Kinetics of Non-Rapid Eye Movement Delta Production Across Sleep and Waking in Young and Elderly Normal Subjects: Theoretical Implications

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INTRODUCTION

THE OBSERVATION THAT THE DELTA (0.3-3 HZ) ENCEPHALOGRAM (EEG) OF NON-RAPID EYE MOVEMENT (NREM) sleep increases with prior waking duration and decreases across sleep1 provided the cornerstone of the homeostatic model of NREM delta.2 According to this model, NREM delta EEG is a correlate of a homeostatic process that reverses “neurometabolic” changes produced in plastic neuronal systems during waking. The hypothesized homeostatic events restore the brain for renewed plastic activities. The intensity of the homeostatic process is proportional to the intensity of NREM delta EEG (stage 4 EEG or computer-measured delta power or integrated amplitude). Changes in the intensity of delta EEG, therefore, indicate the kinetics of sleep homeostasis. Borbely3 incorporated these ideas in a “two-process” model of sleep, which proposes that a circadian process interacts with the homeostatic process to regulate sleep-wake propensity. The quantification of “process-S,” the homeostatic process, states that delta intensity increases with increasing prior wake duration at a saturating exponential rate and that it declines exponentially across sleep.

In spite of many studies based on the two-process model, the kinetics of the increase in delta propensity across waking and the decrease across sleep have not been statistically established. Dijk et al4 fit a saturating exponential function to the delta increase across naps taken at different times of day in 6 young adult female subjects. While they judged its fit “satisfactory,” they did not test statistically whether a saturating exponential fit their data significantly better than a linear or logistic model. We5 plotted the delta increase across daytime naps using cross-sectional data from several studies. These plots produced a logistic (S-shaped) curve. We noted that Dijk et al’s data also appeared logistic, but a firm conclusion would require statistical analyses of nap data using a within-subject design with an adequate N.

Many more studies have been published describing the delta decline across NREM periods (NREMPs). Early investigations measured this change as the decline in number of visually scored stage 4 epochs across hours of sleep.1,2,6 Beginning in 1978, the decline of computer-measured delta has been analyzed statistically, typically as the trend across NREMPs.7-10 Most of our own studies have shown only the linear component of this decline to be statistically significant. However, we1,8 and others16 have sometimes observed weaker but statistically significant quadratic trends. As discussed below, a significant quadratic component indicates the presence of curvature but does not by itself demonstrate exponential change. However, the absence of a significant quadratic component in arithmetic plots of delta across NREMPs argues strongly against exponential change. One recognizes, of course, that linear delta growth or decline cannot continue indefinitely. When the duration of waking is extended beyond a normal 16-hour day, the curve for delta propensity flattens. Similarly, the curve for the delta decline across sleep flattens late in the sleep period (in NREMP5) and remains at this level when sleep is extended.

In addition to its dependence on prior waking, NREM delta is substantially lower in normal elderly than in young adults.11 This difference was first demonstrated with visual scoring of stage 4 sleep.2,6,12-14 It was subsequently confirmed and elaborated with direct computer measurement of delta EEG using period-amplitude (PA)16 or power spectral analysis with the fast Fourier transform (FFT).17-19 We have long empha-
sized (c.f. 20) that the close relation of delta to age holds fundamental clues both to its biologic function and to the nature of brain aging.

The present investigation of baseline, nap, and postnap sleep in two age groups used orthogonal components analysis of variance to examine the increasing delta production rate across daytime naps and its decrease across sleep in young normal (YN) and elderly normal (EN) subjects. Specifically we wished to determine whether these rates were linear or showed a curvilinear (quadratic) component that would be consistent with exponential rates of change. Preliminary descriptions of these findings were presented at the 2001 and 2002 annual meetings of the Association of Professional Sleep Societies.

METHODS

Study Design

Sleep EEG was recorded on four separate 2-day sessions, each consisting of a baseline night, a nap the following day, and a postnap night. Nap starting times were 0900, 1200, 1500, and 1800. We had intended to systematically vary the nap times across subjects, but conflicts with the subjects’ schedules made this impractical. Following the subjects’ scheduling needs produced a good variation in the nap orders. Of the subjects, 9 subjects took one of the early naps first and 10 subjects took one of the late naps first. For YNs, the numbers were 7 and 12, respectively. ENs, 9 subjects took one of the early naps first and 10 subjects took one of the late naps first. For YNs, the numbers were 7 and 12, respectively. The median interval between 2-day recording sessions was 11 days for the YNs and 9 days for the ENs.

Subjects

Table 1 describes 19 YN and 19 EN subjects who completed the entire study. YNs were undergraduate and graduate students recruited from the University of California Davis (UCD) campus by newsletters. ENs were living independently in the immediate geographic area and were recruited with announcements in the local newspaper and in senior citizen centers. All subjects were paid for their participation, and the UCD Institutional Review Board approved this research.

Baseline Sleep Schedules

Subjects’ time in bed for the baseline and postnap nights was 11:00 PM – 7:00 AM except for 13 YNs who were in bed between 11:30 PM and 7 AM. The latter was our intended time-in-bed schedule for all subjects. However, we recruited YNs more rapidly than ENs and had studied 13 YNs on the 11:30 AM – 7 AM schedule before initiating study of the ENs. When the ENs entered the study, they strongly preferred an earlier bedtime and so the schedule for the 6 remaining YNs and all 19 ENs was set at 11 PM - 7 AM. This schedule kept constant the time between the end of the sleep period and the first nap, but it resulted in 30 minutes less time in bed for the first 13 YNs. We show below that this difference in sleep period did not affect the results. For both schedules, subjects maintained the laboratory time-in-bed at home for at least 3 nights prior to each recording session. Subjects were instructed on the importance of maintaining the prescribed sleep schedule and avoiding daytime naps at home. They were also questioned regarding naps when they reported to the laboratory. Sleep schedules were further documented by requiring the subjects to telephone the laboratory on going to bed and arising in the morning. These calls were recorded and time stamped. In addition our subjects appeared highly motivated and conscientious. They did, in fact, occasionally report an inadvertent nap that required rescheduling the recording session. The high internight reliability and relatively small absolute differences in delta EEG across baseline nights in these data indicate that subjects complied well with the experimental requirements.

