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Postural Stability in Cigarette Smokers and During Abstinence from Alcohol

Thomas P. Schmidt*, David L. Pennington*, Timothy C. Durazzo, and Dieter J. Meyerhoff

Background: Static postural instability is common in alcohol-dependent individuals (ALC). Chronic alcohol consumption has deleterious effects on the neural and perceptual systems subserving postural stability. However, little is known about the effects of chronic cigarette smoking on postural stability and its changes during abstinence from alcohol.

Methods: A modified Fregly ataxia battery was administered to a total of 115 smoking (sALC) and nonsmoking ALC (nsALC) and to 71 smoking (sCON) and nonsmoking light/nondrinking controls (nsCON). Subgroups of abstinent ALC were assessed at 3 time points (TPs; approximately 1, 5, 34 weeks of abstinence from alcohol); a subset of nsCON was retested at 40 weeks. We tested whether cigarette smoking affects postural stability in CON and in ALC during extended abstinence from alcohol, and we used linear mixed effects modeling to measure change across TPs within ALC.

Results: Chronic smoking was associated with reduced performance on the Sharpened Romberg eyes-closed task in abstinent ALC at all 3 TPs and in CON. The test performance of nsALC increased significantly between 1 and 32 weeks of abstinence, whereas the corresponding increases for sALC between 1 and 35 weeks were nonsignificant. With long-term abstinence from alcohol, nsALC recovered into the range of nsCON and sALC recovered into the range of sCON. Static postural stability decreased with age and correlated with smoking variables but not with drinking measures.

Conclusions: Chronic smoking was associated with reduced static postural stability with eyes closed and with lower increases of postural stability during abstinence from alcohol. Smoking cessation in alcohol dependence treatment may facilitate recovery from static postural instability during abstinence.

Key Words: Ataxia, Balance, Postural Stability, Alcohol Dependence, Cigarette Smoking, Abstinence.

LOWER STATIC POSTURAL stability is common among persons with alcohol use disorders (AUD; Durazzo et al., 2006b; Sullivan et al., 2000b). Cross-sectional performance on ataxia tasks has been described at different lengths of sobriety within the first 12 to 18 months of abstinence from alcohol, with better gait and balance function after longer durations of sobriety (Smith and Fein, 2011). Longitudinal studies assessing performance on ataxia measures in abstinent alcohol-dependent individuals (ALC) have yielded varying results depending on the duration of abstinence (Fein and Greenstein, 2013; Rosenbloom et al., 2004, 2007; Sullivan et al., 2000a). Nonsignificant improvements were observed in 10 abstinent ALC on an ataxia eyes-closed

composite score between 4 months and 2 years of abstinence (Rosenbloom et al., 2007). Between 1 and 2 to 12 months of abstinence, 20 ALC showed statistical trends for improvements on the Sharpened Romberg eyes-closed (SREC) task and on the Walk-on-Floor eyes-open task (Sullivan et al., 2000a). ALC, however, did not improve on these tasks and Stand-on-One-Leg when examined later between 10 weeks ($n = 25$) and up to 4 years ($n = 13$) of abstinence (Fein and Greenstein, 2013; Rosenbloom et al., 2004). The generalizability of these longitudinal studies is limited by substance use comorbidities and rather small sample sizes at baseline and follow-up, the latter due to significant attrition from alcohol relapse.

Chronic cigarette smoking is highly comorbid with AUD, and 60 to 90% of treatment-seeking ALC are chronic smokers (Durazzo et al., 2007a; Hurt et al., 1994; Kalman et al., 2005; Le, 2002; Romberger and Grant, 2004). However, the potential effects of chronic smoking on static postural stability during abstinence from alcohol are poorly understood (Durazzo et al., 2006b). In treatment-naïve individuals with AUD (Fein et al., 2012), smoking and nonsmoking individuals did not differ significantly on the Romberg Stand-on-One-Leg and Walk-on-Floor tasks, neither with eyes open nor eyes closed. However, in 1-month-abstinent treatment seekers (Durazzo et al., 2006b), we found that smoking ALC (sALC) performed worse than nonsmoking ALC (nsALC) on the SREC task, but not on the eyes-open condition and

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that worse performance correlated with more cigarettes smoked per day. Additionally, in middle-aged normal controls, chronic smokers showed significantly poorer performance than nonsmokers on the SREC task, with worse performance in smokers related to more lifetime years of smoking (Durazzo et al., 2012b).

