ORIGINAL ARTICLE

Recorded and Reported Sleepiness: The Association Between Brain Arousal in Resting State and Subjective Daytime Sleepiness

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Objectives: Daytime sleepiness is a significant public health concern. Early evidence points toward the computerized VIGALL (Vigilance Algorithm Leipzig) as time-efficient tool to assess sleepiness objectively. In the present study, we investigated the association between VIGALL variables of EEG vigilance (indicating brain arousal in resting state) and subjective daytime sleepiness in the LIFE cohort study. Additionally, we validated VIGALL against the self-rated likelihood of having fallen asleep during the conducted resting EEG and against heart periods.

Methods: Participants of the primary sample LIFE 60+ (*N* = 1927, 60–79 years) and replication sample LIFE 40+ (*N* = 293, 40–56 years) completed the Epworth Sleepiness Scale (ESS). After an average interval of 3 weeks (LIFE 60+) and 65 weeks (LIFE 40+), respectively, participants underwent a single 20-minute resting EEG, analyzed using VIGALL 2.1.

Results: Analyses revealed significant associations between ESS and EEG vigilance in LIFE 60+ (rho = −0.17, *p* = 1E–14) and LIFE 40+ (rho = −0.24, *p* = 2E-5). Correlations between EEG vigilance and self-rated sleep likelihood reached rho = −0.43 (*p* = 2E-91) in LIFE 60+ and rho = −0.50 (*p* = 5E–20) in LIFE 40+. Overall, strongest correlations were obtained for EEG vigilance variable "slope index." Furthermore, lower EEG vigilance was consistently associated with longer heart periods.

Conclusions: The present study contributes to the validation of VIGALL. Despite the considerable interval between ESS and EEG assessment dates, the strength of ESS-VIGALL association approximates prior ESS–Multiple Sleep Latency Test results. In this light, VIGALL might constitute an economical choice for the objective assessment of daytime sleepiness in large cohort studies. The discriminative power to identify disorders of hypersomnolence, however, remains to be addressed.

Statement of Significance

Electroencephalography (EEG) is a common methodology to determine sleep stages. Beyond that, the EEG is a valuable tool to discriminate levels of arousal preceding sleep onset. Recently, the computerized Vigilance Algorithm Leipzig (VIGALL) has been introduced, a tool measuring EEG vigilance as an indicator of brain arousal in resting state. Typically, VIGALL analyses are based on a single 15- to 20-minute resting EEG recording, keeping the burden on the subject at a minimum. The present study provides strong evidence for an association between VIGALL variables of EEG vigilance and subjective daytime sleepiness. Notably, association strength approximates prior multiple sleep latency test results, suggesting VIGALL as an economical choice possibly suitable for the objective assessment of daytime sleepiness in large cohort studies.

Keywords: arousal, vigilance, VIGALL, daytime sleepiness, Epworth Sleepiness Scale, EEG, ECG.

INTRODUCTION

Daytime sleepiness is a significant public health concern and constitutes a frequent complaint in both clinical and nonclinical contexts. It is associated with reduced quality of life,[1,2] increased risk for occupational injuries,[3,4] motor vehicle accidents,[5,6] cardiovascular and cerebrovascular events,[7–9] and is linked to higher mortality.[10–12] While the Epworth Sleepiness Scale (ESS) is an established and time-efficient technique to measure daytime sleepiness subjectively,[13] the objective assessment of daytime sleepiness with limited economic resources remains a challenge.

The Multiple Sleep Latency Test (MSLT) is widely considered the gold standard for assessing disorders of hypersomnolence objectively, although criticism has been voiced in this regard.[14,15] The MSLT typically involves simultaneous electroencephalography (EEG), electrocardiography (ECG), electromyography (EMG), and electrooculography (EOG). It consists of five consecutive 20-minute nap recordings conducted at 2-hour intervals. Its main objective is to measure the average elapsed time from lights turned off to the onset of sleep. While the American Academy of Sleep Medicine suggests the MSLT as standard tool for confirming the diagnosis of narcolepsy,[16] insufficient evidence supporting its routine use was found in terms of several other sleep disorders including idiopathic hypersomnia and obstructive sleep apnea.[17,18] Importantly, disorders of hypersomnolence are characterized by subjective complaints of daytime sleepiness.[18] Yet, prior research revealed modest associations between the MSLT and the ESS, with an estimated true correlation (95% confidence interval [CI]) ranging between −0.18 and −0.36.[19] Despite its substantial contribution to diagnostic decisions in narcoleptic patients, when investigating daytime sleepiness in large cohort studies, the question might be raised whether the costs of the MSLT are in reasonable proportion to its benefits.

