Original Paper

Unfavorable Polysomnographic Sleep Patterns Predict Poor Sleep and Poor Psychological Functioning 3 Years Later in Patients with Restless Legs Syndrome

Serge Brand[a]   Johannes Beck[a]   Martin Hatzinger[a–c]   Mirjana Savic[a]
Edith Holsboer-Trachsler[a]

[a]Psychiatric Hospital of the University of Basel, Depression Research Unit, and [b]Psychiatric Outpatient Department, University Hospital, Basel, and [c]Psychiatric Hospital, Solothurn, Switzerland

Abstract

Background: Amongst the variety of disorders affecting sleep, restless legs syndrome (RLS) merits particular attention. Little is known about long-term outcomes for sleep or psychological functioning following a diagnosis of RLS. The aim of the present study was thus to evaluate sleep and psychological functioning at a 3-year follow-up and based on polysomnographic measurements. **Method:** Thirty-eight patients (18 female and 20 male patients; mean age: 56.06, SD = 12.07) with RLS and sleep electroencephalographic recordings were followed-up 33 months later. Participants completed a series of self-rating questionnaires related to sleep and psychological functioning. Additionally, they completed a sleep log for 7 consecutive days. **Results:** Age, male gender, increased light sleep (S1, S2) and sleep onset latency, along with low sleep efficiency, predicted psychological functioning and sleep 33 months later. Specifically, sleep fragmentation predicted poor psychological functioning, and both sleep fragmentation and light sleep predicted poor sleep. **Conclusions:** In patients with RLS, irrespective of medication or duration of treatment, poor objective sleep patterns at diagnosis predicted both poor psychological functioning and poor sleep about 3 years after diagnosis. The pattern of results suggests the need for more thorough medical and psychotherapeutic treatment and monitoring of patients with RLS.

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Introduction

Restoring sleep is strongly associated with daily well-being and functioning [1], memory [2, 3], emotional intelligence [4], learning capacity, and academic performance [5]. By contrast, chronic sleep disturbances adversely affect physical and psychological functioning in both adolescents [6] and adults [7, 8]. Furthermore, sleep complaints and insomnia in adults seem to be on the increase worldwide [9, 10].

Amongst the variety of possible factors adversely affecting sleep, restless legs syndrome (RLS) has been described as 'the most common disorder you ever heard of' [11]. RLS is a distressing sensorimotor disorder. An alteration of iron-dopamine connections [12, 13] as well as genetic factors [14] have been implicated in its etiology.

Serge Brand, PhD
Psychiatric Hospital of the University of Basel, Depression Research Unit, Switzerland
Wilhelm Klein-Strasse 27
CH–4025 Basel (Switzerland)
Tel. +41 61 325 51 14, Fax +41 61 325 55 13, E-Mail serge.brand@upkbs.ch

For several reasons, RLS demands particular attention. First, prevalence rates range from 5 to 10% in the United States and other Western countries [15, 16]. Second, RLS does not only affect adults: it is also observed in children and adolescents [17–19]. Third, RLS is associated with a broad variety of additional psychiatric disorders. Several studies have reported the co-occurrence of RLS and depressive symptoms [11, 18, 20–26]. In particular, patients suffering from RLS have shown poor polysomnographic sleep patterns, compared both to healthy controls [27] and patients suffering from major depressive disorders [25, 26]. In this respect, Hornyak et al. [26] observed that several antidepressants may trigger or aggravate RLS. By contrast, mild to moderate depressive symptoms often seem to be relieved, with improvements in RLS symptoms, after administration of dopamine receptor agonists. Furthermore, 83.3% of the patients with dysthymia, 63.6% of those with general anxiety disorders, and 60% of those with panic disorder reported the occurrence of RLS before the onset of the psychiatric disorder [24]. Recent findings from a population-based survey in South Korea suggest that the prevalence of RLS there may be substantially lower than in Western countries, though the occurrence of RLS was strongly associated with major depressive disorders, panic disorders, and posttraumatic stress disorder [28].

The occurrence of RLS is associated with poor quality of life and with particular personality traits. Happe et al. [29], for example, assessed 519 patients suffering from RLS in a cross-sectional study and observed that health-related quality of life was substantially affected, compared to indices for the general population. Severity of RLS and depressive symptoms had the most significant influence on deteriorated health-related quality of life. Likewise, a series of cross-sectional studies have identified poorer quality of life and psychological functioning among patients suffering from RLS as compared to controls [for a comprehensive overview, see ref. 29]. In a similar vein, based on the 5-factor model of personality proposed by Costa and McCrae [30], Kalaydjian et al. [31] investigated differences in personality traits between patients suffering from RLS and controls. The results showed significant differences on neuroticism, but not on openness, agreeableness, conscientiousness, or extraversion, i.e., compared to controls, patients suffering from RLS had higher scores for anxiety, anger/hostility, and depression.