Given the lack of studies with larger samples in this area, our previous work on the effects of smoking on postural stability in normal controls and ALC (Durazzo et al., 2006a, 2007b, 2012b; Pennington et al., 2013) as well as the empirical (Cargiulo, 2007; Jahn et al., 2010; Stolze et al., 2008) and intuitive relevance of balance to quality-of-life and safety in everyday tasks, long-term assessment of a large cohort with repeated ataxia measures may advance our understanding of brain-behavior relationships following excessive alcohol consumption. Therefore, the goal of this study was to assess the effects of chronic smoking on postural stability in a large cohort of ALC over an average of 34 weeks of abstinence from alcohol and in matched nonalcoholic controls. We tested 2 primary hypotheses: (i) sALC demonstrate less recovery than nsALC on measures of static postural stability over the first 34 weeks of abstinence from alcohol; and (ii) across ALC and light-drinking control (CON), smokers per-

form worse than nonsmokers on cross-sectional measures of static postural stability.

MATERIALS AND METHODS

Participants

ALC individuals were recruited from the VA Medical Center and the Kaiser Permanente substance abuse outpatient clinics in San Francisco. Controls (CON) were light/nondrinking individuals recruited from the local community, who had no history of biomedical and/or psychiatric conditions known to influence study measures. All research participants provided written informed consent according to the Declaration of Helsinki and underwent procedures approved by the University of California San Francisco and the San Francisco VA Medical Center. A total of 115 unique ALC participants were enrolled in this study. A subset of 67 ALC (40 sALC, 27 nsALC) was studied at 7 ± 4 days of abstinence (time point 1 = TP1); 100 ALC (59 sALC, 41 nsALC) were studied at an average of 33 ± 9 days of abstinence (TP2), including 66 with TP1 data; 35 ALC (17 nsALC and 18 sALC) were studied after an average of 235 ± 56 days (34 weeks) of abstinence (TP3), and all had TP2 data. Eighteen ALC had data for all 3 TPs. Seventy-one light-drinking healthy controls (35 sCON and 36 nsCON) were studied with the same measures once; of these, 13 nsCON completed follow-up assessments 281 ± 95 days after baseline to assess potential age-related effects on our measures, their stability over time, and poten-

Table 1. Group Demographics and Psychiatric History: Mean (SD) [Min, Max]

Measure	nsALC	sALC	nsCON	sCON
Number of participants (female)	41 (7, 17%)	59 (2, 3%)	39 (7, 18%)	35 (5, 14%)
Age [min, max]	52 (10) [28, 67]	49 (9) [28, 67]	45 (9) [26, 59]	49 (9) [33, 64]
Education (years) [min, max]	15 (2) [12, 19]	13 (2) [9, 20]	16 (2) [12, 21]	15 (2) [12, 20]
AMNART [min, max]	115 (9) [95, 129]	113 (9) [91, 128]	120 (6) [101, 129]	117 (6) [100, 128]
Percent Caucasian/African Amer./Latino/Asian/Polynesian	84/0/12/0/2/2/0	73/22/3/0/0/0/2	72/15/3/5/5/0/0	69/11/9/11/0/0/0
Pacific Islander/Native Amer./Declined				
Percent with current medical comorbidity	52	47	N/A	N/A
Percent with comorbid substance dependence (sustained full remission)/abuse (lifetime) diagnosis	17/0	5/5	N/A	N/A
Percent with current psychiatric comorbidity	34	22	N/A	N/A
Beck Depression Inventory [min, max]	9 (9) [0, 31]	11 (8) [0, 37]	4 (4) [0, 13]	6 (4) [0, 17]
State-Trait Anxiety Inventory—Trait [min, max]	44 (11) [24, 62]	44 (12) [21, 71]	33 (7) [21, 47]	33 (7) [20, 56]

AMNART, American National Adult Reading Test; nsALC, nonsmoking alcohol-dependent participants; sALC, smoking alcohol-dependent participants; nsCON, nonsmoking light-drinking controls; sCON, smoking light-drinking controls; NA, not applicable.

