EXPERIENTIA

Volume 39/No. 6 Pages 551-686 June 15, 1983

Reviews

Sleep in normal and pathological aging

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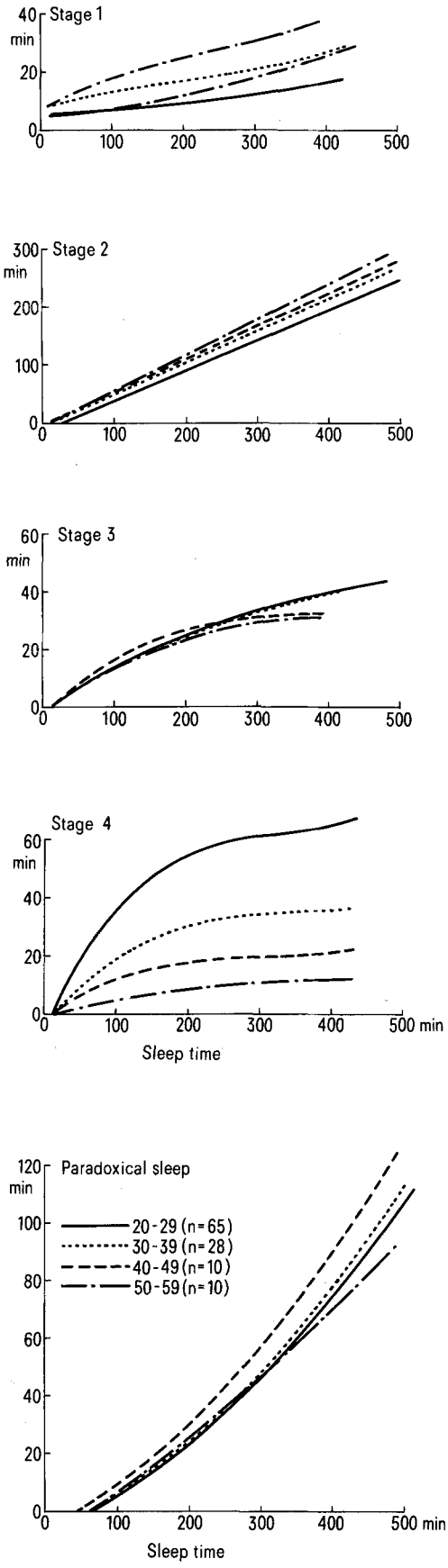
Introduction

The increasing proportion of elderly people in our population makes it necessary for us to pay more attention to changes in physiological functions with respect to age. However, to age is not only to become elderly, and it is now well established that sleep undergoes changes at all stages of life. It is usual to separate the modifications associated with maturation from those occurring in adulthood and advanced age. This distinction is in part arbitrary, and it is likely that maturational processes partially overlap with involutional processes.

The evolution of the main classical sleep parameters with age is known in broad outline, but there are still several points on which perfect agreement has not yet been reached. One of the best known modifications of sleep with age is the decrease of slow wave sleep; it is not known at present whether it represents a maturational or an involutional modification, although the first possibility is the most likely. In addition, it is not known whether these modifications are primarily related to changes in the amplitude, density or total number of slow waves. This point has important implications for the consideration of possible mechanisms responsible for this evolution. The comparison of EEG and subjective estimates of sleep indicates better correlations for some of them, such as sleep latency, than for others, such as within-sleep awakenings. Thus, the subjective awareness of the various components of sleep shows large differences. Not only aging modifies normal sleep, but pathological conditions as well. An interaction exists between depression and aging, suggesting that age-related changes in sleep are not merely superimposed on depression-induced changes, but that age-related changes observed in depressed people are different from those seen in normal subjects. Thus, rapid-eye-movement (REM) sleep latency is stable as a function of age in normal people but shows a striking linear decrease in depressed patients. This observation not only has consequences for the use of biological measures for the diagnosis of depression, but may also have considerable implications concerning the physiopathology of this condition.

