AN ABSTRACT OF THE THESIS OF

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Narcolepsy is a complex of physiological and behavioral symptoms. The most striking of these are: excessive daytime sleepiness; extremely short latency to rapid eye movement (REM) sleep; hypnogogic hallucinations; sleep paralysis; and cataplexy, which is loss of skeletal muscle tonus in response to intense emotions such as surprise, anger, laughter, competition, or sexual intercourse. What unifies these symptoms is that they are components of the REM phenomenon and narcolepsy has come to be know as REM disorder.

The cause(s) of narcolepsy is unknown. A genetic aspect is possibly involved (Carskadon, 1982; Guilleminault, 1989) and, historically, the pandemic encephalitis lethargica resulted in many reported cases of narcolepsy. Typically, onset of symptoms appear in teenage years although diagnosis usually takes place many years after the actual onset (Navelet, 1976). There are over 200,000 diagonosed cases in the U.S. (Dement, 1979). Studies using lesions and microelectrode recordings followed by definitive

immunohistochemical staining methods have located structures that are possibly involved in the generation of REM components. Pharmacological studies complement the neuroanatomical data by the exogenous induction and suppression of REM and suggest that the cholinergic and catecholaminergic neurotransmitter systems are involved. These same systems are implicated in cognitive behavioral functions of alerting and attention.

Narcoleptics have not been extensively studied with cognitive testing, despite the fact that their catecholaminergic and cholinergic systems are impaired as evidenced by the mechanisms of their effective therapies (Mitler, 1986; Soldatos, 1983; Phillips, 1983) and animal studies of receptor number and serum levels of neurotransmitter metabolites (Baker and Dement, 1985; Kilduff et al., 1986; Faull et al., 1986). A case study presented in this thesis attempts to assess the ability of a narcoleptic individual to shift covert attention, respond to a warning cue and perform an increasingly difficult response. These tests were given on two different days. On the first day, the subject was using protriptyline, a tri-cyclic antidepressant which potentiates the monoamines and controls cataplexy in the narcoleptic. The second day of testing took place two months after the subject had taken a "drug holiday" from protriptyline. The results may indicate this individual displays a left hemispheric effect that manifests in difficulty in disengagement, longer reaction times to contralateral targets, and slower motor responses. This case study, suggests future study of cognitive function in the narcolpetic population.

Narcolepsy: An Interdisciplinary Approach

by

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DEFINING THE DISORDER

The French physician Jean Baptiste Edouard Gelineau is credited with the first medical definition of narcolepsy in 1880 (Passouant, 1981). There are also earlier references to such a disorder in 1878, 1877, 1862 and as early as the 1600's (Carlson, 1981). In his monograph of 1881, Gelineau described ideopathic and symptomatic forms of narcolepsy and associated the former with a neurosis. He also carefully distinguished between epilepsy and narcolepsy by the states of consciousness during the respective seizure events. Gelineau observed the epileptic seizure to be concurrent with unconsciousness and followed by sleep with no memory of the seizure event. He contrasted this with narcoleptic siezure in which the patient was conscious and remembered the entire event. Narcolepsy remained obscure and infrequently reported until the 1920's when many became afflicted as a consequence of the pandemic encephalitis lethargica. Between 1928 and 1933, 388 cases were published. The flood of reported cases influenced the evolving definition of narcolepsy in two ways. Because these cases of narcolepsy occurred after the tremendous viral insult to the brain, opinion swayed to the view that narcolepsy was a secondary rather than primary disease. Also, the

huge increase in incidence resulted in an amplification of symptomology and a clear definition of narcolepsy escaped medical understanding.

Eventually, a delineation of the symptom complex arose (Yoss and Daly, 1957) which came to be known as the classic tetrad. It consists of the following four components:

1. Excessive daytime somnolence (EDS)--the urge to sleep even while in the midst of activity;

2. Sleep paralysis--inability to move just before sleeping and just after waking;

3. Hypnogogic hallucination-- and occurring at the sleep/wake interface like sleep paralysis and usually terrifying;

4. and Cataplexy--loss of muscular tone caused by events of intense emotion.

Despite the tetrad outline, confusion persisted in narcolepsy research. Some have insisted that all four symptoms be present for the condition to be called narcolepsy while others have included in their studies subjects who have some but not necessarily all of the above symptoms. Of the four only cataplexy is pathognomonic for narcolepsy, and in fact, many researchers specify its presence by using it in hyphenated form: "narcolepsy-cataplexy".

The most clarifying and definitive description of narcolepsy comes out of research of the 1950's and 1960's when the course of sleep was characterized polygraphically with distinct features in the electroenchephalogram, electro-oculogram and electromyogram.

A detailed description of the tetrad is best accomplished in the light of that work.

Rapid Eye Movement and Narcolepsy

One of the most important findings in sleep research was the discovery of rapid eye movement (REM) by Aserinsky in 1952 in the laboratory of Kleitman, a pioneer whose early work included sleep deprivation studies and artificial sleep-wake cycles experienced in deep cave surroundings (cited in Dement, 1976). Instructed to watch through the night for the slow rolling motion of the eyes that characterize the beginning of sleep, Aserinsky instead observed the electrooculogram (EOG) of a polygraph display wild movements at various times through the night. This phenomenon which came to be known as REM served as a useful marker and measure of sleep. It provided an empirical means to study the otherwise mysterious and amorphous enigma of sleep.

It is now viewed that there are two kinds of sleep: non-REM sleep (NREM) and REM sleep. NREM sleep is broken into stages I-IV. These stages identified by their electroencephalogram (EEG) forms. They constitute a progression from beta wave activity of waking which is desynchronous, low amplitude and high frequency to more and more synchronous, high amplitude and low frequency forms. Stage IV is the deepest, and marked by theta activity. NREM stages I-IV usually occupy the first 90 minutes of sleep in normals, at which time REM occurs.

REM cycles with the NREM stages II-IV through the night, occurring 3-4 times and occupying about 25% of the total time spent in sleep. The REM episodes tend to increase in length, with the longest episode characteristically occurring in the period just prior to the morning awakening. Besides the high frequency, high amplitude conjugate eye movements recorded in the EOG, REM is correlated with additional changes in the EEG and the electromyogram (EMG) including EEG activity similar to waking (low amplitude, high frequency) and an EMG that displays no activity, indicating a state of paralysis.

When individuals are awakened during REM, they report vivid dreams. While the dreaming that occurs during NREM periods is not as vivid or fantastic, researchers now recognize that REM and dreaming are not exclusively concurrent as was initially believed and that NREM is not a mental void. However, when one is awakened from either state, dream reportage and quality of content differs (Dement, 1976). REM dreaming tends to be fantastic and visual. NREM tends to be ordinary and more like fragmented thinking. In the thinking of Hobson and McCarley (1977, 1988) who interpret dreaming as mentation that is a consequence of cortical activation, the bizarreness of REM appears to reflect greater activation especially of the visual cortical areas.

Although researchers have not yet determined the functions of REM, they have amassed information about its nature. Time spent in REM appears to be of an optimal quantity. Some drugs like alcohol and many "sleeping pills" suppress REM If these are

administered for a period of time and then stopped, the subject will experience a "rebound" of excessive amounts of REM. It has also been conjectured that depressives experience excessive amounts of time in REM and that the effectiveness of antidepressants is through the suppression of REM (Vogel,1989).

EDS and REM Sleep Onset

Clinically, the difference between the excessive daytime sleepiness of narcolepsy and regular sleep is the onset of the REM period. In normal sleep (besides being synchronous with the night), the individual enters and passes through the four stages of NREM sleep and after about 90 minutes, REM sleep onset (REMSO) occurs. The hypersomnolence of narcoleptics is distinguished by immediate entry into REM (Dement, 1976). This important finding had two important consequences for narcolepsy research: 1) immediate REMSO has become a diagnostic tool for narcolepsy and 2) narcolepsy can now be seen as disordered REM. Dement coined the term "REM attack" to characterize the narcoleptic seizure. The Multiple Sleep Latency Test (MSLT) is given to test for narcolepsy. During a 12 hour period, the suspected narcoleptic is asked to go to sleep every two hours. If narcoleptic, the individual enters REM within 10 minutes. It has also been reported that a shortened REM latency occurs in those who have been psychologically diagnosed as having obsessive compulsion and panic anxiety as well as endogenous depression (Vogel,1989; Weitzman 1981a). Narcolepsy is distinguished from these other disorders by immediate entry

into REM from the waking state while the other three disorders exhibit a latency of greater than zero but less than 20 minutes which is still far less than the normal latency of 90 minutes.

Clearly, narcolepsy is not the only cause of EDS. The EDS symptom is also displayed in winter depressives and CNS hypersomnolence of various origins as well as those mentioned in the Vogel study.

Sleep Paralysis

Sleep paralysis is the conscious sensation of an inability to move limbs on the verge of entering sleep or awakening. In the context of viewing narcolepsy as a REM disorder, this is readily explained as another abnormal, desynchronous REM event. A distinguishing electrophysiological component of the REM period is no activity in the electromyogram trace. The muscles are atonic and a conscious awareness of that would be a sense of paralysis. Jouvet's now classic cat experiments (cited in Dement, 1976; Morrison, 1983) demonstrated a neural substrate that if lesioned, would result in motor behavior during REM, as if the cat were dreaming of stalking and attacking prey. This also offeres a teleogical explanation for loss of muscle tone during REM: it would be quite dangerous to act out dreams in the sleep state. It is normal for individuals to experience loss of muscle tone during REM and not be conscious of the phenomenon. Frequently the narcoleptic, maintains consciousness during this event and the sensation is interpreted as paralysis.

The desynchrony of narcolepsy manifests itself in an increased amount of REM and in a disruption of normal patterns of the sleep-wake cycle. Thus, the narcoleptic is not only in REM more of the night, but also the narcoleptic can be aware during the REM characteristic of atonia or loss of muscle tone. REM and consciousness which are usually mutually exclusive, are mixed for the narcoleptic.

What appears to be happening for the narcoleptic is a loss of the clear dividing line between sleeping and waking. Arousal and consciousness should be complete during the day and inhibited during the night. Conversely, REM sleep should occur during the night. In the case of narcolepsy the sleep/wake interface is blurred.

Hypnogogic Hallucination

The hybrid sleep/wake state also explains the occurrence of hypnagogic hallucinations which, like sleep paralysis, occur at the interface of sleeping and waking, those periods in which the states of consciousness are mixed and disjointed from the normally correlated physiological states. At sleep onset, the narcoleptic is abnormally experiencing REM dream state, but is still semi-conscious as in Stage I of NREM sleep. This results in hallucinations that are often terrifying; the subject feels conscious and the hallucination is a vivid mix of the real world environment and fear, e.g. a stranger in the room, a fire in the house. The subject is not aware that the current sensations are

dream mentations as in cases of "lucid dreaming" in which the dreamer can consciously discern and define the dream scene as not real. The fear is compounded with the sense of being paralyzed and unable to respond to the intense fright, or the sense that the subject cannot willfully summon the power of arousal from the state of sleep.

With regard to psychotherapeutic help for reducing the fright of the hypnagogic hallucination, expanded awareness on the part of the sufferer might be helpful. If it is possible to teach people to be aware and manipulate the lucid dream-state as was once been reported (Tholey, 1983), then perhaps a similar approach could be taught to narcoleptics to control the panic that accompanies the hypnogogic hallucination.

Cataplexy--the "Falling Seizure"

As narcolepsy evolves in the individual, cataplexy tends to appear after the other tetrad symptoms. Like sleep paralysis, its phenomenological context is the REM component of atonia. During REM, the alpha motor neuron is inhibited and consequently, the EMG is inactive.

