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Cardiac autonomic function during sleep: effects of alcohol dependence and evidence of partial recovery with abstinence

Massimiliano de Zambotti, PhD[1], **Adrian R. Willoughby, PhD**[1], **Fiona C. Baker, PhD**[1,2], **David S. Sugarbaker, MPH**[1], and **Ian M. Colrain, PhD**[1,3,*]

[1]Center for Health Sciences, SRI International, Menlo Park, CA, USA

[2]Brain Function Research Group, School of Physiology, University of the Witwatersrand, Johannesburg, South Africa

[3]Melbourne School of Psychological Sciences, University of Melbourne, Parkville, Victoria, Australia

Abstract

Chronic alcoholism is associated with the development of cardiac and peripheral autonomic nervous system (ANS) pathology. The aim of the present study was to evaluate the extent to which recovery in ANS function could be demonstrated over the first 4 months of abstinence. Fifteen alcoholics (7 women) were studied on three occasions: within a month of detoxification, at approximately 2 months post-detox, and at 4 months post-detox. Thirteen control subjects (6 women) were also studied on three occasions with inter-study intervals matching those of the alcoholics. Six alcoholics relapsed, 48.7 ± 27.9 days following the initial PSG session. ANS function was assessed in the first part of stable non-rapid eye movement sleep. Frequency-domain power spectral analysis of heart rate variability (HRV) produced variables including: heart rate (HR), total power (TP; an index representing total HR variability), High Frequency power (HF_a; an index reflecting cardiac vagal modulation), HF proportion of total power (HF_{prop} sympathovagal balance), and HF peak frequency (HF_{pf}; an index reflecting respiration rate). Overall, high total and high frequency variability and low sympathovagal balance and myocardial contractility are considered as desired conditions to promote cardiovascular health. At initial assessment, alcoholics had a higher HR ($p < 0.001$) and respiratory rate ($p < 0.01$), and lower vagal activity (HF_a; $p < 0.01$) than controls. Alcoholics showed evidence of recovery in HR ($p = 0.039$) and HF_a ($p = 0.031$) with 4 months of abstinence. Alcoholics with higher TP at the initial visit showed a greater improvement in TP from the initial to the 4-month follow-up session ($r = 0.75$, $p < 0.05$). Alcoholics showed substantial recovery in HR and vagal modulation of HRV with 4 months of abstinence, with evidence that the extent of recovery in HRV may be partially

*Corresponding author: Ian M. Colrain SRI International 333 Ravenswood Avenue Menlo Park, CA 94025 **Telephone:** +1 650 859 3915 **Fax:** +1 650 859 2743 ian.colrain@sri.com.

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determined by the extent of alcohol dependence-related insult to the cardiac ANS system. These data support other studies showing recovery in a number of ANS, central nervous system, and behavioral domains with abstinence, even in those with long-term dependence.

Keywords

recovery; alcoholism; heart rate variability; sleep; autonomic nervous system; abstinence

Introduction

Alcoholism is strongly associated with chronic sleep disturbances (Brower & Perron, 2010); insomnia (for a review see Arnedt, Conroy, & Brower, 2007) is the most common complaint and persists or even worsens during both acute withdrawal from alcohol and longer-term abstinence (Brower, 2003; Currie, Clark, Rimac, & Mahlotra, 2003). Polysomnographic (PSG) measures in sober alcoholics indicate suppressed slow wave activity during the night (Roehrs & Roth, 2001), consistent with results from electroencephalographic (EEG) studies in abstinent alcoholics showing alterations in both nocturnal and diurnal brain activity, primarily a reduction in delta and theta power over the frontal regions (Colrain, Turlington, & Baker, 2009; Coutin-Churchman, Moreno, Añez, & Vergara, 2006).

Cardiovascular (CV) disease is one of the most common risk factors associated with alcoholism (Rehm, 2011). The CV system is regulated by the sympathetic and parasympathetic branches of the autonomic nervous system (ANS), centrally located in the medulla oblongata in the lower brainstem. Classical tests have demonstrated impaired autonomic nerve function in recently detoxified alcoholics (Barter & Tanner, 1987; Duncan, Johnson, Lambie, & Whiteside, 1980; Johnson & Robinson, 1988; Matikainen, Juntunen, & Salmi, 1986; Miralles, Espadaler, Navarro, & Rubiés-Prat, 1995; Monforte et al., 1995), with higher likelihood of serious deficits such as autonomic neuropathies with more severe alcohol dependence (Monforte et al., 1995; Rechlin, Orbes, Weis, & Kaschka, 1996; Villalta, Estruch, Antúnez, Valls, & Urbano-Márquez, 1989). Despite these findings, several studies have demonstrated improvements in tests of ANS function during wakefulness following prolonged periods of abstinence (Hirsch, Bishop, & York, 1993; Tan, Johnson, Lambie, & Whiteside, 1984; Villalta et al., 1989; Weise, Müller, Kreel, Kielstein, & Koch, 1985) including possible recovery from neuropathy (Villalta et al., 1989).

