Eur Arch Psychiatry Clin Neurosci (2011) 261:559–566
DOI 10.1007/s00406-011-0195-5

ORIGINAL PAPER

Sleep homeostasis in alcohol-dependent, depressed and healthy control men

Kirk J. Brower · Robert Hoffmann · Deirdre A. Conroy · J. Todd Arnedt · Roseanne Armitage

Received: 10 September 2010 / Accepted: 26 January 2011 / Published online: 11 February 2011

Abstract Visually scored and power spectral analyses (PSA) of polysomnography (PSG) recordings reveal abnormalities in alcohol dependence (AD) and major depressive disorder (MDD), including deficiencies in slow wave activity (SWA) during non-rapid eye movement (NREM) sleep. SWA parameters reflect the integrity of the homeostatic sleep drive, which have not been compared in those with AD or MDD. Ten men with AD were compared with 10 men with MDD and 10 healthy controls (HCs), all aged 20–40 years. They maintained an 11 pm to 6 am sleep schedule for 5–7 days, followed by 3 consecutive nights of PSG in the laboratory: night 1 for adaptation/screening; night 2 for baseline recordings; and night 3 as the challenge night, delaying sleep until 2 am. SWA was quantified with PSA across 4 NREM periods. Men with AD generated the least SWA at baseline. In response to sleep delay, HC men showed the expected SWA enhancement and a sharper exponential decline across NREM periods. Both the MDD and the AD groups showed a significantly blunted SWA response to sleep delay. Men with MDD had the least SWA in the first NREM period (impaired accumulation of sleep drive), whereas men with AD had the slowest SWA decay rate (impaired dissipation of sleep drive). These results suggest that both SWA generation and its homeostatic regulation are impaired in men with either AD or MDD. Finding interventions that selectively improve these different components of sleep homeostasis should be a goal of treatment for AD and MDD.

Keywords Alcohol dependence · Depression · Polysomnography · Sleep · Slow wave activity · Sleep homeostasis

K. J. Brower (✉) · D. A. Conroy
Department of Psychiatry, University of Michigan,
4250 Plymouth Rd, SPC 5740, Ann Arbor, MI 48109-2700, USA
e-mail: kbrower@umich.edu

K. J. Brower · D. A. Conroy
Addiction Research Center, Ann Arbor, MI, USA

R. Hoffmann · J. T. Arnedt · R. Armitage
Department of Psychiatry, University of Michigan,
4250 Plymouth Rd, SPC 5766, Ann Arbor, MI 48109-2700, USA

R. Hoffmann · J. T. Arnedt · R. Armitage
Sleep and Chronophysiology Laboratory, Ann Arbor, MI, USA

Introduction

Sleep disturbances are common in both depressed [1, 2] and alcohol-dependent [3–6] patients. Between 36 and 91% of alcohol-dependent patients report insomnia [7, 8] as do 50–90% of depressed patients [2, 9, 10]. In addition to subjective reports of insomnia, patients with major depressive disorder (MDD) and alcohol dependence (AD) manifest similar abnormalities in visually scored polysomnography (PSG) including impaired sleep continuity, decreased slow wave sleep (SWS), shortened latency to rapid eye movement (REM) sleep (REML), and increased amounts of REM sleep [11]. Computer-analyzed sleep electroencephalography (EEG) abnormalities, particularly deficiencies in delta activity in non-REM (NREM) sleep, known as slow-wave activity (SWA), have also been reported both in those with MDD [2, 12] and in those with AD [13, 14].

Slow-wave activity provides an important measure of sleep regulation. According to the two-process model [15], sleep regulation involves a balance between a homeostatic sleep drive (Process S) and a circadian rhythm that maintains wakefulness (Process C). Sleep drive accumulates

with the duration of wakefulness, resulting in increasing sleepiness as the day progresses from morning to evening. The circadian rhythm counters the sleep drive, especially in the late afternoon and early evening when it peaks to maintain wakefulness. Process C subsequently begins to decrease as bedtime approaches, at which time sleep drive (Process S) is at its maximum. Experimental evidence suggests that the stronger the sleep drive, the more SWA power is observed during the first NREM period of the night [15]. Thus, SWA during the first NREM period is taken as a measure of sleep drive generation. As sleep progresses during the night, the drive for sleep as well as SWA dissipates in an exponential manner in healthy individuals.

The standard approach to quantifying SWA regulation is to assess the response to a sleep challenge such as sleep restriction or deprivation [16]. Compared with a baseline night of sleep, SWA is typically increased in response to these sleep challenges, particularly in the first NREM episode in recovery sleep, reflecting an increase in homeostatic sleep drive. Our own work has shown that men with MDD have an abnormal SWA response to sleep challenge when compared with healthy controls (HCs), characterized by a lower accumulation of SWA in the first NREM period and a slower dissipation across subsequent NREM periods during sleep [17]. Thus, both the power or amplitude and regulation of SWA are impaired in MDD men. Irwin and colleagues [16] demonstrated that alcohol-dependent men also show reduced total SWA power and an overall blunted response to partial sleep deprivation, compared with healthy controls. Although it appeared that SWA impairment was greater in men with AD as reported by Irwin and colleagues [16] than in the MDD men from our own studies [17], procedural differences between the two studies limit the comparability of SWA in these two clinical groups.