In the instance of cataplexy, atonia is occurring during the day when the individual is engaged in wakeful behavior rather than embedded in the sleep cycle. Moreover, the wakeful behavior is of a certain type: Cataplexy is precipitated by emotionally ladened situations such as surprise, anger, laughter, sexual intercourse,

athletic competition, etc. In his discussion on the brainstem Morrison (1983) wrote of the common cataplectic-like situations in which we may be "frozen with fear" or stopped "dead in our tracks" in emergency situations. His inference is that brainstem mechanisms of emotion and arousal are linked to motor inhibition.

Cataplectic attacks may last only a few seconds or up to 30 minutes. An attack might consist of a fall or it might be only a slight nod of the head or a sagging at the knees. The duration of the attack may be short enough and the narcoleptic so practiced at "catching" or "propping" themselves the temporary loss of muscle tone may go unnoticed. On the other hand, if the narcoleptic goes into a total collapse they are still aware, and the stress of being surrounded by gathering strangers may be enough to precipitate attack after attack, prolonging the cataplexy. The cataplectic attack is perceived by many narcoleptics to be the most debilitating symptom. They often report that they fear others will not understand or accept this particular aspect of their disorder. Functionally, it is the limiting factor in these individuals' employability.

Of the tetrad, only cataplexy is pathognomonic for narcolepsy. Clinicians do not necessarily require all four symptoms for a diagnosis. While some researchers have insisted that all four symptoms be present for the condition to be called narcolepsy, others have included subjects in their studies who only have some symptoms of the tetrad. In keeping with its history, narcolepsy still evades a definitive nosology.

NEURAL SUBSTRATES OF NARCOLEPSY

It is difficult to consider mechanisms of sleep without considering mechanisms of wakefulness. The following discussion on the neural systems that are involved in narcolepsy is intertwined with the work on neural structures of arousal. Brainstem area lesions and transections only a few millimeters apart lead to dramatic changes in states of behavior.

Neural Mechanisms of Arousal

In 1937, Bremer performed a midcollicular transection between the inferior and superior colliculi of a cat, a preparation called cerveau isole'. The cat survived a few days in a state of sleep. In contrast, a transection at the caudal end of the medulla called encephale isole' produced a cat whose EEG showed alternating synchronous and desynchronous cortical activity indicating sleep and waking respectively. Moreover, the cat's eyes would track a moving object during the desynchronous period. Bremer concluded that the area between the two cuts which left sensory input intact was responsible for the waking state. He thought that the brain was essentially inactive unless tonically aroused by sensory input.

However in 1959, Batini et al. established that the sensory input did not figure in an aroused state. Batini performed a midpontine pretrigeminal transection just caudal to the midcollicular cut of the cerveau isole preparation. The result was

the opposite: a state of insomnia. The midpontine preparation had the same loss of sensory input as the midcollicular cut and yet produced wakefulness. Even when the remaining afferent sensory pathways were removed, the cat still exhibited wakefulness. Thus, it was established that an area associated with wakefulness was located somewhere in the short distance between the midpontine transection of Batini's preparation and the rostral cerveau isole preparation of Bremer, and the mechanism of waking was not a passive reception of sensory input as Bremer originally thought. Further, somewhere between the midpontine cut and the caudal encephale isole preparation was an area associated with sleep.

In 1949 Moruzzi and Magoun found that electrical stimulation of the brainstem reticular formation would produce arousal. Their seminal work led to other studies that characterized the morphology and function of the reticular formation so named for its intricate net-like appearance. The reticular formation has diffuse connections to the thalamus, cortex and spinal cord. It begins rostrally in the mesencephalic ventral tegmentum, runs through the pontine area and on to the medulla. It is comprised of over 90 nuclei which include sites of production of the monaminergic neurotransmitters norepinephrine, dopamine, and serotonin and also those located in the medulla that control vital processes such as cardiovascular activity, breathing, and skeletal muscular tone.

Many subsequent studies have confirmed the role of the reticular formation in wakefulness. Jones, (1969) showed that destruction of the locus coeruleus (LC), populated with

noradrenergic neurons, resulted in hypersomnolence. The electrodes that Moruzzi and Magoun placed in the reticular formation were very near the dorsal pons which is the location of the locus coeruleus. These experiments give evidence that arousal may be noradrenergically facilitated by the locus coeruleus and that its activation appears to suppress sleep. As will be discussed in more detail in the section on cognitive function and narcolepsy, recent drug studies suggest the locus coeruleus plays an important role in human arousal and attention.

Jones, Bobillier and Jouvet (1969) also experimented with lesioning the substantia nigra which is rich in dopaminergic neurons. The result is a comatose state, which Jouvet interpreted as evidence that dopamine contributes to arousal. However, this did not occur with species other than the cat (Simpson and Iverson, cited by Carlson, 1981). In humans, the contribution of the dopaminergic system to arousal is now regarded as the facilitation of an attentional system (Carlson, 1981). The efficacy of dopaminergic antagonists in the treatment of schizophrenia is the basis for a hypothesis that it is an attentional disorder brought about by hyperactivity of the dopaminergic system. Conversely, children who are hyperkinetic are seen as unable to focus attention. Their disorder is regarded as an attentional deficit and they respond to dopamine agonists such as amphetamine and methylphenidate. The only other recognized therapeutic use of these drugs is in the treatment of the excessive daytime somnolence of narcoleptics (Goodman and Gilman, 1986).

Steriade, et al. (1982) showed that the rostral projections from the midbrain reticular formation depolarize inhibitory relay neurons of the thalamus and thereby eliminate the EEG characteristic of sleep spindles during waking and paradoxical sleep. They equate these neuronal sites with the rostral reticular substrate that Moruzzi and Magoun first proposed as the neural substrate of tonic thalamocortical activation responsible for waking. Further studies by Steriade et al. (1990a) confirmed a hypothetical ascending cholinergic thalamocortical system that correlated to the desynchronous EEG activity of both waking and REM sleep. They ascertained the identity of these neurons of the peribrachial area of the pedunculopontine tegmental nucleus and the laterodorsal tegmental nucleus as comprising part of an ascending cholingergic system through retrograde transport and acetylcholine transferase immunohistochemistry in the cat and rat. Their studies (1991a) also determined that stimulation of these neurons would result in the lateral geniculate component of the PGO spike associated with REM about which more will be said in the next section.

For the narcoleptic symptom of excessive daytime sleepiness, increasing compensatory arousal during the day may be pharmacologically achieved by the use of amphetamines which cause the release of the catecholamines (Soldatos, 1983). Methylphenidate, methamphetamine and dexedrine are used to control excessive daytime somnolence, but are not effective in

controlling cataplexy. The most effective drugs used to suppress cataplexy are the tri-cyclic antidepressants.

Neural Mechanisms of Sleep

Most relevant to narcolepsy are the structures that facilitate REM sleep. Jouvet (1962) transected the cat brain through the rostral pons and produced REM and loss of neck muscle tone. A more caudal transection to the first but rostral to the medulla which is the site of motor inhibition produced REM but not loss of muscle tone. This suggested that a site for REM control lies between the upper pons and medulla. It was in this methodical search that Jouvet found a site caudal to the pontine reticular formation wherein small lesions produced REM dissociated and released from atonia. However, because of the intricate and complex nature of the reticular formation and the relatively poor resolution that available methods allowed, several locations have been proposed as executive centers of REM generation.

Single cell electrophysiological readings in the caudal pons added to Jouvet's findings that REM behavior was controlled somewhere in the pontine area. Hobson and McCarley (1974) found that neurons in gigantocellular tegmental field (FTG) fired at rate fastest during REM sleep. This finding led the authors to speculate the FTG cholinergic cells were responsible for generating REM. It was proposed that the physiological correlate of REM known as PGO spiking which is a burst of electrical activity in the pons, the lateral geniculate bodies and the visual occipital cortex were

generated in the pons via an activating cholinergic system that projects profusely through the thalamus to the cortex.

The PGO activity was interpreted as the neural basis for the vivid dreaming of the REM state as the lateral geniculate bodies and occipital cortex comprise the relay and processing sites respectively for the visual neural circuitry. In other words, the sensation of visual imagery was being processed without the daytime sensory input from the eyes. This work led to McCarley and Hobson's "activation-synthesis" hypothesis of dreaming that proposes the cortex is cholinergically activated by the FTG neuronal projections and that the behavioral experience is a dream composed of associated, i.e., synthesized images. Hobson et al. (1983) also conducted studies in which cholinergic mimetics were injected into the pontine area and caused REM, thereby confirming the role of acetylcholine.

Morrison (1983) also demonstrated that pontine lesions in the cat prevents atonia during REM and the cats proceed to apparently act out their dreams. He further concluded there are two separate neural systems that produce atonia. One is the simpler and well known center in the medulla that inhibits the motor neuronal system and produces atonia. The other is a locomotory drive that appeared to manifest in the awake post-lesion cat which was extra exploratory for no reason from the external environment. Morrison theorizes a locomotion generator in the spine that is under control of a locomotion center in the brainstem. He cites other work that confirms such a center in the cunieform nucleus with tracts

running down each side of the brainstem. There is also a region near the midline upon which lesions can be made so as to release the center from inhibitory input. Morrison feels these are the sites he and Jouvet have damaged and consequently released atonia from its usual concurrent place in REM.

Morrison's laboratory, also established that the nature of the PGO spike is identical to EEG activity called eye movement potentials that are recorded over the occipital visual cortex during wakefulness. Previously thought to be a consequence of changes in illumination, they found the awake cat exhibited eye movement potentials in absolute darkness. They redefined the response as one of alerting to multi-sensory stimuli. It is now accepted (Hobson, 1990) that this one activity characterizes a startle response during waking, is absent during NREM sleep, and in contrast, occurs in clusters during REM sleep. The PGO of REM sleep is not externally derived by sensory stimuli, but is somehow internally generated and results in excitation of the forebrain. This connection of the REM-related cholinergic PGO spike to the normal process of alerting during waking was an important finding in that a physiological event could be related to a behavioral process. It also has implications that a person afflicted with disordered REM may have consequential behavioral anomalies. The hypnagogic hallucination may be such an anomaly, i.e., a cluster of electrical bursts that should be occurring in the context of sleep may intrude upon a waking moment and the awake person would experience an hallucination instead of a dream. Another possible anomaly might

occur in cognitive tasks that require an alerting response. These implications of behavioral aspects of disordered REM will be discussed again in the section on cognitive function in narcolepsy.

Jones (1985) has investigated the neural basis of REM sleep. She employed a computerized three-dimensional cluster analysis of physiological correlates (EEG amplitude, EMG amplitude, and PGO spike rate) consequent to the lesion. Jones destroyed the FTG and decreased the PGO spike component but did not eliminate the cluster-state of REM sleep. This finding established that the FTG cannot be the generator of REM as Hobson and McCarley thought. Jones also found that lesions of the lateral tegmental field were the most effective in eliminating the cluster-state of REM sleep. Of the lesions studied, the most effective abolishment of REM sleep came from the dorsolateral pontine tegmentum, which is also the site of the laterodorsal tegmental nucleus that Steriade et al. have investigated (1982, 1990a&b), between the motor trigeminal nucleus and the FTG (crossing the coronal section at the level of motor trigeminal nucleus).

Jones described the ascending and descending projections of the dorsolateral pontine tegmentum as widespread enough to certainly affect state changes such as entry into REM sleep. Rostrally, these cells project to the intralaminar and midline thalamic nuclei, the subthalamic region, lateral hypothalamus, and basal forebrain and septum. Caudally, the projections extend through and collateralize in the ventral medial medullary reticular formation and project to the length of the spinal cord. Thus,

lesions in the dorsolateral pontine tegmentum effectively eliminate REM sleep because of the disruption in the pontomedullary reticular formation.

