Rapid Eye Movement Density is Reduced in the Normal Elderly

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Study Objectives: While there is general agreement on the age changes in non-rapid eye movement sleep, there is conflicting evidence on whether eye movement density (EMD) in rapid eye movement sleep is affected by aging. We therefore performed computer measurement of EMD in young and elderly normal subjects.

Design: Sleep electroencephalogram and electrooculogram were recorded in each subject on 4 nonconsecutive baseline nights. Eye movement density in the elderly subjects was compared to that in young adults.

Setting: A sleep research laboratory with 4 separate bedrooms.

Interventions: Not applicable.

Participants: Subjects were 19 young normal adults and 19 elderly normal adults.

Measurements and Results: Digitized electrooculograms were analyzed with the extensively validated zero-cross period-amplitude module of PASS PLUS software. The EMD was measured as 0.3 to 2 Hz integrated amplitude per 20-second stage of rapid eye movement sleep. Eye-movement incidence was the number of half waves. Eye-movement amplitude was the sum of peak-trough excursions (curve length) in the average half wave. We also counted visually the number of 2-second epochs with eye movements for 1 baseline night in both groups. The EMD in the elderly subjects was substantially and significantly lower than in the young subjects. Visual scoring of EMD on 1 baseline night confirmed the statistically significant difference between age groups. Period-amplitude analysis revealed that a lower eye-movement incidence rather than reduced amplitude caused the lower EMD in the elderly. The EMD was significantly correlated within subjects across the nonconsecutive baseline nights in both groups; in both, subjects' EMD average across 2 nights provided a correlation greater than .90 with the 4-night mean.

Conclusions: The incidence of eye movements during rapid eye movement sleep is substantially reduced in the elderly. We hypothesize that this reduction is due to degenerative (aging) rather than developmental brain changes. The correlation analysis indicates that EMD is a reasonably stable individual trait in both young and elderly adults. These results encourage normative studies of EMD over a wider age span and continued exploration of the relation of EMD to cognitive function in the elderly.

Key Words: REM sleep, aging, eye movement density, computer analysis

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INTRODUCTION

UNDERSTANDING THE MECHANISMS GOVERNING THE TIGHT LINK OF SLEEP TO AGE OVER THE HUMAN LIFE SPAN COULD SHED LIGHT ON 2 FUNDAMENTAL PROBLEMS IN NEUROSCIENCE: THE FUNCTION OF SLEEP AND THE NATURE OF BRAIN AGING. Research over the past 40 years has documented substantial and reliable age-dependent changes in the electroencephalogram (EEG) of non-rapid eye movement (NREM) sleep. Compared to young adults, normal elderly subjects have markedly reduced levels of NREM delta. This age difference was first demonstrated with visual scoring of stage 4 sleep.[1-3] It was subsequently confirmed and elaborated with direct computer measurement of the 0.3- to 3-Hz EEG on which the stage 4 scores are based.[4, 5] Other major changes in the NREM EEG of the normal elderly are marked reductions in the density and duration of sleep spindles and increases in the number and duration of awakenings.[6-9] Accumulating evidence also suggests that total sleep capacity is reduced in old age (c.f.[10]). The contribution of illness rather than aging to those latter changes remains controversial.

Compared to these marked NREM changes, the effects of age on rapid eye movement (REM) sleep are more subtle. The 2 distinctive features of REM sleep are its recurrent periods of low-voltage EEG and its rapid eye movements, which occur singly or in bursts. The stage REM EEG of the elderly visually resembles that of young adults. However, both fast Fourier Transform (FFT) and period-amplitude (PA) computer analyses demonstrate that the EEG frequency spectrum in stage REM of the elderly differs from that of young adults.[11] Low-frequency EEG power in the elderly is below that of young adults, but high-frequency power is above the young-adult level; the FFT spectral curve for stage REM in the elderly crosses the young-adult curve at about 8 Hz. A similar crossing pattern occurs in the NREM EEG spectra.

