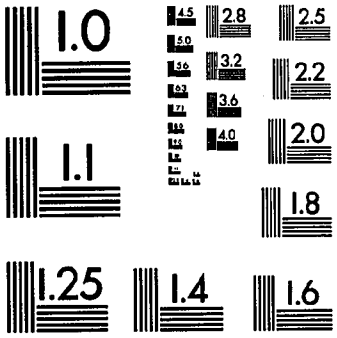

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AUDITORY LATERALITY IN DEPRESSION: RELATION TO CIRCADIAN PATTERNS

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AUDITORY LATERALITY IN DEPRESSION : RELATION TO CIRCADIAN PATTERNS

by

PAUL BERGER-GROSS

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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Abstract

AUDITORY LATERALITY IN DEPRESSION: RELATION TO CIRCADIAN PATTERNS

by

PAUL BERGER-GROSS

Advisor: Professor Gerard Bruder

The purpose of this study was to investigate the relationships between measures of auditory laterality and circadian rhythm disturbance in depressives. Unmedicated endogenous (ED) and nonendogenous depressed (ND) patients were tested in the morning and evening on monotic and dichotic click detection, dichotic consonant-vowel (CV) discrimination, Purdue Pegboard, and visual (letter and dot) matching tasks. Both ED and ND patients displayed morning dichotic click detection lateral asymmetries suggestive of right hemisphere dysfunction. Both groups showed a morning-to-evening shift in lateral asymmetry for detecting dichotic clicks, which was opposite in direction to that previously seen for normal subjects.

The abnormal lateral asymmetry for dichotic click detection in the morning was significantly correlated with EEG sleep characteristics (sleep latency, REM period latency, REM time) and ratings of diurnal variation on the Hamilton Depression Scale. ED and ND patients displayed the normal right ear advantage for dichotic CV's and there was no morning-to-evening shift in CV asymmetries.

There was also a significant lateral asymmetry for detecting monotic click stimuli in ED patients that was not correlated with dichotic click detection asymmetries. This monotic asymmetry was not found in ND patients in this study or normal subjects in a prior study. The ED patients displayed significantly poorer left ear as compared to right ear sensitivity in the morning, but not in the evening. The monotic detection finding again suggests the importance of cyclical mechanisms in abnormal perceptual asymmetries in depressives.

A right hand advantage seen on the Purdue Pegboard may also support a right hemisphere deficit hypothesis of depression, especially considering the significant correlation between faster left hand (right hemisphere) speed and lower (i.e. healthier) Hamilton Depression Scale scores. In the evening, faster visual matching speed, faster

Purdue Pegboard placement, and decreased total (both ears) CV discrimination were correlated with reduced sleep efficiency. These relationships suggest overarousal in the evening, a circadian disturbance which may also affect the continuity of sleep.

This study suggests that some right hemisphere deficits seen in depressed patients fluctuate with time-of-day in a pattern which is the opposite of that previously observed in normal subjects. This abnormal circadian shift in asymmetries was related to disturbances of other cyclical phenomena such as sleep/wake patterns and diurnal mood changes. Symptom, sleep and endocrine variables provided the basis for preliminary speculation on the mechanism of such abnormal patterns of hemisphere efficiency in ED and ND patients.

ACKNOWLEDGEMENTS

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My dissertation committee endured five years of stop-and-start work on this project. Dr. Essman provided direction and insights in neuroendocrinology, but, was sufficiently flexible to recognize the constraints of my dependance on other's work. Dr. Parlee provided encouragement and thoughtful editing throughout. Dr. Mitchell Kietzman has my most sincere thanks for his friendship and guidance throughout my graduate career. Dr. Goetz made the sleep data available to me. His advice on both the analysis and interpretation of this data was invaluable.

Finishing a dissertation, despite full-term employment, would be near-impossible without the support of one's employers. In my case, Drs. Arthur Rose and Roger Cracco my immediate and departmental superiors in Neurology at Downstate Medical Center provided me with ample, indeed generous,opportunities to finish this and other research projects. They have my profound thanks.

Finally, I wish to thank and commend the two individuals who figured most prominantly in the accomplishment of this project. The first, Dr. Gerard Bruder, supervised my teaching and research activities almost from the beginning of graduate school. His care and thoroughness in research has been a necessary balance to my own, more scattered efforts. Without Dr. Bruder's extensive help this dissertation and the research report based upon it may never have been completed. Above all, there is no way to measure the contributions of my beloved wife, Vicky. A Ph.D. herself, there was no task so menial that she would not do it if there was a chance it would hasten the completion of my dissertation.

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I. INTRODUCTION

Affective illnesses vary considerably in their expression. Symptom severity, association with non-endogenous events (e.g., alcohol or drug abuse, traumatic loss), and polarity (i.e., unipolar versus bipolar) represent the major variants in the depressive presentation. Such variants may have particular patterns of ontogenic expression, genetic predisposition, and clinical course. Their salient common feature, depressed mood, may or may not be accompanied by disturbances of several vegetative functions (e.g., psychomotor, sleep, or appetitive abnormalities). These vegetative, or "endogenous" features are inherently biopsychological phenomena, likely to be related to hormonal and electroencephalographic (EEG) sleep correlates of depression. Depression is also often associated with morning to evening changes in mood and daily (circadian) rhythmic fluctuations of REM sleep, neurotransmitter metabolite concentrations, activity, and hormone concentrations (basal and challenge responses) are distorted during depressive episodes.

More controversial, but of considerable interest, has been neuropsychological research suggesting abnormal right

hemisphere function in affective illness. Asymmetrical EEG parameters, average evoked potentials(AER), eye movements, electrodermal responses, unilateral electroconvulsive therapy (ECT), dichotic listening, and neuropsychological tests have all been interpreted as indicating right-hemisphere involvement in depression.

Evidence of altered right-hemisphere function in depression has been provided in a series of studies showing that the "ear" advantage for dichotic click detection is reversed in depressives as compared to normal controls tested during the day. In control subjects, dichotic click detection asymmetries shift from the "normal" pattern in the morning to a reduced asymmetry in the evening. This shift in normal subjects is towards the abnormal asymmetry seen in depressed groups (tested during the day), suggesting the possibility to be investigated in this dissertation that depressed patients may display deviant dichotic listening changes from morning to evening.

The objective of this dissertation is to study perceptual and cognitive rhythms, especially of asymmetrical hemispheral processing, in depression. An additional goal is to demonstrate some external validity of these behavioral changes by correlating them with

endocrine and sleep architecture variables known to undergo (cyclic) alteration in depression. Lastly, we will investigate the symptoms and subtypes of depression (especially endogenous versus nonendogenous) that may relate most strongly to any morning versus evening behavior shifts.

The introduction that follows will review a tremendously heterogeneous literature in order to suggest the following points:

(1) Negative affect involves right hemisphere (RH) functioning and in psychiatric depression RH functioning is altered;

(2) Diurnal anomolies affecting sleep, neurotransmitter and endocrine levels, temperature, activity and sleep indicate a disturbance of a central pacemaker during the depressive episode;

(3) Perceptual and cognitive circadian rhythms exist, including rhythms of relative hemispheric advantage.

The Neuropsychology of Depressed Mood

Neurology and Affect. Asymmetry in the cognitive functions of the cerebral hemispheres is a consistent research finding. A wide variety of measures (e.g., dichotic listening, visual half-field studies, evoked potential and psychological testing) support the view that the left hemisphere is specialized for verbal, analytic, and sequential processing (e.g., Bever, Hurtig, & Handel, 1976; Kimura, 1961; Kimura, 1967). In contrast, the right hemisphere plays a primary role in processing non-verbal, multi-modal, and novel information (e.g., Bogen, 1969, Milner & Taylor, 1972). Attentional (Kinsbourne, 1970), structural (Galaburda, Lemay, Kemper & Geshwind, 1978), or neurochemical (e.g., Oke, Keller, Mofford & Adams, 1978) differences known to exist between the hemispheres are presumed to underlie these cognitive asymmetries.

While there is some consensus of opinion about lateralization of cognitive and perceptual functions, the same can not be said for affective functions. Clinical neurological examinations of the effects of unilateral brain damage showed that catastrophic reactions with depression were more frequently associated with left hemisphere, whereas right hemisphere damage correlated with anosagnosia (i.e., denial of illness) and

inappropriate joking (Gianotti, 1972). Recent research indicated that clinically significant depression is correlated with the closeness of the lesion to the frontal pole (Robinson & Szetelea, 1981). The severity of depression is related to proximity to the left frontal pole (Robinson, Kubos, Starr, Rao, & Price, 1984). In a similar vein, sedation of the left hemisphere during the Wada test (unilateral carotid injection of barbituate) produces depressive affect; right hemisphere sedation is likely to result in a euphoric response (Terzian, 1964; Rossi & Rosadini, 1967). Other studies of unilateral lesions (Dikman & Reitan, 1977) and unilateral barbituate intoxication (Milner, 1967) have failed to demonstrate consistent hemisphere specific affective correlates. Sackeim, Weiman, Gur, Greenbeg, & Hungerbuhler (1983) have reviewed a consensus of evidence suggesting that "shutting-off" the left hemisphere produces disinhibition of the right-hemisphere predilection for negative affect

Right hemisphere damage also affects the processing of affectively charged material. Memory of such material is selectively impaired by NDH lesions (Wechsler, 1972). Comprehension of affective valence in speech is similarly decreased with NDH damage (Heilman, Scholes & Watson, 1975). Finally, while fluency and syntax of spoken

langauge are dependent on the integrity of the left hemisphere, RH lesions can produce a disorder of the melody (i.e., prosody) and emphatic elements (gesturing) of speech (Ross & Mesulam, 1979).

Experimental Neuropsychology and Affect. Davidson, Schwartz, Sero, Bennett, and Goleman (1979) showed lateralized EEG changes occur in normal subjects during periods of reminiscing over happy or sad episodes. Specifically, alpha desynchrony suggested right frontal activation during negative emotion, with left frontal activity during positive affect. Using hypnotic induction procedures Tucker (1981) has produced similar results. He showed right frontal activation with induced depressed mood, but also found a coincident decrease in right hemisphere visuo-spatial processing. Tucker speculated that right frontal activity was inhibitory, supressing coqnition in the right posterior regions. This is consistent with the frontal "disinhibition" syndrome reported by numerous clinical researchers (e.g., Hacaen, 1964; Luria, 1968). Harmon and Ray (1977) found similar hemispheral EEG differences, with EEG power increased in the left hemisphere (relative to the right hemisphere) for listening to accounts of personal events involving positive affect and decreasing power for those involving

negative affect. Lateral eye movements (LEMS), reflecting hemispheric activation contralateral to the direction of the gaze have been used to investigate emotional asymmetries with mixed and highly criticized results (Ehrlichman & Weinberger, 1978). Nevertheless, LEM studies support the hypothesis of right (especially frontal) hemispheral involvement in negative emotions.

Experiments employing lateralized stimulus presentation have supported the notion of affective asymmetries. For example, Beaton (1979) found that music and poetry were judged more pleasant when heard in the left ear (right hemisphere) as compared to the right ear (left hemisphere) when white noise was presented coincidentally (dichotic presentation). Similarly, Carmen and Nachson (1973) reported a left-ear-advantage for non-verbal emotional stimuli. Recently, Ladavas, Nicoletti, Umilta, and Risolatti (1984) described two experiments in which reaction times (RTs) to lateralized visual stimuli were measured during negative affect and during recollection of everyday events. Both experimental procedures increased RT latency over the non-interference control condition. However, during negative affect there was an asymmetrical interference effect, with LVF presentations (right hemisphere) producing longer RTs.

Taken together, these experimental studies reinforce the special role of the right hemisphere in affective processing, especially for negative (i.e., sad) feelings.

Psychiatric Depression and Lateralized Asymmetries. Psychiatric depression and mania are naturally occurring states that provide fairly stable levels of particular affects. Thus, they provide a unique subject pool for assessing neuropsychological theories of affect. This has not been lost upon the research community which has approached affective disorders through a variety of methods including, neuropsychological testing, EEG, AER's, and lateralized perceptual and autonomic responses. Unfortunately, as John Gruzelier (1981) has pointed out in a recent editorial, the neuropsychological study of psychiatric groups is subject to innumerable methodological pitfalls. These include inadequate diagnostic criteria, problems of sampling, inappropriate comparison groups, difficulty in controlling drugs, and difficulty maintaining attention through extensive test batteries.

Flor-Henry (1969) first noted the correlation of particular psychiatric disorders in patients with lateralized temporal lobe epilepsy (i.e., schizophrenia with LH foci and affective disorders with RH foci). This

work was followed by the Flor-Henry (1976) finding of neuropsychological test results consistent with right fronto-temporal dysfunction in patients with affective disorders. A subsequent study employing a research diagnostic criteria confirmed the prior finding of greater right hemisphere (RH) impairment in depressed patients as compared to a group of schizophrenic patients (Taylor, Greenspan, and Abrams, 1979). Several studies suggest that clinical improvement following ECT is associated with improvement on RH sensitive neuropsychological tests (Goldstein, Filskov, Weaver, & Ives, 1977; Kronfol, Hamsher, Digre, & Wiziri, 1978). Unilateral ECT has itself provided evidence of association of right hemisphereinvolvement in depression. For example, Deglin and Nikalcenko (1975) found that while right ECT improved mood level, left ECT increased depressive complaints. ECT produces a generalize convulsion that decreases metabolism temporarily. If RH ECT decreases depression and LH ECT increases it, that suggests that (pre-ECT) the RH maintains depressed mood and that normally the left-hemisphere inhibits RH negative affect biases.

There is considerable disagreement over interpretation of electrophysiological studies of depression (i.e., EDR, EEG, AER). A likely contributor to

inconsistencies may be the associations between particular psychophysiologic response components (e.g., Perris and Monakohv, 1979). Also, lateral differences in electrophysiology are frequently difficult to conceptualize in simple terms such as dysfunction or overactivation. A third problem is the enormous complexity of these data sets. For example, EEG studies frequently employ up to 20 recording sites; with numerous frequency ranges containing significant power, hundreds or even thousands of contrasts and coherence measures are possible. Such studies tax understanding and violate conservative standards of experiment-wide alpha rates.

In a series of EEG studies Perris and his associates (D'Elia & Perris, 1973, 1974; Perris, 1975) consistently found greater alpha desynchrony on the left side (as compared to right) in depressed patients. Differential hemispheral activation, as measured by alpha desynchrony, was correlated with degree of depressed mood (Perris, 1975). This correlation suggests that patterns of lateralized hemispheric activation are directly linked to pathological affect states.

A few studies have presented data on average evoked response (AER) asymmetries in depressed patients. For example, Perris (1974) reported that depressed patients

had lower visual ERP amplitude in the LH than the RH. This effect was more pronounced in psychotic depressives as compared to neurotic depressives. Also, the ERP asymmetry in psychotic depressives was reversed following antidepressant treatment, suggesting that the asymmetries were a state (depression specific) not trait variable. More recently, Perris and his associates (Tueting, Kaskey, Buchsbaum, Connolly, Perris, & Roemer, 1984) reported replicating the ERP amplitude asymmetry finding in a sample of unmedicated depressed patients. However, Perris and Eisman (1980) were unable to show that ERP asymmetries differed significantly between depressed patients and normals.

Several studies have suggested that ERPs to visual, auditory and median nerve stimulation are more variable in the left hemisphere than the RH of depressed patients (Roemer, Shagass, Straumanis, & Amadeo, 1978; Shagass, Roemer, & Straumanis, 1980). Invariant RH ERPs in depressives like increased EEG synchrony, may indicate underarousal of the RH. However, the failure to replicate findings of asymmetrical ERP stability in a large sample of depressed patients (Roemer, Shagass, Straumanis & Amadeo, 1979) is a caution. These ERP studies are all deficient in that they failed to present stimuli in

procedures (e.g., tachistoscopic visual hemifields) designed to stimulate the brain unilaterally.

Since the mid 1970's, Bruder and his associates have studied auditory perception in psychiatric patients. Their interest has focussed on lateralized stimulus presentation in different affective disorders and relationships between perceptual asymmetries and symptom ratings. Yozawitz et al. (1979) first demonstrated a reversal of the normal lateral asymmetry on a non-verbal dichotic listening test in psychotic depressed patients. The non-verbal dichotic listening test developed by Bruder and Yozawitz is unlike other commonly used dichotic techniques, and requires a thorough explanation. Bender and Diamond (1975) demonstrated impaired perceptual resolution of successive clicks in patients with temporal lobe lesions. They found that click resolution was a function of the lesion side (hemisphere) and which ear was stimulated first. Specifically, when the initial click was presented to the ipsilateral (favored) side, poorer resolution resulted for the perception of a dichotic click pair (i.e., a greater interaural delay was necessary for the perception of the contralateral lagging click). Bender and Diamond's method shows patient groups to perform more poorly (e.g., requiring longer intraural

delays) and fails to separate sensory from non-sensory (i.e., response criteria) contributions. Yozawitz, Bruder, Sutton, Sharpe, Gurland, Fleiss, & Costa (1979) used an analogous method and circumvented these problems. They employed a forced-choice measurement of intensity thresholds for the detection of dichotic click pairs.Detection thresholds were measured for two dichotic click conditions. In one, a click was presented to the right ear followed after a delay of 60 msec, by a click to the left ear. In the other dichotic condition, the left ear click preceded the right ear click by 60 msec (see Figure 1). On this dichotic click detection task patients with affective psychotic disorders and right temporally lesioned patients displayed an advantage, for (i.e., needed less intensity to detect) the right ear first (RL) condition. Conversely, normals needed less intensity when the left ear click (LR) occurred first (Yozawitz, et al., 1979).

Subsequent research has replicated and extended the Yozawitz, et al. (1979) findings. Bruder, Sutton, Berger-Gross, Quitkin, & Davies (1981) reported that RDC diagnosed bipolar depressed patients were most likely to show reversed asymmetry and that unipolar depressives were more heterogeneous with respect to this abnormality.

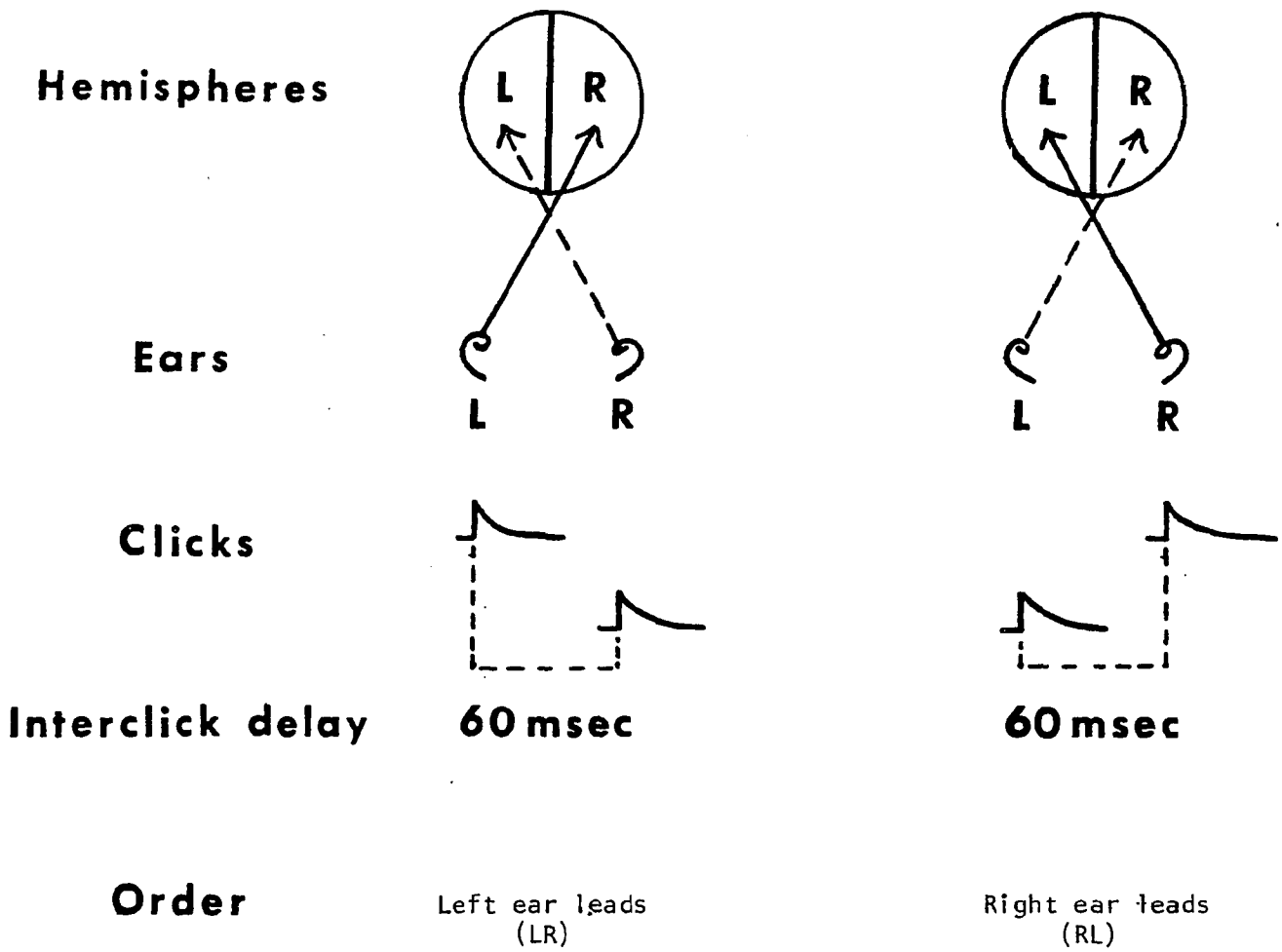


Figure 1. An illustration of dichotic click stimulation and contralateral pathways to the cerebral hemispheres.