As utilized by the MSLT, recording and analyzing the human EEG is the most common methodology to determine sleep stages. Changes in the power of the spectral frequency bands have robustly been demonstrated to correlate with alterations in arousal.[20–24] Recently, the novel low-resolution electromagnetic tomography (LORETA)-based computer algorithm VIGALL (Vigilance Algorithm Leipzig) has been introduced, a tool to assess brain arousal by means of electroencephalic activity.[25,26] Its development has been put forward within the framework of validating the arousal regulation model of affective disorders and

ADHD.[27] According to this model, arousal regulation is a promising biomarker for treatment response predictions and for the identification of biologically more homogenous patient groups in psychiatry.[28–31] VIGALL also ties in with the NIMH's Research Domain Criteria Project (RDoC), suggesting that arousal is a principal construct to describe psychiatric disorders.[32] By incorporating information on the spectral composition and cortical distribution of electroencephalic activity, VIGALL automatically determines stages of EEG vigilance (indicating brain arousal) corresponding to active wakefulness (stage 0), relaxed wakefulness (stages A1, A2, A3), drowsiness (stages B1, B2/3), and commencing sleep (stage C). Typically, VIGALL analyses are based on a single 15- to 20-minute resting EEG recording, keeping the burden on the subject at a minimum. While previous versions of the algorithm have been validated in a simultaneous EEG-fMRI study,[33] in a PET study,[34] against evoked potentials,[35] and against parameters of the autonomous nervous system,[36] the association with subjective ratings is still understudied.

Recently, Olbrich et al.[37] compared the scores of the ESS with results derived from both the MSLT and VIGALL 2.0. The authors observed the MSLT and VIGALL with similar ESS correlations and concluded that VIGALL might be a time-efficient choice to assess sleepiness in large cohort studies. Notably, the small sample comprising 25 subjects enabled only vague inferences regarding the true strength of the underlying association. Additionally, it remains uncertain whether the observed link is robust over time; that is, does self-reported daytime sleepiness correlate with the outcome variables of VIGALL even if weeks or months elapse between the dates of both assessments? Addressing this issue is vital because observed associations might arise from an individual's temporal condition (state) affecting the results of both assessments when conducted chronologically close to each other. Aiming to make reliable predictions on an individual's future (pathological) behavior, the assessment of a relatively stable characteristic (trait) may be preferred.

On this basis, we set out to investigate the association between subjective daytime sleepiness and brain arousal using VIGALL 2.1 in the LIFE cohort study,[38] with an interval of days to months spanning the dates of the subjective and objective assessment. Additionally, we sought to validate the VIGALL-based assessment of brain arousal against the self-rated likelihood of having fallen asleep during the conducted resting EEG. Regarding the assessment of sleepiness, results were assumed to shed light on VIGALL as a putative time-efficient tool for large cohort studies. Furthermore, VIGALL classifications were compared against heart periods. In accordance with findings on previous VIGALL versions,[36] we expected lower stages of EEG vigilance to correlate with longer heart periods.

METHODS

Samples

Subjects were volunteers from two samples of the LIFE-Adult study, a population-based cohort study including 10 000 randomly selected inhabitants of Leipzig, Germany.[38] The first sample was composed of subjects aged 60–79 years, with resting EEG data obtained from 3119 subjects (hereinafter referred to as LIFE 60+). The second sample was composed of subjects aged 40–56 years, with resting EEG data obtained from 343 subjects (hereinafter referred to as LIFE 40+). We selected those who did not report current intakes of psychoactive medication and who had no history of apoplexy, epilepsy, multiple sclerosis, Parkinson's disease, skull fracture, cerebral tumor, or meningitis (leaving 2435 subjects in LIFE 60+ and 328 subjects in LIFE 40+). Within LIFE 60+, subjects underwent a structured clinical interview for DSM-IV axis I disorders. We selected elderly, who were free of current affective and anxiety disorders and without a history of substance dependence and psychotic disorders (leaving 2338 subjects in LIFE 60+). Further, EEGs with substantial artifacts (≥15% of all EEG segments) and those displaying pathological activity, low-voltage alpha or alpha variant rhythms were not included in subsequent analyses. The final LIFE 60+ sample comprised $N = 2096$ eligible subjects (1074 male; mean age: 69.9 years) with valid data from ECG recordings ($n = 1967$), self-rated sleep likelihood ($n = 2039$), or the ESS ($n = 1927$), respectively. In terms of LIFE 40+, the final sample comprised $N = 296$ eligible subjects (131 males; mean age: 49.4 years) with valid data from ECG recordings ($n = 289$), self-rated sleep likelihood ($n = 291$), or the ESS ($n = 293$). Participants gave written informed consent and received an expense allowance. All procedures were conducted according to the Declaration of Helsinki and were approved by the Ethics Committee of the University of Leipzig (263-2009-14122009).

Procedure

Subjects completed the ESS on the first LIFE-Adult assessment date. In LIFE 60+, the resting EEG was conducted after an average time interval of 2.7 weeks (range: 0.14–17.0 weeks). In LIFE 40+, 64.9 weeks (range: 16.7–137.9 weeks) passed between ESS completion and EEG assessment date. As previously described,[39] EEG recordings were carried out in a sound-attenuated booth at approximately 08:00 am, 10:30 am, and 01:00 pm, respectively. Subsequent to attaching EEG and ECG electrodes, subjects were brought into reclined position, light was dimmed, and standardized auditory instructions were given via speakers using Presentation software (Neurobehavioral Systems Inc., Albany, USA). Subjects underwent a Berger Manoeuver and a brief cognitive activation task, during which they were asked to count backwards by six starting at 100. Following this, participants were instructed to close their eyes, to relax, and not to struggle against any upcoming feelings of drowsiness. Next, the 20-minute resting EEG was recorded. Afterward, subjects were asked to rate the likelihood of having fallen asleep during the resting EEG. Ratings were made on a four-point scale ("I definitely did not fall asleep"–"I probably did not fall asleep"–"I probably fell asleep"–"I definitely fell asleep").