Age changes in the eye movements of stage REM are less well established. Our own studies[1,2] and some subsequent reports from others[12,13] did not find reduced eye movement density (EMD) in the elderly. However, Vegni and coworkers[14] recently reported significantly reduced EMD in a small sample of elderly subjects; in addition, they replicated their earlier finding that eye movement bursts in the elderly are shorter than those of young adults.[13] Vegni et al's findings are of potential clinical as well as basic interest. The EMD in the elderly appears to be positively correlated with cognitive function[15,16] and may predict the development of age-related cognitive impairment.

Because of the conflicting evidence in prior studies, and because Vegni et al studied relatively small samples, we thought it would be useful to compare EMD in larger groups of young and elderly subjects using the computer measurement described by Tan et al.[17] This straightforward method simply measures all low-frequency (.3-2 Hz) waves in the electrooculogram (EOG) during visually defined epochs of artifact-free stage REM. The measurements can be performed with either FFT or PA computer analysis, the 2 most widely used methods of computer analysis.

We used Tan et al's method with PA to analyze EOG on 4 baseline nights that had been recorded in a study of naps in young normal and elderly normal subjects.[10] The PA integrated amplitude (IA) provides roughly the same information as FFT power in the low frequencies that contain most of the EOG potentials. The IA and FFT power are homologous in that both reflect the combined contributions of the incidence and amplitude of EOG potentials. We used PA because, in contrast to

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FFT, it can also measure separately the incidence and amplitude of EOG waves.[18]

METHODS

Subjects and Study Design

Nineteen young (10 women and 9 men) normal subjects with a mean age (SD) of 22.4 (1.4) years and 19 elderly (11 women and 8 men) normal subjects with a mean age of 71.4 (4.9) years participated in a study of the effects of naps on postnap sleep. The young normal subjects were students at the University of California, Davis. The elderly normal subjects were retired individuals living in the Davis community. All subjects were paid volunteers, and the study was approved by the University of California Davis Committee for Human Research Protection. Each subject 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 4 baseline nights were used for the analyses presented here.

Screening

Prior to enrollment in the study, each subject was screened on 2 recording nights to rule out sleep apnea, myoclonus, and other sleep disorders. No subject was using hypnotics or other psychoactive drugs. Random urine screening was also carried out. An individual psychiatric interview was performed with particular attention to the possibility of depression. The young subjects were in excellent health, and the elderly subjects were in generally good health for their age, although some subjects had age-related illnesses such as osteoarthritis and hypertension. Some of the hypertensive subjects were taking angiotensin converting enzyme inhibitors, diuretics, or both. These drugs are not known to affect the sleep EEG.

Baseline Sleep Schedules

Baseline time in bed was 11:00 PM to 7:00 AM for all elderly subjects. Seven young adults were also in bed from 11:00 PM to 7:00 AM, and the remaining 12 young subjects were in bed from 11:30 PM to 7:00 AM. The different sleep schedules in the 2 subgroups of young adults did not affect the EMD results. The EMD in the subjects (90.20μV•sec) with 7.5 hours of time in bed did not differ from that in the subjects (92.81μV•sec) with 8 hours of time in bed (P = .876). Although the elderly subjects had a longer mean time in bed, they averaged less total sleep than did the young subjects. All subjects were instructed to maintain the laboratory time-in-bed schedule at home for at least 3 nights prior to each recording session. Subjects were informed of the importance of complying with this schedule and also avoiding daytime naps. To encourage compliance with the sleep schedules, subjects were required to phone the laboratory on retiring and waking up. The time of these calls was automatically recorded. In addition, when the subjects reported to the laboratory, they were carefully quizzed about the possibility of inadvertent daytime naps.