Jones also demonstrated a non-noradrenergic system around the LC alpha--"peri locus coeruleus alpha"--could be cut and eliminate REM atonia whereas cuts in the noradrenergic tract from the LC did not as was previously believed. A transection of the tegmental fiber systems at the pontomedullary junction, which interrupts the catecholamine longitudinal bundle and all short interconnecting as well as long projecting reticular fiber systems, eliminated the cluster-state of REM sleep. Jones concluded that pontomedullary interconnection must be intact for REM sleep to occur.

Steriade et al. (1990b) have used single-cell recordings in chronically implanted, behaviorally intact cats to correlate peribrachial and laterodorsal tegmentum activity to both the PGO spiking of REM sleep and tonic discharging that they believe serve to maintain arousal during waking. Their studies have described six different classes of cholinergic neurons based on firing rates and timing with thalamic PGO waves. Their immunohistochemical techniques have also identified the area around the locus coeruleus be to have cholinergic neurons closely situated and mixed with adrenergic neurons. In a recent review Hobson (1990) concludes that the cholinergic facilitation of regulation and generation of REM does not occur at any one site; instead, the phenomenon is derived from multi-site activity.

Cornwall et al. (1990) have reported on their studies of immunohistochemical identification of the afferent and efferent connections to the the laterodorsal tegmental nucleus. Together with the pedunculopontine nucleus, the Laterodorsal tegmental nucleus is seen as basic to the reticular cholinergic activating system (Steriade et al., 1990a). The results portray a highly differentiated ascending system that includes projections to: nuclei involved in visual function such as the paramedian pontine reticular formation which is associated with eye movement during paradoxical sleep; thalamic nuclei; and structures of the limbic system and basal ganglia. The import of their findings on understanding the physiology of narcolepsy is that the laterodorsal tegmentum may be an anatomical link between REM generation and the limbic structures associated with emotionality. For example, the amygdala, a limbic structure involved in emotions such as fear and anger has projections to and from the laterodorsal tegmentum (Calvo et al., 1986). This might in part explain why cataplexy is precipitated by intense emotion and why the hypnogogic hallucination has a terrifying quality.

Neural Mechanisms for the Sleep/Wake Interaction

So far, the discussion has covered mechanisms for arousal and sleep--especially REM sleep. The interface of these states is of prime importance when considering the condition of narcolepsy in which the transition between the two states is poorly controlled. The integration of the wakeful and sleep state may

involve structures of the forebrain. For example, in the above mentioned experiments that used protocols aimed to disrupt putative brainstem control of the normal sleep/wake cycle such as the cerveau isole' some correction at the intact higher brain level would still take place. Other studies have shown that administration of parachlorophenylalanine which inhibits the synthesis of serotonin in the cat produced an insomnia marked by intrusions of PGO spikes (Dement et al., 1972). This disruption occurs presumably at the brainstem level, but once again some correction still takes place. Neuroanatomical support for this kind of higher brain level involement lies in the fact that structures that are integral to REM generation are innervated by forebrain structures among others (Cornwall et al., 1990).

There are undeniably higher structures involved in rhythmic behavior, notably the suprachiasmatic nucleus which receives afferents from the retina, ventrolateral geniculate nucleus and the raphe' nuclei and projects to the ventromedial and posterior hypothalamus, interpeduncular nucleus, dorsomedial thalamus, lateral habenula, the lateral septum and the diagonal band. These connections support the belief that the suprachiasmatic nucleus is the "zeitgeber" (time-giver) of the brain that sets the organism to a circadian rhythm (Carlson, 1981).

Lewy (1980) demonstrated that diurnal activity in humans is sensitive to light and that there is a correlation between melatonin production in the sympathetically innervated pineal gland and depression. This is of note because of the link between depression

and shortened REM sleep latency found by Vogel (cited in Weitzman, 1981). It is also noteworthy because of the frequency of depression in narcoleptics. If application of the light therapy that Lewy developed could ameliorate the symptoms of narcolepsy, possibly an ancillary non-drug therapy could be developed. This would be desirable because thhe current drug regimens while symptom reducing can have undesirable side effects such as tolerance, dry mouth, reduced libido, and impotence.

Lesion work in animals has indicated sites that are putative regulatory or executive centers for sleep, wakefulness and REM generation. In order to consider the integration of these behavioral states, the focus now shifts to the interaction of these nuclei, their projections to higher structures of the midbrain and cortex and the neurotransmitter systems that may facilitate the integration of the sleep/wake cycle.

Two major systems which appear to be involved in wakeful behavioral activity are the noradrenergic and serotonergic (Aston-Jones and Bloom, 1981). Both systems arise from specific reticular cell groups and project extensively throughout the cortex, innervting virtually all cortical areas and layers. The noradrenergic locus coeruleus has been shown to undergo quiescence during REM (Chu and Bloom, 1973; Hobson et al., 1975) as does the serotonergic dorsal raphe' (Trulson and Jacobs, 1979). Both groups show tonic firing rates related to the circadian rhythm, and show virtual cessation of firing during REM periods.

Hobson (1983) has offered a theory of the sleep/wake cycle that incorporates the fluctuating levels of the monaminergic systems. He proposed the hypothalamus (site of the SCN) serves as a regulator of the 24-hour circadian rhythm, and the pontine tegmentum serves as site for an ultradian rhythm regulator that controls the 90 minute cycling of NREM and REM sleep. These two oscillatory systems interact with each other (hence the theory's name: reciprocal interaction) such that oscillation of the ultradian is at its greatest when the circadian oscillation is at its lowest. He also proposed the circadian rhythm and the ultradian rhythm are mediated by noradrenergic and cholinergic systems respectively. Hobson suggests that imbalances in this model would explain such disorders as narcolepsy. For example, if the circadian oscillation were too low in amplitude because the noradrenergic system was dysfunctional, then its zenith during daytime would not be great enough to mask the ultradian cycling of NREM and REM. And if the cholinergic system were sensitized, the amplitude of the ultradian oscillation would also be greater than normal with the greater likelihood that its peaks would result in REM events surfacing above the cover of what should be daytime behavior and showing a periodicity of 90 minutes. Hobson's theory is compatible with Kleitman's ultradian basic rest-activity cycle (cited by Hobson) and supported experimentally by De Koninck et al. (1986) in a study of the daytime REM cycles in narcoleptic patients in which it was found that REM interval periods of the night were significantly similar to the occurrences of REM episodes of the day.

Hobson's theory is in keeping with other studies that form a cholinergic-aminergic imbalance hypothesis first proposed by Janowsky in 1972 (cited by Gillin, 1989) regarding the cause of endogenous depression and sleep abnormalities . Gillin discusses evidence such as the muscarinic antagonist scopolamine induced sleep abnormalities that characterize depression. Of special interest is the shortened REM latency that characterizes endogenous depression and is most acute in narcoleptic sleep with its immediate entry into REM.

A battery of assays have been done (Baker and Dement, 1985; Kilduff et al., 1986; Faull et al., 1986) to determine if monoaminergic and cholinergic levels differed between narcoleptic and normal dogs. The findings are also compatible with the cholinergic-aminergic imbalance hypothesis. Norepinephrine levels were significantly reduced in the narcoleptic canine model and muscarinic receptor number was significantly increased. The lowered norepinephrine levels would explain the benefits seen in methamphetamine or methylphenidate therapy (Soldatos, 1983; Mitler, 1986) and begins to define the possible system(s) involved in narcolepsy. For example, other therapies such as the β-adrenergic receptor blocker propranolol (Kales et al., 1979), the opioid codeine (Fry et al., 1986) and the serotonergic blocker fluoxetine (Baker and Dement, 1989) have not been successful.

Baker and Dement also found increased levels of 3,4-dihydroxyphenylacetic acid (DOPAC) and DA but inferred from ratios of homovanillic acid (HVA)/DA that turnover appeared to be lower

in narcoleptic dogs, pointing to an inhibition of release of DA. This finding is compatible with the beneficial effects of DA agonists such as dextroamphetamine and methylphenidate. It is also compatible with the phenomenon that exogenously applied gamma-hydroxybutyrate (GHB) inhibits DA release (Gessa, 1966; Roth, 1970a; Altar, 1983; Bloom, 1986). If this system is impaired, GHB may somehow be interactive with this system. In fact, nocturnally taken GHB is a therapy for narcoleptics in Canada and European countries (Broughton and Mamelak, 1979; Mamelak, 1986, Iahno et al., 1985) and is currently being researched in clinical trials in the United States (Scharf et al., 1985; Scrima et al., 1989) with results compatible with the Canadian studies.

The original work of Laborit (1964), who initially synthesized GHB, listed inhibition of the monosynaptic reflex as one of its many properties. This finding was later confirmed in humans (Mamelak and Sowden, 1983), and that GHB induced REM (Mamelak, 1977). The monosynaptic inhibition of the alpha motor neuron is the cause of atonia during REM and is a natural concomitant in normal individuals (Chase and Morales, 1985) but an abnormal manifestation in the cataplectic attack of narcolepsy (Guilleminault, 1989).

Broughton and Mamelak reasoned that the effectiveness of GHB treatment was to consolidate REM events to the night and improve the sense of restfulness. This is in accordance with a theory formulated to account for the phenomenon known as REM rebound (Dement, 1976) wherein if REM is suppressed for a period

of time, excessive amounts of REM appear when the suppressor is taken away. The theory holds that REM occurs in defined amounts and if not expressed builds up in "pressure". When GHB is applied nocturnally, it is seen as facilitating events during the night so that the pressure for diurnal sleep and REM components is relieved.

Broughton and Mamelak departed from the established regimen which emphasized increasing daytime alertness and suppressing daytime REM, viz. methylphenidate and tri-cyclic antidepressants respectively. They reasoned the pathogenesis of narcolepsy involved disturbed sleep and therefore looked for ways to treat sleep itself. They chose to work with GHB because unlike other narcotics, GHB induces a state that approximates a natural state of sleep specifically because it does not suppress REM as do the barbiturates and is non-toxic.

They reported a marked reduction in the symptoms with few adverse clinical effects such as tolerance, reduced libido or impotence. Moreover, because GHB is endogenous (Bessman and Fishbein, 1963) it is metabolized by existing pathways. Broughton and Mamelak do cite the following side effects: a sense of weakness upon awakening--hypotonia due perhaps to presence of unmetabolized GHB; urinary urgency; and a dream-like confusional state. They also comment that an improvement in the therapy would be some kind of timed release form so that the patient would not have to waken during the night for the dose of this short acting (about 1 hour) compound.

Mamelak (1989) feels the role of GHB is that of regulating the orientation of the cell metabolism to a quiescent, energy conserving and anti-hypoxant state as Laborit originally contended (1964) and Zaretskaya demonstrated (1983). Hobson (1990) currently believes, as Hess originally thought in 1954, that the aminergic system controls energy expending functions, whereas the cholinergic system controls energy conserving functions. The connection between these two potentially compatible theories may be the fact that GHB has an inhibitory effect upon the dopaminergic systems in the brain and the adrenergic systems in other tissues (Mamelak, 1989). The production of GHB could be part of the regulation and integration of the states of waking, NREM sleep and REM sleep; and the primary difference between the the fast EEG-wave states of waking and REM sleep that Hobson has sought to define. He proposes that during wakefulness, catecholaminergic systems are functioning to optimize neuronal processes involved with daily attentional state-dependent tasks such as vigilance, learning and memory. But during the night when this system theoretically undergoes a mandatory restorative or anaplerotic phase, the disinhibition of the cholinergic system results in spontaneous firing activity known as PGO spiking which heralds and distinguishes the REM sleep state.