Daytime Naps

Subjects were required to remain in bed in a darkened but not entirely light-proof room for 2 hours at each scheduled nap time. The a priori criterion for a “successful” nap was 25 minutes of sleep. If a subject failed to meet this criterion on 3 attempts, he was dropped from the study. Two ENs and two YNs (in addition to the 19 subjects per group) were unable to complete all the naps.

EEG Recording

The C3-A2 and C4-A1 EEG were recorded continuously on a Grass model 78 polygraph throughout the time in bed. Electrode impedance measured with a Grass impedance meter was <5 Kohms at the start of each recording. The C3-A2 lead was used for the analyses here except when excessive artifact was present, in which case the C4-A1 lead was used. For any given subject, only the C3 or C4 lead was used for all analyses. C3 was used in 24 subjects and C4 in 14. The high-pass filter was set at 0.3 Hz and the low-pass filter at 100 Hz. The 60-Hz notch filter was disabled at all times. In addition to C3/C4, an O1-A2 lead and an EOG lead recorded from the left outer canthus to the forehead were used in sleep stage scoring.

Data Acquisition and Scoring

EEG was digitized at 200 Hz and saved to hard disk by PASS PLUS (Delta Software, St. Louis). FFT and PA analyses (see below) were
simultaneously performed on-line, and these outputs were also saved to the hard disk. The digitized data and the FFT and PA results were subsequently transferred to compact disk. Consecutive 20 second epochs of the digitized EEG were scored off-line on a computer monitor for NREM, REM, waking, and artifact. A second rater checked this scoring and a third experienced EEG scorer reconciled any differences. Visual sleep-stage scoring was performed according to modified Rechtschaffen and Kales criteria\(^{22}\) without knowledge of the EEG computer analyses. PASS PLUS calculated NREMPs and REM periods (REMPs) according to modified Feinberg and Floyd criteria.\(^{23}\) The database with each 20 second epoch’s visual scores (sleep stage, artifact notation) was linked with the database of signal-analysis results, making it possible to tabulate FFT and PA measurements for each epoch by frequency band, sleep stage, and NREM.

“Skipped” First REMPs

When delta kinetics are measured as the decline across NREMPs, the issue of a “skipped” first REMP can crucially determine whether the delta decline appears linear or exponential (c.f.\(^{24,25}\) and discussion below). “Skipped” first REMPs occur when REM sleep is not scored in the first trough of the cyclic delta curve across sleep. To rule out contributions of a skipped first REMP to the trend analyses here, we examined scattergrams of visually scored NREM1 durations in each group. When outlying values were found, both authors examined the corresponding smoothed delta curves. Curves that contained two distinct peaks separated by a clear-cut trough were treated as two NREMPs. The effects of these analyses are discussed further below.

FFT Analysis

We configured PASS PLUS to perform FFT analysis on 5.12 second Welch tapered windows with 2.62 second overlap, yielding 8 windows per 20-second epoch. For fundamental reasons, FFT analysis does not, in general, yield integer frequency bands. For example, the 0.3-3 Hz delta band used for the PA analyses corresponded most closely to 0.29 to 3.03 Hz in the FFT measurements. To simplify the presentation, the FFT delta band is also reported as 0.3-3 Hz.

PA Analyses

In addition to FFT, PASS PLUS simultaneously analyzed the EEG with both zero-cross and zero-first derivative PA algorithms. Both methods apply a specifiable smoothing constant (here 5 \(\mu\)V) to eliminate spurious waves caused by electrical jitter. PA frequency resolution is greatly enhanced by the use of linear interpolation, which avoids the storage burden that would result from the oversampling otherwise required for equivalent resolution (J. D. March, unpublished analyses). Our laboratory normally uses zero-cross PA to analyze delta frequencies and the zero-derivative PA to analyze higher frequencies. Since this study concerns only the delta band, the following four PA zero-cross measures are reported for this frequency band: (1) Integrated amplitude (IA) in \(\mu\)V\(\cdot\)sec. This measure sums the areas under all rectified delta halfwaves. IA is essentially a composite measure that reflects the combined contributions of wave incidence and amplitude and, therefore, corresponds to FFT power. (2) Time in band (TIB) in seconds. This is the total time occupied by the delta-frequency halfwaves. TIB is a measure of wave incidence, since it is almost entirely determined by the number of waves occurring in the frequency band; variations in wave period, while often statistically significant, have extremely small effects on TIB compared to variations in the number of waves. (3) Average sample amplitude (ASA) in \(\mu\)V. This is a measure of the average amplitude of the waves in 0.3-3 Hz. Delta IA is the product of wave amplitude and time occupied by the frequency band; i.e. IA = ASA \times TIB. For details, see\(^{7}\).

(4) Mean frequency (Hz) of waves within the delta band: This is half the number of zero-crosses (two zero-cross halfwaves = a full wave) divided by TIB.

Measures of Delta Growth and Decline

We measured the increasing intensity of delta production across daytime naps and its decreasing intensity across the NREMPs of baseline night sleep as power/minute and IA/minute. In addition we measured the growth and decline of wave incidence (TIB/minute) and wave amplitude (ASA). The across-night trends for each of these delta measures were analyzed across successive NREMPs, and the trend of the growth of delta production with increasing prior waking was analyzed across successive naps. The final point of the nap (growth) curve for each delta measure was its value in NREM1 of baseline sleep (mean of the 4 baseline nights). This final point represents the delta increase from the level in the 1800 nap.