To our knowledge, no studies have analyzed differences in SWA between individuals with AD and those with MDD. We reasoned that similarities or differences in SWA abnormalities in men with either AD or MDD may have important clinical implications. First, MDD and AD frequently co-occur [18], which may represent a common genetic vulnerability [19, 20]. Comparing sleep regulation between these groups, therefore, is a first step in dissecting and understanding diagnosis-specific contributions versus common vulnerabilities to sleep dysregulation. Second, residual sleep disturbances following acute treatment of either MDD or AD are associated with relapse/recurrence of the respective disorder [7, 21, 22]. Whether recurrence and relapse are related to a common abnormality of sleep regulation across disorders is unknown but may have additional value in understanding their comorbidity. Third, similarities in sleep dysregulation would suggest that both diagnostic groups might respond to similar treatments for their sleep disturbance, whereas differences would suggest that specific tailoring of treatment to each diagnostic group is needed. At present, measuring SWA is neither a diagnostic tool nor a guide to differential therapies, and most pharmacotherapies for treating sleep complaints in patients with either AD or MDD target symptoms, not underlying mechanisms of sleep dysregulation. Nevertheless, behavioral therapies that employ sleep restriction techniques are designed to increase homeostatic drive. Providing therapy based on underlying mechanisms rather than manifest symptoms is a worthwhile goal of future treatment as these mechanisms and their specificity across diagnoses become better understood.

The present study investigated SWA response to a mild sleep challenge, using a 3-h sleep delay paradigm in 20- to 40-year-old men with either MDD or AD, compared with HC men. We hypothesized, on the basis of studies reviewed above [16, 17], that alcohol-dependent individuals would have greater impairments in both SWA generation (baseline night) and regulation (delay night) than either individuals with MDD or HC.

Methods

Participants

Participants were 30 men, between 20 and 40 years of age, who met criteria for inclusion into one of the three study groups: AD, MDD, or HCs. The study was restricted to this age range and sex group, because SWA varies significantly in relation to these variables among depressed patients [23]. All participants were recruited through a combination of advertisement, posted flyers in affiliated clinics, and clinician or self-referral. Participants with MDD as well as HC participants were recruited separately for another study comparing these two groups [24]; however, all participants were recruited from the same community and followed identical laboratory procedures at the same sleep laboratory. The research described was approved by the Medical Institutional Review Board at the University of Michigan. All participants signed an informed consent document prior to undergoing study procedures.

Diagnoses of MDD and AD were determined by the Structured Clinical Interview for DSM-IV [25, 26]. Participants with AD met past-year DSM-IV diagnostic criteria [27] for AD. They were excluded if they met DSM-IV criteria for dependence on any other substance except nicotine; if they met current criteria for any mood disorder, anxiety disorder, or eating disorder; or if they had a lifetime diagnosis of bipolar disorder or any psychotic disorder. Comorbid diagnoses for men with MDD were also exclusionary, including a previous history of substance

dependence. HCs had no personal or family history of psychopathology. All potential participants that had a medical illness or took medication known to affect sleep were excluded. Potential participants who were suicidal or thought to require antidepressant medication sooner than the study protocol allowed were also excluded and referred to appropriate psychiatric treatment.

Eligible participants with MDD were unmedicated for a minimum of 4 weeks (6 weeks for fluoxetine) and were currently symptomatic as indicated by scores ≥17 on the 17-item Hamilton Rating Scale for Depression [28]. Men with AD were studied 1–3 months after their last drink (mean 61.6 days, SD = 17.6, range 34–91 days), as determined by the time-line follow-back interview [29, 30] and breath testing. On average, their age at onset of problem drinking was 17.9 (5.7) years with a duration of problem drinking continuing for 12.1 (10.0) years. They scored 16.0 (7.3) on the Obsessive–Compulsive Drinking Scale [31] and 18.1 (10.1) on the Short Inventory of Problems [32], indicating a moderate degree of severity and problems.

Sleep procedures

All participants kept an 11 pm to 6 am schedule for 5 days prior to their studies in the sleep laboratory. No daytime napping was permitted, and adherence to the schedule at home was verified by actigraphy and sleep diaries. Caffeine was restricted to 2 cups per day. Participants were asked not to drink alcohol or take drugs of abuse during the study. In addition to self-reported intake using the time-line follow-back interview [33], abstinence was confirmed by breath testing and urine drug screen collection upon arrival to the sleep laboratory each night of study.

Subjects spent 3 consecutive nights in the sleep laboratory for PSG recording. The first night was an adaptation and screening night to rule out primary sleep disorders such as sleep apnea and periodic limb movements in sleep. The second night collected baseline sleep parameters from 11 pm to 6 am, and the third night recorded sleep after a 3-h sleep delay (bedtime at 2 am and rise time at 9 am). The major difference in sleep challenge techniques between early partial sleep deprivation and sleep delay protocols is that time in bed, and consequently the total time available for sleep, is held constant across all nights with the latter protocol. EEG was recorded from C3 and C4, referenced to the earlobes, and connected to a 10-kΩ resistor to minimize non-homogeneous current flow. The electrode montage also included left and right electro-oculogram (EOG) leads placed on both the upper and lower canthi; a bipolar, chin-cheek electromyography (EMG) lead; leg leads; chest and abdomen respiration bands; and a nasal-oral thermistor.

