

# Kinetics of NREM Delta EEG Power Density Across NREM Periods Depend on Age and on Delta-Band Designation

Nato Darchia, PhD<sup>1</sup>; Ian G. Campbell, PhD<sup>2</sup>; Xin Tan, MD<sup>3</sup>; Irwin Feinberg, MD<sup>2</sup>

<sup>1</sup>*I. Beritashvili Institute of Physiology, Tbilisi, Georgia;* <sup>2</sup>*Department of Psychiatry, University of California, Davis, CA;* <sup>3</sup>*Department of Psychophysiology, National Center of Neurology and Psychiatry, Tokyo, Japan*

**Study Objectives:** (1) To determine whether children and elderly exhibit the atypical kinetics of very low frequency (VLF) power found in young adults, (2) to test the hypothesis that variations in “delta” bandwidth designations can explain discrepancies in whether normalized delta power density declines across non-rapid eye movement periods (NREMPs) linearly or shows the curvature expected of exponential change, and (3) to test our hypothesis that the decline in normalized delta power density in children across NREMPs would have a slope similar to that which we had previously found in young adults and elderly.

**Methods:** In 3 age groups (mean ages 11, 22, and 71 years) NREM electroencephalograms were analyzed with fast Fourier transform for frequencies between 0.3 and 4 Hz in bands. Across-NREMP trends of normalized power density for various “delta” bands were analyzed by analyses of variance for linearity, curvature, and age interactions.

**Results:** We replicated the atypical kinetics of VLF power (~0.3-0.9 Hz) in young adults reported by others and showed that this pattern exists in children and normal elderly. As frequencies increased above 0.7 Hz,

power showed first a linear and then a concave-upward curvilinear decline across NREMPs in children and young adults; the decline across NREMPs in the elderly became linear but never developed curvilinearity. For all designations of delta, the across-NREMP decline in children was significantly steeper than in young adults.

**Conclusions:** The findings that all normalized “delta” electroencephalogram bands in children showed a curvilinear decline across NREMPs that was steeper than that in young adults confirms observations of others and refutes our hypothesis that the decline would be linear with the same slope we found in young adults and elderly. Whether the decline in normalized power in young adults appears linear or curvilinear depends on whether the convex trend of VLF power is included.

**Keywords:** EEG, adolescent, elderly, FFT

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## INTRODUCTION

THE KINETICS OF NON-RAPID EYE MOVEMENT (NREM) DELTA ELECTROENCEPHALOGRAPH (EEG) HAVE BEEN OF SPECIAL INTEREST IN SLEEP physiology because these EEG frequencies behave homeostatically in response to waking.<sup>1,2</sup> Delta increases (to a limit) as the duration of prior waking increases, and it decreases across successive NREM periods (NREMPs) as though brain changes produced during waking are “consumed” or reversed. A second indication that delta plays a critical sleep role is that it is conserved, i.e., delta expressed in daytime naps reduces delta in postnap sleep. Rapid eye movement (REM) sleep does not behave homeostatically in these respects.<sup>1</sup> REM does not increase with prior waking duration, it becomes more prevalent as sleep progresses, and its quantity is not conserved.<sup>3</sup> A third indication that delta represents an important brain function differing from that of REM is that the EEG in the delta frequency range changes strikingly with age. After reaching a peak in childhood, delta declines steeply across adolescence and then more slowly—but still substantially—across adulthood.

In a recent study of sleep EEG in young adult and elderly subjects, we analyzed the kinetics of normalized delta (0.3 to 3

Hz) power density across daytime naps and its decline across NREMPs. Delta power was normalized by expressing each subject’s NREMP data points as percentages of that individual’s all-night NREM delta power density.<sup>4</sup> We found that normalized 0.3 to 3 Hz power density increased linearly with increasing waking duration and declined linearly across NREMPs. The slopes of the delta increase and decline were similar in the young adults and elderly. These similar slopes of normalized delta accumulation and decline led us to hypothesize that across the lifespan a given duration of waking produces the same proportionate increase in delta power and a given duration of NREM sleep produces the same proportionate delta decrease. We therefore predicted that the decline of delta power across NREMPs in children would also be linear with a slope similar to that we found in the 2 older groups.

However, Gaudreau et al<sup>5</sup> reported directly contrary observations. Using fast Fourier transform (FFT) analyses, they found that normalized delta declines across the night more steeply in children (mean age 7 years) and adolescents (mean age 15 years) than in young and middle-aged adults (mean ages 24 and 45 years). They also found significant curvature in the delta decline across the night in children and young adults, whereas we had observed a purely linear trend. Gaudreau et al used EEG and statistical analyses similar to those we employed for young adults and elderly. However, one potentially important difference was their definition of “delta”. They defined “delta” as 0.75 to 4 Hz, whereas we used 0.3 to 3 Hz.

The data of Achermann and Borbély<sup>6</sup> on the kinetics of less than 1 Hz EEG suggest a possible explanation for these discrepancies. They reported that, in young adults, power in these very low frequencies (VLF) exhibits a different pattern of change across NREMPs from that of the higher delta frequencies. Rather than being at its highest level in NREMP1 and declining sharply to

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Address correspondence to: Ian G. Campbell, PhD, University of California Davis Sleep Lab 1712 Picasso Ave, Suite B, Davis, CA 95616; Tel: (530) 752-7216; Fax: (530) 757-5729; E-mail: igcampbell@ucdavis.edu

**Table 1**—Age and Sex Characteristics of the Subjects in the 3 Age Groups

Group	Age, y
Children (n = 40)	10.8 ± 1.5 (8.9-12.5)
Female (n = 20)	10.9 ± 1.6 (8.9-12.5)
Male (n = 20)	10.8 ± 1.5 (9.0-12.5)
Young adult (n = 19)	22.4 ± 1.4 (20.2-25.1)
Female (n = 10)	22.6 ± 1.7 (20.2-25.1)
Male (n = 9)	22.2 ± 1.0 (20.8-24.2)
Elderly (n = 19)	71.4 ± 4.9 (65.3-81.8)
Female (n = 11)	72.3 ± 4.8 (66.4-81.8)
Male (n = 8)	70.2 ± 5.0 (65.3-78.8)

Data are presented as mean ± SD (range).

