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HEALTHY AGING RESEARCH

Principal component scoring of the resting EEG spectrum provides further evidence for age-associated disinhibition of the wake drive

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Abstract

Background: Aging is often accompanied by increasingly occurrence of profound sleep–wake disturbances. However, normal 'sleep aging' can also be advantageous to older people, for example, they have a better ability to tolerate sleep deprivation than to younger people. In previous work, we compared the principal component structure of the electroencephalographic (EEG) spectra of Non-Rapid-Eye-Movement (NREM) sleep in young and elderly people, and found that the decrease in slow-wave activity, which is the most earliest and most obvious age-related modification of the sleep EEG spectrum, can be viewed as a consequence of a reduced rise of the first principal component score combined with an insufficient fall of the second principal component score. It was suggested that such changes in principal component scores can be caused by disinhibition (i.e. strengthening) of the wake drive due to weakening of the sleep drive. It is possible that the second principal component score remains higher in older people compared to younger people not only during NREM sleep, but also during normal and extended wakefulness.

Methods: To test this suggestion, principal component analysis was applied to the spectra of resting EEG signals obtained with a three-hour interval during the course of sustained wakefulness of 130 and 33 participants of two independent sleep deprivation experiments.

Results: The second principal component score was positively linked to participants' age.

Conclusions: Elevation of score can reflect age-associated strengthening of the sleep drive, which predisposes older people to develop certain disturbances of their sleep–wake cycle and, on the other hand, to tolerate sleep deprivation better than younger people.

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Introduction

A computerized analysis of the human electroencephalographic (EEG) signal provides possibilities to relate the sleep aging process to certain quantitative changes in the spectral composition of EEG records. Indeed, age-associated variation in almost every range of the EEG power spectrum (delta, theta, low alpha, high alpha, etc.) has been well documented in the EEG literature [1–4]. Principal component structuring of this spectrum allows a more parsimonious quantitative description of the spectral composition of EEG signals by representing it as a set of just 2–4 scores of the largest (first, second, etc.) principal components. However, age-associated variation in the principal component structure of the

human EEG power spectrum has not yet been systematically explored.

Exploration of the effects of aging on principal component scores might provide deeper insights into age-related changes in the regulation of the human sleep–wake cycle that are usually linked to gradual worsening of night sleep quality across lifespan. It has been recognized that the kinetics of slow-wave activity can serve as the major physiological marker of the homeostatic process of sleep regulation [5, 6], and the decrease of slow-wave activity can be regarded as the most obvious age-related modification of the sleep EEG spectrum [4, 7]. Chronologically, it signifies the earlier phase of sleep aging [8]. Principal component structuring of the EEG spectrum has shown that slow-wave activity closely correlates with the difference between scores of the first and second principal components and such a difference can reflect a balance between the competitive drives for sleep and wakefulness, respectively [9–16]. To our knowledge, we have made the first attempt to compare the principal component structure of the EEG spectrum in young and elderly people [17] by exploring the effect of aging on the principal component structure of the EEG spectrum in the first episode of non-rapid eye-movement (NREM) sleep. We have shown that age-associated attenuation of slow-wave activity during the first 75 minutes of sleep can be viewed as a consequence of both a reduced rise of the first principal component score, and an insufficient fall of the second principal component score. Therefore, such a consistent age-related change in sleep as the decrease of slow-wave activity can originate from the simultaneous weakening of the sleep drive and strengthening of the wake drive [17]. Further changes in the strengths of these drives can lead to sleep problems such as a lowered threshold for arousal from sleep, reduced night sleep, repeated awakening during a night sleep episode, and so on. On the other hand, age-related strengthening of the wake drive may be an explanation as to why older people can tolerate sleep deprivation and feel less sleepy during the daytime compared to younger people [17]. Unfortunately, this study [17] was focused on describing the principal component structure of the EEG signal in the first episode of NREM sleep, and it did not provide any information on the principal component structure of the waking EEG spectrum.