All electrophysiological signals were transduced by Vitaport III™ digital amplifiers with an equivalent sensitivity of 5 (50 μV, 0.5-s duration calibration) corresponding to a gain of 50,000. For EEG, filter settings were set at 0.3 and 70 Hz. Digital filters attenuate electrical noise. EOG was recorded at a sensitivity equivalent to 5 on AC amplifiers with filter settings at 1 and 35 Hz. EMG was recorded at a sensitivity of 1 with filters at 30 and 100 Hz. All data were digitized at 256 Hz. All digitized signals were displayed in real time in analog form on a computer monitor.

Sleep recordings were scored in 30-s epochs using standard criteria [34]. Sleep continuity variables included sleep-onset latency (SOL), defined as the time from lights out to the first 10-min block of sleep with 8 or more minutes of any sleep stage; total sleep period (TSP) from sleep onset to morning awakening; percentage of TSP spent awake and/or moving; total sleep time (TST), defined as the TSP minus time spent awake and/or moving; and sleep efficiency (SE), defined as the TST divided by the time in bed X 100%. Sleep stage variables included the percentages of TSP spent in stage 1 and stage 2, slow-wave sleep (SWS; defined as stage 3 + stage 4 sleep), and REM sleep (REM%). REM latency was defined as the minutes from sleep onset to the first epoch of REM sleep. REM density, reflecting the number of eye movements in REM sleep, was scored on a 0–5 scale.

Quantifying SWA

During visual scoring, epochs were tagged for artifact rejection. Epochs with any movement or electrical artifact, baseline shift, or electrode problems were excluded from analysis. Power spectral analysis (PSA) was performed on digitized EEG signals. Although the full EEG spectrum was quantified at all sites, primary statistical analyses focused on delta (0.5 to < 4 Hz) power from PSA.

The PSA algorithm, based on a fast Fourier transform, was taken from Press et al. [35], processing data in 2-s epochs (512 samples for each 2 s) with a Hanning window taper. The PSA generates power (area under the curve) in the delta band (0.5–3.9 Hz), expressed as μV^2. Delta power was then averaged in 30-s epochs to provide identical epoch lengths to the stage-score data.

The delta power data were then sorted by NREM period (determined by stage-score data), separately for each subject on baseline and sleep delay nights to compare SWA among groups. The definition of NREM periods closely follows that outlined by Dijk et al. [36–42] and Feinberg's group [43]. NREM periods were defined as the succession of stages 2, 3, or 4 of ≥15 min in duration and terminated by REM sleep or a period of wakefulness of at least 5 min. Stage 1 sleep epochs were excluded from delta power

calculations. No minimum REM duration was required for the first or last REM period. For each subject, delta power was summed and then averaged relative to the number of epochs in each NREM period, henceforth referred to as SWA.

Data analyses

Data were coded for group (AD, MDD, and HC), and a repeated-measures multivariate analysis of variance (MANOVA) was performed entering the two nights as the within-subject repeated measure, the three diagnostic groups as the between-subject variable, and visually scored PSG measures as the dependent variables. Main and interaction effects were considered significant in the multivariate analysis using a P value of 0.05.

To analyze SWA measures, repeated-measures ANOVA testing was performed separately for each night of study using NREM periods as a four-level repeated measure. To insure that potential SWA differences across NREM periods were not an artifact of differences in either the duration or time to onset of each NREM period, we compared these measures between groups. No significant differences were found. For the baseline night, the SWA measure was entered for each NREM period. For the 3-h sleep delay night, SWA for each NREM period was computed as a percentage of each participant's average SWA across the baseline night (%SWA) to normalize power across subjects. Regression analyses were used to describe the time course of %SWA in each group. All SWA statistical analyses were conducted using SAS^{TM} general linear models, or mixed model analysis, and regression routines.

Results

Demographic data for the three groups are shown in Table 1. The three groups did not differ in terms of age, ethnicity, and employment status but did differ in their education and marital status. Men with AD were less educated than either the MDD or HC group, and they were less likely to be married and more likely to be divorced than the other two groups.

The visually scored PSG variables for the three diagnostic groups and two nights of study are presented in Table 2. A repeated-measures MANOVA, including all visually scored PSG variables except TSP, revealed an overall significant group effect (F [18, 38] = 2.10, $P = 0.027$), a significant sleep delay effect (F = [9, 19] 2.59, $P = 0.039$), and no significant overall interaction between sleep delay and diagnostic group. Significant differences from the baseline to delay nights included SL ($P = 0.033$), stage 2% ($P = 0.023$), and REM latency ($P = 0.003$). All three measures were significantly shortened on the delay night compared with the baseline night. Post hoc comparisons using the Tukey honestly significant difference test revealed significant group differences ($P < 0.05$) for SE, stage 1%, stage 2%, and REM latency. All of these differences involved the AD group except stage 2%, for which the MDD group scored significantly lower than HCs. The AD group had significantly lower SE than the MDD group, but otherwise did not differ from it. Compared with the HC group, however, the AD group had significantly less stage 1% sleep and a shorter REM latency.

