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# Internight Variability of REM Latency in Major Depression: Implications for the Use of REM Latency as a Biological Correlate

Marc Ansseau, David J. Kupfer, and Charles F. Reynolds III

*The internight variability in REM latency in 92 drug-free inpatients with major depressive illness was recorded for 4 consecutive nights and subsequently assessed. Individual coefficients of variation in REM latency [CV = (standard deviation of mean REM latency for 4 recording nights/4-night mean REM latency) × 100] ranged from 5.1 to 121.7, with a mean of 37.0 (SD = 27.3) and a median of 27.4. CV was positively correlated with both age ($p < 0.05$) and age at onset of depressive illness ($p < 0.01$). Male patients showed more variability in REM latency than female patients ($p < 0.05$); likewise, the subgroups of patients who either were incapacitated or had bipolar II illness showed greater variability in REM latency in comparison with the remainder of the sample ($p < 0.05$). When the entire patient sample was stratified by CV into three equal subgroups, the subgroup of patients defined by the highest CV presented the longest sleep latency ($p < 0.05$) and the shortest REM latency ($p < 0.0001$). No other clinical or polysomnographic correlates of REM latency variability were noted nor was REM latency variability related to severity of illness, other subtypes of illness, or clinical response to antidepressant therapy.*

*In selecting REM latency data for assessment of diagnostic sensitivity, the use of the shortest REM latency from* at least 3 consecutive nights *yielded a higher sensitivity (74%–81%) than did the use of any one individually specified night (50%–56%) or different internight means (49%–52%). The same conclusion applied when patient age was taken into account. These results have implications for standardizing the use of REM latency as a biological correlate in major depression.*

## Introduction

Among the various abnormalities of sleep architecture that have been noted in major depressive disorders, a shortening of the time from the onset of sleep to the first REM period (REM latency) is the most specific feature (Kupfer 1976). Mean REM latency in

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Supported in part by NIMH Grants MH 24652, 30915, and 00295, and by a grant from the John D. and Catherine T. MacArthur Foundation Research Network on the Psychobiology of Depression.
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Received June 18, 1984; revised November 2, 1984.


0006-3223/85/$03.30

patients with primary or endogenous depression averages 40–50 min (Kupfer and Thase 1983) compared with a mean value of 90 min in the normal population. Numerous investigators have replicated the finding of shortened REM latency in depressed individuals, both inpatients and outpatients. In addition, shortened REM latency has been reported in all of the major clinical and research subtypes of major depression: primary, secondary, endogenous, unipolar, bipolar, melancholic, autonomous, delusional, and schizoaffective depression (reviewed in Kupfer and Thase 1983). Shortened REM latency has also been reported in some borderline (Akiskal et al. 1982; McNamara et al. 1984) and obsessive-compulsive patients (Insel et al. 1982).

The high sensitivity and specificity of shortened REM latency for major depressive disorders has led some investigators to test its possible use as a biological marker for these illnesses (Akiskal et al. 1982; Berger et al. 1982; Blumer et al. 1982; Feinberg et al. 1982; Kupfer et al. 1982; Rush et al. 1982; Reynolds et al. 1983; Ansseau et al. 1984a). Results of these trials have been divergent, with sensitivity ranging from 35% to 95% and specificity from 62% to 100% (Table 1). However, methodologies have differed among studies on a number of variables, including number of recording nights, REM threshold, and selection of REM latency data for diagnostic assessment. In fact, a major problem in the interpretation of these results is that so little is known about the night-to-night variability (or stability) of REM latency, especially in depressed patients. Prolongation of REM latency has been described as one of the most characteristic features of the "first night effect" (i.e., the influence of the environmental and technical conditions of the sleep laboratory on data collected during the first night) in normal subjects (reviewed in Ansseau et al. 1985). The "first night" effect on REM latency in depressed patients is more controversial: it has been reported to be absent in primary depressives (Coble et al. 1976), reduced (Mendels and Hawkins 1967), and even "paradoxical" or shortened during the first night in psychotic or bipolar depressives (Kupfer et al. 1974),

Some data have suggested that the internight stability of REM latency in normal subjects is limited (Moses et al. 1972; Clausen et al. 1974; Spiegel 1981). Spiegel (1981) classified REM latency as an "unstable" sleep characteristic. No systematic study of the individual night-to-night variability of REM latency in depressed patients has been published to date. However, longitudinal studies of REM latencies have shown a bimodal distribution of REM latencies (with peaks just after sleep onset and 40–60 min later), suggesting that some patients exhibit a large variability in REM latency values (Schulz et al. 1979; Coble et al. 1981). Kupfer et al. (1983b) have suggested that depressive patients who show sustained shortened REM latency night after night require somatic treatment to achieve a complete remission and are likely to be the group most responsive to tricyclic antidepressants. In contrast, patients whose REM latencies oscillate could suffer from atypical or cyclothymic depression and could require treatments other than tricyclic antidepressants.

Another possible source of REM latency variability is patient age. REM latency shows a linear decrease with age in normal subjects (Gillin et al. 1981), a phenomenon that could be more pronounced in depressives (Ulrich et al. 1980; Gillin et al. 1981; Kupfer et al. 1982), with the consequence that the diagnostic utility of REM latency measures could be limited if the subject's age is not known (Gillin et al. 1981). To rule out this possible source of error, Kupfer et al. (1982) proposed the "rule of 90" model, stipulating that if the sum of a patient's age and REM latency equals 90 or less, the patient shows a shortened REM latency, which is usually associated with depression.