NREMP2, VLF power is roughly equal in the first 2 NREMPs and then declines. Including VLF power within the “delta” band, (as we do by designating delta as 0.3 to 3 Hz) could reduce or nullify the curvature that would characterize an exponential decline, since this requires much higher delta power in NREMP1 than in NREMP2. As illustrated by the different delta bandwidths used by various investigators, there are no empirically “established” frequency bands for NREM delta computer analysis. Different designations of delta bandwidth affect the shape of the decline in delta power across NREMPs.

In this paper, we test the following hypotheses: (1) the VLF kinetics found in young adults also exist in children and normal elderly; (2) excluding or including VLF in the delta bandwidth affects the shape of the decline in delta power density across NREMPs; and (3) the decline in normalized 0.3 to 3 Hz power density has the same slope in children, young adults, and elderly. Some of these findings were reported in preliminary form at the 2004 meeting of the European Sleep Research Society.

## METHODS

### Subjects and Study Design

Table 1 lists the numbers, age, and sex compositions of the preadolescent and early-adolescent children (“children”), young adults, and elderly. All subjects were paid volunteers. The UC Davis Committee for Human Research Protection approved the studies. Adult subjects signed informed consent. The parents of the children signed consent forms, and the children 12 years or older signed assent forms that described the purpose and procedures of the study. No subject was using hypnotics or drugs of abuse, and random urine screens were performed on all subjects.

The child subjects are subsamples (n = 20 each) drawn from an ongoing longitudinal study of sleep EEG across adolescence in 2 cohorts: a 9-year-old group (n = 31) and a 12-year-old group (n = 38). Without knowledge of the results of sleep EEG analyses, equal numbers of boys and girls were selected on the basis of minimal artifacts in the EEG recordings. In this ongoing project, ambulatory (home) recordings of sleep EEG are being obtained twice yearly, at approximately 6-month intervals. Each recording period consists of 4 consecutive nights: 2 nights with baseline (habitual) time in bed followed by 2 nights with extended (goal = 12 hours) time in bed. At each time point, Tanner stage, daytime sleepiness, and other measures are obtained. Child subjects were recruited by newspaper reports of the project and

word of mouth. Subjects selected had normal sleep patterns and negative psychiatric and neurological histories. Each subject was performing at grade level or better in school. A full description of this study has been published<sup>7</sup>.

Analyses of variance (ANOVAs) revealed no differences in kinetics in the samples (n = 20 each) drawn from the preadolescent (9-year-olds) and early adolescents (12-year-olds). The data of these 2 groups were therefore combined in the single children group (n = 40) described in Table 1. This similarity between the 2 subgroups of children replicates the prior findings of Gaudreau et al, who also combined similar age groups. Data for the young normal and elderly normal groups were from our previously published studies of nap and postnap sleep.<sup>4</sup> Young adults were students at UC Davis. The elderly subjects were retired individuals living in the Davis community. After a 2-night screening for sleep apnea, myoclonus, and normal sleep times, these subjects participated in four 2-day experiments, each consisting of a baseline night, a nap the next day, and a postnap night. These 2-day experiments were separated by intervals that ranged from 4 days to several weeks (mean interval between baseline nights = 11.5 days). The data for young adults and elderly are means of the 4 (separated) baseline nights.

As we have previously noted,<sup>8</sup> the stability of the 4 baseline night recordings was very high for all night NREM 0.3 to 3 Hz power per minute in young adults and elderly. The average 1-night difference from the 4-night mean was 7.9% ± 0.8% in young adults and 9.2% ± 0.8% in the elderly. Similarly, in children we found very high stability in the 2 nights of EEG recordings. The average 1-night difference from the 2-night mean in 0.3 to 3 Hz NREMP1-4 power per minute was 5.7% ± 0.8%.

### Sleep Schedules

Children were recorded on their habitual sleep schedules. We used actigraphy watches (Mini Mitter Actiwatch™ 16, Mini Mitter Co., Inc., Bend, OR) to ensure that children maintained their habitual sleep schedules and did not nap in the 5 days prior to recording. In the elderly subjects, time in bed was 11:00 PM to 7:00 AM. This was also the schedule for 6 of the young adults. For the remaining 13 young adults, time in bed was 11:30 PM to 7:00 AM. It had been our intention to use the 11:30 PM to 7:00 AM schedule for all the adult subjects, but the elderly subjects insisted on a bedtime no later than 11:00 PM. As it turned out, the different sleep schedules within the young adult group did not affect the results (cf<sup>1</sup>). These schedules differed from the subjects’ habitual sleep schedules as follows. In the young adults, the average difference between habitual bedtime and laboratory bedtime was 43 ± 6 minutes, and the average difference in wake-up time was 48 ± 11 minutes. In the elderly, the average difference between habitual bedtime and laboratory bedtime was 40 ± 6 minutes, and the average difference in wake-up time was 40 ± 5 minutes. These subjects were instructed to maintain the laboratory-based time-in-bed schedule at home for at least 3 nights prior to each recording session. They were informed of the importance of maintaining this schedule and of avoiding daytime naps. To encourage compliance with the preexperiment sleep schedules at home, young and elderly subjects phoned the laboratory each night when they went to sleep and again when they awoke. The times and locations of these phone calls were recorded and checked daily.