Table 2. Group Alcohol Variables: Mean (SD) [Min, Max]

Measure	nsALC	sALC	nsCON	sCON
Number of days abstinent at TP1 ^a	6 (3) [1, 13]	7 (5) [1, 30]	N/A	N/A
Number of days abstinent at TP2 ^a	34 (9) [16, 58]	33 (8) [16, 58]	N/A	N/A
Number of days abstinent at TP3 ^a	225 (42) [139, 299]	244 (70) [112, 413]	N/A	N/A
1-year average alcoholic drinks/mo ^b	309 (198) [20, 870]	447 (253) [64, 1,320]	15 (16) [0, 60]	21 (19) [0, 75]
Lifetime average alcoholic drinks/mo ^b	170 (104) [54, 532]	267 (121) [45, 543]	17 (14) [1, 51]	25 (13) [4, 52]
Onset of heavy drinking [years] ^c	28 (11) [15, 59]	22 (7) [14, 50]	N/A	N/A
Duration of regular drinking [years] ^d	35 (11) [10, 54]	32 (9) [10, 49]	N/A	N/A

NA, not applicable; nsALC, nonsmoking alcohol-dependent participants; sALC, smoking alcohol-dependent participants; nsCON, nonsmoking light-drinking controls; sCON, smoking light-drinking controls.

^a $p = n.s.$

^b $p < 0.001$ for ALC.

^cHeavy drinking = drinking in excess of 100 alcoholic drinks (containing 13.6 g of ethanol) per month for males (80 for females).

^dRegular drinking = consuming at least 1 alcoholic drink per month.

Table 3. Group Smoking Variables: Mean (SD) [Min, Max]

Measure	sALC	sCON
FTND at TP1	5.1 (1.8) [2, 10]	5.0 (3.0) [2, 8]
FTND at TP2	5.1 (1.8) [2, 10]	N/A
FTND at TP3	5.1 (1.5) [2, 9]	4.0 (3.0) [1, 6]
Cigarettes per day at TP1	19 (8) [2, 40]	19 (10) [4, 30]
Cigarettes per day at TP2	19 (8) [2, 40]	N/A
Cigarettes per day at TP3	18 (6) [6, 30]	11 (8) [4, 20]
Smoking duration (years)	26 (12) [2, 54]	25 (14) [5, 44]

FTND, Fagerström Test of Nicotine Dependence; NA, not applicable; sALC, smoking alcohol-dependent participants; sCON, smoking light-drinking controls; TP, time point.

tial practice effects. None of our smoking controls were studied twice. Descriptive data for the largest group of ALC participants (those participating at TP2 and representative of the whole cohort of 115 ALC) and our CON group are described in Tables 1–3.

Primary inclusion criteria for ALC were current DSM-IV-TR diagnosis of alcohol dependence, fluency in English, consumption of >150 standard alcoholic drinks per month for at least 8 years before enrollment for men and >80 drinks per month for at least 6 years before enrollment for women. Primary exclusion criteria were fully detailed earlier (Durazzo et al., 2004). In brief, all participants were free of general psychiatric, neurological, and physical injuries to the back, hip, knees, and/or foot, and free of any medical conditions known or suspected to influence performance on a task of static postural stability, with the exceptions of hepatitis C, hypertension, and unipolar mood disorders. Major depression and substance-induced mood disorder were not exclusionary given their high comorbidity with both alcohol dependence (Gilman and Abraham, 2001) and chronic cigarette smoking (Fergusson et al., 2003). All subjects were specifically screened for history of peripheral neuropathies and vestibular disorders. In addition to self-report, the medical records of all ALC participants were reviewed prior to all TPs to search for indications of any alcohol and other substance use (e.g., results of urine toxicology and alcohol breathalyzer tests). ALC who had consumed any amount of alcohol after TP1 or who stopped smoking after TP1 were not included in analyses at TP2 or TP3. All CON participants were screened for recent use of illicit substances, with smoking status and alcohol consumption history determined via self-report. For all ALC participants, dependence on any drug in the past 5 years other than alcohol or nicotine was exclusionary. No participant was positive for alcohol or other substances at any TP.

Psychiatric/Behavioral Assessments

At the time of enrollment, all participants were administered the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition, version 2.0 (American Psychiatric Association, 1994), and standardized questionnaires assessing depressive (Beck Depression Inventory [BDI]; Beck, 1978) and anxiety symptomatology (State-Trait Anxiety Inventory, Y-2 [STAI]; Spielberger et al., 1977), lifetime alcohol consumption (Lifetime Drinking History; Skinner and Sheu, 1982), lifetime substance consumption (Abé et al., 2013), and level of nicotine dependence via the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991; see Tables 1–3).

