40 HZ EEG AND FOCUSED AROUSAL BEHAVIOR IN THE CAT

A Thesis

Presented to

the Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

By

Paul M. Kaufmann

December, 1985

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ABSTRACT

The relationship between 40 HZ EEG and focused arousal behavior has been investigated in 6 cats. Indwelling chronic electrodes were implanted in the nucleus parabrachialis (PB) of the rostral pons, lateral geniculate nucleus (LGN) of the thalamus, and visual cortex (VC). After recovery, EEG and behavior were recorded across the following experimental phases: 1) baseline, 2) presentation of a novel 7 cps visual stimulus and habituation to this stimulus, and 3) UCS - CS pairing of this visual stimulus with a mildly aversive event and adaptation to the pairing. An increase in the frequency of 40 HZ peaks was observed in the initial stages of phase 2 and phase 3 in comparison to phase 1. 40 HZ activity in the LGN and VC was strongly correlated with 40 HZ activity in PB. These results replicate previous findings that a high frequency low amplitude EEG signal is highly correlated with focused arousal, attention, and the acquisition phase of learning. Furthermore, results suggest that PB functions, through excitatory post synaptic potential (EPSP) biasing, to increase the probability of firing of fast frequency EEG between the LGN and VC during UCS-CS pairing of a visual stimulus. Ascending cholinergic input from PB is a critical neural substrate for focused arousal. Applications to learning and cognitive dysfunction are discussed.

Key words: 40 HZ - focused arousal - parabrachialis - EPSP biasing

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CHAPTER I

INTRODUCTION

A high frequency, low amplitude electroencephalographic (EEG) signal centered at a frequency of 40 hertz (HZ) is highly correlated with concentration, attention and the acquisition phase of learning, in animals and humans (Coleman & Lindsley, 1975; Galambos, 1958; Rowland, 1958; Freeman, 1963, Killam & Killam, 1967; Dumenko, 1961; Sheer, 1970, 1974, 1976; Sheer & Grandstaff, 1970; Bauer & Jones, 1976; Skinner & Yingling, 1977; Bird et al., 1978 a, b; Ford et al., 1980, Sheer, 1977; 1984; Loring & Sheer, 1983; Spydell & Sheer, 1982; Spydell, et al., 1979). These various cognitive abilities require a state which has been referred to as "focused arousal" (Sheer, 1975; 1984).

Forty HZ EEG activity was first recorded in various structures in the rhinencephalon (Gerard & Young, 1937). Early studies generally recorded discharges of 40 HZ activity from the olfactory bulbs in response to a variety of stimuli. The findings of Adrian and Ludwig (1938) are typical. These investigators recorded 40 HZ activity from the olfactory bulb of catfish when they were exposed to a meaningful olfactory stimulus. More recently 40 HZ activity has been recorded in rhinencephalic structures of numerous species including cat (Gault, 1963), monkey (Hughes & Mazurowski, 1962), chimpanzee (Adey, 1963), and human (Brazier, 1961).

Others have observed 40 HZ activity in various regions of the nervous system. Galambos (1958) recorded 40 HZ activity in the caudate nucleus and globus pallidus of cats in response to clicks which the animals had learned were predictive of an unavoidable shock. Rowland (1958), using a similar paradigm, observed an increase in 40 HZ activity in the medial geniculate nucleus and auditory cortex in the cat in response to clicks which predicted an unavoidable shock. He then used the absence of clicks to signal an unavoidable shock and saw an increase in 40 HZ activity during the non-click periods. In both conditions, 40 HZ activity increased as the animal learned the association between a conditioned stimulus (CS) and meaningful unconditioned stimulus (UCS).

Freeman (1963) recorded 40 Hz activity in prepyriform cortex of cats following the successful pairing of a tone (CS) with a food odor (UCS).

Furthermore, he noted that the maintenance of airflow through the nostrils is essential for successful pairing and increased 40 HZ activity. The efficacy of food odor as an UCS increases with the number of hours of food deprivation. As the duration of food deprivation lengthens the UCS is presumed to become more meaningful.

Killam and Killam (1967) observed increased 40 HZ activity in the lateral geniculate nucleus of cats during presentation of the correct visual pattern in a three choice visual discrimination task. Again, the increased 40 HZ activity only appeared after the correct discrimination had been learned.

These findings indicate that as the animal learns the association between a CS and an UCS an increase in 40 HZ activity is observed within the appropriate sensory pathways. This increased activity may be the result of additional processing required as the CS becomes meaningful. If the increase in 40 HZ activity is truly the result of the association, then it should be observed again when a new CS is employed. Rowland's (1958) reversal procedure demonstrated this to be the case. The findings of Freeman (1963) and Killam and Killam (1967) are at least suggestive that similar processes are operating in other sensory modalities.

Forty HZ activity is not limited to subcortical structures. Hess, Koella, and Akert (1953) found increased 40 HZ activity over frontal, parietal, and occipital areas of cortex in cats which were "fully alert" when compared to subjects that were simply awake, drowsy, or asleep. Sakakura and Doty (1969) noted bursts of 40 HZ activity from striate cortex in squirrel monkey in response to sudden changes in illumination in the testing chamber. These investigators observed that changes in attention or eye movements will block or sharply curtail these bursts of 40 HZ. Furthermore, 40 HZ activity ceases in striate cortex with bilateral enucleation of the eyes.