Within this general context, then, our investigation had three purposes: (1) to study



Table 1. Diagnostic Performance of RL as a Biological Marker of Depression

| | Inpatients | Outpatients | Criterion group (*n*) | Control group (*n*) | *n* Rec N | Data used | Cut-off RL (min) | Sensitivity | Specificity | PV |
|---|---|---|---|---|---|---|---|---|---|---|
| Feinberg et al. 1982 | + | + | ED (33) | non-ED (28) | 2 | Mean N 1–2 | <35 | 48 | 93 | 89 |
| | | | | | | | + age <75 | 35 | 93 | 85 |
| Rush et al. 1982 | (+) | + | ED (32) | non-ED (38) | 2 | Mean N 1–2 | ≤62 | 66 | 79 | 72 |
| Akiskal et al. 1982 | | + | PD (49) | SD (19) | ≥2 | | <70 on 2 consec. N | 62 | 88 | 90 |
| | | | | Other psych. dis. (13) | | | | | | |
| | | | | Normals (18) | | | | | | |
| Blumer et al. 1982 | | + | D + pain (20) | — | 1 | N 1 | <60 | 40 | — | — |
| Kupfer et al. 1982 | + | + | MD (108) | Normals (36) (Gillin et al. 1982) | 2 | Mean N 1–2 | + age <90 | 65 | 95 | 92 |
| Berger et al. 1982 | + | | ED (20) | ND (19) | 5 | N 1, 3, 5 | <50 on 1 N | 65 | 62 | 50 |
| | | | | Unclassified D (6) | | | | | | |
| | | | | Normals (9) | | | | | | |
| Reynolds et al. 1983 | + | (+) | eld MD (9) | Demented (9) | 2 | Mean N 1–2 | <30 | 67 | 89 | 86 |
| Svenden, in Kupfer et al. 1983b | ? | ? | ED (20) | ND (3) | ? | ? | <50 | 95 | 100 | 100 |
| | | | | Normals (10) | | | | | | |
| Ansseau et al. 1984a | + | | ED (12) | — | 6 | N 1–6 or 3–6 | <50 on 1 N | 67 | — | — |

ED, endogenous depressive; PD, primary depressive; SD, secondary depressive; ND, neurotic depressive; MD, major depressive; N, night; PV, predictive value.

internight REM latency variability over 4 consecutive nights in a large sample of depressed inpatients; (2) to determine possible demographic, clinical, and/or polysomnographic correlates of REM latency variability; and (3) to compare the diagnostic sensitivity of different methods of selecting REM latency data, with or without taking age into account, in order to define or standardize the procedure with the greatest sensitivity for using REM latency as a biological correlate of major depression.

## Methods

### *Sample and Procedure*

The characteristics of the sample and of the evaluation and treatment procedures have been described in detail elsewhere (Ansseau et al. 1984b). Briefly, we studied 92 inpatients on the Clinical Research Unit of Western Psychiatric Institute and Clinic. These patients represented consecutive admissions who met Research Diagnostic Criteria (RDC) for a major depressive disorder according to the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L) (Spitzer and Endicott 1977) and who had a score of at least 30 on the Hamilton Depression Scale (using the sum of two raters on the first 17 items of the scale) at the end of a 2-week drug-free period.

All-night polygraphic sleep recordings were obtained for 4 consecutive nights for each patient and were scored according to the criteria of Rechtschaffen and Kales (1968). Sleep onset was defined by the first minute of Stage 2 sleep that was followed by at least 10 min of Stage 2 sleep, interrupted by no more than 2 min awake or in Stage 1 sleep. REM latency was defined as the time between sleep onset and the first REM period (which had to last at least 3 min), minus any intervening wake time.

Patients were treated with either amitriptyline ($n = 73$) or nortriptyline ($n = 19$) under double-blind conditions. During a 4-week period, the drug dosage was increased in a stepwise fashion from 50 to 200 mg of amitriptyline and from 25 to 100 mg of nortriptyline. The dosage of nortriptyline was consistently half that of amitriptyline. The Hamilton Depression, Brief Psychiatric (BPRS), Raskin, and Beck Rating Scales were administered weekly throughout the study. Patients were defined as treatment responders ($n = 65$) if their final Hamilton score was 19 or less and as nonresponders if their final Hamilton score was 20 or higher (two-rater sum).

The study included 31 male and 61 female patients, from 19 to 69 years of age (mean ± SD = 36.5 ± 12.6). The characteristics of the sample according to RDC subtypes of major depressive disorder are shown in Table 4.

### *Data Analysis*

The individual variability of REM latency values across the 4 consecutive nights was assessed by means of a coefficient of variation (CV), expressed as the following ratio:

$$\frac{\text{Standard deviation (SD) of mean REM latency of 4 nights} \times 100}{\text{4-Night mean REM latency}}$$

This index controls for the effect of mean REM latency on internight variability. The Pearson correlation coefficient was used to assess the relationship between CV and clinical variables having continuous distribution. The sample was then stratified by CV into three



equal subgroups: (1) patients with a CV <18.5 ($n = 30$), (2) patients with CV between 18.5 and 45.0 ($n = 32$), and (3) patients with CV >45.0 ($n = 30$). Clinical characteristics having continuous distribution were compared among the three subgroups using univariate analysis of variance (ANOVA). To test for differences in the handscored sleep data among the three subgroups, we performed a two-factor analysis of variance (using group and night as factors) with repeated measures (the four recording nights) for each variable. We then made a posteriori nonorthogonal contrasts using the Newman-Keuls comparison procedure. The CV in subgroups defined by either gender or RDC subtype was compared to the CV in the remainder of the sample using univariate ANOVA. When subgroup variances differed significantly, the ANOVA was adjusted by the Brown-Forsythe statistic.

### *Assessment of Diagnostic Sensitivity*

The sensitivity of REM latency as a biological correlate of major depression was defined, according to Vecchio (1966), by the percentage of patients exhibiting an REM latency value shorter than or equal to the threshold. Different methods for the selection of REM latency data for assessment of diagnostic sensitivity have been compared: each of the 4 consecutive nights; mean REM latency of nights 1–2, 1–3, 1–4, 2–3, 2–4; and night with shortest REM latency from nights 1–2, 1–3, and 1–4.