Postural Stability and Balance Assessments

To assess postural stability and balance, participants were administered a version of the Fregly Ataxia Battery (Durazzo et al., 2006b; Fregly and Graybiel, 1968; Fregly et al., 1972; Sullivan

et al., 2000a). For the Sharpened Romberg, a measure of static postural stability, participants were required to stand heel-to-toe, with arms folded across the chest, for a maximum of 60 seconds, first with eyes open and then with eyes closed. The task was discontinued if participants were unable to maintain the required position for at least 3 seconds on any of the 4 trials. If they successfully maintained this position for 60 seconds on any of the 4 trials, they were given the maximum score of 60 for any remaining trials. For trials in which the 60-second criteria were not achieved, but the participant was able to maintain the required position for at least 3 seconds, the times were recorded and summed across all 4 trials to obtain the final total score. The maximum possible score for Sharpened Romberg eyes-open or SREC was 240 seconds.

For Walk-on-Floor eyes-open and Walk-on-Floor eyes-closed (WFEC), participants were required to walk heel-to-toe with arms folded across the chest and follow a straight line on the ground for 10 consecutive steps. The task was discontinued if the individual was unable to complete any 1 of 3 trials for eyes open or eyes closed. If a participant was able to complete all 3 trials, the total deviation in inches from the straight line at the end of 10 consecutive steps was summed across 3 trials. The maximum possible score for eyes open or eyes closed was zero inches. Raw scores were used for all analyses, as there are no appropriate norms for these balance and postural stability measures. In addition, standing-on-one-foot was attempted with ALC at TP1 but had to be discontinued early for safety reasons, particularly for the eyes-closed condition.

Data Analyses

Due to a restriction in the range of scores on the eyes-open tasks, our statistical analyses focused on the SREC task. Additional analyses compared proportions of group members able to perform the WFEC task.

Longitudinal change on the SREC for sALC and nsALC over an average of 34 weeks of abstinence from alcohol was tested via linear mixed effects modeling (random intercepts and slopes with an autoregressive covariance structure). We specifically tested for an interaction of smoking status-by-duration of abstinence (in days) to determine whether sALC and nsALC demonstrated a differential level of change during abstinence. This linear mixed effects modeling is well suited for evaluating longitudinal change in data sets that do not have identical numbers of observations for all cases (Pinheiro and Bates, 2000). Significant main effects and interactions were further examined via within-group comparison across time (i.e., days of abstinence) as indicated.

In cross-sectional analyses at each TP, we assessed alcohol status (ALC or CON)-by-smoking status (smoking or nonsmoking) interactions and main effects using univariate analysis of covariance (ANCOVA), controlling for age. We compared sALC and nsALC performance at all TPs to baseline sCON and nsCON data. Initial comparisons between nsALC and sALC on the SREC were controlled for age, BDI (Bishop et al., 2009; Iaboni and Flint, 2013), and alcohol consumption variables, as these variables may influence postural stability. Only age emerged as a significant predictor of SREC performance and was therefore used as a covariate in all cross-sectional and longitudinal analyses directly comparing nsALC and sALC. Effect sizes (ES) for pairwise group comparisons were calculated using Cohen's *d* (Cohen, 1988). Unless otherwise indicated, all *t*-tests were 1-tailed as a priori hypotheses were tested. For tests that had ceiling effects (both eyes-open tasks) or could not be performed by the majority of participants for meaningful statistical analyses (WFEC), we performed Fisher's exact tests at each TP to assess for differences in proportion of individuals per group achieving maximum scores and being unable to perform the task. Correlations between performance on the SREC and smoking variables used Spearman's rank testing. All statistical analyses were conducted with R v3.0.1 (R Foundation for Statistical Computing,

Vienna, Austria) and SPSS v19 (IBM, Armonk, NY); $p < 0.05$ was considered statistically significant.