Long-term treatment outcomes of RLS have focused exclusively on the impact of medication [32–38], though with conflicting results: whereas some studies have reported a marked decrease in RLS [37] and exceptional efficacy for RLS-related medication [32], others have reported either increased severity of symptoms [35] or only symptomatic relief rather than any curative effect [32]. However, nothing is known about the extent to which polysomnographic sleep patterns may predict long-term development of sleep or psychological functioning in patients with diagnosed RLS. The aim of the present study was thus to relate sleep electroencephalographic (EEG) values to self-reported sleep and psychological functioning about 3 years later.

Since specific long-term data have not been available until now, no hypotheses were formulated. As a consequence, an exploratory approach was adopted.

Methods

Sample and Procedure

A sample of 63 patients (30 females and 33 males) was diagnosed in our Sleep Research Unit between April 2001 and October 2005 (mean age 51.76 years, SD = 15.34) [25]. At first contact, a thorough assessment was made, including a brief psychiatric interview, diagnosis of RLS, and polysomnographic EEG recordings. These patients were subsequently recontacted, the follow-up occurring on average 33 months later (SD = 13.28; range 18–63 months). The response rate was 61% (38 participants[1]: 18 female (47.5%) and 20 male (52.5%) patients; mean age 55.32 years, SD = 12.33)[2].

Patients were contacted by telephone and asked to participate in a follow-up study consisting of a set of questionnaires (see below) concerning current sleep, quality of life, medication intake and psychological functioning. The purposes of the study were fully explained. Participants received the questionnaires and the informed consent by mail. All participants received a reward of CHF 40.00 for participation. The experimental protocol was approved by the local ethics committee.

Materials

Initial Assessment of Sleep by Polysomnography

All patients slept in the Sleep Research Unit for one night. Sleep was recorded between 11 p.m. (lights off) and 7 a.m. (lights on) using standard polysomnography procedures, namely a horizontal electrooculogram, a submental myogram and an EEG recording: C3–A2, C4–A1, C3–C4) as well as an electrocardiogram. The sleep records were visually scored by two experienced raters

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[1] Of the 25 nonparticipants, 2 had died, 6 were hospitalized, 7 could not be contacted, and 10 refused to participate due to lack of interest or time.
[2] Participants at follow-up did not differ from nonparticipants with respect to gender distribution (participants: male:female = 18:20; nonparticipants: male:female = 12:13; $\chi^2(1) = 0.002$, p = 0.961), age (participants: 55.32 years (SD = 12.33); nonparticipants: 57.67 years (SD = 10.21) = t(61) = 0.65, p = 0.52), or initial sleep EEG profiles (all ts < 1). Thus, there was no systematic bias between participants and nonparticipants.

Table 1. Dimensions of FEPS I and II

Dimensions	Poles	
	positive pole	negative pole
FEPS I		
Attitude towards life	Satisfied, confident, positive	Depressive, dissatisfied, resigned, lacking emotion
Self-confidence	Self-confident, resolute, carefree	Anxious, unsure, indecisive, easily irritated
Mental arousal	Relaxed, balanced, calm	Tense, irritable, exhausted, burdened
Physical arousal	Relaxed, balanced, without any complaints	Nervous, over-agitated, complaining
Aggressive behavior[1]	Externalizing, competitive, asserting own opinion	Internalizing, over-controlling, inhibited, evasive
Self-perception of body sensations	Easy-going, carefree, confiding	Hypochondriac, complaining
Subjective sleep quality[2]	Regenerative, undisturbed, unimpaired	Impaired, disturbed, not regenerative
FEPS II		
Focusing	Easy-going, carefree, confiding with regard to sleep	Concerned about sleep; preoccupied about not falling asleep, not sleeping enough to feel restored
Rumination	Optimistic about coping with problems	Concerned and preoccupied about unresolved problems

FEPS = Fragebogen zur Erfassung allgemeiner Persönlichkeitsmerkmale Schlafgestörter [45].
[1] The expression 'aggressive behavior' proposed by the test authors, may be misleading; the dimension should perhaps be translated as 'assertive behavior'. [2] To avoid artificial associations between this dimensions and target variables related to sleep, the dimension Subjective sleep quality was not included in the statistical computations.

according to standardized criteria [39]. Twenty percent of the sleep records were independently rescored. Inter-rater reliability was r = 0.92. The sleep parameters were analyzed according to the definitions in the standard program described by Lauer et al. [40; also see ref. 25][3].

Assessments at Follow-Up
Depressive Symptoms
Participants completed the Beck Depression Inventory [41] providing self-rating of depressive disorders. The higher the overall score, the more the respondent is taken to suffer from depressive symptoms (Cronbach's α = 0.89).

