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# Sleep changes in smokers before, during and 3 months after nicotine withdrawal

**Andreas Jaehne[1], Thomas Unbehaun[1], Bernd Feige[1], Stefan Cohrs[2,3,4], Andrea Rodenbeck[3,4] & Dieter Riemann[1]**

Department of Psychiatry and Psychotherapy, Freiburg University Medical Center, Freiburg, Germany[1], Department of Sleep Medicine, St. Hedwig Clinic, Berlin, Germany[2], Department of Physiology, Sleep Medicine and Chronobiology, Charité, Berlin, Germany[3] and Department of Psychiatry and Psychotherapy, Georg-August University, Göttingen, Germany[4]

## ABSTRACT

Nicotine may affect sleep by influencing sleep-regulating neurotransmitters. Sleep disorders can increase the risk for depression and substance dependency. To detect the influence of sleep disturbances on the effect of smoking cessation, we investigated polysomnographically (PSG) the sleep of smoking subjects during a period of smoking, during withdrawal and after a period of abstinence from nicotine. Thirty-three smokers (23 male, 10 female, median age 29 years, Fagerström Test for Nicotine Dependence score 6.3) were examined during smoking, 24–36 hours after smoking and 3 months after cessation. All subjects had an adaptation night followed by the PSG night. Compared with the smoking state, we found increased arousal index and wake time during nicotine withdrawal. Smokers who later relapsed (11) presented a higher degree of nicotine dependence and more withdrawal symptoms than those who abstained (22) and were characterized by less rapid eye movement (REM) sleep, a longer REM latency as well as by more intense sleep impairments in the subjective sleep rating during the withdrawal. Impairments of sleep during the withdrawal phase may reflect more severe nicotine dependence and may contribute to earlier relapse into smoking behaviours.

**Keywords** nicotine, sleep, smoking.

*Correspondence to:* Andreas Jaehne, Department of Psychiatry and Psychotherapy, Freiburg University Medical Center, Hauptstrasse 5, 79106 Freiburg, Germany. E-mail: andreas.jaehne@uniklinik-freiburg.de

## INTRODUCTION

Besides craving for tobacco, nicotine withdrawal can induce not only dysphoria, fear, anhedonia, irritability, restlessness and increased appetite but often also remarkable sleep disturbances (Hughes 2007; Jaehne *et al.* 2009), as reported by up to 25 percent of smokers during the first weeks after quitting (Okun *et al.* 2011). Subjectively experienced sleep disturbance is viewed as a consequence of frequent, ultra-short awakenings (arousals), a typical symptom of insomnia and a result of an imbalance of sleep protecting and inhibiting mechanisms (Riemann *et al.* 2010), which constitute a risk factor to develop depressed mood (Baglioni *et al.* 2011). Depressive symptoms, in turn, are associated with more severe nicotine withdrawal symptoms. It is assumed that this could increase the relapse risk during periods of smoking cessation (Colrain, Trinder & Swan 2004; Nakajima & al'Absi 2012; Weinberger *et al.* 2012). Studying large cohorts of smokers, a subjectively reduced quality of sleep and more insomnia-like symptoms (reduced sleep quality, longer time to fall asleep, less restorative sleep; Riedel *et al.* 2004, Cohrs *et al.* in press; Sabanayagam & Shankar 2011) compared with non-smokers have been observed. Only a few studies have used polysomnographic (PSG) methods to investigate sleep changes in smokers. In a sleep laboratory study, Soldatos *et al.* (1980) found that smokers had longer sleep latency and spent more time awake during the night than non-smokers. These findings were confirmed in a large longitudinal cohort study by Zhang *et al.* (2006), in which unattended PSG studies were conducted at home; smokers showed longer sleep latency and rapid eye movement (REM) sleep latency, shorter total sleep time (TST) and less slow-wave sleep (SWS) than non-smokers, and sleep efficiency was reduced. A spectral analysis of sleep electroencephalograms (EEGs), which allows a more detailed analysis of the spectral power of several EEG frequencies, showed an increase in α-frequencies (8–12 Hz) and a reduction in δ-frequencies (4–7 Hz) in smokers