Epworth Sleepiness Scale

The ESS is a widely used eight-item self-administered questionnaire designed to assess the degree of general daytime sleepiness.[13,40] Subjects rate the chance of falling asleep in different situations (eg, "sitting and reading," "sitting and talking to someone"). Ratings are made on a four-point scale. The total score ranges between 0 and 24 with higher sum scores indicating higher daytime sleepiness. The ESS has been shown with good internal consistency (Cronbach's α between 0.73 and 0.86), weak to moderate external validity (0.11–0.43), and moderate test-retest reliability (0.73–82).[19] Normative values were previously reported for the entire LIFE-Adult cohort.[41]

Physiological Data Collection and Processing

The physiological data were collected as previously described.[39] Electroencephalic activity was recorded by 31 electrodes according to the extended international 10–20 system, amplified using a QuickAmp amplifier (Brain Products GmbH, Gilching, Germany), referenced against common average and sampled at 1000 Hz with a low-pass filter at 280 Hz. Impedances were kept below 10 kΩ. In addition, EOG was recorded by two electrodes above and beneath the right eye for vertical eye movements, and two electrodes lateral to the right and left eye for horizontal eye movements. Further, ECG was recorded by two electrodes attached to the right and left forearm. ECG and EEG data processing was performed using Brain Vision Analyzer 2.1 (Brain Products GmbH, Gilching, Germany). Heart periods were obtained by measuring the interbeat interval (IBI), that is, the time difference between two consecutive R peaks. R peaks were detected using the Brain Vision Analyzer 2.1 function "cardioballistic artifact correction" and were verified by visual inspection. Heart periods were determined for each 1-second segment of the 20-minute resting condition by averaging the IBIs between R peaks that occurred within the respective segment plus the nearest R peak preceding and following this segment. EEG data processing included filtering (0.5 Hz high-pass, 70 Hz low-pass, and 50 Hz notch with 5 Hz range), manually identifying and removing cardiac and eye movement artifacts by extracting the respective independent components, and segmenting the 20-minute EEG recordings into 1200 consecutive 1-second segments. Segments with remaining muscle, eye, and sweating artifacts were excluded. Graph elements (K-complexes and sleep spindles) were marked by experienced raters. A K-complex was defined with the following criteria: a negative sharp wave followed by a positive component standing out from the background EEG, 0.5–1.6 second total duration, maximum amplitude at frontal areas, peak-to-peak amplitude of at least 100 µV, no dominant alpha activity in previous segments, and not being attributable to eye movements. A sleep spindle was defined with the following criteria: distinct waves with frequency 11–15 Hz standing out from the background EEG, 0.5–1.5 second total duration, peak-to-peak amplitudes of at least 10 µV, and no dominant alpha activity in previous segments.

Assessment of Brain Arousal

Brain arousal regulation was assessed using the Brain Vision Analyzer add-on VIGALL 2.1 (https://research.uni-leipzig.de/vigall),[26] a novel LORETA-based computer algorithm that utilizes the spectral composition and topographic distribution of electroencephalic activity to determine the level of EEG vigilance (indicating brain arousal) in resting state. To each 1-second EEG interval, VIGALL assigns one out of seven EEG vigilance stages, which corresponds to active wakefulness (stage 0), relaxed wakefulness (stages A1, A2, A3), drowsiness (stages B1, B2/3), and sleep onset (stage C). EEG characteristics of VIGALL stages of EEG vigilance are more detailed in Supplementary Figure S1. Please see also the VIGALL 2.1 manual.[26] Assigned EEG vigilance stages were transformed into values ranging from 7 (active wakefulness) to 1 (sleep onset) and were subsequently averaged in five consecutive blocks of 4 minutes each, which enables repeated-measures analyses of variance (ANOVAs). Further, we calculated three primary outcome variables as described previously[42,43]: the mean vigilance and two variables focusing on the steepness of EEG vigilance decline during the 20-minute resting condition, the stability score and the slope index. All three primary outcome variables were found test-retest reliable and have been established as an adequate way to summarize VIGALL resting EEG results.[42,44,45]

Statistical Analyses

Analyses were conducted using SPSS Statistics 20.0 (IBM Corp., Armonk, New York). We report two-sided levels of significance. The nominal level of significance was set at $p < .05$. Greenhouse-Geisser corrected degrees of freedom were reported where appropriate.

First, we conducted 21 pairwise comparisons of the averaged z-standardized heart periods in the seven EEG vigilance stages. Heart periods were standardized against the mean and standard deviation of heart periods recorded during stage A1. Only subjects with sufficient (≥10) A1 segments were selected. We performed paired *t*-tests within LIFE 60+, LIFE 40+, and in pooled samples. Furthermore, Spearman correlations were conducted between heart periods (unstandardized) and the following variables: EEG vigilance variables (see below), the self-rated likelihood of having fallen asleep, and the ESS score. For this purpose, heart periods were averaged for each subject in five consecutive blocks of 4 minutes each and across the entire 20-minute resting condition. In addition, the slope of a linear function was calculated with the regression line passing through the individual set of heart periods derived from the 20-minute resting condition. Spearman correlations were carried out in separate and pooled samples.