Furthermore, greater severity of depressive or endogenous symptoms was correlated with less lateral asymmetry.

Several laboratories have documented a relationship between severity of depressive symptomatology and magnitude of ear asymmetry. Both non-verbal (Bruder et al., 1981) and verbal (Wexler & Heninger, 1979) dichotic listening studies show an association between reduced ear asymmetry and higher symptom ratings of depression. Recovery from depression is associated with normalization of ear asymmetries (Johnson & Crocket, 1982; Moscovitch, Strauss, & Olds, 1981). This suggests that the magnitude of dichotic listening asymmetry, like the previously mentioned neuropsychological test changes, reflect transient, depressive state correlates, not a persistent "marker" of depression (Johnson & Crocket, 1982).

Circadian Rhythms and Affective Disorders

Advances in methodology (Weitzman, Czeiler & Moore-Ede, 1979) and the neurophysiological basis of endogenous rhythms (Block & Page, 1978) have provided the tools and theory necessary for psychiatric research. The importance of periodicity in psychiatric disorders was recognized by Kraeplin (1913) in his Lectures on Clinical Psychiatry. Recent rhythm research on affective illness

has focussed on patterns of interepisodic intervals and intraepisodic chronophysiological anomalies (Corfman, 1979). It is the latter which is of predominant interest herein.

The activity-rest cycle is often disturbed in depressed patients with interrupted sleep at night, and decreased activity during the day, apparent even to the casual observer. More refined measurements show that during mania the length and intensity of activity is much greater than during depression (Wehr & Goodwin, 1979). Activity records accumulated over 1-2 years indicated that the daily activity phase occurs progressively earlier during a depressive episode. The depressed patients also displayed an abnormal activity peak in the evening. Also, temperature minima occurred earlier in the night when individuals are depressed, as compared to when they are in remission (Avery, Wildschiedtz, & Rafaelson, 1982).

What support exists for the theory that abnormal rhythms in depressive illness are more than an epiphenomenon, secondary to symptomatic changes? After all, stress (e.g., Calhoun, 1977) and social factors (Wever, 1975) have induced biochemical phase shifts. Several lines of evidence suggest the primary nature of the rhythm change in depression. One is the elegant

cosinar analysis of longitudinal measurements showing a predictable set of phase changes within an individual across numerous episodes (Wehr & Goodwin, 1979). The second is based on the cycle-specific effects of antidepressant medications. Kripke, Mullaney, Atkinson, & Wolf (1978) showed that manic patients with fast circadian free-running rhythms responded to lithium carbonate therapy with cycle slowing. Two patients with slower rhythms failed to respond clinically or cyclically to lithium treatment. Futhermore, in rapidly cycling (rapidly alternating depressive and manic episodes) bipolar depressed patients, tricyclic antidepressants produce more rapid cycling (Wehr & Goodwin, 1979; Tondo, Laddomado, Serra, Minnoi, & Kukopulos, 1981).

The central pacemaker(s) entraining biological rhythms (e.g., suprachiasmatic nucleus) appears to be resistant to most pharmacological manipulation (Wirz-Justice, Wehr, Goodwin, Kafka, Naber, Marangos & Campbell, 1980); however, Wirz-Justice and her colleagues found that the monamine oxidase inhibitor (clorgyline) and a tricyclic antidepressant (imipramine) slowed cycle frequency in hamsters. They showed that both drugs lengthened the free-running period of circadian rest-activity cycle and delayed the phase position of

circadian rhythms in alpha and beta-adrenergic, cholinergic, dopaminergic, and benzodiazepine receptor binding (receptor number, not apparent affinity) in brain membranes. It is worth noting that the maximal daily peak to trough amplitude of receptor change is of similar amplitude to the changes reported with chronic administration of the aforementioned antidepressants.

Neuroendocrine Rhythms. A variety of endocrine anomalies have been reported in affective disorders. For many of these, including the pituitary hormones cortisol and melatonin, there are interrelated circadian cycles of secretory activity. As appropriate assay techniques have developed, they have been applied in comparisons of rhythms in depressives and normals.

Plasma cortisol level is high in groups of depressed patients and frequently normalized following effective treatment (e.g., Ruben & Mandell, 1966). Recent theoretical formulations concerning cortisol abnormalities have focussed on the biological factors associated with a central hypothalmic-pituitary-adrenal axis (HPA) activity (e.g., Shlesser, Winokur, & Sherman, 1980).

The feedforward endocrine pathway for rhythmic cortisol secretion is well known. Diurnal variation of hypothalmic corticotropin releasing hormone (CRH)

underlies the circadian cycle of ACTH release from the pituitary (Hiroshige & Sakakura, 1971). The release of ACTH, in turn, modulates cortisol secretion. Dense intraindividual sampling has revealed abnormal circadian profiles of cortisol secretion in depressed patients (Sachar, Hellman, Roffwarg, Halpern, Fukishima, & Gallagher, 1973) characterized by cortisol hypersecretion, increased numbers and duration of secretory episodes. Evening cortisol elevation in depressives (as compared to normals) is much more frequent than morning hypersecretion (Wigar, Kolakoska, & Quinlan, 1979), suggesting an alteration of cortisol levels at just about the time (near midnight) that cortisol rhythms are approaching their minima. Kishimoto et al. (1977) failed to find any anomaly of cortisol rhythm in a small sample of (8) depressed patients. However, Kishimoto's conclusion was based on a comparison of group means not individual cycle analyses, and as such, is not particularly useful.

The dexamethasone suppression test (DST), measurements of plasma cortisol levels the day after the steriod is administered, show abnormally early release from suppression in depressed patients. Schlesser and his collegues (1980) showed that early DST release was particularly likely to occur in bipolar depressed patients and unipolar

depressives with a family history of depressive illness, suggesting a biochemical similarity characterized by overactive HPA activity. Similarly, Schatzberg (1983) reports that dysthymic disorders, excluding major depression, are associated with normal DST responses.

Hypothalmic-pituitary-thyroid (HPT) axis dysfunction has also been implicated in depression. Serum thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH) is diminished in depressed patients. This finding has been supported in over 41 studies describing 917 patients and reviewed by Loosen and Prange (1982). The night (2400 h) increase in serum TSH is inversely related to the degree of endogenous depression (Weeke & Weeke, 1978). Weeke and Weeke (1980) argue that diminished night time secretion of TSH is not related to a circadian phase shift; but they support this contention with data recorded for only four patients monitered for one twenty-four hour period.

In addition to anomalous HPT and HPA response, the hypothalamic-pituitary-gonadal (HRG) axis response to leutinizing releasing hormone (LRH) injections is abnormal in depressed patients (Linnoila, Lamberg, & Rosberg, 1979). Growth hormone (GH) responses to insulin-induced hypoglycemia have been found in a smaller proportion of depressed patients (Gruen, Sachar, & Altman, 1975). Early

endocrine studies focussed on individual hormone responses, but in an effort to characterize the mechanism of these numerous response abnormalities, recent studies have recorded basal and challenge levels of several hormones in the same individuals (e.g., Winokur, Amsterdam, Caroff, Snyder, & Brunswick, 1982; Extein, Pottash, & Gold, 1981). These later studies have reaffirmed that few normals have a single abnormal endocrine response while over 90% of unipolar depressed patients have one or more abnormal responses. Unfortunately, no pattern of abnormal levels or response has yet been identified, suggesting that multiple pathophysiological pathways are responsible for the various endocrine findings in depressives. Research on circadian hormone rhythms (other than cortisol) in depressives has been limited to date.

Neurotransmitter Rhythms. Postmortem examination, breakdown product concentrations in CSF, and antidepressant effects have implicated the catecholamines (norepinephrine, NE; and dopamine, DA) and the indole, serotonin (5-HT), in affective illness. For example, 3-methoxy-4-hydroxy-phenyglycol (MHPG), a breakdown product of NE is found in lowered concentration in the urine of depressed patients, and higher concentrations in

mania and remission from depression (Goodwin & Post, 1975). Wehr et al. (1980) studied the circadian rhythm of MHPG in normals and depressed patients. They argued that previous findings of reduced MHPG in depressives (as compared to normals) may be caused by lower production, an earlier phase peak or some combination of the two factors. Their findings of cyclic differences between depressives and normals points to the inherent flaws in single, fixed-time sampling data. Like the previously cited transmitter binding rhythms in animals (Wirz-Justice, et al., 1980), the amplitude of circadian MHPG changes is similar to the level of discrepancy between mean MHPG levels for groups of depressed and normal subjects.

Similar results obtained in a group of manic-depressive patients (Wehr, Muscettola, & Goodwin, 1980). In this study, both normal controls and bipolar depressed patients displayed a daily rhythm of MHPG excretion, with daytime peaks and nightime lows. As before, changes in excretion levels across time of day was at least as great as the pathological changes associated with bipolar disorder. While rhythm patterns between groups were similar, manic-depressives displayed motor, temperature, and MHPG rhythms whose phase was displaced up to three hours earlier compared to the controls.

But do MHPG rhythm alterations reflect a central pathophysiology which may be related to sleep, endocrine mood and cognitive disturbances in depression? After all, monoamine transmitter rates of synthesis are influenced by the availability to the brain of tryptophan and tyrosine (Fernstrom, 1979). Non-pathological events like meal ingestion can modify amino acid availability. Therefore, alterations of meal timing may antedate monoamine transmitter rhythm changes. At least we can be reassured that MHPG urinary excretion rates in depressed patients reliably reflects norepinephrine rates (Linnoila, Karoum, & Potter, 1982). Clearly, complex technical and procedural issues will continue to obfuscate interpretations of clinical transmitter rhythm research.

In addition to the noradrenergic metabolites, serotonergic precursers and platelet serotonin have been investigated for circadian abnormalities in depression. Studying eight endogenous depressives, Kishimoto, Hama, Takeuchi, and Sakai (1977) demonstrated low mean free plasma tryptophan in the morning (8 a.m.) which was apparently related to the most severe mood disturbance of the day occurring at that time. Normal controls showed an 8 a.m. maximum (for free plasma tryptophan) and fell off to a minumum at 4 p.m. Kishimoto et al. collected blood

every four hours between 8 a.m. and midnight, but another study (Malatino, Calandra, Costa, Bongiono, Petrone, & Fiore, 1979) measured typtophan over a 24-hour period. Melatino et al. (1979) observed that plasma tryptophan levels were low during the night in endogenous depressives, while high at the same hours in normals. While intraindividual monitoring across several days is warranted, the early studies suggest a significant distortion of the normal tryptophan rhythms in depressives. Platelet serotonin uptake in depressed patients is a complicated research area. Several studies have reported decreased uptake (e.g., Tuomisto, Tukiainen, & Ahlfors, 1979); others, increased uptake (Oxenkrug, 1979) while still others found no level difference between normals and depressives (e.g., Wirz-Justice & Puhringer, 1978). A more recent study has suggested a circadian rhythm of platelet serotonin uptake in depressives (Rausch, Shah, Burch & Donald, 1982). The small sample size (n = 7) and inadequate numbers of sampling times (4 in one day) lessen the strength of this result.

The pharmacologic effects of tryicyclic antidepressants and MAO-inhibitors has served to focus attention on noradrenergic and serotonergic mechanisms in depression. Nevertheless, Skutsch (1981) has hypothesized

that manic depression is a disorder of a central dopaminergic rhythm. He explains that both manic and depressed patients have abnormal perspiration K+/Na+ ratios. These anomalous anion ratios may result from a disorder of the circadian rhythm of the adrenal glands. Skutsch argues that this would be caused by a distorted central dopamine rhythm perhaps from abnormal responses to ambient temperature changes. Indeed, the normal circadian rhythm of dopamine-beta-hydroxylase is disrupted in mania and the cycle maximum of cyclic AMP is shifted 6 hours earlier (at 8 a.m.) independent of the phase of the illness (Markianos & Lykouras, 1981).

Sleep and Sleep Deprivation

Polygraph recordings of muscle activity (EMG), body temperature, brain electrical activity (EEG) and eye movements are physiological measures used to study sleep architecture (i.e., stages) in depression. Research employing these variables show that major depressions (bipolar and unipolar) result in reduced sleep time, less stage 4 (deep sleep), extended sleep latency, reduced REM latency, increased early sleep REM density, frequent awakening and early morning awakening. During the manic phase total sleep time is further reduced, especially the night prior to the switch into mania, when sleep may

be absent altogether (Bunney, Murphy, & Goodwin, 1972). What is remarkable about the decreased sleep times recorded in manics is the paradoxical increase in waking activity levels.

Reduced REM latency is not confined to depression. However, patients with primary sleep disorders such as narcolepsy and sleep apnea are likely to show sleep onset REM, an unlikely finding with depression (Reynolds, Coble, Kupfer & Holzer, 1982). Schulz and his colleagues (Shulz, Lund, Cording, & Dirlich, 1979) have offered a theory in explanation of REM latency abnormalities in depression. They argue that the REM disturbances may be a function of reduced amplitude of the circadian rhythm of the arousal system. This amplitude dampening would account for the observation that, on the one hand, the behavior and mentation of these patients appear to be slowed down during the day while on the other hand, sleep is shortened and interrupted by many spontaneous awakenings. Thus, a disturbance of arousal rhythms. This would explain overarousal during sleep (Hawkins, 1977) and reduced (EEG) vigilance while awake (Bente, 1976) in depressed patients.

REM sleep periods oscillate with other sleep stages with mathematical precision. Displacement of REM periods

(especially the initial one) represents a disturbance of this oscillatory pattern. Two pertinent questions regarding this rhythm disturbance have been resolved recently. The question of specificity (with diagnosis) has been addressed in a paper by Akisal, Lemmi, Yerevanian, Kings & Belluomini (1982). Monitoring across two nights, REM latency discriminated primary depressives from other pschiatric groups with 88% specificity; no false positives were found amongst the normal controls (Akiskal et al., 1982). Another important question, which may be generalized to variables other than REM latency measures is: Do disturbed behaviors result from abnormal rhythms or do mood disturbed people alter their schedules resulting in rhythm anomalies? The answer with respect to REM latency has been provided by Kupfer and his associates (Kupfer, Gillin, Goble, Spiker, Shaw & Holzer, 1981). They showed that depressed patients had reduced REM latencies during daytime naps (versus normal controls). Furthermore, measures of sleep time and frequency of awakening suggest that endogenous depressives who (will subsequently) respond to tricyclic treatment remain poor sleepers during their daytime naps. Therefore it is not an institutionalized pattern of napping that disturbs night time sleep patterns.

Amitriptyline prolongs REM latencies and increases ease of falling asleep in those depressives who will remit, far before actual clinical remission. If sleep cycle recovery preceeds symtomatic recovery, it suggests that rhythmic disturbances (including sleep disturbance) are central not secondary features of depression. It is possible that mood and cognitive alterations are the secondary disturbances.

The proportion of sleep time spent in REM is generally higher in groups of depressed patients (Vogel, Vogel, McAbee & Thurmond, 1980). Unfortunately, this is a very variable finding which has a peculiarly inverse relationship with ratings of depression severity. Hauri and Hawkins (1971) monitored 9 depressed inpatients (with no history of mania) over 10 to 32 nights; higher REM percentage was associated with reduced clinical ratings of depression. McGinty and Siegel (1983) argue that REM percentage variability reflects desynchronization and resynchronization of circadion oscillators in relation to sleep. They claim that aspects of sleep structure other than stage percentages (e.g., stage coherence and transitions) are more deviant in depressives. Little use can be made of this claim because there is so little theoretical understanding about stage coherence and transitions.

Several circadian rhythm disturbance have been described in affective illness, the most obvious implication of such disturbances were that some direct manipulation of the timing of sleep and waking might have beneficial clinical effects. For example, temporary remission of depressive symptoms have been found with one night's total sleep deprivation (Pflug & Tolle, 1971).

While sleep deprived patients typically report improving status between 3 and 6 a.m. with remission the following day, a relapse generally occurs over the course of the recovery night. Wehr and his colleagues (e.g., Wehr, Goodwin, Wirz-Justice, Craig, & Breitmeier, 1982) carried out sleep derivation in rapidly cycling manic-depressives. The effects were especially noteworthy during the depressive phase, when one night's sleep deprivation resulted (in a majority of patients) in a "switch" into mania or hypomania. The natural history of the "switch" from depression to mania in rapid cycling patients includes uncoupling of endogenous rhythms (temperature and sleep-wake) and a 48 hour sleep-wake cycle. Wehr and colleagues (Wehr, Sack, Rosenthal, Duncan, & Gillin, 1983) argue that sleep deprivation simulates a 48-hour sleep-wake cycle and that the induced depression to mania switches may be a model of the mechanism that causes the "natural" switch.

Sleep-wake cycles and the embedded oscillations of sleep stages are clearly altered in depression. The relationship of these alterations to neuropsychological disturbances has only been broached in a preliminary way (Shipley, Kupfer, Spike, Coble, Neil, & Cofsky, 1981). Its relation to (possibly) rhythmic lateral asymetries of brain function is unknown.

There is also no accepted theory unifying the various disturbances of periodicity in affective illness. Still, cyclic anomalies pervade the depression literature on sleep, endocrinology, and neurotransmitters. The relation between these altered neurophysiologic variables and the mood and neuropsychologic attributes characteristic of depressives remains largely uninvestigated.

Behavioral Rhythms in Normals

Rhythms in Sensory Perception. A wide variety of cyclical behavior has been reported in the psychological literature (see for example, Brown & Graeber, 1982). Circadian and ultradian fluctuations in critical flicker frequency, visual-sensitivity, vigilance, tapping speed, and other simple sensory and psychomotor measures have also been observed (e.g., Froberg, 1977; Rosenwasser et al., 1979; Podnieks & Lovett-Doust, 1975). These rhythmic

changes have been explained in terms of arousal, hemispheric activity cycles and information-processing strategy changes. The wide range of behaviors sampled to date may be responsible for the heterogeneity in time of day functions across studies. For example, evoked potential and psychophysical measures of pain perception have shown an increase in pain sensitivity in the evening (Davis, Buchsbaum, & Bunney, 1978; Rogers & Vilkin, 1978). This change in pain sensitivity is correlated with rhythms of plasma ACTH and may be related to circadian changes in engodenous opiate concentrations. On the other hand, Browman's (1979) study of auditory evoked potentials found that the sensory components of auditory evoked potentials decreased in amplitude in the evening.

Several prior studies of changes in auditory sensitivity as a function of time of day have reported different findings. Blake (1967) found a rise in the auditory detection rate during the day. Blake's procedure was a vigilance task, requiring the identification (i.e., counting) of a low probability "signal" tone randomly presented during a lengthy session of repeated "noise" tones. The tones in Blake's study were fairly loud and easy to detect. Blake studied how well subjects maintained concentration on a lengthy repetitive task as a

function of time of day. This is not necessarily relevant to measures of auditory detection thresholds which measure the minimum stimulus intensity necessary for a subject to detect the presence of a stimulus with a specified probability.

Harris and Myers (1954) and Ward (1964) both claimed to find no diurnal effect on auditory thresholds. Yet, the data reported in these studies appear to suggest otherwise. Harris and Myers employed a method of limits procedure to measure thresholds hourly for 3 frequencies for five days. They reported that at the highest frequency (8192 hz) two of the three subjects had a reliable decrease in sensitivity in the afternoon. Ward also employed the method of limits and a small number of subjects. Ward presented figures (but not statistical analysis) of group mean thresholds at noon and midnight. The mean sensitivity decreased between noon and midnight on 3 of the 4 days. This pattern was <u>not noted</u> by Ward himself. Both of these studies labored under inadequate sample sizes and used classical threshold procedures that confound sensory and decision criterion contribution to stimulus detection. Moreover, their statistical methods would not be considered appropriate at this time. Nevertheless, there is data in both the Harris and Myers

study and the Ward study to suggest a decrease in auditory sensitivity in the evening.