## Signal Recording

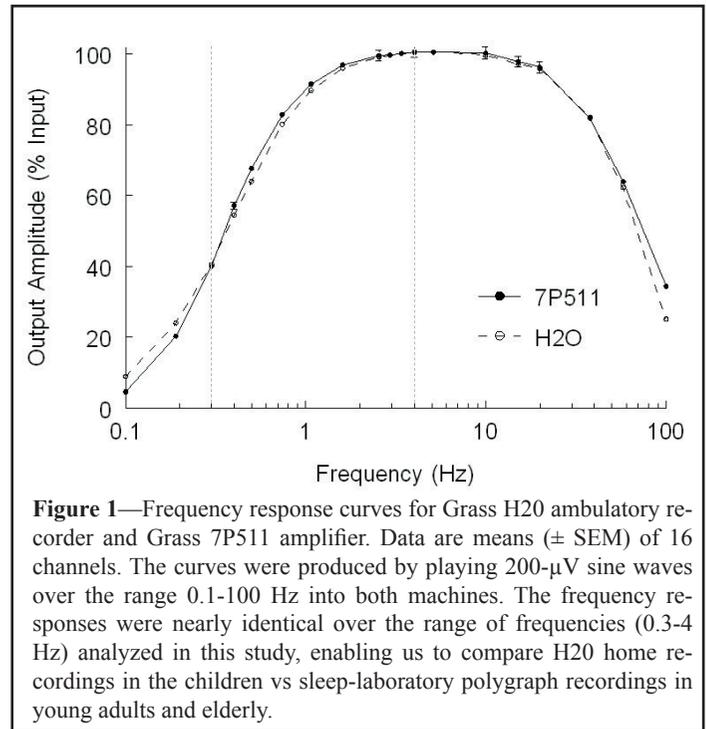
Electrooculogram leads from the outer canthi were referred to the forehead. Several monopolar EEG leads were recorded. We used the cleaner of the signals from C3-A2 or C4-A1 for computer EEG analysis. Electrode impedance was below 5 k $\Omega$  at the start of recording.

Children were studied at home with Grass H2O ambulatory recorders (Grass-Telefactor, Astro-Med, Inc., West Warwick, RI), which digitized the signals and stored data on a mini-hard disk. Hardware filters were half-amplitude, 0.3-Hz low frequency and 100-Hz high frequency. The low-frequency filter is a single pole filter with a 6-dB decrease per octave. EEG and electrooculograms from the young adult and elderly subjects were recorded in the sleep laboratory with Grass Model 78 polygraphs (Grass-Telefactor, Astro-Med, Inc.). Amplifier filter settings (Grass 7P511, Grass-Telefactor, Astro-Med, Inc.) were half amplitude, 0.3 Hz low frequency and 100 Hz high frequency. The low-frequency filter is a 3-pole filter with a 12-dB decrease per octave. The low-frequency filters affect frequency bands that are the focus of this paper. We generated frequency-response curves using calibrated sine waves to determine if the H2O and Grass 7P511 amplifiers responded similarly. Figure 1 shows that, over the 0.3- to 4-Hz range, which is the focus of this article, the frequency-response curves were nearly identical for the 2 recording systems. The greatest difference in this range was at 0.5 Hz, where the H2O output amplitude was 64.0% of input and the 7P511 output amplitude was 67.6% of input.

## Sleep-Stage Scoring

Each 20-second epoch of digitized data was scored visually on a computer monitor as wake, stage 1, NREM, REM, or movement according to modified Rechtschaffen and Kales<sup>9</sup> criteria. Epochs were scored for the presence of artifacts independently of vigilance state. A second scorer checked all scoring. A third experienced scorer reconciled any differences. The PASS PLUS sleep analysis system (Delta Software, St. Louis, MO) automatically defined consecutive NREMPs according to modified Feinberg and Floyd<sup>10</sup> criteria. Only data for artifact-free 20-second epochs visually scored as NREM in the first 4 NREMPs are included in this report. The average number of epochs per night excluded due to artifact in NREM was 24, 30, and 28 for children, young adults, and elderly, respectively.

Whether the delta decline across NREMPs appears linear or exponential can depend critically on where the first and second NREMPs are divided.<sup>11,12</sup> A "skipped" first REM period<sup>13</sup> occurs when REM sleep is not scored in the first trough of the cyclic delta curve across sleep; this phenomenon is frequently seen in children and also in young adults after sleep deprivation.<sup>11,12</sup> To avoid the distorting effects of skipped first REM periods, we divided the first and second NREMPs at the first significant trough in the smoothed across-night delta curve even when stage REM epochs were not scored.<sup>4,12</sup> Similar procedures are being adopted by others.<sup>14,15</sup> Only nights that included 4 complete NREMPs were included in the analyses. The criterion for a complete fourth NREMP was the presence of a fourth REM. All 80 nights from the children, 75 of 76 nights from the young adults, and 68 of 76 nights from the elderly had 4 complete NREMPs. All 19 elderly subjects had at least 2 nights with 4 complete NREMPs.



**Figure 1**—Frequency response curves for Grass H2O ambulatory recorder and Grass 7P511 amplifier. Data are means ( $\pm$  SEM) of 16 channels. The curves were produced by playing 200- $\mu$ V sine waves over the range 0.1-100 Hz into both machines. The frequency responses were nearly identical over the range of frequencies (0.3-4 Hz) analyzed in this study, enabling us to compare H2O home recordings in the children vs sleep-laboratory polygraph recordings in young adults and elderly.

## FFT Analysis

In the children, the digitized (200-Hz) EEG was transferred to a PC hard disk and analyzed off line with the FFT and period amplitude analysis components of PASS PLUS (Delta Software). In young adults and elderly, these analyses were performed on line at the time of data collection. For all subjects, FFT analysis was on 5.12-second Welch-tapered windows with a 2.62-second overlap, producing 8 windows per 20-second epoch. With these settings, FFT computations do not yield exact integer or decimal Hz frequency bands. For example, delta in "0.3 to 3 Hz" was actually 0.293 to 3.027 Hz. For simplicity of presentation, we rounded all frequencies to the nearest 0.1 Hz.