Restless Legs Syndrome
Following the International RLS Study group [42], a diagnosis of RLS is given if patients answer 'yes' to the following 6 questions: (1) symptoms of leg restlessness; (2) unpleasant creepy/crawly feelings in the legs; (3) co-occurrence of leg restlessness and unpleasant feelings in the legs; (4) occurrence of these feelings mainly at rest, (5) improvement with movement, and (6) worsening of these sensations in the evening or at night as compared to the morning [43; Cronbach's α = 0.88].

Sleep Disturbances
Five items were taken from the Insomnia Severity Index [44; Cronbach's α = 0.90]. (1) To assess insomnia, participants were asked the following questions: 'In the last two weeks, how much did you suffer from the following disturbances: difficulty falling asleep, difficulties maintaining sleep, early morning awakening,

increased daytime sleepiness?' Answers were given on a 5-point rating scale ranging from 0 = 'not at all' to 4 = 'very much'. (2) 'How satisfied are you with your sleep?' Answers were given on a 5-point scale ranging from 0 = 'very satisfied' to 4 = 'very dissatisfied'. (3) 'How much does sleep disturbance have a negative impact on your daily performance?' Answers were given on a 5-point scale ranging from 0 = 'not at all' to 4 = 'very much'. (4) 'How much do you think that other people are aware that your sleep disturbance negatively influences your daily performance?' Answers were given on a 5-point scale ranging from 0 = 'not at all' to 4 = 'very much'. (5) 'How much are you actually worried about your sleep disturbance?' Answers were given on a 5-point scale ranging from 0 = 'not at all' to 4 = 'very much'. The higher the mean score, the more the person is assumed to suffer from insomnia. This mean score was labeled 'Insomnia Severity'.

Sleep-Related Personality Traits
Participants also completed a single sleep-related personality questionnaire, i.e. a questionnaire specifically designed to assess personality traits of patients with sleep complaints (Fragebogen zur Erfassung allgemeiner Persönlichkeitsmerkmale Schlafgestörter; Questionnaire for Assessing General Personality Traits of Patients Suffering from Sleep Disorders; FEPS-I and II) [45; Cronbach's α for internal consistency for both FEPS I and II = 0.89]. The FEPS-I questionnaire consists of 64 items describing 6 sleep-related personality traits and subjective sleep quality. Answers are given on a 5-point scale ranging from 'is not true at all' to 'is completely true'. The dimensions are presented in table 1. The underlying rationale for these two dimensions is that dysfunctional, or negative cognitions such as continually worrying about not being able to sleep or about unresolved problems are the main factors in the development and persistence of sleep problems [45–47]. The sleep-related personality questionnaire was chosen because it has been shown to be suitable both for patients suffering from sleep disorders and for healthy subjects [45, 48, 49].

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[3] With respect to the medication during polysomnographic assessment, as in the former study [25], no systematic bias between sleep-altering and non-sleep-altering medications on sleep EEG profiles was observed.

Daily Sleep Log

The sleep log was based on the Pittsburgh Sleep Quality Index [50] the German adaptation of which was taken from a conventional and widely used manual for psychological treatment of sleep complaints [51]. In contrast to this index, the adapted sleep log was completed consecutively. Participants were asked to fill it out twice a day for a week – in the evening and in the morning. In the evening, participants responded to questions about daytime sleepiness (1 = 'high daytime sleepiness'), physical activity (1 = 'low physical activity'), concentration (1 = 'low concentration'), and mood (1 = 'very bad mood') on 8-point scales. In the morning, the questionnaire asked about sleep quality (1 = 'very bad sleep quality'), mood (1 = 'very bad mood'), using the same scales. In addition, sleep onset latency (SOL, in minutes), awakenings after sleep onset (number), and total sleep time (in hours) was requested (Cronbach's α = 0.89). Nights were defined as weekday nights if the participant went to work the following day; accordingly, weekend nights were Friday and Saturday nights. Two separate composite variables were calculated for weekdays and weekend days, respectively.

Assessment of Current Medication

Participants were asked to record any current medications. In particular, they were asked whether they were currently taking any medications relating to RLS or depressive symptoms. Medications were labeled as follows: medication 1 (antidepressants, such as mirtazapine, duloxetine, trimipramine, 'yes' vs. 'no'), medication 2 (RLS-related medications, such as pramipexole, gabapentine, ropinirole, 'yes' vs. 'no'), and medication 3 (benzodiazepines, such as midazolame, diazepame, clonazepame, 'yes' vs. 'no').