## Results

### *Variability of REM Latency Across Nights*

REM latency values across the 4 consecutive nights for the whole sample are presented in Table 2. Individual CVs ranged from 5.1 to 121.7, with a mean of 37.0 (SD = 27.3) and a median of 27.4 (Figure 1).

### *Clinical and Polysomnographic Correlates*

With regard to clinical characteristics and severity ratings, CV showed a significant correlation between age ($r = 0.23$, $p < 0.05$) and age at onset of depressive illness ($r = 0.29$, $p < 0.01$) (Table 3). With respect to gender, clinical response to tricyclic antidepressants, and RDC subtypes (Table 4), depressed men presented a higher mean CV than depressed women ($p < 0.05$). Depressed individuals exhibiting either incapacitating features or bipolar II illness showed higher CVs than the remainder of the sample ($p < 0.05$).

Table 2. REM Latency Across 4 Consecutive Nights in 92 Depressives

| | Night 1 | Night 2 | Night 3 | Night 4 |
|---|---|---|---|---|
| Mean | 48.1[a] | 50.7 | 43.9 | 46.8 |
| Standard deviation | 24.9 | 32.1 | 23.3 | 21.8 |
| Minimum | 2 | 3 | 0 | 0 |
| Maximum | 123 | 167 | 143 | 136 |

[a]REM latency in minutes.

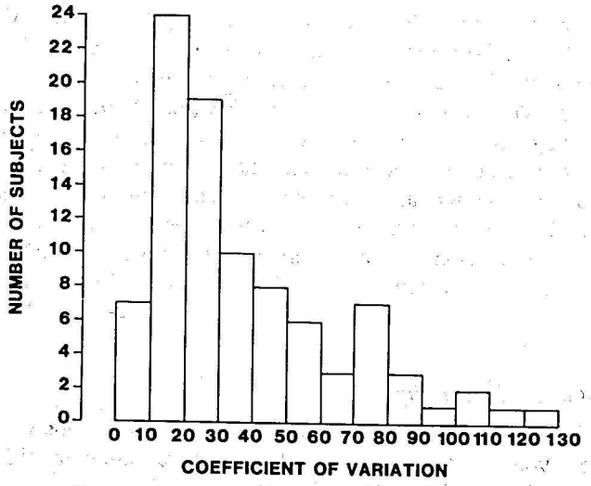


Figure 1. Distribution of individual REM latency variability (measured by the coefficient of variation) across 4 consecutive recording nights in 92 major depressives.

When the clinical characteristics of our sample were analyzed according to stratification of the sample into three equal subgroups based on CV, those patients in the subgroup with the lowest CV had a younger age of onset ($p < 0.05$) (Table 5). The subgroup with the highest CV had the highest baseline BPRS ($p < 0.05$). With regard to sleep parameters, the subgroup with the highest mean CV presented longer sleep latency ($p < 0.05$) and shorter REM latency ($p < 0.0001$) than the other two subgroups (Table 6).

Table 3. Relationship Between Variability in REM Latency Across 4 Consecutive Nights (Coefficient of Variation[a]) and Selected Clinical Characteristics in Major Depressives

| Clinical characteristics | |
|---|---|
| Age | 0.23[b] |
| Age at first onset | 0.29[c] |
| Illness duration | −0.10 |
| Number of episode | −0.14 |
| Duration of current episode | −0.03 |
| *Severity ratings* | |
| Baseline Hamilton | 0.15 |
| Final Hamilton | 0.07 |
| Baseline Raskin | 0.08 |
| Final Raskin | 0.03 |
| Baseline BPRS | 0.15 |
| Final BPRS | 0.19 |
| Baseline Beck | −0.13 |
| Final Beck | −0.04 |

[a]CV = SD mean nights 1–4 REM latency × 100/mean nights 1–4 REM latency.
[b]$p < 0.05$.
[c]$p < 0.01$.



Table 4. Variability in REM Latency Across 4 Consecutive Nights (Coefficient of Variation)[a] in Subgroups of Major Depressives Defined by Gender, Clinical Response, and RDC Subtype

| Variable | Comparison of CV | | F | p |
|---|---|---|---|---|
| Male ($n$ = 31)/female ($n$ = 61) | 45.9 (32.7) | 32.5 (23.2) | 5.1 | <0.05 |
| Responders ($n$ = 65)/ nonresponders ($n$ = 27) | 34.0 (27.1) | 44.3 (27.1) | 2.8 | NS |
| Primary ($n$ = 68)/ secondary ($n$ = 24) | 36.6 (27.4) | 37.6 (28.5) | 0.0 | NS |
| Recurrent ($n$ = 57)[b] | 34.7 (25.4) | 40.7 (30.2) | 1.0 | NS |
| Endogenous ($n$ = 80)[b] | 38.1 (27.9) | 29.9 (23.4) | 0.9 | NS |
| Psychotic ($n$ = 6)[b] | 38.0 (26.7) | 36.9 (27.5) | 0.0 | NS |
| Incapacitating ($n$ = 82)[b] | 38.5 (28.1) | 24.7 (16.9) | 5.0 | <0.05 |
| Agitated ($n$ = 45)[b] | 41.4 (29.2) | 32.8 (25.1) | 2.3 | NS |
| Retarded ($n$ = 46)[b] | 39.2 (26.6) | 34.9 (28.2) | 0.6 | NS |
| Situational ($n$ = 54)[b] | 33.7 (26.7) | 41.7 (27.9) | 2.0 | NS |
| Simple ($n$ = 48)[b] | 36.9 (27.6) | 37.1 (27.4) | 0.0 | NS |
| Unipolar ($n$ = 83)[b] | 35.9 (25.9) | 48.5 (39.7) | 0.8 | NS |
| Bipolar I ($n$ = 4)[b] | 22.4 (14.2) | 37.7 (27.7) | 1.2 | NS |
| Bipolar II ($n$ = 5)[b] | 64.0 (42.5) | 35.5 (25.7) | 5.4 | <0.05 |

[a]CV = SD mean nights 1–4 REM latency × 100/mean nights 1–4 REM latency.
[b]Compared with the remainder of the sample.