Hobson goes on to say that a piece of information is missing from his theory: what regulates the interaction of the circadian rest activity phase with the NREM-REM ultradian rhythms. If Mamelak's assessment of GHB as a regulator of energy metabolism

is accurate, then GHB might be part of the missing piece of information to which Hobson refers. GHB may contribute to the regulation of the sleep/wake cycle by its inhibitory effects upon dopamine release (Gessa, 1966; Roth, 1970b), and the consequent decline of the aminergic inhibition on the cholinergic activity may be the source of REM components. Supporting GHB's regulatory action is the fact that exogenous GHB induces REM (Mamelak, 1977) and its components such as cataplexy (Broughton and Mamelak, 1979), inhibition of the monosynaptic response (Laborit, 1964) and also potentiates the loss of the righting reflex in hibernating animals (Popova, et al., 1984).

The logical question to follow is what regulates GHB production. Laborit and Zaretskaya believe that the pyridine nucleotides NAD^+ and NADH exist in a fixed total pool. These metabolic cofactors are converted from one to the other as respective products of cellular reductive and oxidative reactions and therefore exist in a ratio that reflects the metabolic stage. Their fluctuating levels are a source of regulation of the Krebs cycle (Matthews, 1990) and can influence the direction of shunts away from the oxidative phase of metabolism. Specifically, GHB can be an alternate product from succinic semialdehyde in a reaction of the GABA shunt that is catalyzed by succinic semialdehyde reductase when NAD^+ levels are depleted by the activity of the Krebs cycle. Coupled to this reaction in redox flux is the production of succinate which is catalyzed by succinic semialdehyde dehydrogenase and participates in the Krebs cycle. In

this manner, these two reactions reflect the energy state of the cell by consequently producing either a substance that reportedly induces REM sleep behavior or a substance that feeds into the Krebs cycle that supports active, wakeful behavior. If this metabolic theory of the regulation of the sleep/wake cycle is accurate, then the switch-like production of either GHB or succinate is an example of a reaction that sits at the interface of two states of behavior.

The effectiveness of nocturnal application of GHB as a treatment of daytime narcolepsy-cataplexy suggests there may be faulty induction of either succinic semialdehyde dehydrogenase or reductase; or there is dysfunctional feedback controls that would keep GHB production in check during the day. Such a metabolic error could be genetic in origin. This in fact appears to be the case in GHB aciduria in humans (Jakobs et al., 1984) and may possibly correlate to the evidence that some animal strains pass narcolepsy along in a recessive autosomal fashion (Baker, 1985) and that human narcolepsy may be familial (Guilleminault, 1989). The link between genetic transmission and narcolepsy may be the very significant incidence of the class II human leucocyte antigen known as HLA-DR2 and DQw1 which has been shown to be 100% in narcoleptics of various nationalities compared to 21.8-36.0% of the control groups as studied (Honda et al., 1986; Langdon et al., 1986; Billiard et al., 1986; Poirier et al., 1986). While this indicates some connection between narcolepsy and autoimmune processes of the body, there is still no concrete explanation for this highest correlation between a disease and the HLA.

Other GHB research that is relevant in the context of neural systems is distribution of sites of synthesis and receptors. Maitre et al. (1987) found that high affinity binding sites for GHB exist in highest densities in the olfactory bulbs, frontal cortex, striatum and hippocampus, than the caudal portion consisting of the hypothalamus, cerebellum, pons-medulla, and spinal cord. This distribution pattern is roughly opposite to the distribution of the specific succinic semialdehyde reductase that catalyzes the production of GHB (Rumigny, 1981) which is highest in the cerebellum, septum, hypothalamus and lowest in the cortical areas measured.

Since application of exogenous GHB causes components of REM like inhibition of alpha-motor neurons (Laborit, 1964; Mamelak & Sowden, 1983), endogenous GHB must somehow play a role in the integration of REM with NREM and waking. If this is an associated system of REM control, it would add another link between emotionality and cataplexy given its distribution of synthesis and receptor sites among several structures of the limbic system. The other model of cataplexy that can be induced pharmacologically is by injection of the cholinergic agonist carbachol into the peri- and sub coeruleus regions which produces atonia in the wakeful animal (Quattrochi, cited by Hobson, 1990). The ascending cholinergic reticular activating system depicted by Steriade et al., (1990a) and Cornwall et al., (1990) is an extensively innervated and profusely projecting system that also includes structures of the limbic system and nuclei that are probable candidates for the generation

of REM (Steriade et al., 1990b; Jones. 1985). It interacts with the ascending dopaminergic system which is subject to inhibition by the presence of GHB. If GHB is produced cyclicly and inhibits dopamine, then perhaps the consequence on the cholinergic system is the manifestation of REM components. For narcoleptics, an imbalance at the level of the peri- or sub-coeruleus might result in cataplexy.

COGNITIVE FUNCTION IN NARCOLEPSY

Like many other neurological disorders that display a far-ranging symptomology, narcolepsy may also have effects in addition to disruption of the sleep-wake cycle; e.g., narcoleptics commonly exhibit depression and a tendency to being overweight. Besides looking at the mechanisms of the acute manifestation of its seizure-like symptoms, several reasons warrant looking for other tonic effects that might be manifested in general cognitive function.

As discussed earlier in the section on neural mechanisms, both attention and alertness share some common pathways with those involved in sleep and wakefulness. Researchers of alertness and arousal often look to the sleep-wake continuum as a model-system (Posner, 1978; Woodruff, 1985), because no single distinction affects the behavioral responsivity of an organism more dramatically than whether it is awake or asleep. This same area of research is of considerable interest with respect to the narcolepsy syndrome of disordered sleep, viz. REM sleep. The rest of this thesis is devoted to addressing the issue of whether or not state-dependent cognitive processes affected in the narcoleptic.

In addressing the issue of cognitive function, the discussion will focus on the catecholaminergic and cholinergic systems which appear to figure prominently in both the sleep-wake cycle and behavioral response modes affected by attention and alertness. The discussion will also describe an experimental methodology that

allows precise assessments of the processes involved in attention and arousal (Posner, 1978). These techniques have been developed across the last 30 years and have proven to be reliable and reproducible in characterizing the normal population. In the 1980's it is also being used to study pharmacological effects such as with dopamine and norepinephrine agonists and antagonists (Clark et al., 1986, 1989) and many neurological disorders including visual neglect, progressive supranuclear palsy (Rafal et al.,1984; Posner et al., 1984) hyperactivity (Swanson, in press), lesion patients (Posner,1987) schizophrenia (Posner, 1988), Parkinson's disease, (Wright et al., 1986). Although this is the first time these techniques have been aimed at narcolepsy, they seem to be an appropriate tool to look at this disorder that apparently involves catecholaminergic and cholinergic imbalances. Hopefully, future studies can shed some light on attentional and arousal components as they might be affected in narcolepsy.

Attention

Evidence suggests that the catecholaminergic systems are impaired for the narcoleptic. Animal model studies indicate lowered norepinephrine levels and impaired dopamine release (Baker and Dement, 1989; Kilduff, et al., 1986; Faull et al., 1986); and many narcoleptics respond to amphetamines and tri-cyclic antidepressants (Soldatos, 1983; Guilleminault, 1989) to control excessive daytime somnolence and cataplexy respectively. The

therapeutic effects of both these classes of drugs is to potentiate the effects of catecholamines (Weiner, 1985; Baldessarini, 1985)

Besides being considered the main facilitators of arousal and wakefulness (Hess, 1954; Hobson, 1983; Gillin, 1989), catecholamines appear to facilitate cognitive tasks. Pharmacological and ablation studies with young and aged monkeys implicate lowered norepinephrine levels projecting to the prefrontal cortical α_2-adrenergic receptor system cause cognitive deficits involving short term memory and attention (Arnsten and Goldman-Rakic, 1985). In a study of Alzheimer patients, lowered performance on picture recognition and attention focusing tasks correlated to those who had lowered 3-methoxy,4-hydroxyphenyl glycol, an assayable metabolite of norepinephrine in cerebrospinal fluid, (Freed et al., 1988).

Apparently the same neural systems that facilitate the waking state also provide the optimal conditions for behavioral responses to the environment. It is reasonable that wakefulness provides the context for an organism's activities to "get its business done"; in the case of humans, this "business" can be a complex array of cognitive processes. Results from cognitive psychology studies suggest that attention orchestrates these processes by "spotlighting" the urgent stimulus and delimiting the numerous other unimportant stimuli that constantly bombard the perceptual organism. Thus, neural systems such as the catecholamines, by means of their ascending projections may physically adjust processing in the cortex so that the most

important channels are facilitated. For example, norepinephrine reduces the spontaneous background activity of cortical and cerebellar cells and augments the cells evoked response to sensory stimuli (Tucker & Williamson, 1984).

A widely used methodology introduced by Posner et al. (1978) is directed at quantifying the covert shift of attention, i.e. the central processing that accompanies attending to a change in the expected spatial location of a target. The processing is called a covert shift of attention because it is separable from the overt movement of eyes. The subject is asked to sit in front of a computer monitor onto which six different kinds of trials are presented. The trials consist of a presentation of one of three centrally located cues followed by an interval of variable length or stimulus onset asynchrony (SOA) and then the target is presented on either side of the central point in the LVF or RVF. The three kinds of cues consist of an arrow pointing left, an arrow pointing right or a "plus" sign in the middle of a 1 cm square of white against a dark screen. Thus, the six kinds of trials are a combination of these three different cues with followed by a target in the LVF or RVF. Of the total number of trials, each trial occurs at the following approximate frequencies:

1. 40% = Arrow pointing left, target in LVF--a valid cue
2. 40% = Arrow pointing right, target in RVF--a valid cue
3. 5% = Arrow pointing left, target in RVF--an invalid cue
4. 5% = Arrow pointing right, target in LVF--an invalid cue
5. 5% = Plus sign, target in LVF--a neutral cue
6. 5% = Plus sign, target in RVF--a neutral cue

The subject is asked to fixate on a central point and respond as quickly as possible by depressing one lever to the target regardless of the side on which it appears. Subjects are instructed about the frequency of the cue conditions so that they know a valid cue occurs 80% of the time, an invalid cue occurs 10% of the time and a neutral cue occurs 10% of the time with an equal probablility that the target will be on either side. For trials with a valid cue, reaction times show a "benefit" of being set in advance by the correctly pointing arrow. These validly cued reaction times are faster than those for trials with a neutral cue which offer no information about where the target will likely occur. In contrast, trials with invalid cues cause longer reaction times compared to neutral, the inference being that the subject was miscued and must take time to disengage from the opposite side and move to attend to the target in its real place (Posner, 1978).

To reiterate, these covert shifts of attention are distinct from the neuromuscular mechanisms of attending eye movements because during fixation, which is determinable by electro-oculogram and electronic eye movement scanners, there is a measurable benefit in reaction times to the target that has been validly cued by a correctly pointing arrow. And, conversely there is a measurable cost in reaction times to the target that has been invalidly cued by an incorrectly pointing arrow.

The Posner paradigm offers a method to study then the abstract concept of attention. By this means attention becomes a measurable entity because it is locked in time, i.e., it takes a finite

amount of time to move, and engage on a validly cued target; and an additional finite amount of time to disengage, move and re-engage on an invalidly cued target. In this view, attention becomes similar to an effector organ that can be moved in response to environmental cues. The survival value of such an evolutionary development is obvious.