Table 1—Internight correlation for eye movement density* in young and elderly subjects

Young normal subjects			
Night	N2	N3	N4
N1	0.75†	0.89†	0.74†
N2		0.69†	0.59†
N3			0.73†
Elderly normal subjects			
N1	0.42‡	0.55§	0.56§
N2		0.74†	0.69†
N3			0.78†

*0.3- to 2-Hz electrooculogram integrated amplitude per epoch
†P < .0001
‡P < .01
§P < .001
N1 refers to night 1; N2, night 2; N3, night 3; N4, night 4

Recording

The EEG and EOG were amplified and filtered with Grass 7P511 amplifiers and digitized and saved to the hard disk of the personal computer. Amplifier filter settings were 0.3 Hz (high pass, TC = 0.25 seconds) and 0.1 kHz (low pass). The eye-movement lead (left outer canthus to midforehead) responded to both vertical and horizontal eye movements. The EOG potentials were digitized at 50 Hz and analyzed simultaneously with FFT and PA analysis by PASS PLUS (Delta Software, St. Louis, MO). The C3-A2 lead was used for identification of vigilance states according to standard criteria.[19] When excessive artifact was present on C3-A2, the C4-A1 lead was used. Supplemental information for visual sleep staging was provided by an O1-A2 lead that was also continuously recorded and digitized. Electrode impedance measured with a Grass impedance meter was less than 5 kOhm at the start of each recording. Electromyography was not recorded.

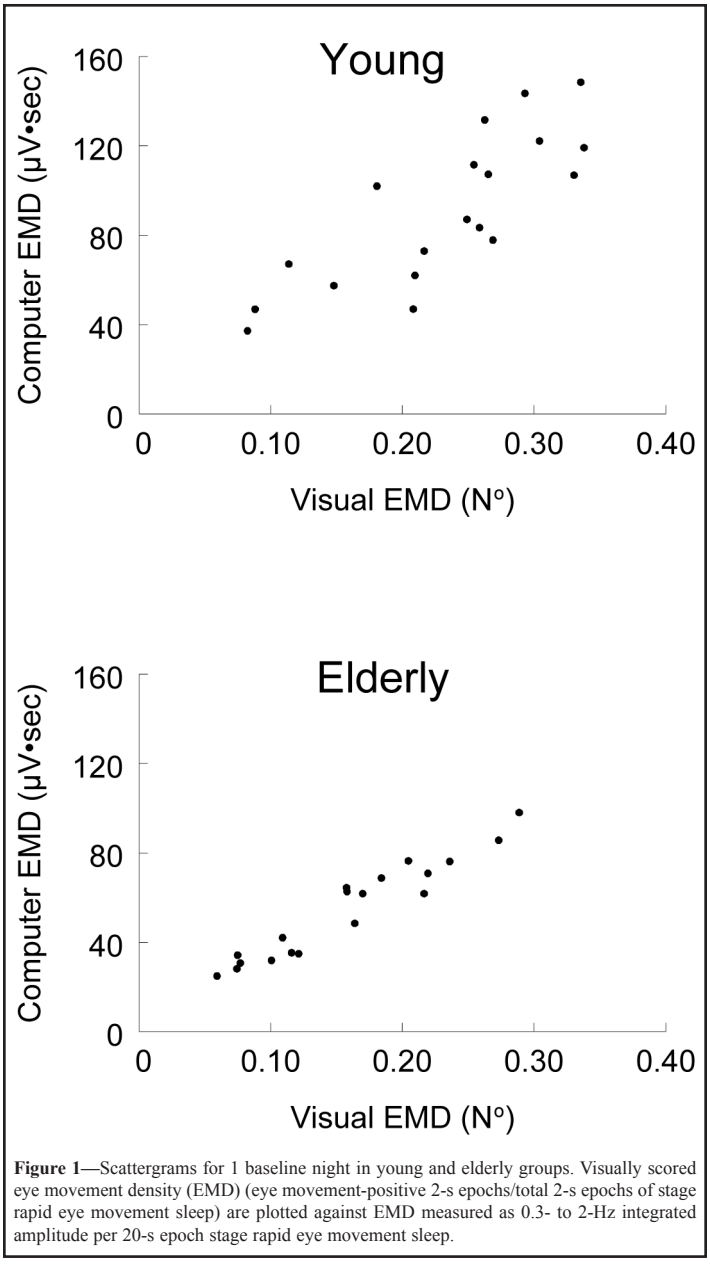

Figure 1—Scattergrams for 1 baseline night in young and elderly groups. Visually scored eye movement density (EMD) (eye movement-positive 2-s epochs/total 2-s epochs of stage rapid eye movement sleep) are plotted against EMD measured as 0.3- to 2-Hz integrated amplitude per 20-s epoch stage rapid eye movement sleep.