Table 5. Selected Clinical Characteristics Among Three Subgroups of Major Depressives Defined According to Their Variability in REM Latency Across 4 Consecutive Nights (Coefficient of Variation[a])

| | Low CV (<18.5) ($n$ = 30) | Intermediate CV (18.5–45.0) ($n$ = 32) | High CV (>45.0) ($n$ = 30) | F | p |
|---|---|---|---|---|---|
| *Clinical characteristics* | | | | | |
| Age | 32.3 (10.9) | 38.4 (11.9) | 38.6 (14.1) | 2.5 | NS |
| Age at first onset | 22.9 (11.4) | 28.8 (13.1) | 30.4 (13.1) | 3.0 | <0.05 |
| Number of episodes | 3.0 (2.5) | 2.8 (2.5) | 2.2 (1.7) | 1.0 | NS |
| Duration of current episode (weeks) | 69.4 (86.0) | 59.8 (56.7) | 51.5 (68.1) | 0.5 | NS |
| *Severity ratings* | | | | | |
| Baseline Hamilton[b] | 32.9 (10.1) | 33.2 (10.6) | 37.2 (10.4) | 1.6 | NS |
| Final Hamilton[b] | 14.2 (10.4) | 17.0 (11.2) | 17.5 (10.7) | 0.8 | NS |
| Baseline Raskin | 9.6 (2.1) | 9.7 (1.6) | 10.3 (2.2) | 1.1 | NS |
| Final Raskin | 6.8 (2.1) | 7.3 (2.6) | 7.1 (1.9) | 0.4 | NS |
| Baseline BPRS | 11.2 (4.2) | 11.0 (4.4) | 13.6 (4.9) | 3.3 | <0.05 |
| Final BPRS | 7.6 (5.2) | 7.7 (5.0) | 10.2 (6.0) | 2.2 | NS |
| Baseline Beck | 19.1 (8.9) | 16.5 (7.2) | 16.9 (7.1) | 1.0 | NS |
| Final Beck | 12.0 (8.5) | 11.9 (8.1) | 11.0 (6.8) | 0.1 | NS |

[a]CV = SD mean nights 1–4 REM latency × 100/mean nights 1–4 REM latency.
[b]Sum of two raters.

Table 6. Selected Sleep Parameters Among Three Subgroups of Major Depressives Defined According to Their Variability in REM Latency Across 4 Consecutive Nights (Coefficient of Variation[a])

| | Low CV (<18.5) ($n$ = 30) | Intermediate CV (18.5–45.0) ($n$ = 32) | High CV (>45.0) ($n$ = 30) | $F$ | $p$ |
|---|---|---|---|---|---|
| *Sleep continuity* | | | | | |
| Sleep latency (min) | 33.1 (24.2) | 33.9 (20.6) | 43.8 (28.5) | 3.4 | <0.05 |
| Time spent asleep (min) | 394.4 (42.1) | 342.7 (43.8) | 329.7 (48.2) | 2.7 | NS |
| Sleep efficiency[b] (%) | 85.3 (9.2) | 84.5 (9.4) | 81.4 (11.3) | 2.3 | NS |
| Sleep maintenance[c] (%) | 93.0 (9.0) | 92.3 (9.6) | 91.2 (10.4) | 0.4 | NS |
| *Sleep architecture (%)* | | | | | |
| Stage 2 | 63.6 (8.1) | 64.7 (8.3) | 61.6 (8.8) | 1.5 | NS |
| Stage 3 and 4 | 3.5 (5.9) | 1.4 (2.6) | 2.3 (4.2) | 1.8 | NS |
| Stage REM | 25.7 (5.8) | 25.1 (6.7) | 25.1 (7.3) | 0.1 | NS |
| *REM measures* | | | | | |
| REM latency (min) | 53.2 (14.1) | 54.0 (23.6) | 34.5 (30.6) | 10.7 | <0.0001 |
| REM activity (units) | 111.7 (50.7) | 116.2 (54.3) | 115.5 (67.1) | 0.1 | NS |
| REM density[d] | 1.25 (0.48) | 1.33 (0.48) | 1.35 (0.52) | 0.5 | NS |
| Number of REM periods | 3.7 (0.7) | 3.5 (0.7) | 3.7 (0.8) | 1.5 | NS |

[a]CV = SD mean nights 1–4 REM latency/mean nights 1–4 REM latency × 100.
[b]Time spent asleep/Total recording period.
[c]Time spent asleep/Total recording period − Sleep latency.
[d]REM activity/REM time.

### *Comparison of Diagnostic Sensitivity of Different Methods for the Selection of REM Latency Data*

The diagnostic sensitivity of various REM latency threshold levels was generally similar during all four individual recording nights (Figure 2), except for the higher threshold values (60–80 min), where the performance on night 1 and, to a lesser extent, on night 2 was slightly lower than on nights 3 and 4. For example, with a REM latency threshold of 50 min (a value suggested by Kupfer 1976 and applied by Berger et al. 1982; Kupfer et al. 1983b; Ansseau et al. 1984a), the diagnostic sensitivity across the 4 consecutive nights was 50% (night 1), 53% (night 2), 56% (night 3), and 55% (night 4). The diagnostic sensitivity of averaged REM latency values was also similar, regardless of the combination of nights used in the calculation (Figure 3). For example, the comparative diagnostic sensitivity of a REM latency threshold of 50 min was 49% (mean nights 1–2), 50% (mean nights 1–3), 52% (mean nights 1–4), 51% (mean nights 2–3), and 49% (mean nights 2–4). However, the use of the shortest REM latency from the 4 consecutive nights was a more sensitive measure than the arbitrary use of any single night or the use of mean values. Moreover, sensitivity increased with the number of nights taken into account (Figure 2). For example, with a REM latency threshold value of 50 min during at least 1 night of the 4, the sensitivity of the measure increased from 65% (nights 1–2) to 74% (nights 1–3) and 81% (nights 1–4).