As mentioned earlier Posner and his colleagues have used this basic paradigm to characterize the normal population. Variations of ths paradigm, patient population studies and pharmacological studies have afforded a finer dissection of the entire phenomenon of attentional shift into three discreet parts and their possible underlying neural substrates. In order to shift attention, one must first "disengage"from the current location, "move" to the new location, and finally "engage" on the new location of the target. Although a complete discussion of these advanced techniques goes beyond the scope of this paper, reference is made to this body of research so as to offer the context in which a cognitive study of narcolepsy would easily fit.

In a study (Posner et. al., 1984) of progressive supranuclear palsy, a form of Parkinsonism resulting from degeneration of a midbrain nucleus that controls saccadic eye movements, patients showed an ability to shift attention even to targets that were spatially located in the direction of the impaired saccade ability (vertical) although it was a delayed shift. Posner posited this disease of brainstem nuclei impairs the "move" component of shifting attention. This study also included patients with parietal

lesions who exhibited normal reaction times with the notable exception of marked delays to contralateral targets. The size and location of parietal lesion as determined by CT scans and behavioral deficits in orienting to the environment correlate to the delayed reaction time in a manner that suggests the posterior parietal lobe plays a distinct role in the act of disengaging. Another study (Posner et.al., 1987) appears to confirm this putative structure-function relationship in parietal lesion patients and goes on to suggest that visual spatial attention is a component in a network of distinct neural structures. Posner's studies (1990) conclude that damage to the posterior parietal lobe, the lateral pulvinar nucleus of the posterolateral thalamus or the superior colliculus of humans result in slowing of visual processing of events in an attended locale. He theorizes that these structures form an anatomical circuit that facilitates the cognitive operation of covert visual attention shifts to spatial locations. In this manner, these simple techniques have led to a better understanding of the deficits involved in these disorder, and also a better understanding of the anatatomical components of the attentional system.

Posner has also used his covert orienting methodology on the schizophrenic patient population. Because positron-emission tomography studies of never medicated schizophrenic patients showed left basal ganglia abnormalities (Early et al., cited in Posner, 1988) and the view that schizophrenia is a disorder of attention, Posner et. al. (1988) looked for a corresponding left

hemispheric defect in processing. Results of longer reaction times to the right visual field targets in both medicated and unmedicated patients supported his hypothesis. In this manner, Posner has sought to link neural substrate to attentional behavior. He conjectures that the neural pathway that is being affected is the one that connects the prefrontal cortex and the posterior parietal cortex, and involves the basal ganglia as well.

Other groups have also pursued this method of inquiry. Clark, et al., (1989) point out that both dopaminergic and noradrenergic neurons project to the parietal region that forms the tectopulvinar-juxtastriate axis distinct from the geniculostriate and inferotemporal structures that are involved in feature processing and are not innervated by the catecholaminergic systems. Using Posner's methodology, they have shown that the dopamine antagonist droperidol, and the norepinephrine antagonist clonidine, not only increase reaction times but also in a manner suggesting involvement of the catecholamines in the disengage component of attention (1989a, b); and that the catecholamine agonist methylphenidate, gives the subject a feeling of increased attentional ability. Wright et al., (1986) have shown that Parkinson's disease patients show this same pattern in attention impairment. Since Parkinson's disease show low dopamine and norepinephrine levels, this provides converging evidence that these catecholamines are central to attention.

In a similar manner it is worth considering if and how attention is affected in the narcoleptic, given that methylphenidate

and other amphetamines are an effective therapy for excessive daytime sleepiness. Further, if GHB becomes a therapy in the U.S. does its inhibitory effect on dopamine release have implications for an undesirable effect on attention during the day.

Alertness

For normal individuals, the alerting response to novel stimuli is accompanied by activation of the noradrenergic locus coeruleus (Foote and Bloom, 1979). It has been shown that this system (Chu and Bloom, 1973; Hobson, et al., 1975) and the serotonergic dorsal raphe' (McGinty and Harper, 1976; Trulson and Jacobs, 1979), are in the nadir of cyclical activity during REM. This diminished activity is seen as disinhibiting the pedunculopontine cholinergic neurons whose spontaneous burst pattern firing projects to the thalamus and cortex and results in the fast wave desynchrony of REM (Steriade, 1990a; Hobson, 1990). During waking, these neurons fire most strongly to novel stimuli concurrently with and regulated by the locus coeruleus and the phasic activity of the dorsal raphe'. Apparently, this activation by brainstem nuclei as an alerting response serves to enhance early stages of sensory detection and processing (Foote et al., 1983).

It follows from the discussion above and the evidence that narcolepsy involves impaired catecholaminergic systems that the narcoleptic is at risk from a physiological standpoint in that the role of the aminergic systems as inhibitory modulators contribute to the generation of REM when their levels are lowered. The

individual in whom these systems are impaired might well display disordered REM episodes. A symptom of the classic tetrad that may result directly from this impairment is the hypnagogic hallucination. Recall that Morrison discovered the eye movement potentials recorded from the visual cortex were in fact identical to the PGO component of REM, but occurred in the awake state and resulted from a sudden change in the environment. In normal individuals this "startle" response occurs during the wakeful zenith of the aminergic systems which appear to dampen the firing of cholinergic neurons of the brainstem; whereas the PGO spike is embedded in normal REM sleep during which time these systems are in the nadir of activity. The PGO spike is seen as causal to the intense and prolonged cortical activation that comprises vivid dreaming (Hobson, 1988). But in the case of the narcoleptic, the eye movement potential may result in a generalized activation of the cortex that becomes instead a hypnagogic hallucination during wakefulness as opposed to a vivid dream during nighttime sleep.

The cholinergic antagonist scopolamine which is known to reduce REM sleep (Weiner, 1985; Hobson, 1988) has also been used in psychopharmacological studies with humans (Wesnes and Revell, 1984; Callaway et al., 1985). These studies showed that scopolamine reduced performance at the stages of processing that affect event-related potentials and imply that cholinergic mechanisms facilitate this early detection phase. Given the common mechanisms of REM and alerting as evidenced by these pharmacological results and aforementioned identity of the eye

movement potential and the PGO spike, it is compelling to explore whether alerting is affected by narcolepsy and if the individual is disadvantaged from a cognitive behavioral standpoint.

The Posner methodology lends itself to the study of alertness in that a warning cue such as a flash prior to the target presentation will decrease the reaction time in a time-locked manner depending upon the time between the warning stimulus and the onset of asynchrony (SOA) brought about by the response process. In other words, when a subject is alerted by a warning that the target is about to come on, there is a phasic activation which can be measured in time and facilitates quicker responses to the target. This "alerting" effect differs from the covert attentional effects described earlier in that it is nonspecific; i.e., a warning will speed RT's to all subsequent stimuli, regardless of whether they are in the LVF or RVF. Also, many studies have shown that this general alerting builds and then decreases across time. It is relatively small at SOA's of 100-200 msec, peaks in strength at about 500 msec. and then decreases at longer SOA's This is inferrable from a reproducible, predictable effect of alertness produced by an optimal SOA. Shorter or longer SOA's will have less effect, which is graphically apparent as a U-shaped curve. In this manner, the effects of alerting can be quantified and compared across normals, drug studies or a patient population. These studies on alerting suggest that it is facilitated by cholinergic and catecholaminergic systems which may tend to be lateralized anatomically (Tucker and Williamson, 1984) and brought out under

certain circumstances such as positive and negative emotional states (Derryberry, 1989) or sustained vigilence (Whitehead, 1992). This possibility of lateralization fits with the clinical observation that parietal lesions on the right side result attentional deficits such as visual neglect, impaired vigilence or reduced alerting effects (Posner, 1990, 1987).

A Cognitive Approach to the Study of Narcolepsy

The reasons described above justify a cognitive study of narcoleptics. A study was done on a single subject who was able to participate in the study while on and off protriptyline medication. Although no statistical conclusions can be deduced from a single subject, she can serve as her own control in two ways: comparing the the on and off conditions; and comparing left hemispheric to right hemispheric processing for which the many possible inter-subject variables such as age, medication history etc., are the same intra-subject. Also, her results can be compared to what is already known about the normal population and other patient populations. Information about this one individual is intrinsically interesting because so little is known about cognitive function in narcolepsy and it may serve to guide future studies. In fact, this is the main advantage of the case study as a research form: it can by itself break ground from the expected patterns in the normal population (Elmes et al., 1981) and generate hypotheses (Ellingstad & Heimstra, 1974). The case study is a venerable form for psychology research and instruction and it recurs in medical

literature e.g., the work on GHB aciduria began with a single case whose report generated diagnoses in other cases. Sometimes because of the rarity of the example, a case study is the only possible route for research to take (Dukes, W.F., 1965) and information to spread. The historical recording of narcolepsy itself began with a case study report by Doctor Gelineau. It might even be argued that a neurological disorder cannot escape the individualized treatment of a case study because individual differences are so high. Symptoms are grouped together into syndromes for the grasp of the researcher while the clinician daily faces patients with supposedly the same disease yet present very differently from one another and require inidvidualized medication regimens.

A presentation of the study and its results follows. It must be borne in mind that any interpretation of the results are made within the limitations of a study comprised of one person. By itself, it can claim no relavance beyond that one subject as she performed on two days. However, it can also have value as a pilot study pointing the way to further research.

CASE STUDY: IS REACTION TIME AFFECTED IN NARCOLEPSY AND TREATMENT WITH PROTRIPTYLINE?

Introduction

Narcolepsy is a symptom complex that involves disordered facets of Rapid Eye Movement (REM) sleep. Its most overt symptoms are excessive daytime somnolence (EDS) and cataplexy (alpha motor neuron inhibition) precipitated by events of high emotionality. Current drug treatments are aimed at these two symptoms which appear to be separate neurochemical entities because a treatment for one symptom does not alleviate the other. Generally speaking, compounds which cause a release of the catecholamines such as methylphenidate or amphetamine are effective in combatting EDS while the tri-cyclic antidepressants are effective in suppressing cataplexy (Mitler et al., 1986; Soldatos et al., 1983; Phillips, 1983).

The subject of this study takes dexedrine (dextroamphetamine, preferred for its greater effects on the CNS than the periphery as opposed to the l-isomer form) for EDS symptoms and protriptyline to combat cataplexy which has been shown to be most effective of the tri-cyclic antidepressants in an animal model (Baker & Dement, 1986). Dexedrine is associated with an increase in alertness and ability to sustain attention in hyperactive boys (Rapoport et al, 1978); and the attentional deficit hyperactive disorder is the only other condition in which methylphenidate is used as a drug regimen.

Although dexedrine was used on the day of the study, we thought that reaction time (RT) tests in attention might still illuminate several questions of interest:

1. Are there tonic cognitive differences as well as the obvious phasic event of the REM "attack"?

2. At the reduced level of milliseconds of reaction, will there be a detectable difference in performance in a narcoleptic?

3. If an impairment in performance can be detected in someone who has narcolepsy, can a locus of attention be hypothesized?

4. Does medication for cataplexy affect performance?

5. Are any differences in performance attributable to time of day?

Methods and Materials

The subject was a 36-year old schoolteacher who under the supervision of her physician slowly phases off protriptyline each summer. She responded right-handed to 10/10 activities of the shortened Edinburgh Inventory (Oldfield, 1971), has no ambidextrous tendencies, subjectively reported that she is "very right-handed", has both right-handed mother and father, right-handed brother and sister, and a right-handed son and left-handed daughter. She was highly motivated to participate in this study.