In previous work we showed that the first principal component score remains low during wakefulness and Stage 1 sleep, , and exhibits a rapid rise during Stage 2 sleep [9–11, 14–16]. Compared to such changes in the first principal component score, the time course of the second score appears to be much simpler. This score is highest during wakefulness and rapidly declines during the transition from wakefulness to Stage 1 sleep to reach its lowest point somewhere in the middle of the first ultradian sleep cycle, i.e. when the sleep process reaches its deepest level [9–14, 16]. Findings from the study of NREM sleep EEG, which indicated that sleep aging is associated with the insufficient fall of the second principal component score [17], allows us to predict that during normal or extended wakefulness this score also remains higher in older people compared to younger people.

Therefore, the aim of the present analysis was to test this prediction to further support the hypothesis of age-associated strengthening of the wake drive due to its disinhibition by the weakened sleep drive.

Methods

We analyzed a database containing data from resting EEG recordings collected in two experimental studies of the effects of sleep deprivation on the characteristics of the human EEG signal. Both studies were performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Protocols for these studies were approved by the Ethics Committee of the Medical Institutes of the Siberian Branch of the Russian Academy of Sciences. Informed written consent was obtained from each of the participants studied, who were paid volunteers. The study designs and the methods of data collection have been detailed in previous publications [18–21].

Participants in the first study were healthy adolescents and adults. Fifty-four males and 76 females took part in the study, ranging in age from 15 to 55 years, and from 16 to 66 years, respectively (average ± standard deviation: 27.4 ± 10.1 and 30.8 ± 13.4). In the experimental morning (between 08:00 and 08:30), each participant was admitted to a research unit at our Institute and remained there until approximately 11:00 the next morning. Over the next 24 hours each study participant completed nine 3–4-minute EEG recording

sessions divided by three-hour intervals. The EEG recordings were taken at frontal and occipital scalp sites, corresponding to derivations Fz and O2, referenced to the right mastoid, A2, of the International 10–20 system of electrode placement. For half of the participants, recordings with closed eyes were obtained prior to the recordings with eyes open, and for the other half the eyes closed recordings were made following the eyes open recordings. To fix the electrodes, Ten20 conductive paste was used (Nicolet Biomedical, Madison, WI, USA). The exact positions of active electrodes were preliminary inked with a permanent marker, and the electrodes were removed after each recording session. The EEG signals were recorded via a 16-channel electroencephalograph (Neuron-Spectrum-2, Neurosoft, Ivanovo, Russia), conditioned with high-pass, low-pass and notch filters (0.5 Hz, 35 Hz, and 50 Hz, respectively). Recordings were sampled and stored on a hard disc with a frequency of 200 Hz. To calculate the EEG power spectra, at least one minute of data recorded with eyes closed, and at least one minute with eyes open were recorded from each active electrode.

Pre-experimental self-reports consisted of a seven-day sleep history and self-assessments on the 72-item Sleep-Wake-Pattern Assessment Questionnaire (SWPAQ) [22, 23]. The individual mean clock times for going to bed and waking were obtained by averaging over five pre-experimental days (from -6 to -2). Other five-day reports included times of nap episodes, sleep latency (the self-perceived time interval between going to bed and falling asleep), total sleep duration, and sleep satisfaction (scored from 1= "not satisfied at all" to 5= "excellent"). The SWPAQ was completed again immediately after arrival at the institute. Items in the questionnaire are sorted into six 12-item scales: M and E (Morning and Evening Lateness), W and V (Anytime and Daytime Wakeability), and F and S (Anytime and Nighttime Sleepability). Immediately following each EEG recording, participants self-rated their alertness/sleepiness on the Karolinska Sleepiness Scale (KSS) – this is a nine-point verbally anchored scale with the following scores: 1 = very alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy, but no problem staying awake, and 9 = very sleepy, great effort to keep awake. Intermediate steps were not anchored verbally [24]. For the present analysis, individual KSS scores were averaged over nine sessions.