Assessing Quality of Life

The Skala zur Erfassung der Lebensqualität (Scale for the Assessment of Quality of Life, SEL) [52] was administered to assess quality of life. The questionnaire consists of 67 items and assesses current mood (e.g. 'At the moment, I feel abysmal'), objective and subjective physical state (e.g., for objective, 'I have difficulties or I have observed changes in the heart and lungs, such as shortness of breath, heart irregularity; for subjective, 'Over recent weeks, I have had a lot of pain'), objective and subjective social environment (e.g., for objective, 'I wish I had more people to share my sorrows with'; for subjective, 'Over the last weeks, it has been comforting to talk to my family'), global mood (e.g. 'Over the last weeks, I have been quite happy') and orientation to life (e.g. 'I think that also in the future I'll have many interesting things to do'). Answers are given on a 5-point rating scale ranging from 1 (= not at all true) to 5 (= definitely true; scoring was reversed for some items). For the dimensions Mood, Subjective social environment, Global attitude, and Orientation to life, higher mean scores reflect a favorable position on the dimension. For the dimensions Objective physical state, Subjective physical state, and Objective social environment, higher mean scores reflect an unfavorable position on the dimension.

Statistical Analyses and Preliminary Computations

First, to compress and reduce the psychological functioning outcome variables [Beck Depression Inventory (BDI), SEL, FEPS I and II], a factor analysis was performed with orthogonal rotation [53]. A factor analysis of 16 items from the BDI (total sum score), the questionnaires related to quality of life (SEL) and to sleep-re-

lated personality traits (FEPS I and II) yielded 15 factors. The first 3 had eigenvalues greater than 1, together accounting for 78.4% of the overall variance. The first factor, with an eigenvalue of 8.48, labeled 'Psychological arousal and depressive symptoms', explained 56.53% of the total variance. The second factor, labeled 'External locus of control and rumination' (eigenvalue 1.97), explained 13.14% of the total variance. The third factor, labeled 'Social withdrawal and low social support' (eigenvalue 1.29) explained 8.66% of the overall variance. The term 'Psychological functioning' embraces the dimensions 'Psychological arousal and depressive symptoms', 'External locus of control and rumination', and 'Social withdrawal and low social support'.

Next, to compress and reduce the results extracted from the sleep log, a factor analysis with orthogonal rotation was again performed. The factor analysis of 9 variables yielded 8 factors; the first 3 had eigenvalues higher than 1, together accounting for 84.50% of total variance. The first factor, labeled 'Sleep quality and sleep-related mood and behavior' (eigenvalue 5.56) explained 59.28% of the total variance. The second factor, labeled 'Sleep duration and sleep fragmentation' (eigenvalue 2.13) explained 17.24% of the total variance. The third factor, labeled 'Sleep onset latency' (eigenvalue 1.09) explained 7.98% of the overall variance.

Next, the influence of possible confounding variables was examined. To this end, a series of multiple-regression analyses (excluding stepwise backwards) were performed with the 6 new factors identified above as dependent variables whereas the possible confounding variables were identified as independent variables. Possible confounding variables considered were age, gender, difference in years between first assessment and follow-up (termed 'RLS duration'), medication 1 (antidepressants 'yes' vs. 'no'), medication 2 (RLS-related medicaments 'yes' vs. 'no'), and medication 3 (benzodiazepines 'yes' vs. 'no'). It turned out that for all 6 multiple regression analyses, age, gender, and 'RLS duration' were of predictive value whereas this was not the case for the variables related to medications. Thus, medications were not introduced as covariates.

Next, we examined whether current medication was in any way related to former sleep EEG profiles and whether medications should thus have been introduced as a factor confounding the relation of sleep EEG variables and current sleep patterns and psychological functioning. To this end, an ANOVA with the factors medication 1, medication 2, and medication 3 and the sleep EEG profiles as dependent variables was performed. Current medication was found to be unrelated to former sleep EEG profiles (all Fs <1.2). Thus, current medication was not introduced as a possible confounding factor between former sleep EEG profiles and current sleep patterns and psychological functioning.

Last, to predict psychological functioning at follow-up ('Psychological arousal and depressive symptoms'; 'External locus of control and rumination'; 'Social withdrawal and low social support'), sleep at follow-up ('Sleep quality and sleep-related mood and behavior', 'Sleep duration and sleep fragmentation'; 'Sleep onset latency'; 'Insomnia Severity'), and occurrence of RLS at follow-up, a series multiple-regression analyses were performed with age, gender, RLS duration and the sleep variables derived from polysomnographic sleep recordings as predictors.

Pearson correlations were computed and analyses were conducted using SPSS 17.0 for Windows.