More recently, Browman (1979) reported a reduction in the amplitude of the N_1 - P_2 component of the averaged auditory evoked potential (AEP) in the evening as compared to the morning. It is noteworthy that while these early sensory components (N_1 - P_2) of the AEP changed from morning to evening, a late "endogenous" component that is not modality specific (P_{300}) does not change with time of day (Werner, 1980). Berger-Gross and Bruder (1984) found that sensitivity to monotically presented clicks was reduced in the evening as compared to the morning. There were no differences between the sensitivity for the two ears within or between (morning versus evening) sessions. The correspondence between our behavioral measures and Browman's (1979) AEP's (N_1 - P_2) suggest that morning to evening reduction in auditory sensitivity may reflect changes in physiologic arousal.

Reduced sensitivity for monotic click detection has been reported in affective psychotic patients (Bruder et al., 1980). Given the preceding review, indicating reduced responsiveness in the evening to threshold level stimuli, and biological (e.g., cortisol and activity) studies of rhythms in depression, it may be suggested that

higher (daytime) detection thresholds in depressives were the result of a shift in daily rhythms of auditory perception.

Rhythms of Cognition and Lateral Asymmetries.

Circadian performance rhythms have repeatedly been correlated with the body temperature rhythm (e.g., Blake, 1967). However, recent research has demonstrated that task attributes affect this relationship. Simple repetitive perceptual-motor tasks do demonstrate a high correlation with temperature rhythm, peaking during the late afternoon and evening (Colquhoun, 1971; Blake, 1967). However, those tasks which are cognitively more complex (e.g., verbal reasoning) usually reach performance maxima in the late morning (Monk, Weitzman, Fookson, Moline, Kronayer, & Gander, 1983). Such complex tasks demonstrate a periodicity influenced by both the temperature and basic rest activity cycles. The validity of this multioscillator theory (of biological rhythm influence on cognition) has been supported by shift-work, jet-lag, and temporal isolation induced desynchronization studies. Still other cognitively relevant rhythms are just being charted (Folkard, Wever & Wildgruber, 1983).

Lateralized cognitive rhythms have rarely been reported. Several reports have been published in the area

of EEG sleep. First, Goldstein, Stotzfus and Gardocki (1959) reported a relative increase in EEG amplitude over the right hemisphere during REM sleep as compared to the left. Cognitive cycles corresponding to those interhemispheric EEG changes have now been described (Gordon, Frooman, & Lavie, 1982; Bertini, Violani, Zoccolotti, Antonelli, & Di Stefano, 1984). Gordon et al. found a significant increase in performance levels in the direction of tasks associated with left hemisphere functioning (i.e., digit span, sound sequencing, and word fluency) following waking from NREM sleep relative to waking from REM sleep (when RH tasks, i.e., point localization, closure, and spatial orientation predominated). The hemispheric specificity of these tasks in non-lesioned individuals is controversial. Nevertheless, the findings of Gordon et al., have been strongly supported by Bertini et al. (1984) which shows a shift from left hand (RH) superiority on a tactile recognition test following awakening from REM sleep to no hand difference following NREM awakening. Bertini et al., like Gordon, suggest that these cognitive shifts in hemisphere advantage were related to the REM/NREM cycle, a temporal relation that they believe persisted into the waking (day) period.

A daytime rhythm of relative hemispheric advantage was reported by Klein and Armitage (1979). They demonstrated a 90-minute oscillation of visual matching speed, alternately favoring visually matching letters or abstract dot patterns. This time period (90 minutes) corresponds to the average inter-REM interval. It also corresponds to the period of a number of waking rhythms, including pupillary response, electroencephalographic, urine flow, electrolyte concentration, motor behavior and the perception of visual illusions (Kripke, 1972; Lavie, 1972, 1976, 1979; Lavie, Lord & Frank, 1974).

Bruder and his associates have documented sensory, psychomotor, and lateralized disturbance in the processing of auditory stimuli amongst depressed patients. Perhaps the most interesting of these findings has been the evidence suggestive of right hemisphere dysfunction in the performance of depressed patients on a measure of dichotic click detection (Yozawitz et al., 1979; Bruder et al., 1981). The avalanche of recent papers linking clinical and biochemical aspects of depression to circadian rhythm disturbances made us consider the possibility that evidence of altered right hemisphere function (on dichotic click testing) might represent a time-of-day aberration in depressives. Therefore, in advance of embarking on a

study of diurnal changes in depressed patients, we carried out a study of diurnal changes in dichotic asymmetries in normal volunteers (Berger-Gross & Bruder, 1984, see Appendix 1).

In this study, the threshold asymmetry for detecting dichotic clicks shifted from morning to evening (Berger-Gross & Bruder,1984). As in previous studies (Bruder et al., 1981; Yozawitz et al., 1979), the normal subjects displayed a greater sensitivity for the LR condition than the RL condition during the morning. In the evening, however, the asymmetry shifted in the direction of that found previously for right handed depressed patients during the day (Yozawitz et al., 1979; Bruder et al., 1981). This suggests the intriguing possibility that the altered dichotic click asymmetry for depressed patients may be related to the hypothesized timing advance in their circadian patterns (Wehr et al., 1980). In contrast to the results with non-verbal stimuli, dichotic CV syllable asymmetries did not vary between the morning and evening session (Berger-Gross et al., 1984).

Research into morning to evening shifts of lateralized performance with the exception of Berger-Gross et al. (1984), appears to be nonexistent in the published literature. However, Mary Parlee (personal

correspondence, 1983) has found time-of-day effects on finger tapping speed that differ between the right and left hand. This suggests that fine motor speed may (like dichotic click detection) depend upon some lateralized hemispheric process that changes from morning to evening.

Broughton's (1982) recent review argues that ultradian and diurnal cognitive cycles, like those reviewed in this section, may be related to sleep/walking rhythms and are of theoretical and clinical relevance to neuropsychology. Certainly daily lateralized performance shifts merit investigation in depression, a psychiatric disorder that is manifested clinically as a disturbance of normal sleep patterns and altered waking activity levels.

Diagnostic Issues

Until recently research in psychiatric disorders has suffered from a lack of agreement upon diagnostic criteria. Vastly different subject samples made comparisons from study to study difficult. The acceptance of standardized Research Diagnostic Criteria (RDC), while hardly ending nosological controversies, goes far in rectifying difficulties in study comparability. For even if one disagrees with part of a set of objective diagnostic criteria, the patient sample is at least

adequately described. Clinical diagnosis in the form of the American Psychiatric Association's DSM III (APA, 1983) has also benefited from the behavior-based criteria first appearing in the RDC's.

The patients in this study all received DSM III and,in most cases, RDC (Spitzer, Endicott & Robbins, 1978) diagnoses. This means they were divided according to behaviorally anchored criteria rather than with unsubstantiated etiologic or metapsychological criteria. Several subdiagnoses of major depressive disorder have been found to be relevant in psychobiological studies. For example, primary and endogenous depressions are more frequently associated with abnormal DST results than are reactive (e.g, secondary) and non-endogenous depressives (Carrol, Feinberg, Steiner, Haskett, James, & Tarika, 1981;Brown & Sheuy, 1980). Delusional depressives respond poorly to tricyclic antidepressants (Charney & Nelson, 1981). Bipolar depressed patients are more likely than unipolar depressed patients to show abnormal dichotic listening asymmetries (Bruder et al., 1981). The greater frequency of affective disorder in the relatives of bipolar patients (versus unipolar patients) was not upheld when RDC (Feighner, Robins, & Guze, 1972) were applied to a large sample (Winokur, Tsuange, & Crowe, 1982).

The vegetative features of endogenous depression (ED) such as sleep and activity disturbances might be expected to be associated with rhythm anomalies that are related to the basic sleep-wake cycle. Those ED patients displaying diurnal variations of mood, in particular, might be more likely to show a disturbance of circadian patterns when compared to nonendogenous (ND) patients. Nevertheless, any hypotheses regarding specific subtypes or symptoms and their role in perceptual cycles must be considered extremely speculative at this early stage of research. For that reason, we adopted a dual strategy. First, morning to evening changes are compared across ED and ND subgroups. Second, a variety of symptom variables, assessed objectively on either of two semi-structured interview schedules (i.e., the Hamilton Rating Scale for Depression or the Schedule for Affective Disorder and Schizophrenia; SADS, Endicott & Spitzer, 1978), will be compared across ED and ND subtypes and correlated with the laterality and performance variables measured in the morning and evening.

The Plan and Purpose

Monotic and dichotic click detection and dichotic CV syllable perception will be assessed in ED and ND

depressives in a morning and evening session in a similar manner as the Berger-Gross and Bruder (1984) study of normal adults. This will allow us to describe the nature of morning-evening shifts in auditory sensitivity and cognitive asymmetries in depressives, to test diagnostic (ND vs. ED) subtype differences, and to make inferences about hemispheric changes in affective disorders. Two other "auxillary" measures not employed in the Berger-Gross study, the Klein and Armitadge visual matching task and Purdue Pegboard, will be administered when patients are cooperative and as time allows.

We will attempt to support our hypothesis that depressives will show a shift between morning and evening in hemispheric advantage for detecting dichotic clicks that differs from that previously described for normals. Furthermore, abnormal dichotic click asymmetries (RH deficits) and anomalous morning to evening asymmetry shifts (reduction in RH deficit from morning to evening) are hypothesized to be related (correlated) with clinical variables whose circadian pattern is thought to be disturbed in depression (e.g., sleep variables, cortisol levels, and measures of diurnal mood swings). Conversely, cognitive variables that are static with respect to time of day (especially dichotic CV

asymmetries) may be related to measures of depression severity (see e.g., Wexler & Heninger, 1979), but should not correlate with symptoms, neuroendocrine levels and sleep variables that have a basis in daily rhythms.

We anticipate replicating decreased sensitivity for clicks in this depressed sample, however it is not clear how this might be related to abnormal rhythms of hemispheral advantages. The change in monotic thresholds from morning to evening, left versus right ear differences as a function of time of day, and clinical variable correlations may provide some insights into the basis of (previously reported) threshold increases in depressives.

The study of visual matching and Purdue Pegboard speed is exploratory (rather than hypothesis-testing oriented). We hope that these quick measures, known to yield lateralizing information, may contribute to the investigation of circadian rhythm disturbance and its correlates in clinical depression.

II. METHOD

Subjects.

Subjects were 27 patients at NYS Psychiatric Institute who were diagnosed as having an affective disorder (currently in the depressed phase). The basis for diagnosis was both the American Psychiatric Associations' Diagnostic and Statistical Manual, third addition (DSM-III, 1982) and RDC (Spitzer,Endicott & Robins, 1978). Only patients who were 60 years old or less, and had no relevant medical or neurologic disorder were tested. Demographic characteristics of the patients are listed in Table 1. Table 2 shows the DSM-III and RDC diagnoses for each patient. The DSM-III and RDC diagnoses were done by research psychiatrists in the Depression Evaluation Service (NYSPI), all of whom had extensive experience in interviewing and diagnostics. Both inpatients and outpatients were used.

Patients were unmedicated for at least 7 days prior to testing. All the patients were right handed as determined by their Laterality Quotient (LQ) on the Edinburgh Handedness Inventory (Oldfield, 1971). All patients admitted with a provisional diagnosis of major affective disorder were asked to participate in the study. They were informed of the general nature of the

Table 1. Characteristics of patients

	Endogenous	Nonendogenous
N		
Males	7	6
Females	9	4
Age (years)		
$\bar{X}$	36.3	34.1
SD	10.2	10.4
Education (years)		
$\bar{X}$	14.9	15.4
SD	2.2	1.6
Handedness (LQ)		
$\bar{X}$	83.8	91.8
SD	15.8	10.6
Hamilton Depression Scale Scores		
$\bar{X}$	27.2	14.2
SD	7.5	5.8

TABLE 2

INDIVIDUAL DSM-III AND RDC DIAGNOSES

SUBJECT	DSM III DISORDER	RDC DISORDER	SUBTYPES
1	MAD	BII, MDD	ED, secondary, retarded, psychotic
2	MAD	MDD	Primary, retarded, psychotic alcholism
3	MAD	MDD	Secondary, recurrent, alcoholism
4	Other Specific Affective Disorder	BI - Min DD	Cyclothymic
5	MAD	MDD	ED
6	MAD	BI, MDD	Primary, retarded, simple
7	Atypical Affective	----------	
8	MAD	BII, MDD	Agitated, primary, situational
9	MAD	MDD	Secondary, recurrent, psychotic anxious
10	MAD	MDD	Situational, primary, simple
11	Atypical Affective	----------	
12	Atypical Affective	Other Psychiatric	Drug use disorder, phobic
13	MAD	Unspecified Functional Psychosis	Phobic
14	MAD	MDD	Recurrent
15	MAD	MDD	Secondary, recurrent, alcoholism

TABLE 2

INDIVIDUAL DSM-III AND RDC DIAGNOSES (CONT.)

SUBJECT	DSM III DISORDER	RDC DISORDER	SUBTYPES
16	MAD	MDD	Primary
17	MAD	MDD	Simple, primary
18	Schizoaffective	Schizoaffective	Depressed
19	MAD	MDD	Primary, simple
20	MAD	MDD	Primary, recurrent, agitated anxious
21	MAD	MDD	
22	MAD	MDD	Atypical
23	MAD	MDD	Secondary, recurrent, retarded, drug use
24	MAD	MDD	Atypical, primary
25	Other Specific Affective	Int. D.D.	Dysthymic
26	MAD	BI, MDD	
27	MAD	BII, MDD	Primary, psychotic, agitated

Key:

MAD	Major Affective Disorder
MDD	Major Depressive Disorder
BI	Bipolar Depression with Mania
BII	Bipolar Depression with Hypomania
Min. DD	Minor Depressive Disorder
Int. DD	Intermittent Depressive Disorder
ED	Endogenous

study, that testing was not physically harmful, their participation was irrelevant to their treatment, their performance would remain confidential, and that they could withdraw from the study at any time. Participating subjects signed an informed consent form which had been approved by the hospital's institutional review board.

Not all patients were tested on both the verbal and nonverbal tasks, as some patients were not available for the amount of time necessary to complete both tasks in either the morning or evening session. There were three ED patients and one ND patient who were not tested on the click detection task, and two ED patients and one ND patient were not tested on the CV syllable task. The loss of these patients from the ED and ND samples did not alter the subject characteristics given in Table 1 for the total samples.

Apparatus

Monotic & Dichotic Click Detection. Patients were tested in a sound attenuating booth that was situated in the middle of a room lined with acoustic tile. The click stimuli were shaped by negative-going saw tooth electrical pulses with exponential return to base. The decay time constant, i.e., the time required to reach 1/e of peak

amplitude was 0.1 msec. The rise time was .0125 msec. A switch steered pulses to the right or left channels (for monotic presentation) or both channels (for dichotic presentation). Two Hewlett-Packard atteruators (5-N, 60052) adjustable in 1 db steps over a range of 110 db were used to manipulate pulse intensity independently for each channel.

Dichotic clicks were produced simultaneously in the separate channels. Subsequently one click was delayed by 60 msec as per Figure 1 by a crystal controlled timer (local design) calibrated with a systron Donner counter ($\pm$.05%). The shaped electrical pulses were transduced as clicks by a pair of Sharpe circumaural head phones (HA-10, MKII).

A Bruel and Kjoer condenser microphone (1/2 inch) mounted in a flat lucite coupler was used to calibrate output at the headphone in db (peak equivalent SPL). Details of the procedure are specified by Deatherage and Hirsh (1959). Care was taken to monitor the peak right and left channel voltages to each phone, pulse configuration and interclick intervals (for dichotic clicks). Oscilloscope pictures of the rarefaction clicks transduced by each earphone, particulars of the various calibration procedures, and diagrammatic representation of

the apparatus are described in detail by Yozawitz (1978).

Dichotic Consonant Vowel (CV) Perception. A Tandberg stereo tape deck (3500 X) was used to play a pre-recorded stero tape. The recorded material consisted of natural consonant-vowel syllables (e.g., Ba, Ta, Pa) provided by Dr. Charles Berlin (Berlin et al., 1973). The voltage outputs from the right and left channel of the tape deck were separately attenuated by two Hewlett-Packard attenuators (3500). Attenuation was provided over a range of 110 db; each channel could be adjusted in 1 db steps. The output from the attenuators was further modified by a 60052 termination resistor. Following attenuation, the two channels were independently amplified by a Kenwood stereo integrated amplifier (Model KA-4006) and transduced as CV's by a set of matched Sharpe circumaural earphones (model MK-II-S). A diagram of the CV presentation equipment may be found in Yazowitz (1978). Voltage output to the phone was monitored before each session on an RMS meter. Appropriate changes in attenuation were made to insure equal level of 67 db SPL in each channel. The output from these phones was calibrated in a similar manner to that described for the click apparatus.

The three different response sheets each consisted of 30 sequentially numbered lines; each line contained all of the 6 possible stop consonant-vowel pairs (i.e., ba, ga, da, pa, ka, ta). The order of the CV pairs within each numbered trial "line" was randomly determined. A copy of a response sheet can be seen in Appendix 2

Auxillary Tasks

Purdue Pegboard: A Purdue Pegboard was obtained from the Lafayette Instrument Company. The pegboard consists of 1/2 x 12 x 18 inch thick pressed wood board with two vertical rows of 25 indentations and metal pegs which fit them. The pegs are held in two circular troughs above the rows of indentations. This board was similar to those described elsewhere (Purdue Research Foundation, 1948).

Visual Matching Materials. Three hundred different response sheets were provided by Drs. Klein and Armitage (see Klein & Armitage, 1979). Each sheet contained either 48 randomized pairs of letters (one upper case, one lower case) or 48 randomized pairs of dot patterns. A sample of the dot and letter response sheets appears in Appendix 3.

Procedures

Each patient was tested during a morning session (between 8:00 and 11:30 AM) and an evening session (between 4:00 and 7:30 PM). The order of the sessions was counterbalanced across the total sample of patients such that alternate patients were tested initially either in the morning or evening.

Monotic & Dichotic Click Detection. A three-interval temporal forced-choice procedure was employed to assess auditory sensitivity for monotic and dichotic clicks. The advantages of the three-interval forced choice technique, compared to the classical yes no procedure for assessing sensitivity, is that it yields sensitivity measures without confounding by response criterion (Green & Swets, 1966; Clark, Brown & Rutschmann (1967). The clicks were presented in one of three observation intervals and the S had to indicate which of the intervals contained the signal by pressing one of three response buttons.

The following sequence of events occurred for each trial. A 0.5 sec. duration red light signalled the S that E was ready. The S would then initiate each trial by pressing a round button, which produced another red light, signaling the beginning of the trial. After 3.6 sec.,

three red lights were presented in temporal sequence, 0.5 sec. on and 0.7 sec. off. Each auditory signal was presented 0.1 sec. after the onset of one of the three lights which demarcated the observation intervals. The S indicated his choice of which one of the observation intervals contained the signal by pressing one of three square response buttons. When a S made a correct choice, a blue feedback light was presented.

A Block-Up-and-Down-Two Interval Forced-Choice stepping procedure (BUDTIF) (Campbell & Lasky, 1968) was adapted for use in this study. The utilization of this procedure permits an accurate estimation of the signal intensity needed for 67% correct rsponses (50% adjusted for chance) in the three-interval forced-choice task. Campbell (1963) suggested that such a procedure might quickly provide information comparable in precision and magnitude to that obtained through the implementation of more exhaustive experimental procedures.

A constant signal intensity was used during each block of three trials. The signal level used in a block was determined by the S's performance in the prior block according to the following stepping rules.

0 or 1 correct - increase the signal intensity level for the next block of trials;

2 correct - maintain the same signal intensity level for the next block of trials;

3 correct - decrease the signal intensity level for the next block of trials.

At the initiation of the monotic threshold measurements, the signal intensity levels were set at approximately 60 db SL (sensation level). This high level of signal intensity was maintained until the E was convinced that the S was accurately performing the task (by achieving a level of 100% correct detections in both ears). The signal intensity was then reduced in 5 db steps per trial until the first incorrect response was recorded. From that point, the conventional blocking rules, which were previously described, were invoked. Signal intensity was adjusted according to these blocking rules in 5 db steps to achieve a bracketing of the S's threshold. Trial blocks were randomly alternated between ears with the constraints that no more than two blocks in a row were presented to one ear and that in every 8 blocks there were an equal number of right and left ear blocks.

After the S was presented with a fourth block at the same level of signal intensity, the stepping size was reduced to 1 db. The same blocking rules governing this procedure continued until the S was again presented with a fourth block at the same level of signal intensity. The median of all the revisited signal intensities, in db attenuation, was recorded as the threshold estimate. Subjects whose single click thresholds were 20 db or more above our normative standard or who had an ear difference of greater than 10 db were excluded from the study.