(Zhang *et al*. 2007), indicating a reduction of the deeper sleep stages. Furthermore, sleep may also be disturbed by sleep-related breathing disorders such as oxyhaemoglobin desaturation (Conway *et al*. 2008) and the sleep apnoea syndrome, which is found more frequently in smokers (Kashyap, Hock & Bowman 2001), and by the restless legs syndrome (RLS), a neurological disorder with periodic leg movements (PLMs; Montplaisir *et al*. 1997) that is also more prevalent in smokers (Ohayon & Roth 2002). Using polysomnography to investigate PLMs in smokers, the results are inconsistent. One study found no differences in RLS and PLMs compared with non-smokers (Lavigne *et al*. 1997), whereas another found a 10-fold higher leg movement index and a higher number of arousals caused by leg movements in smokers (Jaehne *et al*. 2012). Besides this inconsistency in the results regarding PLMs, there are methodological differences between the studies (PSG at home rather than in a sleep laboratory, the use of an adaptation night in the sleep laboratory to avoid first night effects, differences in age and other sleep-influencing parameters such as medication intake between investigated groups, measurement of degree of nicotine dependence and withdrawal symptoms with regard to psychometric instruments used). Furthermore, most of the previous studies examined ex-smokers regardless of the duration of abstinence (Zhang *et al*. 2007; Conway *et al*. 2008) or started the sleep laboratory session 1 month after smoking was stopped (Moreno-Coutino, Calderon-Ezquerro & Drucker-Colin 2007). PSG studies that investigated nicotine withdrawal had a small sample size, included only a short follow-up of a few days after smoking was stopped and were contradictory regarding sleep duration, sleep efficiency, frequency of sleep stage changes and arousal frequency (Soldatos *et al*. 1980; Prosise *et al*. 1994). Our knowledge about how nicotine withdrawal affects objective sleep parameters and about the relationship between insomnia complaints during withdrawal and relapse rates in smoking cessation is unfortunately very limited. The aim of the present study is to analyse the sleep in otherwise healthy smokers during tobacco consumption, during acute nicotine withdrawal and 3 months after smoking cessation in a structured sleep laboratory setting. We hypothesized that compared to smoking (baseline), acute withdrawal would decrease subjective and objective sleep efficiency but increase arousal, REM pressure (decrease REM latency, increase REM duration and REM density) and increase PLM index. Patients with more pronounced sleep alterations (i.e. increased number of PLMs) during acute withdrawal would have an increased relapse risk in the succeeding 3-month follow-up interval. Sleep abnormalities initially present would be attenuated by successful long-term cessation compared to acute withdrawal.

## METHODS

This observational study was performed in 2007 and 2008 at the Sleep Center of the Department of Psychiatry and Psychotherapy, Freiburg University Medical Center, Germany. We included 44 participants, recruited via postings and advertisements, who smoked cigarettes daily and had a high level of tobacco dependence, as indicated by a sum score in the Fagerström Test for Nicotine Dependence—FTND (Heatherton *et al*. 1991) of 5 or higher. An additional diagnosis of tobacco dependence was made according to the DSM-IV criteria (APA 1994). We recruited study subjects aged between 18 and 52 years because of the well-known effects of older age on sleep, i.e. the amount of SWS decreases over the lifetime and especially at higher ages (Ohayon *et al*. 2004). Subjects gave written informed consent to participate in the study. The study was approved by the local ethics committee.

To rule out any relevant somatic disorder that may affect sleep, before starting the study, all participants underwent an extensive physical and neurological examination, electrocardiography and laboratory screening. This included measures of blood cell count; liver, renal and thyroid function; ferritin; folic acid; vitamin B12; and glucose. Body mass index (BMI) was calculated from body weight and height. Exclusion criteria were presence of any other sleep disorder (e.g. sleep apnoea syndrome, RLS, narcolepsy, circadian rhythm disorders, organic or psychiatric insomnia as defined by DSM-IV); apnoea-hypopnoea index (AHI) or PLMs index with arousal >5.0 per hour of TST; variable shift work or travel between time zones 4 weeks before the investigation; clinically relevant medical, psychiatric or neurological disorders (such as liver disease or epilepsy); electrocardiogram conduction abnormalities; pregnancy; a positive urine drug screen for benzodiazepines, barbiturates, amphetamines or opiates; consumption of psychotropic, hypnotic or somatic medication known to affect sleep in the 4 weeks before or during the sleep laboratory examination; and changes in other medication during the preceding 4 weeks. Absence of any psychiatric Axis I disorder was confirmed by experienced psychiatrists using the Mini-International Neuropsychiatric Interview (Sheehan *et al*. 1998), a structured interview that includes ratings of depressive, maniac, psychotic and schizophrenic symptoms; anxiety, obsessive-compulsive, post-traumatic stress and eating disorders; alcohol and substance abuse and dependency; and anti-social personality disorders. Participants were asked to document their subjective sleep routine 2 weeks prior to investigation including bed and sleep time, subjective sleep latency, time awake during the night by the sleep diary 'Schlaftagebuch STB' (Kloepfer 2004), which also includes a documentation of

 

daily alcohol and caffeine intake. Subjects with elevated alcohol consumption levels were excluded from the study.