Period-amplitude Analysis

We measured the EOG with the zero-cross algorithms of PASS PLUS.[18] Their reliability has been documented for EEG[11,18,20,21] and EOG measurement.[17] We increased the 5-μV smoothing constant we use for EEG to 50 μV for the EOG analyses. This minimizes the contributions of EEG to the EOG leads. The following variables were measured in 0.3 Hz to 2 Hz for each 20-second epoch of visually defined artifact-free stage REM: IA, number of half waves (HW) and curve length (CL: the sum of peak-trough amplitudes). The EMD was computed by dividing each of these measures by the number of 20-second stage-REM epochs. In addition, we computed eye-movement incidence as HW per 20 seconds and eye-movement amplitude as CL per HW.

Cross-validation of Computer Measurement

We cross-validated the computer-measured age difference in EOG by performing visual scoring of eye-movement activity on 1 baseline night, using the night that preceded the 9 AM nap. We counted the number of 2-second epochs of stage REM containing any eye-movement activity greater than 25 μV[17] in all 19 young and elderly subjects. The EMD was the number of 2-second epochs with eye-movement activity divided by the total number of 2-seccond stage-REM epochs.

Statistical Analysis

We tested the EMD differences between age groups with *t*-tests. To compare groups, the EMD for each subject was averaged across the 4 baseline nights. These 4-night subject means were used to compute the elderly and young group means. We tested the EMD reliability across nonconsecutive baseline nights with Pearson correlation coefficients and calculated the mean number of baseline nights required to obtain a correlation coefficient greater than 0.90 with the 4-night mean.

RESULTS

Stability of Computer-measured EMD Across Nonconsecutive Nights

Table 1 presents the internight correlation matrix for EMD measured as IA per epoch of 0.3- to 2-Hz EOG. All of the correlation coefficients were statistically significant. In both the young and elderly groups, the mean of 2 nights was sufficient to provide a correlation greater than .90 with the 4-night mean. We also used the visual scoring of eye movements in 2-second epochs on 1 baseline night to confirm Tan et al's finding that computer-measured EMD (IA per epoch) is strongly correlated with visually scored EMD. In the group of young normals, r was .80; in the elderly, it was .96 ($P < .001$). These scattergrams are presented in Figure 1.

Age Effects on EMD

Table 2 shows that EMD in elderly normal baseline sleep, measured as 0.3- to 2-Hz IA per 20 seconds of stage REM, was 39% lower than in the young normals ($P = .0002$). As would be expected from the significant correlations between the visual and computer measures of EMD reported above, visually scored EMD in 2-second epochs on a single baseline night corroborated the difference found with computer analysis. Visually scored EMD was significantly higher in the young than in the elderly subjects (0.232 vs 0.158, $P = .006$). There were no significant sex differences in EMD ($P = .145$).

Integrated amplitude in 0.3 to 2 Hz is roughly equivalent to spectral power with FFT. Both FFT power and PA IA represent the combined effects of wave incidence and amplitude. Period amplitude can distinguish between these effects. Its application (Table 2) shows that the lower IA per epoch in the elderly resulted from a lower incidence of EOG waves. The amplitude of the average EOG wave (CL per HW) did not differ significantly in the 2 groups.

Figure 2 shows that the EMD difference (IA per epoch) between age groups was present on each of the 4 baseline nights. The age difference in eye-movement incidence (HW) was clearly present on each night (Figure 2). The amplitude (CL per HW) of EOG potentials was slightly lower on each night in the elderly, but these differences were not statistically significant.