A second procedure, capable of concurrently yielding four independent threshold estimates was initiated. This procedure used blocking and a stepping size of 1 db, beginning from the previously determined monotic threshold level of signal intensity for each ear. S's were instructed to listen carefully for the faint click that they heard at the conclusion of the prior test period. They were told to listen carefully to both ears. This second procedure entailed four threshold measurements, consisting of single click determinations for each ear and dichotic click determinations for each ear leading condition (see Figure 1), i.e., right-left (RL) and left-right (LR) independently charted as four separate staircases. Each of the four staircases was randomized

across blocks of trials with the constraint that each dichotic ear lead condition be presented twice and each monotic condition once within every sequence of 6 blocks. This prevented any one staircase from inordinately suffering the effects of any momentary shift in sensitivity or attention. All staircases were continued, utilizing the blocking rules which were described earlier, until the last of the four staircases reached the point where a block was presented for the fifth time (not necessarily congruently) at the same intensity level. The threshold estimate for each staircase, in dB attenuation, was taken as the median of all signal levels revisited during the measurement of that staircase.

Since the dichotic click procedure was begun at threshold levels for each ear, the stability of each of the four staircases was carefully monitored to assure that the S was accurately performing the task. Each staircase was continued for a minumum of 10 blocks. All four staircases were discarded if the single click thresholds, which had been equated prior to each session, were divergent by 3 dB or more at the conclusion of a session. Two patients who were unable to perform this task adequately were discontinued from the study; one other patient had to be retested the next evening.

Dichotic CV Syllable Perception. Subjects received 16 monaural trials (8 to each ear). They were required to achieve 87% accuracy in each ear (to assure normal speech sound discrimination) on the monaural trials. Fourteen dichotic practice trials were followed by 3 "blocks" of 30 dichotic test trials for a total of 90 test trials per session. Each block of trials was followed by a 2 minute rest period. Patients were required to use a pencil to cross off two of the 6 CV choices that appear on the response sheets for each trial. Dichotic CV trial presentations consisted of two CV's presented simultaneously, one (CV) to the right ear and one to the left. Trials were separated by a 3 second silent interval. Other procedural details were consistent with Berlin et al. (1973).

Auxillary Tasks: Purdue Pegboard. Subjects placed 10 pegs in the Pegboard with each hand for practice. Then they were told to place pegs in the right vertical row with their right hand as quickly as possible, 30 seconds were allowed. Thirty seconds were allowed for peg placement in the left vertical row with the left hand as well.

Auxillary Tasks and Visual Matching Task. Subjects were asked to circle "S" for stimuli that matched and "D"

for those that did not. Following 24 practice trials with the letters, subjects were asked to perform the visual letter matches as quickly as they could for 5 minutes. The procedure for the dots was identical, 24 practice trials followed by 5 minutes of testing.

Clinical Research Variables

Sleep Procedures. Subjects admitted to the Sleep Unit at the NY State Psychiatric Institute remained for one to three days (generally, at least 2) during which time their sleep was polysomnographically recorded for each night.

Electrode placement for a standard polysomnographic recording (Rechtschaffen & Kales, 1968) was carried out one hour before their stated bedtime. Skin was cleaned with alcohol, and electrodes were applied with electrode gel and kept in place by electrode paste (scalp electrodes) or adhesive collars (face electrodes). Ten electrodes were placed for each night: 2 scalp electrodes (C_3 and C_4), 2 mastoid (A_1 and A_2), three periocular (ROC, LOC, and right superior) 2 chin and one ground (nasium). Seven polygraph channels were recorded: C_3 to A_1A_2, C_4 to A_1A_2, ROC-A_1, LOC-A^2, LOC-ROC, RS-ROC, RM-LM.

Subjects were allowed to sleep ad lib. They requested lights out when they chose to and were not

awakened until they spontaneously awoke. In a few cases where the subject had not awakened by 8:30 a.m. after the 2nd night, he/she was awakened for the intravenous catheter placement (see Endocrine Procedures).

During the night, if the polygraph indicated that an electrode was not functioning, an attempt was made to replace it without awakening the subject. All recordings were made at 10 mm/sec using Grass polygraph models 78D or 8, which were calibrated every evening prior to actual recording and again the morning following a night of recording.

A 2-way intercom connects the subject's room to the control room and allows for bi-directional communication throughout the night.

Sleep records were scored by a highly trained sleep researcher (Ray Goetz) for 60 second epochs, using Rechtschaffen and Kales methods (968). Each sleep record is paginated 001 to 1000, with each page representing 30 seconds in actual time. Each page of the polysomnographic recording was assigned a stage number: stage awake = 0 /stage 1 sleep = 1/stage 2 sleep = 2 / stage 3 sleep =3 / stage 4 sleep = 4 / stage REM sleep = 5/ missing data = 6 / body movement = 7. The epoch by epoch data was entered onto a computer archive stored on computer disk and

magnetic tape for subsequent analysis. Eye movement activity during REM sleep was scored in 60 second epochs

The following list provides definitions of all the sleep variables that were used in correlations with our experimental measures (i.e., dichotic, monotic, Purdue, and matching). Total sleep time: total time spent in stages 1 through 5 sleep during sleep period time. Sleep latency: time from lights-out until sleep onset. Sleep efficiency: the percentage of sleep-period time spent asleep. REM efficiency: total time divided by total of REMP times, multiplied by 100%. REM cycle length: time from the midpoint of an REMP to the midpoint onset of the first REMP. REMP latency: time from sleep onset to the onset of the first REMP. Vogel's r: a measure of temporal distribution of REM sleep; the Pearson's correlation of each REMP's length with the duration of all non-REMP sleep preceding the REMP.

Endocrine Procedures. The endocrine procedures varied in number of daily samples, hormones sampled, and site of sample collection according to which research project the individual patient was enrolled in. However, sample collection and assay methods were equivalent across the research projects.

In order to collect hormone samples, an Angiocath heparin lock was inserted in the antecubital vein. Blood samples (1.5 ml) were drawn for cortisol determination every half-hour for a period of 24 hours (beginning at 8 a.m), 12 hours (beginning at 9 a.m.), or 3 hours (from 1 to 4 p.m.). Plasma was separated promptly by centrifuge and stored at -20°C for hormone assay. Cortisol was assayed by a competitive protein binding procedure described by Novacenko, Halpern, & Sachar (1980). For correlation purposes, the following variables were constructed: average morning cortisol (8-1 am), average afternoon cortisol (1-4 pm), and average evening cortisol (6-9 pm).

DST responses to 1 mg dexamethasone administered at 11 p.m. was assessed the following day at 4 and 11 p.m. Five hundred micrograms of thyrotropin-releasing hormone was administered, then bloods were drawn at half hour intervals between 0 and 10:30 a.m. Thytrotropin-stimulating hormone (TSH) and prolactin (PRL) were assayed in each of these samples (following TR4). TSH assays were carried out by a double antibody radioimmunoassay technique with ammonium sulfate precipition (Loosen & Prange, 1982).. PRL was determined

by a double antibody radioaimmunoassay technique, using ^{125}I-prolactin and PRL standard (Winokur et. al., 1982).

All hormone samples were assayed in duplicate. Intra-assay coefficients of variation (for PI's entire research sample) ranged from 2.2% for cortisol to 7.1% for PRL.

III. RESULTS

Monotic Click Detection

A four-way analysis of variance with one grouping factor and three repeated measures was carried out. The one grouping factors was diagnosis (i.e., endogenous versus non-endogenous). The three repeated measures were ear of presentation (i.e., left versus right), two separate thresholds determinations (factor referred to as repetition) and morning session versus evening session (time of day). Table 3 summarizes the results of this ANOVA. None of the main effects (i.e., diagnosis, ear difference, repetition, and time-of-day) reached significance ($p > .05$). Only the three-way interaction, Time-of-Day X Ear Difference X Diagnosis, was significant ($F = 5.54$; $df = 1/20$; $p = .0289$). The lack of a significant repetition effect indicates no significant practice effects on detection levels and the reliability of the threshold procedure.

The nature of this interaction is not simple; therefore the effect is not completely elucidated by Figure 2. However, a post-hoc statistical analysis of the interaction reveals two signficant underlying effects. The difference between the left and right ear thresholds (i.e., less sensitive left ear) was significantly greater

Table 5

Four-way ANOVA for the monotic click detection of Endogenous and Nonendogenous depressives

Source	Degrees of Freedom	Mean Square	F	2 - Tail Probability
(ED/ND) Diagnosis (Dx)	1	36.306	0.28	*NS
Error	20	129.831		
Ear Difference (E)	1	39.618	2.84	NS
A X Dx	1	20.484	1.47	NS
Error	20	13.928		
Time (T)	1	2.078	0.32	NS
T X Dx	1	15.982	2.45	NS
Error	20			
T X E	1	3.884	2.94	NS
T X E X Dx	1	7.306	5.54	.0289
Error	20	1.319		
Repitition (REP)	1	3.613	3.47	NS
REP X Dx	1	3.584	3.44	NS
Error	20	1.041		
T x REP	1	0.007	0.06	NS
T X REP X Dx	1	0.423	0.29	NS
Error	20	1.472		
A X REP	1	0.044	0.14	NS
E X REP X Dx	1	0.196	0.61	NS
Error	20	0.320		
T X E X REP	1	0.016	0.03	NS
T X A X REP X Dx	1	0.620	1.11	NS
Error	20	0.561		

* NS : NOT SIGNIFICANT

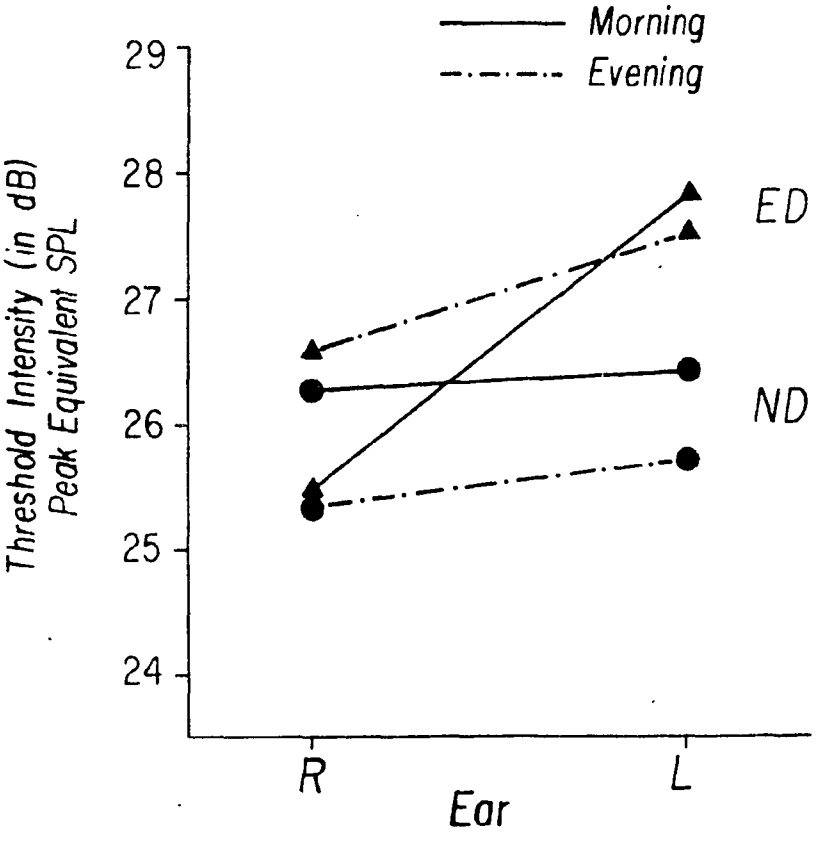


Figure 2. Mean threshold intensitities for monotic clicks as a function of diagnosis and time of day.

in the endgenous patients as compared to nonendogenous patients in the morning (Newman-Keuls, $p < .05$). Also, this ear difference (less sensitive left ear), which was large in the endogenous depressives in the morning, was significantly reduced in the evening, i.e., less difference between right and left ear sensitivity for ED depressives in the evening as compared to morning (Newman-Keuls, $p < .05$).

Dichotic Click Detection.

A three-way ANOVA was carried out on the dichotic click detection thresholds (Table 4). The analysis included one grouping factor (i.e., diagnosis) and two repeated measures (i.e., ear order and time-of-day). The ANOVA did not show a difference in sensitivity between the two orders of click presentation (right ear first: RL; left ear first: LR) or between ED and ND groups. While time-of-day did not significantly affect performance level (threshold sensitivity) it did interact significantly with the ear order factor ($F=10.55$; $df=1/20$; $p=.004$). No other interactions reached significance.

Figure 3 clearly displays the aforementioned interaction. Both the endogenous and nonendogenous groups were more sensitive (i.e., less intensity required) in the RL condition as compared to the LR condition in the

TABLE 4.

Three-way ANOVA for the dichotic click detection of ED and ND depressives.

Source	Degrees of Freedom	Mean Square	F	2 - Tail Probability
(ED/ND) Diagnosis (Dx)	1	38.397	0.63	*NS
Error	20	60.969		
(RL/LR) Ear Order (O)	1	0.006	0.02	NS
O X Dx	1	0.152	0.54	NS
Error	20	0.280		
Time-of-Day (T)	1	0.174	0.04	NS
T X Dx	1	0.75	0.02	NS
Error	20	4.023		
T X O	1	2.926	10.55	.004
T X O X Dx	1	0.026	0.09	NS
Error	20	0.277		

* NS : Not significant

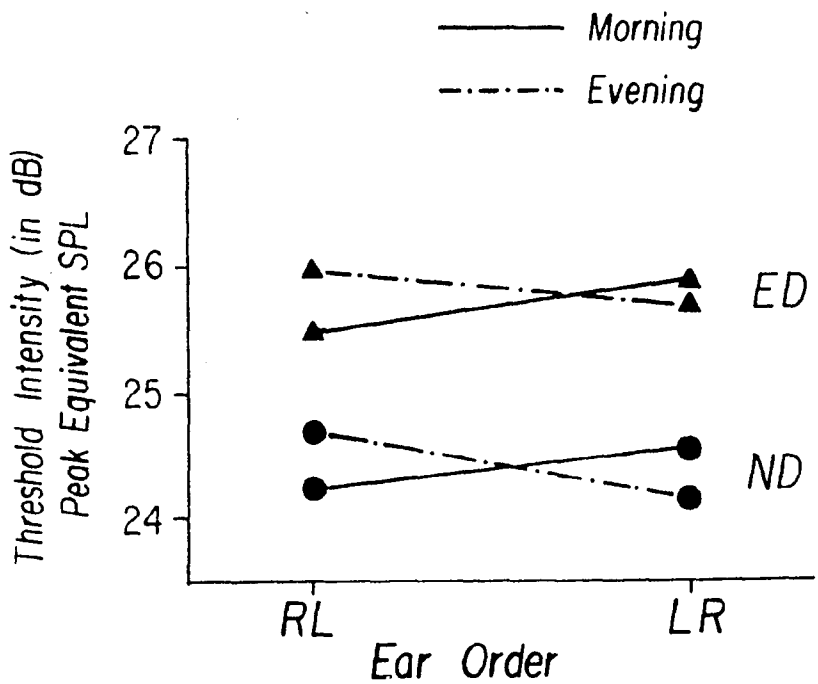


Figure 3. Mean dichotic click threshold intensities as a function of ear order, diagnosis, and time of day.

morning, and less sensitive in the RL condition as compared to LR condition in the evening. As with the left ear monotic thresholds, the mean sensitivity of endogenous depressives in both dichotic conditions appears to be reduced compared to nonendogenous depressives. However, this difference is not statistically significant.

A series of correlations between the dichotic and monotic thresholds is shown in Table 5. These correlations are extremely large, indicating the high level of reliability of the threshold measures. Note also that left monotic thresholds correlate equally with both dichotic click (ear order) conditions in morning and evening. This suggests that the time-by-ear order interaction in the dichotic click ANOVA is not merely another expression of the left monotic threshold differences between groups or sessions. The same conclusion, that monaural threshold levels do not affect the dichotic click asymmetries, is supported by the low, non-significant correlations between monotic thresholds and the difference between the RL and LR conditions (dichotic click asymmetry).

TABLE 5. CORRELATIONS BETWEEN MONAURAL AND DICHOTIC CLICK THRESHOLDS.

		DICHOTIC THRESHOLDS		
		RL	LR	ASYMMETRY (RL - LR)
AM (n=23)	Right Mono.	.84*	.84*	-.19
	Left Mono.	.92*	.91*	-.25
PM (n=22)	Right Mono	.88*	.88*	-.26
	Left Mono.	.88*	.89*	-.27

* Correlations significant at p=.001 level.

Dichotic CV Syllables: Total Discrimination

A two-way ANOVA with one grouping (i.e., diagnosis) factor and one repeated measure (i.e., time-of-day) was carried out on the accuracy of CV discrimination (total percent correct). This measure was the sum of the percent single right and left correct trials plus two times the percent of trials with two correct responses ("double corrects"). This total discrimination reflects the depressive patients' level of performance on this verbal discrimination task. There was no significant effect in the CV total discrimination ANOVA (Table 6). The morning and evening mean total percentages for endogenous and nonendogenous depressives were remarkably similar (see Table 7).

Table 6.

Two-way ANOVA of the total CV percent correct in the morning and evening

SOURCE	DF	MEAN SQUARE	F	TWO-TAILED P
(ED/ND) Diagnosis(Dx)	1	218.91	0.27	*NS
Error	21	813.55		
Time (T)	1	48.32	0.31	NS
T X Dx	1	0.99	0.01	NS
Error	21	156.48		

* NS : NOT SIGNIFICANT

Table 7.

Mean total CV percent correct
in the morning and evening

		ED	ND
Morning	$\bar{X}$	118.7	114.5
	Sd	21.6	14.0
Evening	$\bar{X}$	116.9	112.1
	Sd	25.6	23.0

Dichotic CV Syllable Asymmetry

A three-way ANOVA with one grouping factor (i.e., diagnosis) and 2 repeated measures (ear and time-of-day) was carried out on the "single correct" CV trials (see Table 8). The "single correct" trials were those in which the subject correctly identified either the CV presented to the right ear or the one presented to the left ear. Trials in which neither or both CV's were identified correctly do not contribute to ear asymmetry and therefore were not included in this analysis. Endogenous and nonendogenous depressives had no significant difference in the number of single correct CV identifications. Time-of-day did not have any relation to the rate of single CV identification, nor were there any significant interactions involving any of the three factors (i.e., diagnosis, ear, time-of-day). Only the ear factor, which tests for a difference between the number of right and left single correct trials, produced a significant F test ($F = 17.97$, $df = 1/20$, $p = .0004$). Figure 4 shows that right ear single corrects are predominant (REA) in all diagnostic and time conditions.

Table 8

Three-way ANOVA for the single CV correct trials of ED and ND depressives in the morning and evening.

Source	Degress of Freedom	Mean Square	F	Tail Probability
(ED/ND) Diagnosis (Dx)	1	42.246	0.33	*NS
Error	21	128.231		
(E)	1	5431.422	17.97	0.0004
E X Dx	1	1.983	0.01	NS
Error	21			
Time (T)	1	9.406	0.46	NS
T X Dx	1	0.605	0.03	NS
Error	21			

* NS = not significant.