The 40 HZ EEG response occurs in cortical areas that are required for processing of information and execution of behavior. Dumenko (1961) established a conditioned defensive response in dogs by using a tone as a CS and induction current excitation as the UCS. Forty HZ activity was recorded from auditory, somesthetic, and motor cortex, following acquisition of the CR. However, this activity was only observed in that portion of the motor cortex associated with the body area which had been trained. When the CR had been conditioned on the posterior limb, 40 Hz activity was noted over the cortical motor area associated with that limb and 20-25 HZ activity was observed over the area controlling the anterior limb. When this response was re-conditioned on the anterior limb, 40 HZ activity occurred in the anterior motor area and 20-25 Hz activity in the motor area controlling the posterior limb. Some investigators have concluded that 20-25 HZ activity indicates inhibitory processing, while 40 HZ activity represents excitatory processing (Sheer, 1984).

In a series of studies using a successive visual discrimination task with cats, Sheer (1970) reported 40 HZ activity was associated with facilitation, while 20 HZ activity was linked to inhibition. Ten second presentations of a light stimulus flashing at 7 cycles/ second (positive stimulus) predicted a milk reward for bar pressing in deprived animals. However, 10 second presentations of the light stimulus flashing at 3 cycles/ second (negative stimulus) was not predictive of milk reward. Hence, bar pressing was brought under disriminative control of a visual stimulus. Increases in 40 HZ power were recorded in both visual and motor cortex when the presentation of the positive stimulus and the bar press response occurred simultaneously. Concurrent with this increase was an expected decrease in 20 HZ EEG power. This concurrent decrease in 20 HZ power was more marked over the visual cortex. During the presentation of the negative stimulus an increase of 20 HZ EEG power was observed over the same cortical areas if the animal correctly inhibited the bar press response.

In summary, it appears that 40 HZ EEG activity is correlated with the following three conditions: 1) the presentation of a novel stimulus (olfactory, somesthetic, auditory, and visual), 2) the acquisition phase of learning the association of a stimulus with a novel event which is meaningful for the animal, and 3) the execution of a learned motor response which is rewarding within the meaningful context mentioned above. Furthermore, 40 HZ activity is associated with specific sensory and motor areas of the brain required in detection and execution of this learned response. Finally, evidence suggests that 40 HZ activity indicates excitatory processing or "arousal" of neural substrates.

Focused Arousal Behavior

Lindsley and his co-workers (Anchel and Lindsley, 1972; Macadar, Chalupa, & Lindsley, 1974; Coleman and Lindsley, 1975) have described two distinct behavioral arousal patterns which can be observed in ongoing free behavior. The first, pattern I, was characterized as "alerting, orienting, scanning, and investigatory activity". Pattern II was characterized as "activiation of attentive processes, but in a more focused and restrictive manner...seeming to narrow the field of view, whether external or internal...attention is temporarily 'locked on' to specific aspects of the environment." This second pattern is manifested by "fixation of gaze and an attentive posture".

Before proceeding to describe the electrical correlates of these behavioral arousal patterns, it is important to define and understand some of the terminology which has been used historically in EEG research. The vague term "desynchronization" is used frequently in the older literature in reference to faster frequency EEG patterns which appear as irregularly thickened black lines on visually inspected EEG records. This crude distinction was as much a result of slow paper speed as it was actual discription of the EEG record. With the advent of recording techniques and computer analysis it has been demonstrated that this "desynchronized" EEG clearly represents a number of different electrical patterns. The 40 HZ pattern, described above, represents one such distinct pattern (Sheer, 1984).

Patterns I and II, described above, are correlated with tonic and phasic arousal (Sharpless and Jasper, 1956), as expressed in cortical EEG desynchronization. In tonic arousal, diffuse desynchronized cortical EEG and hippocampal theta EEG are observed (Macadar, et al.,1974). Stimulation of the brainstem-hypothalamic zones - locus coeruleus, nucleus reticularis pontis caudalis, and medial hypothalamus - produced behavioral arousal pattern I and EEG tonic arousal, simultaneously (Coleman and Lindsley, 1975). This desynchronization corresponds to lower frequency (13-35 HZ) beta EEG signal. Behavioral arousal pattern I and tonic arousal EEG activity, when taken together, has been described as "general arousal" (Sheer, 1975; 1984).

In phasic arousal (Sharpless and Jasper, 1956), EEG desynchrony is restricted to cortical areas appropriate to the stimulus inputs, and it is much more brief, a second or less as compared with a minute or more in tonic arousal (Sheer, 1984). Furthermore, hippocampal EEG activity is desychronized in phasic arousal (Macadar, et al., 1974). Stimulation of the brainstem-hypothalamic zones - nuclei of raphe, nucleus reticularis pontis oralis (which overlaps with nucleus parabrachialis), and lateral hypothalamus - produced behavioral arousal pattern II and EEG phasic arousal, simultaneously (Coleman and Lindsley, 1975). This desynchronization corresponds to higher frequency (36-44 HZ) EEG signal. Behavioral arousal pattern II and phasic arousal EEG activity, when taken together, has been described as "focused arousal" (Sheer, 1975; 1984). See Table A for a comparison of the correlates of these two arousal patterns.

FOCUSED AROUSAL(phasic)	GENERAL AROUSAL(tonic)
Produced by stimulation of:	
locus coeruleus	raphe nuclei
nucleus reticularis pontis caudalis	nuc. ret. pontis oralis
medial hypothalamus	lateral hypothalamus
EEG correlates:	
36-44 HZ cortical EEG	13-35 HZ cortical EEG
36-44 HZ hippocampal EEG	4-8 HZ hippocampal EEG
(measured electronically)	(visual inspection)
Behavioral correlates:	
fixation of gaze, execution and maintenance of an attentive preparatory posture	alerting, scanning, orienting, and investigation

Table A -- Anatomical, electrophysiological and behavioral correlates of general and focused arousal.