A standardized procedure was used for all PSG investigations. All subjects underwent two consecutive nights of PSG sleep monitoring: the first night allowed them to adapt to the sleep laboratory conditions and to be screened for sleep apnoea and PLMs; the second was used to gather sleep recording data. To take into account that nicotine withdrawal symptoms usually begin after 6–12 hours after discontinuation, reach maximum intensity within 1–3 days and can last up to 3 weeks (Hughes 2007), subjects were asked to complete three different sleep laboratory sessions: during smoking (baseline), 24–36 hours after they stopped smoking (withdrawal) and 3 months after the date of cessation (follow-up). Smokers were allowed to smoke *ad libitum* before and between each of the two baseline nights, but smoking was not permitted during the PSG recording night as well as before and between the withdrawal sleep laboratory sessions. All subjects had the chance to take part in a structured behavioural group therapy programme for smoking cessation with six weekly lessons, but except for one no participant took this chance up. The use of nicotine replacement therapy was not allowed before the withdrawal sleep laboratory session (end of the fourth night) was completed. We noticed no use of nicotine products for smoking cessation support in our participants at follow-up. The use of bupropion or varenicline was not allowed in this study. Abstinence of smoking and of other nicotine intake was confirmed by a qualitative urinary cotinine test (ulti med Products, Ahrensburg, Germany; sensitivity of 200 ng/ml) before the withdrawal as well as before the follow-up sleep laboratory session. Abstinence after 3 months was defined to smoke less than five cigarettes after the target date of cessation and a negative cotinine test at follow-up.

### Polysomnography

Sleep recordings including EEG (C3–A2; C4–A1; sampling rate 200 Hz), electrooculogram (horizontal and vertical) and electromyography (sub-mental) were performed from 10:30 PM to 6:30 AM. The recordings were scored according to standard criteria (AASM 2007) by experienced raters who were blinded to the clinical condition of the subjects. All raters participated in weekly meetings to discuss and solve scoring problems. Inter-rater reliability for all technicians involved in scoring polysomnograms was checked bimonthly. Coefficients of agreement between two raters were required to be higher than 85 percent. A combination of finger pulse oximeter, nasal and oral thermistor airflow, and thoracic and abdominal breathing effort was used to document sleep-associated breathing abnormalities. The following variables of sleep continuity and architecture were assessed: sleep-onset latency, defined as the period between when the lights were turned off and the first 30-second epoch of stage 2 sleep (sleep latency); sleep period time, defined as the period between sleep onset and the final awakening; sleep efficiency, defined as the ratio of TST to time in bed × 100 results in a percentage; and time spent in waking and in sleep stages 1, 2, slow-wave sleep (combined stages 3 and 4) and REM sleep, as a percentage of the sleep period time. REM sleep latency was defined as the period between sleep onset and the occurrence of the first 30-second epoch of REM sleep, including intermittent waking times (REM latency). REM density was calculated as the ratio of 3-second mini-epochs of REM sleep containing rapid eye movements to the total number of 3-second mini-epochs of REM sleep × 100 results in a percentage. The arousal index is the number of arousals per hour of sleep.

### Subjective scales

The German version of the Pittsburgh Sleep Quality Index (PSQI; Buysse *et al.* 1989) was used to assess sleep habits and quality in the 2 weeks before screening and follow-up nights as well at during the withdrawal period 4 weeks after the cessation date. Target variables for analysis were subjectively reported sleep onset latency, TST and sleep efficiency, as well as the PSQI sum score (ranging from 0 to 21, with values above 5 denoting reduced sleep quality and above 10 severely impaired sleep). Participants with a score of 5 or higher at screening were excluded at screening.

The 'Schlaffragebogen A' SF-A (Görtelmeyer 1981) assesses subjective aspects of sleep in the preceding nights. Subjects completed the SF-A after each night of recorded sleep, a few minutes after they had woken up. The questionnaire asks about subjective estimates of wake times and the frequency of awakenings and includes five subscores for the items sleep quality, feeling refreshed in the morning, well-being in the evening, feeling exhausted in the evening and 'psychosomatic symptoms' (e.g. the experience of palpitations, sweating, myalgia) during sleep. Items are rated on a scale of 1–5, with higher values denoting better sleep or well-being in all subscales except 'psychosomatic symptoms', which was reverse-scored. Subjective TST and sleep efficiency were calculated using SF-A wake times and PSG-documented bed times because SF-A records the beginning but not the end of bed time.

The FTND (Heatherton *et al.* 1991) assesses behavioural aspects of smoking and resulted in score between 1 and 10, which reflects the degree of nicotine dependence. Scores of 5 and higher corresponded to a more severe dependence and more frequent relapses after stop

smoking attempts. The six items ask for the number of daily smoked cigarettes (rated from 0 to 4), time to first cigarette after awakening (rated from 0 to 3), the amount of cigarette consumption in the morning, which cigarette could be most easily avoided and the hurdles with smoking restrictions (rated from 0 to 1).

The Perceived Stress Scale (PSS; Cohen, Kamarck & Mermelstein 1983) rates the subjective experienced stress level during the last four weeks. The 10 items in the scale inquire about feelings and thoughts that tap the degree to which respondents find their current life situation unpredictable, uncontrollable and stressful. Respondents indicate how often in the past month they have felt or thought a certain way on a 5-point Likert scale (0 = never, 4 = very often). The higher the score, the higher the perceived stress is. PSS was conducted before baseline, withdrawal and follow-up.