Absolute and Normalized Measures of Decline and Increase in Delta Production Rates

Declines and increases in both absolute and normalized measures of delta were calculated. Data were normalized for each subject by converting the absolute value for each data point to its percentage of that subject’s 4-night baseline mean for that measure. This normalization permits analysis of delta kinetics with the age differences in baseline delta levels controlled.

Statistical Analyses

These analyses addressed two main questions. (1) Are the decline and increase in absolute and normalized rates of delta production linear or do they show significant curvature (quadratic component) or inflections (cubic component)? (2) Do the kinetics of the absolute and normalized delta measures differ between age groups in shape or slope? Both questions were investigated with a repeated measures ANOVA with orthogonal components.\(^{26,27}\) In addition, we used simple t-tests to evaluate the significance of the age differences in the main baseline sleep measures. A detailed age comparison of computer-measured sleep EEG in the two groups will be presented in a later paper. The problem of multiple statistical tests has not fully been resolved. Because of the large number of statistical comparisons required by our data, we set the alpha level a priori at 0.01 for all ANOVA and t-test results.

RESULTS

Baseline and Nap Sleep in YN and EN Groups

Table 2 presents the 4-night baseline means for the relevant visually scored sleep variables in the two groups. Although 13 of the 19 YN subjects spent 30 minutes less time in bed than the EN group, the YNs obtained significantly more total, NREM, and REM sleep. In addition there was no difference in total sleep time between the 6 YNs who spent 8 hours in bed and the 13 YNs who spent 7.5 hours in bed. Thus, differences in time in bed did not affect the results of this study. Table 2 also

Table 4—Computer-measured delta EEG in baseline NREM sleep in young normal (YN) and elderly normal (EN) subjects.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Power/minute</th>
<th>IA/minute</th>
<th>TIB/minute</th>
<th>ASA (\mu V)</th>
<th>Mean delta freq. (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power (\mu V\cdot sec)</td>
<td>92,740</td>
<td>310</td>
<td>209,765</td>
<td>706</td>
<td>9,141</td>
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<td>YN Mean</td>
<td>s.e.</td>
<td>10,430</td>
<td>33</td>
<td>12,269</td>
<td>38</td>
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<tr>
<td>EN Mean</td>
<td>s.e.</td>
<td>33,851</td>
<td>102</td>
<td>118,686</td>
<td>431</td>
</tr>
<tr>
<td>ASA (\mu V)</td>
<td></td>
<td>2,541</td>
<td>8</td>
<td>5,787</td>
<td>17</td>
</tr>
<tr>
<td>t-test (t_0)</td>
<td></td>
<td>5.49</td>
<td>5.55</td>
<td>6.71</td>
<td>6.61</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</tr>
</tbody>
</table>
| IA, integrated amplitude; TIB, time in band; ASA, average sample amplitude

shows that ENs and YNs did not differ in sleep latency. The lower sleep durations in the ENs were caused by significantly higher wake time after sleep onset.

Table 3 presents the NREM durations for the 4 naps. It shows that ENs consistently obtained less NREM sleep in the naps (p<0.01) than did YNs. NREM durations did not differ significantly across the 4 nap times in either age group.

Table 4 shows that the rates of delta production within NREM sleep were substantially and significantly lower in the ENs. Power/min was reduced by 60.3% and IA/min by 38.9% (p<0.0001 for both measures). Significantly lower levels of both delta TIB and amplitude ASA in the ENs caused their lower levels of power and IA. Wave frequency and amplitude are inversely related in the NREM EEG.21,28 Table 4 shows that the mean frequency of the lower amplitude delta waves in the ENs was significantly higher than the mean frequency of the delta waves in the YNs.

**Kinetics of Delta Decline Across NREMPs and its Increase Across Daytime Naps**

Figures 1-3 plots absolute and normalized declines across NREMPs for FFT and PA delta measures and their increases across daytime naps. The highest (final) point in each waking curve is the value of the measure in NREMP1 on the baseline night (4-night mean). The statistical analyses of these data are presented in Tables 5 and 6.

Figure 1A plots the decline in absolute FFT power/min across NREMPs and its increase across daytime naps. Tables 5B and 6B show that the decline and increase were both linear without significant quadratic or cubic components. Figure 1A and the significant age-x-linear trend interaction (Tables 5B and 6B) demonstrate that the slopes of quadratic or cubic components. Figure 1B plots the FFT power/min data of Figure 1A after they were normalized as the proportion of each subject’s baseline level increased across waking and decreased across sleep at the same rate in YNs and ENs.

Figures 1 C-D illustrate the results for absolute and normalized PA IA/min. As noted previously, IA is homologous with FFT power; each is determined by the combined effects of wave amplitude and incidence. While therefore expected, the similarity of the IA/min curves in Figures 1C-D with the corresponding FFT curves in Figures 1 A-B was nonetheless striking. Tables 5B and 6B show that the statistical analyses for IA/min yielded the same results as those for FFT power/min: absolute IA/min declined linearly across NREMPs and increased linearly across naps. Both the declining and increasing linear slopes for absolute IA/min were significantly steeper in the YNs. As with normalized FFT power/min, the linear slopes of normalized IA/min did not differ significantly in the two age groups. Similarly the decline in IA/min lacked significant quadratic or cubic components.

Figures 2 A&B illustrate the decline in delta incidence (TIB/min) across NREMPs and its increase across naps. In addition to its significant linear trend, TIB/min was the only measure of delta decline that showed a significant (p=0.01) quadratic component; this was present in both the absolute and normalized trend. Examination of Figure 2B indicates that the quadratic trend resulted from a disproportionately low TIB/min value in NREMP1 of the ENs. The NREMP1 value for the ENs was below that for NREMP2. The EN curves for absolute and normalized TIB/min across NREMPs 2-4 were almost perfectly linear. The interaction with age of the linear decline of TIB/min approached significance for the absolute but not for the normalized data (Table 5B). The increase across waking for absolute and normalized TIB/min (Figure 2B) was linear in the two age groups and did not differ in slope. This increase did not have significant quadratic or cubic components.