RESULTS

Characterization of Study Participants

Of the 100 ALC participants at TP2, 9 were female, 77 were Caucasian, 13 African American, 7 Latino, 1 Native American, 1 Polynesian/Pacific Islander, and 1 declined to disclose ethnicity (see Tables 1–3). nsALC had more years of education than sALC ($p < 0.001$). The ALC groups were equivalent on age, AMNART score, total lifetime years drinking, and days of abstinence at TP1, TP2, and TP3 (all $p > 0.21$). sALC drank more than nsALC over 1 year prior to study (+31%) and over lifetime (+36%, both $p < 0.001$), and sALC began drinking heavily at a younger age than nsALC (22 vs. 28 years, $p < 0.001$). These alcohol consumption variables were not significant predictors of SREC performance in comparisons between nsALC and sALC. Of the 115 unique ALC participants in the study, nsALC and sALC did not differ on the densities of family history of nicotine dependence ($p = 0.389$) or on the densities of family history of problem drinking ($p = 0.248$), social drinking ($p = 0.875$), or abstinence from alcohol ($p = 0.155$; only mother, father, and paternal and maternal grandparents were included in the density calculations). At TP2, which had the largest number of ALC participants, DSM-IV-TR criteria for recurrent major depression were met for 14/41 nsALC (34%) and 7/59 sALC (12%); 4 nsALC (10%) and 2 sALC (3%) met criteria for substance-induced (alcohol) mood disorder with depressive features. These percentages were similar for the ALC sample at TP1. Criteria for amphetamine dependence in full remission were met for 3/41 nsALC and 2/59 sALC (<8%); criteria for lifetime cocaine abuse were met for 3 of 59 sALC and no nsALC (<6%); criteria for cocaine dependence in full remission were met for 1 of 59 sALC and 3 of 41 nsALC (<8%). Hepatitis C antibody was present in 5 of 41 nsALC (12%) and 11 of 59 sALC (18%). The proportion of comorbid conditions was equivalent in smoking and nonsmoking groups at all TPs and did not contribute to variance on the task. The groups were not significantly different on BDI, STAI, or any other clinical laboratory variable at either TP. Total FTND scores were virtually identical across sALC samples at all TPs, indicating a stable and medium-to-high level of nicotine dependence during abstinence. One of the sALC participants stopped smoking after TP1 and was not included in any analyses of TP2 or TP3 data; none of the nonsmoking participants started smoking during the study. Of the 74 CON participants at baseline, 12 were female (16%), 52 were Caucasian (70%), 10 African American (14%), 6 Asian (8%), 4 Latino (5%), and 2 Polynesian/Pacific Islander (3%), a distribution statistically similar to that in ALC. nsCON were older than sCON ($p = 0.03$) and had more years of education ($p < 0.001$), but they were similar on alcohol consumption and other clinical variables. Smok-

ing duration, number of cigarettes smoked per day, FTND score, and age were not significantly different between sCON and sALC (Table 3).

Longitudinal Changes on SREC in sALC and nsALC

No smoking status-by-duration of abstinence interaction was observed for the SREC, $t(81) = -0.27$, $p = 0.78$, (see Table 4). However, there were significant main effects for smoking status, $t(82) = -2.26$, $p = 0.03$, and duration of abstinence, $t(82) = 2.14$, $p = 0.04$. Higher age was related to smaller increases in test performance with increasing abstinence, $t(115) = -5.30$, $p < 0.001$. Follow-up within-group tests revealed nsALC and sALC showed differential changes in SREC performance over 34 weeks. nsALC showed a significant overall increase in SREC performance ($p = 0.03$), whereas sALC showed no significant changes ($p = 0.22$). Specifically, nsALC scores increased significantly between TP1-2 ($p = 0.04$) and tended to increase between TP2-3 ($p = 0.08$). By contrast, sALC showed no significant increases between any of the TPs (all $p > 0.21$). When women were removed from the statistical analyses, the results were essentially unchanged and the pattern of findings virtually identical.

Cross-Sectional Findings on SREC

At TP1, an alcohol status (ALC or CON)-by-smoking status (nonsmokers or smoker) interaction was not observed (see Table 4). There were significant main effects for both alcohol ($p < 0.001$) and smoking status ($p = 0.006$). Specifically, sALC performed significantly worse than nsALC ($p = 0.034$, $ES = 0.46$, -25%), sCON ($p = 0.008$, $ES = 0.56$, -31%), and nsCON ($p < 0.001$, $ES = 1.16$, -47%); nsALC were inferior to nsCON ($p = 0.004$, $ES = 0.65$, -32%) but not significantly different from sCON ($p = 0.345$, $ES = 0.10$, -9%). sCON performed worse than nsCON ($p = 0.006$, $ES = 0.60$, -23%). Notably, smoking in CON contributed to a similar decrement in SREC performance than alcohol consumption in nonsmokers, and the effects of smoking and

Table 4. Sharpened Romberg Eyes-Closed by Group: Raw Scores in Seconds for Each Time Point (TP), Mean (SD)

Group	TP1 or baseline	TP2 (5 weeks)	TP3 (mean 34 weeks) or nsCON follow-up (40 weeks)
sALC	107 (48)	118 (45)	136 (58)
nsALC ^a	140 (67)	149 (77)	185 (47)
sCON	154 (69)	N/A	N/A
nsCON	201 (56)	N/A	203 (41)

sALC, smoking alcohol-dependent participants; nsCON, nonsmoking light-drinking controls; sCON, smoking light-drinking controls; nsALC, nonsmoking alcohol-dependent participants.