Evolution of sleep in normal adults between 20 and 60 years

Although a number of studies of sleep and aging have been published, relatively few of them have systematically covered a large age range and an adequate set of sleep parameters (Williams et al.[2]; Miles and Dement[3]). A study in normal adults between 20 and 60 years old seemed likely to be interesting, because this is the age of most of the patients investigated for sleep disturbances. In addition, the decrease of slow wave sleep is one of the most prominent modifications of sleep in this age range. However, the validity of visual scoring of stages 3 and 4 is limited by the relatively low interscorer agreement. Automatic sleep scoring with electronic devices for measuring slow waves provides a greater precision in the assessment of these stages.



General trends of sleep stages as a function of sleep time in 4 age groups of normal subjects.

Male (n = 70) and female (n = 46) normal subjects were recorded in the laboratory for 2 nights after 1 habituation night. They were subdivided into 4 age groups (20–29, n = 65; 30–39, n = 28; 40–49, n = 13; 50–59, n = 10). Sleep was monitored with standard methods and scored with an automatic system previously described (Gaillard and Tissot[4]). The hypnograms and sleep parameters were stored in a data base; statistical estimations of age-related modifications were realized by calculating the significance of the trend across all groups, with a significance level of $p < 0.05$. In addition, the functions describing the evolution of sleep stages as a function of sleep time were calculated by fitting with orthogonal polynomials (Gaillard[5]).

Total sleep time was longer in the 20–29-year-old subjects (490 min) and decreased similarly in the other 3 groups (469, 471 and 465 min respectively). There was no significant reduction of this parameter as a function of age, although the first 2 groups were significantly different from each other ($p < 0.05$, unpaired Student's t-test).

Interestingly, waking revealed a significant age trend ($p < 0.01$) with values of 24, 30, 36 and 45 min in the 4 age groups. Similarly, stage 1 ($p < 0.05$) and stage 2 ($p < 0.01$) showed an age-related increase. Stage 3, although slightly reduced in the 2 older groups, did not yield any significant trend, whereas stage 4 was clearly diminished as a function of age ($p < 0.05$). The average values of stage 4 were 67, 36, 21 and 12 min respectively. REM sleep remained perfectly stable in this sample between 20 and 60 years.

Sleep latency was calculated as the interval of time between the start of the recording and the onset of the first episode of sleep lasting more than 1 min and containing at least 1 min of stage different from stage 1. This parameter was remarkably constant among all 4 age groups, with values of 13, 16, 11 and 18 min. As usual, a relatively large variability was evident. The latency of stage 2 was independent of age, as opposed to the latency of stage 3, which increased significantly as a function of age ($p < 0.05$). The latency of stage 4 could not be accurately compared across age groups since several subjects of the older group had no stage 4. The latency of REM sleep remained stable with aging. Waking latency, which is a measure of sleep stability, was markedly shortened with increasing age; not significantly so, however, because the change was not regular (415, 368, 355 and 233 min respectively). The efficiency index, that is the ratio of total sleep time over time in bed, also measures sleep stability. This index decreased regularly with age ($p < 0.05$); rather interestingly, the organization index was also significantly decreased ($p < 0.01$). This index is the ratio of the number of minutes within complete cycles over the total number of minutes of sleep. According to our definition, a

complete cycle ends with REM sleep and is considered as aborted if it contains more than 3 min of intervening wakefulness. Thus, the organization index is sensitive to bouts of waking interrupting NREM sleep before the onset of a REM sleep episode. This index is also sensitive to disruptions of REM sleep, but as we have seen above, this is not the case in aging. The number of persomnic awakenings was 3.99, 3.71, 4.92 and 5.80 in the 4 age groups. The trend was not significant.

The analysis of the evolution of sleep stages as a function of total sleep time confirms the observations made with the classical sleep parameters (fig.). The increase of stage 1 and stage 2 was regularly distributed during the night. Stage 3 showed a remarkable stability with age, contrasting to the marked decrease of stage 4. The modifications of REM sleep were not related to age in a simple way. The general trend of this stage was slightly increased in the 40–49 years group, and slightly decreased in the 50–59 years group.