Questionnaire of Smoking Urges (QSU; Tiffany & Drobes 1991) consists of 32 items comprising four putative features of craving, including anticipation of relief of nicotine withdrawal, anticipation of positive outcomes of smoking, desire to smoke and intention to smoke. Thirty-two items were rated between 1 (not at all) and 7 (totally agree) before every sleep session.

The Beck Depression Inventory (BDI; Beck & Steer 1987) is a self-report measure designed to assess depression and was used before every sleep session. It consists of 84 self-evaluative statements grouped into 21 categories. These assess the affective, cognitive, motivational and physiological symptoms of depression. Items are rated in terms of increasing severity from 0 to 3, with 0 indicating the absence of a particular symptom. Scores for each item are summed, giving a range from 0 to 63.

The State-Trait-Anxiety-Inventory (STAI; Spielberger, Gorsuch & Lushene 1970) contains 20 state anxiety items and 20 trait anxiety items. The state anxiety items are each rated on a 4-point intensity scale, from 1 for 'not at all' to 4 for 'very much so'. The trait anxiety items are rated on a 4-point frequency scale (from 'almost never' to 'almost always'). Respondents are asked to indicate how they generally feel. Scoring is reversed for anxiety-absent items (e.g. 'I feel calm'). The range of scores for each of the two scales is 20–80.

### Statistical analysis

For descriptive purposes of the sample and outcome variables, mean values and standard deviations (SDs) were calculated.

In SPSS Statistics 19 & 20 (IBM-Version, Ehningen, Germany), a two-factor general linear model for repeated measurement was used in order to differentiate between the effect of the three points in time, both groups of subsequent abstainers and relapsers, and the interaction between time and group. For all variables, the *F*-value, level of significance and effect size in terms of $\eta^2$ were calculated. The $\alpha$ level for this study was set up at 5 percent.

## RESULTS

### Sample characteristics

We screened 65 smokers and identified 51 subjects who met the inclusion criteria. Fourteen smokers were excluded for the following reasons: iron deficiency (one subject), elevated liver enzymes in laboratory testing (one subject), use of psychotropic medication (two subjects), FTND score <5 (two subjects), withdrawal of consent (seven subjects) and time shift work that includes working during the night. After baseline night, another six subjects withdrew their consent, one was excluded because of use of psychotropic medication and two subjects were lost to follow-up. Forty-two subjects had their follow-up nights in the sleep laboratory, but records of one could not be analysed because of technical difficulties. Another six smokers were excluded because of a positive cotinine test before the withdrawal session and three who reported abstinence but had no cotinine test after 3 months. Of the remaining 33 subjects, 22 stayed abstinent after 3 months, 74 percent of men but only 60 percent of women. The smokers (23 men and 10 women) were 29.4 ± 9.6 years old, had a BMI of 23 ± 2.7 kg/m$^2$, had smoked daily for a median of 12.4 ± 9.5 years, had a mean Fagerstroem score of 6.2 ± 1.1 and consumed an average of 20 ± 6.2 cigarettes per day during the 2 weeks before the investigation. Regarding these demographic variables, we found no differences between abstinent and relapsing smokers after 3 months. The participants' habitual bedtime was between 10:00 PM and 12:00 PM. None of the remaining smokers indicated that they typically woke up because of cravings or had to smoke during sleep periods and none had a positive cotinine test before the withdrawal nights. Both relapsing and abstinent smokers gained some weight between baseline and follow-up, but no significant differences were found regarding the BMI differences (abstinent +0.96 kg/m$^2$; relapsers +0.94 kg/m$^2$).

Relapsing smokers had a higher Fagerstroem score at baseline compared to those who stayed abstinent after 3 months (6.9 ± 1.1 versus 6.0 ± 1.3; $P = 0.031$) and at all times a higher urge to smoke assessed by the QSU than abstinent subjects (see Table 1). In smokers, we found very few depressive symptoms by using the BDI (mean 3.6 ± 3.6) but smokers who relapsed 3 months later had, at baseline, non-significantly higher BDI scores than abstinent subjects (see Table 1). BDI scores of both abstinent and relapsed smokers declined from baseline to follow-up ($F = 4.860$, $P = 0.011$). Furthermore,

 

**Table 1** Polysomnographic characteristics of sleep parameters in smokers before (baseline), during (withdrawal) and 3 months after (follow-up) nicotine withdrawal (mean with standard error of the mean, statistically significant findings are bold and the lines are marked in grey).