Finally, we used the sum of REM latency and age to compare the sensitivity of different methods of selecting REM latency data. With single night values alone, the diagnostic



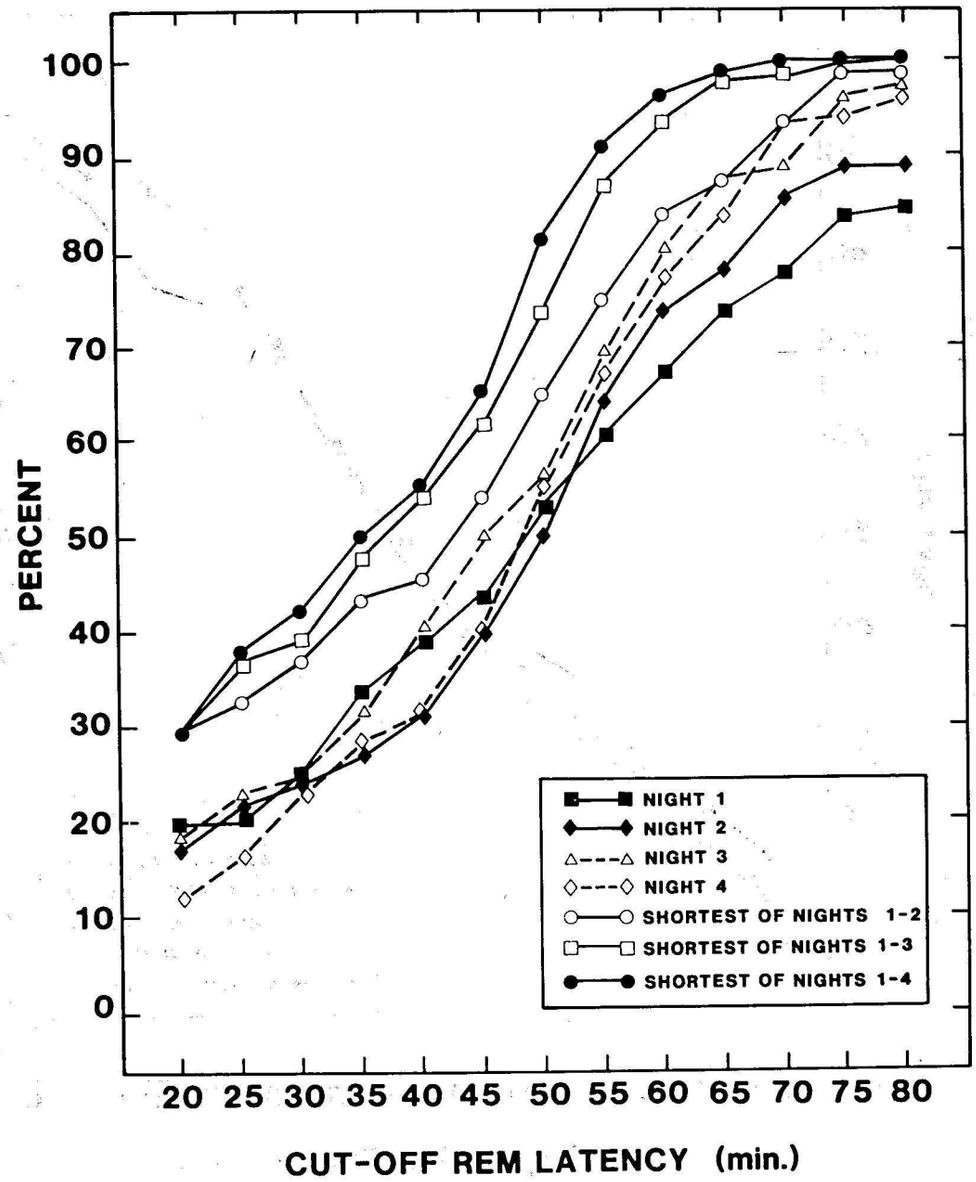


Figure 2. Diagnostic sensitivity of various cut-off REM latencies for the diagnosis of major depression according to the selection of REM latency data.