Table 2. Multiple linear regression models to describe the influence of age, gender, duration to follow-up, and objective sleep on psychological functioning

Dimension	Variables	Coefficient	Standard error	Coefficient β	95% CI	t	p	R	R²	Durbin-Watson-statistics
Psychological arousal and depressive symptoms	Intercept	−1.58	0.72	–	−3.16 to −0.01	−2.21	0.049	0.92	0.85	1.79
	Age	0.049	0.014	0.625	0.02–0.08	3.52	0.005			
	WASO	0.126	0.034	2.13	0.05–0.20	3.68	0.004			
	WASO, time	0.0039	0.008	2.63	0.057 to 0.021	4.82	0.001			
	SOL	0.062	0.005	1.72	0.04–0.62	5.00	0.000			
	S1	0.028	0.006	0.455	0.016–0.641	5.06	0.000			
	S2	0.016	0.007	0.455	0.001–0.030	2.29	0.043			
	Excluded variables: SWS, S3, SE, gender, S4, SPT, REM-S, RLS duration									
External locus of control and rumination	Intercept	22.88	6.74	–	11.86–41.90	3.99	0.003	0.87	0.76	1.61
	Age	0.074	0.027	0.823	0.015–0.133	2.78	0.020			
	SPT	−0.017	0.006	−1.315	−0.030 to −0.004	2.85	0.017			
	SE	−0.16	0.045	−2.63	−0.264 to −0.064	3.67	0.004			
	WASO	0.265	0.075	4.24	−0.432 to −0.099	3.55	0.005			
	WASO, time	0.044	0.014	2.57	0.013–0.074	3.21	0.009			
	S3	−0.049	0.016	−1.25	−0.084 to −0.014	3.14	0.01			
	S4	−0.088	0.20	−1.076	0.043 to −0.132	4.35	0.01			
	Excluded variables: SWS, gender, S1, S2, REM-S, SOL, RLS duration									
Social withdrawal and low social support	Intercept	9.039	2.78	–	2.987–15.09	3.25	0.007	0.83	0.68	2.395
	Age	0.041	0.018	0.416	0.002–0.080	2.31	0.040			
	SPT	−0.018	0.006	−1.309	0.006–0.031	3.15	0.008			
	SOL	0.029	0.008	1.496	0.012–0.046	3.80	0.003			
	S1	0.042	0.011	0.965	0.019–0.065	3.99	0.002			
	Excluded variables: SWS, WASO, gender, RLS duration, S2, S3, S4, SE									

SOL = Sleep onset latency; SPT = sleep period time; S1 etc. = stage 1 etc.; WASO = wakening after sleep onset; light sleep (min) = S1 + S2; slow-wave sleep (min) SWS = S3 + S4; REM-S = REM sleep; SE = sleep efficiency; CI = confidence interval; R = multiple correlation coefficient; R² = multiple coefficient of determination.

Results

Predicting Psychological Functioning

Table 2 summarizes the multiple-regression analyses with Psychological functioning as outcome variable and age, gender, RSL duration, and polysomnographic EEG variables as predictors.

Increased psychological arousal and depressive symptoms were predicted by greater age, more awakenings after sleep onset (amount and duration), a prolonged SOL, and increased light sleep (S1 and S2). Greater external locus of control and rumination were predicted by lower age, decreased sleep period time and sleep efficiency, more awakenings after sleep onset (number and duration), and shortened SWS (S3 and S4).

More marked social withdrawal and lower social support were predicted by greater age, shortened SPT, a prolonged SOL, increased S1 and decreased S4.

Taken together, along with age, both an increased sleep fragmentation and increased light sleep predicted poor psychological functioning about three years later.

Prediction of Sleep

Table 3 gives an overview of the multiple regression analyses with Sleep (as extracted from the daily sleep log) as outcome variable and age, RLS duration, gender, and polysomnographic EEG variables as predictors.

Poorer sleep quality and sleep-related mood and behavior were predicted by prolonged RLS duration, male gender, lower age, an increased sleep fragmentation, along with increased light sleep (S1, S2), decreased S4, and increased rapid eye movement (REM)-sleep. Shortened Sleep duration and increased sleep fragmentation were predicted by increased RLS duration, male gender, more awakening after SO (sleep onset; number and duration), increased light sleep (S1, S2), decreased S4, and increased

Table 3. Multiple linear regression models to describe the influence of objective sleep, age, and gender on subjective sleep from the daily sleep log