These results are in good agreement with previous data of the literature (Williams et al.[2]). The most obvious modification of sleep as a function of age is the decrease of stage 4, contrasting with the stability of stage 3. A decrease of slow wave sleep has been observed in chronic primary insomnia, but more accentuated since it involved both stages 3 and 4 (Gaillard[6]). These 2 stages are distinguished by the amount and amplitude of slow waves, that is by a quantitative difference. Therefore, it is possible that the insomnia-related and the age-related decrease of slow wave sleep are of the same nature and differ only in a quantitative way. A qualitative difference between the 2 conditions could be another possibility, less likely than the former one, however, because in both conditions the decrease of slow wave sleep is associated with a lenghtening of the latency of stage 3 (and of stage 4). This evolution is characterized by large variability between individuals, which could imply that there are large individual differences in the rate of aging, at least for this physiological parameter.

Contrasting with the decrease of slow wave sleep is the very good stability of REM sleep in all its characteristics: total amount in minutes, latency and rhythmicity of the ultradian sleep cycle. This stability is opposed to the current opinion of a slight and progressive decrease during adult life.

It has been hypothesized that slow wave sleep is the expression of a physiological hypnogenic mechanism (Gaillard[6]). If this hypothesis is true, a relationship should exist between the parameters describing the sleep-waking balance and the amount of slow wave sleep. This relationship seems to exist, but not in the form of a simple correlation (Gaillard[7]). The present data further suggest that all the parameters describing the sleep-waking balance are not similarly affected. No clear age-related modification was observed for total sleep and sleep latency, and although the number of persomnic awakenings tended to be greater on older subjects, no age-related increase could be demonstrated here. The parameters showing a significant age-related change are total waking, stage 1, efficiency index and organization index. Thus it is possible that the decrease of stage 4 is related to the decrease of sleep stability, but not necessarily to the onset and total duration of sleep.

The relationships between brain serotonin neuronal systems and sleep appear to be more complex than was believed until recently (Jouvet[8]). Serotonin neurons may control the synthesis or activation of a hypnogenic factor, perhaps of a peptidergic nature. It is possible, but purely speculative at present, that the synthesis of this factor (or factors) decreases with age, or alternatively that the systems involved in sleep generation become less sensitive to this factor.

EEG waveform profiles in NREM sleep in young and elderly normal subjects

It is well known that elderly subjects show much lower amounts of high-voltage slow (delta) EEG waves during stage 1–4 (i.e. Non-REM- or NREM-sleep) than young adults (Feinberg[9]). However, the extent to which these differences depend upon changes in the amplitude, density or total number of delta waves has not previously been determined. Neither have there been quantitative comparisons between young and elderly subjects for the waveform characteristics of the other EEG frequency bands occurring in NREM sleep. Here, we present the waveform profile of the main EEG frequency bands in 41 young normal (YN) and 46 elderly normal (EN) subjects.

The YN subjects were male college or medical students in good health. They ranged in age from 18 to 29 years with a mean of 22 years. For a further description of these subjects, see Walker et al.[10] and Feinberg et al.[11].

The EN subjects were retired school teachers participating in an extensive study of sleep in relation to psychobiologic function in normal old age. For a detailed description of the rationale and methods in this investigation, see Feinberg et al.[12]. The EN subjects ranged in age from 66 to 78 years with a mean of 72 years. 12 subjects were male and the remainder were female. (None of the age differences in the sleep variables that are described below depend upon the sex composition of the 2 groups; a separate analysis of elderly males and females, matched for age, revealed that the males showed greater deviations from the young adult values than did the females. Thus, the data reported below, which compare young males with a group made up largely of older females, *underestimate* the age effects.)