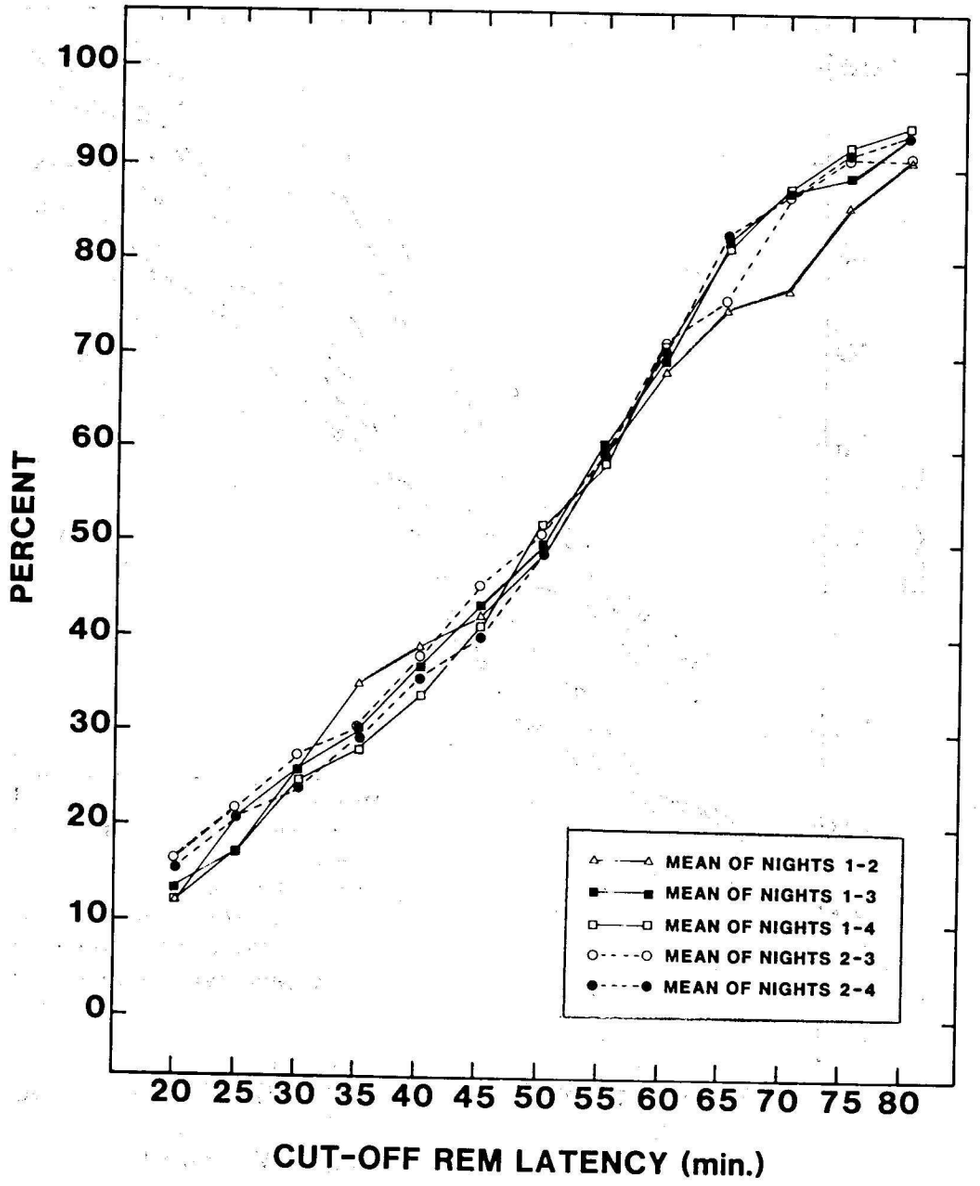


Figure 3. Diagnostic sensitivity of various cut-off REM latencies for the diagnosis of major depression according to the selection of REM latency data.



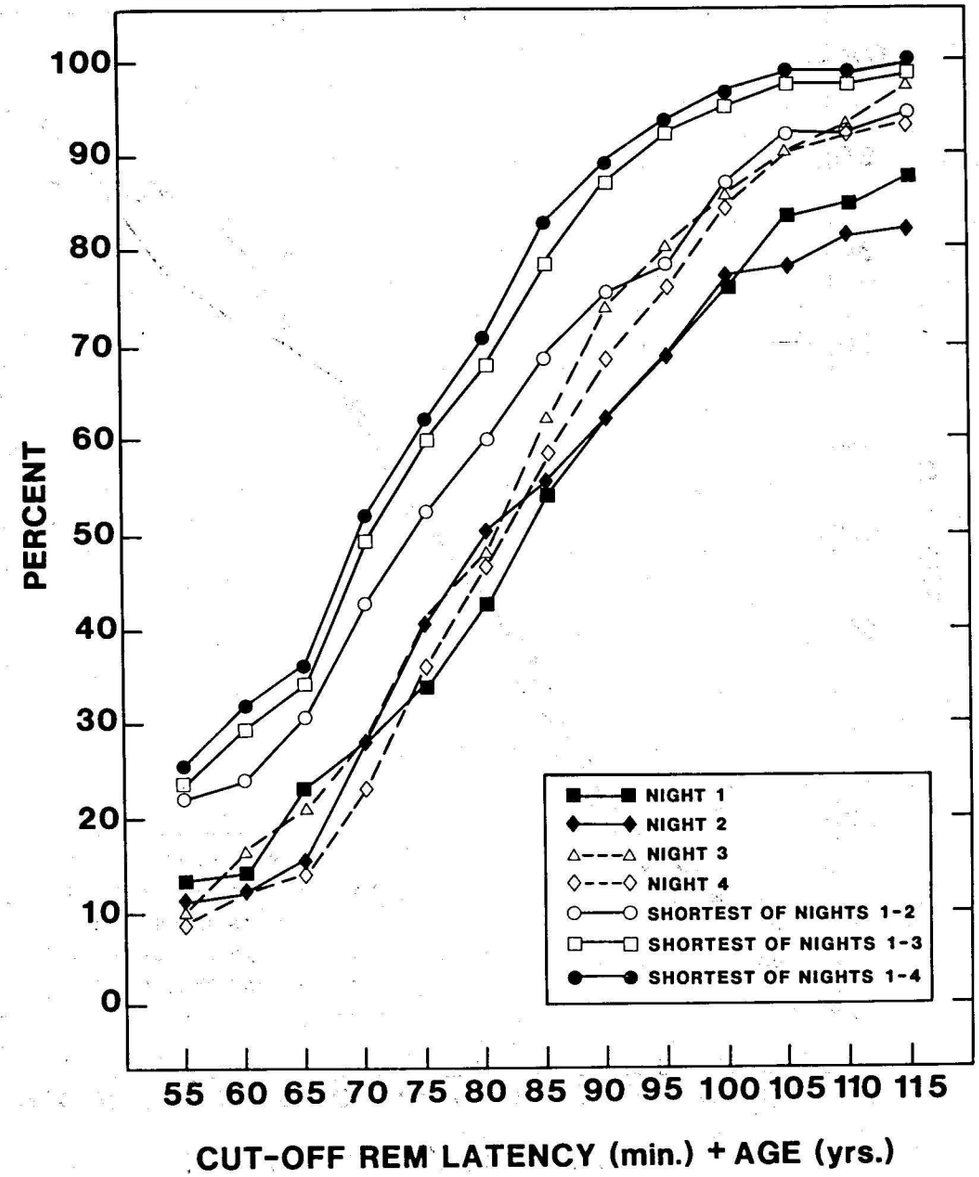


Figure 4. Diagnostic sensitivity of various cut-offs of the sum of REM latency and age for the diagnosis of major depression according to the selection of REM latency data.

