Sleep Deprivation as a Probe of Homeostatic Sleep Regulation in Primary Alcoholics

Michael Irwin, J. Christian Gillin, Jeff Dang, Jeffrey Weissman, Evie Phillips, and Cindy L. Ehlers

Background: Alcoholic patients show prominent disturbances of sleep electroencephalograms (EEGs) with a marked loss of slow wave sleep that is even more profound in African American alcoholics as compared to European Americans. Using partial sleep deprivation, this study examined the extent to which abnormal sleep is reversible in alcoholic subjects.

Methods: In a sample stratified on ethnicity, polysomnographic and spectral sleep EEG measures were compared in male primary alcoholic patients (n=46) and age-matched comparison controls (n=32) at baseline--and recovery sleep following a night of partial sleep deprivation.

Results: As compared to controls, alcoholic patients showed a loss of slow wave sleep and more spectral power in beta frequencies. Following sleep deprivation, slow wave sleep and delta power differentially changed between the groups. European American controls showed increases of slow wave sleep that were more robust than responses found in African American controls, whereas both alcoholic groups failed to show increases of slow wave sleep from baseline to recovery. Spectral EEG analyses revealed similar results; sleep deprivation induced significant increases of delta power during NREM-1 in the controls, but not in the alcoholics.

Conclusions: Alcohol dependence compromises the augmentation of slow wave sleep and delta power seen in healthy adults following sleep deprivation. The differential effect of alcoholism on sleep stage physiology suggests a defect in the regulation or plasticity of slow wave sleep with implications for theories linking sleep depth to morbidity and outcome in alcoholics. Biol Psychiatry 2002;51:632–641 © 2002 Society of Biological Psychiatry

Key Words: Sleep, alcohol dependence, sleep deprivation, spectral analyses, ethnicity

Introduction

Considerable evidence indicates that sleep is abnormal in alcohol dependence. Alcoholic patients commonly report sleep difficulties and this problem is one of the most refractory symptoms to resolve over the course of alcoholic recovery (Zarcone 1979; Brower et al 1998; Drummond et al 1998; Gillin et al 1994). EEG sleep studies reveal a reduction of total sleep time, fragmentation of sleep, loss of Stages 3 & 4 (delta) sleep, and less robust changes in rapid eye movement (REM) sleep in alcoholics as compared with age-matched controls (Allen et al 1971; Snyder et al 1985; Johnson et al 1970; Williams et al 1981). Age and severity of alcohol dependence correlate with abnormal sleep in alcoholics (Gillin et al 1990a). Furthermore, recent data indicate that ethnicity is a critical factor in mediating the effects of alcohol dependence on sleep; African American ethnicity and alcohol dependence interact to produce a more profound loss of delta sleep as measured by polysomnographic and spectral sleep analyses than that found in European American alcoholics (Irwin et al 2000b). The severity of sleep disturbance and the extent of sleep abnormalities in alcoholics contrasts with the limited effort to understand sleep regulatory processes in these patients. Whereas studies of depressed patients have probed sleep regulation using naturalistic strategies such as sleep deprivation (Reynolds et al 1987; Buysse et al 1988), there are no data to our knowledge that have examined the effects of sleep deprivation on EEG sleep in alcoholics.

In healthy adults, sleep deprivation leads to a selective enhancement of the slow wave sleep fraction of non-REM sleep with robust increases in stage 4 sleep (Borbély et al 1981) and delta power (Armitage 1995). Indeed, the generality of this finding across various species (e.g., human, monkey, cat, and rat) has prompted the hypothesis of a specific relationship between prior waking, sleep capacity, and slow wave sleep in which both neuronal and...
humoral mechanisms (i.e., the accumulation of possible sleep promoting substances such as cytokines) regulate sleep (Borbély 1982; Krueger et al 1993). In contrast, in depressed patients where macro and micro-architectural analyses support the notion of delta sleep deficits as compared to controls, depressives show a diminished augmentation of delta sleep following sleep loss (Reynolds et al 1987; Buysse et al 1988). Whether alcoholics show similar impairments in the plasticity of slow wave sleep in concert with delta sleep deficits at rest are not known.