Sleep EEG and eye movements were recorded with the usual methods. The C3 EEG lead was recorded on an analog FM tape recorder and analyzed off-line with a period and amplitude analysis program (PANV35). This program computes various measures for the waveforms in each of several frequency bands using a baseline crossing method. PANV35 was described in detail in Feinberg et al.[13] and its repeatability in independent groups of young adults was reported in Feinberg et al.[14]. In addition to the excellent consistency across similar groups of subjects described in the latter article, PANV35 yields data with high within-subject night-to-night reliability.

All subjects were recorded in the absence of daytime naps or psychoactive drugs while carrying on their usual daily activities.

Table 1 gives the results for 3 waveform measures. The values are means across subjects for a night on which at least 4 complete NREM periods (NREMPs) occurred and represent the means for these 4 NREMPs. Because of the interest of the low frequency EEG activity of NREM sleep, the waves between 0.5 and 4 Hz were analyzed in 1 Hz increments.

Table 1 shows that the average sample amplitude (integrated amplitude/time in band) was significantly lower in the EN group between 0.5 and 4 Hz. In the frequency bands above 4 Hz, the groups did not differ significantly in amplitude. It may seem surprising that alpha (8–12 Hz) and sigma (12–15 Hz) waveforms in the elderly were not significantly smaller than in young adults. We believe that separate measurement of *organized* alpha and sigma bursts would indeed demonstrate that these patterns are of higher amplitude in young subjects. However, our computer program 'sees' and averages all waves in the 8–12 and 12–15 Hz bands whether or not they are organized into sinusoidal patterns. We plan to develop pattern-recognition algorithms to measure the waveform characteristics of sinusoidal alpha and sigma bursts.

Table 1 shows that the EN subjects had higher mean frequencies of NREM EEG waves in each frequency band except 8–12 Hz. Table I also shows that the decreased number of delta waves in the EN subjects was limited to the 0.5–2 Hz range. The groups showed equal numbers of 2–3 Hz waves. For each of the frequency bands above 3 Hz, the EN subjects had substantially more waves in the average 20-sec epoch of NREM sleep.

It seemed possible that the difference between YN and EN subjects in the faster frequency bands might have been artificially exaggerated because in the YN subjects fast EEG waves in the early hours of sleep are often superimposed on high-voltage activity and therefore are not detected by baseline crossing analysis. To evaluate this possibility, we examined the waveform profile in the 4th NREMP, where EEG amplitudes approach their asymptote (Feinberg et al.[15]) and where most waves cross the baseline. The relative amounts of activity in the 2 groups were quite similar – for all frequency bands – to the values shown in table 1. However, the absolute levels differed as a consequence of the changing EEG characteristics across NREM sleep.

These data reveal that NREM EEG waveforms are markedly different in young and elderly subjects. In addition to their well-known reduction in delta amplitude (Agnew[16], Smith et al.[17]), the elderly have fewer delta waves in the 0.5–2 Hz range and the average frequency in this particular band is higher. In the higher frequency bands, beginning at 4 Hz, the EN subjects show more waves of significantly higher frequency. The one exception to this generalization is in the alpha (8–12 Hz) range where mean wave frequency in the elderly does not differ significantly from the YN adult value; however, the EN subjects again have substantially more alpha waves.

In the near future, we shall test the relation of these NREM EEG patterns to cognitive function in the EN subjects. Over the longer term, it may become possible to relate these age effects on the NREM sleep EEG to changes in brain neurotransmitter levels or metabolic rate.

Subjective measures of sleep in older populations

As we move from our laboratories to respond to sleep in the clinic of the day to day world, we can no longer be content with the relatively impersonal and objective EEG measures of sleep. We must concern ourselves also with the subjective aspects of sleep. These include such descriptive statements as estimates of length of time it takes to get to sleep, qualitative statements such as 'I sleep very lightly', 'I awake refreshed', or 'I slept poorly'. Such subjective observations often serve as incentives for seeking drugs or professional help. The 'quality of life' relative to sleep is mediated by such evaluative states. They also are of theoretical interest in that they give us hints as to which aspects of the sleep structure or patterns carry the main weight in engendering such responses.