Hence, all EEG desynchrony is not the same. Lower frequency desynchronous EEG is longer-lasting, spontaneous, and indicative of general arousal. While higher frequency desynchronous EEG, that which is operationally centered at a frequency of 40 HZ, represents focused arousal. Focused arousal is more brief and requires specific stimulus-response contingencies or meaningful environmental events, e.g. a warning signal (Sheer, 1984).

Putative Neural Substrates of Focused Arousal

Sheer (1984) has proposed subcortical brain circuitry which is involved in focused arousal. It involves an ascending cholinergic reticular system originating in the nucleus parabrachialis (PB) of the rostral pons, passing through the lateral hypothalamus, synapsing in the basal forebrain and then distributing widely to cortex from the nucleus basalis of Meynert (Kimura, 1981; Saper, 1981, 1982, Saper and Loewy, 1980, 1982). Cortical facilitation was directly demonstrated by the excitatory effects of brainstem reticular stimulation upon cortical cells (Singer, 1979, 1980; Steriade, 1980), which appears to be cholinergic in function (Spehlman, 1971; Spehlman and Downes, 1974). Furthermore, cholinergic agonists increase and antagonists decrease levels of acetylcholine and EEG desynchronization (Celesia and Jasper, 1966; Montplaisir, 1975). However, a wakeful, alert behavioral state persists under the conditions of cholinergic blockade and increased slow-wave EEG. This dissociation of electrocortical and behavioral arousal suggests two arousal systems: 1) a lower brainstem system mediating general arousal and 2) a more rostral system focusing arousal on the processing of stimulus inputs. These two systems can also be dissociated on the basis of differential brainstem lesions (Chatrian, Bickford, & Uihlein, 1964; Kaada, Rasmussen, & Kreim, 1961; Kimura, 1964; Landsell and Mirsky, 1964; Loeb and Poggio, 1953; McDonald and Burns, 1964).

Nucleus PB also projects to thez nuclei of raphe, lateral hypothalamus (Kimura, et al., 1981; Saper, 1981; Saper and Loewy, 1980) and to nucleus reticularis and specific sensory nuclei of the thalamus (Singer, 1985). These projections are thought to be cholinergic (Singer, 1985) and have implications for proposed central gating mechanisms underlying selective attention (Skinner and Yingling, 1977).

Measurement of Focused Arousal

Focused arousal, a functional component of attention, represents the interaction of ascending cholinergic brainstem reticular projections contingent with specific sensory inputs and/or memory traces at cortical and subcortical levels. It can be measured by recording a narrow band of EEG, centered at 40 HZ, from chronic in-dwelling brain electrodes in animals and/or by direct behavioral observations (Sheer, 1984). The behavioral manifestation of focused arousal includes a wide variety of actions which result in appropriate posturing for receptor orientation and fixation on novel and/or meaningful environmental events.

Initial interest in the 40 HZ EEG pattern had its beginnings in the large amplitude, highly synchronous bursts recorded from the olfactory bulbs and other rhinencephalic structures during sniffing, exploring, and orienting behaviors observed in a wide variety of species (described above). In the olfactory bulb of the cat, the necessary and sufficient stimulus for 40 HZ activity is airflow (Freeman, 1963; Pagano, 1966; Sheer, Grandstaff, & Benignus, 1966). However, as olfactory input ascends towards higher levels of processing in the CNS a certain level of arousal becomes necessary for the generation of this EEG pattern. Forty HZ activity in the amygdala requires both airflow and a certain level of arousal (Pagano, 1966; Sheer, et al., 1966), while at even higher levels, i.e. prepyriform cortex, this EEG pattern can be conditioned to a stimulus (CS) that is independent of airflow (Freeman, 1975). These mechanisms have far-reaching implications for understanding the behavior of quadraped animals. Sniffing, in these animals, is an important component of an orienting response needed for exploring the environment and searching for food, safety, and a mate. The evolutionary significance of learning which environmental stimuli (CS) predict the occurance of food, safety, and a fertile mate (UCS) is obvious.

Simple three layered laminar structure is first encountered in the olfactory bulb. Freeman (1975) has demonstrated, with mathematical equations and empirical recordings in the cat, that the optimal level of sensitivity in the olfactory bulb, which is compatible with stability, gives rise to a rhythmic oscillation at 40 HZ. Rall and Shepard (1968) and Shepard (1970) have made a detailed analysis of a dendrodendritic synaptic interaction as a mechanism for this activity in the olfactory bulb. An airflow-induced steady background input excites bipolar receptor cells in the olfactory mucosa. The axons of these receptor cells ascend and synapse within encapsulated glomeruli of dendrites originating from tufted and mitral cells. Impulse discharge in mitral cells results in synaptic excitation of granule cells, which, in turn, feedback to mitral cells delivering a graded inhibition. This inhibition attenuates the source of synaptic excitatory input to the granule cells. As granule cell activity subsides, the inhibition delivered to the mitral cells is reduced, permiting the mitral cells to respond again to the excitatory input from the glomeruli. Hence, a sustained excitatory input from the receptors would be converted to a rhythmic excitation-inhibition sequence, which would be determined by a timed rhythmic activation of the granule cell pool. This phemonenon has been referred to as recurrent inhibitory processing (Andersen, Eccles, & Loying, 1963; Sheer, 1984).