## Data Selection and Normalization

For the young adult and elderly groups, we used the data from the 4 baseline nights. Data were normalized for each night by expressing the power density (power/minute) in each NREMP in each frequency band as a percentage of the all-night NREM power density (power/minute) in that frequency band. For each subject, we then calculated the 4-night mean of the normalized data. For children, we used the data from night 2 (the second baseline night) and the first 4 NREMPs of night 3 (the first extended night). Data were normalized for night 2 by expressing power density in each NREMP in each frequency band as a percentage of the all-night power density in that frequency band. To control for the additional sleep time resulting from the extended time in bed, night 3 data in NREMPs 1 to 4 were normalized as a percentage of all-night power density of night 2. In this way we were able to calculate a 2-night mean of normalized data for each child subject. Normalization allows comparison of power-density trends across NREMPs while controlling for the massive differences in EEG power between age groups and between frequency bands. Subject means, across 2 nights for the children and across 4 nights for the young adults and elderly, were used for the statistical analyses below.

**Table 2**—Duration of NREMPs for the 3 Age Groups

NREMP	Children	Young adults	Elderly
1	81.71 <sup>a</sup> ± 2.89	67.71 <sup>b</sup> ± 2.01	64.56 <sup>b</sup> ± 2.62
2	81.50 <sup>a</sup> ± 2.71	69.72 <sup>b</sup> ± 2.49	80.51 <sup>ab</sup> ± 3.94
3	75.08 ± 2.00	72.60 ± 2.36	75.14 ± 3.10
4	64.30 <sup>a</sup> ± 2.05	58.51 <sup>ab</sup> ± 1.97	51.01 <sup>b</sup> ± 1.68

Data are presented as mean ± SEM durations, in minutes.

<sup>a,b</sup>Across-group differences: for each non-rapid eye movement period (NREMP), means that do not differ significantly between age groups share a common superscript.

Within-group differences: in all 3 age groups, NREMP4 was significantly shorter than NREMP3. In the elderly, NREMP1 was significantly shorter than NREMP2.

### Statistical Analysis

We tested age-group differences in NREMP durations with an ANOVA using NREMP duration as a repeated measure and age group as a grouping factor. We also conducted a repeated-measures ANOVA for NREMP durations in each age group and tested for differences within age groups with paired *t* tests between successive NREMPs using a Bonferroni correction to  $\alpha = .05$  to account for the 3 comparisons.

We tested power-density trends across NREMPs with an ANOVA for each delta range subfrequency band using age group as a grouping factor and NREMP as a repeated measure. Many of these analyses showed significant interactions between age group and NREMP effects. For each age group, at each delta range subfrequency, we conducted a repeated-measures ANOVA with orthogonal components to test for change across NREMPs and to determine whether curvature was present. We also performed these ANOVAs on composite “delta” bands 0.3 to 3 Hz, 0.7 to 4 Hz, 0.9 to 4 Hz, and 1.1 to 4 Hz to test for differences between age groups.

## RESULTS

### NREMP Durations

It has long been known that NREMP durations change systematically across sleep and that the resulting patterns differ by age group. Table 2 lists the NREMP durations for the 3 age groups studied here, along with statistical analyses of differences across and within groups. Although a full analysis of NREMP durations is beyond the scope of this paper, we think it is useful to emphasize a finding that has been extraordinarily consistent in our laboratory: in every age group studied, the fourth NREMP is significantly shorter than the third.

### Slow-Wave EEG Power Density Differs in the 3 Age Groups

Although this paper is concerned with the kinetics of normalized power density, we list here the average absolute power density values for the 3 groups. It is well established that slow-wave EEG power decreases with age. The average all-night NREM power density in 0.3 to 4 Hz in children was 111,000  $\mu\text{V}^2\text{sec}$  per minute of NREM. In the young adults (33,000  $\mu\text{V}^2\text{sec}$ ), it was 70% lower than in children, and in the elderly (13,000  $\mu\text{V}^2\text{sec}$ ), it was 60% lower than in young adults. Age-group differences were present in every 0.2-Hz band between 0.3 and 4 Hz.

### Patterns of Decline in Normalized Power Density for Subfrequencies Within 0.3 to 4 Hz

To examine trends across NREMPs for frequencies comprising the “delta” band, we analyzed these trends in successive narrow bands (0.2-Hz width) above 0.3 Hz. Power density below 0.3 Hz was uninterpretable because of pervasive ultra-low-frequency recording artifact (DC drift).

Figure 2 shows patterns for 6 representative narrow frequency bands for the 3 age groups. The 3 groups had virtually identical levels of normalized power density in frequencies between 0.3 and 0.7 in each NREMP. In these VLFs, power density in NREMP2 was slightly (nonsignificantly) higher than in NREMP1. Power density then showed a shallow linear decline from NREMP2 to NREMP4. The resulting trends across NREMPs 1 to 4 for these VLFs were therefore slightly convex-upward (henceforth referred to as “convex”) with statistically significant curvature (for all groups, 0.3-0.5 Hz and 0.5-0.7 Hz had a quadratic orthogonal component significant at  $p < .002$ ).