Second, we conducted Spearman correlations between the self-rated likelihood of having fallen asleep during the resting EEG and eight variables of EEG vigilance, including the three primary outcome variables (mean vigilance, stability score, and slope index) plus the means of EEG vigilance in five consecutive blocks of 4 minutes each. Analyses were performed within LIFE 60+, LIFE 40+, and in pooled samples. To differentiate between time course and level effects, we additionally conducted repeated-measures ANOVAs in both samples, with self-rated sleep likelihood serving as between-subjects factor and the five block variables of EEG vigilance serving as within-subjects factor time in rest.

In the main step, we performed Spearman correlations between the ESS score and the abovementioned eight variables of EEG vigilance. Analyses were run within LIFE 60+, LIFE 40+, and in pooled samples. Further, in both samples, we compared ESS extreme groups regarding the eight variables of EEG vigilance by conducting Kruskal–Wallis (KW) tests. Level and time-course effects were additionally investigated by conducting repeated-measures ANOVAs, with ESS extreme groups serving as between-subjects factor daytime sleepiness and the five block variables of EEG vigilance serving as within-subjects factor time in rest. ESS extreme groups were derived from the first and fourth quartile of the ESS score distribution. They were matched by age based on their propensity scores calculated from a generalized additive model (nearest neighbor matching algorithm, caliper 0.2).[46] Exact matching was carried out for sex. Subsequent to matching, ESS extreme groups did not differ regarding sex, age, and daytime of EEG assessment

(age: KW test, all $p \geq .569$; sex: χ^2 test, all $p = 1.000$; daytime: KW test, all $p \geq .208$).

RESULTS

The descriptive statistics of VIGALL 2.1 variables of EEG vigilance are provided in Supplementary Table S1 for separate and pooled samples.

Heart Periods

In pooled samples, analyses of z-standardized heart periods across EEG vigilance stages revealed significant differences for 20 out of 21 possible pairwise stage comparisons ($.002 \geq p \geq 2E{-}129$, $-0.169 \geq d_z \geq -1.137$), with lower EEG vigilance stages consistently associated with longer heart periods. Only heart periods in stage 0 versus A1 did not significantly differ ($t = -1.072$, $p = .284$, $d_z = -0.025$). Furthermore, Spearman correlations revealed significant associations between variables of heart period (average in block 1–5 and slope) and EEG vigilance ($-0.064 \geq \text{rho} \geq -0.194$, $.002 \geq p \geq 2E{-}20$), the self-rated likelihood of having fallen asleep ($-0.083 \geq \text{rho} \geq -0.134$, $1E{-}4 \geq p \geq 3E{-}10$), and the ESS score ($0.047 \leq \text{rho} \leq 0.063$, $.032 \geq p \geq .004$), with some exceptions for the slope of heart periods: Subjects with longer heart periods (and steeper increases of heart periods) exhibited lower EEG vigilance, reported a higher likelihood of having fallen asleep, and were characterized by higher ESS scores. Detailed results including findings from separate sample analyses are provided in the Supplemental Materials (Supplementary Figure S2, Table S2, Table S3).

Self-Rated Sleep Likelihood

Correlation Analyses

Spearman correlations revealed significant associations between the self-rated likelihood of having fallen asleep and each of the eight EEG vigilance variables, both in LIFE 60+ ($0.171 \leq \text{rho} \leq 0.428$, $7E{-}15 \geq p \geq 2E{-}91$) and in LIFE 40+ ($0.309 \leq \text{rho} \leq 0.534$, $8E{-}8 \geq p \geq 7E{-}23$): subjects who were more confident of having fallen asleep showed lower levels and steeper declines of EEG vigilance. The enhanced power in pooled sample analyses further reduced the type-I error probabilities of these associations ($0.189 \leq \text{rho} \leq 0.438$, $3E{-}20 \geq p \geq 9E{-}110$). Detailed association results are presented in Table 1. Partialling out effects of sex, age, and daytime of EEG assessment did not substantially alter association results (Supplementary Table S4). In addition, similar results were obtained when applying VIGALL without graph element markers (no C stage classification; Supplementary Table S5).

Repeated-Measures ANOVA

In LIFE 60+, repeated-measures ANOVAs of EEG vigilance revealed a significant main effect of self-rated sleep likelihood ($F_{3,2035} = 133.581$, $p = 5E{-}79$, $\eta^2 = 0.165$) and a significant self-rated sleep likelihood × time in rest interaction ($F_{8.7,5916.2} = 44.922$, $p = 2E{-}76$, $\eta^2 = 0.062$), with subjects being more confident of having fallen asleep showing generally lower levels and steeper declines of EEG vigilance. Further support was provided by LIFE 40+ analyses, showing a significant self-rated sleep likelihood main effect ($F_{3,287} = 35.721$, $p = 1E{-}19$, $\eta^2 = 0.272$) and a self-rated sleep likelihood × time in rest interaction ($F_{8.1,775.0} = 11.907$, $p = 3E{-}16$, $\eta^2 = 0.111$). The time courses of EEG vigilance stratified by the self-rated sleep likelihood are shown in Figure 1A (LIFE 60+) and Figure 1B (LIFE 40+).