ANS control of the heart can be assessed noninvasively by measuring heart rate variability (HRV). Several approaches have been used for the HRV analysis. The simplest method is probably the time domain approach; it is based on the calculation of the normal-to-normal (NN) inter-beat-intervals (IBIs), i.e., intervals between adjacent R waves, recorded from the ECG signal over standard short-term (5 min) and long-term (24 h) periods. It allows the derivation of several indices reflecting total variability (e.g., the standard deviation of the NN intervals [SDNN] which reflect all the components responsible for the HRV in a defined period), as well as short-term high frequency variability (e.g., the square root of the mean squared differences of successive NN intervals [RMSSD]). One of the most commonly used approaches to analyze the HRV, most suitable for short-term recordings (from 2 to 5 min), is

the frequency domain method; it usually applies a Fast Fourier Transform (FFT) on the IBIs series and decomposes the variance of the total heart period in specific frequency bands. The variation in the high frequency activity (HF; 0.15–0.40 Hz) is considered a reliable index of vagal modulation of the sinoatrial node. The oscillation in the low frequency range (LF; 0.04–0.15 Hz) is considered a mixture of sympathetic and vagal activity, whereas the total power (TP; 0.00–0.40 Hz) reflects the total variance in the heart rate pattern, according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). Disruption in normal HRV patterns, i.e., suppression of both total HRV and HF-HRV and elevated LF-HRV, is associated with a number of pathological (e.g., immune dysfunction, inflammation) and psychological conditions (e.g., depression, anxiety) and is typically used to assess the relationship between changes in the sympathetic or parasympathetic systems and CV problems and disease (Thayer, Yamamoto, & Brosschot, 2010).

Several studies have provided evidence of a reduction in HRV, particularly in the vagal-related indices, in abstinent chronic alcoholics during daytime electrocardiographic (ECG) recordings (for a review, please see Karpyak, Romanowicz, Schmidt, Lewis, & Bostwick, 2014; Quintana, McGregor, Guastella, Malhi, & Kemp, 2013). HRV has also been suggested as a potential marker of relapse in alcohol-dependent patients, showing greater HF-HRV reactivity to stress-primed alcohol cues in relapsing patients compared to patients who did not relapse (Garland, Franken, & Howard, 2012).

Studying HRV during sleep offers the advantage of stable periods to evaluate ANS functioning free from wake-related external influences (Brandenberger, Buchheit, Ehrhart, Simon, & Piquard, 2005; Orr, Elsenbruch, & Harnish, 2000). Previous studies investigating ANS activity during sleep in recently sober alcoholics (de Zambotti et al., 2014; Ganesha, Thirthalli, Muralidharan, Benegal, & Gangadhar, 2013; Irwin, Valladares, Motivala, Thayer, & Ehlers, 2006) show suppressed HRV in alcoholic patients consistent with findings from daytime studies. In addition, results suggested greater vagal HRV suppression (low HF component of HRV and RMSSD), especially at the beginning of the night (de Zambotti et al., 2014; Irwin, Valladares, Motivala, Thayer, & Ehlers, 2006), and a greater increase in HRV over the course of the night (de Zambotti et al., 2014) in alcoholics compared to controls, suggesting a beneficial role of sleep on ANS function in alcoholism.

The largest differences between detoxified alcoholics and healthy controls in ANS functioning thus appear to be particularly pronounced at the beginning of the night; the same time that the differences in EEG power spectrum, melatonin, and cortisol secretions are most prominent (Armitage, Hoffmann, Conroy, Arnedt, & Brower, 2012; de Zambotti et al., 2014; Irwin et al., 2006). Difficulties in falling asleep have been reported as one of the leading causes of relapse in both short- and long-term abstinent alcoholic patients (Currie et al., 2003). Therefore, sleep onset, where cortical and cardiac functioning seems to be particularly compromised in alcoholics, may be a suitable period in which to investigate recovery during a prolonged period of sobriety in alcoholism.

To our knowledge, no studies have yet investigated recovery in ANS functioning during sleep across months of sobriety in alcoholism. The present study investigated

electrocardiographic (HRV) activity in recently detoxified alcoholic men and women during stable sleep, immediately after the sleep onset, after short (less than a month) and prolonged (2 and 4 months) periods of sobriety. Overall, we hypothesize a suppression of HRV at the initial assessment in alcoholics compared to controls, followed by a progressive improvement in HRV after 2 months and 4 months of sobriety in the alcoholics group, with no changes over time in control subjects. We also explored the relationship between ANS function at the initial assessment and changes in ANS activity at 2 and 4 months of sobriety compared to the initial status of the alcoholics.