| *After 3 months* *Abstinent* n = *22* *Relapse* n = *11* | *Baseline* | | *Withdrawal* | | *Follow-up* | | *Time* | | | *Time × Group* | | | *Group* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Relapse* | *Abstinent* | *Relapse* | *Abstinent* | *Relapse* | *Abstinent* | F | P | $\eta^2$ | F | P | $\eta^2$ | F | P | $\eta^2$ |
| **Objective sleep parameters by polysomnographic analysis** | | | | | | | | | | | | | | | |
| Sleep period time (minutes) | 451.0 ± 13.8 | 442.0 ± 34.0 | 460.1 ± 16.2 | 451.2 ± 45.9 | 464.8 ± 7.0 | 456.6 ± 17.2 | 2.27 | 0.130 | 0.07 | 0.00 | 0.990 | 0.00 | 1.30 | 0.264 | 0.04 |
| Total sleep time (minutes) | 424.5 ± 17.3 | 408.6 ± 45.0 | 413.2 ± 44.0 | 406.0 ± 59.3 | 432.6 ± 20.4 | 415.8 ± 31.3 | 1.39 | 0.256 | 0.04 | 0.19 | 0.772 | 0.01 | 1.29 | 0.265 | 0.04 |
| Sleep efficacy (percent) | 88.8 ± 3.7 | 85.2 ± 9.4 | 86.0 ± 8.4 | 84.6 ± 2.1 | 90.2 ± 4.1 | 86.6 ± 6.7 | 1.39 | 0.256 | 0.04 | 0.19 | 0.772 | 0.01 | 1.29 | 0.265 | 0.04 |
| Stage 1 latency (minutes) | 18.3 ± 14.3 | 21.9 ± 18.9 | 21.9 ± 18.9 | 15.5 ± 13.0 | 16.1 ± 19.0 | 16.1 ± 19.0 | 2.79 | 0.069 | 0.08 | 0.41 | 0.665 | 0.01 | 0.77 | 0.387 | 0.02 |
| Stage 2 latency (minutes) | 25.9 ± 13.5 | 28.3 ± 20.4 | 19.7 ± 12.2 | 26.4 ± 45.4 | 13.1 ± 6.5 | 21.6 ± 17.7 | 1.52 | 0.229 | 0.05 | 0.15 | 0.775 | 0.00 | 0.69 | 0.413 | 0.02 |
| REM-Latency (minutes) | 78.7 ± 28.4 | 72.8 ± 22.3 | 99.5 ± 44.3 | 72.0 ± 36.5 | 95.9 ± 27.0 | 66.7 ± 28.8 | 0.99 | 0.378 | 0.03 | 1.66 | 0.198 | 0.05 | 6.64 | **0.015** | 0.18 |
| REM-Density (percent) | 28.6 ± 5.0 | 30.9 ± 9.3 | 30.7 ± 5.8 | 30.0 ± 10.3 | 27.0 ± 5.6 | 30.3 ± 7.5 | 0.77 | 0.469 | 0.02 | 1.09 | 0.344 | 0.03 | 0.44 | 0.513 | 0.01 |
| Percent wake SPT | 5.9 ± 3.1 | 7.7 ± 5.2 | 10.4 ± 7.1 | 10.3 ± 7.5 | 6.9 ± 4.2 | 9.0 ± 5.5 | 5.28 | **0.008** | 0.15 | 0.56 | 0.575 | 0.02 | 0.54 | 0.467 | 0.02 |
| Percent S1 in SPT | 6.3 ± 2.0 | 8.4 ± 4.8 | 6.4 ± 2.5 | 8.7 ± 4.0 | 6.0 ± 2.7 | 8.4 ± 5.1 | 0.16 | 0.809 | 0.01 | 0.02 | 0.968 | 0.00 | 2.88 | 0.100 | 0.08 |
| Percent S2 in SPT | 54.7 ± 6.7 | 55.0 ± 5.5 | 51.6 ± 8.2 | 49.4 ± 7.5 | 57.9 ± 6.8 | 50.4 ± 6.2 | 8.28 | **0.001** | 0.21 | 5.93 | **0.007** | 0.16 | 2.17 | 0.151 | 0.07 |
| Percent SWS in SPT | 10.1 ± 10.4 | 8.0 ± 6.6 | 11.3 ± 8.7 | 8.7 ± 7.1 | 9.3 ± 8.1 | 9.5 ± 6.9 | 1.26 | 0.290 | 0.04 | 2.73 | 0.073 | 0.08 | 0.30 | 0.585 | 0.01 |
| Percent REM in SPT | 22.6 ± 5.3 | 20.5 ± 4.6 | 19.9 ± 5.2 | 22.4 ± 6.3 | 19.5 ± 4.8 | 22.5 ± 5.8 | 0.18 | 0.833 | 0.01 | 4.00 | **0.023** | 0.11 | 0.44 | 0.513 | 0.01 |
| Arousal per hour SPT | 8.8 ± 3.0 | 12.8 ± 5.6 | 12.7 ± 6.8 | 14.4 ± 6.9 | 11.7 ± 5.1 | 14.2 ± 5.7 | 6.09 | **0.004** | 0.16 | 1.02 | 0.365 | 0.03 | 2.02 | 0.165 | 0.06 |
| Leg movements per hour SPT | 3.3 ± 9.9 | 6.2 ± 13.5 | 3.7 ± 9.0 | 7.8 ± 19.9 | 3.9 ± 8.1 | 4.8 ± 8.1 | 0.43 | 0.595 | 0.01 | 0.52 | 0.545 | 0.02 | 0.34 | 0.565 | 0.01 |
| Apnoeas per hour SPT | 0.8 ± 0.6 | 1.3 ± 1.5 | 1.2 ± 1.8 | 1.9 ± 3.1 | 1.0 ± 0.9 | 2.1 ± 2.9 | 1.01 | 0.371 | 0.03 | 0.29 | 0.748 | 0.01 | 1.34 | 0.255 | 0.04 |