Subjective Daytime Sleepiness

Correlation Analyses

Regarding LIFE 60+, Spearman correlations revealed significant associations between the ESS score and variables of EEG vigilance, with subjects reporting higher daytime sleepiness exhibiting lower EEG vigilance during the 20-minute resting EEG. Depending on EEG vigilance variable, the association strength ranged between rho = −0.130 and rho = −0.174 (with $9E{-}9 \geq p$

Table 1—Spearman Correlations Between EEG Vigilance Variables and the Self-Rated Likelihood of Having Fallen Asleep.

	LIFE 60+		LIFE 40+		Pooled samples	
	rho	*p*	rho	*p*	rho	*p*
n	**2039**		**291**		**2330**	
Averaged EEG vigilance						
Block 1 (min 1–4)	0.171	7E–15**	0.309	8E–8**	0.189	3E–20**
Block 2 (min 5–8)	0.297	1E–42**	0.379	2E–11**	0.308	2E–52**
Block 3 (min 9–12)	0.346	1E–58**	0.487	9E–19**	0.366	7E–75**
Block 4 (min 13–16)	0.374	1E–68**	0.523	8E–22**	0.395	6E–88**
Block 5 (min 17–20)	0.373	3E–68**	0.469	3E–17**	0.386	1E–83**
Primary outcome						
Mean vigilance (min 1–20)	0.382	1E–71**	0.500	8E–20**	0.398	4E–89**
Stability score	0.386	2E–73**	0.534	7E–23**	0.406	3E–93**
Slope index	0.428	2E–91**	0.503	5E–20**	0.438	9E–110**

**$p < .001$ (two-tailed).
EEG = electroencephalography.

≥ 1E–14), except for EEG vigilance in block 1 (min 1–4) where no significant association was found (rho = −0.036, p = .116). Concerning LIFE 40+, analyses revealed significant associations across all EEG vigilance variables (−0.188 ≥ rho ≥ −0.252, .001 ≥ p ≥ 1E–5), again with higher daytime sleepiness being linked to lower EEG vigilance. Pooled sample analyses revealed significant ESS score associations for all EEG vigilance variables (−0.055 ≥ rho ≥ −0.183, .009 ≥ p ≥ 3E–18). Table 2 shows detailed correlation results of EEG vigilance variables and the ESS score. Partialling out effects of sex, age, and daytime of EEG assessment did not substantially alter association results (Supplementary Table S6). In addition, similar results were obtained when applying VIGALL without graph element markers (no C stage classification; Supplementary Table S7).

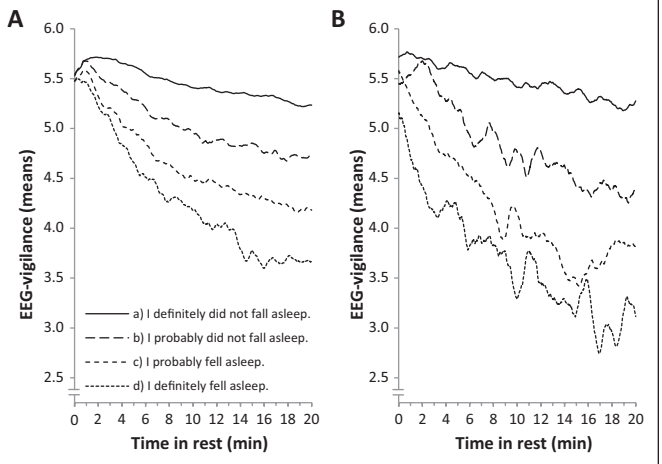

Figure 1—Simple moving averages of EEG vigilance across the 20-minute resting condition stratified by the self-rated likelihood of having fallen asleep. (A) LIFE 60+; (a) n = 1313; (b) n = 355; (c) n = 247; (d) n = 124. (B) LIFE 40+; (a) n = 177; (b) n = 47; (c) n = 51; (d) n = 16. EEG = electroencephalography.

Extreme Group Comparisons

Applying KW tests, significant ESS extreme group differences were found for seven of the eight EEG vigilance variables in LIFE 60+ ($17.120 \leq \chi^2_1 \leq 29.876$, 4E–5 ≥ p ≥ 5E–8, $0.019 \leq \eta^2 \leq 0.032$) and LIFE 40+ ($4.641 \leq \chi^2_1 \leq 11.610$, .031 ≥ p ≥ 7E–4, $0.048 \leq \eta^2 \leq 0.121$). No group differences were found regarding EEG vigilance in block 1, neither in LIFE 60+ ($\chi^2_1 = 2.301$, p = .129, $\eta^2 = 0.002$) nor in LIFE 40+ ($\chi^2_1 = 2.471$, p = .116, $\eta^2 = 0.026$). Table 3 presents detailed results of ESS extreme group comparisons. Additionally, in LIFE 60+, repeated-measures ANOVAs revealed a significant main effect of daytime sleepiness ($F_{1,922} = 19.796$, p = 1E–5, $\eta_p^2 = 0.021$) and a significant daytime sleepiness × time in rest interaction ($F_{2.8,2585.8} = 10.621$, p = 1E–6, $\eta_p^2 = 0.011$), with subjects scoring high on the ESS exhibiting generally lower levels and steeper declines of EEG vigilance. LIFE 40+ analyses showed a significant main effect of daytime sleepiness ($F_{1,94} = 9.890$, p = .002, $\eta_p^2 = 0.095$) and a significant daytime sleepiness × time in rest interaction ($F_{2.8,264.0} = 3.103$, p = .030, $\eta_p^2 = 0.032$) with effect directions consistent with LIFE 60+. Figure 2, A and B show the time courses of EEG vigilance for LIFE 60+ and LIFE 40+, respectively.