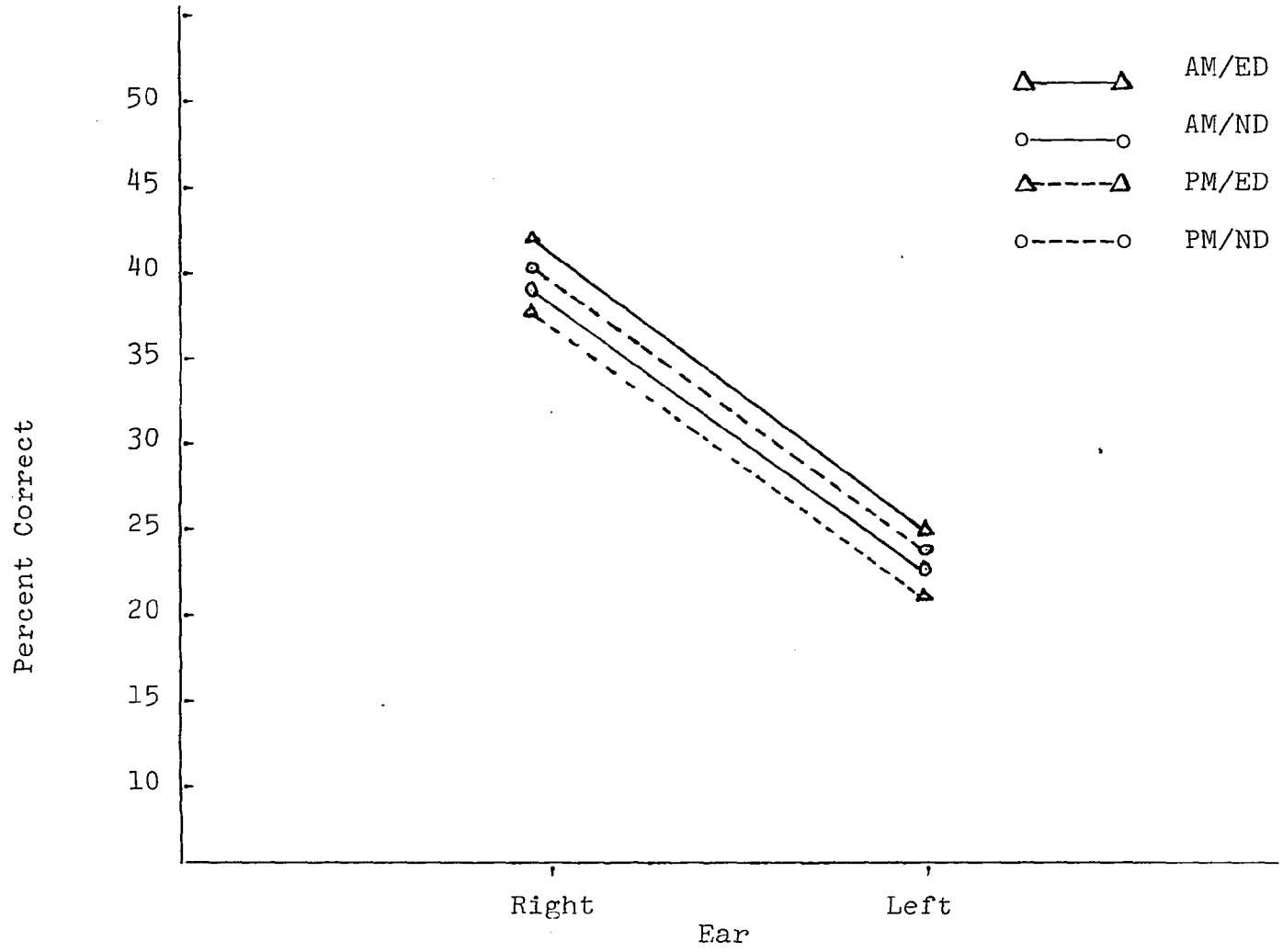


Figure 4. Mean percent single correct responses for each ear as a function of time of day.

Auxillary Measures

Purdue Pegboard. Thirteen patients were tested on the Purdue, therefore grouping by diagnosis was inappropriate. The 2-way ANOVA (Table 9) revealed a significant superiority of the right hand over the left hand condition, but no significant time-of-day effect or time-by-hand interaction. The cell means derived from this analysis are displayed in Figure 5. Visual inspection suggests a non-significant trend for patients to be faster in the evening.

Visual Matching. Only 10 patients were tested in both the morning and evening on the Klein & Armitradge (1981) matching tasks. The two-way ANOVA (Table 10) with two repeated measures (i.e., material type and time-of-day) indicates that only the letter versus dot (material type) condition was significant, an unsurprising finding because dot pattern matching is much more difficult than letter matching. Figure 6 displays the mean performance on this task broken down by time and material type.

Table 9.

Two - way ANOVA of the Purdue Pegboard performance in the morning and evening.

Source	df	Mean Square	F	2 - tail Probability
Hand (H)	1	17.308	31.03	.0001
Error	12	.558		
Time (T)	1	6.231	.83	*ns
Error	12	7.481		
H X T	1	.692	1.32	ns
Error	12	.526		

* ns : Not significant

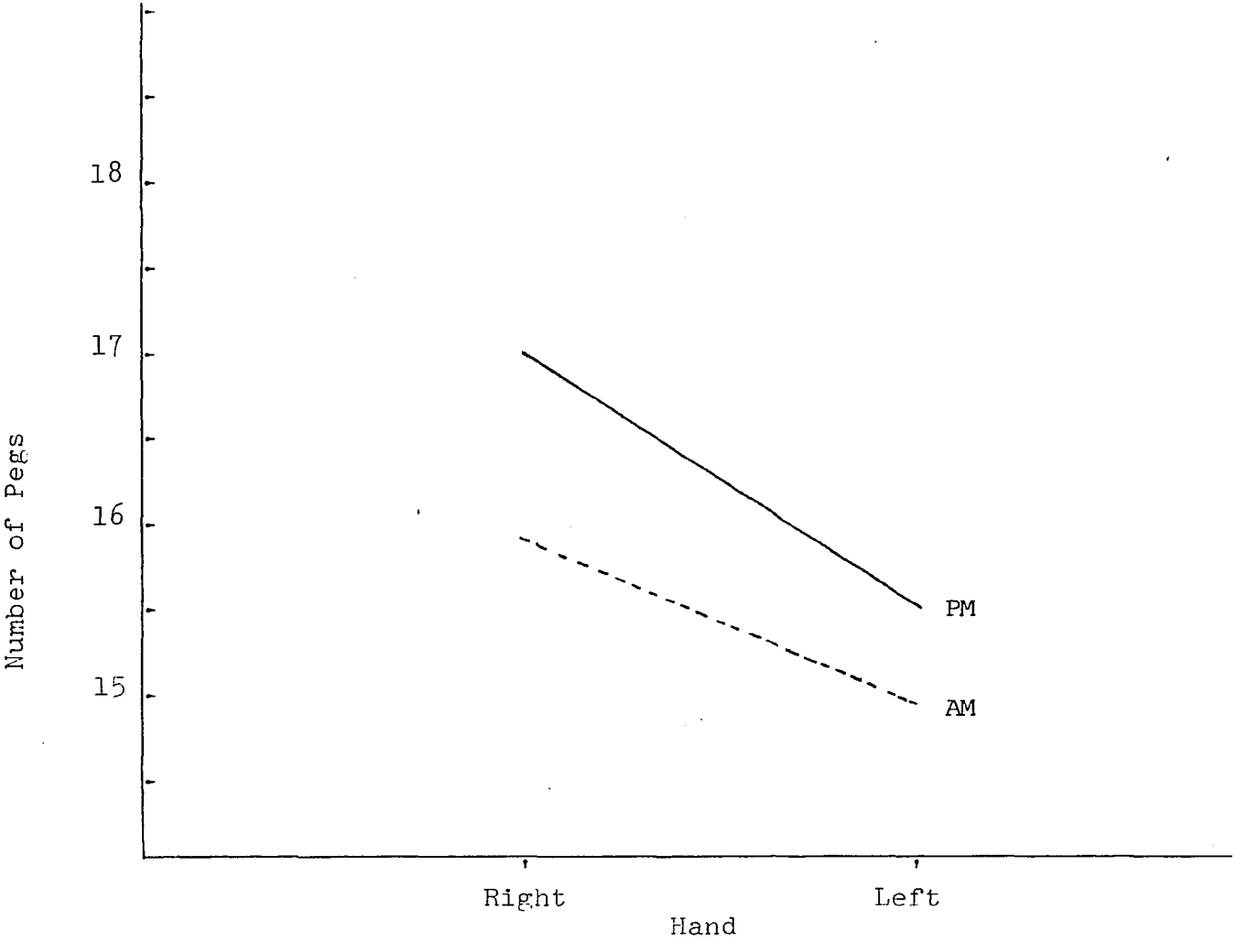


Figure 5. Mean Purdue Pegboard performance in each hand as a function of time of day.

Table 10.

Two-way ANOVA of the visual matching test in the morning and evening

Source	df	Mean Square	F	2-tail Probability
Material Type (M)	1	63,520.90	75.34	.0001
Error	9	843.18		
Time (T)	1	409.60	.48	*ns
Error	9	857.21		
M X T	1	44.10	.39	ns
Error	9	111.93		

* ns : not significant

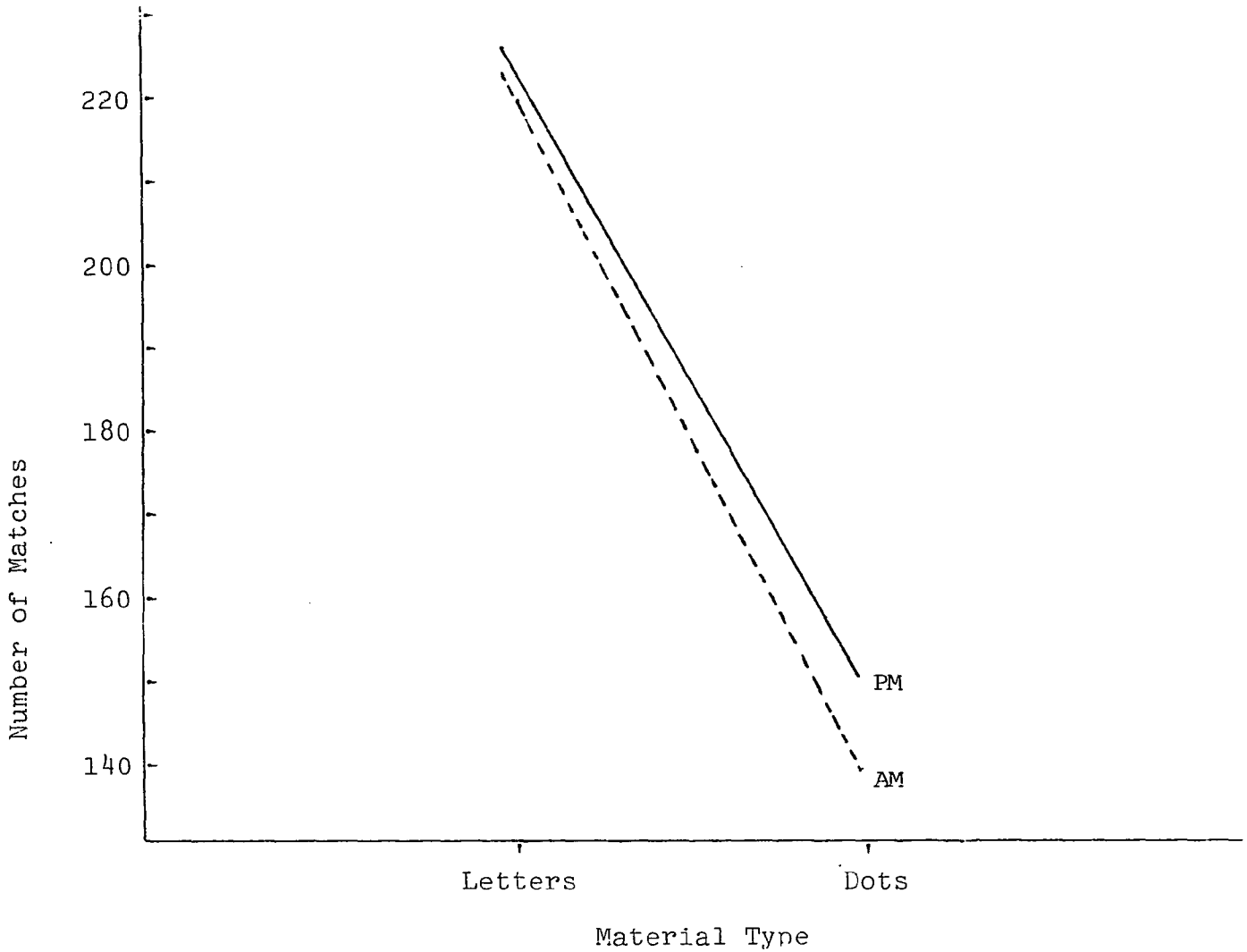


Figure 6. Mean letter and dot matches as a function of time of day.

Correlational Analyses and Clinical Research Variables.

Hamilton Depression Scale item and total scores, sleep variables, and hormone levels were correlated with performance on the various experimental tasks in the morning, evening and AM-PM change scores (morning minus evening score). Little is known about these biobehavioral associations. Therefore correlations were computed on every possible "experimental" variable - clinical correlate pair. Thus, our intention was an exploratory descriptive analysis, rather than specific hypothesis testing. By using every variable and its transforms (e.g. asymmetries and morning-evening) an enormous number of correlations were created. Many of these were trivial or had too few subjects. Still, 9.1% of the sleep variable correlations were significant; significantly more than would be expected by chance alone ($X^2=6.60$, $p<.02$). The proportion of significant Hamilton Depression Scale and endocrine correlations was 6.8% and 4.9% respectively. These frequencies of significant findings were not beyond the level expected based on chance alone. This finding suggests that caution is warranted with regard to the reliability of our significant correlations. However, it is not surprising, given the original premise of unbiased variable selection in order to most completely screen for possible relationships.

Hamilton Depression Scale. On the Hamilton Scale, higher scores on "individual items" or on the total (test) score, indicates a greater degree of pathology. Tables 11 and 12 show the significant Pearson correlation coefficients between Hamilton items and our (experimental) dependent variables. Many of these correlations indicated that reduced speed (i.e., lower total AM visual dot and letter matches and lower total PM visual dot and letter matches; Table 12) or reduced accuracy (i.e., lower total AM CV discriminations; Table 11) are associated with higher (worse) symptom ratings. For example, suicidal ideation and Hamilton total score was correlated with matching speed, and reduced work and activities with CV discrimination.

There were, however, several correlations showing abnormal perceptual or motor asymmetries to be associated with particular symptomatic complaints. For example, (Table 11) increasing (more abnormal) advantage for the RL dichotic click condition in the morning was associated with increased reports of diurnal variation in symptoms (most often "symptoms worse in the morning"). In the evening, more abnormal (lower LR threshold) dichotic click asymmetry was significantly correlated with higher levels of somatic complaints (i.e., hypochondriasis; Table 11).

Larger dichotic CV REA in the evening were associated with decreased reports of agitation (Table 11). Slower left hand performance on the Purdue in the morning was correlated with higher total Hamilton scores and, in the evening, with higher ratings of guilt (see Table 12). Discussion of individual correlations will be included in the Discussion subsection dealing with the relevant experimental measure.

Sleep Measures. The correlations with sleep variables are depicted in Tables 13 and 14. Total sleep time was positively correlated with two measures of performance level, i.e., PMCV total discrimination (Table 13) total Purdue speed (Table 14). Similarly, sleep efficiency measures were related inversely to evening performance (i.e., PM visual matches, PM Purdue; Table 14). The time spent in REM sleep and the proportion of sleep that was REM correlated positively with several visual matching speed variables (Table 14).

Hamilton Depression Scale Correlates of Click Detection and CV Variables #

	Work & Activities	Psychomotor Retardation	Agitation	Hypochondriasis	Diurnal Variation
AM Dichotic Click Asymmetry	r= n= p=				.571 17 .017
PM Dichotic Click Asymmetry	r= n= p=			-.610 17 .009	
AM-PM Dichotic Click Asymmetry	r= n= p=			.593 16 .016	
PM L. Monotic Click Threshold	r= n= p=	.571 17 .017			
PM CV Asymmetry	r= n= p=		-.482 18 .043		
AM CV Discrimination	r=-.539 n=18 p=.021			-.538 18 .021	
PM Monotic Threshold Asymmetry	r=.600 n=17 p=.011	.599 17 .011			

Empty cells are not significant or n<8.

Table 12.

Hamilton Depression Scale Correlates
of Auxillary Variables. *

	Suicide	Guilt	Work & Activities	Depersonalization	Total Score
AM Vis. Match	r=-.515 n=16 p=.041			-.497 16 .050	-.516 17 .034
PM Vis. Match	r=-.569 n=17 p=.017	-.546 17 .023			-.528 18 .024
AM L. Purdue	r= n= p=				-.742 9 .022
PM L-R Purdue	r= n= p=	-.630 10 .051			
Lat. Quotient (LQ)	r= n= p=			-.497 19 .030	

* Emply cells are not significant or n<8.

Monotic click threshold asymmetries (greater rightear sensitivity relative to left ear) in both the morning and evening, were correlated with increased REM cycle length (Table 13). Abnormal dichotic click advantages (RL) in the morning were correlated with both REM latency and sleep latency. A higher rate of CV discrimination in the evening was correlated with shorter sleep latency and longer sleep times. On the other hand, an increase in CV discrimination from the morning to evening session correlated with prolonged sleep latencies.

TABLE 13.

SLEEP CORRELATES OF CLICK AND CV MEASURES *

	REM			SLEEP		
	LATENCY	CYCLE LENGTH	TIME	LATENCY	TIME	STAGE 2 EFFICIENCY
AM Monotic Asym.	r= n= p=	.657 11 .028				
PM Monotic Asym.	r= n= p=	.668 13 .013				
AM Dichotic Clk. Asym.	r=.741 n=11 p=.009		-.706 11 .015	.709 11 .015		
AM-PM Dichotic Clk. Asym.	r=.713 n=11 p=.014		-.670 11 .024			
PM CV Total Discrimination	r= n= p=			-.581 13 .037	.654 13 .015	
AM-PM CV Discrimination	r= n= p=			.650 12 .022		
AM-PM CV Asym. Ratio	r= n= p=		.594 12 .042		.732 12 .007	.642 11 .033

* Empty cells are not significant or n<8.

TABLE 14.

SLEEP CORRELATES OF AUXILLARY MEASURES *

	REM TIME	REM %	SLEEP TIME	SLEEP STAGE 2	EFFICIENCY ALL NIGHT
AM Letter Matches	r=.748	.771			
	n=11	11			
	p=.008	.006			
AM Dot Matches	r=.600	.635			
	n=11	11			
	p=.051	.036			
PM Letter Matches	r=.712	.717			
	n=13	13			
	p=.006	.006			
PM Dot Matches	r=.664	.672			
	n=13	13			
	p=.012	.012			
PM Letter + Dot Matches	r=			-.545	
	n=			13	
	p=			.054	
Purdue	r=		.697		
AM + PM Total	n=		8		
	p=		.055		
PM Purdue	r=				-.840
	n=				8
	p=				.009

* Empty cells are not significant or n<8.

Endocrine Measures. As with the symptom correlations, most endocrine correlations (see Table 15) indicate that abnormal endocrine responses (i.e., higher secretion) are associated with reduced performance levels (i.e., AM letter match, PM letter and dot matching). Still, there were correlations between morning-to-evening (AM-PM) cognitive shifts (i.e., CV discrimination and CV asymmetry ratio) and endocrine levels. These correlations indicated that greater morning CV discrimination and REA ratios, as compared to greater levels, are associated with higher endocrine levels. There was also an association between RL advantage on the dichotic click detection task in the evening and cortisol hypersecretion in the afternoon. An analysis of daily blood cortisol level changes in this sample of depressed patients is presented in Appendix IV.

Table 15.

Endocrine Correlates

	11 DEX PM Resp.	Aft. Cort.	Even. Cort.	Peak PRL	Base-to-peak PRL
PM Dichotic Click Asym.	r= n= p=ns	.470 n=15 .055	ns	ns	ns
AM-PM CV Tot.% Discrimination	r=.537 n=15 p=.039	.497 17 .040	.797 8 .018	ns	ns
AM-PM CV Asymm. Ratio	r= n= p=ns	ns	ns	.591 9 .055	.636 9 .036
AM Letter Match	r=-.658 n=11 p=.014	-.532 13 .041	ns	ns	ns
PM Letter Match	r=-.588 n=13 p=.021	-.510 15 .037	ns	ns	ns
PM Dot Match	r=-.528 n=13 p=.043	-.461 15 .063/ns		-.701 9 .016	-.629 9 .038

Additional Analyses: The click detection and CV analyses were recalculated with age employed as a covariate and sex added as a grouping factor. In no case was age a significant covariate. On the monotic click detection task, there was a trend for lower left ear sensitivity (relative to right) to be found in the male patients (F=3.66, df=1/19, p=.07).

IV DISCUSSION

Monotic Click Detection

The average level of monotic sensitivity did not shift significantly between morning and evening sessions. This contrasts with the morning-to-evening drop in sensitivity reported in normals by Berger-Gross et al. (1984) and Browman's (1979) early AEP component amplitude decreases. It is possible that the small shifts (i.e. about 1 dB) in sensitivity reported previously in normals were obscured by the increased variability extant in patient performance. However, the failure of average monotic thresholds (in the morning or evening) and the morning to evening shift in average thresholds to correlate with any of the clinical research variables (i.e. Hamilton scores, sleep and endocrine measures) suggests that sensitivity level, per se is not related to any integral aspect of affective disorders.

ED patients showed a threshold asymmetry for detecting monotic click stimuli that was not seen for ND patients in this study or normal subjects in our prior study (Berger-Gross & Bruder, 1984). Also, this monotic threshold asymmetry was related to time of day. ED patients displayed significantly poorer left ear as compared to right ear sensitivity in the morning but not in the evening. Although

Bruder and his associates have previously reported evidence of reduced sensitivity for monotic click detection in affective psychotic patients, there was no evidence in these studies that this was a lateralized effect (Bruder et al., 1980). However, the patients in these studies were more heterogenous in their diagnostic characteristics and they were medicated at the time of testing. In a study of the effects of electroconvulsive therapy (ECT), unmedicated depressed patients in a pre-ECT phase also showed significantly poorer left ear as compared to right ear sensitivity for monotic click detection (Epstein et al., 1983). Most of the patients in this ECT study were severely depressed and had an endogenous major depressive disorder. Monotic stimulation of various types has elicited perceptual asymmetries suggestive of asymmetrical hemispheric contributions. Thus, poorer left-ear sensitivity may be another manifestation of right hemisphere dysfunction in depression.