Table 1 Demographic characteristics

	Healthy controls ($n = 10$)	Major depression ($n = 10$)	Alcohol dependence ($n = 10$)
Age (year)	28.7 (5.9)	29.4 (6.9)	29.6 (7.4)
Ethnicity			
Black	0	1 (10)	1 (10)
White	8 (80)	7 (70)	7 (70)
Other	2 (20)	2 (20)	2 (20)
Education (year)	16.9 (1.5)	15.7 (1.8)	12.5 (1.4)
Marital status			
Never married	4 (40)	5 (50)	6 (60)
Married[a]	6 (60)	4 (40)	1 (10)
Divorced	0	0	3 (30)
Employment			
Employed	5 (50)	8 (80)	5 (50)
Unemployed	5 (50)	2 (20)	5 (50)

Means (SDs) shown for continuous variables and frequencies (%) shown for categorical variables. Continuous and categorical variables analyzed by independent samples T tests and chi-square tests, respectively

[a] Married or living with partner; missing data for 1 participant with major depression

With regard to SWA at baseline, significant multivariate effects were observed for NREM period (F [3, 25] = 39.79, $P < 0.0005$) and group (F [2, 27] = 10.8, $P < 0.0005$), but not for an interaction between them. Post hoc contrasts revealed that men with AD had significantly lower SWA averaged across the four NREM periods than either the HC (mean difference ± SE = 96.4 ± 23.4 μV^2; $P = 0.001$) or MDD (92.4 ± 23.4 μV^2; $P = 0.001$) groups. When examined by period, the AD group had the lowest SWA which was statistically significant compared with HC men in the first, third, and fourth NREM periods and with MDD men in the third NREM period (Fig. 1). Moreover, there was no evidence of a systematic decline in SWA across the night for the AD group. By contrast, HC and MDD men had more SWA in the first NREM period than in latter NREM periods.

Table 2 Visually scored sleep variables on baseline and delay nights

Characteristic	Healthy controls ($n = 10$)		Major depression ($n = 10$)		Alcohol dependence ($n = 10$)		Night (N)/Group (G)
	Baseline	Delay	Baseline	Delay	Baseline	Delay	Effects
Total sleep period (min)	407.1 (9.6)	403.0 (60.7)	410.6 (18.8)	414.1 (7.0)	393.8 (31.6)	401.6 (18.2)	
Total sleep time (min)	389.3 (10.3)	382.8 (60.8)	400.6 (18.4)	401.0 (12.0)	375.5 (33.9)	384.2 (17.0)	
Sleep latency (min)	8.1 (7.3)	5.7 (3.3)	4.7 (3.9)	5.0 (4.1)	24.6 (31.4)	6.8 (6.2)	N*
Sleep efficiency (%)	93.9 (2.3)	92.9 (3.1)	95.5 (4.0)	95.5 (3.0)	89.9 (8.2)	93.0 (3.5)	G*
Awake and/or movement time (%)	4.4 (2.3)	5.0 (2.5)	2.4 (1.9)	3.2 (2.6)	4.7 (2.5)	4.4 (2.7)	
%Stage 1	9.9 (5.1)	10.3 (7.0)	5.6 (4.8)	7.8 (7.8)	5.0 (3.0)	3.4 (2.0)	G*
%Stage 2	58.9 (6.3)	57.6 (4.3)	52.6 (10.3)	46.8 (8.3)	53.4 (7.8)	51.2 (10.1)	G*/N*
%Slow wave sleep	4.5 (5.8)	3.7 (5.8)	12.7 (10.6)	13.5 (11.7)	13.1 (9.7)	14.9 (10.2)	
%REM	22.4 (4.5)	23.5 (11.8)	26.7 (5.6)	28.6 (3.8)	23.8 (6.2)	26.2 (7.3)	
REM latency	79.5 (17.9)	78.3 (25.5)	79.3 (13.3)	56.1 (29.4)	61.4 (25.5)	42.3 (34.1)	G*/N**
REM density	2.5 (0.7)	2.3 (0.7)	3.5 (1.2)	3.4 (0.9)	2.6 (1.2)	2.6 (1.3)	