REM = rapid eye movement sleep; SPT = sleep period time = total time between sleep onset and final awakening; SWS = slow-wave sleep; TST = total sleep time = amount of actual sleep time in a sleep period, i.e. the total sleep period less awake time.

relapsing smokers showed a higher level of state-related anxiety in the STAI at baseline, during withdrawal and follow-up, and had higher scores during withdrawal compared to baseline than those who would remain abstinent. The self-rated level of stress in the PSS did not differ between the groups and over the time.

### Sleep characteristics

Overall, we found a number of sleep changes during smoking abstinence (see Table 1); whereas sleep efficiency, latency and sleep duration were not affected by nicotine withdrawal, we noticed increased percentage of wake time after sleep onset during withdrawal and an increase of the arousal index during withdrawal and follow-up a whole. Leg movements and apnoeas did not differ over time and between the groups. Relapsing smokers, compared to the abstinent, had a higher REM latency at all times, and an increase of the REM latency during withdrawal that persisted at follow-up. In contrast to abstinent smokers in relapsing smokers, the percentage of REM sleep was reduced after they ceased smoking. Whereas we found no reduction of the amount of SWS during withdrawal and only a non-significantly reduced SWS proportion in abstinent compared to relapsed smokers, the percentages of stage 2 sleep was reduced in abstinent smokers at all times and for both groups during withdrawal.

By using the PSQI to rate the TST, we observed an increase in both groups between baseline and follow-up (see Table 2). Regarding PSQI sum scores and sleep efficiency, abstinent smokers rated sleep better at follow-up when compared to relapsed smokers, but the difference did not reach statistical significance. Although the SF-A sum score did not differ significantly over time or between the groups, we found a trend towards an increase of the subjectively rated sleep time between baseline and follow-up but also a reduced duration during withdrawal compared to baseline. In the same way, the sleep latency was rated: increase during withdrawal, decrease at follow-up to a comparable degree in both groups. During withdrawal, we noticed also an elevated wake time after sleep onset, reduced sleep efficiency, sleep quality and a reduced feeling of well-being in the evening using the SF-A (each most in the relapsers but significant only for the feeling of well-being in the evening).

## DISCUSSION

In a sample of healthy young subjects and by control of many other sleep-affecting variables such as mental illness, psychotropic medication, other drug and alcohol consumption, we documented slight withdrawal effects after smoking ceased. In accordance with Prosise *et al.* (1994) and in contrast to Soldatos *et al.* (1980), smokers of our investigation spend more time awake during the night and had more arousal during the withdrawal nights in comparison to the night while they were still smoking. Because Soldatos *et al.* (1980) had also noticed shorter sleep latency during withdrawal, adaptation effects from our baseline night to the withdrawal night, which was always the night after the baseline night, could probably overlap the results of this study. In addition, we found subjective sleep impairment during withdrawal that is more pronounced than that of the PSG. In the SF-A, smokers rated their SE lower during withdrawal. Wetter *et al.* (1995) found a similar discrepancy between the intensity of objective and subjective sleep impairments when analysing sleep of smokers during withdrawal when wearing a nicotine patch. Even if none of our subjects indicated that he woke up during the night by craving for a cigarette, symptoms like this could have affected sleep quality in a more subtle way even if the PSG was nearly normal. Again, in contrast to Soldatos *et al.* (1980) and to our hypothesis, we found REM sleep reduced and REM latency increased during withdrawal in relapsing subjects only. According to the reciprocal interaction model of McCarley & Hobson (1975), REM sleep results from cholinergic stimulation of neurons in the gigantocellular tegmental field, whereas noradrenergic neurons of the raphe nucleus inhibit REM and induce non-REM sleep. The direct stimulation of the central acetylcholine receptors by nicotine corresponds to the findings of reduced SWS time, an increase of the non-REM stages 1 and 2, and a decreased power of low sleep EEG frequencies in favour of high-frequency activity in smokers (Zhang *et al.* 2006, 2007). So, in our study, withdrawal of nicotine seems not to result in any kind of REM rebound but in a reduced cholinergic stimulation in those who relapsed within 3 months, marked by a reduced amount of REM sleep. Even if we found no changes in the amount of SWS, the stage 2 amount in abstinent smokers was reduced during withdrawal. Despite there being a strong relationship between insomnia and depression (people with depression have a reduced TST and sleep efficiency, a greater number of nighttime and early morning awakenings, increased REM sleep; Baglioni *et al.* 2011) and that depressive symptoms are a risk factor for a relapse after smoking cessation (Nakajima & al'Absi 2012; Weinberger *et al.* 2012) with the exception of the wake time, we found no evidence of depression such as sleep changes in our population. Underlining this, BDI scores were, on a non-clinical level, differing initially between abstinent and relapsed smoker in a non-significant way and declined over time. Nevertheless, we noticed a higher degree of nicotine dependence, more urge to smoke, higher anxiety levels and a reduced feeling of well-being in the evening