At the neocortical level, where laminar structure is more complex, the 40 HZ rhythm is at a much lower amplitude and is embedded in a much more complicated electrical background. However, it can still be recorded from epidural electrodes and observed visually on an oscilloscope and records recorded at fast paper speeds.

Recurrent inhibition has also been demonstrated in the lateral geniculate nucleus (LGN) (Famiglietti, 1970; Fertziger and Purpura, 1971), hippocampus (Andersen, <u>et</u> <u>al</u>., 1963) and in thalamo-cortical interactions (Andersen and Andersson, 1968). Mechanisms of recurrent inhibition at the neocortical level have not been elucidated. Hypothetically, the ascending cholinergic brainstem reticular system may provide the steady background input to the neocortex in a functionally analogous manner to that observed for airflow in the olfactory bulb (Sheer, 1984). In the olfactory bulb, concerned with one sensory modality, airflow is the background input, while at the multi-sensory neocortex the biasing input of the ascending brainstem reticular system is multi-sensory, determined by the collaterals into the brainstem reticular from specific sensory pathways. In human and cat, the narrow frequency band of rhythmic oscillations that results from the optimal level of sensitivity compatible with stability has been proposed to center at 40 HZ (Sheer, 1984). In other species it centers at different frequency bands, depending upon the geometry of the local neuronal pool (Bressler and Freeman, 1980).

This hypothesis suggests that the electrical activity in simple laminar structure of the olfactory bulb provides a simple model of the electrical activity in the complex laminar structure of the neocortex. The efficacy of this hypothesis remains to be fully demonstrated.

A neural model for the generation of 40 HZ activity in attention has been detailed by Freeman (1975, 1979, 1980) and further elucidated by Basar (1980). A balance of sensitivity and stability in functionally connected cell assemblies is required to achieve maximum sensitivity to stimulus inputs while avoiding uncontrolled excitation. Sheer (1984) refers to this maximum sensitivity as focused arousal and describes the hypothetical interaction of excitatory and inhibitory processing in the generation of the 40 HZ EEG in the following:

> "Sensitivity in the form of neural gain depends on the level of depolarization bias as a consequence of steady background input. As cell assemblies become excited by background input, the neural gain increases, driving the neurons closer to their firing threshold. Hence, the probability of a subsequent signal input firing a neural response is increased. However, as sensitivity increases, their is a concommitant increase in instability. If numerous cells with excitatory connections were driven into a state of increased gain, an uninterupted series of excitation would exist. One neuron would deliver an excitatory pulse to adjacent cells where it would stimulate neurons with heightened gain. This, in turn, would then feed back to the first cell, further increasing its excitatory gain. To prevent runaway excitation, inhibition of approximately equal magnitude interupts the cycle of mutual excitation. This balance between excitatory and inhibitory influences provides system stability. The feedback loops resulting from mutually excitatory cell connections, mutually inhibitory connections, and excitatory-inhibitory interactions, i.e. recurrent inhibition, gives rise to periodic oscillations, recorded as EEG."

Specific and nonspecific connections in the visual system may provide an example of the interaction between excitatory and inhibitory processing, which is analogous to that which has been detailed in the olfactory bulb. In this model, visual excitation traveling from the retina would serve as the specific excitatory input, while nucleus PB would serve as the nonspecific excitatory input. These two inputs converge at the LGN of the thalamus. Here, cholinergic input from PB would serve a depolarization biasing function. That is, PB input would raise the probability of firing of LGN cells in response to a retinal input. This increased sensitivity in the form of neural gain would occur through excitatory post synaptic potential (EPSP) biasing at the LGN. However, inhibition would be required to control runaway excitation and provide stability to the input. Hippocampal and/or cortical input could provide this inhibition, thereby modulating the output of the LGN to the visual cortex (VC). PB has reciprocal connections with VC (Kimura, et al., 1981; Saper, 1981; Saper and Loewy, 1980; Singer, 1985). Therefore, nonspecific input from PB could activate VC, which in turn could provide the inhibition required for stability of the input at the level of the LGN. Input from the VC may be functioning through inhibitory post synaptic potential (IPSP) biasing.

In summary, PB may provide input in the form of

EPSP biasing, while VC could furnish IPSP biasing and this interaction of excitatory and inhibitory processing would result in a stable coherent signal from the LGN in response to a visual stimulus. The effects of excitatory-inhibitory interactions, from PB and VC respectively, could result in recurrent inhibition at the level of the LGN, in a similar fashion to mitral-granule cell interaction in the olfactory bulb. Hence, the coherent signal emerging from the LGN, modulated by recurrent inhibition, would then be analogous to the 40 HZ signal which has been observed in the olfactory bulb. The results of subcortical and cortical EEG findings, described above, would suggest that this could be the case. However, the efficacy of this hypothesis remains to be fully demonstrated.

The purpose of this experiment is to explore the validity of this hypothesis. EEG has been monitored from chronically implanted electrodes in PB, VC, and LGN of the awake, behaving cat in response to three environmental situations: 1) baseline, 2) presentation of a novel visual stimulus and the eventual habituation to this stimulus, and 3) pairing of the visual stimulus with an uncontrollable, unavoidable, mildly aversive event and gradual adaptation to this pairing as a function of time. Forty HZ activity would be expected to increase in all three locations during phase 2 and decline in PB and VC during habituation. Additionally, 40 HZ activity would be expected to increase in PB and VC during the acquisition phase of learning the CS-UCS association in phase 3, with a gradual decline in this activity during adaptation. Furthermore, focused arousal behavior should be correlated with the increase of 40 HZ activity in PB and VC during phases 2 and 3.