Table 2—Period-amplitude measurements of baseline sleep eye movement density in young and elderly subjects

Group		IA/20s	HW/20s	CL/HW
Young	Mean	91.61	19.66	34.26
	s.e.	7.49	0.48	1.78
Elderly	Mean	56.02	14.45	31.92
	s.e.	4.52	0.84	2.11
Young vs Elderly	t_{36}	4.07	5.40	0.84
	P	.0002	< .0001	.41

IA/20s refers to integrated amplitude per 20-s epoch; HW/20s, number of half waves per 20-s epoch; CL/HW, curve length (sum of peak-trough amplitudes) per half wave

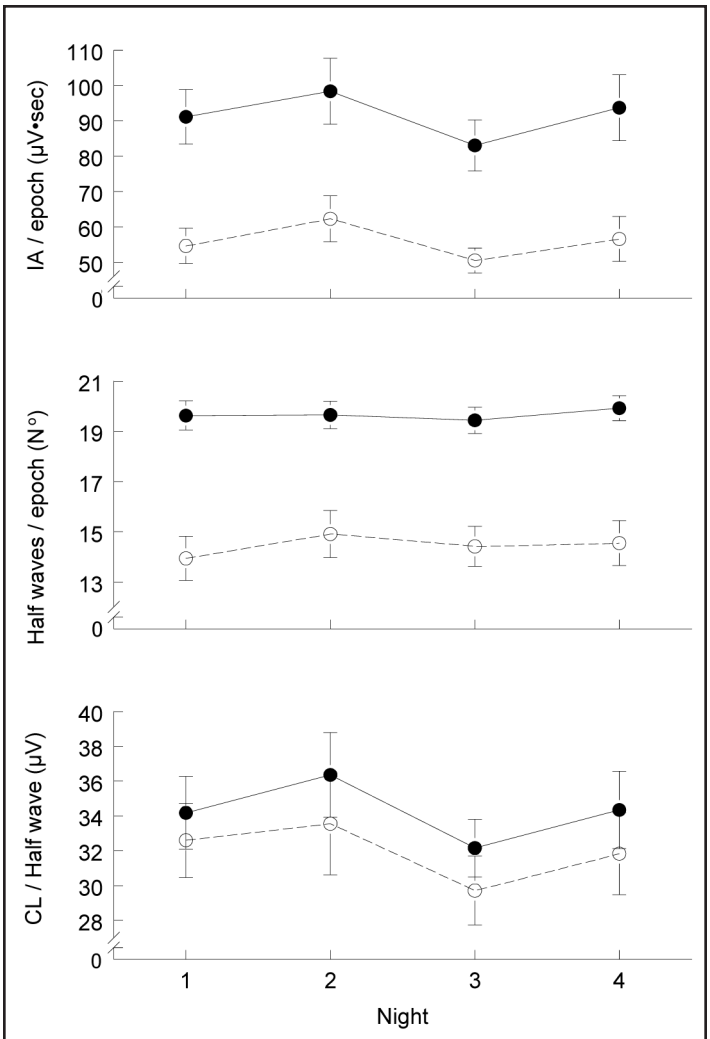

Figure 2—Measures of electrooculographic (EOG) activity in 4 nonconsecutive baseline nights in 19 young (filled circles) and 19 elderly (open circles) normal subjects. Top: Integrated amplitude (IA) in 0.3-2 Hz per 20-s epoch of rapid eye movement sleep. This measure of eye-movement density (EMD) correlates well with visually scored EMD. The IA represents the combined contributions of half-wave incidence and amplitude. These contributions can be measured separately by period-amplitude analysis. Middle: Wave incidence is significantly lower in the elderly on all 4 nights. This accounts for their reduced IA since the amplitude of the EOG waves does not differ significantly (Bottom Figure). Bottom: The amplitude of EOG waves did not differ between groups. These results were consistent across the 4 baseline nights. Curve length (CL) is the sum of peak-trough excursions of each half wave.