 

**Table 2** Rating of general condition and subjective sleep rating in smokers before (baseline), during (withdrawal) and 3 months after (follow-up) nicotine withdrawal (mean with standard error of the mean) by using the SF-A and the PSQI (mean with standard error of the mean, statistically significant findings are bold and the lines are marked in grey).

| *After 3 months*<br>*Abstinent* n = *22*<br>*Relapse* n = *11* | *Baseline* | | *Withdrawal* | | *Follow-up* | | *Time* | | | *Time × Group* | | | *Group* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Relapse* | *Abstinent* | *Relapse* | *Abstinent* | *Relapse* | *Abstinent* | F | P | $\eta^2$ | F | P | $\eta^2$ | F | P | $\eta^2$ |
| **Questionnaires for general condition** | | | | | | | | | | | | | | | |
| QSU (sum score) | 128.0 ± 25.6 | 116.2 ± 25.5 | 114.0 ± 42.9 | 99.4 ± 35.4 | 95.5 ± 43.0 | 44.8 ± 14.2 | 25.97 | **0.000** | 0.46 | 4.30 | **0.018** | 0.12 | 11.91 | **0.002** | 0.28 |
| PSS (sum score) | 13.1 ± 3.8 | 11.5 ± 5.4 | n.a. | n.a. | 13.8 ± 4.0 | 11.9 ± 5.7 | 0.33 | 0.572 | 0.01 | 0.02 | 0.896 | 0.00 | 1.30 | 0.263 | 0.04 |
| STAI (state) | 36.9 ± 7.1 | 34.2 ± 7.5 | 45.1 ± 7.2 | 35.9 ± 9.5 | 35.6 ± 3.9 | 31.8 ± 6.8 | 14.07 | **0.000** | 0.33 | 3.44 | 0.039 | 0.11 | 4.63 | **0.040** | 0.14 |
| BDI (sum score) | 4.0 ± 3.1 | 2.4 ± 2.7 | 4.1 ± 2.9 | 2.7 ± 2.9 | 2.9 ± 2.3 | 1.4 ± 1.8 | 4.30 | **0.030** | 0.14 | 0.03 | 0.931 | 0.00 | 2.81 | 0.106 | 0.10 |
| **Subjective sleep ratings by using the PSQI** | | | | | | | | | | | | | | | |
| Sleep latency (minutes) | 17.0 ± 7.5 | 18.2 ± 13.3 | n.a. | n.a. | 19.5 ± 13.4 | 32.4 ± 91.7 | 0.31 | 0.584 | 0.01 | 0.15 | 0.701 | 0.01 | 0.23 | 0.637 | 0.01 |
| Sleep period time (minutes) | 7.0 ± 0.8 | 7.4 ± 0.9 | n.a. | n.a. | 7.7 ± 1.8 | 7.8 ± 0.7 | 4.57 | **0.041** | 0.14 | 0.36 | 0.553 | 0.01 | 0.72 | 0.402 | 0.03 |
| Total sleep time (minutes) | 420.0 ± 49.0 | 444.9 ± 52.7 | n.a. | n.a. | 461.7 ± 110.1 | 468.3 ± 40.3 | 4.57 | **0.041** | 0.14 | 0.36 | 0.553 | 0.01 | 0.72 | 0.402 | 0.03 |
| Sum score | 4.6 ± 2.2 | 4.3 ± 2.1 | n.a. | n.a. | 4.3 ± 1.3 | 3.4 ± 1.6 | 2.26 | 0.144 | 0.07 | 0.61 | 0.441 | 0.02 | 1.19 | 0.285 | 0.04 |
| **Subjective sleep ratings by using the SF-A** | | | | | | | | | | | | | | | |
| Sleep quality (1–5) | 3.5 ± 0.5 | 3.4 ± 0.7 | 3.1 ± 0.5 | 3.1 ± 0.7 | 3.5 ± 0.4 | 3.6 ± 0.5 | 5.07 | **0.010** | 0.16 | 0.15 | 0.862 | 0.01 | 0.00 | 0.962 | 0.00 |
| Refreshed at morning (1–5) | 3.8 ± 0.7 | 3.8 ± 0.7 | 3.2 ± 0.7 | 3.7 ± 0.5 | 3.8 ± 0.7 | 3.9 ± 0.7 | 10.31 | **0.000** | 0.28 | 3.23 | **0.047** | 0.11 | 0.67 | 0.420 | 0.02 |
| Sleep efficiency (percent) | 94.2 ± 3.3 | 94.1 ± 6.3 | 89.5 ± 8.4 | 91.0 ± 7.5 | 94.7 ± 2.6 | 95.3 ± 2.8 | 6.53 | **0.003** | 0.20 | 0.18 | 0.836 | 0.01 | 0.14 | 0.713 | 0.01 |
| Wake time after sleep onset (minutes) | 15.4 ± 11.9 | 15.3 ± 21.4 | 32.0 ± 21.6 | 26.7 ± 29.8 | 17.0 ± 10.5 | 11.6 ± 9.9 | 5.88 | **0.005** | 0.18 | 0.18 | 0.832 | 0.01 | 0.39 | 0.539 | 0.01 |
| Sleep latency (minutes) | 12.5 ± 10.4 | 11.5 ± 11.3 | 17.7 ± 17.7 | 14.5 ± 15.3 | 7.9 ± 8.7 | 9.9 ± 8.1 | 4.05 | **0.023** | 0.13 | 0.53 | 0.594 | 0.02 | 0.04 | 0.848 | 0.00 |
| Total sleep time (minutes) | 454.4 ± 21.1 | 444.4 ± 47.2 | 428.4 ± 47.7 | 428.5 ± 44.2 | 462.9 ± 30.5 | 453.9 ± 17.9 | 5.47 | **0.007** | 0.17 | 0.18 | 0.836 | 0.01 | 0.29 | 0.592 | 0.01 |