Participants in the second study were healthy females (n=17) and females with a diagnosis of winter seasonal affective disorder (n=16). Their ages ranged from 21 to 57 and from 18 to 54 years old (32.0 ± 11.0 and 35.1 ± 10.5, respectively). Participants arrived at to the Institute's research unit at 09:00–09:30, and left the laboratory shortly after 16:00 the following day. The 30-hour experimental procedure included 11 EEG recording sessions of 3–4 minutes duration per procedure. The EEG signal was recorded in the eyes open condition with a three-hour interval starting from 10:00. Over the following six days the participants were treated in the afternoon with either melatonin or a placebo to test whether this treatment is able to stabilize the antidepressant action of sleep deprivation in patients. They returned to the research unit to repeat the first (12-hour) part of the study protocol, which included the first four EEG recording sessions. Waking EEG signals were obtained from derivations Fz-Cz and C4-A1. They were sampled and computerized via a multi-channel physiological signal recorder, BI-01R (produced by the Research Institute for Molecular Biology and Biophysics, Novosibirsk, Russia). In the present analysis, the EEG power spectra were calculated from the EEG data obtained from each derivation for an interval of at least one minute with eyes open (Table 1).

Immediately after completing each of 15 EEG recordings, the participants self-rated their alertness/ sleepiness according to the KSS. Mean scores were obtained by averaging across scores reported between 10:00 and 19:00 (days +1 and +8). The individual mean clock times for going to bed, waking and napping were obtained by averaging over three pre-experimental days (from day -4 to day -2) and over three days between the first and second visits to the Institute (from day +4 to day +6). To measure the level of depression in both controls and patients, the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version [25] was completed before and after the treatment (days +1 and +8).

Table 1. Correlation of age with score on the second principal component of the waking EEG spectrum

Sample	First sample				Second sample	
Condition	Closed eyes		Open eyes		Open eyes	
Derivation	Fz-A2	O2-A2	Fz-A2	O2-A2	Fz-Cz	C4-A1
All participants (n=130/33)	0.428***	0.144	0.400***	0.119	0.469**	0.657***
Two subsamples:	Males or females				Patients or controls	
Males/Patients (n=54/16)	0.413**	0.218	0.299*	0.194	0.685**	0.788***
Females/Controls (n=76/17)	0.409***	0.054	0.430***	0.023	0.327	0.520*

Note. EEG data from the First and Second samples. Scores were calculated separately for each derivation and each condition (closed eyes or open eyes). Asterisks denote significance ($^{***}p<0.001$; $^{**}p<0.01$; $^{*}p<0.05$) according to Pearson's coefficients of correlation

The EEG signals were inspected visually and epochs containing artifacts were removed from further analysis. Power spectra for artifact-free two-second epochs were computed using the Fastest Fourier Transform in the West (FFTW) package [26]. Absolute spectral powers (μV^2) were calculated for single-Hz frequency bandwidths (i.e., 0.50–1.49 Hz, 1.50–2.49 Hz, etc.). Thereafter, spectra of the artifact-free epochs were averaged within, at least, one-minute intervals. The absolute power values in the frequency, which ranged between 1 and 16 Hz, were converted into a natural logarithmic scale.

All statistical analyses were performed with the SPSS statistical software package (IBM, Armonk, NY, USA, version 20.0). Principal component analysis was run on sets of spectra obtained for each experimental condition and derivation. A set consisting of 16 log-transformed power values was decomposed into four principal component scores, but only the score on the second principal component was used for the present analysis, aimed at testing the prediction of its age-associated elevation. In order to calculate this score, the 16 power values were optimally weighted in accord with their loadings on this component, and then summed. More details regarding the methodology of principal component analysis of the EEG spectrum can be found in earlier reports [9–11, 17].

Preliminary analysis of the EEG data showed the absence of significant interaction between age and timing of EEG session, i.e. the aging process failed to significantly change the time course of the second principal component score. Therefore, the individual scores were averaged over all EEG sessions (nine in the first study and 15 in the second study). The participants of each study were sorted into three age groups (adolescents, younger and older adults). Significance of difference between these three age groups was tested by applying either four- or three-way repeated measure ANOVA (rANOVA). For the analysis of data recorded in the first experimental study (four-way rANOVA), other than "Age" (<20, 20–40, and >40) factors were a between-subjects factor "Subsample" (male vs. female) and two within-subjects factors, "Derivation" (Fz-Cz vs. C4-A1) and "Condition" (eyes open or closed). For the second experimental study (three-way rANOVA), other factors were "Subsample" (patients vs. controls) and "Derivation" (Fz-Cz vs. C4-A1). The Bonferroni multiple comparison test was used in the *post hoc* analysis to examine significance of pairwise differences between age groups. Figure 1 illustrates the differences between subsamples (male vs. female or patients vs. controls) and age groups from the example of scores obtained in the eyes open condition from frontal derivations (Fz-O2 or Fz-Cz).