DISCUSSION

The main goal of the present study was to investigate the association between subjective daytime sleepiness and brain arousal using VIGALL 2.1, a novel EEG-based computer algorithm. Additionally, we validated VIGALL against the self-rated likelihood of having fallen asleep during the conducted 20-minute resting EEG and against heart periods. Analyses revealed

Table 2—Spearman Correlations Between Variables of EEG Vigilance and ESS Score.

	LIFE 60+		LIFE 40+		Pooled samples	
	rho	p	rho	p	rho	p
n	1927		293		2220	
Averaged EEG vigilance						
Block 1 (min 1–4)	−0.036	.116	−0.198	7E–4*	−0.055	.009*
Block 2 (min 5–8)	−0.130	9E–9**	−0.188	.001*	−0.136	1E–10**
Block 3 (min 9–12)	−0.148	7E–11**	−0.207	4E–4**	−0.155	2E–13**
Block 4 (min 13–16)	−0.147	1E–10**	−0.195	8E–4**	−0.153	4E–13**
Block 5 (min 17–20)	−0.136	2E–9**	−0.193	9E–4**	−0.145	7E–12**
Primary outcome						
Mean vigilance (min 1–20)	−0.143	3E–10**	−0.220	2E–4**	−0.153	4E–13**
Stability score	−0.138	1E–9**	−0.252	1E–5**	−0.152	6E–13**
Slope index	−0.174	1E–14**	−0.244	2E–5**	−0.183	3E–18**

*p < .050 (two-tailed).
**p < .001 (two-tailed).
EEG = electroencephalography; ESS = Epworth Sleepiness Scale.

Table 3—Kruskal-Wallis Test Results Comparing EEG Vigilance Among Subjects With Low (ESS-) Versus High (ESS+) Self-Reported Daytime Sleepiness.

	LIFE 60+					LIFE 40+				
	ESS-	ESS+	χ^2	η^2	*p*	ESS-	ESS+	χ^2	η^2	*p*
n	**462**	**462**				**48**	**48**			
Group characteristics										
Sex (f/m)	203/259	203/259	0.000	0.000	1.000	24/24	24/24	0.000	0.000	1.000
Age (years)	69.95 (4.7)	69.79 (4.6)	0.325	<0.001	.569	48.90 (4.1)	48.70 (4.2)	0.008	<0.001	.878
EEG daytime (hours:minutes)	10:51 (2:04)	10:53 (2:03)	0.002	<0.001	.969	10:22 (1:56)	10:55 (1:59)	1.588	0.017	.208
Averaged EEG vigilance										
Block 1 (min 1–4)	5.61 (0.8)	5.53 (0.8)	2.301	0.002	.129	5.66 (0.7)	5.34 (0.9)	2.471	0.026	.116
Block 2 (min 5–8)	5.44 (1.0)	5.22 (1.0)	17.120	0.019	4E–5**	5.55 (1.0)	4.85 (1.3)	6.503	0.068	.011*
Block 3 (min 9–12)	5.32 (1.0)	5.01 (1.1)	24.565	0.027	7E–7**	5.46 (1.1)	4.58 (1.4)	8.293	0.086	.004*
Block 4 (min 13–16)	5.23 (1.0)	4.87 (1.1)	26.897	0.029	2E–7**	5.32 (1.1)	4.50 (1.5)	6.062	0.063	.014*
Block 5 (min 17–20)	5.10 (1.1)	4.75 (1.2)	22.722	0.025	2E–6**	5.14 (1.2)	4.42 (1.5)	4.641	0.048	.031*
Primary outcome										
Mean vigilance (min 1–20)	5.34 (0.9)	5.08 (0.9)	24.222	0.026	9E–7**	5.42 (0.9)	4.74 (1.2)	6.805	0.071	.009*
Stability score	10.01 (3.6)	8.76 (3.9)	21.475	0.023	4E–6**	10.63 (3.3)	7.75 (4.6)	10.281	0.107	.001*
Slope index	−1.33 (0.8)	−1.61 (0.8)	29.876	0.032	5E–8**	−1.22 (0.8)	−1.97 (1.1)	11.610	0.121	7E–4**

Descriptive statistics are presented as mean (standard deviation). Effect sizes are shown as η^2 (referring to ranked data) and were computed squaring r as calculated from χ^2 according to Rosenthal and DiMatteo.[67] All χ^2 distributions are specified by 1 degree of freedom.
EEG = electroencephalography; ESS = Epworth Sleepiness Scale.
*$p < .050$ (two-tailed).
**$p < .001$ (two-tailed).

compelling evidence for an association between subjective daytime sleepiness and brain arousal, with higher daytime sleepiness being linked to lower levels and steeper declines of EEG vigilance (indicator of brain arousal). Moreover, subjects who were more confident of having fallen asleep showed lower levels and steeper declines of EEG vigilance. In addition, we found lower EEG vigilance consistently associated with longer heart periods.