* $P < 0.05$; ** $P < .005$

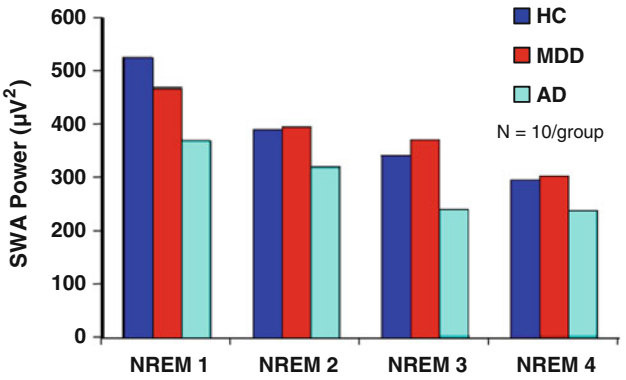

Fig. 1 SWA power as a function of diagnostic group and NREM period on the baseline night of recording. Repeated-measures MANOVA revealed a significant between-group difference (F [2, 27] = 10.8, $P < 0.0005$) with AD men having lower SWA than the HC and MDD men. A significant decline in SWA across NREM periods was also found (F [3, 25] = 39.79, $P < 0.0005$)

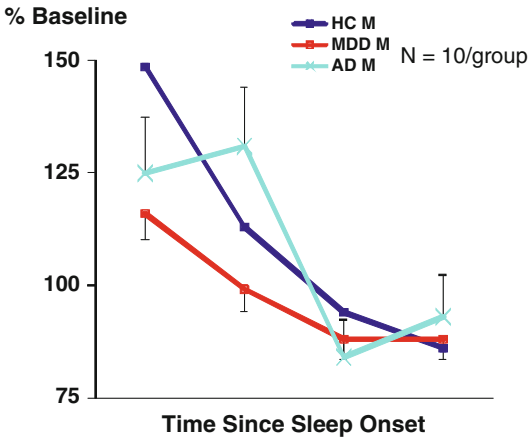

Fig. 2 %SWA power after sleep delay, expressed relative to baseline SWA by group. Amounts > 100 indicate an enhancement over baseline. The interaction between diagnostic group and time-of-night is significant (F [6, 50] = 2.7, $P = 0.027$). The HC group showed the largest SWA response to delay with a rapid decline over NREM sleep time. The MDD men showed the lowest SWA response to delay with a flatter decline across the night. The AD men showed an intermediate SWA response to delay but showed the slowest decline in %SWA of all groups

With regard to SWA regulation (Fig. 2), the repeated-measures ANOVA on %SWA (SWA on the delay night expressed relative to baseline) revealed a significant time-of-night by group interaction (F [6, 50] = 2.64, $P = 0.027$). HC men showed the greatest response to challenge, accumulating 150% of baseline SWA in the first NREM period of the delay night, with a very rapid decline over total NREM sleep time (Fig. 2). The MDD men showed a blunted response to sleep delay with minimal differences from the first to fourth NREM periods. By contrast, the men with AD showed an intermediate SWA response to sleep delay in the first NREM period, although still significantly lower than HC men. Moreover, %SWA did not decline significantly from the first to second NREM period in the AD group.

Regression analyses were used to quantify between-group differences in the accumulation and dissipation of SWA in response to challenge. Exponential regression analyses were computed on %SWA response to sleep delay, separately for each group, using the model $y = b * e^{c * \text{time}}$, where b is the predicted %SWA value at time 0, c is the exponential change, and time is the minutes of NREM sleep since sleep onset. A negative value of c indicates a decay of %SWA over NREM time. The resultant equations indicated a significantly higher accumulation of %SWA in the HC men, with a faster dissipation than AD or MDD men ($y = 176.53e^{-0.19}$). MDD men showed a lower initial

accumulation and slower dissipation of %SWA ($y = 137.57e^{-0.15}$) outside the 95% confidence interval of HC men. Those with AD showed a significantly lower accumulation of %SWA than HC men, but higher than those with MDD. The rate of decay was slower in AD men than in either HC or MDD men ($y = 159.52e^{-0.03}$). However, the shape of the decline in %SWA appeared different visually (Fig. 2); exponential in HC, linear in MDD, and curvilinear in the AD group. To evaluate this possibility, linear and polynomial equations were also applied to the %SWA data.

A linear equation provided the best fit for those with MDD ($r^2 = 0.91$) compared with HC ($r^2 = 0.81$) and the worst fit in the ADD group ($r^2 = 0.70$). By contrast, a fourth-order polynomial provided the best goodness fit for %SWA in the AD group ($r^2 = 0.99$), compared with HCs ($r^2 = 0.77$) or the MDD group ($r^2 = 0.49$).

Discussion

This study had three major findings. First, baseline SWA was lower in AD men than in either HC or MDD men, indicating impaired generation of SWA and sleep drive. Second, homeostatic regulation of SWA was impaired in both MDD and AD men when compared with HC men, as indicated by their decreased accumulation of %SWA in the first NREM period as well as their abnormal course of %SWA dissipation across NREM periods on the delay night. Third, the regulation of SWA was most abnormal in men with AD, who had the slowest %SWA dissipation across NREM sleep time. Moreover, neither linear nor exponential functions provided a good fit for the %SWA changes across the night for the AD group, in contrast to the MDD and HC groups.