This study examined the effects of partial sleep deprivation as a probe on sleep-stage physiology in controls, contrasted with alcoholic patients. The following hypotheses were tested: a) alcoholics will show macro- and micro-architectural evidence of a “decay” of delta sleep as compared to controls at baseline; b) sleep deprivation, as a naturalistic probe of sleep regulatory processes, will reveal a loss of delta sleep plasticity in alcoholics as compared to controls.

**Methods and Materials**

**Participants**

A total of 99 men fulfilled screening eligibility criteria, gave informed consent and entered the research protocol. Of this total, 6 participants were excluded due to medical history and/or medication use, 2 controls and 4 alcoholics were dropped due to positive toxin screens during the sleep protocol or within the two week period prior to assessment, 7 subjects were excluded due to medication use, 2 controls and 4 alcoholics were dropped due to positive toxin screens during the sleep protocol or within the two week period prior to assessment, 7 subjects were excluded due to medical history and/or medication use, 2 controls and 4 alcoholics were dropped due to positive toxin screens during the sleep protocol or within the two week period prior to assessment, 7 subjects were excluded due to medical history and/or medication use, 2 controls and 4 alcoholics were dropped due to positive toxin screens during the sleep protocol or within the two week period prior to assessment, 7 subjects were excluded due to medical history and/or medication use, 2 controls and 4 alcoholics were dropped due to positive 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Sleep records were visually scored according to the criteria of Rechtschaffen and Kales (Rechtschaffen et al. 1968). Data from each 30-second epoch were entered into a computer program that tallies the summary statistics for each subject. Sleep onset was defined as the first minute of stage 2 or rapid eye movement (REM) sleep followed by at least eight minutes of sleep in the next nine minutes. A REM period was defined by not less than three consecutive minutes of REM sleep. Sleep efficiency was the ratio of total sleep time to the time in bed, multiplied by 100. Sleep architecture was defined as the duration of time spent asleep in non-REM (NREM) sleep. Stages 1 through 4, REM density was an estimate of the number of eye movements per minute of REM sleep, scored on a scale of 0 to 4 per 30-second epoch but expressed on a scale of 0 to 8 per minute. Sleep research technicans were regularly tested on scoring reliability and high standards were maintained: sleep latency (r = .96), REM latency (r = .99), REM density (r = .91), amounts of stages 3 and 4 (r = .85), and total sleep time (r = .99).

To quantify EEG frequency characteristics, the sleep EEG, from sleep onset to good morning time, was digitized (128 Hz) and power spectra for 4 sec epochs were then determined for a .25-64.0 Hz range. The transformed data were then further compressed into 6 frequency bands (.75-4.5 Hz [Delta], 4.5-7.5 Hz [Theta], 7.5-11 Hz [Alpha], 11-12.5 Hz [Slow spindle frequencies], 12.5-16 Hz [fast spindle frequencies], 16-40 Hz [Beta]) and mean power density (microvolts²/octave), and peak frequency (Hz) was calculated for each band as previously described (Ehlers et al. 1989; Ehlers et al. 1998; Irwin, et al. 2000b). Power in each frequency band was determined for the following five epochs after good night time (1) first NREM period; (2) first REM period; (3) second NREM period; (4) second REM period; and (5) the time from good night time to good morning time (whole night). Of the total sample (n = 78), 71 subjects aged 27-65 years (African American n = 35 vs. European Americans, n = 36; alcohol dependent subjects n = 46 vs. controls n = 25) had electronic EEG data suitable for EEG spectral analyses.

**LIVER FUNCTION TESTS.** Values of liver function tests were obtained and measured by previously described methods (Irwin et al. 1990).