Individuals with poorer left ear sensitivity (compared to right ear) in the evening reported lower rating of ability to engage in work and activities and a greater degree of psychomotor retardation on the Hamilton Depression Scale (Table 11). The monotic click threshold asymmetries were unrelated to our endocrine measures

(Table 13). These correlations indicated that relatively inferior left ear detection was associated with longer REM sleep periods, suggesting that right hemisphere deficits are associated with temporal anomalies in REM sleep architecture.

The threshold asymmetry for monotic click stimuli exhibited by the ED patients raises the question as to whether this effect was related to their abnormal threshold asymmetry for dichotic click stimuli. There is no evidence that this was the case. The monotic click thresholds for each ear and the ear asymmetry scores did not correlate significantly with the dichotic threshold asymmetry scores for either ED or ND patients in the morning or evening session (see Table 5). It should also be noted that the ED and ND patients displayed the same morning to evening changes in threshold asymmetry for dichotic click stimuli (Figure 3), and yet, these groups differed in their findings for monotic click stimuli (Figure 2). Although this could mean that the threshold asymmetry measures for monotic and dichotic click stimuli may tap different aspects of hemispheric function, further research would be needed to clarify this issue.

Dichotic Click Detection

Prior studies have found a reversal of the normal direction of dichotic threshold asymmetry in depressed

patients tested once during the day (Bruder et al., 1981; Yozawitz et al., 1979). Three findings of the present study support the hypothesis that this abnormal pattern of perceptual asymmetry is related to a shift in circadian rhythm. First, the dichotic threshold asymmetry for endogenous and nonendogenous depressed patients was dependent on time of day. Most importantly, the direction of the morning to evening shift for depressed patients was different than that previously observed for normal subjects. Depressed patients showed an advantage for detecting the right ear lead condition in the morning and the left ear lead condition in the evening, which was opposite the direction of the morning to evening shift previously reported for normal subjects (Berger-Gross & Bruder, 1984).

Second, support for the circadian hypothesis was found in correlations between dichotic threshold asymmetry and EEG sleep in depressed patients. A reversal of threshold asymmetry (i.e., a right ear lead advantage) in the morning was associated with abnormally long sleep latency (see Figure 7). Although REM period latency, total REM and percent REM were also correlated with dichotic threshold asymmetry (Table 13), patients with reversed asymmetry generally had REM measures in the normal range. Shipley et al. (1981) similarly examined the correlation between neuropsychological test performance and EEG sleep in depressed patients. While their tests did not

provide information concerning the locus of dysfunction, a high level of impairment on neuropsychological tests was associated with prolonged sleep latency but not with REM abnormality. The correlation with sleep latency represents a disturbance of the most fundamental daily rhythm, the sleep/wake cycle. The failure of dichotic click asymmetries to correlate with REM abnormalities is understandable in this context, since REM cycles are ultradian, not circadian.

Third, additional evidence for the circadian hypothesis was evident in the significant correlation between dichotic threshhold asymmetry in the morning and self-ratings of diurnal variation on the Hamilton Depression Scale (Table 11). Namely, an abnormal reversal of threshold asymmetry was associated with diurnal variation in the symptoms of depressed patients. Also, the evening shift to a LR threshold advantage was associated with a increase in somatic complaints (i.e. hypochondriasis), suggesting the possibility that altered circadian variation may underlie the many minor physical complaints of depressed patients.

While a two-point examination (morning vs. evening) over the 24 hour cycle can hardly provide definitive evidence for this circadian hypothesis, it should give impetus for more fine grained examination.

Our theoretical interpretation of the morning to evening changes in dichotic threshold asymmetry is based upon three assumptions. First, we assume that the normal advantage for

detecting the left ear leading condition during the day is related to a right hemisphere advantage for hemispheric activation. It has previously been suggested that cerebral activation or arousal is mediated primarily by a mechanism centered in the right hemisphere (Heilman & Van Den Abell, 1979; Jutai, 1984). As a result, stimuli in the left hemispace may be more effective for yielding bilateral cerebral activation compared with stimuli in the right hemispace (Bowers & Heilman, 1980; Prohovnik, 1980; Heilman & Van Den Abell, 1979). Second, we assume that the disappearance of the advantage for detecting the left ear lead condition in the evening for normal subjects is due to a daily rhythm that diminishes right hemispheric activation (Berger-Gross & Bruder, 1984). This daily rhythm is normally associated with heightened cerebral arousal during the day but diminished arousal during the evening. Third, we assume that the opposite direction of morning to evening shift in dichotic threshold asymmetry for depressed patients is related to a difference in their daily rhythm of cerebral arousal. The significant correlation (Table 15) between the evening dichotic click asymmetry and (average) afternoon cortisol levels (there were too few morning cortisols for adequate comparisons) suggests a neuroendocrine mechanism for modulation of this hypothesized cerebral arousal cycle. A disturbance of the circadian rhythm of arousal has been hypothesized to explain EEG sleep abnormalities in depression and may be one of several biological

rhythms that are not synchronized in the normal fashion with day-evening cycles (e.g., Kripke et al., 1978; Schulz et al., 1979; Wehr et al., 1980).

Dichotic CV Syllables : Total Discrimination

There was no morning-to-evening shift in total accuracy of discrimination for either ED or ND depressives. Nor was there any significant difference in discrimination between these two diagnostic groups. While depressives' discrimination levels were poorer than for a previously reported normal group (Berger-Gross & Bruder, 1984) the differences (from the normal group) were generally less than one standard deviation . Furthermore, the lack of time-of-day effects was seen both in the depressed and normal groups.

Morning CV discrimination was inversely related to reports of hypochondriasis (Table 11). Also, the higher the evening CV discrimination level , the greater the amount of sleep (and reduced sleep latency) the patient was likely to obtain (Table 13). Therefore, in both sessions (AM and PM) good CV discrimination performance was associated with lesser evidence of abnormalities associated with depression. On the other hand, the correlational evidence indicates that when CV discrimination fell between the morning and evening sessions, it was associated with longer sleep latencies and

higher cortisol levels (i.e. afternoon, evening and Dexamethasone Suppression Test). Because there were no time-of-day shifts in CV discrimination the meaning of these correlational findings is somewhat obscure. Still, there evidence from the CV discrimination correlates that better cognitive efficiency was related to fewer biological indicators of affective illness and that anomalous (individual) shifts in cognitive efficiency from morning to evening were associated with both sleep and endocrine abnormalities. These findings emphasize the importance of controlling for time-of-day in future studies which correlate CV performance with clinical aspects of depression.

Dichotic CV Syllables : Asymmetry

As in most studies of normals (Berlin et al., 1976). ED and ND depressives displayed significant REAs for dichotic CV syllables. The difference between right ear and left ear accuracy was similar for morning and evening sessions, a finding comparable to that found in a previous study of normals (Berger-Gross & Bruder,1984)

The degree of evening REA was positively correlated with ratings of agitation (Table 11). This is the only correlation between morning or evening REA and the symptom variables. The correlation indicating that larger (evening)

REAs in depressives are associated with a greater amount of agitation contrasts sharply with a prior study which showed a decrease in dichotic REA with increasing levels of psychopathology in a mixed group of schizophrenics and affective disorder patients (Wexler & Heninger, 1981). It is possible that there is a special relationship between agitation and CV asymmetries, or that this is an isolated spurious correlation. While morning-evening REA advantage differences were not significantly correlated with endocrine or sleep measures, the morning-evening CV asymmetry ratio (i.e. ((L. correct - R. correct)/(L. correct + R. correct)) X 100) difference did correlate with several sleep and endocrine measures. The asymmetry ratio formula is used to control for performance level effects on lateral asymmetries. The device, which may be useful when comparing REAs in groups with putatively different performance levels (e.g. brain damaged versus normal controls), obfuscates the meaning of the correlations reported herein. That is, the reported correlations are affected by total CV discrimination (as suggested by the ratio denominator), and therefore the correlation for ratio scores represents the same direction of findings as those described in the total dichotic CV discrimination discussion (e.g. individuals with poorer evening discrimination have more abnormal sleep and endocrine findings). Diurnal changes in CV asymmetry do not appear regularly in normals (Berger-Gross & Bruder, 1984) or depressives;

any individual variation that does exist does not appear to be related to cyclic alterations in sleep or endocrine variables.

Auxillary Measures : Purdue Pegboard

Right hand speed was better than left hand speed on the visually guided fine motor movements of the Purdue Pegboard for ED and ND patients in both sessions (AM and PM). While patients tended to place more pegs and had a greater right hand advantage in the evening session than in the morning session, neither of these differences approached statistical significance. The failure to reject these null hypotheses (i.e. no time or time-by-hand effects) may be due in part to a inadequate patient sample size and the notoriously variable performance of psychiatric patients on "power" (speed of performance) tests.

As might be expected on a "power" test, how quickly a patient performs on the Purdue Pegboard (AM plus PM score) was positively correlated with amount of sleep. More interestingly, evening Purdue speed was negatively correlated with sleep efficiency. This is consistent with the theory (Shulz et al., 1979) that a circadian disturbance resulting in hyperarousal (indicated here by increased speed) in the evening is responsible for sleep deficits in depressed patients. Left

hand speed (am) and hand speed asymmetry (pm: left minus right) correlated negatively with total score and guilt ratings respectively on the Hamilton score. These correlations suggest that poorer right hemisphere mediated performance (i.e. left hand speed) is associated with a increased depressive symptomatology. Another study that used neuropsychological tests in depressed patients (Henig, 1981), which employed a finger tapping test and depression ratings (Carroll), found no relationship between right hemisphere deficits (slower left hand tapping speed) and depression severity. Whether this difference is due to task or sample differences or some other factor can not be resolved as yet.

No correlations of Purdue speed with endocrine variables were significant (Table 15), nor did any morning-evening difference correlations reach significance.

Auxilliary Measures : Visual Matching

Letter matching was much faster than dot matching, but this difference was not effected by time-of-day or diagnosis (ED versus ND). The mean letter as well as dot matches in the evening were larger than in the morning. This higher performance level on a simple timed task in the evening, as with the Purdue, failed to approach statistical significance. Even so, the morning-to-evening increase in mean per-

formance are in the direction found for numerous other simple tasks in normals (e.g. Blake, 1967).

Just as the ANOVA carried out on the Klein and Armitage (1979) visual matching task gave no indication of circadian or hemisphere specific changes, correlations with morning-to-evening changes and letter-dot differences were consistently non-significant. However, faster visual matching speed was consistently correlated with lower symptom ratings and more normal sleep and endocrine levels. Thus, the matching task, appears to be the most non-specific with respect to lack of daily fluctuations or laterality effects, but most generally correlated with symptom and physiologic measures. Further studies concerned with rhythms, hemisphericity and depression might employ the Klein and Armitage procedure in its original, ultradian cycle context; this could be especially valuable in rapidly cycling patients (see: "Suggestion for Further Research").

Conclusions

The most interesting findings of this dissertation are those supporting the hypothesis that there is a disturbance of right hemisphere function in depression (e.g., Flor-Henry et al, 1976 Bruder et al., 1981) and that it is influenced by time of day (Berger-Gross and Bruder, 1984). Specifically, lower left ear sensitivity for monotic clicks in the morning in ED depressives and the morning RL dichotic click advantage in both ED and ND depressives are suggestive of right hemisphere dysfunction. While these two findings are statistically unrelated, possibly indicating multiple mechanisms of RH deficiency, both the monotic and dichotic asymmetries show a diminishing of RH disadvantage in the evening. Abnormal dichotic click asymmetries in the morning (RL advantage) were associated with lengthened sleep latencies and increased reports on the Hamilton Depression Scale of diurnal variation. These correlations support the notion that anomalous dichotic click asymmetries (i.e., RH disturbances) are related to altered diurnal patterns of physiology and mood. The unusually large right hand advantage observed on the Purdue Pegboard may also be interpreted as supporting the RH deficit hypothesis, especially in light of the relationship between faster left hand (RH) speed and lower (better) Hamilton Depression Scale scores.

Several generalizations appear to apply to the various relations among the cognitive, perceptual, motor, sleep, endocrine, and symptom investigated in this study. First, Purdue hand, Dichotic CV, monotic click and dichotic click asymmetries were all significantly correlated with symptom severity and sleep variables. These asymmetries did not correlate consistently with endocrine levels, nor did performance levels (i.e. total Purdue speed, CV discrimination, average click threshold levels) correlate with REM sleep or (consistently) with symptom severity. Does this mean that hemispheric asymmetries in depression, symptom severity and aspects of sleep are all modulated by some, as yet unspecified central mechanism? A larger sample subjected to cluster analysis (e.g. facter analysis) techniques could test this speculation. Secondly, the timed tests, Purdue and visual matching, were, when measured in the evening session inversely related to sleep efficiency. This suggests that increased arousal in the evening ,indicated by faster speed on simple tasks, may represent a disturbance of circadian arousal rhythm which also affects the continuity of sleep (Schulz et al., 1979).

As with normal subjects tested in a prior study (Berger-Gross & Bruder, 1984), depressed patients showed no morning

to evening shift in dichotic CV discrimination or REA. The Purdue Pegboard and Visual Matching task were not employed in the previous study, but they too failed to show an asymmetry that shifted with time of day. The fact that some measures of hemispheric advantage display a significant daily fluctuation in depressives and others do not, does not disconfirm the importance of the significant findings. Rather, those tasks not displaying the hypothesized affect may be mediated by fairly static hemispheric processes (e.g. stable LH dedication to the verbal, CV task) or another oscillator (e.g., Folkard et al., 1983).

In summary, this study has replicated previous findings of RH deficits in depressed patients tested during the day. The RH deficit for click detection was found to decrease by evening, a change precisely opposite of that previously observed in normal individuals. Symptom, sleep and endocrine variables provided the basis for some initial speculation on the mechanism of these abnormal patterns of hemispheric efficiency in ED and ND depressed patients.

Suggestions for Future Research

There are obvious technical and procedural improvements that would, if used in a replication, strengthen our findings. One obvious limitation is the use of two point (morning versus evening) assessment of the 24 hour cycle. The use of quicker, automated threshold procedures would allow more frequent performance assessment, and the direct statistical evaluation of 24 hour cycle attributes (e.g. minima, maxima, and phase angle). Other non-verbal dichotic measures, such as spatial localization, offer the promise of reduced test time while tapping cognitive dimensions similar to the dichotic click detection task.The use of automated temperature and activity monitors (which were on order, but not delivered) would clarify which of the multiple centrally determined cycles (e.g. sleep/wake and temperature) is related to daily monotic threshold and dichotic click detection asymmetry fluctuations in depressed patients.

The honing of technical aspects of this research area could be complemented by the use of a rare, but important, patient sample, rapidly cycling manic-depressive (i.e. bipolar) patients. Sleep and temperature monitoring in

these patients has already been used to illustrate recurrent patterns of circadian rhythm disturbance across episodes of the alternating bipolar phases (i.e., depression and mania). Intensive perceptual and cognitive monitering in these patients would not only provide a unique cross-validation of our findings regarding alterations of daily behavior rhythms in depression and extend the investigation to the manic period; but would, more generally, highlight the (largely ignored) importance of time-of-day effects in human neuropsychology.

Finally, the reported relationships between sleep variables and morning and evening perception and cognition in depressives, suggests another line of research. Specifically, are sleep disorders, which share some sleep characteristics with depression, associated with analogous (to our depressed patients) mood and neuropsychological fluctuations? The implications of that question are twofold; first the obvious (primary) question as to whether sleep/wake cycle anomalies, of themselves, lead to altered circadian mood and performance rhythms. The second implication is again directed at the role of time-of-day effects in neuropsychology.

APPENDIX 1

Berger-Gross & Bruder, 1984

APPENDIX II

Dichotic CV Response Sheet

Page 3

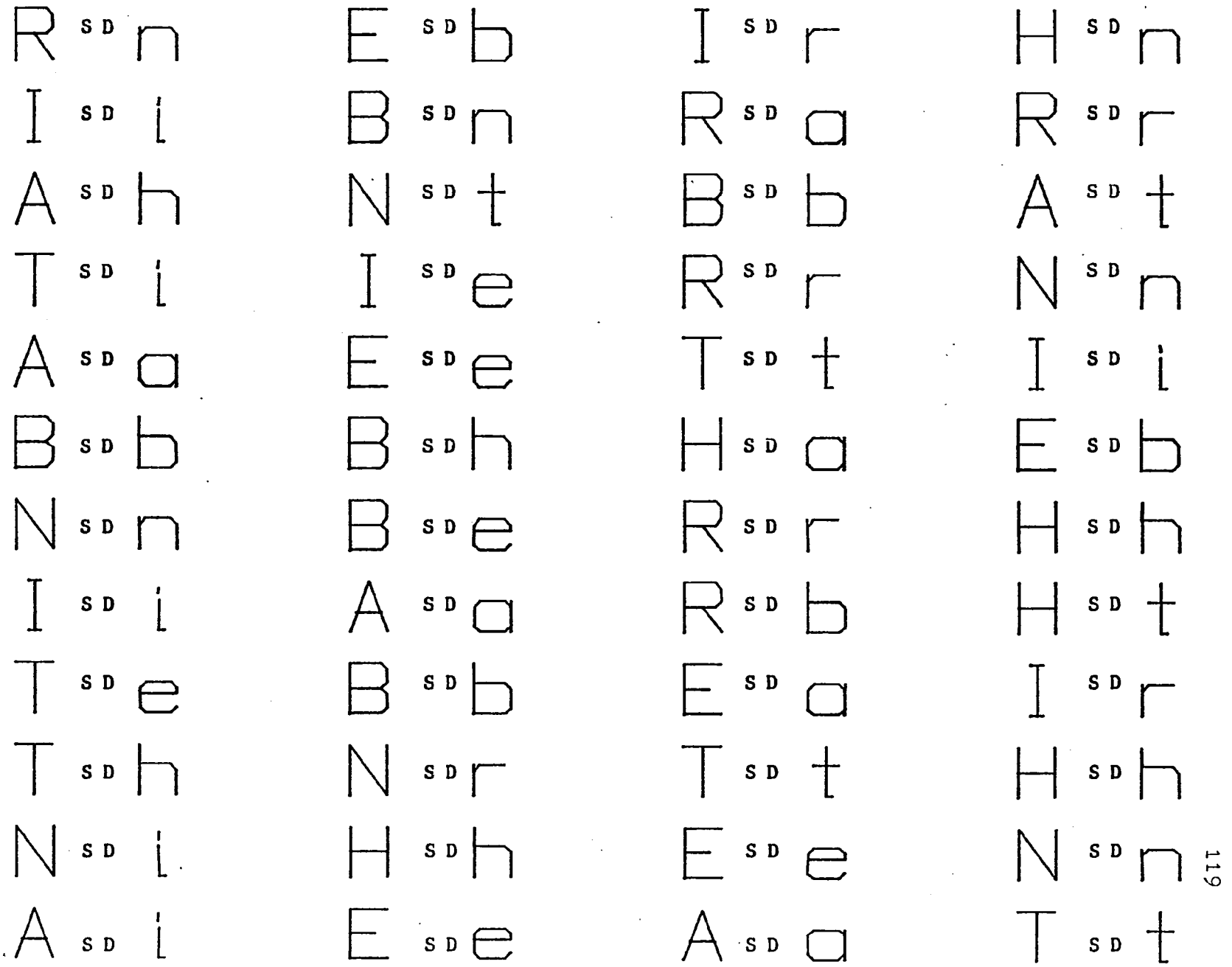
Name _____

Date _____

1	DA	BA	GA	PA	KA	TA		16	PA	DA	TA	KA	BA	GA
2	BA	TA	PA	GA	KA	DA		17	DA	KA	BA	GA	PA	TA
3	TA	GA	DA	BA	PA	KA		18	GA	TA	DA	KA	BA	PA
4	PA	KA	TA	BA	GA	DA		19	BA	GA	DA	TA	KA	PA
5	PA	BA	TA	GA	DA	KA		20	DA	BA	TA	PA	GA	KA
6	KA	DA	PA	GA	TA	BA		21	TA	KA	PA	GA	BA	DA
7	GA	KA	DA	PA	TA	BA		22	TA	KA	PA	GA	BA	DA
8	TA	PA	GA	BA	KA	DA		23	PA	DA	GA	TA	BA	KA
9	GA	KA	DA	PA	BA	TA		24	KA	DA	GA	PA	TA	BA
10	PA	BA	KA	DA	TA	GA		25	TA	GA	DA	BA	PA	KA
11	DA	GA	BA	TA	PA	KA		26	KA	PA	TA	DA	GA	BA
12	GA	PA	BA	KA	DA	TA		27	KA	TA	BA	PA	GA	DA
13	GA	BA	KA	TA	DA	PA		28	BA	TA	PA	DA	KA	GA
14	BA	GA	DA	TA	PA	KA		29	DA	GA	BA	TA	KA	PA
15	BA	TA	PA	GA	DA	KA		30	TA	BA	PA	DA	KA	GA