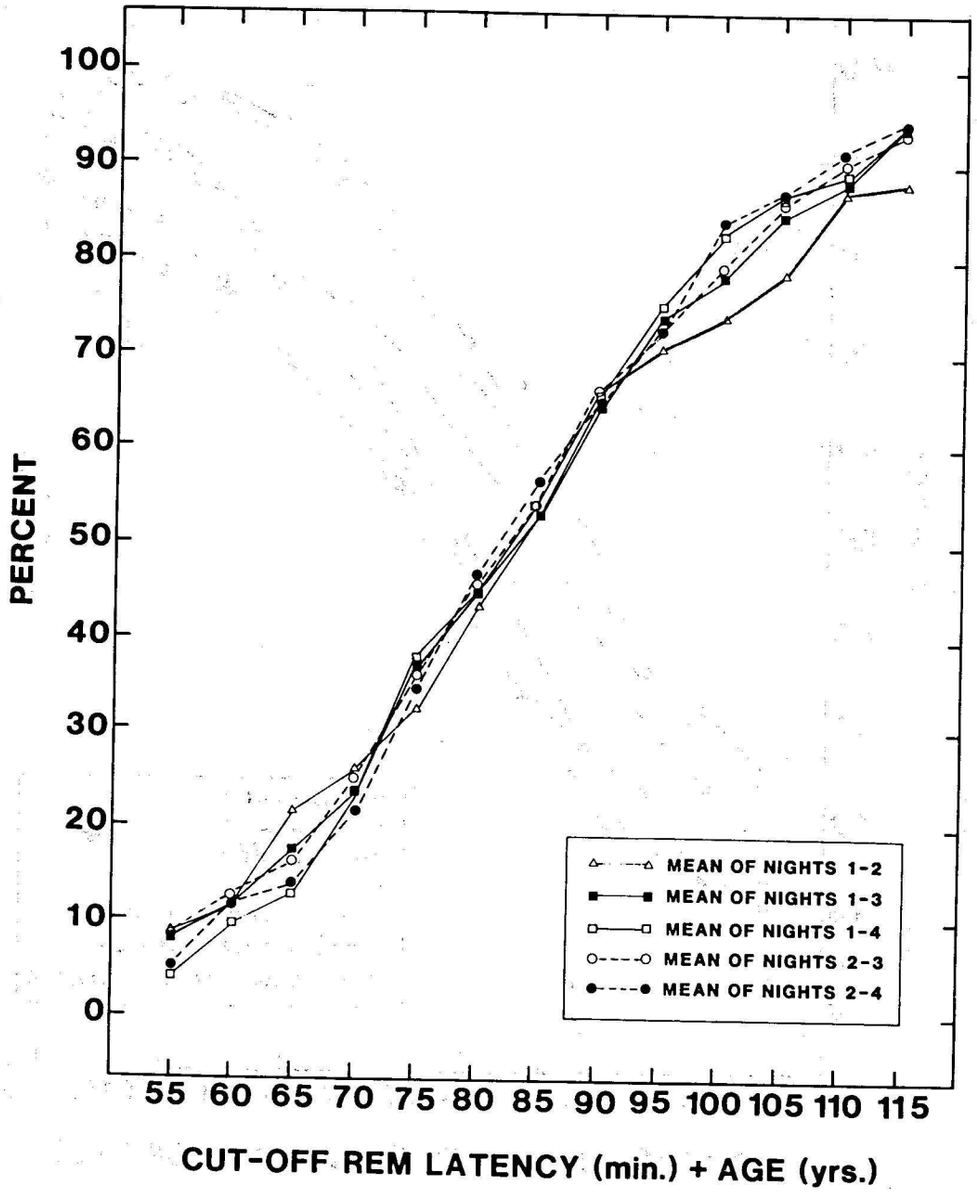


Figure 5. Diagnostic sensitivity of various cut-offs of the sum of REM latency and age for the diagnosis of major depression according to the selection of REM latency data.



performance was lower during the first 2 nights than during the last 2 nights for threshold levels between 85 and 115 min (Figure 4). For example, the threshold recommended by Kupfer et al. (1982) yielded sensitivities of 62% (night 1), 62% (night 2), 74% (night 3), and 68% (night 4). Furthermore, the use of averaged REM latency values yielded generally similar sensitivity rates for different combinations of nights (Figure 5). For example, using a threshold of 90, sensitivity was 66% for the mean of nights 1–2, 65% for the mean of nights 1–3, 66% for the mean of nights 1–4, 66% for the mean of nights 2–3, and 65% for the mean of nights 2–4. In contrast, the use of the shortest value of REM latency plus age from consecutive nights yielded an increase in sensitivity parallel to the number of nights taken into account, with the greatest increment in sensitivity from the addition of the third recording night and only limited improvement from the addition of night 4 (Figure 4). Using a threshold score of 90, the diagnostic performance increased from 75% (nights 1–2) to 87% (nights 1–3) and 89% (nights 1–4).

## Discussion

This study shows stable mean REM latencies across 4 consecutive nights in a sample of 92 inpatients with major depressive disorder. The standard deviations of mean REM latency are similar on the consecutive nights, with the exception of a slightly higher value on night 2. These results support the conclusions of Mendels and Hawkins (1967) and Kupfer et al. (1974) that major depressives do not show a consistent adaptation pattern to the sleep laboratory as compared with normals (discussed previously, Ansseau et al. 1985). However, these stable mean REM latency values conceal large individual internight variability, at least in some patients. In fact, we found the variability in REM latency across 4 consecutive nights to differ widely among patients, from very stable values to widely different ones, as shown by the distribution of the CV.