**Statistical Analyses**

Two way analyses of variance (ANOVA) were used to evaluate main effects of diagnosis (alcohol dependence, control), and ethnicity (European American, African-American) on the dependent variables (i.e., age, education, depressive symptoms, alcohol consumption history, and liver function tests). In view of the multivariate experimental approach in which multiple dependent sleep variables were collected simultaneously in a repeated

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**Table 1. Age, Education, Severity of Depressive Symptoms, and Alcohol Consumption Histories in Control and Alcoholic Groups**

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
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<tbody>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 14)</td>
<td>(n = 24)</td>
<td>(n = 22)</td>
<td>(n = 24)</td>
<td>(n = 22)</td>
<td>(n = 24)</td>
<td>(n = 22)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.6 (11.8)</td>
<td>39.1 (7.5)</td>
<td>43.3 (11.0)</td>
<td>42.9 (7.0)</td>
<td>52.3 (11.0)</td>
<td>51.5 (6.7)</td>
<td>51.8 (12.2)</td>
<td>51.3 (7.6)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.0 (1.5)</td>
<td>14.3 (1.5)</td>
<td>12.8 (1.7)</td>
<td>13.0 (1.0)</td>
<td>11.6 (1.5)</td>
<td>12.0 (1.0)</td>
<td>13.0 (1.5)</td>
<td>12.4 (1.0)</td>
</tr>
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<td>Depressive symptoms (HRSD scores)</td>
<td>1.6 (1.8)</td>
<td>1.3 (1.9)</td>
<td>1.8 (2.0)</td>
<td>1.0 (1.5)</td>
<td>1.6 (1.8)</td>
<td>1.3 (1.9)</td>
<td>1.8 (2.0)</td>
<td>1.0 (1.5)</td>
</tr>
<tr>
<td>Alcohol consumption (last 3 months)</td>
<td>8.4 (8.0)</td>
<td>4.3 (7.7)</td>
<td>27.3 (4.4)</td>
<td>26.9 (5.5)</td>
<td>8.4 (8.0)</td>
<td>4.3 (7.7)</td>
<td>27.3 (4.4)</td>
<td>26.9 (5.5)</td>
</tr>
<tr>
<td>Drinking days/month</td>
<td>1.4 (1.0)</td>
<td>1.1 (9.0)</td>
<td>13.1 (5.8)</td>
<td>15.3 (12.0)</td>
<td>1.4 (1.0)</td>
<td>1.1 (9.0)</td>
<td>13.1 (5.8)</td>
<td>15.3 (12.0)</td>
</tr>
<tr>
<td>Days since last drink</td>
<td>45.8 (116.3)</td>
<td>110.6 (167.1)</td>
<td>22.4 (12.0)</td>
<td>23.0 (12.2)</td>
<td>45.8 (116.3)</td>
<td>110.6 (167.1)</td>
<td>22.4 (12.0)</td>
<td>23.0 (12.2)</td>
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HRSD, Hamilton Rating Scale—Depression.
measures design, multivariate ANOVAs (MANOVA) were employed as a first step in the analyses of the sleep data. Within each of the three domains of sleep including sleep continuity (total sleep time, sleep latency, and sleep efficiency), sleep architecture (duration of Stages 1-4 and REM sleep), and REM measures (REM latency, density and REM duration), main effects of diagnosis, ethnicity, night and their interaction were tested by MANOVA covarying for age, education, and depressive symptoms. These covariates were selected because the groups differed in these variables and/or the covariate has been found to correlate with sleep disturbance. For those sleep domains in which main- and/or interaction effects were found by the MANCOVA, subsequent three-way (ANCOVAs) were performed on the individual sleep EEG variables and spectral EEG results. For the spectral EEG results in which only a subset of the total sample was available for analyses, statistical power was limited. Thus, planned comparisons were also used to test group differences in the spectral analytic measures at baseline- or recovery nights, when main effects by ANOVA and/or a priori predictions generated by analyses of sleep EEG data supported this exploratory statistical approach.

**Results**

**Demographic and Clinical Characteristics**

Table 1 summarizes the demographic characteristics, severity of depressive symptoms and alcohol consumption histories in the control- and alcoholic groups. The alcoholic and control groups were similar in age, whereas the African-American groups were younger than the European American groups. The alcoholic groups were similar in age, whereas the European American and African American groups differed in these variables and/or the covariate has been found to correlate with sleep disturbance. The alcoholic and control groups were similar in age, whereas the European American and African American groups differed in these variables and/or the covariate has been found to correlate with sleep disturbance. The alcoholic and control groups were similar in age, whereas the European American and African American groups differed in these variables and/or the covariate has been found to correlate with sleep disturbance. The alcoholic and control groups were similar in age, whereas the European American and African American groups differed in these variables and/or the covariate has been found to correlate with sleep disturbance. The alcoholic and control groups were similar in age, whereas the European American and African American groups differed in these variables and/or the covariate has been found to correlate with sleep disturbance. The alcoholic and control groups were similar in age, whereas the European American and African American groups differed in these variables and/or the covariate has been found to correlate with sleep disturbance.