APPENDIX III

Visual Matching Response Sheets


R SD n
I SD i
A SD h
T SD i
A SD a
B SD b
N SD n
I SD i
T SD e
T SD h
N SD i
A SD i
E SD b
B SD n
N SD t
I SD e
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B SD h
B SD e
A SD a
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120
S D
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120

APPENDIX IV

Analysis of Cortisol Rhythms

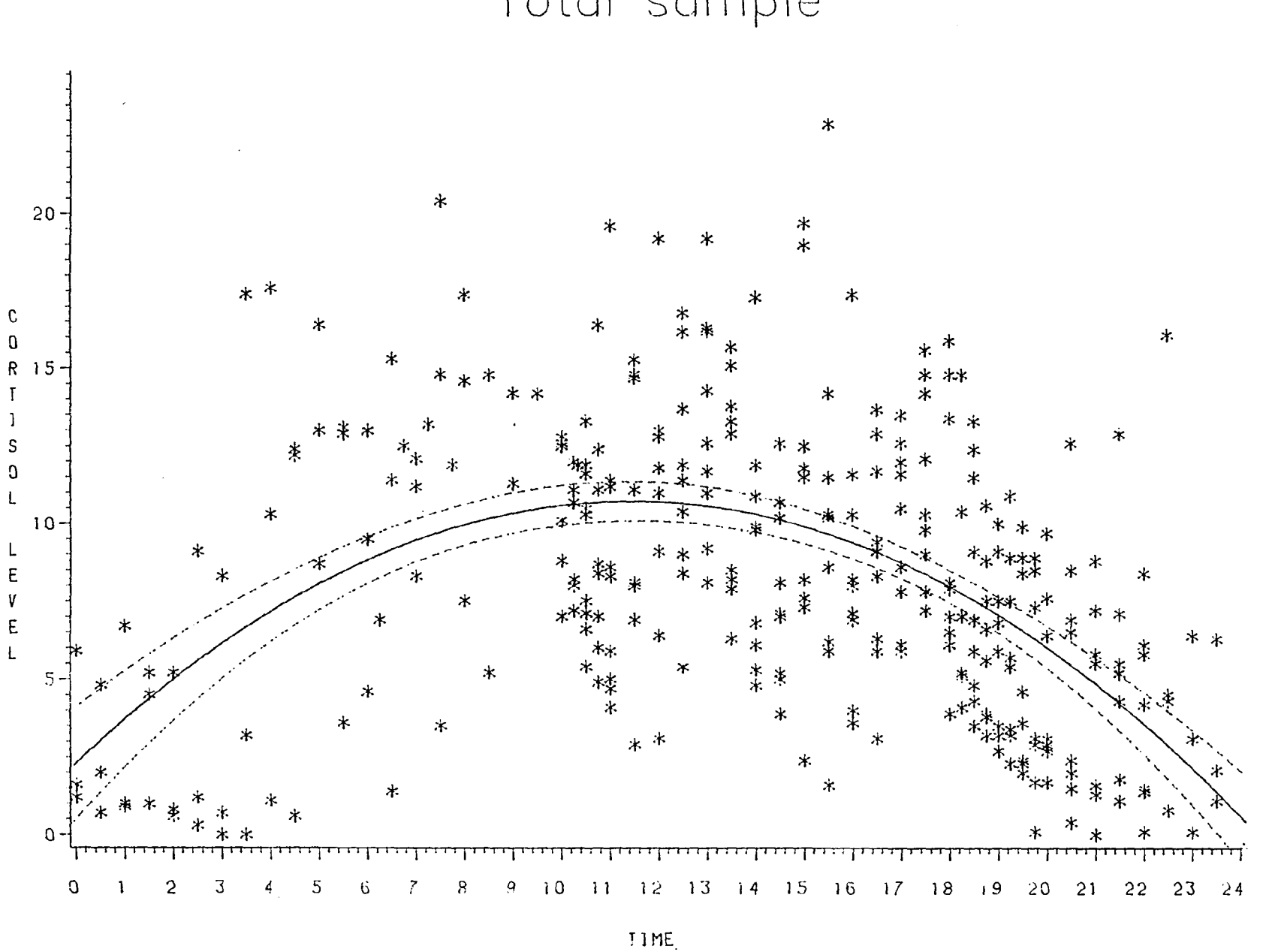

Figure 10. Cortisol levels as a function of time of day.

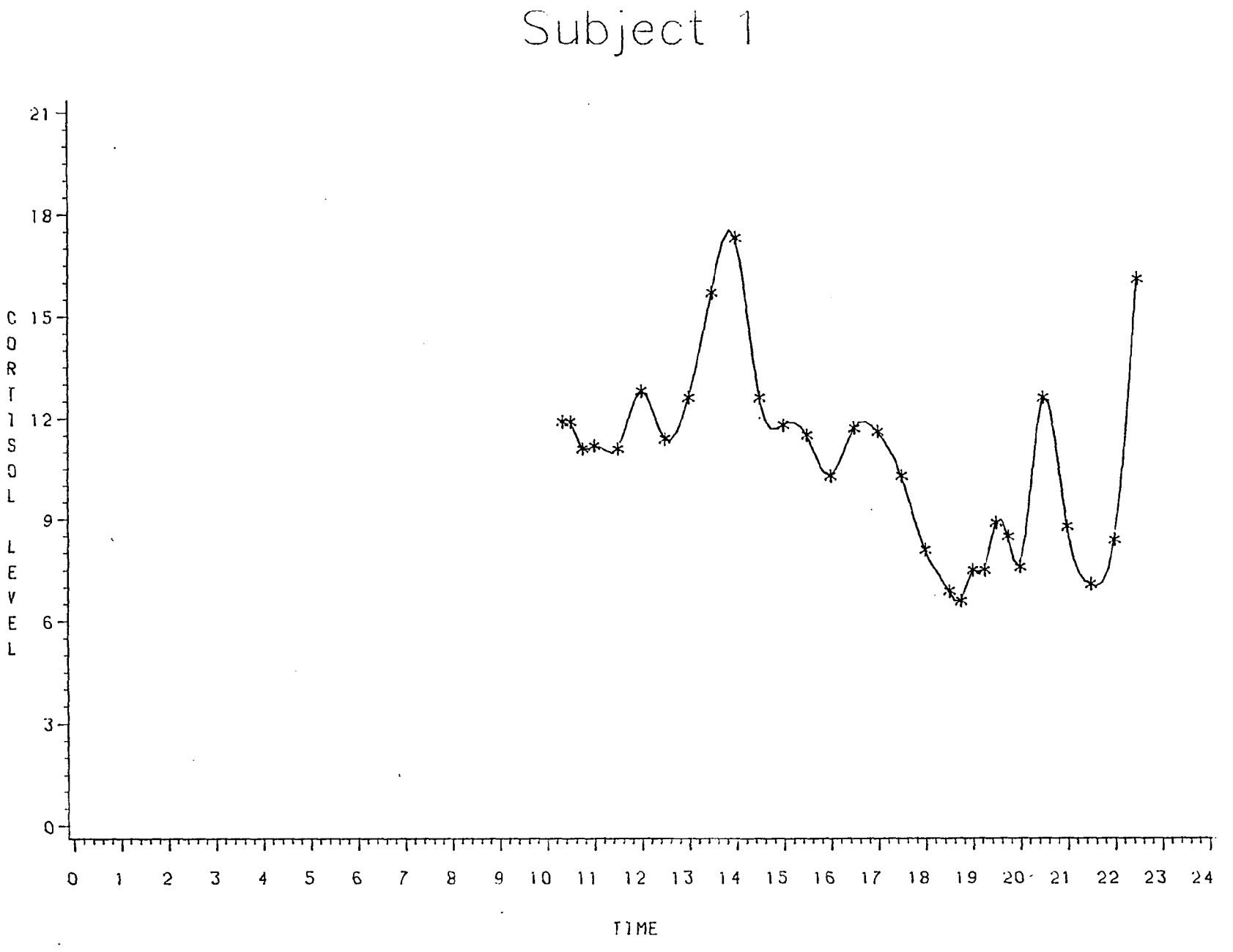

Figure 1. Cortisol levels as a function of time of day.

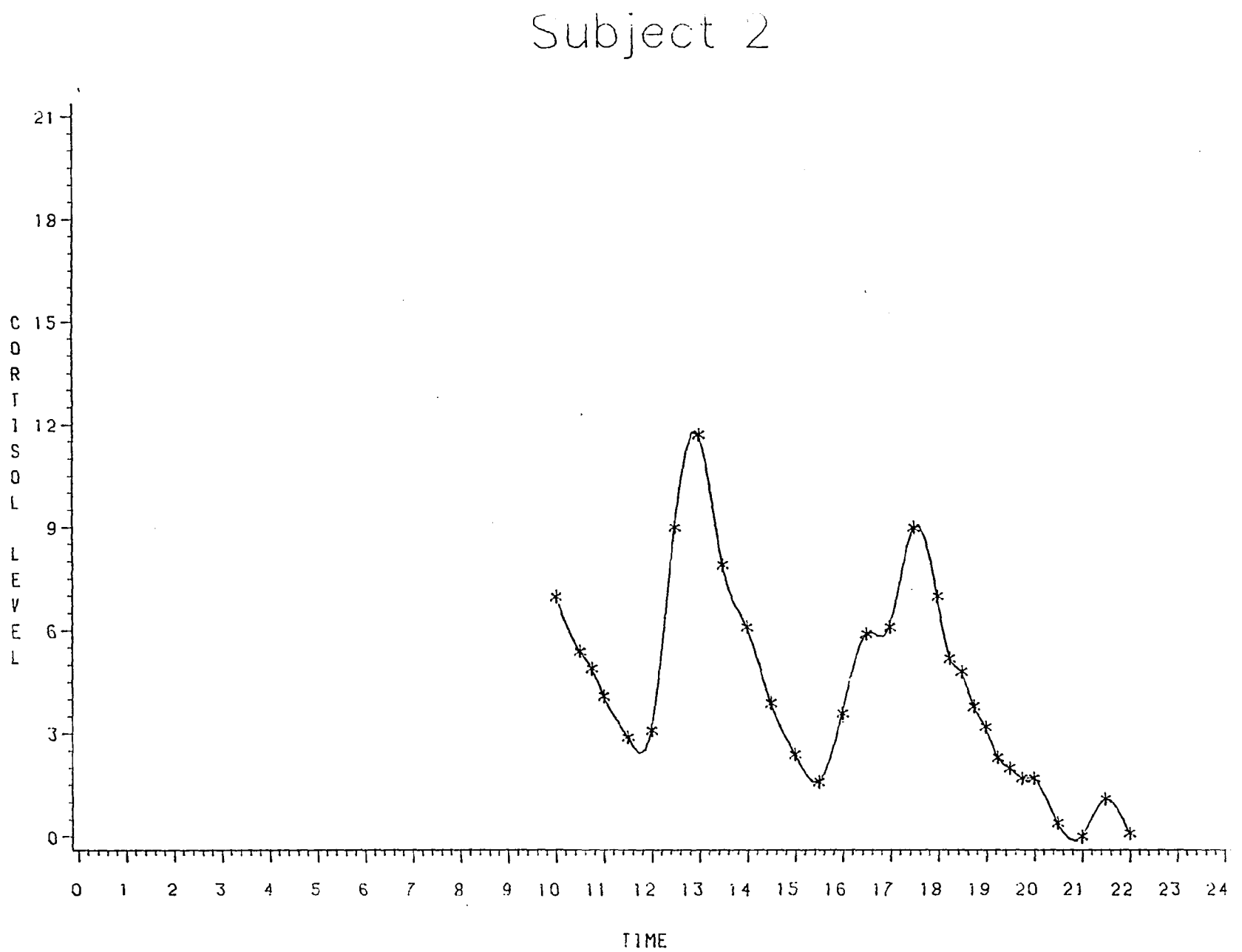

Figure 2. Cortisol levels as a function of time of day.

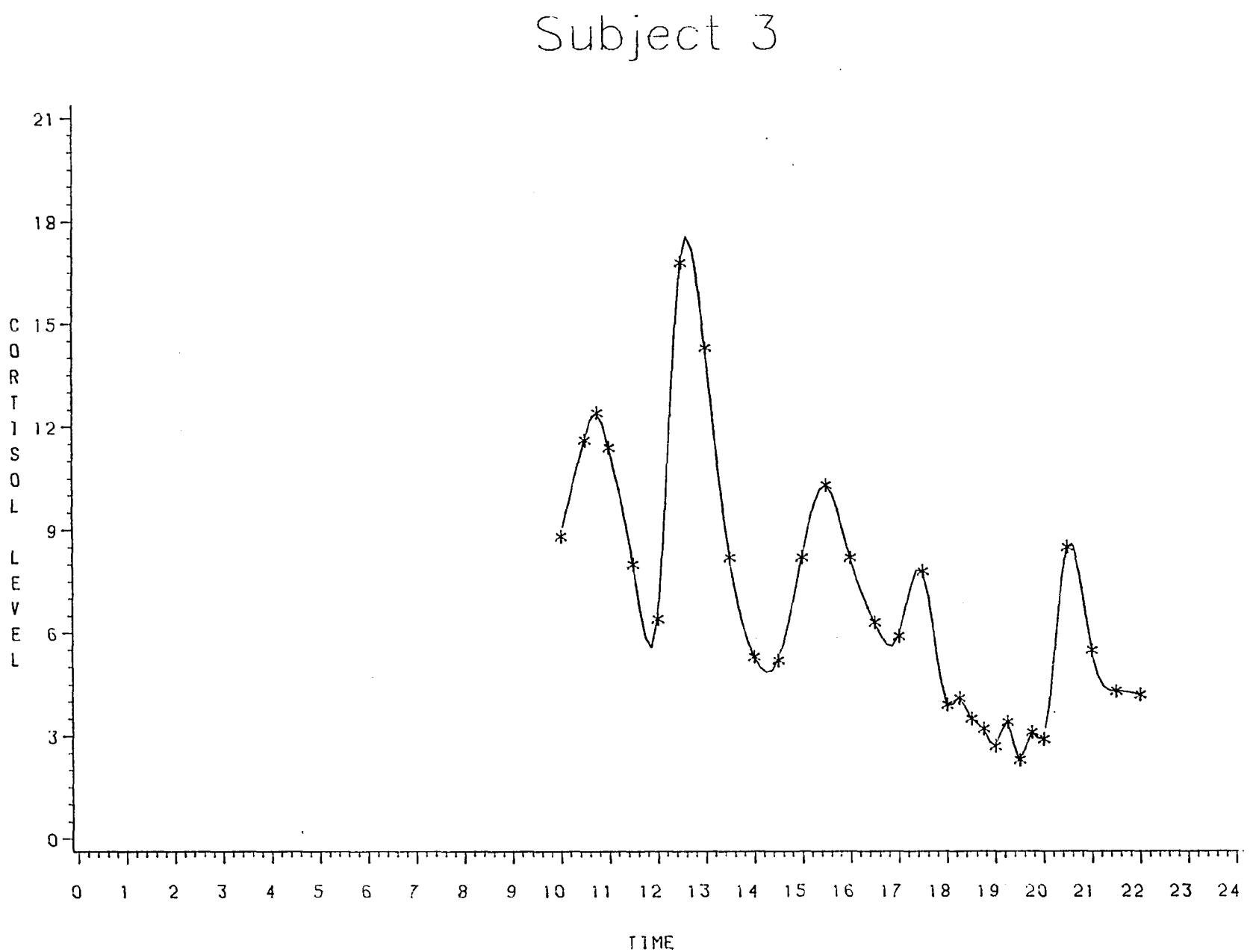

Figure 3. Cortisol levels as a function of time of day.

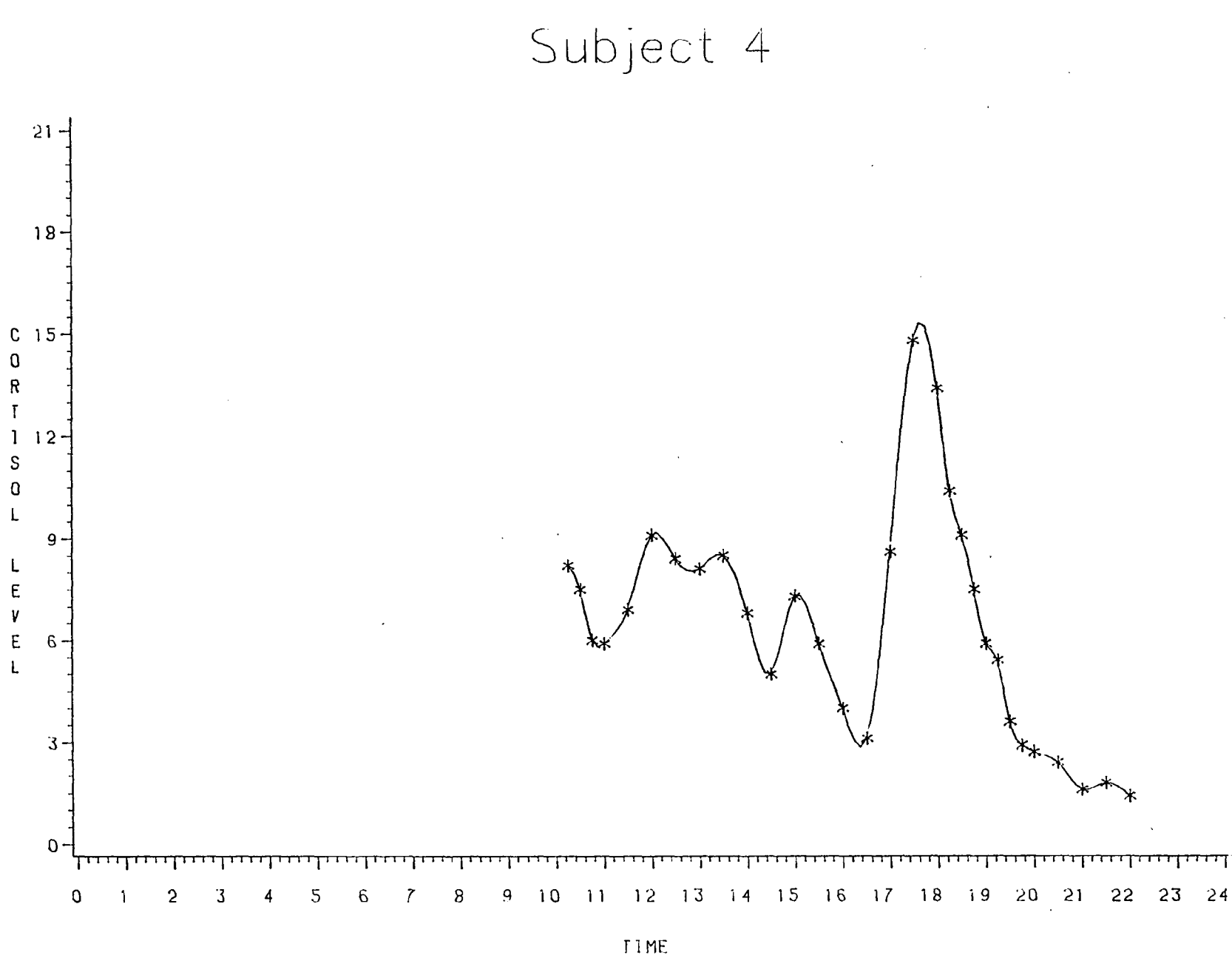

Figure 4. Cortisol levels as a function of time of day.