Regarding daytime sleepiness, the average interval between the date of completing the ESS and the date of the resting EEG was 3 weeks in LIFE 60+, and 65 weeks in LIFE 40+. Accordingly, we deduce that the present and previously reported VIGALL-ESS associations do not only mirror an individual's temporal condition (state) but also suggest the contribution of a relatively stable characteristic (trait). In keeping with this, the regulation of arousal has been proposed to constitute a state-modulated trait,[27,42] and De Valck and Cluyds[48] previously emphasized the relevance of state and trait components for sleepiness. Besides, the impact of endogenous and environmental factors is reflected by heritability estimates derived from prior family and twin studies, suggesting that a proportion of 29%–48% of excessive sleepiness is due to genetic variation.[49] Notably, aiming to make reliable predictions on an individual's future behavior, the assessment of stable characteristics may be preferred.

Although VIGALL-ESS associations surpassed conventional levels of significance by a clear margin, the amount of common variance between both measures appeared small (eg, ESS × slope index: rho = 0.18, $p = 3E{-}18$), particularly when compared to correlations reported by Olbrich et al.[37] (eg, ESS × EEG vigilance cluster: rho = 0.45, $p = .026$). Notably, there are considerable content-related differences between both assessments: the ESS measures the self-reported chance of falling asleep across different everyday situations. In contrast, variables of EEG vigilance reflect a broad range of arousal stages and their dynamics during the transition from wakefulness to sleep onset in a laboratory setting. Further, the strength of association between different measures is limited by the reliabilities of each measure, which have been found moderate (0.7–0.8) for both the ESS[50–52] and VIGALL variables of EEG vigilance.[42] Additionally, self-report data can be subject to cognitive and emotional bias. Comparing our findings to results provided by Olbrich et al.,[37] several reasons might account for effect size discrepancies. First, subjects of Olbrich et al. completed both assessments on two consecutive days. Second, Olbrich et al. examined younger subjects and our own analyses suggest larger effect sizes among the younger age groups (as discussed below). Third, estimates provided by Olbrich et al. were drawn from a small sample ($N = 25$), which is to the disadvantage of effect size reliability (ie, given rho = 0.45 and $N = 25$: $CI_{95\%}$ [0.07, 0.90]). An adequate benchmark for ESS-VIGALL associations might be provided by prior MSLT results.

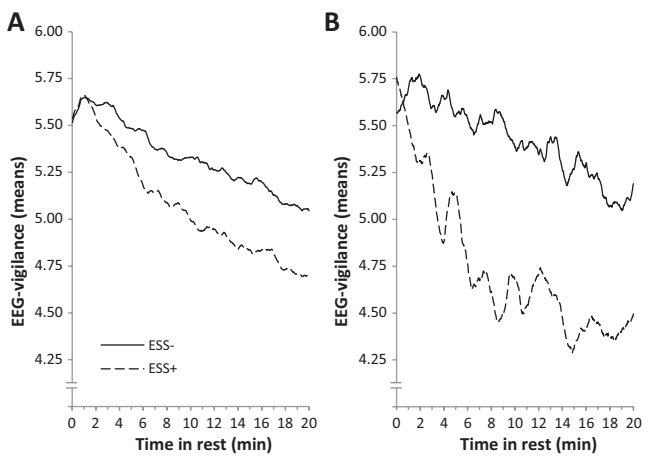

Figure 2—Simple moving averages of EEG vigilance across the 20-minute resting condition among subjects reporting low (ESS−) and high (ESS+) daytime sleepiness (lower and upper quartile of the ESS score distribution). (A) LIFE 60+ (ESS-: *n* = 462; ESS+: *n* = 462). (B) LIFE 40+ (ESS−: *n* = 48; ESS+: *n* = 48). EEG = electroencephalography; ESS = Epworth Sleepiness Scale.

Despite its substantial contribution to diagnostic decisions in narcoleptic patients, modest ESS associations were reported for the MSLT, with an estimated true correlation (95% CI) ranging between −0.18 and −0.36.[19] Since both the MSLT and the ESS focus on sleep onset, MSLT-ESS associations might be expected stronger relative to VIGALL-ESS associations. However, present findings suggest relatively comparable VIGALL-ESS associations, especially regarding LIFE 40+, with VIGALL variables of EEG vigilance reaching correlations of about −0.25 with $CI_{95\%}$ (−0.14, −0.37). This appears remarkable considering that (1) VIGALL results were obtained from one single 20-minute resting recording, (2) there was a 65-week interval between both assessments in the respective sample, and (3) we examined nonclinical subjects and thereby possibly induced some bias toward lower effect sizes. Regarding the latter, we additionally compared subjects with scores in the lower versus upper quartile of the ESS score distribution. This comparison revealed a moderate amount of variance explanation (of ranked variables) reaching 12% in LIFE 40+. Future investigations may clarify the value of VIGALL for diagnosing disorders of hypersomnolence, which is related to—but not congruent with—VIGALL's primarily intended field of application, the assessment of brain arousal regulation.

The present study is the first addressing the relationship between VIGALL variables of EEG vigilance and the self-rated likelihood of having fallen asleep during the resting condition: Subjects with higher confidence of having fallen asleep exhibited generally lower levels and steeper declines of EEG vigilance. Associations were also evident when referring to the averaged EEG vigilance within the first 4 minutes of rest (block 1 with p = 3E–20). This implies that sleepy and nonsleepy groups of subjects can be identified by conducting relatively short EEG recordings, which may be suitable for large cohort studies with a tight schedule. However, explained variance (of ranked variables) increases fivefold when contrasting EEG vigilance in block 1 ($\eta^2 = 0.189^2 = 0.036$) against primary outcome variables (eg, slope index: $\eta^2 = 0.438^2 = 0.192$), which underlines the advantages of longer recordings. Thus, we encourage future investigators to budget for a decent period of 15 or 20 minutes of rest.