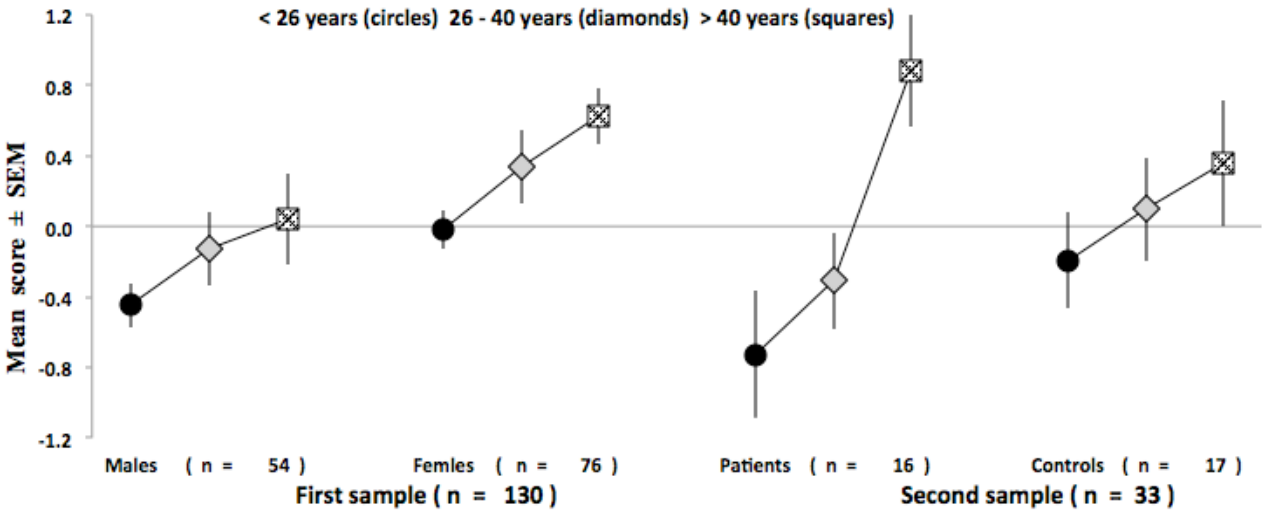

Figure 1. Example of age-associated changes in score on the second principal component of the waking EEG spectrum

Data from frontal EEG recorded in the eyes open condition. Scores were calculated separately for the first and second samples (derivations Fz-A2 and Fz-Cz, respectively). Scores were averaged within and then across participants, sorted into three age groups within a given subsample (males or females, and patients or controls). Vertical bars: standard errors of mean (SEM).

To confirm the rANOVA results of associations between age and second principal component scores, these associations were evaluated with the Pearson coefficients of correlation (Table 1). In the analysis of assessments obtained in the first study, stepwise linear regression analysis was additionally used to predict either age or principal component score from other measurements. In order to compare the effects of treatment on self-reports in subsamples of patients and controls, a paired *t*-test was applied to pre- and post-treatment KSS scores and sleep times. Moreover, correlation between changes in depression levels and self-ratings was measured with the Pearson coefficients of correlation test (*r*).

Finally, each self-rating was analyzed by means of two-way ANOVA with the same between-subjects factors, "Age" and "Subsample" (male vs. female or patients vs. controls).

Results

Irrespective of the experimental study, the significant effect of the 'Age' factor on the second principal component score was revealed by rANOVA ($F_{2,124}$=4.1, p<0.05, and $F_{2,27}$=8.3, p<0.01, for data from the first and second study, respectively). Pairwise differences were found to be significant between older adults and adolescents (0.419, p<0.05, the first study) and between older adults and either adolescents or younger adults (1.318, p<0.01, and 0.932, p<0.05, the second study). Analysis of data from the first study also revealed the significant main effect of the 'Subsample' factor ($F_{1,124}$=9.5, p<0.01) indicating a lowered score in male participants. By contrast, this effect was insignificant in the second study ($F_{1,27}$=0.0, p>0.1), suggesting the absence of differences between patients and controls on the second principal component score. According to results of the first study, the main effect of the 'Condition' factor was insignificant. "Derivation" did not interact significantly with "Age" when the frontal and central derivations were compared (the second study), but the interaction was found to be significant (p<0.001) when frontal derivation was compared with occipital derivation (the first study). This result, reflecting the absence of significant influence of age on occipital score, was contrasted with the result

suggesting a highly significant influence of age on frontal score (Figure 1).