Dimension	Variables	Coefficient	Standard error	Coefficient, β	95% CI	t	p	R	R^2	Durbin-Watson-statistics
Sleep-related mood, concentration and sleep quality	Intercept	16.951	7.36	–	3.489–37.391	2.30	0.08	0.99	0.97	1.31
	RLS duration	0.066	0.020	0.715	0.010–0.122	3.26	0.031			
	Gender	–1.152	0.362	–0.503	–2.157–0.0147	3.18	0.033			
	Age	0.047	0.013	0.527	0.01–0.0185	3.53	0.024			
	WASO	0.0174	0.041	1.74	0.060–0.289	4.22	0.013			
	WASO, time	0.075	0.009	4.40	0.049–0.101	7.90	0.001			
	SOL	0.031	0.007	1.77	0.011–0.051	4.31	0.013			
	SE	0.175	0.064	2.803	0.002–0.353	2.74	0.052			
	S2	0.064	0.010	4.11	0.036–0.092	6.31	0.003			
	S4	–0.100	0.028	–1.227	–0.178–0.022	–3.56	0.024			
	REM-S	0.0139	0.025	4.09	0.079–0.209	5.54	0.005			
	Excluded variables: SWS, S1, S3, RLS duration									
Sleep duration and sleep fragmentation	Intercept	1.449	2.087	–	3.272–6.171	0.694	0.51	0.86	0.74	1.47
	RLS duration	0.092	0.028	0.895	0.028–0.156	3.26	0.010			
	Gender	–1.538	0.673	–0.601	–3.061 to –0.016	2.28	0.048			
	SPT	0.037	0.012	2.597	0.010–0.064	3.06	0.014			
	WASO	0.154	0.050	1.374	0.042–0.0266	3.11	0.012			
	S1	0.055	0.018	1.249	0.015–0.059	3.14	0.012			
	S4	–0.049	0.034	–1.028	–0.016 to –0.172	2.72	0.024			
	Excluded variables: SWS, Age, S2, S3, REM-S, SOL									
Sleep onset latency	Intercept	16.275	4.935	–	5.280–27.270	3.29	0.008	0.90	0.81	1.80
	Gender	–0.943	0.355	–0.549	–1.734 to –0.153	2.68	0.024			
	SE	–0.15	0.044	–3.219	0.054–0.248	3.46	0.006			
	WASO	0.053	0.018	0.706	0.013–0.093	2.94	0.015			
	WASO, time	0.069	0.025	1.465	0.013–0.125	2.75	0.020			
	SOL	0.026	0.005	1.945	0.014–0.038	4.70	0.001			
	S3	–0.026	0.010	–0.885	–0.004 to –0.049	2.59	0.027			
	Excluded variables: SWS, S1, S2, S4, RLS duration									

SOL = Sleep onset latency; WASO = wakening after sleep onset; light sleep (min) = S1 + S2; slow wave sleep (min) SWS = S3 + S4; REM-S = REM sleep; SE = sleep efficiency; S1 etc. = Stage 1; CI = confidence interval; R = multiple correlation coefficient; R^2 = multiple coefficient of determination.

REM-sleep. A prolonged SOL was predicted by age, female gender, reduced SE, increased wakening after sleep onset (amount and duration), a markedly prolonged SOL, and shortened S3. In sum, poor sleep as extracted from the sleep log was predicted by gender, age, RLS duration, and by fragmented sleep, increased light sleep and decreased deep sleep.

Prediction of Occurrence of RLS, Depressive Symptoms, and Sleep Complaints at Follow-Up
Further computations showed that at follow-up, RLS, depressive symptoms (BDI sum score) and sleep complaints (sum score, Insomnia Severity Index, ISI) were intercorrelated; RLS, BDI; r = 0.47, p < 0.001; RLS, ISI: r = 0.59, p < 0.001; BDI, ISI: r = 0.77, p < 0.001. Thus, the question arose as to whether polysomnographic sleep variables could predict RLS, depressive symptoms, and sleep complaints. Multiple regression analyses with the polysomnographic variables as predictors and the occurrence of RLS, depressive symptoms (sum score BDI) and sleep complaints as dependent variables showed that neither the polysomnographic sleep variables as a whole, nor specific polysomnographic sleep variables were of predictive value. R's and R^2's were between 0.75 and 0.85, though ANOVAs revealed that multiple correlation coefficients did not significantly differ from 0 (p > 0.1). Thus, polysomnographic values could predict neither RLS, nor depressive symptoms, nor sleep complaints.

Discussion

The key findings of the present study are that greater age, polysomnographically assessed increased light sleep and decreased deep sleep, along with sleep fragmentation, could predict poor sleep and poor psychological functioning of patients with diagnosed RLS about three years after diagnosis. Moreover, RLS duration and medication did not alter the pattern of results.