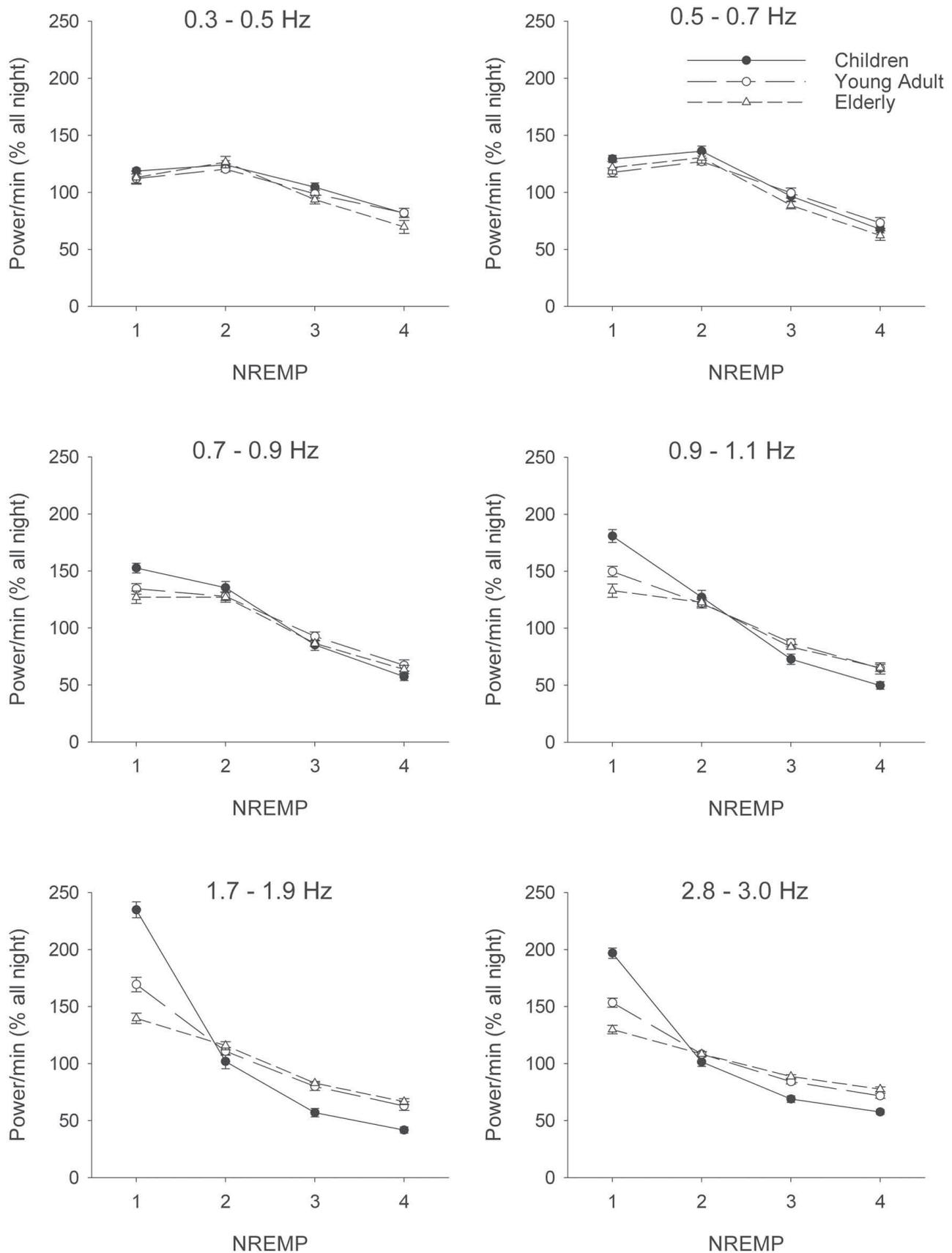
The similarity of trends in the 3 age groups ended at 0.7 to 0.9 Hz. In the children, the trend across NREMPs became linear in 0.7 to 0.9 Hz (quadratic orthogonal component  $p = .24$ ). Between 0.9 Hz and 3 Hz, all bands in the children exhibited strong concave-upward (henceforth “concave”) trends across NREMPs (quadratic orthogonal component,  $F_{1,39} > 9$ ,  $p < .005$ ) with a significantly steeper decline than in the other 2 age groups (interaction age  $\times$  NREMP,  $F_{6,225} > 8$ ,  $p < .0001$ ).

In young adults and elderly, convex curvature was maintained through 0.7 to 0.9 Hz (quadratic orthogonal component,  $F_{1,19} = 5.0$ ,  $p = .039$ , and  $F_{1,19} = 6.7$ ,  $p = .018$ , respectively). The next higher band, 0.9 to 1.1 Hz, showed strong linear declines ( $p < .0001$  in young and elderly) without significant curvature in either group (quadratic orthogonal component,  $p = .48$  and  $p = .32$ , respectively). The decline in young adults then became significantly concave for all frequencies between 1.1 Hz and 4 Hz (quadratic orthogonal component,  $p < .009$ ); however, their curvature was less marked than in the children. In the elderly, across-NREMP trends through 4 Hz remained linear and did not exhibit significant concave curvature for any delta frequency except for  $p < .02$  for 3.3 to 3.7 Hz. These group differences are illustrated by the plots for the 1.7 to 1.9 Hz and 2.8 to 3.0 Hz bands in Figure 2.