Table 2 presents mean values of laboratory tests of liver function in the control and alcoholic groups. In this sample of medically healthy, detoxified alcoholics, only values of aspartate aminotransferase (SGPT) (F(1,74)=4.9, p<.05) and alkaline phosphatase (F(1,74)=4.6, p<.05) were elevated in the alcoholic groups as compared to the controls, whereas other measures of liver function including alanine aminotransferase (SGOT) and bilirubin (direct and total) were statistically indistinguishable between the four groups. Importantly, mean values for all of the liver injury tests were within the normal range for the four groups. The EEG sleep measures in the four groups who were sampled across the two nights. For the sleep

**Egg Sleep**

Table 3 shows the EEG sleep measures in the four groups who were sampled across the two nights. For the sleep...
Table 3. Sleep EEG Measures in the Control and Alcoholic Groups

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
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<th>Alcoholic Patients</th>
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<tr>
<td></td>
<td>European Americans</td>
<td>Africa Americans</td>
<td>European Americans</td>
<td>Africa Americans</td>
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<tr>
<td></td>
<td>(n = 18) Mean (SD)</td>
<td>(n = 14) Mean (SD)</td>
<td>(n = 24) Mean (SD)</td>
<td>(n = 22) Mean (SD)</td>
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<tr>
<td>Sleep continuity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total sleep time (min)</td>
<td>33.72 (65.2)</td>
<td>38.50 (45.9)</td>
<td>34.88 (66.1)</td>
<td>37.33 (52.5)</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>26.43 (33.0)</td>
<td>11.00 (12.2)</td>
<td>10.91 (9.9)</td>
<td>9.60 (8.4)</td>
</tr>
<tr>
<td>Sleep architecture</td>
<td></td>
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<tr>
<td>Stage 1 (min)</td>
<td>27.0 (11.5)</td>
<td>21.1 (12.0)</td>
<td>22.4 (13.1)</td>
<td>23.0 (13.2)</td>
</tr>
<tr>
<td>Stage 2 (min)</td>
<td>216.6 (59.5)</td>
<td>239.3 (38.8)</td>
<td>245.4 (48.2)</td>
<td>250.8 (56.9)</td>
</tr>
<tr>
<td>Stage 3 (min)</td>
<td>64.1 (8.0)</td>
<td>62.4 (8.8)</td>
<td>70.7 (7.3)</td>
<td>66.6 (10.5)</td>
</tr>
<tr>
<td>Stage 4 (min)a</td>
<td>3.9 (7.4)</td>
<td>11.6 (16.6)</td>
<td>3.5 (6.0)</td>
<td>4.7 (10.1)</td>
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<tr>
<td>Delta (min)b</td>
<td>1.2 (2.5)</td>
<td>3.0 (4.4)</td>
<td>.98 (1.6)</td>
<td>1.4 (3.0)</td>
</tr>
<tr>
<td>REM (min)/%</td>
<td>67.9 (23.6)</td>
<td>81.0 (22.4)</td>
<td>60.0 (25.8)</td>
<td>73.4 (24.0)</td>
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<tr>
<td>REM Measures</td>
<td></td>
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<tr>
<td>Latency (corrected)</td>
<td>77.6 (47.6)</td>
<td>70.9 (36.1)</td>
<td>74.7 (28.6)</td>
<td>68.8 (22.4)</td>
</tr>
<tr>
<td>Density</td>
<td>1.7 (1.0)</td>
<td>1.6 (7.3)</td>
<td>1.3 (3.5)</td>
<td>1.4 (1.0)</td>
</tr>
<tr>
<td>Duration (1st period)</td>
<td>22.7 (12.4)</td>
<td>19.9 (9.5)</td>
<td>14.0 (7.5)</td>
<td>18.1 (9.1)</td>
</tr>
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REM, rapid eye movement.