Materials and methods

Participants

Fifteen recently detoxified alcoholic patients and 13 healthy controls participated in this study. Alcoholic patients were recruited from residential treatment centers and controls were recruited from advertisements placed in the local community. Full details of screening procedures are described in de Zambotti et al. (2014). Potential participants completed a structured alcohol history (Pfefferbaum, Rosenbloom, Cruzan, & Jernigan, 1988) and a structured clinical interview for DSM-IV-TR for Axis I DSM IV Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 1998). Alcoholic patients had to meet the DSM-IV-TR (American Psychiatric Association, 2000) criteria for alcohol dependence for at least 3 years and to be recently sober (less than 1 month since their last drink). Exclusion criteria for the alcoholics were: current use of psychoactive medication, severe current/past medical/psychiatric conditions (e.g., hypertension, cancer, major depression, and schizophrenia), withdrawal symptoms, and head injury with associated loss of consciousness for longer than 30 min. Of the sample, 3 alcoholics also met DSM-IV-TR criteria (American Psychiatric Association, 2000) for nicotine and/or cannabis dependence (60.0 ± 43.3 months since last meeting criteria) and/or 5 for cocaine and/or amphetamine dependence (174.0 ± 129.6 months since last meeting criteria) and/or 1 for Anxiety disorder NOS (84 months since last meeting criteria). Eight alcoholics met DSM-IV-TR criteria for current nicotine and/or cannabis dependence, 5 for cocaine and/or amphetamine dependence, and/or 8 for anxiety/depression-related disorders. Control participants were matched to the alcoholics by age and sex and did not meet the criteria for any Axis I psychopathology. Screening procedures also included a clinical polysomnography (PSG). None of the participants had obstructive sleep apnea (apnea-hypopnea index, AHI > 5) or severe periodic limb movements (PLMS; PLMS index > 10).

Demographic and clinical data are provided in Table 1. This study was approved by the Institutional Review Board at SRI International. All participants gave their written informed consent and received payment for their participation.

Procedure

Participants meeting eligibility criteria completed 4 PSG nights at the SRI International Human Sleep Laboratory (adaptation/clinical, initial, 2-month and 4-month follow-up). For alcoholics, after their adaptation/clinical night, the initial night was within a month of their last drink (23.7 ± 6.2 days), and the second and third nights were respectively at 2 months

(54.2 ± 7.9 days) and 4 months (111.1 ± 7.5 days) of sobriety. The time of the follow-up recordings relative to initial assessment for controls was matched to the intervals used for the alcoholic participants.

All participants completed adaptation and initial PSG nights. Five participants failed to complete the 2-month follow-up night. Three controls missed the appointment and 2 alcoholics relapsed. Five other participants failed to complete the 4-month follow-up night. One control participant decided to withdraw from the study and 4 further alcoholics relapsed.

The sample at the 2-month follow-up therefore consisted of 13 alcoholics and 10 controls, and at the 4-month follow-up consisted of 9 alcoholics and 12 controls. Overall, 100 nights were successfully completed: 48 for controls and 52 for alcoholics.

As expected in our sample, a large proportion of alcoholics failed to remain sober for the entire duration of the study. Forty percent of alcoholics (n = 6) relapsed 48.7 ± 27.9 days following the initial PSG session, in line with previous studies showing that almost 60% of patients relapse after commencing treatment (Brower, 2003).

Breath alcohol concentration was measured before each PSG night using a breathalyzer; all participants scored 0.0%.

PSG recording—The PSG montage included standard EEG, electromyogram (EMG), and electro-oculogram (EOG), to allow 30-s epoch sleep staging (wake, N1, N2, N3, rapid-eye-movement [REM] sleep), according to standard criteria (Iber, Ancoli-Israel, Chesson, & Stuart, 2007), as well as ECG in lead II Einthoven configuration, recorded using Compumedics Neuroscan SynAmps amplifiers (El Paso, TX, USA). EEG, EMG, and EOG signals were sampled at 1000 Hz; EEG and EOG were filtered at 0.3–30 Hz; EMG was filtered at 10–100 Hz; ECG signals were sampled at 256 Hz and off line-filtered at 0.3–70 Hz.

Analyses—The current study is part of a large project investigating the recovery in brain function across several months of sobriety in alcoholic patients using event-related potentials elicited by tones played during the night. For the current investigation, we restricted the window of analysis to the first part of stable N2 sleep after sleep onset and before any tones were played. Example windows selected for the analysis are shown in Fig. 1. The windows were selected according to the following rules: 1) consecutive 2-min windows were selected in stable N2 sleep free from arousals and sleep stage transitions; 2) once the tone started no further windows were selected; 3) to guarantee no biases in the length and time of the period analyzed (mainly driven by the fact that alcoholics have reduced N3 sleep and more fragmented sleep) we restricted to 5 the max number of 2-min windows that have been selected.

No significant differences ($p > 0.10$) were found in the number of selected 2-min epochs for the analyses (Table 1) (indicating no differences in the amount of time considered in the analyses), as well as the average start time of the selected epochs (indicating no differences in the between-epochs time), lights-out time and sleep onset time (indicating no confounding

due to the time of the night and time spent in bed prior to sleep) between groups at both initial and follow-ups (Mann-Whitney *U* tests) and within the recovery period in the two groups separately (Wilcoxon signed rank tests).