CHAPTER II

METHODS

SUBJECTS: This study required six cats (Felus domesticus) within the weight range of 2.5 - 3.5 kilograms. The animals were healthy alley cats secured from the city pound. The cats were housed in an air-conditioned animal colony in the animal care facility of the University of Houston prior to and during the study. The health and nutritional requirements of these animals were monitored daily by full-time trained staff and veterinarian at the animal care facility. Food and water were available to the animals ad-lib basis throughout the course of this study.

ELECTRODES: Parallel bipolar electrodes made of .0092 inch diameter untempered steel wire with a tip separation of approximately 1 mm were employed to record EEG from subcortical structures. Monopolar stainless steel screw electrodes were used to record EEG from the surface of the cortex. Procedures for construction of electrodes are described elsewhere (Skinner, 1971).

<u>SURGERY</u>: Stereotaxic surgery and electrode implantation were executed using standard sterile technique (Skinner, 1971). Ketamine hydrochloride was administered intramuscularly as a general anesthetic at a dose of 11 mg/ kg of body weight and 5 mg supplements were administered about every 90 minutes during surgery. Xylocaine was applied locally to the scalp incision to reduce the post-surgical pain.

The surgical procedure involved placing the animal in a stereotaxis, making a 3 inch longitudinal scalp incision and exposing the skull. Six 1/8th inch holes were drilled in the skull to expose the dura mater. The dura was punctured and a small incision was made for the passage of the depth electrodes. Surface cortical electrodes were placed without opening the dura. The subcortical electrodes were packed with sterile Gelfoam and cemented and anchored to the skull with dental cement. Electrode connectors were inserted into a connector base and it was cemented to the animals' skull. Then the scalp incision was sutured at both ends with the connector base being exposed in the middle (Skinner, 1971). The animals were given a standard antibiotic intramuscular injection to reduce the risk of post-operative infection. The animals were allowed to recover at least two weeks before under going any experimental manipulations. Stereotaxic surgery and electrode implantation are described in greater detail elsewhere (Skinner, 1971).

ELECTRODE SITES: Electrodes were implanted in nucleus parabrachialis (PB), lateral geniculate nucleus (LGN) of the thalamus and visual cortex (VC). Stereotaxic coordinates were as follows: PB - 0.9 mm posterior, 4 mm lateral, -0.5 mm vertical (depth), LGN - 7.0 mm anterior, 10 mm lateral, 4 mm vertical (depth), and VC - 4 mm posterior, 2 mm lateral and in contact with the dural surface. All electrode locations were measured from the interaural line origin of 0 mm A-P, 0 mm lateral, and 0 mm vertical depth (Snider and Niemer, 1961; Reinoso-Suarez, 1961; Berman, 1968). Electrode sites were verified through histological examination of the brain. Standard techniques of perfusion and histology were employed (Skinner, 1971). Photographs of the PB electrode site are provided for two subjects in the Appendix.

EXPERIMENTAL APPARATUS AND EQUIPMENT: Similar laboratory equipment has been described in detail by Grandstaff (1975) and Hix (1969). Subjects were placed in a sound-proof, dimly illuminated experimental chamber constructed of steel, insulation, and plexiglass during the experimental sessions. The chamber was equiped with a three inch speaker and 30 db white noise was produced during the experimental sessions to mask laboratory sounds. Subjects were observed in this one cubic meter chamber through a 12 inch square one way glass window. A strobe, controlled by a Grass Model PS 22C photic stimulator, was situated in front of a 4 inch square plexiglass port in the front of the chamber. A seven-analog and two-event channel Grass Model 78 EEG and polygraph system and a four channel Grass Model 10 ERS evoked responce system were used to produce a visual record of the EEG and evoked responses. The EEG was stored on 1/2 inch magnetic tape for further analysis using a seven-analog and/or event channel Ampex SP-300 recorder/reproducer. On-line computer analysis of the 36-44 HZ EEG window was conducted by a special purpose microprocessor which has been described elsewhere (Raghavan, Glover, & Sheer 1985; Sheer, 1984).

EXPERIMENTAL PROCEDURE: Subjects were placed in the experimental chamber and exposed to three experimental phases following recovery. The animals skull connector base was fused will another connector base in order to monitor EEG from the depth and surface electrodes during experimental manipulations. Observations of behavior and EEG records were taken across the following three experimental manipulations: 1) free bahavioral situation (baseline), 2) presentation of a novel 7 cps visual stimulus and habituation to this stimulus, and 3) UCS - CS pairing of this visual stimulus with a mildly aversive event and adaptation to the pairing. All EEG measures were taken with the subjects' nostrils plugged with foam rubber to eliminate volume conduction of airflow-induced olfactory 40 HZ EEG. The duration of the 7 cps stimulus was 10 seconds across all phases of the experiment except baseline. The aversive event was a mild shock delivered from a Grass model S10SCM stimulator through a Grass model SIU8TB stimulus isolation unit and applied to the chest of animal through standard EKG plate electrodes. A train of electrical impulses was delivered at a rate of 100 pps for a duration of 2 seconds. The absolute intensity of the aversive stimulus varied between sessions and animals depending upon various areas of resistance, i.e. amount of electrode cream, fur, etc. The intensity of the aversive stimulus was set by the behavioral reaction of the animal. When the animal began to show a response, such head-turning, twitching, and arching its back, then the stimulus was of an appropriate intensity (usually between 20-50 volts).