Figures 2 C&D and Table 5 present the data for delta wave amplitude (ASA). Both the absolute and normalized values for ASA declined linearly across NREMPs. In contrast to the other measures of delta decline, the normalized as well as the absolute slope for ASA across NREMPs was significantly steeper in the YNs. Quadratic or cubic trends were not significant for these amplitude measures. However, Figures 2 C-D show that the values for ASA in NREMP1 in the ENs appeared disproportionately low. This finding for ASA resembles the low value for TIB/min in NREMP1 in the ENs, although it was not sufficient to produce a significant quadratic component. The relatively low TIB/min and ASA values in NREMP1 in the ENs produced relatively low values for power/min and IA/min, although they were not sufficiently low to produce significant quadratic trends in the composite measures.

Figure 2C shows that absolute ASA increased linearly across naps. The slope for the increase in absolute ASA was significantly steeper in the YNs (Table 5B). The curve for normalized ASA was also linear, but its slope did not differ significantly between age groups. Normalized ASA showed no significant quadratic or cubic trends (Table 5B).

The curve for mean delta frequency (Figure 3A) in ENs was above and parallel to the YN curve. In both groups, delta frequency was at similar levels in NREMPs 1 and 2 then
increased linearly across NREMPs 2-4. The similar levels of mean frequency in NREMPs 1 and 2 in both groups and their linear increase across NREMPs 2-4 produced robust quadratic as well as linear trends. The cubic component was also significant.

While the change in mean delta frequency across NREMPs has been reported in earlier studies of young and elderly subjects, the change in delta frequency across daytime naps has not previously been described. Figure 3B shows that mean delta frequency decreased across successive naps as delta amplitude increased. The trends were linear for both the absolute and normalized data, and these slopes did not differ in the two age groups. The quadratic and cubic components of those trends were not significant.

Qualitative Tests for Exponential Rates of Change in Delta

The two-process model assumes that delta declines exponentially across NREMPs and increases across waking as a saturating exponential. Our failure to find significant quadratic components in the ANOVAs for delta decline and growth argued against these exponential assumptions. Because of its theoretical importance, we evaluated this issue further by examining the magnitudes of the successive changes in delta power/min across NREMPs. If the decline was exponential, the difference between NREMPs 1 and 2 should be substantially larger than the differences between NREMPs 2-3 and 3-4. This was not the case. The successive differences in the YNs were 68, 104, and 81 µV^2*sec/min per NREMP. In the ENs, the corresponding differences were 13, 44, and 23 µV^2*sec/min per NREMP. In both groups, the decline from NREMP1 to NREMP2 was actually smaller than the subsequent declines. This pattern is, qualitatively, the opposite of an exponential decrease.

We performed the same analysis for the increase in delta power/min across waking. Differences between successive points on a saturating exponential curve should become progressively smaller. Neither the YN nor EN nap data exhibited this pattern. For YNs, mean differences in delta power/min per hour of waking, based on changes between successive naps and between the last nap and the first NREMP of baseline sleep, were 16, 21, 20, and 23 µV^2*sec/min/hr. For the ENs the corresponding values were 12, 0.2, 9.4, and 7.6 µV^2*sec/min/hr. Similar results were obtained for the growth and decline of IA/min, ASA, and TIB/min. Thus, neither the statistical trend analyses nor the qualitative patterns of delta kinetics supported the hypothesized exponential decline across sleep or the saturating exponential increase across waking.

DISCUSSION

One short methodologic point deserves mention before discussing the data presented above. The linear changes in delta across sleep and the increase in delta across daytime naps are seen in the mean group data but not in data from individual subjects. As previously discussed, individual subject-night data are more variable, and delta often does not decline monotonically. The pulsatile appearance of computer-measured delta on individual nights may suggest a different interpretation of the underlying physiologic processes from that pointed to by averaged data.

Age Differences in Vigilance States in Baseline Sleep

The present data are consistent with many previous studies of baseline sleep EEG in YNs and ENs.2,6,12-15,29 This work shows that elderly subjects fall asleep as readily as young adults but awaken more frequently after sleep onset. Arousals occur more frequently later in the sleep period. Regression analyses, although thus far based on limited data, indicate that the number of awakenings increases linearly between childhood and old age.30 Time in bed awake after sleep onset remains at relatively low levels until about age 40 years, and then it increases with positive acceleration producing a parabolic age curve.30,31 When time in bed is controlled, as was done here for baseline sleep and naps, ENs consistently produce significantly less sleep than do young adults.

Age Effects in Rate of Delta Production

Decreased NREM delta in the elderly was initially demonstrated with visual scoring (see references cited above) and subsequently corroborated with computer analyses.16,18,19,32 In the present study, PA and FFT analyses both replicate the robust age differences in delta previously reported with sleep-stage scoring. Visually scored stage 4 (which is highly correlated with FFT and PA measured delta7,33) declines hyperbolically from its peak in early childhood.30,31 The decline is steep during late childhood and adolescence and then continues more slowly through adulthood, reaching a plateau in the fifth to sixth decade of life. While the delta decline is much slower during adulthood than during adolescence, it is nonetheless appreciable: the rate of delta production (integrated amplitude or power) at age 72 years is half or less than that at age 22 years. The magnitude of this age effect is illustrated by the fact that the absolute rate of delta production in YNs at the end of the night (in NREM4) is higher than that of ENs at the beginning of the night (in NREM1).

It has been traditional in the sleep literature to regard the delta decline over adulthood as caused by “aging” (degenerative changes) and the delta decline across adolescence as “developmental.” There is, however, no evidence that suggests qualitatively different processes operate in the two age periods.34 If a single process is involved, it must in some sense be “developmental,” since the inevitable delta decline during adolescence cannot be caused by pathologic age change.