If one decides to use such measures, one has to find ways and means to gauge their level significance. How well do they measure what they are proported to measure? In this instance, how well do they measure important aspects of sleep? There are 3 general aspects of validation: 1. Construct or content validity involves the selection of prima facie measures of a variable and its interrelations; 2. concurrent validity evaluates alternative methods of measuring the same construct; 3. predictive or criterion validity assesses the power of measures as predictors of selected crucial independent variables. Here, we explore some aspects of the validity of 2 subjective measures – sleep onset latency and awakenings within sleep.

The population under study consisted of healthy subjects between the ages of 50 and 60 years. There were 40 male and 40 female subjects.

The subjects gave post-sleep subjective responses for 2 weeks at home to the questions: 'How many minutes would you estimate it took you to go to sleep last night?' and 'About how much total time did you spend awake after going to sleep? (None, less than 5 min, 5–15 min, 16–30 min, 31–60 min, more)'. In addition, the males were asked: 'Do you remember waking up last night? Yes, No, Number of times'. The questions were also answered after each laboratory recording night. Subjects slept in the laboratory for 4 successive nights of EEG recordings and measures of sleep latency and awakenings were derived from the EEG recordings.

Table 2 presents the onset latency data from the post sleep estimates (PSE) and the EEG estimates. The 1st set are the correlations of the measures for laboratory nights 2, 3, 4, and their averages (M). The 2nd set are reliability estimates of the PSE measures. The N/N figures are the average night to night correlations; the 14 days estimates are Spearman-Brown formula extrapolations from these correlations. The 3rd set gives the reliability data for EEG measures. The last column presents the correlations between the PSE 2 week means and the 3 night EEG means.

These data and other studies indicate that the nightly latencies are perceived with considerable accuracy by normal subjects. The data also indicate that, while both measures fluctuate from night to night, reasonably stable perceptions of individual latencies and objectively measured latencies are developed. There was, particularly in the males, a low correlation between PSE averages and average EEG measures of latencies. Some lack of correspondence may be attrib-

Table 1. Means and SD of 3 computer measures of sleep EEG waveforms

Frequency band (Hz)	Age group	Average sample amplitude (μV)		Mean frequency (Hz)		No. halfwaves per 20-sec epoch	
		Mean	SD	Mean	SD	Mean	SD
0.5– 1	YN	29.66	6.52	0.752	0.047	5.23	1.80
	EN	20.11*	4.33	0.779*	0.037	3.12*	1.69
1– 2	YN	21.54	6.73	1.44	0.032	16.84	3.10
	EN	15.07*	3.67	1.49*	0.034	13.66*	3.01
2– 3	YN	14.76	3.90	2.44	0.019	15.04	2.05
	EN	11.74*	2.83	2.46*	0.024	15.41	1.78
3– 4	YN	11.88	2.55	3.47	0.015	12.28	2.45
	EN	9.76*	2.34	3.46*	0.014	13.31*	1.90
4– 8	YN	8.87	1.77	5.51	0.088	32.38	8.51
	EN	8.16	2.06	5.71*	0.098	47.14*	9.74
8–12	YN	6.85	1.34	9.69	0.055	26.45	8.28
	EN	6.29	1.72	9.71	0.055	38.28*	10.71
12–15	YN	4.92	0.91	13.28	0.022	14.00	4.88
	EN	4.72	1.45	13.32*	0.028	18.86*	5.65
15–23	YN	3.37	0.68	17.86	0.069	19.69	6.38
	EN	3.48	1.42	18.15*	0.124	30.02*	9.94

*$p < 0.0001$; F test with 1, 85 degrees of freedom. The results are means across NREMPs 1–4 in young normal (YN; n = 41) and elderly normal (EN; n = 46) subjects.