DATA ANALYSIS: The incidence and power of a narrow band (36-44 HZ) of EEG were analyzed, across all experimental phases by a microprocessor system described in detail elsewhere (Raghavan, *et al.*, 1985; Sheer, 1984). Pearson product-moment correlation coefficients were calculated for the frequency of 40 HZ EEG between PB and LGN, and PB and VC.

CHAPTER III

RESULTS

An increase in the frequency of 40 HZ EEG was observed in response to the initial presentation of the 7 cps visual stimulus in phase 2 and the initial CS-UCS pairings in phase 3. Results are presented for two subjects (See Table 1 and Graph 1).

These changes in 40 HZ EEG activity were closely correlated with the behavior of the animal. Subject behavior varied greatly during the baseline phase. However, decreases in 40 HZ activity were observed when subjects were drowsy or asleep. During phase 2 increases in 40 HZ EEG were observed concurrent with orientation, initiation and maintenance of an attentive posture, and fixation on the 7 cps visual stimulus. There was a rapid decline in this pattern as the animal became habituated to the stimulus. Scanning, orienting, appropriate posturing, and fixating on the stimulus were again correlated with increases in the frequency of 40 HZ activity in phase 3, when the 7 cps visual stimulus was paired with a mildly aversive event. In this case, there was a gradual decline in this pattern as the animal adapted to the situation.

Forty HZ activity in PB, LGN, and VC was highly correlated across the trials presented in Table 1. Pearson product moment correlation coefficients between PB - VC, and PB - LGN, in subject B3, were r = .72 and r = .87, respectively. Trials 3 and 4 of the 7 cps visual stimulus were excluded from this analysis for subject G4. Behavioral observations indicated that there had been a tonic shift in attention, i.e. the animal became drowsy, thereby indicating a rapid habituation to the stimulus. Excluding these trials yielded correlation coefficients r = .61 for 40 HZ activity in PB - VC, and r = .59 for PB - LGN 40 HZ activity (See Table 2). Correlations decrease significantly with the inclusion of trial 3 and 4 described above.

FREQUENCY OF 40 Hz PEAKS

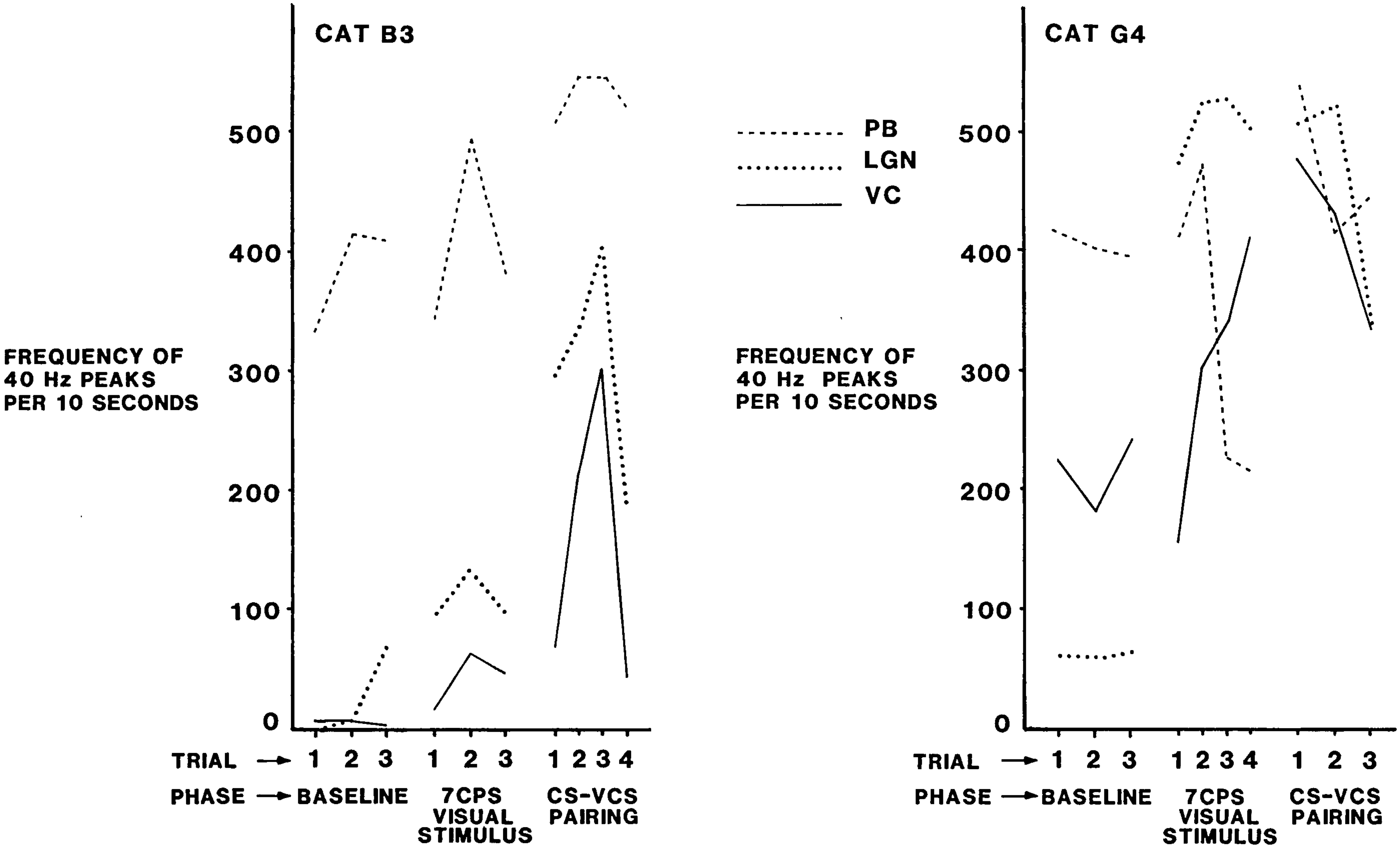
		CAT B3			CAT G4		
PHASE	TRIAL	VC	LGN	PB	VC	LGN	PB
BASELINE	1	5	0	331	225	61	417
	2	5	5	413	184	60	403
	3	1	68	409	241	64	395
7CPS VISUAL STIMULUS	1	16	94	364	157	476	412
	2	61	133	493	301	527	477
	3	47	97	378	341	529	288*
	4	—	—	—	413	504	219*
CS-VCS PAIRING	1	68	296	510	477	509	542
	2	215	335	546	434	521	417
	3	298	403	546	335	348	447
	4	42	191	521	—	—	—