Although type-I error probabilities were low, abovementioned effect sizes suggest considerable discrepancies between EEG vigilance variables and sleep perception. Again, this appears reasonable given the fact that both measures only partly overlap in content: While variables of EEG vigilance reflect the dynamics of brain arousal in resting state, subjective sleep likelihood ratings focus on the occurrence of sleep onset. Aside from this, the objective-subjective mismatch in sleep detection is a well-known phenomenon, with cortical sleep often being experienced as wake. This particularly applies when subjects are physically roused from early sleep stages such as Rechtschaffen and Kales' stage 2 sleep,[53] which compares to VIGALL stage C. For instance, Yang et al.[54] showed that when awakened after the onset of stage 2 sleep, only 45% of subjects felt as though they had been asleep. Several further studies revealed similar proportions of perceiving stage 2 sleep.[55–58] In the present study, we observed 467 of 2330 subjects with VIGALL C stages. Of those, 20.1% (94) reported definite sleep, 29.8% (139) reported probable sleep, 21.6% (101) reported probable wake, and 28.5% (133) reported definite wake. These data underline that when awakened during the sleep onset period, there is a considerable degree of uncertainty among subjects required to report the prior sleep/wake state.

Notably, classifications of VIGALL C stages are based on the occurrence of graph elements, that is, sleep spindles and K-complexes, which were marked by experienced raters. To examine whether observed associations might be inflated by manual ratings, we repeated the application of VIGALL without graph element markers. As a consequence, no C stages were classified. Analysis revealed only marginal alterations of EEG vigilance correlations with the ESS and the self-rated sleep likelihood (Supplementary Tables S5 and S7), suggesting no considerable inflation by manual ratings.

Throughout our analyses, we observed stronger associations in LIFE 40+ relative to LIFE 60+. In a post hoc approach, we sought to find out whether this phenomenon is of statistical relevance. Using R package cocor[59] with the formula provided by Hittner et al.,[60] we found five out of eight EEG vigilance variables to correlate with sleep likelihood ratings at significantly higher levels in LIFE 40+ ($.141 \geq p \geq .003$). Despite the considerably larger interval between assessment dates, ESS correlations were significantly stronger in LIFE 40+ regarding one out of eight variables ($.432 \geq p \geq .009$). Two possible explanations for stronger correlations in the younger age group might be taken into account: First, previous studies suggest that EEG power decreases as subjects grow old[61–63] and our own analyses show a marginal age-related decline in alpha power as derived from the VIGALL reference segment (rho = −0.094, p = 4E–6). Second, we observed subjects of LIFE 60+ with generally higher levels of EEG vigilance, which was accompanied by lower variance in EEG vigilance across subjects (see Supplementary Table S1 for means and standard deviations). Both the lower EEG power and lower variance in EEG vigilance might attenuate the reliability of observed interindividual differences among the elderly. Consequently, effect size discrepancies might result from age-related result reliabilities.

Additionally, we observed lower stages of EEG vigilance consistently associated with longer heart periods. This finding is well in line with data derived from previous VIGALL versions.[36] Only heart periods occurring with stage 0 (corresponding to active wakefulness) and A1 (corresponding to relaxed wakefulness) did not significantly differ. Similar heart periods in these stages might be explained by the fact that participants were not given a task but were instructed to relax, so that during stage 0, which indicates cognitive activity, the mental workload was low and mobilizing substantial physiological resources (ie, oxygen and glucose) by elevating cardiovascular function was not required.[cf.64–66] The present results also indicate that considerable proportions of intraindividual (see stage comparisons) but only minor proportions of interindividual variability in heart period (see correlation analysis) can be explained by EEG vigilance. Importantly, variables of heart period showed substantially lower associations with the self-rated sleep likelihood and the ESS score relative to EEG vigilance variables, underpinning the incremental validity of EEG recordings.

A limitation of the present results refers to the small effect sizes obtained from ESS analyses. Above, we addressed several potential reasons such as content-related discrepancies between assessments. One further limitation is that ESS and EEG assessments were not repeated for each subject after several intervals, so that an estimate for the potential decrease in association strength with increasing time interval between assessments cannot be derived from longitudinal data. Noteworthy, by analyzing the present data using SPSS add-on process v.2.16.3,[67] we did not obtain evidence for time interval to moderate VIGALL-ESS associations (see Supplementary p. 8, Table S8). Moreover, the present inferences were drawn from nonclinical subjects. Thus, the discriminative power to identify pathological conditions such as narcolepsy and other disorders of hypersomnolence remains to be addressed.

In conclusion, the present study contributes to the validation of VIGALL. Despite the considerable interval between ESS and EEG assessment dates, the strength of VIGALL-ESS association approximates prior MSLT-ESS results. In this light, the application of VIGALL might be an economical technique for the objective assessment of daytime sleepiness in large cohort studies. The discriminative power to identify disorders of hypersomnolence, however, remains to be addressed in future studies.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *SLEEP* online.

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The authors have no financial or competing interests to declare.