Table 2. Subjective and objective estimates of sleep onset latency

	PSE/EEG				PSE		EEG		PSE (14)/EEG (3)
	II	III	IV	M	N/N	14 days	N/N	3 days	
M	0.65	0.85	0.36	0.65	0.18	0.75	0.28	0.54	0.16
F	0.52	0.70	0.78	0.65	0.22	0.74	0.45	0.71	0.40

PSE: post-sleep estimates; EEG: EEG estimates. See text for explanation.

Table 3. Correlational data relative to awakenings

	PSE/EEG				PSE		EEG		PSE (14)/EEG (3)
	II	III	IV	M	N/N	14 days	N/N	3 days	
	PSE (time awake)/EEG (mins of W)								
M	0.35	0.43	0.70	0.52	0.24	0.82	0.33	0.47	0.04
F	0.01	0.54	0.27	0.28	0.10	0.59	0.11	0.28	0.13
	PSE (N awake)/EEG (NW > 1)								
M	0.19	0.01	0.36	0.19	0.15	0.72	0.55	0.78	0.17
	PSE (N awake)/EEG (NW > 5)								
M	0.03	0.28	0.00	0.16	0.15	0.72	0.23	0.47	0.15

PSE: post-sleep estimates; EEG: EEG estimates. See text for explanation.

uted to the atypical laboratory measurement conditions. However, these figures indicate inaccuracies of over and under ratings, which result in incongruent overall perceptions of sleep latencies relative to the objectively measured latencies.

The subjective ratings of awakenings are more complex. Awakenings, unlike latencies, may vary in number, amounts of time within awakenings and at times of the night and from different conditions of sleep. One person may awaken 10 times in 1 min intervals near sleep onset, another 1 time for a single 10 min interval late in the sleep period.

Table 3 presents the correlational data relative to awakenings. The sets of data are comparable to the table of latency data. Amount estimates and number estimate relations are shown separately. Two 'number' criteria for the EEG were used: all awakenings of more than 1 min in length ($NW > 1$) and only awakenings which exceeded 5 min ($NW > 5$).

The data indicate that there were limited relationships between estimates of amount of wakefulness and EEG measures for the females. The males showed moderate relationships but essentially no relationship between average estimates. The subjective measures of the number of awakenings of the males, using either criterion, had little relationship to the EEG measures although these yielded reliable individual differences. Again, the average estimates were not significantly related.

These data on normal subjects indicate, with the exception of nightly latency estimates, a limited correlation between subjective measures and electrophysiological measures of latency and within-sleep wakefulness. The literature indicates that these relations are yet more attenuated in insomniacs. Clinically and practically the findings indicate the necessity of choice, comparison and caution. Philosophically, they thrust on us many hoary and unresolved problems of mind/body relations. Technically, they point to a long road ahead in the development of valid means of assessing the quality of sleep. It is our suspicion that this path will be one in which psychological determinants will have considerable weight.

Aging, EEG sleep and depression

Despite the considerable activity in elucidating the electroencephalographic (EEG) sleep characteristics of depression, until recently sparse attention has been paid to the possible age-dependent relationships of these EEG sleep measures. This state of affairs is in contrast to the large number of normative studies on aging. In spite of differences in method, these normative studies have demonstrated that age is a very powerful determinant of sleep patterns, affecting the length of sleep, its distribution within the 24-hour-day, and sleep-wake architecture. In a recent report examining the correlation with age of sleep variables in 87 inpatients with major depressive disorders, the variables sleep efficiency, intermittent wakefulness, delta sleep percent, and REM latency showed significant linear decreases with age (Ulrich et al.[18]). This apparent age-related variability in the EEG sleep of patients with depression is important for several theoretical and pragmatic reasons. First, as is well known in clinical psychiatry, the phenomenology of depression shows age-related variability; hence, EEG sleep measures may provide information regarding the developmental psychobiology of depressive disorders. In this regard, it has been observed that the EEG sleep characteristics of depression appear to mirror changes of sleep in the elderly. Second, by controlling for age effects, it is reasonable to expect improved sensitivity, specificity and diagnostic confidence from the use of sleep measures in the differential diagnosis of depression.