BDI = Beck Depression Inventory; n.a. = not applicable; PSQI = Pittsburgh Sleep Quality Index; PSS = Perceived Stress Scale; QSU = Questionnaire of Smoking Urges; SF-A = Schlaffragebogen-A; STAI = State-Trait-Anxiety-Inventory.

during withdrawal in our relapsing smokers, indicating a more severe nicotine withdrawal and therefore it could be possible that more severely dependent smokers suffer from more impaired sleep during withdrawal. No changes were detected regarding sleep-related breathing abnormalities and leg movements during and after withdrawal. In contrast to the previously documented relationship of AHI (Conway *et al.* 2008), PLM (Jaehne *et al.* 2012) and smoking status, those parameters did not change over time in our investigation. Two possible explanations could be proposed: for both disorders, a time longer than 3 months is required to normalize after smoking was stopped, or a pre-existing coincidence between a habitual and behavioural risk factor is not influenced by quitting the habit.

Our analysis is limited by a small sample size. Even if we doubled the number of participants compared to previous studies (Soldatos *et al.* 1980), we had only 11 relapsing and 22 abstinent smokers to analyse. Therefore, other aspects may overlap the results of our analysis, i.e. uncontrolled gender aspects. When looking at gender differences, an exacerbation of withdrawal symptoms was observed in women during the luteal cycle phase (Perkins *et al.* 2000), and Wetter *et al.* 1999 observed a temporal linear decrease of sleep fragmentation in men during nicotine replacement after smoking was stopped, while it remained constantly increased in women. Another limitation is the sleep recording of the first two nights after smoking ceased (the first was not analysed because of adaptational processes) so that only the initial part of the withdrawal phase was covered. Even if the maximum of withdrawal symptoms occurs after 24–36 hours (Hughes 2007), sleep changes could persist longer (Moreno-Coutino *et al.* 2007). Furthermore, we observed abstinence for 3 months only; therefore, no statement could be made for a longer abstinence and for longer adaptation processes regarding sleep. If sleep changes reflect some kind of neuroendocrinological regulating mechanisms, it would be interesting to correlate the results of PSG sleep investigations and neuroendocrine analyses to detect changes in sleep-regulating mechanisms. Relevant neurotransmitters, such as acetylcholine, dopamine, serotonin, noradrenaline and glutamate, and hypothalamic-pituitary-adrenal axis functions are not only known to be influenced by nicotine but also play a crucial role in sleep-wake regulation (for overview, see Steriade 2003).

To sum up, we documented in a cohort of young healthy smokers and by control of many other sleep influencing parameters a subjectively impaired sleep during withdrawal with only few changes in the PSG. So far, we have found indices for predictive value of PSG-documented sleep changes and their subjective rating for abstinence in smoking cessation, probably reflecting the degree of nicotine dependence. Nevertheless, this fact should be brought more into the focus of research to understand the consequences of reduced sleep quality on affect and relapses during smoking cessation.

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**Conflict of Interest**

None declared.

**Authors Contribution**

SC, AR and DR were responsible for the study concept and design. AJ and TU contributed to the acquisition of data, performed data analysis and interpretation of findings. BF performed and interpreted the spectral analysis of sleep EEG data. AJ drafted the manuscript. BF, SC, AR and DR provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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