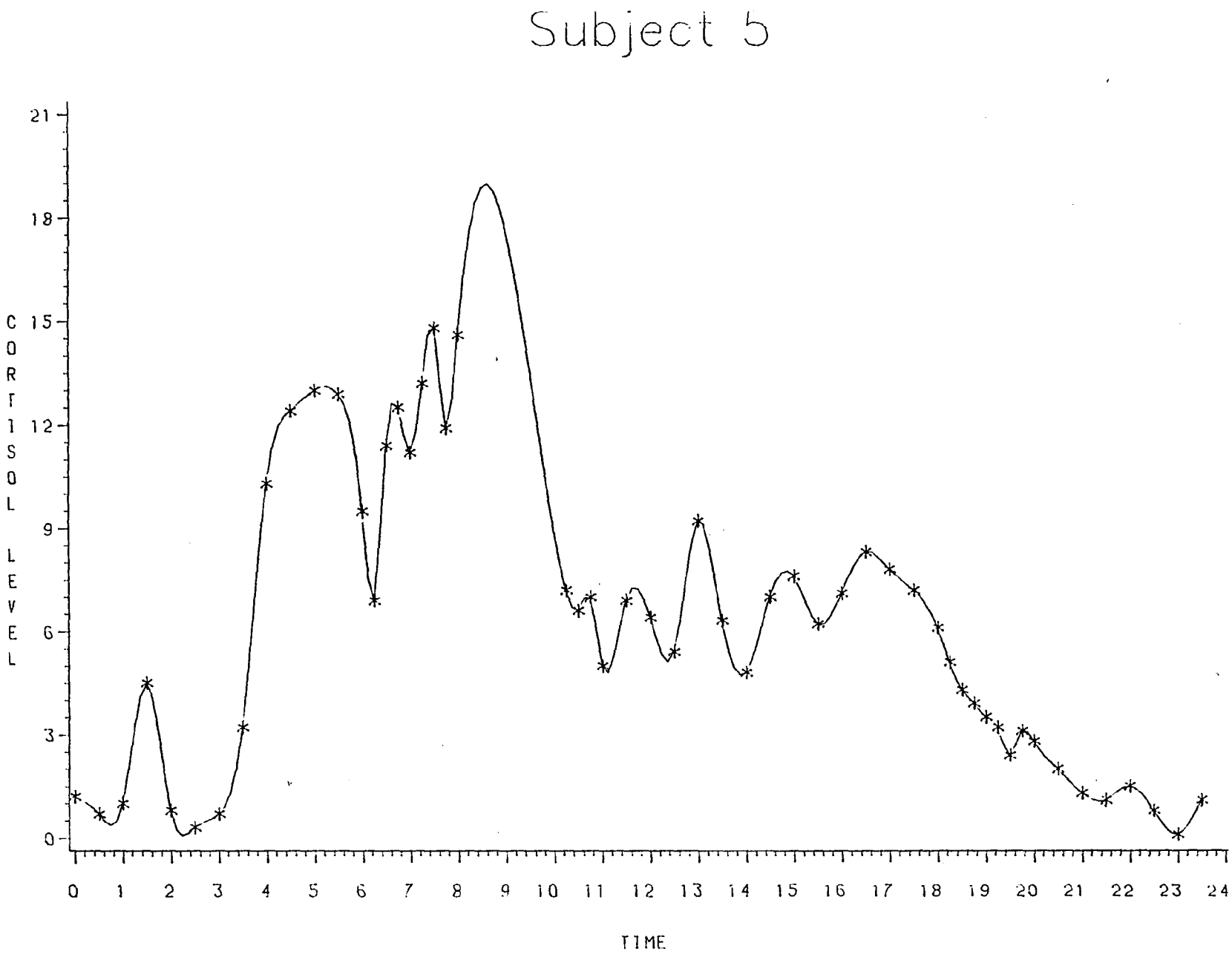

Figure 5. Cortisol levels as a function of time of day.

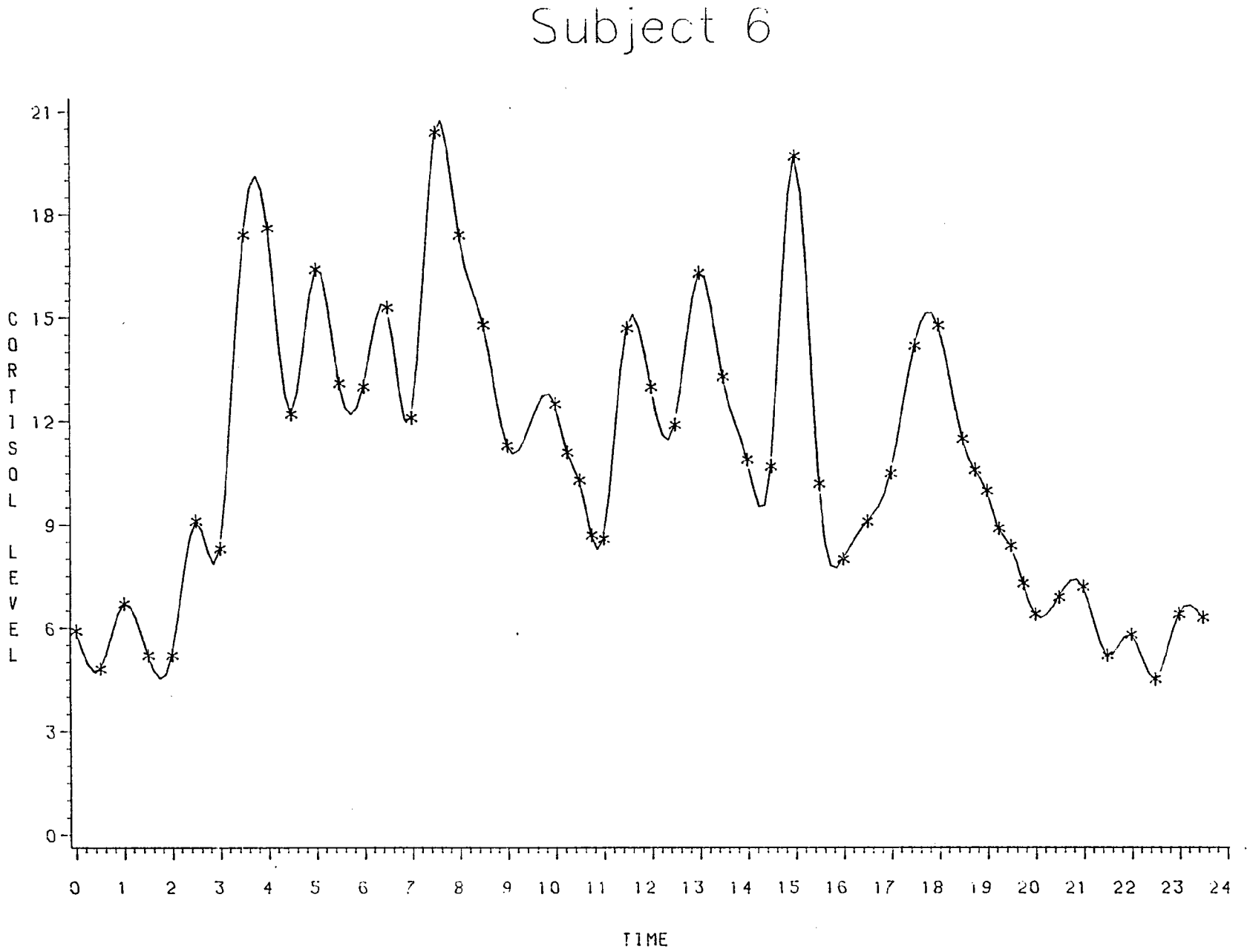

Figure 6. Cortisol levels as a function of time of day.

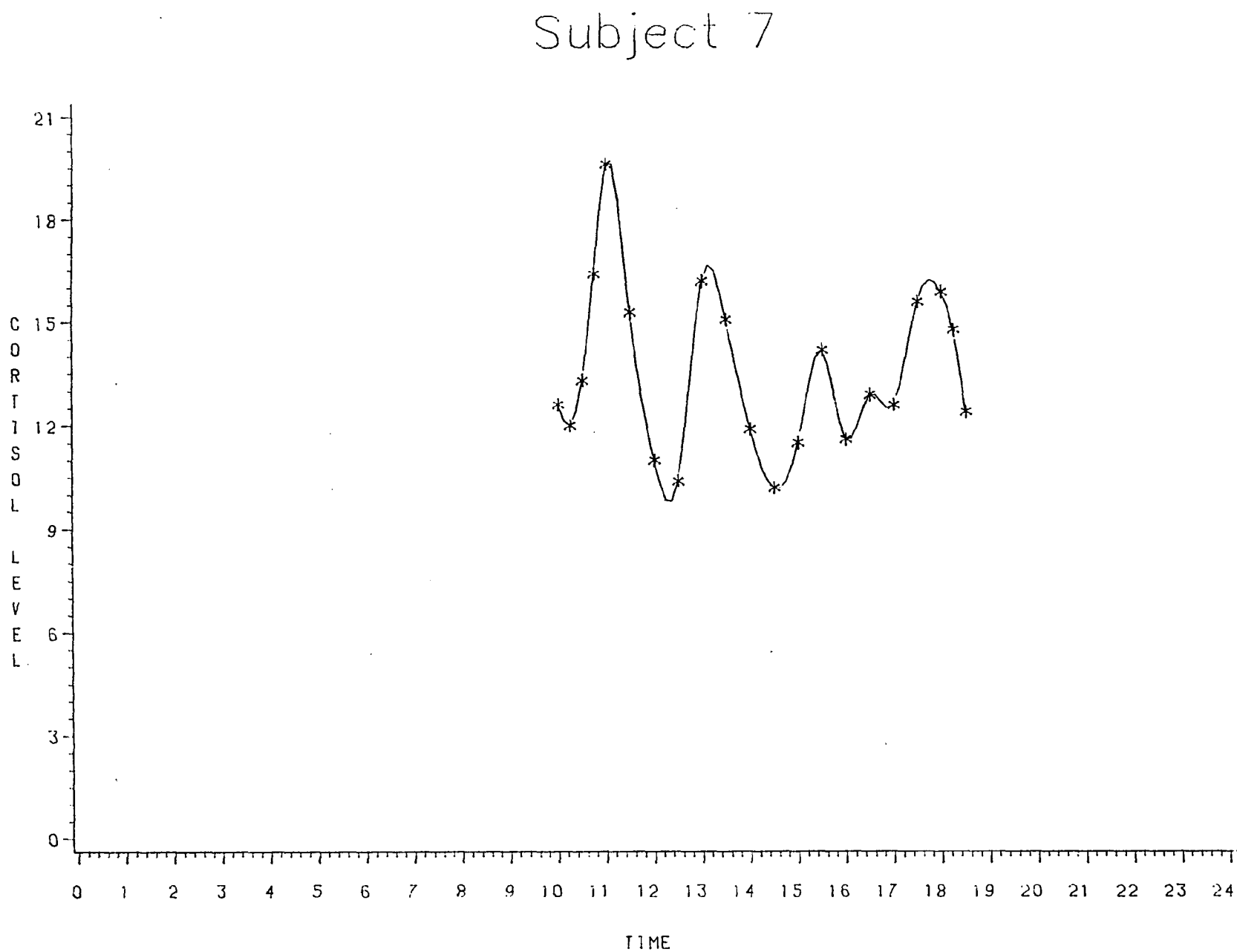

Figure 7. Cortisol levels as a function of time of day.

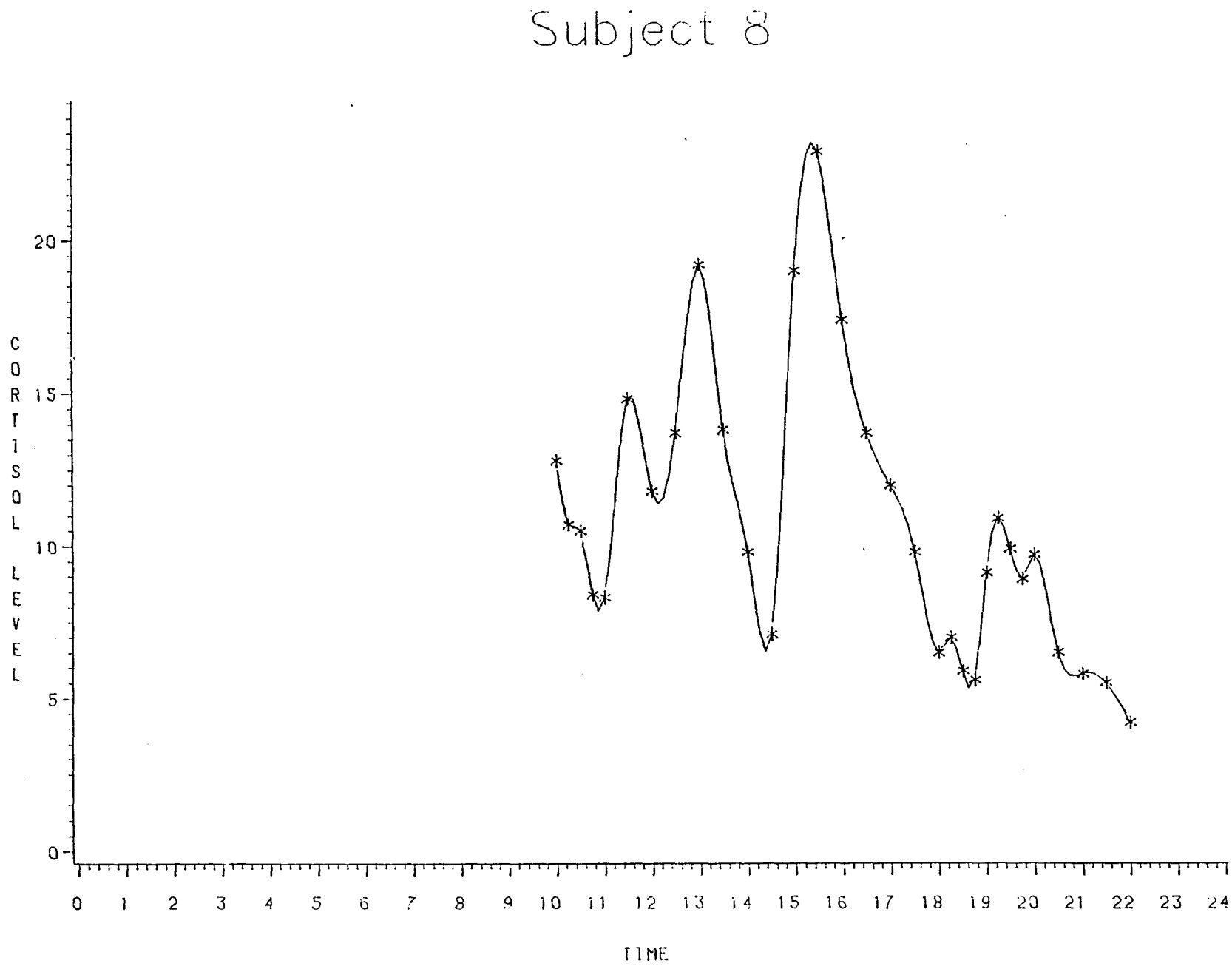

Figure 8. Cortisol levels as a function of time of day.

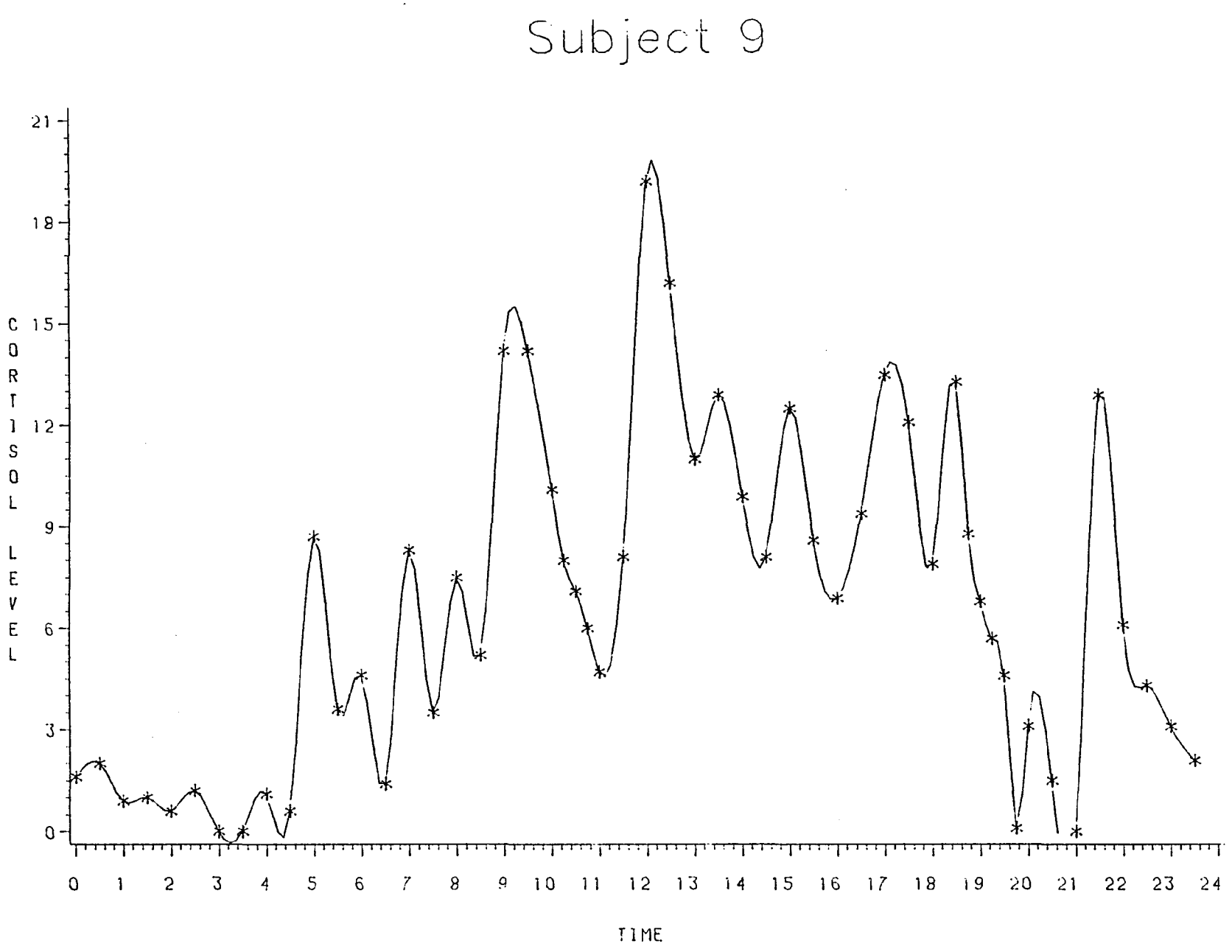

Figure 9. Cortisol levels as a function of time of day.

The DST and time-of-day of measurement

Brown & Shuey (1980) 49 depressives
non-suppression= more than 6ug/dL
11 non-suppressors 3 @ 8am
6 @ 4 pm
6 @ 11 pm

Hamilton severity = between suppressors and non-sup.

Schlesser,Winokur, & Sherman (1980) over 100 depressed and psychiatric/other Ss
8 am testing
non-sup.=more than 5 ug/dL
non-sup. occurred in 45% of pure unipolar disease
76% of " " " w. fam hx.
85% of bipolar pure dep. illness
0 % of 2 depressions,manias,schizophrenics

Carroll,Greden et al. (1980) sample=14 primary psychotic unipolar depressives
non-sup.= more than 5ug/dL
non-sup. : 7 @ 8 am
7 @ 4 pm
8 @ 11 pm

Sternbach, Extein, & Gold (1982) 124 major depressive disorders
non-sup.= more than 5 ug/dL
cortisol measured at 8 am,4 pm,and 12 pm

total non-suppression 51%
non-sup. at all 3 test times 16%

BJ Carroll (1982) a review article on the DST for melancholia (i.e. endogenous dep.)

Conclusions: DST abnormalities may precede bipolars "switch" into depression

Normal Ss remain below 5ug/dL of cortisol following dexameth. administration for at least 24 hours

Depressives release from dexameth. at variable times throughout the next 24 hours.

Sherman, Pfohl, & Winokur (1984) 25 major dep. dis. (see enclosed partial copy)

depressed supressors had the same daily cortisol rhythm as normal controls

non-supressors had an abnormal (unchallenged) cortisol rhythm

release from suppression can occur at any time, with certain hours better (8 am,12 noon, 4 pm) because of normal pattern of cortisol release at that time.

I would conclude that non-suppression to dexamethasone is best tested at multiple times throughout the following day. This results in maximal "capture" of abnormal neuroendocrine responsivity. However, and this may be one of your concerns, 8 am is the time when the fewest normals and psychiatric controls show non-suppression.

DEXAMETHASONE SUPPRESSION AND NON-SUPPRESSION:RELATION TO CLICK DETECTION THRESHOLDS AND SELECTED VARIABLES.

		Hamilton Total	Laterality Quotient	AM Sensitivity	PM Sensitivity	AM Dich.Clk. Asymm	PM Dich.Clk. Asymm
Suppressors	$\overline{X}$	21.9	87.9	26.55	26.55	.50	-.58
	SD	8.1	9.4	4.6	4.2	.82	.69
	n	13	16	16	16	15	16
Non-Suppressors (>5 mg)	$\overline{X}$	31	81.3	27.45	27.25	.30	-.11
	SD	6.4	18.0	1.2	1.1	.69	.70
	n	4	7	5	6	5	6

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