In reporting age-related curves for sleep variables in depressed inpatients ranging in age from 18 to 60 we concluded that there are definite differences in various age groups despite the common feature of a diagnosis of major depressive syndrome. REM latency was shown to have a distinctive decline with age in this group of patients. The findings on sleep continuity and wakening supported the previously published data derived from normals at different ages. Although these data on depressed inpatients further our understanding of sleep-age relationships, a key question was whether studies on inpatients, including delusional inpatients, are applicable in understanding age-related phenomena in depressed outpatients. As has been well documented, the majority of depressed patients are non-psychotic outpatients who may possibly show different age-depressive relationships than hospitalized depressed patients. Therefore a group of non-psychotic inpatients were compared with a group of outpatients to answer this question.

The evaluation of 108 non-psychotic patients with major depressive syndrome (67 inpatients and 41 outpatients) ranging in age between 18 and 60 (mean age 35.3 (12.0)) years demonstrated important age-related curves for sleep variables in depression. Few major sleep differences between outpatients and inpatients are found if they are matched for severity of illness.

Based on these results, showing few differences between the 2 groups, the data for the inpatients and the outpatients were combined and age-sleep relationships were examined in the entire group of 108 non-psychotic depressed patients. As in previous studies of inpatients alone (Ulrich et al.[18]), the EEG sleep in these depressed patients demonstrated definite age-group differences in a number of aspects of sleep continuity, sleep architecture and REM sleep. Most measures were either stable or revealed changes which were progressive with age. In table 4, which includes only the so-called age-stable measures, sleep

Table 4. Sleep variables without age trends in 108 depressed patients

	Mean ± SD	Centiles 1%	10%	25%	50%	75%	90%	99%
Sleep continuity								
Total recording period (min)	408.1 ±28.0	348	376	387	406	426	450	476
Sleep latency (min)	40.9 ±35.5	5	13	21.5	31	52.5	69	294
Sleep architecture								
Percent of stage 2	61.69± 9.0	28	52	58	63	68	72	80
REM percent	24.90± 6.07	5.6	18	21	25	29	33	37
REM measures								
Number of REM periods	3.51± 0.83	1	2.5	3	3.5	4	4.5	5.5
REM time (min)	83.1 ±23.6	10.5	52.5	68	84	99	113	138
REM activity*	116 ±62.4	3.5	55	78	102	146	184	394

*Each minute of REM sleep is rated on a 9-point scale (0–8) for the relative amount of rapid eye movements occurring; the sum for the whole night provides the REM activity.

Table 5. Sleep variables with age trends in 108 depressed patients

	Mean ± SD	F, Linear trend	Median (50%)	Range (1–99%)	Number of cases at 0
Sleep continuity					
Early morning awakening (min)	13.7 ±28.0	13.5[a]	1	0–164	44
Awake (min)	20.6 ±26.0	15.6[a]	10	0–158	5
Time spent asleep (min)	332 ±55.0	13.6[a]	343	88–445	
Sleep efficiency	0.82± 0.12	18.7[a]	0.85	0.19–0.97	
Sleep maintenance	90.4 ±11.7	23.1[a]	95	40–100	
Scaled sleep maintenance	34.4 ±21.1	57.6[a]	27	2–100	
Sleep architecture					
Stage 1 percent	9.1 ± 6.4	4.13[b]	7	1– 48	
Delta percent	2.7 ± 4.81	24.3[a]	0	0– 26	63
Percent of stage 2 REM	1.35± 1.43	3.6[c]	0	0– 8	7
REM measures					
REM latency (min)	49.6 ±21.5	15.1[a]	51	0–112	

[a] $p < 0.001$; [b] $p = 0.05$; [c] $p = 0.06$.

latency and duration of REM periods did not differ with age. Measures of sleep continuity were again noteworthy for their absence from this age-stable set.

