VB) thalamic neurons in anesthetized and awake rat (21,22). We demonstrated that focal suppression of S1 cortex reduced the number of discharges of VB neurons in response to electrical stimulation of the medial lemniscus or the somatic receptive field. This data provides evidence that somatosensory transmission to VB neurons is primarily facilitated by S1 corticothalamic neurons.

Bowsher (2) also reviewed evidence for reticular formation and tectal inputs to somatosensory thalamus. Scheibel, et al.(18) and others suggest an anatomical substrate for modulation of the thalamic ventrobasal complex via connections with both cortex and the adjacent

thalamic reticular nucleus. Anatomical studies show a projection of cortical efferents to VB and to the thalamic reticular nucleus that parallels the topographic projection to the thalamic relay nuclei (7,11,19). Thus the thalamic reticular nucleus receives inputs from the cerebral cortex organized so that any cortical area projects to the thalamic reticular and neighboring VB complex with these two corticothalamic sites interconnected by thalamo-reticular and reticulo-thalamic fibers (3,9,11).

In summary, there is considerable evidence many systems may be involved in the modulation of somatosensory transmission through the VP thalamus. The underlying mechanisms responsible for changes VP responsiveness during shifts in arousal as reported here are yet to be determined.

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FIGURE LEGENDS

FIGURE 1. Schematic representation of data acquisition during a typical unit recording session. Note how the behavioral state, defined by the EEG and movement traces, rapidly and continually changes during the period of data acquisition as a stimulus is presented. Shown in the lower boxes, computer processing (PETH software) sorts the evoked unit discharges into separate groups, based on the specific behavioral state during which the stimulus was given. The vertical lines (upper four traces) represent the divisions imposed by the software for sorting each stimulus evoked unit discharge into three distinct groups as defined by the arousal states described in the methods. (LVF = EEG desynchronized with low voltage fast activity, SYNC = EEG synchronized with high voltage, slow wave activity, MOV = movement)

FIGURE 2. VP unit responding to hair movement produced by calibrated puffs of air to the contralateral receptive field on the dorsal surface of the toe (inset). Reduced responses are seen to SL stimulation (Upper PSTH panels) and to somatic input (lower PSTH panels and rate meter records) during drowsy state (RIGHT) as compared to quiet waking (LEFT). Vertical line extending from top to bottom of horizontal axes in each PSTH represents time of each stimulus onset.

FIGURE 3. VP unit responding to hair movement within the receptive field on contralateral dorsal forearm shown (inset). Both somatic (air puff stimulation, upper panels) and SL (lower panels) responses show reduced responses as the level of arousal increases from drowsy to quiet waking to waking with movement. Vertical line extending from top to bottom of horizontal axes in each PSTH represents time of stimulus onset.