*a p < .05 group x time interaction.

continuity variables (total sleep time, sleep efficiency, and sleep latency), the MANCOVA found significant effects for age (F(3,69) = 5.3, p < .01) and depressive symptoms (F(3,69) = 3.4, p < .05), but there no main effects for alcohol dependence, ethnicity, night, or their interactions. Thus, subsequent three-way ANCOVAs were not performed on the individual sleep continuity measures.

For the sleep architecture domain (duration of Stages 1-4 sleep and REM sleep), multivariate analyses showed main effects for age (F(5,67) = 3.0, p < .05), diagnosis (F(5,67) = 4.0, p < .01), and ethnicity (F(5,67) = 2.9, p < .05). In addition, the MANCOVA identified a trend for the interaction of alcohol dependence x night (F(5,67) = 2.1, p = .07) and ethnicity x night (F(5,67) = 2.2, p = .06).

In view of these significant main effects on the sleep architecture domain, subsequent ANCOVAs were performed on the duration and percentage of Stages 1-4, delta, and REM sleep. Analyses of the sleep architecture variables revealed main effects of alcohol dependence on duration and percentage of Stage 1 (F(1,71) = 6.5, p < .01; F(1,71) = 6.5, p < .01), percentage of Stage 2 (F(1,71) = 3.9, p < .05), duration and percentage of Stage 3 (F(1,71) = 4.1, p < .05; F(1,71) = 5.5, p < .05), delta (F(1,71) = 3.2, p = .08; F(1,71) = 4.2, p < .05) and REM sleep (F(1,71) = 8.2, p < .01; F(1,71) = 11.9, p < .001). The alcoholic groups showed increases in Stage 1 and REM sleep and decreases of Stage 2-, Stage 3- and delta sleep as compared to the controls. In addition, significant main effects of ethnicity were found for duration and percentage of Stage 2 (F(1,71) = 5.0, p < .05; F(1,71) = 11.3, p < .001), Stage 3- (F(1,71) = 8.8, p < .01; F(1,71) = 6.5, p < .01), and duration and percentage of delta sleep (F(1,71) = 7.8, p < .01; F(1,71) = 5.7, p < .05) in which European American groups showed greater amounts of Stage 3- and delta sleep as compared to African Americans.

Interactions between alcohol dependence, ethnicity and night were also found. There were alcohol dependence x night and ethnicity x night interactions found for measures of Stage 4 sleep duration (F(1,71) = 7.9, p < .01; F(1,71) = 8.8, p < .01). Finally, there was a differential change of slow wave sleep from baseline to recovery nights across the four groups; significant alcohol dependence x ethnicity x night interactions were found for duration and percentage of Stage 4 sleep (F(1,71) = 4.6, p < .05; F(1,71) = 3.4, p = .06; Figure 1) European American controls showed a more robust increase of Stage 4 from baseline to recovery night as compared to African Americans, whereas Stage 4 sleep were unchanged or decreased in the two alcoholic groups. A similar pattern of results was also found for duration of delta sleep, although the interaction between alcohol dependence x ethnicity x
night did not reach statistical significance ($F(1,71)=3.2$, $p=.07$).

For the REM sleep measures (REM latency, REM density, and REM duration), the MANCOVA showed a significant effect for age ($F(5,67)=5.0$, $p<.01$), but no main effects for alcohol dependence, ethnicity, night, or their interaction.

**EEG Spectral Analyses**

Spectral analyses of the sleep EEG could be accomplished in 71 subjects, and alcoholics were found to have several spectral indicators of disturbed sleep both on their baseline sleep night as well as on their night of recovery from sleep deprivation. Significant main effects for alcohol dependence were seen for both NREM and REM sleep. For example, alcoholics as a group were found to have more beta power in the beta frequency range over the whole night as well as on their night of recovery from sleep deprivation. Significant main effects for alcohol dependence, ethnicity, night, or their interaction.