Table 1- FREQUENCY OF 40 Hz PEAKS IN A 10 SECOND EPOCH ACROSS THREE EXPERIMENTAL PHASES: 1) BASELINE, 2) PRESENTATION OF A 7CPS VISUAL STIMULUS, AND 3) CS-VCS PAIRING OF 7CPS VISUAL STIMULUS WITH A MILDLY AVERSIVE EVENT. RESULTS SHOWN FOR PARABRACHIALIS (PB), LATERAL GENICULATE NUCLEUS (LGN), AND VISUAL CORTEX (VC). (*INDICATES TRIALS EXCLUDED FROM CORRELATIONAL ANALYSIS).

CORRELATION OF FREQUENCY OF 40 Hz PEAKS

CAT B3 (n=10)		CAT G4 (n=8)	
OC-PB	r=+.72	OC-PB	r=+.61
LGN-PB	r=+.82	LGN-PB	r=+.59

Table 2- PEARSON PRODUCT MOMENT CORRELATION COEFFICIENTS OF FREQUENCY OF 40 Hz PEAKS BETWEEN VARIOUS ANATOMICAL LOCATIONS: PARABRACHIALIS (PB), LATERAL GENICULATE NUCLEUS (LGN), VISUAL CORTEX (VC).



GRAPH 1 - FREQUENCY OF 40 Hz PEAKS IN A 10 SECOND EPOCH ACROSS THREE EXPERIMENTAL PHASES: 1) BASELINE, 2) PRESENTATION OF A 7 CPS VISUAL STIMULUS, AND 3) CS-VCS PAIRING OF 7CPS VISUAL STIMULUS WITH A MILDLY AVERSIVE EVENT. RESULTS ARE SHOWN FOR PARABRACHIALIS (PB), LATERAL GENICULATE NUCLEUS (LGN) AND, VISUAL CORTEX (VC).

CHAPTER IV

DISCUSSION

The results of this study replicate previous findings, that a high frequency, low amplitude EEG signal centered at a frequency of 40 HZ is highly correlated with attention and the acquisition phase of learning (Coleman & Lindsley, 1975; Galambos, 1958; Rowland, 1958; Freeman, 1963, Killam & Killam, 1967; Dumenko, 1961; Sheer, 1970, 1974, 1976; Sheer & Grandstaff, 1970; Bauer & Jones, 1976; Skinner & Yingling, 1977; Bird *et al.*, 1978 a, b; Ford *et al.*, 1980, Sheer, 1977, 1984; Loring & Sheer, 1983; Spydell & Sheer, 1982; Spydell, *et al.*, 1979). These increases in 40 HZ activity were observed when subjects were posturing, orienting, and fixating gaze on the stimulus. This indicates that 40 HZ EEG activity is increased when the animal is in a state of "focused arousal" (Sheer, 1975; 1984).

It is of interest that on some trials after the subjects were habituated to the 7 cps stimulus, they were spatially oriented to the area where the stimulus occured prior to stimulus onset. Under these conditions, 40 HZ activity in LGN increased with stimulus onset, but remained relatively unchanged in PB and VC. This indicates that when the animal is habituated to a stimulus 40 HZ activity is not as wide spread in the CNS. Hence, focused arousal is not solely manifested in behavior, but rather, is the result of the interaction of behavior and cortical EEG tone. There are two components of focused arousal: 1) overt behavioral changes (posturing, orienting, fixating, etc.) and 2) covert changes in the EEG (40 HZ).

Initial pairings of the 7 cps visual stimulus and the mildly aversive event produced dramatic increases in the frequency of 40 HZ activity. During this phase the presiously meaningless visual stimulus acquired a novel meaning, that is, it was predictive of the aversive event. As the animal adapted to the CS-UCS pairing 40 HZ activity gradually declined, however, these data were not included in the results because adaptation occured over many trials, e.g. 25 trials, and varied greatly between subjects. If the stimulus remained predictive, i.e. meaningful, why would there be a decrease in focused arousal? Perhaps this represents an adaptive strategy for coping with a stressful situation. During the initial pairings, the subject would learn the predictive value of the 7 cps stimulus. However, soon thereafter, the subject would also learn that the aversive event was unavoidable and uncontrollable. This decrease in fast frequency EEG may be an electrical correlate of the learned helplessness phenomena (Alloy & Berch, 1979; Maier, 1970; Maier, Seligman, & Solomon, 1969). This decrease in arousal may be a strategy the animal employs in order to reduce its sensitivity to stressful environmental events.