As can be seen in Table 1, highly significant correlations between age and the second principal component score were obtained for the frontal derivations (e.g. the first study) as well as for the central derivation (the second study), but not for the occipital derivation (the second study). The correlations mostly remained highly significant in at least one of the subsamples (e.g. females from the first study and patients from the second study).

Age of participants showed highly significant correlation not only with principal component score (e.g. in frontal derivation, eyes open or closed) but also with some of the self-reports, such as times for going to bed and waking, the SWPAQ scores on morning lateness and both anytime and nighttime sleepability (-0.432, -0.460, -0.406, -0.304, -0.441, $p<0.001$ for all). These negative correlations contrasted with the positive correlation between age and daytime wakeability score (0.212, $p<0.05$). The results of stepwise linear regression analysis suggested that 44.5% of total variation in age can be explained by such significant predictors as time of waking, nighttime sleepability score, second principal component score (frontal derivation, eyes closed), and sleep satisfaction score (standardized betas were -0.406, -0.337, 0.261, and 0.184, respectively, $p<0.001$ for the first three, and $p<0.01$ for the last). Second principal component score (frontal derivation, eyes closed) also correlated with several self-reports, such as times for going to bed and waking, SWPAQ scores on morning lateness and nighttime sleepability (-0.197, -0.176, -0.176, -0.238, $p<0.05$ for the first three, and $p<0.01$ for the last), but the strongest correlate was gender (0.291, $p<0.01$). Stepwise linear regression analysis indicated that only age and gender were significant predictors of this score (standardized betas were 0.374, $p<0.001$, and -0.233, $p<0.01$, respectively). These characteristics of the study participants collectively explained 21.8% of total variation in the score.

Correlations between age and subjective sleepiness (KSS score) were insignificant; ANOVA also did not reveal significant main effect of "Age" on KSS score. The main effect of "Subsample" was insignificant in ANOVA of subjective sleepiness scored in the first study (males vs. females), whereas this effect was significant for scores in the second study (patients vs. controls). This difference suggests that patients were sleepier than controls both before and after the treatment ($F_{1,27}=9.4$, $p<0.01$, and $F_{1,27}=5.5$, $p<0.05$, respectively). A paired t-test indicated that subjective sleepiness did not change significantly in controls, but it significantly decreased in patients ($t=1.539$, $p>0.1$, and $t=3.358$, $p<0.01$, respectively). In controls, changes in depression score was found to correlate with changes in subjective sleepiness ($r=0.532$, $p<0.05$). Despite decrease in level of sleepiness after the treatment, patients also reported a shortened duration of sleep (0.878 hours) due to the shift in waking at an earlier hour ($t=3.027$, $p<0.01$, and $t=2.586$, $p<0.05$, respectively). As a result, pretreatment difference between two subsamples on waking and sleep duration ($F_{1,27}=4.2$, $p<0.05$, and $F_{1,27}=5.7$, $p<0.05$, respectively) became insignificant after the treatment ($F_{1,27}=0.1$, $p>0.1$, for both).

Discussion

The aging process is often accompanied by profound disruptions of an individual daily sleep–wake cycle. An elderly person often experiences a number of sleep–wake disturbances, such as unsatisfactory daytime alertness, undesired daytime sleepiness, too frequent daytime napping, difficulty in falling asleep, insufficient duration of nighttime sleep, unsatisfactory nocturnal sleep quality, disturbed or "light" sleep, frequent nighttime waking, and unwanted early morning waking [27–29]. On the other hand, it was recently shown that the process of normal aging can bring some advantages to older people living in modern 24-hour societies. For instance, they may better tolerate sleep deprivation compared to younger people [30–33]. It seems that research into age-associated changes in principal component structure of the wake and sleep EEG signal can provide deeper insights into the regulatory processes underlying optimal sleep of older people, and their predisposition to both certain sleep disturbances and advantageous waking ability.