Given the lack of long-term studies focusing on sleep and psychological functioning as a function of previously assessed objective sleep profiles in patients suffering from RLS, no specific hypotheses were formulated. In this respect, to our knowledge, only a few studies have focused on long-term outcomes of psychiatric disorders based on polysomnographic recordings at baseline. Hatzinger et al. [54] followed up 15 patients suffering from major depressive disorders. At follow-up, about three years later, both sleep-EEG recordings and the activity of the hypothalamus-pituitary-adrenocortical (HPA) axis were assessed. Results suggested that decreased slow wave sleep (SWS) variables especially in the first sleep period and increased REM density were predictive for the occurrence of depressive symptoms at follow-up. Additionally, these unfavorable sleep-EEG variables were also related to excessive stress hormone response in the DEX/CRH-test. In sum, unfavorable sleep patterns such as decreased SWS and increased REM density were predictive of unfavorable outcomes of depressive disorders 3 years later. By contrast, in our study, REM sleep was of no predictive value. Rather, an entire set of specific sleep patterns relating both to sleep architecture (increased light sleep; decreased deep sleep) and sleep continuation (sleep fragmentation), along with age and gender, was associated with unfavorable sleep and psychological functioning at follow-up. With respect to gender, no clear picture emerged: some unfavorable outcomes were associated both with being male and with being female.

Long-term studies of RLS treatment outcomes have focused primarily on effects of medication [32–38], but the findings have been inconsistent. Whereas some studies have reported a marked decrease in RLS [37] and outstanding efficacy of RLS-related medication [32], others have reported an increase in symptoms [35], or only symptomatic relief rather than any curative effect [32]. The results of our study are in line with those reporting more negative findings [32]. Importantly, as our data suggest, the presence or absence of medications for RLS, depression or sleep difficulties (i.e. benzodiazepines) had no impact on outcomes related to sleep or psychological functioning about 3 years later.

The present data do not allow a closer inspection of the specific regimen pursued by every single patient. Thus, the data do not provide information on who took what compound for how much time at what level of compliance or at what dosage. However, notwithstanding the lack of these details, the overall pattern supports the speculation that patients' compliance was mixed given that medication-based treatment was recommended after the diagnosis of RLS. Moreover, statistical computations indicated that the current medication did not systematically bias either former sleep EEG variables or current sleep patterns and psychological functioning. How should one explain a presumably mixed or unsatisfactory level of compliance? First, there is increasing evidence that antidepressants such as fluoxetine and selective serotonin reuptake inhibitors (SSRIs) may increase periodic leg movements and, consequently, also RLS [for detailed discussions, see ref. 22, 26, 41, 55, 56]. However, in this respect, recent findings suggest that the occurrence and duration of SSRI-induced RLS and periodic leg movements are more complex [56]. Second, recent findings suggest an association between olanzapine and RLS [57]. Third, both medication tolerance and augmentation effects are well-known unwanted, though common side effects [58–60]. Summing up, one may speculate that patients did alter (increase, reduce, interrupt, and/or quit) the regimen, either independently or after consultation with their physician, though for unknown reasons and with unsatisfactory outcomes.

However, the pattern of results ('poor sleep predicts poor sleep and poor psychological functioning') is not necessarily specific to the development of RLS. Rather, our results fit well with a wealth of long-term research related to sleep and psychological functioning. Roberts et al. [6] found that chronic insomnia in adolescents severely impacted upon physical and psychological health over a 12-month period. In a population-based survey of adults, Morphy et al. [7] found that the incidence of insomnia at 12 months was 15% among those without insomnia at baseline and that this was significantly associated with baseline anxiety, depression, and pain. More importantly, of those who did have insomnia at baseline, 69% had insomnia at the 12-month follow-up, suggesting that insomnia is a persisting disorder. Likewise, Leblanc et al. [8] showed that a 1-year insomnia incidence rate was high and several psychological and health factors were associated with new-onset insomnia. Specifically, compared to good sleepers, insomnia syndrome incident cas-

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es presented with premorbid psychological vulnerability to insomnia, characterized by more marked symptoms of depression and anxiety, lower extraversion, higher arousability, and poorer self-rated mental health at baseline. These patients also presented with a higher level of bodily pain and poorer general health. Importantly, this pattern of results indicates that sleep and psychological functioning are highly interrelated. Taken together, findings from longitudinal studies show that poor sleep and poor psychological functioning do persist over time. As our data suggest, this also holds for patients with RLS.

However, the question arises as to why patients suffering from RLS should show a similar pattern of results even 3 years after diagnosis. The present data do not allow a conclusive answer to be drawn. However, the following observations should be taken into account. First, poor sleep, almost by definition, is strongly associated with depressive disorders [54], pain [61–64], and somatoform disorders [65]. Thus, it is highly conceivable that disrupted sleep as a consequence of RLS had resulted in poor psychological functioning. Second, another longitudinal study suggests that depressive disorders may lead to poor sleep, which in turn may lead to depressive disorders, and that poor sleep and depressive disorders may co-occur without common etiology [66]. The observations made the present study may speculatively be explained by a similar pattern of interrelated perturbations. Furthermore, although again speculative, rather than a static if-then relation between poor sleep and poor psychological functioning, a more dynamic process is conceivably at work. As an illustration, the model of Patterson et al. [67] for the development and maintenance of children's coercive behavior proposes that adverse parenting styles such as high behavioral and responsive inconsistency, low control and lack of warmth exacerbate an unfavorable childhood temperament (e.g. easily irritable, irascible, low tolerance of frustration), negative behavior (e.g. oppositional-aggressive, hyperactive), and poor intellectual skills (e.g. low degree of fast and accurate information processing), and vice versa. Thus, this model claims a reciprocal impact and feedback loop between the parents' style and the child's psychosocial, intellectual and behavioral characteristics over time. Similarly, we may speculate that, over time, poor sleep (due to RLS) may lead to poor psychological functioning, and that poor psychological functioning may aggravate poor sleep in a process of reciprocal interaction.