Forty HZ activity in PB is highly correlated with 40 HZ activity in LGN and VC when the animal is presented with a novel situation. This increase can occur when the the subject is presented with a new environmental stimulus or when a habituated stimulus acquires a new meaning. These correlations provide support for the hypothesis that PB may provide input in the form of EPSP biasing to the specific sensory pathway of the visual system. This conclusion is consistent with the anatomy and physiology described above (Kimura, et al., 1981; Saper, 1981; Saper and Loewy, 1980; Singer, 1985).

In summary, these findings suggest that the CNS is predisposed by genetics and prior experience to be sensitive to novel stimuli and stimuli which acquire novel meaning. The CNS is especially sensitive to new meanings which alter the probability of survival in the animal's environment. Similar results have been observed when a visual stimulus (CS) predicted a milk reward (UCS) for bar pressing (CR) in deprived animals (Sheer, 1970). Increases in 40 HZ activity in the appropriate sensory and motor pathways were observed only when animals were deprived. Forty HZ activity and focused arousal behavior declined as the subjects became satiated. Focused arousal, a component of attention, decreased as the animal's physiological requirement for nutrients decreased and the animal could then "re-allocate" its attention to other environmental needs if the situation demanded it. In this study we have simply manipulated a different physiological requirement, that is, defense against aversive environmental events.

The results of this study suggest that high frequency EEG is correlated with the acquisition phase of learning, in the visual system. Furthermore, PB functions, through EPSP biasing, to increase the probability of firing between the LGN and VC during acquisition. These results support the hypothesis that ascending cholinergic reticular input from PB serves an excitatory role in the process of recurrent inhibition at the LGN. The interaction of this excitatory input with the inhibitory corticofugal input from VC results in the resonance of fast frequency EEG within the appropriate sensory pathway. The critical EEG frequency window may vary as a function of individuals, species, and the sensory system being investigated. In conclusion, it would seem that the three layer laminar structure of the olfactory bulb may provide a simple model of recurrent inhibition in the visual system.

Further analysis of these data is warranted to determine the precise frequency window which is correlated with focused arousal and the acquisition phase of learning. The analysis in this study was operationally restricted by the microprocessor unit to the 36-44 HZ window. Slightly lower or higher EEG frequencies may also be implicated in this arousal response. Linear coherence between different structures, e.g. LGN and VC, could also be investigated. Visual inspection of the EEG records and initial spectral EEG analysis suggest the possibility of coherent firing between the LGN and VC during critical trials of the CS-UCS pairing. If this coherence could be demonstrated it may offer a new approach to the investigation of EEG correlates of learning. The data collected in this study could be readily subjected to linear coherence analysis at various EEG frequencies.

Future animal studies could futher investigate the role of PB and cortex in the process of recurrent inhibition in specific sensory nuclei of the thalamus. One such study could investigate the effects of reversible functional blockade of the parabrachialis and/or cortex through the use of a chronically implanted cryoprobe (Skinner, 1971). It would be interesting to observe changes in behavior and the frequency, power, and coherence of fast frequency EEG in a specific sensory system as function is attenuated and restored through the use of this reversible tissue freezing technique.

The results of this study have application in understanding cognition and its dysfunction in humans. Forty HZ activity can be brought under operant control through the use of response-reinforcement contingencies in animals (Bauer & Jones, 1976) and biofeedback procedures in humans (Bird, et al., 1978 a, b; Ford, et al., 1980; and Sheer, 1977). Using a Q-sort procedure, the subjective state consistently reported with 40 HZ conditioning in humans include such words as attentive, concentrating, vigilant, effortful, etc. In contrast, words like active, energetic, excited, restless, etc. were correlated with 21-31 HZ EEG frequency window.

These findings are consistent with behavioral observations of focused and general arousal in animals described in the introduction. Furthermore, subjects who had completed successful biofeedback training could not inhibit 40 HZ activity while problem-solving. Finally, task-dependent lateralization of 40 HZ activity was demonstrated in the left and right cerebral hemispheres in verbal and visual-spatial problem-solving, respectively (Loring & Sheer, 1983; Spydell & Sheer, 1982; Spydell, et al., 1979).

Significant decrements in 40 HZ activity have been observed in learning disabled children (Sheer, 1974; 1976) and patients diagnosed with senile dementia of the Alzheimer type (SDAT) (Largent, 1980; Loring, 1982; Spydell & Sheer, 1983) when compared with appropriate control groups. It is also of interest that Alzheimer's disease is correlated with a loss of choline acetyltransferase and acetylcholinesterase (Price, et al., 1982; Coyle, et al., 1983), two enzymes required for the biochemical synthesis and recycling of acetylcholine. Furthermore, SDAT has been associated with a selective degeneration of cholinergic neurons in the nucleus basalis of Meynert in the basal forebrain (Whitehouse, et al., 1982) which projects to the cerebral cortex.

These clinical observations and the findings presented in this study suggest that the ascending cholinergic reticular pathways originating in the nucleus parabrachialis of the rostral pons is a possible area of degeneration or dysfunction in disorders of learning and memory.

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APPENDIX

Parabrachialis Electrode Site