Table 4. Electroencephalogram Beta Activity (16–40 Hz) in Recovery Sleep in Control and Alcoholic Groups

<table>
<thead>
<tr>
<th></th>
<th>1st NREM</th>
<th>1st REM</th>
<th>2nd NREM</th>
<th>2nd REM</th>
<th>Whole Night</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
</tr>
<tr>
<td>Alcoholic Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n=46$</td>
<td>4.6</td>
<td>(.3)</td>
<td>8.1</td>
<td>(.7)</td>
<td>4.7</td>
</tr>
<tr>
<td>Control Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n=23$</td>
<td>3.7</td>
<td>(.4)</td>
<td>5.0</td>
<td>(.9)</td>
<td>4.0</td>
</tr>
</tbody>
</table>

NREM, non-rapid eye movement.

Figure 1. Effects of partial night sleep deprivation on duration of Stage 4 sleep in control- and alcoholic subjects stratified by European American and African-American ethnicity. A significant alcohol dependence x ethnicity x night interaction was found ($F(1,71)=4.6$, $p<.05$) in which European American controls showed a more robust increase of Stage 4 from baseline to recovery night as compared to African Americans, whereas Stage 4 sleep was unchanged or decreased in the two alcoholic groups.
later in the night, or may reflect a difference in the architecture of REM sleep.

Discussion

Electrophysiological measures in sleeping and waking have been demonstrated to be good indices of risk for alcoholism. Many, although not all (Emmerson et al 1987), studies in alcoholics have found that their resting, wakeful EEG was deficient in alpha activity, was of lower voltage, and tended to contain theta and excessive fast activity (Naitoh 1973; Kaplan et al 1985; Spehr et al 1985; Krauss et al 1991; Pollock et al 1992). It has been suggested that EEG fast frequency activity may also be higher in subjects with alcoholic relatives (Gabrielli et al 1982; Ehlers et al 1990) and related to risk for relapse in abstinent alcoholics (Bauer 1994, 2001; Winterer et al 1998). No previous studies have evaluated EEG fast activity during sleep in alcoholics. In the present study an excess of EEG fast activity was found in alcoholics during their sleep over the whole night and specifically during REM sleep. In a previous study of a large sample of normal adults, it was demonstrated that spectral power distributions during waking were substantially correlated to those seen during REM sleep (Ehlers et al 1998). Taken together, these data suggest that EEG fast activity may be a spectral signature of alcoholics both during their sleep and waking activity.

The present study also replicates prior sleep EEG studies in alcoholics (Gillin et al 1990a; Gillin et al 1994; Irwin et al 2000b). As compared to controls, alcoholics are more likely show alterations in sleep architecture measures with a relative loss of slow wave sleep and increases in the duration of REM sleep. Moreover, consistent with our recent findings, African-American alcoholics show the greatest loss in measures of slow wave sleep as compared to the other groups (Irwin et al 2000b). Finally, a relatively new measure has been developed to estimate the distribution of delta power during the first part of the night, namely delta ratio or the amount of power in the first NREM period divided by the amount of power in the second (NREM-1/NREM-2). In the present study, not only do alcoholics show shifts in power and in their delta patterns, but the distribution of delta power over the night is altered particularly during the recovery night. Delta ratio was found to correlate with poor outcome in a study of depressed patients discontinued from long-term maintenance treatment for depression (Kupfer et al 1990).

The main aim of our study was to use sleep deprivation and evaluate the extent to which alcoholism-related “decay” of slow wave sleep is reversible. Compared with controls, alcoholic patients failed to show increases of slow wave sleep following sleep deprivation. Differences in homeostatic regulation of slow wave, Stage 4 sleep...
were particularly striking in the European Americans; controls showed nearly two-fold increases of Stage 4 sleep whereas alcoholics had recovery levels of Stage 4 sleep that decreased. Similar findings were found in the comparison of the African-American control and alcoholic groups; although African American controls showed less robust increases of Stage 4 sleep than European Americans. These data, taken together with macro- and micro-architectural evidence of delta sleep loss in alcoholics, further implicate abnormalities of delta sleep and its regulation in alcohol dependence. Loss of slow wave sleep is a robust characteristic of alcoholic sleep disturbance that sleep deprivation did not ameliorate. These are the first data, to our knowledge, that reveal a loss of plasticity in the regulation of slow wave sleep in alcoholic subjects. Decreases of slow wave sleep are major effects of healthy aging and are also associated with major depression. Using total sleep deprivation, Reynolds et al (1987) found that depression compromises the augmentation of slow wave sleep seen in healthy elderly. However, even in elderly depressed subjects, there was a significant consolidation of sleep with increases in slow wave sleep after sleep deprivation. In contrast, alcoholics show a complete lack of reversal of slow wave sleep following partial sleep deprivation. Taken together, these findings suggest that there is an impairment of non-REM sleep generating mechanisms in alcoholics that can not be ameliorated by sleep homeostatic factors.