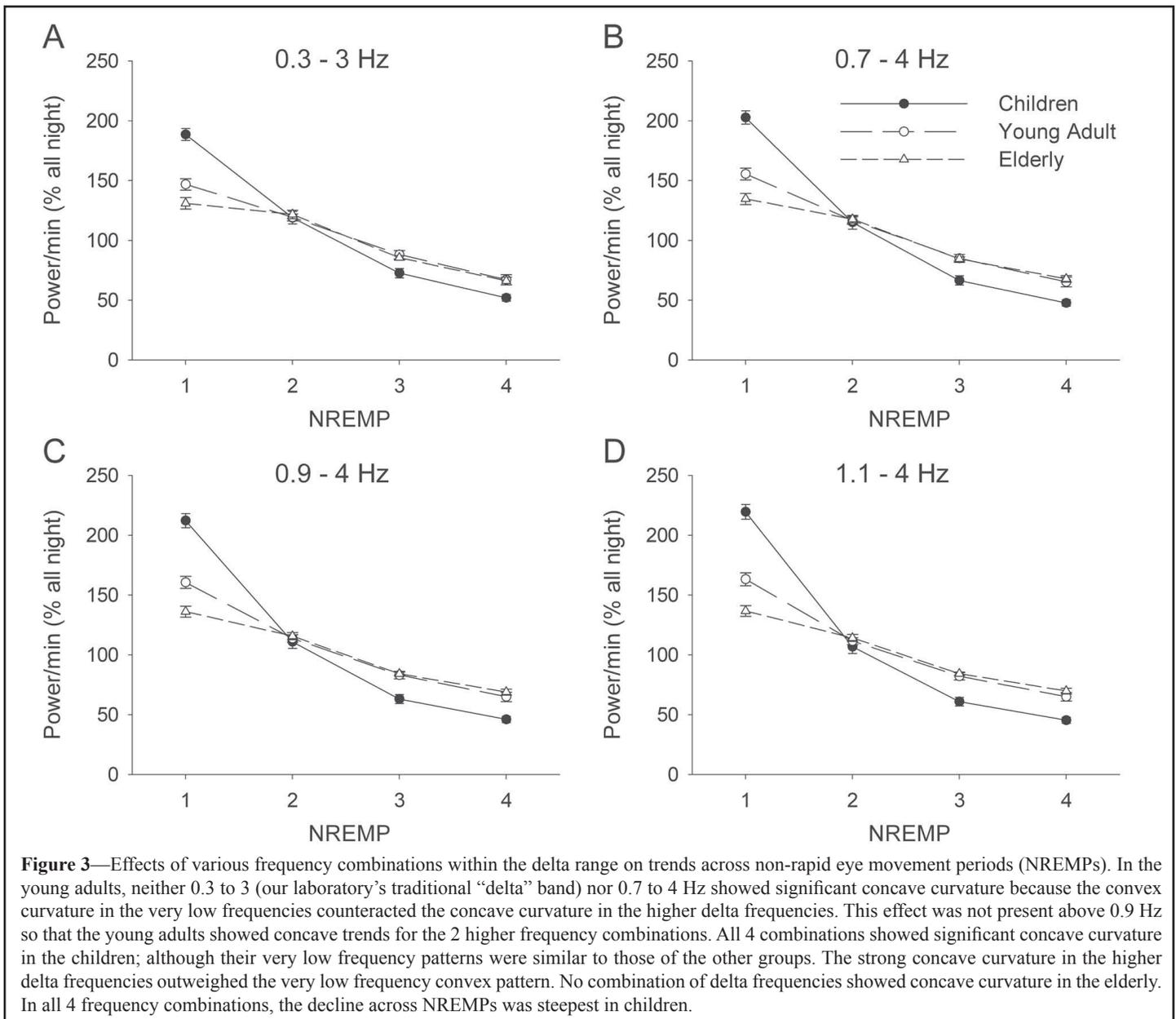
It should be noted that declining trends in EEG power density do not end at 4 Hz. For example, Gaudreau et al have shown that the declining trends in normalized power across the night continue through alpha frequencies. Our unpublished analysis of the present data confirms this finding.

### Trends Across NREMPs for Various Definitions of “Delta Frequency”

Figure 3 illustrates how different combinations of frequencies within 0.3 to 4 Hz yielded different trends across NREMPs. Each of these frequency combinations showed statistically significant NREMP effects ( $F_{3,225} > 200$ ,  $p < .0001$ ) and age  $\times$  NREMP interactions ( $F_{6,225} > 17$ ,  $p < .0001$ ). The children showed significant concave curvature for all 4 frequency-band combinations (quadratic orthogonal component  $F_{1,39} > 37$ ,  $p < .0001$ ). In young adults, concave curvature was significant for 0.9 to 4 Hz ( $F_{1,18} = 13.5$ ,  $p = .0017$ ) and 1.1 to 4 Hz ( $F_{1,18} = 19.5$ ,  $p = .0003$ ) but not for 0.3 to 3 Hz ( $F_{1,18} = 0.73$ ,  $p = .40$ ) or 0.7 to 4 Hz ( $F_{1,18} = 6.0$ ,  $p = .025$ ). None of these delta-frequency combinations showed



**Figure 2**—For the 3 age groups, trends across non-rapid eye movement periods (NREMPs) in normalized power density in representative frequencies between 0.3 and 4 Hz. Normalized power density in narrow frequency bands between 0.3 and 0.7 Hz is at similar levels and shows nearly identical trends for all 3 groups. In 0.7 to 0.9 Hz, the 3 groups begin to diverge. In 1.7 to 1.9 Hz, the children show a markedly concave trend, the young adults show a less marked concave curvature, but the trend for the elderly remains linear. See text for details.



**Figure 3**—Effects of various frequency combinations within the delta range on trends across non-rapid eye movement periods (NREMPs). In the young adults, neither 0.3 to 3 (our laboratory’s traditional “delta” band) nor 0.7 to 4 Hz showed significant concave curvature because the convex curvature in the very low frequencies counteracted the concave curvature in the higher delta frequencies. This effect was not present above 0.9 Hz so that the young adults showed concave trends for the 2 higher frequency combinations. All 4 combinations showed significant concave curvature in the children; although their very low frequency patterns were similar to those of the other groups. The strong concave curvature in the higher delta frequencies outweighed the very low frequency convex pattern. No combination of delta frequencies showed concave curvature in the elderly. In all 4 frequency combinations, the decline across NREMPs was steepest in children.

significant ( $F_{1,19} < 2, p > .19$ ) concave curvature in the elderly.

Thus, the linear trend in the 0.3 to 3 Hz “delta” band of young adults was produced because the convex curvature in 0.3 to 0.7 Hz counteracted the concave curvature in the higher delta subfrequencies. The children showed a convex trend for the VLF paralleling that of the young adults. However, because the concave curvature in children in higher delta frequencies was much more pronounced, it outweighed their VLF convexity. As a result, all delta-frequency combinations in children, even those that included the less than 1 Hz subfrequencies, showed concave curvature.

#### Decline in Normalized 0.3 to 3 Hz Power Density Across NREMPs

Our laboratory has traditionally designated delta as 0.3 to 3 Hz. Figure 3A shows the decline of normalized 0.3 to 3 Hz power per minute across NREMPs in the 3 age groups. Contrary to our hypothesis, normalized power in the children did not decline linearly across NREMPs with a slope similar to those we had previously found<sup>4</sup> in these same young and elderly groups.

Instead, normalized delta power density in 0.3 to 3 Hz in children declined more steeply than in young adults and elderly. The 0.3 to 3 Hz trends differed significantly among groups (age  $\times$  NREMP interaction  $F_{6,225} = 17.3, p < .0001$ ). In addition to being steeper, the decline of the 0.3 to 3 Hz power density in children exhibited significant concave curvature (quadratic component,  $F_{1,18} = 37.9, p < .0001$ ) that was absent in the 2 older groups. Analysis of the age-group differences in power density by NREMP showed that the differences in trends were due primarily to higher 0.3 to 3 Hz power in NREMP1 in children compared with young adults and elderly subjects ( $F_{2,75} = 33.8, p < .0001$ ). Trends across NREMP2-4 showed no significant age  $\times$  NREMP interaction ( $F_{4,150} = 1.34, p = .26$ ).