Frequency-domain HRV analysis of the ECG signal—Frequency-domain power spectrum analysis of HRV was performed on 2-min artifact-free windows of stable N2 sleep. IBIs were derived from the semi-automatic detection of R-wave peaks in the ECG using customized software (Sleep Research System, Melbourne School of Psychological Sciences, University of Melbourne, Australia). IBIs were re-sampled at 4 Hz and then detrended with a third-order polynomial filter to remove the slow non-stationary components before analysis. The power spectrum (0–0.5 Hz) was divided into 0.02-Hz bins. The frequency with the greatest power was identified in both the low frequency (LF; 0.03–0.15 Hz) and high frequency (HF; 0.15–0.40 Hz) bands. The absolute integrated power in arbitrary units was quantified for both LF and HF bands as the area between the first frequency bands on either side of the peak to fall to 50% of the peak value. The following cardiac-autonomic indices were calculated over 2-min windows: heart rate derived from the IBIs (HR; bpm), total power (TP, an index representing the total variability; ms^2), absolute HF power in the narrow band (HF_a, an index thought to reflect cardiac vagal modulation; arbitrary units, ms^2), HF proportion of total power (HF_{prop}, the proportion of HF power over the total power, an index of sympathovagal balance ranging from 0 to 1, i.e., from low to high vagal sympathovagal balance). HF peak frequency (HF_{pf}, a measure of respiration rate; Hz) (see Brown, Beightol, Koh, & Eckberg, 1993; Trinder et al., 2001) was further calculated to control for potential confounding effect of respiration (Cacioppo, Tassinary,& Berntson, 2007). For details about the HRV analysis method we used, and the meaning and calculation of the HRV indices, see Trinder et al. (2001).

Statistical analysis—Demographic data, alcohol history measures, and HRV indices averaged for all 2-min intervals sampled during the initial night, were compared between groups using Mann-Whitney *U* tests.

Differential scores for each of the HRV variables were calculated as follows: 2 month minus initial, 4 month minus initial, and 4 month minus 2 month. Mann-Whitney *U* tests were used to analyze group differences in the differential scores. The Benjamini-Hochberg False Discovery Rate (FDR) was used to correct for multiple comparisons. *Z* values and adjusted *p* values are reported in the results.

Finally, Spearman rank-order correlations were used to explore the association between HRV variables at the initial visit and the rate of change in these variables at the follow-up visits in alcoholics.

For all statistical analyses, results were considered significant at $p < 0.05$.

Results

Demographic and clinical data at the initial visit

Mann-Whitney *U* tests showed no differences between alcoholics and controls in age, BMI, ethnicity, or consumption of caffeinated beverages (Table 2); alcoholics had fewer years of education and higher lifetime alcohol consumption compared to healthy controls ($p < 0.001$) (Table 2).

Mann-Whitney *U* tests failed to show significant differences in demographic or clinical variables between those alcoholics who completed the 4-month follow-up visit ($n = 9$) and those who did not ($n = 6$).

Autonomic measures at the initial visit

Group differences in HRV measures recorded during the initial PSG night are shown in Table 3. Mann-Whitney *U* tests showed that alcoholics had a higher HR ($p < 0.001$) and HF_{pf} indicating a higher respiratory rate ($p < 0.01$) than controls. They also had a lower HF_a ($p < 0.01$), indicating lower vagal activity.

Recovery in autonomic measures in alcoholics with abstinence

Mann-Whitney *U* tests showed no significant differences between alcoholics and controls were detected in the changes in any ANS measures between initial and 2-month assessments (Fig. 2 and Table 4).

Mann-Whitney *U* tests showed evidence of recovery in HR and HF_a with longer abstinence in alcoholics compared to controls. The changes between the initial and 4-month assessment in both HR ($Z = 2.49$, adjusted $p = 0.039$) and HF_a ($Z = -2.56$, adjusted $p = 0.031$) were significantly greater in alcoholics. As shown in Fig. 2, all alcoholics showed decreased HR and increased HF_a (increases in vagal modulation) at the 4-month follow-up compared with the values at the initial assessment. To confirm that the reduction in HR and the increase in HF_a in alcoholics was not biased by the distribution of values in the control subjects, we compared the changes in HR and HF_a against zero using Wilcoxon signed ranks tests in alcoholics; both HR ($Z = 2.67$, $p = 0.007$) and HF_a ($Z = 2.00$, $p = 0.045$) were significantly different from zero.

Mann-Whitney *U* tests showed no significant differences between alcoholics and controls in CV measures between the 2-month and 4-month assessments (Table 4).