The results of this sleep deprivation experiment are relevant for models of sleep regulation. For example, the “two process” model proposes that sleep is regulated by two factors: “process S”, a homeostatic, sleep-dependent factor that increases in strength with the duration of prior wakefulness and that is expressed in slow wave sleep activity; and “process C” a circadian sleep factor expressed in REM sleep propensity (Borbély 1982; Borbély et al 1982). The present data suggest that the accumulation of “process S” is diminished or inhibited in alcohol dependence, which in turn leads to lower amounts of delta sleep and increased amount of REM sleep. Even when the duration of wakefulness is prolonged, “process S” does not appear to be augmented in the alcoholic subjects. The failure to accumulate “process S” might contribute to the persistent severity of sleep disturbances in recovering alcoholics, and identify those recovering alcoholics whose sleep complaints fail to resolve and who may be at increased risk of relapse (Brower et al 1998; Gillen et al 1994; Drummond et al 1998). An alternative explanation for the lack of delta rebound, which is separate from a possible failure to generate “process S”, suggest that the physiological mechanisms responsible for the generation of delta waves has been damaged as discussed below. Nevertheless, because sleep depth is hypothesized to contribute to the maintenance of health and the homeostatic regulation of the autonomic, neuroendocrine and immune systems, (Horne 1988; Dinges et al 1995) studies are underway to evaluate whether alcoholics are at increased risk for physiological abnormalities in association with disordered sleep.

The neurobiological mechanisms that underlie the deficit in the generation of slow wave sleep in association with chronic alcohol exposure remain largely unknown. Steriade and colleagues have shown that during slow-wave sleep (SWS), neocortical neurons display long-lasting periods of silence, whereas they are tonically active and discharge at higher rates during waking and sleep with rapid eye movements (REMs) (Timofeev et al 2001). It is possible that chronic alcohol use interferes with the process of neuronal hyperpolarization that is mediated by a mixture of K⁺ currents and “disfacilitation” processes that together induce periods of silence (Timofeev et al 2001). Indeed, clinical studies support the notion that chronic ethanol exposure causes direct toxic or neuro-adaptive changes in the brain areas that are involved in the regulation of sleep. For instance cerebral atrophy and slow wave sleep have been correlated in abstinent chronic alcoholics (Ishihashi et al 1987). Other work suggests that the complex cytokine network is one system that might contribute to the declines of sleep depth in alcoholics; African American alcoholics have a profound loss of delta sleep (Irwin et al 2000b) that is coupled with alterations in the nocturnal expression of the pro-inflammatory cytokines and a relative shift from T helper 1 to T helper 2 cytokine production across the night as compared to responses in European American alcoholics (Irwin et al 2000a). Animal studies indicate that such cytokine abnormalities can interfere with the depth of sleep (Krueger et al 1994). Regardless of the possible mechanisms, we conclude that alcoholic subjects show abnormal sleep physiology. The amount and plasticity of slow wave sleep and delta power is severely diminished in alcoholics. In contrast, the amounts and maintenance of sleep can be augmented in alcoholics by restricting time in bed.

Limitations of this study include small sample size and gender. Thus, the findings may not apply to other community samples or to female alcoholic patients. In addition, the sleep protocol focused on the effect of sleep loss during the early part of the night, a time of high propensity for slow wave sleep and a low propensity for REM sleep. The interplay between timing of the sleep deprivation, total sleep deprivation and respective effects on non-REM and REM sleep recovery requires further study. Despite these limitations, this report represents an important step in an ongoing investigation to determine the mechanisms underlying disturbed sleep associated with substance use disorders in this understudied ethnic group.
References