#### DISCUSSION

The data above successfully address each of the hypotheses posed in the introduction. Before discussing each hypothesis, we will briefly discuss data on NREMP durations.

## NREMP Durations

Because all analyses of delta here are for normalized NREM power per minute, the varying NREMP durations do not affect the delta power density trends, although they would affect the amount of homeostatic recovery accomplished in each NREMP. The finding that NREMP4 is significantly shorter than NREMP3 in each age group replicates a finding that has been extraordinarily consistent in our laboratory.<sup>1</sup> Feinberg's 1974 homeostatic model noted that the decline in NREMP4 duration is followed by further declines in later NREMPs and hypothesized that, when NREMPs become as short as the REMPs with which they alternate, maximal sleep homeostasis has been achieved. In the elderly but not in children or young adults, NREMP1 was significantly shorter than NREMP2. This also replicates previous findings from our laboratory, but we have no explanation for this strong and consistent finding.

## Kinetics of VLF in Children, Young Adults, and Elderly

The existence of VLF waves in the NREM EEG has long been known.<sup>16</sup> Achermann and Borbély were the first to demonstrate in young adults that VLF power in NREM sleep shows a different trend across NREMPs from that of the higher delta frequencies.<sup>6</sup> Rather than being at its highest level in NREMP1 and then declining, VLF power in NREMP2 is equal to or (nonsignificantly) greater than that in NREMP1. Between NREMP2 and NREMP4, VLF power exhibits a shallow decline. We demonstrate here that this same pattern of VLF power is present in children and elderly. Interestingly, in all 3 age groups, VLF power less than 1 Hz makes up similar proportions of the total NREM power and has virtually identical across-NREMP patterns. Thus, we demonstrate here that the VLF kinetic pattern reported by Achermann and Borbély in young adults is present most of the human lifespan.

The kinetics of VLF power are obviously inconsistent with the exponential decline that we and the 2-process model proposed should characterize homeostatic recovery from waking. Achermann and Borbély<sup>6</sup> raised the question of whether VLF delta should be considered homeostatic. We recently demonstrated<sup>17</sup> that VLF power meets 2 major homeostatic criteria in young adults. First, VLF power increases with increasing prior waking duration across a normal day. Second, VLF power expressed in a late nap reduces VLF power in postnap sleep by an amount about equal to that expressed in the nap.

Steriade et al<sup>18</sup> have shown that less than 1 Hz (VLF) EEG is produced by a mechanism different from that producing 1 to 4 Hz EEG. As discussed in our study of VLF homeostasis,<sup>17</sup> these mechanisms are consistent with our "one-stimulus" model of NREM-REM sleep alternation.<sup>3,11</sup> The VLF EEG may represent an inhibitory state that allows homeostasis to occur, and the 1 to 4 Hz delta may reflect the homeostatic processes themselves.

Whatever their ultimate significance, VLF EEG clearly requires separate measurement and analysis. The amounts of power below 1 Hz are far from trivial. Power in 0.3 to 1 Hz makes up 47%, 56%, and 53%, respectively, of the 0.3 to 3 Hz NREM power in children, young adults, and elderly. The results here support previous suggestions that the sleep EEG should be analyzed in narrower frequency bands than are usually employed.

## Evolution of NREMP Kinetics Across 0.3 to 4 Hz

Our data agree with those of Achermann and Borbély<sup>6</sup> who noted that, for frequencies above 1 Hz, power density in NREMP1 exceeded that in NREMP2. They found that this difference was significant for frequencies between 1.95 and 5 Hz. With our greater sample size, we were able to detect significantly greater power density in NREMP1 in all bands between 0.9 and 4 Hz. We show here that, as frequencies increase above the VLF level, the trend across NREMPs first becomes linear and then develops concave curvature. This pattern is similar in children and young adults although the trend in children becomes linear and then convex at slightly lower frequencies than in young adults.

Trends in power across NREMPs in the elderly differ significantly from those of children and young adults but in a way that reflects a consistent trajectory across the decades of life rather than a new phenomenon in the elderly. The trend in the elderly becomes linear at 0.9 Hz and remains linear throughout the delta range. This latter result is consistent with the prior findings of Gaudreau et al<sup>5</sup> in middle-aged subjects. Gaudreau et al's finding of a linear trend in 45-year-olds demonstrates that the loss of curvature that we found in our elderly subjects (68 years old) develops at a younger age. The trends in higher delta frequencies across NREMPs appear to develop in a consistent manner from childhood through young adulthood to elderly years. With increasing age, there is a gradual flattening of the across-NREMP curve for normalized delta: strong concave curvature is present in children; this curvature is weaker in young adults and is absent in the elderly. Further study is required to determine the precise shape of this trajectory and whether it occurs consistently in individuals or only on average. Its biologic basis is unknown. Perhaps, with maturation and aging, there is a reduced capacity (or need) to produce extraordinary levels of high-frequency delta EEG during NREMP1.

## Different Boundaries for the Delta Band Can Produce Linear or Curvilinear Trends

Our analyses show that different designations of "delta" frequency bands can explain previous disagreements on whether computer-measured delta shows a linear or curvilinear decline across NREMPs. This issue is important in sleep theory because significant curvature would be expected if the decline is exponential. Feinberg's 1974 homeostatic model proposed that the change in delta intensity is indicated by the decline in stage 4 across the night and hypothesized that this decline mirrors the metabolic consumption of a substrate produced by waking brain activity.<sup>1</sup> In this model, the substrate for the homeostatic process (termed S-SW) is proportional to both the duration of waking and the intensity of waking brain activity, with waking intensity indexed by cerebral metabolic rate. Our qualitative model did note that the intensity of a single compartment metabolic process declines exponentially as its substrate is consumed. Using the visual scoring of delta (stage 4) then available, we reported that the decline appeared exponential in children and young adults but linear in elderly. (Skipped first REM periods were not identified in the 1974 experiment and may have contributed to the apparent exponential decline in stage 4 in children and young adults.) The quantitative 2-process model subsequently proposed that delta power declines exponentially across sleep but proposed no underlying biologic process to account for the exponential rate.