Three RT tests were employed to explore the above concerns. The tests are based upon the methodology developed by Posner et al. (1978) and utilize software written by D. Derryberry for the Apple

IIE. A lever board with two levers was used for input of the reaction times from the subject. The tests were restricted to the visual/motor modalities, e.g. an alerting visual cue was chosen over an auditory cue. This was done to delimit the sensory input, reduce confounding effects such as the auditory loop, and maintain focus upon the motor component as a possible means of detecting impairment in someone who experiences cataplexy. The order of administering the tests was intended to reflect increasing difficulty so that learning from one test to the next would not cloud discernible differences. The subject was instructed to fixate on a central point throughout all tests.

The first test, called COST/BENEFIT, required the subject to respond with only one lever whenever the target appeared on the left or the right side of the monitor. This basic paradigm was described earlier in the discussion of attentional benefits and costs. The target was a 1x1 cm white square on the dark screen. A central warning cue flashed for 50 msecs with an interval between the cue and target, or stimulus and onset of asynchrony (SOA) of either 200 or 600 msecs. This cue was also a 1x1 cm white square that had one of three images: an arrow pointing left, an arrow pointing right or a "+" sign. Of a total of 70 trials: in 40 trials the arrow pointed to the side where the target appeared. In other words, this cue was <u>valid</u> and created a benefit to facilitate a faster RT. In 10 trials the arrow was <u>invalid</u> and miscued to the opposite side, thus creating a cost which would result in a slower RT. In 20 trials a <u>neutral</u> "plus" cue appeared. The stimulus

appeared on either the left visual field (LVF) or the right visual field (RVF) an equal number of times. To reiterate, there was no choice involved in that the subject was asked to depress only one lever in reaction to the stimulus appearing on either side of the screen. She always used her right index finger to press the key. Previous studies have shown that attentional benefits are the same regardless of whether the right or left hand is used. They also do not depend on handedness. A typical pattern of benefits (i.e. faster RT's on valid compared to neutral trials) and costs (slower RT's on invalid compared to neutral trials) was predicted.

The second test, called ALERT, consisted of reaction to a stimulus, a white 1x1 cm square shown on either side of the monitor. An alerting cue the same size flashed in the center of the screen for 50 msecs and preceded the target by SOA's of 0, 150, 300, 450, 600, and 750 sec. The SOA conditions were used 10 times each in randomized order. The stimulus appeared in either the LVF or RVF an equal number of times, and was terminated by input from the subject's reaction of pushing one lever (no choice) to either the left of right stimulus. As with the attention effects, much previous research indicates that similar alerting effects are found for both right and left handers, regardless of whether they use their right or left hand. A typical "alerting effect" was predicted with RT's peaking in spead at around 40-500 SOA's, and the effect equal in both left and right visual fields.

The third test consisted of a "Stroop"-like task that required choice by the subject. The subject placed one hand on each of the

two levers that are mounted side by side. The stimulus appeared on either side of the screen an equal number of times. In a compatible format with hands uncrossed (COM_0) for 20 trials the correct response was to depress the lever that corresponded to the hemifield on which the stimulus appeared: the subject was asked to push the right lever in response to the stimulus on the right visual field, and the left lever in response to the stimulus on the left visual field. The subject then crossed hands and repeated the same test, pushing the right lever (with her left hand) to the right visual field target and the left lever (with her right hand) to the left visua field target (COM_X). In the incompatible format, for 20 trials the subject was asked to push the left lever in response to the stimulus in the right visual field and the right lever in response to the stimulus in the left visual field ($INCOM_0$). The subject then crossed hands and was asked to push the left lever (with her right hand) in response to the target in the right visual field and the right lever (with her left hand) in response to the target in the left visual field ($INCOM_X$).

This third test was designed to begin considering the pre-motor response following the initial stages of alerting and attention. Although response deficits are not evident in narcolepsy in contrast to other neurological disorders such as in Parkinson's or Huntington's the presence of cataplexy suggests a post-sensory abnormality of some kind. Unfortunately, the task is much more difficult than the attention and alerting tasks, and the added layer of complexity tends to obscure the underlying processing

mechanisms making it more difficult to identify them and pick out abnormalities. However, much research has shown that Rt's are faster when the stimulus and the response are compatible, i.e., when the target and the lever are on the same side than when they are incompatible. Researchers suggest that this difference reflects the time required to "translate" the sensory input of the target's hemifield of spatial location to the appropriate motor response. Under compatible conditions, stimulus and response are processed by the same hemisphere. Whereas, incompatible conditions require an extra processing step to transfer the input across the corpus callosum to the other hemisphere in order to process the motor response that is to come from the side opposite the stimulus.

The subject took this series of tests in the following order:

1. COST/BENEFIT, no choice with cue
2. ALERT, no choice with cue
3. COM_O, choice, compatible, hands uncrossed
4. COM_X, choice, compatible, hands crossed
5. $INCOM_O$, choice, incompatible, hands uncrossed
6. $INCOM_X$, choice, incompatible, hands crossed

twice on two different days for a total of 4 times. The first of these days (DAY1) took place while she was on a medication regimen of 15 mg of dexedrine in the early morning and 10 mg at noon; and 15 mg of protriptyline in the early morning and night. The second day (DAY 2) of testing took place 2 months later at which time she had completely phased off protriptyline (which has a half-life of 78 ± 11 hours) and used dexedrine as she felt the day necessitated, e.g. 10 mg in the morning and 10 mg in the evening or

15-30 mg if she needed to drive a long distance (50 miles to test site). The total drop in medication during this time was from from 30 to 0 mg of protriptyline while dexedrine stayed the same.

On both days, she took the tests twice, in the morning (AM) and afternoon (PM) to determine if there were any differences in performance that might be attributable time of day.

Results and Discussion

Covert Attention

Comparisons of the grand mean RT of each test were first considered to see if there were striking differences between DAY 1 and DAY 2. The results are represented in Figure 1. Then each test's data were examined separately in more detail, keeping conditions such as cue quality (valid, neutral or invalid), SOA and hemifield of stimulus presentation separate.

Looking at Figure 1, there appears to be no decrement in RT values on DAY2 when she was off protriptyline than when she was in her fully medicated state on DAY1. In fact the overall RT's of DAY2 are faster which may be attributable to a practice effect. In any case, protriptyline does not seem to affect this subject's overall performance.

Figure 2(a) is a composite of all 4 COST/BENEFIT tests. It shows the mean RT's for each cue condition for DAYS 1 and 2 both AM and PM. In this figure, benefits can be seen in the fater RT's under valid compared to neutral conditions; and costs can be seen in

the slower Rt's following invalid compared to neutral cues. The data in Figure 2a looks similar to that seen in normal subjects, where benefits and costs tend to be roughly equal in size. The only difference from the normal pattern evident in this figure is the increase in costs that occurs in the afternoon of day 2, where costs are over twice as large as benefits. Figures 2(b-e) are a closer look at each of the four tests further separating the grand mean RT into it's four component conditions: 200 msec SOA (squares), 600 msec SOA (circles), LVF (solid line), and RVF (dotted line).

The examination of costs and benefits revealed that the difference in DAY1 which was much slower than DAY2 can be traced to the morning trials specifically the valid and neutral cued conditions as shown in Figure 2(a). This might be due to the tremendous effect of initiation into the test environment since this is the first test of the first day. A further look at the differences between hemifields of stimulus presentation allows a distinction in hemispheres. Because of the way retinal afferents are divided, input from each visual hemifield is processed initially in the contralateral hemisphere of the brain. Figure 2(b) suggests the subject was generally slower in response to LVF stimuli/right hemisphere processing. Figure 2(c) shows that by the afternoon, these values were all more similar accross the three cue conditions. Figures 3(d and e) are in an interesting contrast in that the responses to invalidly cued LVF stimuli with 600 msec SOA (circles, solid line) are opposite in the morning compared to the afternoon. Note that in Figure 2(d) the cost of having to switch

from the situation in which attention was invalidly set to the RVF prior to the target in the LVF is much greater in the AM than in the PM which is shown in Figure 2(e). In contrast, the cost of disengaging and switching to the opposite side was greater in the afternoon for the other three conditions. The sum of these three conditions manifests in Figure 2(a) which as pointed out above, showed much greater costs in the PM of DAY2.

It is not apparent why the response to LVF 600 SOA stimuli with an invalid cue would be so contrary to the other conditions. This kind of difference does not show up in a normal population (Posner, 1978; 1987). This may relate to findings from research on other patient populations and drug studies that look at catacholaminergic imbalance and difficulty with attentional shifts. Clark (1989) looked at DA and norepinephrine (NE) antagonists and concluded that low catecholamine levels produced less cost in processing invalidly cued stimuli. Swanson (in press) has proposed that attentional deficit hyperactivity disorder which is associated with DA deficiency would exhibit LVF advantage as opposed to schizophrenics who exhibit high costs in RT to invalidly cued LVF 100 msec SOA and are thought to have left hemisphere abnormality (Posner, 1988).

Although the limitations of this case study must be kept in mind, the data suggest that this subject may also show a difference in RT's to invalidly cued LVF stimuli at the longer SOA. This may be due to levels of catecholamines which appear to fluctuate during the day. Another study has shown a RVF-left

hemisphere slowing in normals at longer SOA, but the times studied were considerably longer: 3 seconds and 12 seconds (Whitehead, 1991) compared to 200 msec and 600 msec of this study. Whitehead proposes sustained visual attention is an advantage the right hemisphere has over the left. Perhaps this subject demonstrates a related laterality effect but to much shorter SOA's.

Figure 3 shows the mean RT for three ALERT tests out of four because, unfortunately, the data for the LVF of DAY2 AM was lost. Points (triangles) for the RVF of DAY 2 AM are still shown on this graph but not included in the comparison of LVF (solid line) and RVF (dotted lines) values at the different SOA's on the x axis.

Alerting

Figure 3 shows a typical alerting effect in this subject. The general facilitiation of reaction occurs to targets in both visual fields and it increases to a peak effect at around 450 msec SOA's and then subsides. RVF targets tend to be faster than LVF targets but this is common when subjects respond with right hand.

The ALERT test which included a warning signal also showed a hemifield difference with respect to SOA time. Figure 3 shows a slowing of the RT to RVF stimuli at longer SOA times. This is not reflective of the normal advantage the left hemisphere has in producing a right hand response and indicates a possible impairment of left hemispheric processing. It may be that the alerting effect is similar in the two hemispheres for the first 450 msec following the warning, but then subsides more quickly within

the the left hemisphere processing of RVF stimuli. The possibility of left hemisphere impairment is actually compatible with the finding that invalidly cued LVF 600 SOA stimuli elicited noticeably slower mean RT's on the morning of DAY2 (Fig. 2d). In the COS/BEN paradigm, the slower RT to invalidly cued LVF stimuli indicates a difficulty in disengagement from the RVF in left hemispheric processing. It is most unfortunate that the LVF points for the DAY2 AM were lost. On the other hand the isolated RVF points (triangles) are still emphasized for the exceedingly slow times compared with the other times of testing.

Response Processing

The results from the "Stroop"-like tasks of DAY2 PM are shown in Figures 4(a) and (b). This piece of the data reflects the same pattern as the other times of testing. The subject's RT's do not reflect the normal effects of compatible stimulus-response conditions. In normals compatibility between stimulus and response has effect regardless of the hemifield of presentation or which hand is used. In the hands uncrossed compatible and incompatible conditions (COM_0 and $INCOM_0$), the compatible LVF-stimulus/left-side response and RVF-stimulus/right-side response should be faster than the incompatible LVF-stimulus/right-side and RVF-stimulus/left-side responses. But in the case of this subject as shown in Figure 4(a), the RT's for COM_0 and $INCOM_0$ are roughly the same. For example, the right-side response to a RVF stimulus is not faster than the right-side response to a LVF

stimulus as would be expected, nor is the left-side response to a LVF stimulus faster than the left-side response to a RVF stimulus.