^aSignificant change from TP1 to TP2 ($p = 0.039$) and from TP1 to TP3 ($p = 0.026$).

drinking were approximately additive, that is, $sALC < nsALC \sim sCON < nsCON$ (see Fig. 1).

At TP2, there was also no alcohol status-by-smoking status interaction. Also at TP2, main effects for both group ($p = 0.001$) and smoking status ($p = 0.002$) were significant, with a similar pattern of group performance as at TP1, although with smaller ES. Specifically, $sALC$ performed significantly worse than $nsALC$ ($p = 0.039$, $ES = 0.42$), $sCON$ ($p = 0.035$, $ES = 0.46$), and $nsCON$ ($p < 0.014$, $ES = 1.00$); $nsALC$ were inferior to $nsCON$ ($p = 0.014$, $ES = 0.47$), but not different from $sCON$ ($p = 0.90$).

In our main TP3 analyses, we compared SREC performance in $sALC$ and $nsALC$ to SREC performance of $sCON$ and $nsCON$ measured at baseline. We did not observe a group-by-smoking status interaction. There was a significant main effect for smoking status ($p = 0.001$), but not for alcohol status. After an average of 34 weeks of abstinence, we observed a pattern of results similar to that at 1 and 5 weeks, except that $nsALC$ tended to perform better than $sCON$ ($p = 0.062$, $ES = 0.56$). Overall, $sALC$ performed significantly worse than both $nsALC$ ($p = 0.046$, $ES = 0.68$) and $nsCON$ ($p < 0.001$, $ES = 0.78$); but $sALC$ were not different from $sCON$ ($p = 0.541$, $ES = 0.28$). $nsALC$ at TP3 and $nsCON$ performed similarly ($p = 0.375$, $ES = 0.12$). As we had 40-week follow-up data on 13 of the 40 $nsCON$ individuals, we repeated the TP3 pairwise comparisons of the ALC groups to this smaller control group (that might have experienced “practice effects” similar to the ALC groups). Also here, $sALC$ performed worse than both $nsALC$ ($p = 0.025$) and $nsCON$ ($p = 0.016$) with large ES ($ES = 0.69$ and 0.81 , respectively), whereas $nsALC$ did not differ from $nsCON$ ($p = 0.375$, $ES = 0.12$). The significances and ES of these group differences were very similar to those observed with the baseline data from the larger $nsCON$ group. Again, removing female participants from these cross-sectional analyses left the results essentially unchanged.

Fig. 1. Group performance on Sharpened Romberg eyes-closed (SREC): Raw scores (mean $\pm$ standard deviation) at TP1 or baseline. TP, time point. $sALC$, smoking alcohol-dependent participants; $nsALC$, nonsmoking alcohol-dependent participants; $sCON$, smoking light-drinking controls; $nsCON$, nonsmoking light-drinking controls.

Table 5. Proportion of Group Participants With Performance Characteristics on 3 Fregly Ataxia Tasks

Group	Sharpened Romberg Eyes-Open: % with max score (total group <i>n</i>)	Walk-on-Floor Eyes-Open: % with max score (total group <i>n</i>)	Walk-on-Floor Eyes-Closed: % able to perform (total group <i>n</i>)
TP1			
sALC	88 (40)	90 (31)	20 (35) ^a
nsALC	93 (27)	96 (23)	48 (25)
sCON	100 (35)	94 (35)	44 (32) ^b
nsCON	95 (37)	97 (36)	86 (36)
TP2			
sALC	93 (59)	94 (52)	29 (56) ^a
nsALC	97 (41)	83 (36)	51 (37)
TP3			
sALC	89 (18)	87 (15)	50 (14)
nsALC	94 (17)	86 (14)	60 (15)
nsCON	100 (13)	88 (13)	85 (13)

$sALC$, smoking alcohol-dependent participants; $nsCON$, nonsmoking light-drinking controls; $sCON$, smoking light-drinking controls; $nsALC$, nonsmoking alcohol-dependent participants; TP, time point.

^a $sALC < nsALC$ proportion, $p = 0.03$.

^b $sCON < nsCON$ proportion, $p < 0.01$.

Within the $sALC$ group, worse SREC performance was related to greater lifetime years of smoking ($r = -0.36$, $p = 0.006$ at TP2; $r = -0.54$, $p = 0.027$ at TP3). Similarly in $sCON$, baseline SREC performance inversely correlated with lifetime years of smoking ($r = -0.46$, $p = 0.007$).