In the previous report [17], we analyzed the principal component structure of the first NREM sleep episode in younger and older adults. We concluded that age-related changes in sleep architecture can be viewed as

a single general process of gradual strengthening of the wake drive, which can be caused by its disinhibition due to gradual weakening of the sleep drive. The results of this previous study particularly suggested that strengthening of wake drive in older adults might manifest itself in the course of the first NREM sleep episode in the form of elevation of the EEG indicator of the wake-promoting processes; a score on the second principal component [17]. Such results, along with some other findings of time courses of the first and second principal component scores [9–16], led us to predict that the aging process is characterized by gradual elevation of the second principal component score; not only during NREM sleep, but also during normal and prolonged wakefulness. In the present report, two independent datasets were analyzed to test this prediction. In general, the results of the principal component analyses of EEG signals can be regarded as supportive of the hypothesis that the sleep drive is strengthened. They, in particular, indicated that aging of the sleep–wake cycle is associated with a gradual rise in score on the second principal component of the resting EEG spectrum. Moreover, some results from the self-ratings were in agreement with this hypothesis. For instance, age of the participants in the first study correlated with a higher daytime wakeability score and lower anytime and nighttime sleepability scores. Besides, significant predictors of advanced age included not only the second principal component score but also nighttime sleepability and sleep satisfaction scores.

However, it is necessary to explain why older people did not report a lowered level of subjective sleepiness compared to younger people. There are at least two reasons for this. The first is the possibility of ambivalent influence of wake drive strengthening on sleepiness levels. When the wake drive is strengthened by its disinhibition due to the weakening of the sleep drive, it decreases sleepiness in the course of wakefulness, but – acting together with the weakened sleep drive on night sleep architecture – the strengthened wake drive disturbs night sleep. In turn, disturbed sleep increases sleepiness in the course of wakefulness.

The second reason is the association between sleepiness and health. In the present results, the second reason can be prompted by the analysis of KSS score in two subsamples of the second sample (patients vs. controls). These results suggested that this score was higher in patients than in controls, and that the treatment of patients, but not controls, was associated with its reduced level. This is in line with the findings of our earlier studies of subjective and objective measures of sleep–wake alternations in patients with seasonal affective disorder. In one of these studies we found that patients tended to self-score well-being, activity and winter mood levels lower than did controls before light treatment, but not after the treatment or during the summer season [34–36]. In another study, despite similar patterns of differences between patients and controls in well-being, activity and mood, there were no significant differences in sleep latency (as objectively measured by means of a 24-hour multiple sleep latency test) between the subsamples before and after light treatment in winter, or during summer [37, 38]. It seems that dependence of sleepiness levels from health status can be regarded as a general characteristic of intra-individual variation in sleepiness in both unhealthy and healthy people. At least, the results indicated that changes in depression rating in controls were significantly related to changes in their subjective sleepiness. Similar findings have been published in KSS literature. For example, Åkerstedt et al. [39] reported that a worse self-perceived health status was the strongest predictor of an increase in sleepiness, whereas shorter preceding sleep duration, earlier time of rising, and lower-rated sleep quality were found to be among the least strongly significant predictors.

Thus, age-associated decrease in sleepiness due to wake drive strengthening can be counterbalanced by an age-associated increase in sleepiness caused, in general, by age-associated worsening of health, and in particular by disturbance of nighttime sleep. Unlike sleepiness level, score on the second principal component of the waking EEG spectrum might be regarded as a reliable objective marker of the sleep aging process.

Further studies could be aimed at confirming gender difference in the second principal component score and topographic differences in its age-associated trend. Implementation of principal analysis in studies aimed at comparing the EEG features in people of different ages can facilitate understanding of the

mechanisms underlying optimal sleep aging, and to relate these mechanisms to older peoples' predisposition to develop certain disturbances of their daily sleep–wake cycle, and to cope with the effects of sleep deprivation.

Conclusions

Principal component analysis of the age-related changes in the strengths of sleep and wake drives can help us to understand the sleep–wake regulating mechanisms underlying the normal and pathological aging processes. It seems that the second principal component score of the waking and sleep EEG spectrum can serve as an objective marker of sleep aging. In accord with the hypothesis of wake drive strengthening, this score increased with advancing age, and the changes in several self-ratings were also in agreement with this hypothesis.

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