It has been suggested that the initial accumulation of %SWA in response to sleep challenge reflects the increased sleep debt accumulated during extended wakefulness [15, 40]. On the other hand, the rate of decay of %SWA has been conceptualized as the speed of recovery from increased sleep debt. Interpreted in this context, our findings suggest that neither men with MDD nor those with AD have accumulated as much sleep debt as HCs when exposed to a mild sleep challenge. However, the recovery from sleep challenge, reflected in the rate of decay of %SWA, is more impaired in AD men than in those with MDD. These findings suggest that both the generation and regulation of SWA are impaired in AD and MDD men, but it is primarily the accumulation of sleep debt that captures homeostatic impairment in men with MDD, whereas men with AD show the greatest impairment in recovery from sleep debt. These findings also suggest that different mechanisms underlie SWA abnormalities in men with either MDD or AD.

This is the first study to our knowledge that compares alcohol-dependent and depressed individuals in terms of their SWA parameters. While both disorders have been shown previously and independently to be characterized by decreased generation of SWA and impaired homeostatic regulation [2, 16], this study suggests that these deficiencies may be more complex in AD than in MDD. The impairment of homeostatic sleep drive functioning may underlie and explain prolonged disturbances in both objectively observed and subjectively perceived sleep among AD patients despite abstinence from alcohol [3, 5, 6]. These sleep disturbances constitute a clinical challenge when treating AD patients [44–46] that are commonly treated with sedating antidepressants, anticonvulsants, and antipsychotic medication [47]. Such treatment is provided without good evidence for effectiveness and in the absence of understanding the mechanisms of sleep disturbance [48]. This study adds to our knowledge about the mechanisms involved and suggests that treatment may need to target and enhance the homeostatic sleep drive in order to be effective.

Further studies would be useful to compare individuals with co-occurring MDD and AD to those with either disorder alone. Several reports by Gillin et al. [49–51] and one report by Gann et al. [52] compared visually scored sleep architecture in patients with AD and those with MDD, but no studies have directly compared these two diagnostic groups in terms of SWA generation and regulation. The study by Gann et al. [52] found that AD patients had significantly less SWS% than both MDD patients and control participants. We did not replicate that result here. In fact, our HC men had a lower percentage of SWS than the men with either AD or MDD, although these differences were not statistically significant (Table 2). It may be that SWA is a more sensitive indicator of differences between the two groups than SWS. To remind the reader, SWS only captures delta waves in excess of 75 μV, whereas SWA measures are derived from EEG activity in the delta frequency regardless of amplitude.

It is also unusual that men with AD in this study had significantly less stage 1% sleep than HC men. The reason for this finding is unexplained, but it was unlikely to have any effect on the primary study results involving SWA and sleep homeostasis.

Short REM latency has been associated with recurrent depression [1] and predicts relapse to drinking in AD patients [53, 54]. While the sleep delay paradigm in the present study elicited shorter REM latency in both the MDD and AD groups, only the AD group showed significantly shorter REM latency than HC men. In terms of sleep microarchitecture, increased β-frequency activity during sleep may predict alcoholic relapse [55] and temporal incoherence may predict recurrent major depression [2].

Nevertheless, evidence that treating sleep disturbances in AD patients will prevent relapse is lacking [7, 46].

Limitations of this study include small sample size and sample selection bias so that it cannot be assumed that these results would necessarily generalize to other samples of AD and MDD. Moreover, the entire sample was men, and studies in MDD suggest that men and women have different SWA characteristics [2, 23]. Specifically, depressed men are more likely to have impaired sleep homeostasis than depressed women. The age range was also restricted in this study from 20 to 40 years, although age effects on sleep are important in both MDD [2, 23] and AD [56]. Finally, there were only two African Americans in the study. One study reported that African Americans with AD have lower baseline delta power than either European Americans with AD or healthy controls [13]. Therefore, future studies will need to employ larger samples that include both men and women of different ages, as well as diverse ethnic groups.

In summary, men with AD have greater impairment in both the generation and regulation of homeostatic sleep drive than either men with MDD or HCs, which may explain in part the commonly described disturbances in their sleep as observed in the laboratory and clinical practice. While the small sample size, restricted age range, and exclusive male representation limit the generalizability of findings, this is the first study to our knowledge that compares the two diagnostic groups with HCs using SWA measures under baseline and sleep delay conditions to describe differences in homeostatic sleep drive. Further studies are indicated to confirm and extend these findings. If confirmed, then interventions for sleep disturbance in men with AD or MDD might optimally need to target SWA dysregulation, and corresponding research should determine the effects of such treatment on the course of the primary disorder as well as on sleep. Finally, the differences between the AD and MDD groups in terms of SWA dysregulation (i.e., accumulation of sleep debt vs. recovery from sleep debt) suggest that treating their sleep disturbances may require disorder-specific approaches.

Acknowledgments This work was supported by National Institutes of Health grants 2 K24 AA00304-10 and R01 AA016117-04 to KJB and R01 MH61515 to RA.

Conflicts of interest The authors report no conflicts of interest.