Findings on Proportional Differences on Other Fregly Ataxia Tasks

There were no differences among the proportions of smoking and nonsmoking participants achieving maximum scores on the eyes-open tasks (see Table 5). However, fewer $sALC$ than $nsALC$ were able to perform the WFEC task at TP1 and TP2 (both $p = 0.03$); this proportional difference was no longer apparent at TP3 after an average of 34 weeks of abstinence (see Fig. 2). Similarly, the number of $sCON$ able to

Fig. 2. Percent of group participants able to perform Walk-on-Floor eyes-closed at 3 time points (TPs). $sALC$, smoking alcohol-dependent participants; $nsCON$, nonsmoking light-drinking controls; $sCON$, smoking light-drinking controls; $nsALC$, nonsmoking alcohol-dependent participants.

perform the WFEC task at baseline was smaller than that of nsCON (44 vs. 86%, $p < 0.01$). At TP3, the proportion of sALC able to perform the WFEC task was similar to that of sCON at baseline (50 vs. 44%, $p = 0.471$). Similarly, the proportion of nsALC at TP3 and nsCON at follow-up able to perform the WFEC task were statistically equivalent (60 vs. 85%, respectively; $p = 0.567$).

The proportion of sALC participants who improved on their ability to perform the WFEC task increased from 20% at 1 week to 50% at 35 weeks of abstinence ($p = 0.077$), similar to the cross-sectional proportion of sCON (44%) who were able to perform the task. The corresponding proportion of nsALC able to complete the task increased from 48% at TP1 to 60% at TP3, but this increase was not statistically significant ($p = 0.522$); the nsALC performance at TP3 was similar to that in long-term abstinent sALC (50%).

DISCUSSION

As hypothesized, static postural stability operationalized by the SREC task increased significantly in nsALC over 32 weeks of abstinence from alcohol into the performance range of nsCON with similar age. By contrast, sALC during abstinence did not exhibit statistically significant recovery on this measure of static postural stability over a similar time interval. Although sALC test scores increased into the performance range of age-matched sCON, their SREC performance after approximately 35 weeks of abstinence remained inferior to that of both nsCON and nsALC. Cross-sectionally, nsALC performed better than sALC at all 3 TPs during abstinence; also among the nonalcoholic controls, nsCON performed better than sCON. Whereas performance was inversely correlated with smoking duration in both smoking groups, it was not related to alcohol consumption across both ALC groups. This is contrary to findings in treatment-naïve heavy drinkers (Smith and Fein, 2011). While the proportion of nsALC able to perform the WFEC task did not increase between TP1 and TP3 (similar to the nsCON proportion), the proportion of sALC able to perform the task more than doubled by TP3. Our analyses show that (i) chronic smoking affects static postural stability with eyes closed, (ii) the bulk of recovery of static postural stability occurs during the initial several weeks of abstinence from alcohol, and (iii) the increases observed on a measure of static postural stability during abstinence are less pronounced in chronic smokers. The latter finding is consistent with the results of an exercise study in the elderly, in which current smokers improved less on self-reported balance and mobility (Bishop et al., 2009).

The SREC task interrogates the ability of the basal ganglia and cerebellum to integrate vestibular and proprioceptive information for maintaining postural stability in the absence of visual input (Maschke et al., 2003, 2006). Accordingly, our results suggest that long-term abstinent sALC may be more prone than nsALC to balance-related physical risks due to dysfunction in the basal ganglia (Maschke et al., 2003, 2006; Visser and Bloem, 2005), cerebellum (Manor

et al., 2010; Maschke et al., 2006; Park et al., 2013; Rosenbloom et al., 2007), and/or vestibular (perceptual) systems (Horak, 2009), which are involved in proprioceptive feedback of position in extrapersonal space. Structural abnormalities of the cerebellum (Brody et al., 2004; Gallinat et al., 2006; Kuhn et al., 2012; Yu et al., 2011) and basal ganglia of smokers (Durazzo et al., 2014; Liao et al., 2012; Yu et al., 2011) may mediate these balance problems. As such, the SREC task appears to be a simple, fast, and sensitive measure of interrogating in clinical and research settings the integrity of balance functions subserved by the basal ganglia and cerebellum and/or their interconnectivity. Additional long-term follow-up with this cohort may establish if SREC performance in this middle-aged cohort is predictive of fall risk later in life and to see whether the ALC groups eventually achieve a level of performance that is fully equivalent to that of their nonalcoholic counterparts. In future studies, our findings in conjunction with neuroimaging of the basal ganglia and the cerebellum may be used to better understand the neuropathogenesis of postural instability associated with chronic drinking and smoking.