DISCUSSION

Trait-like Stability of EMD Across Nights

The stability of individual differences in EMD has received little study. In an early investigation of this question,[22] our laboratory reported internight correlations of *r* equal to .61 to .77 for visually scored EMD (in 20-second epochs) on 3 consecutive nights in 30 normal subjects (age, 16-34 years). More recently, Tan et al[17] reported a correlation coefficient across 2 consecutive nights of *r* equal to .78 for visually scored eye movements in 2-second epochs in 16 young normal subjects aged 19 to 26 years. Tan et al also reported correlation coefficients across 5 consecutive nights for computer-measured EMD in this young normal group. Measuring EMD as IA per 20 seconds, the method used here, correlation coefficients in young normal subjects on 5 consecutive nights were r equal to .82, .81, .85, and .88. These r-values are similar to those found here in 4 nonconsecutive nights in young normals (*r* = .59-.89). With regard to the practical matter of the number of nights of study required to approximate a 4-night mean for EMD recorded on nonconsecutive nights, our data show that 2 nights are sufficient to provide an r-value greater than .90 for both young and elderly subjects. These data demonstrate that the density of rapid eye movements during stage REM sleep is a stable individual characteristic of human subjects. This trait accounts for 50% to 60% of the variance in young subjects, indicating that state or other factors also operate.

Reduced EMD in the Normal Elderly

Our data clearly demonstrate a marked reduction in EMD in the normal elderly, confirming Vegni et al's previous report. The documentation of this age difference with computer measurement in larger numbers of subjects confirms its validity. In addition, our PA analysis demonstrates that a lower incidence rather than decreased amplitude of EOG potentials causes the lower IA in the EOG of the elderly subjects.

The finding of significantly lower EMD in the elderly contradicts earlier reports from our laboratory. These earlier studies scored eye movements visually in either 20-second or 4-second epochs. With these methods, a 20-second or 4-second epoch with continuous eye movements carries the same weight as an epoch with a single eye movement. Visual scoring in these relatively long epochs obviously has lower resolution than does continuous computer measurement or visual scoring of eye-movement activity in short epochs such as the 1-second epochs used by Vegni et al or the 2-second epochs used by Tan et al. In the present study, we also detected a significant age difference in EMD using visual scoring of 2-second epochs on a single baseline night.

The demonstration that the reduced EOG power in the elderly is almost entirely due to a reduced incidence of EOG potentials is biologically meaningful. If EOG amplitude had been reduced, it could have indicated an age-dependent degradation of the corneo-retinal potential difference, a reduction of eye-movement velocity, or both.[23] These possibilities are effectively ruled out by the finding that it is the incidence of eye-movement potentials that is reduced in the elderly; that is, elderly normal subjects produce eye movements during REM sleep at a lower rate than do young adults.

Reduced EMD in the elderly is presumably a degenerative (aging) rather than a developmental (maturational) age change. Raising this issue in a study of adults may seem unnecessary. However, it now appears that at least one sleep EEG change during the adult years—the decline in NREM delta IA (or power)—is a continuation of a developmental reduction that begins in childhood, markedly accelerates in early adolescence, and then continues at a slower but substantial rate through at least the fourth decade.[10,24,25] During the years of its most rapid change, the delta decline parallels reductions in cortical synaptic density and metabolic rate.[26]

Interpreting the EMD reduction in old age as a degenerative change that begins late in life is necessarily provisional. There are no age curves for EMD with high-resolution measurement (visual scoring of 1- or 2-second epochs or continuous computer measurement). If further research confirms that the EMD decline begins in late adulthood, this change would belong in the category of degenerative sleep changes that includes increased awakenings and (probably) decreased sleep spindles and reduced total sleep capacity. If the lower levels of EMD in the elderly subjects are caused by brain aging, it might explain findings of a positive relation between eye-movement activity and cognitive function in the elderly.[1,15,16]

One might wonder whether lower levels of EMD in the elderly cause differences in the mentation reports (dreams) elicited by experimental awakenings from REM sleep. In fact, Fein et al[27] found a significantly lower incidence of visual imagery in reports from REM awakenings in elderly compared to young subjects. However, Fein et al found that the incidence of visual imagery from NREM awakenings was also significantly lower in the elderly. Therefore, one cannot attribute the reduced visual imagery in elderly subjects' dream reports to their lower incidence of eye movements. We think it likely that both the reduced visual imagery and the lower EMD in the elderly are independent consequences of brain aging.