In each of the "Stroop"-like tasks the differences between RT's to LVF and RVF stimuli seemed more correlated to the hand used rather than the hemifield of presentation. Figure 4(b) more clearly shows that the left hand (solid line) tended to give faster RT's than the right hand (dotted line). As mentioned earlier, this is a task that is very complicated and only hypotheses can come forth as to what accounts for this pattern of left-handed advantage in a right-handed person with narcolepsy. The simplest explanation would be some relative impairment in left hemisphere processing because the contralateral efferent pathway to the right hand arises in the left hemisphere. This possiblity of laterality in response processing is compatible with her long RT to RVF targets in the ALERT test, and the difficulty she displayed on the morning of the second day with disengagement of attention invalidly drawn to the right side in the COST/BENEFIT test. Certainly more research with controls and patients is required to determine whether this possible effect is real and is somehow a consequence of the disorder.

Conclusions

Any conclusions that may be drawn from this study are restricted by its inherent limitations. First of all, it is a case study and as such, has results that are relevant to this individual and certainly not readily applicable to any others. A case study can

only put forth hypotheses to serve as a possible interpretation to the results at hand and guide for future studies. Second, with only one subject the limited amount of time for testing is a drawback; but only two visits were possible. Even with this limitation, the number of trials per test were at least comparable to other studies of the normal population. Third, any interpretation of hemifield data relies entirely on the the individual's ability to focus on a central fixation point thoughout the tasks. Other studies have shown that it is relatively easy for subjects to fixate with eye movements occurring on less that 5% of the trials. Given the high level of motivation of this particular individual, the assumption is that she was also able to fixate thoughout the tasks. Fourth, conclusions about hemispheric laterality based on these hemifield data is tentative especially concerning the complicated responses asked for in the "Stroop" tasks. Any elaboration on the basic reaction to a stimulus adds layers of processing that tend to obliterate fine differences. The more complicated a task is, the more time is required to make a response; and the longer the reaction time is, the more likely small differences will disappear in the numbers. Fifth, the methodology makes the assumption that as attention moves through space to the location of a target, a directly proportional amount of time is taken to shift covert attention. For example, in order to break the movement of attention into its components of move disengage and move again, it is assumed that when attention is miscued to the wrong side, it takes twice that amount of time to move it back to center and then

on to the correct side which is the same physical distance from center as the location on the other side. This assumption that Newtonian physics holds true through neural networks may or may not be true and may or may not have consequences on the interpretation of the data. Sixth, the length of total test time tends to get long to accomodate an adequate number of trials. This aspect may introduce uncontrolled variables such as fatigue or habituation to the later trials; and seventh, while fatigue or boredom makes it difficult to increase the number of trials it may be the neutral and invalid cue condition which each occur in only 10% of the trials have too few trials to truly reflect a mean that is not skewed by one or two faulty responses. The interpretation of the results and the conclusions are given with these limitations in mind.

The subject's overall RT's did not differ greatly whether or not she was taking protriptyline. This reemphasizes the apparent separateness of the two symptoms, EDS and cataplexy which are controlled by different medications. The stimulatory effects of dexedrine are independent of the action of protriptyline. The similarity in overall RT's between being on and off protriptyline is a form of reassurance to the subject that at this general level, her performance is not affected. However, a thorough consideration of the differences between all the conditions revealed a possible basis for formulating an hypothesis in future cognitive reaction time studies to see if the results from this one patient carry over to a larger number of the narcoleptic patient population.

1. There is a possible left hemispheric effect, especially at longer SOA's. These effects were observable on DAY2 and might possibly be connected to the cessation of protriptyline. This could be tested in a drug study with normals, and/or a patient study if the narcoleptics could be tested in a drug free state. This is difficult to achieve because narcoleptics do not like to be drug free and have uncontrolled symptoms. But it would be preferred because it must be borne in mind that the subject usually takes two drugs in tandem; and there may be interaction between the effects of protriptyline and dexedrine such that cessation of protriptyline would produce changes that are in fact associated with the change in effects of dexedrine. Another source of possible confusion concerning the effects of protriptyline is the highly integrated and interacting nature of the brain's neural systems. A popular theory of control of the sleep/wake cycle is the monoaminergic-cholinergic interaction (Hobson, 1983; Gillin, 1989). Roughly viewed, the two symptoms that dexedrine and protriptyline ameliorate are seen as being in the domain of each system respectively. Perhaps the monoaminergic potentiating effects of protriptyline differ from the enhancement of release by dexedrine in that a tonic presence of neurotransmitter in the synaptic cleft acts as an inhibitory modulator to symptoms that are cholinergically facilitated as the monoaminergic-cholinergic theory might predict. If protriptyline medication is then stopped in someone who has narcolepsy, the effects might be seen in the

cholinergically facilitated events rather than catecholaminergic as might be initially suspected.

2. The left-hemispheric effect may be attributable to DA levels which are believed to be lateralized with greater amounts in the left hemispheres of normal individuals (Tucker, 1984). These levels appear to fluctuate and are potentiated by current drug therapies prescribed to narcoleptics. This implies that DA levels are lower than normal and left-hemispheric processing may suffer impairment. Again, a drug study or medication-free narcoleptic patients could be studied to test this hypothesis. It would also be interesting to see if there are effects in patients using nocturnally administered GHB since exogenous GHB suppresses synaptic release of DA in animals as discussed earlier.

3. The fluctuation of neurotransmitter levels may well account for the differences in the performance this one subject, but the current test design only grossly distinguished between morning and afternoon. An ultradian rhythm may well be at work, given the rhythmicity of REM occurrence. If a catecholaminergic system modulates phasic appearance of the cholinergic as some believe (Hobson, 1990; Gillin, 1989), and this same system facilitates cognitive behavior as others have shown (Arnsten & Goldman-Rakic, 1985; Clark et al., 1986 & 1986; Posner et al., 1987) then some effects could be seen as phasic as the subject's variable performance of the ALERT test on DAY2 and some effects could be seen as tonic such as a general hemispheric effect as

might be the case for this subject whose had different results on LVF versus RVF targets across all three tests.

4. Efferent motor pathways from the left hemisphere may also be implicated as suggested by the data from the "Stroop" tasks. This particularly unusual design would have to be tested in an adequate control number as well a larger narcoleptic population.

Future studies based on this case study could be planned to provide a sufficient number of patients and controls for statistical comparison to test the above hypotheses of left hemispheric effect and fluctuating catecholamine levels in the narcoleptic patient population.

Figure 1

THE EFFECTS OF PROTRIPTYLINE

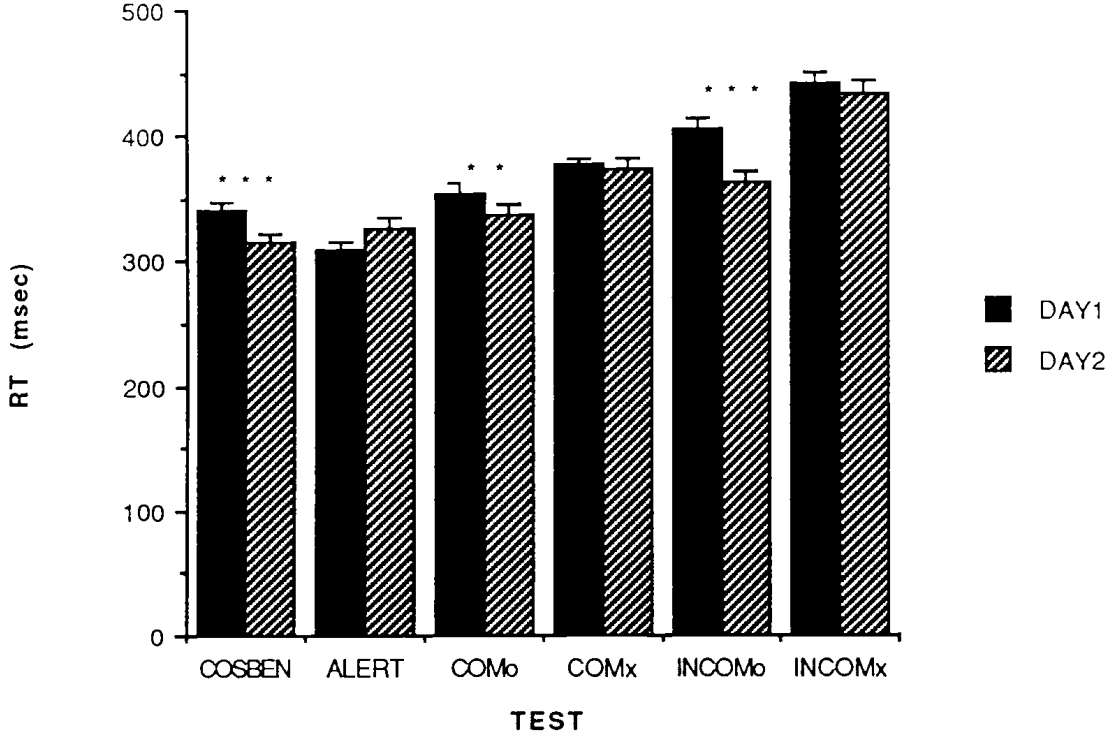
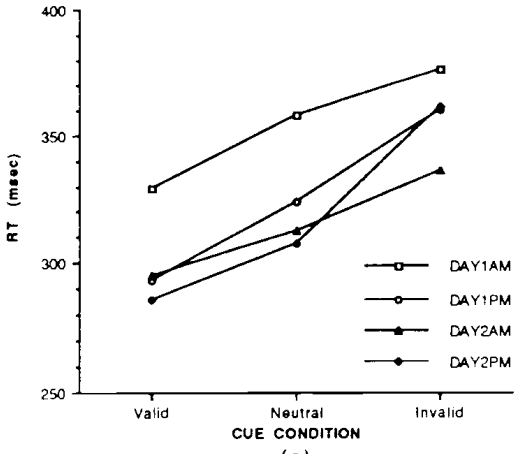


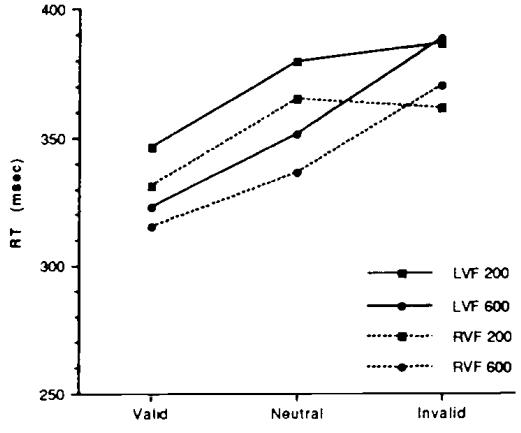
Figure 2

ANALYSIS OF COSTS AND BENEFITS



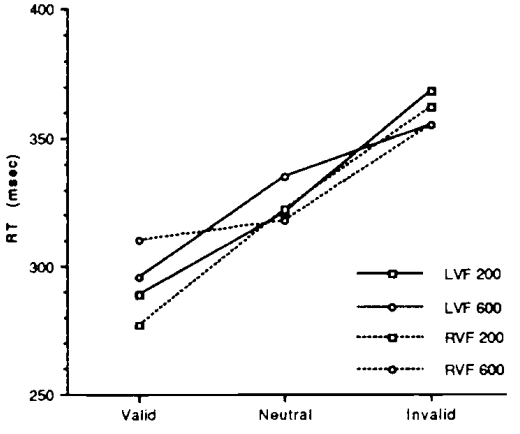
(a)