A few factors limit the generalizability of our results: Only 1 measure of static postural stability was used in this analysis due to ceiling effects or inability to perform on other ataxia measures. Postural sway measures (Sullivan et al., 2010) or functional gait assessments and tests of the balance evaluation systems (Leddy et al., 2011) could provide more robust and varied information in future studies of gait and balance. sCON were not retested, and only a subset of nsCON was retested at follow-up. When comparing repeat data from ALC participants at TP2 and TP3 with baseline data obtained in CON, we did not control for potential practice effects in ALC. However, practice effects in the TP2 to TP3 interval were likely minimized by the long interval between assessments, and practice effects were not apparent in the nsCON subset restudied after 40 weeks (see Table 4). Due to inability to participate at TP1 and attrition from relapse, all ALC participants did not contribute data at all TPs during abstinence. However, analyses showed that the subgroups of ALC at TP1 and TP3 were representative of the largest group at TP2. The smaller number of observations at TP3 increases the risk of model over-fitting and corresponding Type I error, despite all critical model assumptions having been met in the longitudinal analyses of SREC change. Consistent with the main findings of these analyses, the visualization of complete longitudinal data from all 3 TPs of 18 ALC individuals confirms qualitatively that nsALC recover more than sALC over an average of 34 weeks of abstinence. Finally, as the majority of study participants were Caucasian male veterans, race and gender effects could not be evaluated thoroughly.

Notwithstanding these limitations, our study is important in that it describes smoking-related deficits of static postural stability and balance in healthy controls and effects of smoking on these measures in a fairly large sample of ALC with low medical and substance use comorbidities during long-

term abstinence from alcohol. Our findings suggest that abnormalities of static postural stability in sALC cannot be attributed solely to the effects of chronic and hazardous alcohol consumption, but that they are also related to chronic smoking. Specifically, chronic smoking in this cohort exerts nearly as large a decrement on static postural stability performance (~24%) as chronic alcohol consumption (~31%). Longitudinally, in this sample of middle-aged ALC, statistically significant recovery of static postural stability into the range of nsCON took approximately 8 months for nsALC. On the other hand, sALC still retained performance deficits relative to nsALC at that time, and the longitudinal increases in sALC were not statistically significant although they showed recovery into the range of sCON.

Chronic cigarette smokers comprise 60 to 90% of treatment-seeking ALC (Durazzo et al., 2007a; Hurt et al., 1994; Kalman et al., 2005; Le, 2002; Romberger and Grant, 2004). The lack of a significant increase in scores on the SREC task by sALC over approximately 34 weeks of sustained abstinence may reflect persisting abnormalities of structure and/or biochemistry in the basal ganglia and/or cerebellum of sALC. In structural neuroimaging studies of these ALC participants at TP1, we observed that sALC relative to nsALC demonstrated larger putamen volumes (Durazzo et al., 2014), a structure rich in nicotinic acetylcholine receptors, but lower lenticular nuclei (globus pallidus + putamen) *N*-acetylaspartate concentration (a biomarker of neuronal viability; Durazzo et al., 2004). The functional significance of these morphological and metabolite findings will be addressed in future analyses. Additionally, the lack of significant increases observed in sALC may indicate lower white matter microstructural integrity of pathways interconnecting the basal ganglia and cerebellum or those providing proprioceptive and/or vestibular input. As indicated by our previous longitudinal research on the neurobiological and neurocognitive effects of smoking in various populations (Durazzo et al., 2006a, 2007b, 2012a, 2013; Gazdzinski et al., 2008, 2010; Mon et al., 2009; Pennington et al., 2013), this new report provides additional impetus for studying the potentially beneficial effects of smoking cessation on neurobiology, cognition, and balance in AUD and other conditions with high smoking comorbidities.

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CONFLICT OF INTERESTS

The authors have no disclosures and no conflict of interests to report.

AUTHORS CONTRIBUTION

Drs. Dieter Meyerhoff and Timothy Durazzo conceptualized and designed the research and obtained funding for the project. Dr. Meyerhoff had central oversight and overall responsibility for all aspects of the research conducted by Mr. Schmidt and Dr. Pennington. Thomas Schmidt and Drs. Pennington and Durazzo recruited and assessed study participants and prepared all demographic, behavioral, and cognitive data. Dr. Durazzo conducted the statistical longitudinal data analyses and supervised Dr. Pennington on the other analyses. Dr. Pennington mentored Thomas Schmidt in analyzing and preparing the data, reviewing related literature, preparing figures and tables, and writing the first draft of the manuscript. All authors edited the manuscript.

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