Moreover, the eye movements of REM sleep may not have any special significance for dreaming. We have proposed[28] that these eye movements occur only because there is no physiologic requirement that they be inhibited. During REM sleep there is disinhibited firing of neurons in many parts of the brain. The firing in the higher centers that control large somatic muscles would cause awakening if the resulting movements were not blocked by active inhibition at the motor-neuron level.[29-31] Eye movements during REM sleep can occur without awakening the subject and need not be inhibited. We noted that this hypothesis "shifts the question of functional significance from the eye movements to their higher motor centers, which are then seen as behaving in the same way during REM sleep as other motor centers."[28]

Although the average discharge level of neurons in REM and active waking are about equal, their temporal patterns are markedly different. For example, during REM sleep, neurons in the motor cortex of the rhesus show intense irregular firing interspersed with periods of quiescence.[32] If the higher motor centers controlling the oculomotor nuclei behave similarly, one would observe the phasic eye-movement patterns of REM sleep. Under this scenario, decreased eye-movement incidence in the elderly would indicate a decreased number of firing bursts in the motor centers controlling the oculomotor nuclei. Evarts' observation in the rhesus are particularly interesting because the rhesus' response to sleep deprivation closely resembles that of the humans.[33]

The data of Vegni et al[14] show a reduced length of eye-movement bursts, as well as reduced EMD, in the elderly. Both changes could be produced if the overall balance of excitation and inhibition was shifted in the direction of inhibition in the elderly brain. An alternative and, we think, more likely hypothesis is that aged neurons fire less intensely when disinhibited. These possibilities might be distinguished electrophysiologically.

Since the classic work of Pompeiano,[30] sleep research has focused on the cholinergic control of rapid eye movements in subcortical centers. However, eye movements are controlled by complex systems of cortical and subcortical brain structures.[34] Where in these systems aging acts to reduce eye-movement incidence is not known. Evidence of a positive correlation between EMD and cognitive function in the elderly suggests, but does not establish, that aging impairs both cognitive and cortical eye-movement systems.

Reduced cholinergic receptors in the cortex are a cardinal feature of Alzheimer disease.[35] The degenerative changes in this illness may be an extreme form of the changes in cognitive function produced by "normal" aging. It seems possible that some loss of cholinergic transmission also occurs in eye-movement systems in the brainstem. If the extent of this loss is correlated with the more substantial loss of cholinergic receptors in the cortex, it could explain a correlation between EMD and cognitive function in the normal elderly. However, given the large number of cortical and subcortical brain structures involved in eye-movement control,

and the huge preponderance of glutamatergic to cholinergic transmission, one cannot exclude the possibility that reduced excitation mediated by glutamate transmission causes the reduced eye-movement bursts. It is relevant in this regard that blocking mGluR receptors in the rat can totally suppress REM sleep and fast EEG.[36] It is also worth noting that glutamate transmission in REM sleep has been observed in brainstem structures heretofore thought to be totally cholinergic.[37,38]

Whatever its underlying physiologic basis, the strong reduction in EMD in the elderly found here encourages further research in both humans and animals. It seems important to establish age curves for EMD with high-resolution methods and to explore further its relationship to cognitive function in the elderly. It would also be of interest to examine EMD in elderly rhesus, since these primates have sleep patterns resembling those of the human.

Current sleep research uses short time-constant, capacitance-coupled amplifiers to record eye movements. Such recordings are strongly influenced by eye-movement velocity and do not indicate eye position. It would therefore be desirable if future studies supplement the standard short, time-constant, eye-movement recordings with DC or long time-constant amplification.[23,39]

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