Relationship between initial autonomic measures and rate of improvement at the follow-up sessions in alcoholics

Spearman rank-order correlations showed that TP (i.e., an index reflecting the overall HRV) at the initial visit was positively associated with changes in TP from the initial to the 4-month follow-up session ($r = 0.75$, $p < 0.05$, $n = 9$; Fig. 3). Alcoholics who had elevated TP at the initial session showed a greater improvement in TP after 4 months of abstinence. Similarly, TP at the initial visit was positively associated with changes in TP from the 2- to

4-month follow-up sessions ($r = 0.78$, $p < 0.05$, $n = 9$; Fig. 3) confirming the trend of increasing total HRV with abstinence.

Spearman rank-order correlations failed to show other significant associations between initial visit measures and the rate of change at follow-up visits for other HRV variables.

Discussion

Alcoholics compared to healthy controls showed elevated HR and reduced HF activity, reflecting low vagal modulation during early NREM sleep, at about 3 weeks since their last drink (initial assessment). None of the ANS indices significantly improved at 2-months follow-up in alcoholics compared to the minimal changes in controls. However, after 4 months of abstinence, HR was markedly reduced (~8 bpm), and the HRV index (i.e., HF_a, indicative of parasympathetic [vagal] modulation) was increased in alcoholics. Importantly, the level of total HRV at initial assessment was predictive of recovery with abstinence.

Altered autonomic functioning has been implicated in a variety of problems in alcoholics ranging from reduced physical fitness (Herbsleb et al., 2013) to prolonged electrocardiograph QT intervals and associated increased risk of sudden cardiac death (Yokoyama et al., 1992). While many studies have evaluated HRV indices of autonomic function under test conditions, sleep provides a stable period in which to evaluate underlying baseline characteristics of the nervous system. The finding of elevated HR and reduced parasympathetic activity in alcoholics at the initial assessment supports the previous investigation showing altered ANS functioning during sleep in recently sober alcoholics (de Zambotti et al., 2014; Ganesha et al., 2013; Irwin et al., 2006).

The evidence of recovery after 4 months of sobriety indicates that in at least some alcoholics, the altered ANS function associated with abusive drinking and alcohol dependence is reversible. Changes in HR with 2 months of abstinence in alcoholics were distributed around the zero line indicating that not all alcoholics showed the same trend in recovery; however, by 4 months, HR decreased in all the alcoholics compared to the values recorded at the initial assessment. Not surprisingly, the same pattern of results was seen in the measure of vagal modulation, suggesting that the recovery in HR may be via recovery in the parasympathetic system. Again, the present data are consistent with the few studies that have investigated recovery in ANS function during wakefulness in alcoholics across periods of abstinence (Hirsch et al., 1993; Tan et al., 1984; Villalta et al., 1989; Weise, Müller, Kreel, Kielstein, & Koch, 1986; Yokoyama et al., 1991). The good news of recovery with abstinence is tempered by the finding that there is a statistically significant relationship between ANS measures at the initial assessment and changes in ANS functioning at the follow-up sessions in alcoholics, as well as with changes from 2- to 4-months follow-up (Fig. 3). These results indicate that the extent of recovery may be limited by poorer functioning after initial detoxification. This may reflect pre-morbid individual differences in cardiac function or that eventually, chronic alcoholism does enough damage, such that recovery with abstinence is limited. Most likely, there will be individual differences in the susceptibility of the ANS to alcohol that then interact with the duration and extent of alcohol abuse. Investigation of these relations in male and female alcoholics will require a much

larger study. Also, given the frequent coexistence of alcoholism with other addictions and mental conditions (Hasin, Stinson, Ogburn, & Grant, 2007), a larger study is warranted to assess the potential role of comorbidities (e.g., other substance dependencies other than alcohol, mood, and anxiety profile) in affecting the ANS profile in alcohol dependence.

In addition to the sample size, a number of important limitations need to be considered. The conclusions of this paper are based on a small sample size, particularly at the follow-up nights where 40% of alcoholics relapsed. Additional study of whether sleep-related ANS measures are predictive of relapse is warranted, ideally also involving assessment of subjects prior to detoxification. While the alcoholics who relapsed did not differ from those who abstained on any of the clinical variables when measured at baseline, assessment prior to detoxification might reveal differences predictive of a propensity to relapse. Despite these limitations, the changes in HR and HF variability at 4-months follow-up compared to the initial assessment were highly consistent across all alcoholics, as is evident in Fig. 2. However, we cannot exclude that other variables contributed to “normalize” the ANS pattern in alcoholics with abstinence. Further studies should investigate changes in other variables like BMI, mood, and anxiety that may influence HRV (Antelmi et al., 2004; Pittig, Arch, Lam, & Craske, 2013) over the time of the detoxification and link them to the HRV indices. The windows selected for the ANS analysis were restricted to the period immediately after the sleep onset. This limitation did not allow the investigation of the within-night changing in ANS modulation across the period of sobriety. However, the largest differences in ANS modulation between alcoholics and controls have been shown to be at the beginning of the night (de Zambotti et al., 2014; Irwin et al., 2006); therefore, it is unlikely that the results demonstrating recovery in ANS function with abstinence are biased by the time frame of the analysis. Our previous work (de Zambotti et al., 2014) showed evidence of a greater within-night reduction of HR and improvement in total HRV in recently sober alcoholics compared to controls. We hypothesized that sleep may play a strong regulatory control over CV functions in alcoholics, helping the ANS system to recover to some extent. Thus, further studies should clarify the role of sleep in regulating ANS in alcoholics and investigate if the greater within-night ANS recovery seen in alcoholics at the beginning of the detoxification follows a different pattern after a prolonged period of sobriety.