References

1. Giles DE, Jarrett RB, Roffwarg HP, Rush AJ (1987) Reduced rapid eye movement latency. A predictor of recurrence in depression. Neuropsychopharmacology 1(1):33–39
2. Armitage R (2007) Sleep and circadian rhythms in mood disorders. Acta Psychiatr Scand Suppl 115 (s433):104–115
3. Landolt HP, Gillin JC (2001) Sleep abnormalities during abstinence in alcohol-dependent patients. Aetiology and management. CNS Drugs 15(5):413–425
4. Roehrs T, Roth T (2001) Sleep, sleepiness, sleep disorders and alcohol use and abuse. Sleep Med Rev 5(4):287–297
5. Krystal AD, Thakur M, Roth T (2008) Sleep disturbance in psychiatric disorders: Effects on function and quality of life in mood disorders, alcoholism, and schizophrenia. Ann Clin Psychiatry 20(1):39–46
6. Brower KJ (2001) Alcohol's effects on sleep in alcoholics. Alcohol Res Health 25:110–125
7. Brower KJ (2003) Insomnia, alcoholism and relapse. Sleep Med Rev 7(6):523–539
8. Cohn TJ, Foster JH, Peters TJ (2003) Sequential studies of sleep disturbance and quality of life in abstaining alcoholics. Addict Biol 8(4):455–462
9. Tsuno N, Besset A, Ritchie K (2005) Sleep and depression. J Clin Psychiatry 66(10):1254–1269
10. Lam RW (2006) Sleep disturbances and depression: a challenge for antidepressants. Int Clin Psychopharmacol 21(Suppl 1):S25–S29
11. Benca RM, Obermeyer WH, Thisted RA, Gillin JC (1992) Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 49:651–668
12. Armitage R (1995) Microarchitectural findings in sleep EEG in depression: diagnostic implications. Biol Psychiatry 37(2):72–84
13. Irwin M, Miller C, Gillin JC, Demodena A, Ehlers CL (2000) Polysomnographic and spectral sleep EEG in primary alcoholics: an interaction between alcohol dependence and African-American ethnicity. Alcohol Clin Exp Res 24:1376–1384
14. Colrain IM, Turlington S, Baker FC (2009) Impact of alcoholism on sleep architecture and EEG power spectra in men and women. Sleep 32(10):1341–1352
15. Borbely AA, Achermann P (1999) Sleep homeostasis and models of sleep regulation. J Biol Rhythms 14(6):557–568
16. Irwin M, Gillin JC, Dang J, Weissman J, Phillips E, Ehlers CL (2002) Sleep deprivation as a probe of homeostatic sleep regulation in primary alcoholics. Biol Psychiatry 51(8):632–641
17. Armitage R, Hoffmann RF (2001) Sleep EEG, depression and gender. Sleep Med Rev 5(3):237–246
18. Hasin DS, Stinson FS, Ogburn E, Grant BF (2007) Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the united states: Results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry 64(7):830–842
19. Prescott CA, Aggen SH, Kendler KS (2000) Sex-specific genetic influences on the comorbidity of alcoholism and major depression in a population-based sample of us twins. Arch Gen Psychiatry 57(8):803–811
20. Kuo PH, Neale MC, Walsh D, Patterson DG, Riley B, Prescott CA, Kendler KS (2010) Genome-wide linkage scans for major depression in individuals with alcohol dependence. J Psychiatr Res 44(9):616–619
21. Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rossler W (2008) Prevalence, course, and comorbidity of insomnia and depression in young adults. Sleep 31(4):473–480
22. Dombrovski AY, Cyranowski JM, Mulsant BH, Houck PR, Buysse DJ, Andreescu C, Thase ME, Mallinger AG, Frank E (2008) Which symptoms predict recurrence of depression in women treated with maintenance interpersonal psychotherapy? Depress Anxiety 25(12):1060–1066
23. Armitage R, Hoffmann R, Trivedi M, Rush AJ (2000) Slow-wave activity in nrem sleep: Sex and age effects in depressed outpatients and healthy controls. Psychiatry Res 95:201–213