Figure 2—Trends across baseline sleep and daytime naps for period amplitude (PA) measures of delta incidence (Time in bed awake [TIB/min]) and amplitude (average sample amplitude –ASA). NREMP1 data are replotted for the last point on the nap line. 2A-B. Absolute and normalized (percent of baseline mean) TIB/min in young normal (solid line, filled symbols) and elderly normal (dashed line, open symbols) subjects. 2C-D Absolute and percent ASA in the two groups. The results for absolute and normalized incidence and amplitude resemble those shown in Figure 1 for FFT power and PA integrated amplitude, both of which represent the combined effects of wave amplitude and incidence. Some of the statistical details differ. See Tables 5 and 6.
The neuronal changes that produce the ontogenetic decline in delta are unknown. However, the delta age curve appears to parallel that for brain plasticity. Moreover, the ontogenetic curves for delta, cerebral metabolic rate, and synaptic density fit the same statistical model over the first 3 decades of life. These parallel curves might be produced if delta levels at any age reflect the proportion of “uncommitted” to “committed” neurons. The age decline in NREM delta has not yet been recognized as a fundamentally important neuroscience problem. Nevertheless it seems likely that, as envisioned earlier, solving this problem will shed light on delta homeostasis as well as on what appears to be a lifelong process of brain “development.”

The Decline Across NREM Periods in Delta Production is Linear in ENs and YNs and its Slope is Significantly Flatter in the ENs

FFT and PA of 0.3-3 Hz power and integrated amplitude yield virtually identical linear curves for the decline in absolute delta across NREM periods in YNs and ENs. These linear slopes are significantly less steep in the elderly. These findings replicate, at similarly high confidence levels, our previous results in a study of 48 ENs and 41 YNs. They also are consistent with Landolt et al’s recent report that the slope of the decline in delta power in 8 older subjects (mean age 62.0 yrs) was significantly less steep than in 8 YNs (mean age 22.4 yrs).

The normalized data also show linear delta declines and increases. However, normalization virtually eliminates the delta slope differences in the two age groups. Thus, normalized delta FFT/min and integrated amplitude/min decline across sleep and increase across waking at about the same rate in YNs and ENs. This means that an hour of sleep (or an hour of waking) produces roughly equal proportionate delta changes in YNs and ENs even though they differ in mean age by a half century. Although elderly subjects have a lower absolute capacity to produce delta than do young adults, waking and sleep produce similar proportions of delta debt and recuperation relative to this capacity.

The reduced delta in the elderly is often regarded as evidence of reduced homeostatic “drive.” If homeostatic “drive” means the absolute amount of delta produced per hour of waking, then drive is obviously diminished in the elderly. If, however, homeostatic drive means the proportion of one’s delta that increases per hour of waking, homeostatic drive is remarkably similar in young and elderly. A clearer answer to this question awaits identification of the electrophysiologic bases of delta EEG and the cellular mechanisms of the hypothesized restorative process.

One important question is whether the diurnal pattern of delta variation could be produced entirely by the circadian mechanisms that influence sleep-wake propensity. Circadian effects and interaction of circadian and homeostatic mechanisms cannot be adequately evaluated without a forced desynchrony protocol. Such a protocol would have been impractical for this investigation. The literature indicates that a strong circadian effect on delta EEG is unlikely. Dijk et al performed experiments in which homeostatic mechanisms were pitted against circadian factors. Their results show that homeostatic mechanisms predominate for delta, whereas circadian factors strongly determine sigma variations.

The Slopes for the Increase in Absolute Delta Production Across Daytime Naps are Linear in YNs and ENs and are Significantly Flatter in the Elderly

Again, FFT and PA analyses yield highly similar curves for the increase in delta propensity across waking. Both methods show that the absolute rate of delta production increases linearly as prior waking duration increases. The slope of the increase in absolute delta in progressively later naps is significantly flatter in the elderly. The flatter slopes in the ENs for delta decline and growth probably reflect their lower delta levels. Lower levels mean that smaller absolute changes take place over roughly similar sleep durations. This results in lower rates of change in absolute delta for most delta measures. To determine whether rates of delta growth and decline differ in the two age groups when total delta capacity is controlled, we normalized the delta measures by calculating each subject’s data point as the percent of his or her baseline mean.

Table 5A—ANOVA for age and non-rapid eye movement period effects on delta measures for absolute and normalized data. Data used in the ANOVAs were means of 4 baseline nights for each of 19 young and 19 elderly subjects. F and p values are in bold type for p<0.01. 0.0000 is used for p<0.00005.

<table>
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<th></th>
<th>Age</th>
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<tbody>
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<td>F1,36</td>
<td>p</td>
<td>F1,108 p</td>
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<td>IA/min Absolute</td>
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<td>TIB/Min Absolute</td>
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<tr>
<td>IA, integrated amplitude</td>
<td>TIB, time in band; ASA, average sample amplitude</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5B—ANOVA for orthogonal component analysis across non-rapid eye movement periods for absolute and normalized data. Data used in the ANOVAs were means of 4 baseline nights for each of 19 young and 19 elderly subjects. F and p values are in bold type for p<0.01. 0.0000 is used for p<0.00005.