As demonstrated in table 5, many of the linear age trends were present and were extremely significant, with F ratios ranging from 3.6 to 57.6. As expected, the majority of sleep continuity variables were found in this particular table. In addition, with respect to sleep architecture, stage 1 percent, delta percent and the percent of stage 2 REM showed significant linear trends. The most noteworthy REM measure with a linear trend was REM latency, as well as the square root of REM latency. Among the sleep architecture measures, delta sleep percent had the highest correlation with age and it demonstrated that 63 of the 108 patients had no stage 3 or 4 delta sleep at all during the 2 nights recorded. Thus, the majority of patients in all the age-groups did not have any scorable delta sleep. Sleep continuity measures showed systematic age effects which were consistent for most measures. These included such variables as early morning awakening, both in terms of presence and actual number of minutes of early morning awakening. This was also particularly true for the various measures of sleep efficiency, including scaled sleep maintenance and sleep maintenance itself. A transformed variable labeled scaled sleep maintenance had a much higher F ratio than any other measure. This represents a normalized measure of sleep efficiency independent of the effects of sleep latency. A strong age trend existed with the central estimates of REM latency ranging from 58 to 32 min in the oldest group. From these figures, it is apparent that extremely short REM latency, that is, less than 20 to 30 min, was more prevalent with increasing age. The major age linear trend with shortened REM latency confirmed by this study can now allow us to use age corrections to improve the applicability of biologic measures in the specific diagnosis of depression.

The major finding in these studies is that regardless of whether one examines inpatients or outpatients, the relationship between sleep variables and aging in depressed patients appears to be quite similar. These findings support the following conclusions concerning sleep and aging in depression. Sleep latency does not appear to be age-related, but may in fact be more related to environment or to the severity of the patients' clinical condition. The degree of sleep disruption (sleep continuity disturbance) during sleep, which does relate to severity of illness (such as delusional and non-delusional states), also represents a set of age-related measures. With respect to aspects of sleep architecture, the measures in this study confirm that delta sleep and stage 1 percent change

with age; however, this is not the case for REM sleep percent. With respect to specific REM measures, the findings in REM latency continue to confirm and strengthen the notion that REM latency shows a striking linear relationship to age in depressed patients. In contrast to expectations (controlling for delusional states), very few differences were found between depressed inpatients and outpatients.

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0014-4754/83/060551-08$1.50 + 0.20/0

Full Papers

Fetal gastric and colonic implants in syngeneic and allogeneic mice developing typical inflammatory changes

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Summary. Implants of fetal stomach and colon under the kidney capsule of syngeneic, and H-2 compatible and H-2 incompatible allogeneic mice were examined histologically at different time intervals after the procedure. According to the time of implantation typical inflammatory changes were seen in syngeneic stomach and colon implants, which resembled changes seen in chronic atrophic gastritis and chronic ulcerative colitis. Immunofluorescence studies showed that the host developed antibodies against fetal antigens, while there was no evidence for cellular immune response to fetal syngeneic antigens with the direct leukocyte migration inhibition test. Possible explanations for these results are discussed.

Introduction

There are few experimental models of non-infective inflammatory disease of the gastrointestinal tract. One of these models is the orthotopical implantation of fetal gastrointestinal tissue in adult mice. The technique of implantation of fetal mouse intestine under the kidney capsule of adult mice was first introduced by Ferguson and Parrot[3]. Fetal grafts have the great advantage that they have never been exposed to such external antigens as those of food and microorganisms. Using small intestine implants Ferguson and Parrot[3,4] and MacDonald and Ferguson[10] have shown that the morphological development parallels that of the normally sited intestine of the same age, while allografts had typical signs of rejection, such as lymphoid cell infiltration, cell damage and crypt hyperplasia.

In this paper we describe the histopathological changes in fetal colon and stomach implants in syngeneic and allogeneic mice and correlate the morphological changes with humoral and cellular immune reactions. The possible role of fetal intestinal antigens for the development of pathological changes is emphasized.

Material and methods

Mice of inbred strains BALB/c and C57bl/6J were obtained from Simonsen Laboratories, Gilroy, California. DBA/2 mice were obtained from Jackson