The finding of an age-related increase in REM latency variability is a new characteristic to add to the list of age-dependent EEG sleep variables in depression (Ulrich et al. 1980; Gillin et al. 1981; Kupfer et al. 1982). These include age-related decreases in sleep continuity measures (time spent asleep, sleep efficiency, and sleep maintenance), an increase in time awake and early morning awakening, and decreases in delta sleep and REM latency. However, Rush et al. (1982) and Akiskal et al. (1982) did not confirm the inverse relationship between REM latency and age in depressed outpatients. An associated age-related decrease in REM time has also been noted by Gillin et al. (1981) but not by Ulrich et al. (1980) and Kupfer et al. (1982). This age-related variability in the sleep of depressed individuals is similar to that found in normal subjects (reviewed in Miles and Dement 1980; Spiegel 1981).

The previous finding that depressives exhibiting REM latency of less than 10 min (called a sleep onset REM period or SOREMP) during at least 1 night were also older both at the time of study and at the age of onset of depressive illness (Ansseau et al. 1984b) suggests that the presence of SOREMPs may be associated with a higher internight REM latency variability. Indeed, 69% of subjects in the high variability subgroup exhibited a SOREMP during at least 1 of the recording nights, compared with 6.7% in the intermediate variability subgroup and 0% in the low variability subgroup ($\chi^2 = 38.7$, $p < 0.0001$).

Our findings do not demonstrate any relationship between REM latency variability and severity of depressive illness or clinical response to tricyclic antidepressants, with the

exception of a slightly higher BPRS baseline score in the subgroup with the greatest variability. However, the BPRS is a global and nonspecific assessment of psychiatric symptomatology, and this higher score may be related mainly to items assessing psychomotor disturbances, reflecting the somewhat higher CV in the agitated and retarded RDC subtypes of depression.

Surprisingly, this study shows a gender-related difference in REM latency variability, with higher variability among depressed men than among depressed women. This finding is not an artifact resulting from older age in the male subgroup; in fact, in this sample, female depressives have a slightly older mean age (37.5 ± 13.2 versus 34.4 ± 11.2, $F = 1.3$, NS). This parameter is the first to be found that shows a gender difference in depressives. However, the sleep of normal men of middle and advanced age (above 40) has been found to be "older" from polygraphic criteria than the sleep of normal women of similar age, with the men having less time asleep, lower sleep efficiency, less delta sleep, and more awakenings and stage shifts (Williams et al. 1974; Spiegel 1981). The higher REM latency variability found in depressive men compared with depressive women may be related to the finding of more sleep disturbances in normal men than in normal women.

Results from our sample suggest that two RDC subtypes of depression are associated with greater variability in REM latency: incapacitating depression and bipolar II illness. Mean age in these subgroups did not differ significantly from that of the remainder of the sample (36.9 ± 12.6 versus 32.7 ± 12.2, $F = 1.0$, NS and 38.6 ± 16.6 versus 36.3 ± 12.4, $F = 0.1$, NS, respectively). The finding of greater REM latency variability in the bipolar II subgroup may be related to the higher incidence of SOREMPs already found in this subgroup (Ansseau et al. 1984b). However, the low number of bipolar II depressives, added to the fact that bipolar I depressives present lower variability than the remainder of the sample, prevents definitive conclusions.

The patients with the greatest variability in REM latency present longer sleep latency and strikingly shorter REM latency than the rest of the sample. These two findings are generally more prominent in primary than in secondary depressives (Kupfer et al. 1978) and in older than in younger patients (Kupfer et al. 1982). The lack of greater symptom severity in this subgroup is somewhat surprising in view of previous reports suggesting an inverse relationship between REM latency and severity of depression (Kupfer and Foster 1972; Spiker et al. 1978), although these findings have not been replicated in outpatients (Akiskal et al. 1982). These inconsistencies may result from low representation of psychotic depressives in our sample, as well as among the outpatients tested. Psychotic depressives are generally characterized by very short REM latency and usually obtain higher scores on the standard rating scales of depression (Nelson and Bowers, 1978; Glassman and Roose 1981; Kupfer et al. 1983a).

A direct implication of the use of REM latency variability as a biological correlate of major depression is the increased sensitivity associated with the selection of the shortest REM latency from several consecutive nights (especially when at least 3 nights are recorded) instead of the use of a specific individual night or the mean from several consecutive nights.

A question that our study does not address is the possible loss in specificity associated with such methods of selection of REM latency data. In fact, Berger et al. (1982) report poor specificity using the method of selecting the shortest REM latency from several nights for diagnostic confirmation of endogenous depression (62%), but their diagnostic



classification of depressives into endogenous, neurotic, and "unclassified" subgroups was based on the ICD-8 system. This nosology lacks operationalized criteria, and a large number of depressives who were classified as "neurotic" according to the ICD-8 system on the basis of preexisting personality disorders meet RDC or DSM-III criteria for major depression (Klerman et al. 1979). In support of the diagnostic specificity of our method of selecting the shortest REM latency from consecutive nights, it should be noted that none of the nine normal control subjects included in the study experienced any night with a REM latency shorter than 50 min (Berger et al. 1982). The correction of REM latency for patient age according to the "rule of 90" system yields the same conclusion of increased sensitivity when the shortest REM latency from several consecutive nights is selected as the REM latency measure. The gain in sensitivity is large when a third night is recorded, but minimal with the addition of a fourth recording night. The use of the actual "rule of 90" applied to the shortest REM latency of three recording nights yields a sensitivity of 87%. Although the associated specificity of this method remains to be evaluated, our results appear to be promising for the standardized use of REM latency as a biological correlate of major depression.

Our gratitude is due to V. Grochocinski, Ph.D., for her generous assistance in data management; to A.B. McEachran, M.S., who performed the data analysis; and to K. Slomka and B. Bradbury for their technical assistance.

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