24. Armitage R, Hoffmann R, Fitch T, Trivedi M, Rush AJ (2000) Temporal characteristics of delta activity during nrem sleep in depressed outpatients and healthy adults: Group and sex effects. Sleep 23(5):607–617
25. First MB, Spitzer RL, Gibbon M, Williams JBW (eds) (1997) Structured clinical interview for DSM-IV axis I disorders (SCID-I), clinician version: User's guide. American Psychiatric Press, Washington, D.C
26. Kranzler HR, Kadden RM, Babor TF, Tennen H, Rounsaville BJ (1996) Validity of the SCID in substance abuse patients. Addiction 91:859–868
27. American Psychiatric Association (2000) DSM-IV-TR: diagnostic and statistical manual of mental disorders, 4th edn, text revision. American Psychiatric Association, Washington DC
28. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
29. Maisto SA, Sobell MB, Cooper AM, Sobell LC (1979) Test-retest reliability of retrospective self-reports in three populations of alcohol abusers. J Behav Assess 1:315–326
30. Sobell LC, Sobell MB, Leo GI, Cancilla A (1988) Reliability of a timeline method: Assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. Br J Addiction 83:393–402
31. Anton RF, Moak DH, Latham PK (1996) The obsessive compulsive drinking scale: a new method of assessing outcome in alcoholism treatment studies. Arch Gen Psychiatry 53:225–231
32. Miller WR, Tonigan JS, Longabaugh RL (1995) The drinker inventory of consequences (DrInc): an instrument for assessing adverse consequences of alcohol abuse, vol 4. Project match monograph series. National Institutes of Health (Publication No. 95-3911), Rockville, MD
33. Sobell LC, Maisto SA, Sobell MB, Cooper AM (1979) Reliability of alcohol abuser's self-reports of drinking behavior. Behavioral Research and Therapy 17:157–160
34. Rechtschaffen A, Kales AA (eds) (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Government Printing Office (NIH Publication No. 204), Washington, DC
35. Press WH, Flannery BP, Teukolosky SA, Bettering WT (1989) Numerical recipes in pascal. Cambridge University Press, New York
36. Dijk DJ, Beersma DG, Daan S (1987) EEG power density during nap sleep: reflection of an hourglass measuring the duration of prior wakefulness. J Biol Rhythms 2(3):207–219
37. Dijk DJ, Beersma DG, Daan S, Bloem GM, Van den Hoofdakker RH (1987) Quantitative analysis of the effects of slow wave sleep deprivation during the first 3 h of sleep on subsequent EEG power density. Eur Arch Psychiatry Neurol Sci 236(6):323–328
38. Dijk DJ, Beersma DG, Bloem GM (1989) Sex differences in the sleep EEG of young adults: visual scoring and spectral analysis. Sleep 12(6):500–507
39. Dijk DJ, Beersma DG, van den Hoofdakker RH (1989) All night spectral analysis of EEG sleep in young adult and middle-aged male subjects. Neurobiol Aging 10(6):677–682
40. Dijk DJ, Brunner DP, Beersma DG, Borbely AA (1990) Electroencephalogram power density and slow wave sleep as a function of prior waking and circadian phase. Sleep 13(5):430–440
41. Dijk DJ, Brunner DP, Borbely AA (1990) Time course of EEG power density during long sleep in humans. Am J Physiol 258 (3 Pt 2):R650–661
42. Dijk DJ (1999) Circadian variation of EEG power spectra in NREM and REM sleep in humans: dissociation from body temperature. J Sleep Res 8(3):189–195
43. Feinberg I, March JD, Fein G, Floyd TC, Walker JM, Price L (1978) Period and amplitude analysis of 0.5–3 c/sec activity in nrem sleep of young adults. Electroencephalogr Clin Neurophysiol 44 (2):202–213
44. Stein MD, Friedmann PD (2006) Disturbed sleep and its relationship to alcohol use. Subst Abus 26(1):1–13
45. Arnedt JT, Conroy DA, Brower KJ (2007) Treatment options for sleep disturbances during alcohol recovery. J Addict Dis 26(4):41–54
46. Roth T (2009) Does effective management of sleep disorders reduce substance dependence? Drugs 69(Suppl 2):65–75
47. Friedmann PD, Herman DS, Freedman S, Lemon SC, Ramsey S, Stein MD (2003) Treatment of sleep disturbance in alcohol recovery: a national survey of addiction medicine physicians. J Addict Dis 22(2):91–103
48. Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA (2008) A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. Alcohol Clin Exp Res 32:1429–1438
49. Gillin JC, Smith TL, Irwin M, Kripke DF, Brown S, Schuckit M (1990) Short REM latency in primary alcoholic patients with secondary depression. Am J Psychiatry 147:106–109
50. Moeller FG, Gillin JC, Irwin M, Golshan S, Kripke DF, Schuckit M (1993) A comparison of sleep EEGs in patients with primary major depression and major depression secondary to alcoholism. J Affect Disord 27(1):39–42
51. Clark CP, Gillin JC, Golshan S, Demodena A, Smith TL, Danowski S, Irwin M, Schuckit M (1999) Polysomnography and depressive symptoms in primary alcoholics with and without a lifetime diagnosis of secondary depression and in patients with primary major depression. J Affect Dis 52(1–3):177–185
52. Gann H, van Calker D, Feige B, Cloot O, Bruck R, Berger M, Riemann D (2004) Polysomnographic comparison between patients with primary alcohol dependency during subacute withdrawal and patients with a major depression. Eur Arch Psychiatry Clin Neurosci 254(4):263–271
53. Gillin JC, Smith TL, Irwin M, Butters N, Demodena A, Schuckit M (1994) Increased pressure for rapid eye movement sleep at time of hospital admission predicts relapse in nondepressed patients with primary alcoholism at 3-month follow-up. Arch Gen Psychiatry 51:189–197
54. Gann H, Feige B, Hohagen F, van Calker D, Geiss D, Dieter R (2001) Sleep and the cholinergic rapid eye movement sleep induction test in patients with primary alcohol dependence. Biol Psychiatry 50(5):383–390
55. Feige B, Scaal S, Hornyak M, Gann H, Riemann D (2007) Sleep electroencephalographic spectral power after withdrawal from alcohol in alcohol-dependent patients. Alcohol Clin Exp Res 31(1):19–27
56. Brower KJ, Hall JM (2001) Effects of age and alcoholism on sleep: a controlled study. J Stud Alcohol 62(3):335–343