Because intensity of waking brain activity was not a component of the original 2-process model, it had no explanation for the massive age differences in delta.

Although our data with visual scoring suggested an exponential decline of delta in children and young adults, we did not invariably obtain this result when we applied computer measurement. Studies of 2 large samples of young adults<sup>19,20</sup> had revealed a linear decline in most delta waveform measures. However, we had designated the delta band, a priori as 0.3 to 3 Hz. This band includes the atypical kinetics of the VLF and the higher frequencies that show first a linear and then a concave decline. We show here that including the VLF component in a 0.3 to 3 Hz “delta” band produces a linear trend in young adults but not in children. In young adults, the convex trends of the VLF (< 1 Hz) frequencies combine with the concave trend of the 1 to 3 Hz frequencies to produce a linear trend. In contrast, children show a concave curvature in 0.3 to 3 Hz in spite of inclusion of their VLF pattern. This is because the concave curvature in their 1 to 4 Hz frequencies is so powerful that it outweighs the convex VLF curvature. Our analyses here show that, when the delta band is defined to exclude the VLF, young adults show a highly significant concave decline. These findings reconcile the discrepancy between our results and those of Gaudreau et al.<sup>5</sup> Their use of 0.75 Hz as the lower limit of the delta band excluded most VLF power.

### **NREM 0.3 to 3 Hz Power Density Decline is Steeper in Children**

Our findings here also replicate Gaudreau et al’s data<sup>5</sup> that the delta decline across the night in children is significantly steeper than in young adults. This refutes our initial hypothesis based on analysis of normalized 0.3 to 3 Hz in young adults and elderly. The similar linear decline we found in the normalized delta declines in these 2 age groups led us to propose that normalized delta declines across the night at a constant linear rate over most of the lifespan. However, Gaudreau et al’s 0.75 to 4 Hz data show that the decline is curvilinear in children and significantly steeper than in young adults. The finding here of curvature in delta decline in children for 0.3 to 3 Hz as well as 0.7 to 4 Hz leads us to reject our initial hypotheses. In the 0.7 to 4 Hz band, we find differences in slope between all 3 age groups, ie, not only between the children and the adult groups, but also between the young adults and the elderly. We think it important to emphasize that the differences between the rates of decline in power density in the 3 age groups are due to the degree to which delta is concentrated in NREMP1. When NREMP1 is excluded from the analyses, there are no significant differences in normalized across-NREMP delta decline (for any delta-band designation) across the 3 age groups. Essentially the same result was obtained with analysis of the stage 4 decline across NREMPs over a wide age range.<sup>1</sup> We have long emphasized the special importance of the first NREMP in human sleep.<sup>1,21</sup> It is the sleep component that changes most with age and is most affected in psychiatric illness. It is therefore inappropriate to designate NREMP1 duration as “REM latency” as though its only importance is the degree to which it delays REM sleep (cf<sup>21</sup>).

Both Feinberg et al<sup>22</sup> and Dijk et al<sup>23</sup> have shown that the decline in computer-measured slow-wave EEG is less steep in elderly and middle-aged adults than in young adults. However, Feinberg et al reported the declines for absolute rather than normalized EEG. Although Dijk et al did present normalized data, their interpretations

focused on the absolute data. They interpreted the flatter slope as “less efficient” sleep in the middle-aged subjects. Gaudreau et al<sup>5</sup> interpreted the flatter decline in normalized delta in adults as an attenuation of the homeostatic processes of sleep. Feinberg<sup>1</sup> proposed that the exponential decline in slow-wave sleep across NREMPs in children and in young adults could be interpreted as consumption of a metabolic substrate that accumulates during waking. The steeper decline in normalized delta-power density in children could reflect a higher level of substrate (especially at the beginning of the night) for this hypothetical process.

It is interesting that normalized power in the elderly does not decline with concave curvature for any delta designation. It is therefore inappropriate to fit an exponential function to the elderly trend, although this is sometimes done. The fundamental issue is not whether an exponential model can fit the data but whether the data require this fit.

As shown here, when the delta band incorporates frequencies with different patterns, the results may be misleading. Accurate knowledge of sleep EEG kinetics is required to complete an empiric description of sleep EEG that can provide reliable clues to its underlying neurophysiologic and, ultimately, cellular processes. As we have noted elsewhere,<sup>17</sup> we agree with Achermann and Borbély<sup>6</sup> on the importance of separate analysis of the components of low-frequency EEG. We would add that similarly detailed analyses are needed for all the EEG frequencies of both NREM and REM sleep, and we emphasize the importance of including nap studies to challenge homeostasis. We also agree with Amzica and Steriade’s emphasis on the need to go beyond FFT to analyze individual waveform characteristics.<sup>24</sup> Much of the information they call for (albeit not wave shape) is available with existing methods of period-amplitude analysis (cf<sup>19</sup>).

Finally, we reiterate a point we have often made in the past (cf<sup>3</sup>). Although grouped (averaged) data for power or integrated amplitude invariably show systematic declines across NREMPs, the pattern for individual subject nights is highly variable. Both the grouped and the individual data tell compelling stories, but these stories hold different implications for underlying mechanisms. The systematic declines of averaged delta EEG could fit a metabolic process. However, the variability of individual subject nights can differ strikingly from the averaged data and must be explained and modeled. This variability is readily seen in across-night smoothed plots of delta power or integrated amplitude in which the second or even the third NREMP can have higher levels of power than the first. The grouped data have the regularity of a metabolic process. However, we have proposed that individual-night data are more consistent with the variable patterns of neuroendocrine pulses, a possibility consistent with the increasing evidence of hypothalamic control of sleep.

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