<table>
<thead>
<tr>
<th></th>
<th>Linear</th>
<th>Quadratic</th>
<th>Cubic</th>
<th>Linear x age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta Variable</td>
<td>F1,36</td>
<td>p</td>
<td>F1,36</td>
<td>p</td>
</tr>
<tr>
<td>Power/min Absolute</td>
<td>99.1 0.0000</td>
<td>0.08 0.78</td>
<td>6.0 0.02</td>
<td>23.8 0.0000</td>
</tr>
<tr>
<td>Normalized</td>
<td>319.0 0.0000</td>
<td>0.00 0.99</td>
<td>6.4 0.016</td>
<td>2.17 0.15</td>
</tr>
<tr>
<td>IA/min Absolute</td>
<td>303.3 0.0000</td>
<td>0.31 0.58</td>
<td>6.91 0.013</td>
<td>33.8 0.0000</td>
</tr>
<tr>
<td>Normalized</td>
<td>337.5 0.0000</td>
<td>0.58 0.45</td>
<td>6.70 0.014</td>
<td>4.02 0.053</td>
</tr>
<tr>
<td>TIB/Min Absolute</td>
<td>212.0 0.0000</td>
<td>7.18 0.011</td>
<td>6.75 0.014</td>
<td>4.37 0.044</td>
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<tr>
<td>Normalized</td>
<td>170.8 0.0000</td>
<td>7.18 0.011</td>
<td>6.81 0.013</td>
<td>0.21 0.65</td>
</tr>
<tr>
<td>ASA Absolute</td>
<td>304.3 0.0000</td>
<td>0.22 0.64</td>
<td>4.50 0.041</td>
<td>19.74 0.0001</td>
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<tr>
<td>Normalized</td>
<td>383.3 0.0000</td>
<td>0.26 0.61</td>
<td>6.44 0.038</td>
<td>7.68 0.0088</td>
</tr>
<tr>
<td>Mean Freq Absolute</td>
<td>70.4 0.0000</td>
<td>31.4 0.0000</td>
<td>8.76 0.0054</td>
<td>0.40 0.53</td>
</tr>
<tr>
<td>Normalized</td>
<td>68.4 0.0000</td>
<td>31.5 0.0000</td>
<td>8.73 0.0055</td>
<td>0.78 0.38</td>
</tr>
<tr>
<td>IA, integrated amplitude</td>
<td>TIB, time in band; ASA, average sample amplitude</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age Effects on Delta Wave Amplitude, Incidence, and Frequency

One valuable feature of PA analysis is its ability to measure separately the amplitude, incidence, and frequency (period) of EEG waves. We replicate our previous PA finding that delta wave incidence, as well as amplitude, is reduced in the elderly. The data here suggest that aging reduces delta wave amplitude somewhat more than it does delta wave incidence.

We also replicate our previous finding that mean delta frequency in ENs is higher than in YNs. In addition, we confirm our previous descriptions of the trends in mean delta frequency across NREM periods. In both YNs and ENs, delta frequency in NREM periods 1 and 2 is at about the same level but then increases linearly across NREM periods 2-4. The similar mean frequency levels in NREM periods 1 and 2 are puzzling. In view of the overall inverse frequency-amplitude relation in the sleep EEG, one would have expected the lower amplitude delta waves of NREM period 2 to have a higher mean frequency than the higher amplitude waves in NREM period 1.
The finding that delta frequency is at about the same level in NREMPs 1 and 2 in both age groups is not a chance observation. It closely replicates the previous results in 48 ENs and 41 YNs. Similar mean frequency levels in NREMPs 1 and 2 cannot be attributed to poor measurement resolution. In both studies the PA methods were able to demonstrate higher mean delta frequency in the elderly. Both studies also detected strong and reliable linear increases in mean frequency across NREMPs 2-4. Trend analyses of mean frequency across all four NREMPs also yielded reproducible results with highly significant linear and quadratic trends that did not differ by age group.

The mean frequency data indicate that in both YNs and ENs, delta waves oscillate with a fairly constant period across NREMPs 1 and 2 even though their amplitude is lower in NREMP2. In contrast, the decline in amplitude across NREMPs 2-4 is accompanied by reliable increases in mean frequency. These results are consistent with other data that suggest that the delta of the first two NREMPs may differ biologically from that of NREMPs 3 and 4. Acute deprivation of the terminal 4 hours of sleep in human subjects does not increase delta integrated amplitude on the recovery night even though prior waking time has been increased. It appears that loss of delta (or of NREM sleep) from NREMPs 1 and/or 2 is required to produce the powerful delta compensation (“rebound”) that follows a night of total sleep deprivation.

### Delta Frequency Decreases with Increasing Prior Wake Duration

PA analysis demonstrates that mean delta frequency decreases linearly across successively later naps. To the best of our knowledge, this is the first demonstration of the change in delta frequency as a function of prior waking duration. One would expect this result because delta wave amplitude increases with prior waking.

Neither the absolute nor the normalized linear slopes of the delta frequency decline differ in YNs and ENs. Both trends are robust with p levels <0.0001. It is surprising that the slope of the linear change in absolute delta frequency across naps does not differ in the two age groups because the linear increase in absolute amplitude in the ENs is significantly flatter.

### The Linear Patterns of Delta Growth and Decline are Inconsistent with the Exponential Postulates of the Two-Process Model

Absolute and normalized FFT power/min and PA integrated amplitude/min decline linearly across NREMPs. Amplitude and incidence, the waveform components that determine these composite measures, also show a predominantly linear decline. While incidence (TIB/min) exhibits significant curvature, this is due to a disproportionately small difference between NREM1 and NREM2; this pattern is opposite that of exponential decline. Normalized, as well as absolute, delta data show a linear decline. Thus, statistical trend analyses of absolute and normalized delta do not support the exponential delta decline assumed by the two-process model.