While alcoholism is a chronic, long-term disease associated with severely compromised CV health, the finding of recovery in ANS function with 4 months of abstinence adds to other data showing recovery in sleep EEG activity (Colrain, Padilla, & Baker, 2012), brain structure (Cardenas, Studholme, Gazdzinski, Durazzo, & Meyerhoff, 2007), and aspects of alcoholism-related cognitive and motor decline (Fein & McGillivray, 2007; Yeh, Gazdzinski, Durazzo, Sjöstrand, & Meyerhoff, 2007), although recovery in these domains shows substantial individual variability.

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HIGHLIGHTS

- Alcoholism is associated with autonomic nervous system pathology
- Quiet periods of sleep, early in the night provide a perfect opportunity for assessment of resting autonomic activity
- Four months of abstinence from alcohol is associated with substantial recovery in autonomic function.

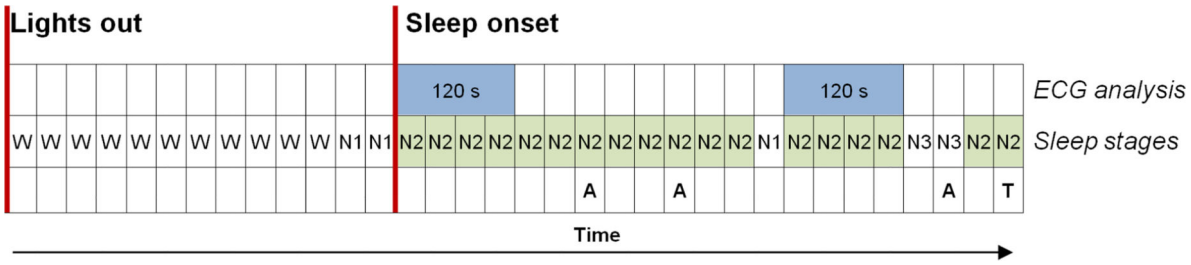

Figure 1.

Example of the windows selected during undisturbed N2 sleep periods for the spectral ECG analysis. Each cell represents a 30-sec epoch, from lights-out to the first tone. ECG analysis was performed on 1 to 5 periods of 4 consecutive 30-sec epochs (120 sec) free of arousals or sleep stage transitions. The last row shows the presence of arousals/tone for each of the 30-sec epochs. In this example, only two 2-min windows of stable N2 were selected for the analysis, being the only 2-min windows (in the period of time starting from the sleep onset to the occurrence of the first tone) free from sleep stage transitions and arousals. A, **arousal**; ECG, **electrocardiogram**; SO, **sleep onset**; T, **first tone**; W, **wake**.