It is of note that sleep EEG recordings predicted neither the degree of RLS, nor depressive symptoms (BDI) or sleep complaints (ISI). How should this pattern of results be interpreted? We think there are five possibilities. One is that the current state of RLS, depressive symptoms, and sleep complaints may be affected by other factors, such as current medication (treatment effects) and use of substances (caffeine, alcohol), and that these factors therefore act as confounds between sleep EEG data at the sleep-EEG assessment and state at follow-up 33 months later. A second possibility is that objective measures and subjective sensations and perceptions may not necessarily correspond. Third, it may be that the disease process of RLS, which is primarily a peripheral movement disorder, is spreading and influencing neural networks and thus sleep and psychological functioning. Fourth, other dimensions related to sleep and psychological functioning, though not assessed in this study, were confounding covariates. The fifth possibility is that there really is no association.

Despite the new findings, several considerations warrant against generalization, and these data should be interpreted cautiously. First, the medication intake between the first sleep EEG assessment and the follow-up, and the possible influence of the medication regimen on the current data, remain unclear. However, to tackle this issue, we examined the possible confounding effect of current medication both on former sleep EEG variables and on current psychological functioning and sleep. It appeared that current medication did not systematically influence the data. It therefore seems likely that current medication was of minor importance. Second, the time lapse between the first and the second assessment showed a high interindividual range, which may have led to a biased pattern of results. To tackle this issue, the interindividual difference between the first and the second assessment (termed 'RLS duration') was introduced as a possible confounding variable; as the pattern of results suggests (tables 2, 3), the time lapse between the first and the second assessment was not a confounding variable. Moreover, in our opinion, the large interindividual differences in the time lapse provide a compelling reflection of both the strengths and the difficulties of naturalistic studies conducted under clinical routine conditions. As a result, long-term observations are rare, though, in our view, they are of considerable practical relevance. Third, data at follow-up relating to psychological functioning were based on self-reports, and it is possible that an increased state of depression may have biased the pattern of response behavior. Thus, any future investigations should employ experts' ratings and a clinical psychiatric interview as well as a thorough physical examination. Though somatic complaints were covered in the questionnaire related to quality of life [52], it is con-

ceivable that somatic complaints not assessed thus far may have negatively influenced current psychological functioning. Fourth, Pearson et al. [68] observed that, in patients suffering from RLS, cognitive performance was decreased compared to controls; thus, it is possible that the pattern of response behavior may have been biased by cognitive impairments. Fifth, sleep patterns were gathered from subjective sleep reports and not from objective sleep registrations such as sleep EEGs or actigraphy, and again a rating bias cannot be excluded. However, the sleep log was completed consecutively rather than retrospectively; thus, this procedure does not heavily rely on memory and is therefore less susceptible to memory failure. Moreover, there is evidence that diary-reported sleep patterns may be as valid as actigraphically estimated sleep behaviors [69, 70]. Additionally, we have been able to show that subjective sleep data from sleep logs provide a good match with sleep EEG recordings [71, 72]. Sixth, no objective assessment of RLS was performed; this may be of particular concern because recent findings suggest that adding response to dopaminergic medication improved the accuracy of RLS diagnosis, that is, the risk of mimics was reduced [73]. Seventh, data may potentially be biased because only patients who were willing and able to complete the questionnaires and the daily sleep log for 7 consecutive days volunteered to participate in the study. Last, the time lag of about 3 years between diagnosis and follow-up is not necessarily comparable to a period of therapy.

Conclusion

In patients with RLS, poor objective sleep almost 3 years earlier predicted current poor sleep and psychological functioning. Moreover, medication regimen seemed to have no influence, either favorable or unfavorable. As a consequence, we propose that an accurate thorough treatment consisting both of psychotherapy and medication is needed. In this view, one may claim that disorders such as RLS are not as easy to treat as it seems, and that monitoring should therefore be performed by specialized sleep centers throughout rather than by residents.

Conflict of Interest

Lundbeck had no influence on the study project; particularly, the sponsor had no influence on data collection, data entry, data analyses, data interpretation or writing and submission of the manuscript, or selection of the journal for possible publication. All authors declare no conflicts of interest.

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