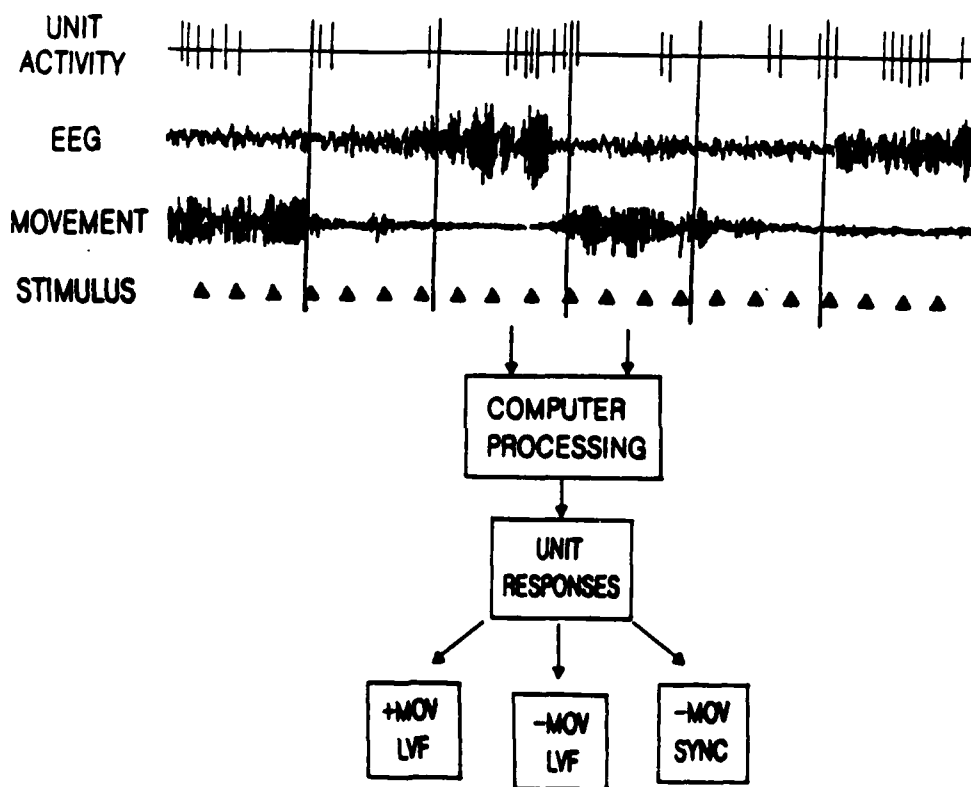


FIGURE 1

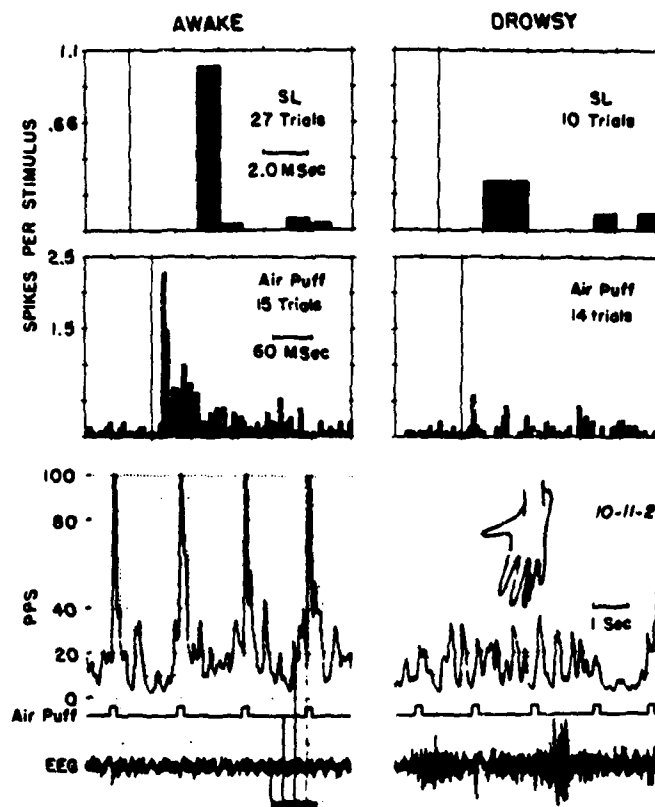


FIGURE 2

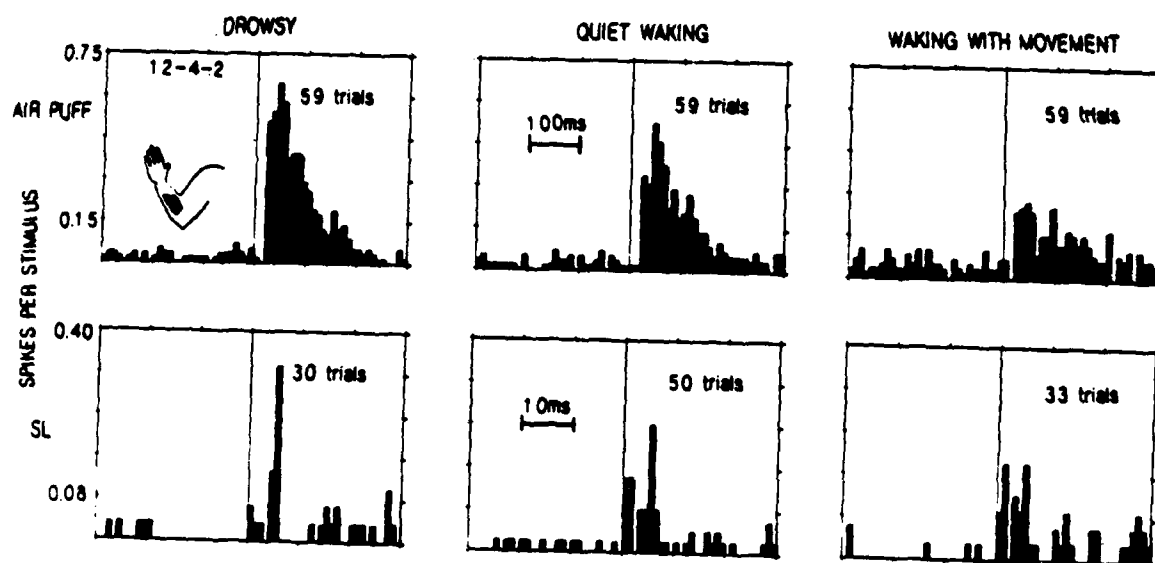


FIGURE 3

TABLE 1. Distribution ARM response changes and response properties of VP neurons.

SOMATICALLY DRIVEN UNITS (n=154)

# TESTED for ARM	93	# WITH ARM	42
# TESTED for SL RESPONSE	129	# RESPONSIVE to SL	54
# SL TESTED for ARM	35	# SL with ARM	15

STIMULUS # with ARM # without ARM

cutaneous	26	36
deep	16	15

ARM = Arousal Related Modulation SL = Spinal Lemniscus