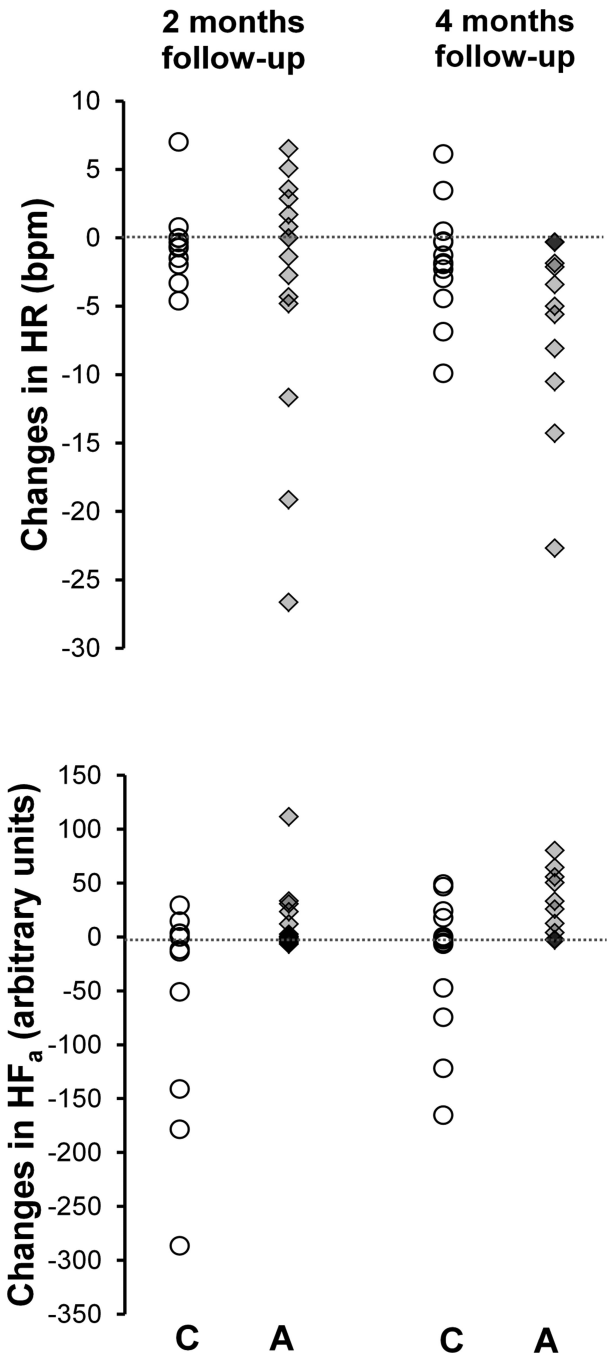

Figure 2.

Distribution of heart rate (**HR**) and HRV absolute high frequency power in the narrow band (**HF_a**) values in both alcoholics (A) and controls(C) at the 2- and 4-month follow-up sessions recorded in stable N2 sleep, compared to the values at the initial visit (zero line).

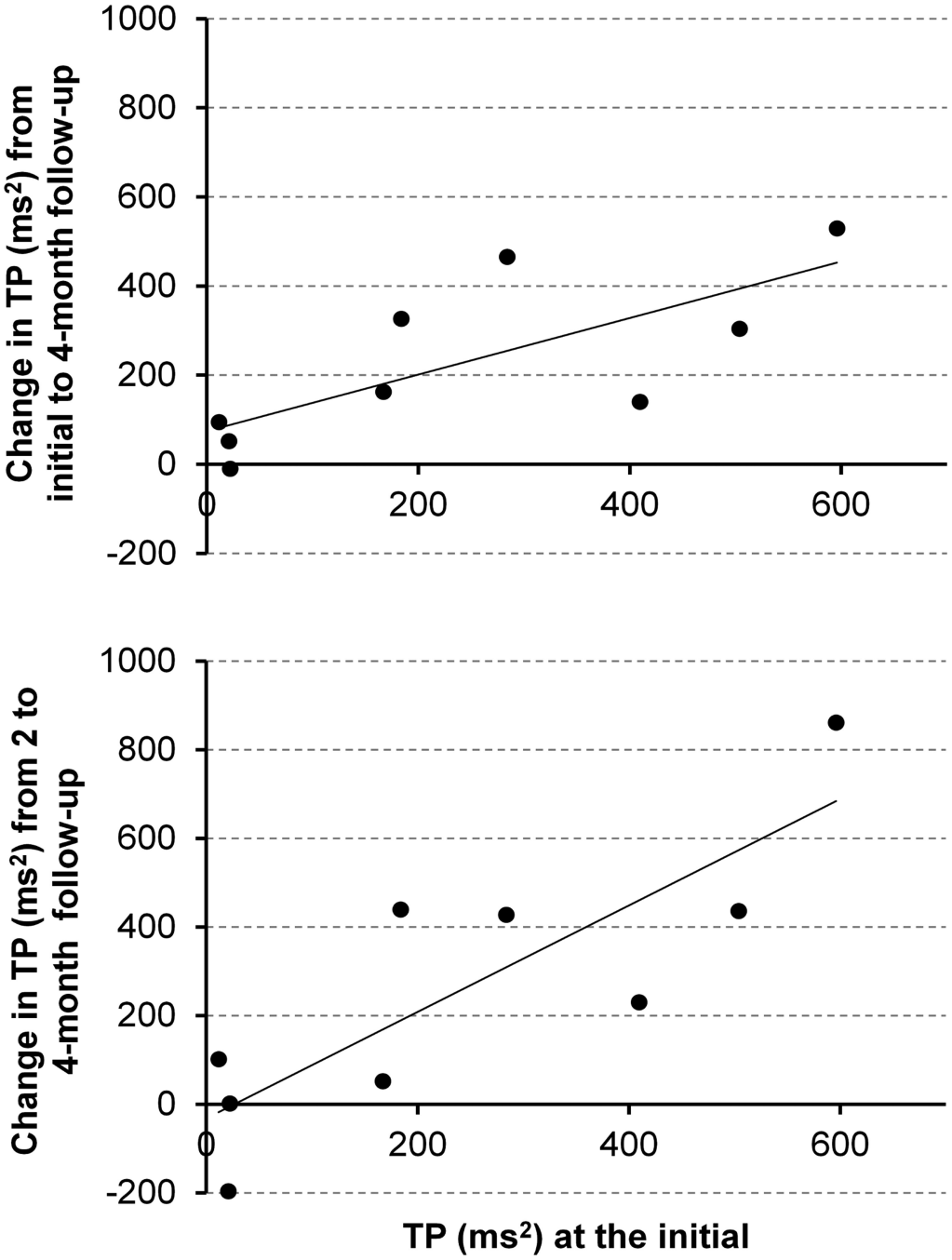

Figure 3.