Data from "DAY 1 AM"



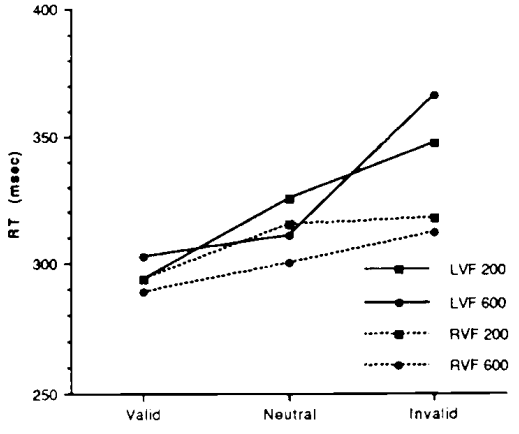
(b)

Data from "DAY 1 PM"



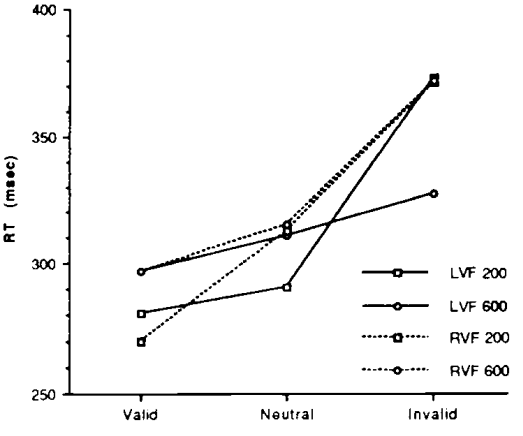
(c)

Data from "DAY 2 AM"



(d)

Data from "DAY 2 PM"



(e)

Figure 3

DATA FROM "ALERT"

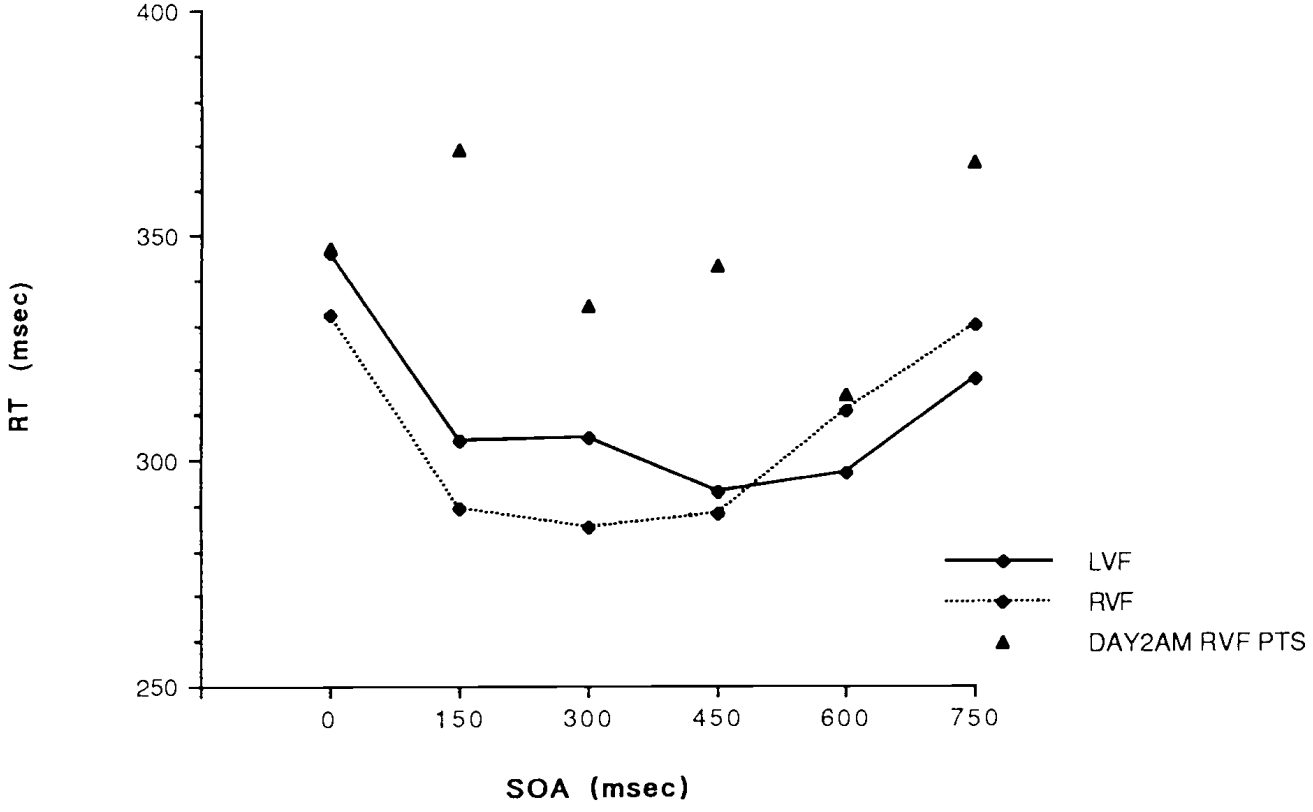
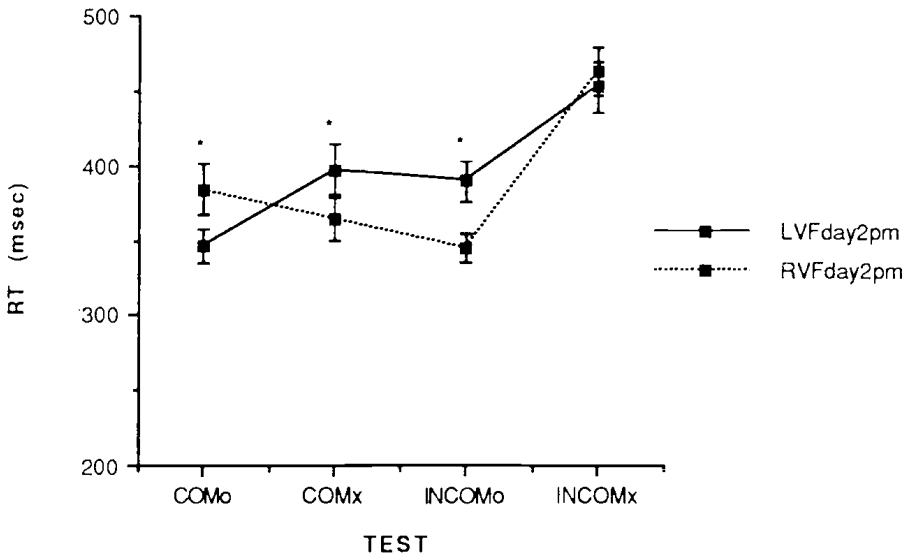


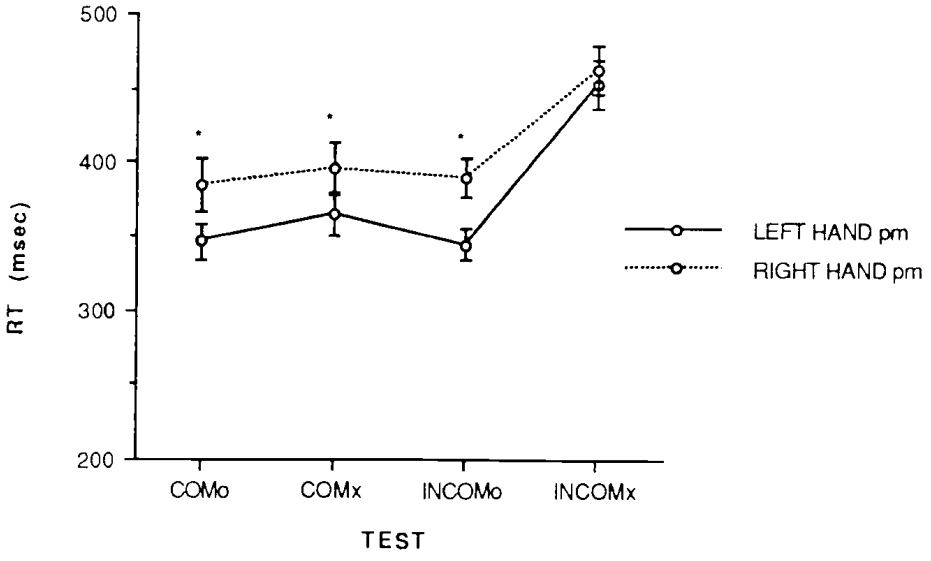
Figure 4

DIFFERENCES IN THE HEMIFIELD OF PRESENTATION: "STROOP" TESTS WITH NO PROTRIPTYLINE



(a)

DIFFERENCES IN HAND USED



(b)

CONCLUSION

The history of narcolepsy research has some fairly distinct divisions that reflect events such as the pandemic encephalitis that swept the world which also produced many cases of theretofore rarely reported Parkinson's disease (Sacks, 1983) and the evolving technology in electroencephalography, single-cell recordings and immunohistochemistry. Passouant's report of 1981 on Gelineau marks a century of research which saw great leaps in understanding the nature of narcolepsy especially during the last 40 years even though a cause and cure evade researchers. During the 50's and 60's the discovery of REM and the polysomnographic characterization of sleep produced much data and the salient finding that narcolepsy was a disorder of REM. The 70's and 80's have been distinquished by the definitive work that single-cell microelectrode recordings have afforded in locating anatomical structures that play prominent roles in the sleep wake cycle. Also during these decades, pharmacological manipulations have discerned the possible neurotransmitter systems that may regulate NREM sleep, REM and waking.

A most significant finding of the last decade's research on narcolepsy was the striking 100% frequency of HLA-DR2 and Dw2 in the narcoleptic patient population. This gives elucidation to the genetic transmission of narcolepsy and may hold a method by which to predict the disorder in the children of narcoleptics. It may also be the basis to research the yet mysterious action of GHB and the manifestation of GHB aciduria which is also genetically transmitted. The ultimate hope would be to restore metabolic or enzymatic

deficiencies in familial narcolepsy or babies that are born with the deleterious succinic-semialdehyde dehydrogenase deficiency. The current drug therapies for narcolepsy are symptom reducing and are by no means a cure. Even GHB therapy, while reportedly having few adverse side-effects, is supplying something that should be endogenously produced and regulated.

The 70's and 80's are also marked by the firm establishment of the field of cognitive psychology. This field seeks to bridge what is known about behavior and neurophysiology and determine structure and function of cognitive activity. While the currently successful Posner test paradigm has been used to look at several patient populations, yet to be done is cognitive testing of the narcoleptic population even though there are several compelling reasons to perform these studies. In this past decade of Reagonomics in which research funding took a steady decline, priority rests with certain projects of which narcolepsy is too rare to figure.

The larger issues of disinterest and underfunding of sleep research in general is something the medical community is urged to address (National Commission on Sleep Disorders Research, 1990; Dement, 1991). Sleep is fundamental to and inextricable from life, yet most research is done in the context of waking. It has been argued that sleep deprivation is society-wide in the U.S. and that many crucial mistakes are made under sleep deprived circumstances (Toufexis, 1990; Rodgers, 1990) At this present moment, while waiting for these breakthroughs in research, the main need of narcoleptics seems to lie in the area of counseling to deal with the characteristic depression and the need to cope with a larger society

that is basically unaware of the total syndrome. As usual the public needs to be educated concerning the disease in order to be understanding to the sufferer and to understand their own needs for sleep hygiene. May this thesis be in some way a contribution along those lines.

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