We recognize that some previous studies with orthogonal components analyses detected significant quadratic components in the delta decline across NREMPs. These include our own early studies, which constitute the first statistical analyses of this question. Skipped first REMPs may have produced this curvature. When sleep is extremely deep, eye movements are sparse or absent in the first delta trough, making it less likely to be scored as REM sleep. This can occur even though the trough meets the criteria for stage REM EEG (e.g., absence of spindles and K-complexes). When a scorer “skips” (i.e., does not detect the first REMP), NREM1 and 2 are summed into a lengthy but spurious “NREM1” and all other periods advance by one. Therefore, NREM4 and 5, which typically have similar delta rates, become NREM3 and 4, causing a flattening of the NREM1-4 curve. We have re-examined our data from the 1978 and 1980 papers and found evidence of a skipped first REMP in at least one subgroup of subjects that had unusually high average NREM1 duration and significantly reduced total eye movement and eye movement density. Skipped first REMPs may have also contributed to the curvature found by Preud’homme et al. Examination of their data shows that the curvature was caused by similar values in NREM1, 3 and 4 after a linear decline in NREM1-3 (their Figure 2). Similarly, Dijk’s data (see baseline data in their table II) show a linear decline in delta power density across NREM1-3 with no further change in NREM3-4. Thus, in both Preud’homme et al and Dijk et al, only the late flattening of the delta curve enabled the authors to fit an exponential function.

### Delta Production Rate Increases Linearly Across Waking Rather than as a Saturating Exponential

The rate of delta production increases linearly as naps are progressively later and prior waking duration increases. This linear rate of change challenges the saturating exponential rate assumed by the two-process model. A saturating exponential requires that delta propensity increase rapidly immediately after waking and then slow monotonically. This pattern would produce strong quadratic trends in the ANOVA, but these were absent. We therefore examined the data qualitatively to seek evidence for a saturating exponential rate. If present, the increases between successive naps should become progressively smaller. This pattern was not observed in either group.

The saturating exponential hypothesis is also counterintuitive. It seems inconsistent with subjective experience that the need for the recuperative powers of sleep increases most intensely during the first few hours of waking. We also note that the linear increase in delta production across daytime naps contradicts our previous hypothesis that this curve is logistic (S-shaped). When we proposed the logistic model, we noted...
that it was provisional since it was based on cross-sectional rather than within-subject nap data.

The literature also indicates that delta increases linearly with waking duration across a normal 16-hour day. Hume and Mills,\(^41\) in a pioneering study of this question, reported a linear increase in slow wave sleep as prior waking increased from 2 to 16 hours. When Knowles et al\(^42\) attempted to fit a saturating exponential curve to cross-sectional, visually scored slow wave sleep from studies of naps, shifted sleep, and sleep deprivation, they obtained negative slow wave sleep values for the first 2 hours of waking. Knowles et al specifically noted that the delta increase is linear across a normal waking day and that curvature appears only when prior waking is extended by sleep deprivation so that the delta plateau is reached. Bess et al\(^3\) studied delta power in naps initiated between 0800 and 2400 h. Delta power showed a linear increase (their Figure 3) that appears slightly slower in the early morning hours than later in the day. We have found no published studies that demonstrate a saturating exponential model is statistically superior to a linear fit for the increase in delta propensity across waking.

**Models of Sleep**

These models are most valuable when they predict quantitative results or point to underlying biologic processes. We found in this study that the growth and decline of delta do not fit the exponential kinetics of the two-process model. The exponential delta changes postulated by this model were not based on any explicit biologic processes. In contrast, the original albeit qualitative homeostatic model of delta proposed that the waking activity of plastic neuronal systems produces a substrate that is metabolized during sleep.\(^2\) Delta is an electrophysiologic correlate of this metabolic process; a one-compartment metabolic model would produce a simple exponential decline. The present findings of linear growth and decline of delta are inconsistent with this as well as the two-process model. Other biologic mechanisms need to be considered.

**Possible Biologic Significance of NREM Delta**

The most important clues to delta’s role in brain function are its homeostatic relation to sleep and waking, its conservation across naps and post-nap sleep (absent for REM),\(^44-47\) its tight link to age (references cited above), and its high night-to-night consistency within individual subjects.\(^7,3,3,48\) To these previously established facts, we add the present findings that the growth and decline of delta are linear. In addition, and perhaps more importantly, we show that these linear rates of growth and decline are approximately equal in YNs and ENs when the data are normalized. This similarity exists despite the massive decrease in absolute delta production in the ENs.

While the neuronal systems underlying these complex physiologic patterns remain unknown, the available data point to some new hypotheses. Steriade\(^49\) and others have shown that delta is produced by cortical neurons. These neurons are the targets of arousal systems that include the reticular activating, forebrain, and hypocretin-orexin arousal systems.\(^50,51\) However, we propose that these arousal systems do not themselves generate (or require) delta. This is a property of their cortical targets.

The kinetic data here are inconsistent with our previous proposal that delta is a correlate of the metabolism of a substrate that accumulates during waking. One alternative possibility is that the linear delta kinetics observed here might result from allosteric changes produced by neurotransmitters in plastic cortical neurons. Reversal of these changes might be a passive process that occurs during the neuronal quiescence of NREM sleep with its functional deafferentation and hypometabolism.\(^52,54\) Evarts has emphasized that, from the neurophysiologic point of view, one of the puzzles of sleep is its protracted nature.\(^55\) Individual neurons can be stimulated to exhaustion and recover within minutes. Why then do we require hours of sleep? Hints of an answer to this question may lie in the growing evidence that long-term as well as short-term changes follow receptor activation, especially in metabotropic receptors.

The decline in delta with age indicates that either the size of the neuronal populations that generate delta are diminishing or else the magnitude of the average potential change per neuron becomes smaller. Despite these age and developmental effects, delta grows and declines at similar rates when the data of the YNs and ENs are normalized. Thus, an hour of waking (or an hour of sleep) produces, on average, similar proportionate changes in these massively different delta-generating systems. Moreover, the nature of the brain activity during waking seems to have little consequence for the amount of delta produced: night-to-night correlations of computer-measured delta are remarkably high.\(^7,3,3,48\) It appears that the amount of delta generated during waking will be the same whether the subject has spent the day studying calculus or whether she has been lolling on a beach in Greece gazing idly at the wine-dark sea.