Scatterplots and regression lines of the significant correlations in alcoholics between total power in HRV (**TP**) at the initial and change at the 4-month follow-up (upper panel), and change from 2-month to 4-month follow-up (lower panel).

Table 1

Number of selected 2-minute epochs for the analyses in both controls and alcoholics at the initial visit and at the follow-ups (mean ± SD).

	Controls	Alcoholics
Initial	3.8 (0.9)	3.6 (1.5)
2-months follow-up	3.3 (1.3)	4.3 (0.9)
4-months follow-up	3.8 (1.3)	4.2 (1.4)

Table 2

Demographic and clinical data (mean ± SD) for 15 alcoholics and 13 controls at the initial visit

	Controls	Alcoholics	Z	
Men/Women (No.)	7/6	8/7	-	
Age (y)	46.6 (9.3)	42.3 (8.2)	1.29	Ns
Caucasian (No.)	7	8	-	
BMI (kg/m^2)	24.4 (3.1)	25.5 (3.5)	−0.69	Ns
Education (y)	17.1 (2.4)	12.5 (2.1)	3.89	***
Length of dependence (y)	-	16.4 (9.0)	-	
Lifetime alcohol use (kg)	53.5 (116.2)	1531.7 (1323.2)	−4.40	***
Days since the last drink	-	23.7 (6.2)	-	
Beverages containing caffeine (cups/day)	1.1 (1.2)	1.80 (2.0)	−0.78	Ns

*** $p < 0.001$; **BMI,** Body Mass Index; **Ns,** not significant

Table 3

HRV spectral indices (mean ± SD) at the initial session (15 alcoholics and 13 controls) during the period of stable artifact-free N2 sleep immediately following sleep onset

	Controls (n = 13)	Alcoholics (n = 15)	Z	
HR (bpm)	57.4 (8.9)	77.3 (12.3)	-3.71	***
TP (ms^2)	550.6 (621.7)	196.1 (182.6)	1.54	Ns
HF_a (arbitrary units)	146.5 (195.1)	18.6 (15.4)	2.83	**
HF_{pf} (Hz)	0.23 (0.04)	0.27 (0.04)	-2.33	*
HF_{prop}	0.57 (0.16)	0.45 (0.20)	1.77	Ns

HF_a, absolute high frequency power in the narrow band; **HF_{pf},** HF peak frequency; **HF_{prop},** proportion of HF over the total power; **HR,** heart rate; **TP,** total power. **Ns,** not significant

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$.

Table 4

Changes in HRV spectral indices (mean ± SD) at 2-months (13 alcoholics and 10 controls) and 4-months (9 alcoholics and 12 controls) follow-up compared to the initial session, and from 2- to 4-months follow-up (9 alcoholics and 9 controls), recorded during the period of stable artifact-free N2 sleep immediately following sleep onset

	Condition	Controls	Alcoholics	Z	
HR (bpm)	2 months vs. initial	–0.52 (3.10)	–3.86 (9.84)	0.25	Ns
	4 months vs. initial	–1.50 (4.28)	–7.93 (6.85)	2.49	*
	2 vs. 4 months follow-up	–1.72 (4.73)	–4.66 (8.57)	1.02	Ns
TP (ms^2)	2 months vs. initial	–23.7 (506.7)	46.6 (286.4)	0.62	Ns
	4 months vs. initial	94.8 (152.5)	229.3 (187.3)	–1.49	Ns
	2 vs. 4 months follow-up	142.4 (492.2)	261.4 (315.7)	–1.19	Ns
HF_a (arbitrary units)	2 months vs. initial	–63.1 (104.4)	14.8 (32.2)	–1.86	Ns
	4 months vs. initial	–21.1 (66.8)	38.5 (28.7)	–2.56	*
	2 vs. 4 months follow-up	35.3 (45.5)	28.9 (27.9)	0.22	Ns
HF_{pf} (Hz)	2 months vs. initial	0.006 (0.011)	–0.010 (0.051)	0.96	Ns
	4 months vs. initial	–0.004 (0.014)	–0.004 (0.044)	1.28	Ns
	2 vs. 4 months follow-up	–0.007 (0.012)	0.004 (0.057)	–1.24	Ns
HF_{prop}	2 months vs. initial	–0.062 (0.131)	–0.017 (0.152)	–0.62	Ns
	4 months vs. initial	–0.047 (0.130)	0.014 (0.106)	–1.35	Ns
	2 vs. 4 months follow-up	–0.008 (0.108)	0.011 (0.123)	–0.22	Ns

*Adjusted $p < 0.05$. **HF_a**, absolute high frequency power in the narrow band; **HF_{pf}**, HF peak frequency; **HF_{prop}**, proportion of HF over the total power; **HR**, heart rate; **TP**, total power. **Ns**, not significant