These hypotheses are obviously speculative. However, the last hypothesis points to one immediately feasible experiment. One can systematically vary cognitive behavior and sensory experience during waking and examine the effects on computer-measured delta during sleep. We predict that these variations would not affect the amount of delta generated. This hypothesis is contrary to the findings of Kattler et al who reported increased delta on the contralateral scalp following tactile stimulation of the hand. We do not consider this result conclusive. Increased delta followed stimulation of the right but not the left hand, and the effect was not statistically robust. Moreover, we think it unlikely that delta is generat-

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**Table 6A**—ANOVA for age and nap effects on delta measures for absolute and normalized data. For each of 19 young and 19 elderly subjects single data points for 0900, 1200, 1500, and 1800 naps were used, and the mean for NREMP1 of 4 baseline nights provided the final data point for the trend across waking. F and p values are in bold type for p<0.01. 0.0000 is used for p<0.0001.

<table>
<thead>
<tr>
<th>Age x Nap</th>
<th>Power/min Absolute</th>
<th>0.0000</th>
<th>0.0000</th>
<th>13.0</th>
<th>0.0000</th>
<th>1.35</th>
<th>0.26</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normalized</td>
<td>2.00</td>
<td>0.17</td>
<td>73.9</td>
<td>0.0000</td>
<td>0.13</td>
<td>0.26</td>
</tr>
<tr>
<td>IA/min</td>
<td>Absolute</td>
<td>51.3</td>
<td>0.0000</td>
<td>60.2</td>
<td>0.0000</td>
<td>5.50</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>Normalized</td>
<td>3.54</td>
<td>0.068</td>
<td>61.7</td>
<td>0.0000</td>
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<td>0.34</td>
</tr>
<tr>
<td>TIB/ Min</td>
<td>Absolute</td>
<td>16.5</td>
<td>0.0003</td>
<td>47.6</td>
<td>0.0000</td>
<td>1.94</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Normalized</td>
<td>3.07</td>
<td>0.088</td>
<td>43.5</td>
<td>0.0000</td>
<td>1.50</td>
<td>0.21</td>
</tr>
<tr>
<td>ASA</td>
<td>Absolute</td>
<td>30.1</td>
<td>0.0000</td>
<td>55.0</td>
<td>0.0000</td>
<td>3.13</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Normalized</td>
<td>1.41</td>
<td>0.24</td>
<td>61.1</td>
<td>0.0000</td>
<td>1.15</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean Freq</td>
<td>Absolute</td>
<td>12.5</td>
<td>0.0012</td>
<td>31.5</td>
<td>0.0000</td>
<td>0.82</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Normalized</td>
<td>2.75</td>
<td>0.11</td>
<td>30.6</td>
<td>0.0000</td>
<td>0.82</td>
<td>0.51</td>
</tr>
</tbody>
</table>

* adjusted for sphericity when necessary

**Table 6B**—ANOVA for orthogonal components in delta tends across naps and through NREMP1 for absolute and normalized data. For each of 19 young and 19 elderly subjects single data points for 0900, 1200, 1500, and 1800 naps were used, and the mean of 4 baseline nights was used for NREMP1. F and p values are in bold type for p<0.01. 0.0000 is used for p<0.0005.

<table>
<thead>
<tr>
<th>Linear x age</th>
<th>Power/min</th>
<th>Absolute</th>
<th>0.0000</th>
<th>0.0000</th>
<th>0.46</th>
<th>0.10</th>
<th>0.76</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normalized</td>
<td>300.2</td>
<td>0.0000</td>
<td>0.44</td>
<td>0.51</td>
<td>0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>IA/min</td>
<td>Absolute</td>
<td>210.3</td>
<td>0.0000</td>
<td>0.19</td>
<td>0.66</td>
<td>0.16</td>
<td>0.69</td>
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<tr>
<td></td>
<td>Normalized</td>
<td>229.9</td>
<td>0.0000</td>
<td>0.23</td>
<td>0.63</td>
<td>0.22</td>
<td>0.64</td>
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<tr>
<td>TIB/ Min</td>
<td>Absolute</td>
<td>232.9</td>
<td>0.0000</td>
<td>0.65</td>
<td>0.42</td>
<td>1.22</td>
<td>0.27</td>
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<tr>
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<td>Normalized</td>
<td>164.0</td>
<td>0.0000</td>
<td>0.61</td>
<td>1.40</td>
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<td>0.07</td>
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<tr>
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<td>Absolute</td>
<td>170.1</td>
<td>0.0000</td>
<td>3.39</td>
<td>0.07</td>
<td>0.03</td>
<td>0.87</td>
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<tr>
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<td>Normalized</td>
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<td>0.0000</td>
<td>3.07</td>
<td>0.09</td>
<td>0.06</td>
<td>0.81</td>
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<tr>
<td>Mean Freq</td>
<td>Absolute</td>
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<td>0.0000</td>
<td>0.00</td>
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<td>Normalized</td>
<td>227.9</td>
<td>0.0000</td>
<td>0.94</td>
<td>0.46</td>
<td>0.50</td>
<td>0.50</td>
</tr>
</tbody>
</table>

ASA, integrated amplitude; TIB, time in band; ASA average sample amplitude
ed by the activity in such hard-wired neuronal systems. Further research could resolve this issue.

Examination of delta kinetics can point to hypotheses regarding functional correlates as well as biologic mechanism. The evidence cited above seems to us consistent with the possibility that delta is a physiologic correlate of the neuronal systems that underlie consciousness. Consciousness seems to march to a steady pace throughout waking. This pace does not seem to differ in YNs and ENs; however, the "depth" and "richness" of consciousness appears to diminish with age. By consciousness we do not imply the simple waking that is produced by arousal systems, although this is a necessary condition for consciousness. We mean, instead, the experience of thoughts and perceptions. The continuity of consciousness indicates that working memory systems also play a crucial role.

ACKNOWLEDGEMENTS

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REFERENCES