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Treadmill exercise improves fitness and reduces craving and use of cocaine in individuals with concurrent cocaine and tobacco-use disorder

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ABSTRACT

Exercise may be a useful treatment for substance use disorders. Participants (N=24) included treatment-seeking individuals with concurrent cocaine and tobacco-use disorder (cigarette smokers). Participants were randomized to either running or walking (30 min per session, 3 times per week) or sitting (control condition) for 4 consecutive weeks. Several metrics indicated significant differences among runners, walkers, and sitters during sessions, including mean distance covered and calories burned. In addition, remote physiological monitoring showed that the groups differed significantly according to mean maximum heart rate (HR), respiration, and locomotor activity. Across the 4-week study, exercise improved fitness measures including significantly decreasing resting HR. Though not statistically significant, exercise improved abstinence from cocaine and increased self-reports of no cocaine use in last 24 h. In general, reductions in tobacco use and craving were not as robust. To our knowledge, this is the first study to evaluate the effects of a multi-week exercise program in individuals with concurrent cocaine and tobacco-use disorder. The data clearly show significant improvements in basic fitness measures and several indices reveal that exercise improved both self-report and biochemically verified reports of cocaine abstinence. Taken together, the data from this study provide preliminary evidence for the efficacy of exercise for improving fitness and reducing cocaine use.

1. Introduction

According to the 2013 National Survey on Drug Use and Health, 20.1% of past month cigarette smokers reported current use of an illicit drug compared with 4.1% of persons who were not current cigarette smokers. Cigarette smoking is ~3 times more prevalent in cocaine abusers than in the general population (Brewer et al., 2013; Budney et al., 1993) and cocaine-dependent individuals who are cigarette smokers report using cocaine more frequently and in greater amounts than those who are non-smokers (Roll et al., 1996).

The problems of cocaine and tobacco use disorders remain as major medical and social concerns, and there is a pressing need for a broadly effective treatment approach. While there are several FDA-approved medications for tobacco use disorder (e.g., varenicline), there has not been a single medication identified that reliably reduces cocaine use (Haile et al., 2012). Behavioral interventions, including contingency management (CM) and cognitive behavioral therapy (CBT), are of particular interest as treatments for cocaine use disorder. A systematic evaluation of 19 studies with a total of 1664 patients showed that CM in combination with standard CBT or other psychological interventions increases cocaine abstinence, improves treatment retention, and may also enhance effects produced by medications (Schierenberg et al., 2012). These promising outcomes indicate that non-pharmacological treatment approaches warrant additional consideration. Among available alternatives, a recent review highlighted data showing that physical activity protects against drug abuse vulnerability (Bardo and Compton, 2015), and exercise has been shown to be reinforcing in humans and rodents and may, therefore, be useful as a treatment for substance use disorders (Lynch et al., 2013). A number of other factors enhance the value of exercise-based behavioral interventions, including that they are relatively low cost and easy to implement in comparison to

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medication studies. Furthermore, these types of interventions likely confer additional benefits to study participants, including improved cardiovascular function and improved mood.

Individual exercise sessions have been shown to attenuate cravings and withdrawal symptoms in cigarette smokers (Janse Van Rensburg et al., 2009; Kurti and Dallery, 2014; Taylor et al., 2007). However, exercise trials lasting several weeks have not consistently shown reductions in craving or improvements in abstinence from cigarette smoking (Abrantes et al., 2014). In a recent meta-analytic review of exercise interventions for smoking, the authors recommended trials with sufficiently intense interventions, equal contact control conditions, and measures of exercise adherence and change in physical activity in both exercise and comparison groups (Ussher et al., 2012).

Several reports have recently emerged evaluating the effects of exercise interventions on methamphetamine use. In one key study, an 8-week exercise intervention was utilized and the data showed that lower severity users (≤ 18 days/month) exhibited reductions in methamphetamine use at three time-points after study completion (Rawson et al., 2015). In a separate study, stationary cycling was also shown to reduce craving and inhibitory deficits in methamphetamine users (Wang et al., 2015). Last, exercise training (3 times weekly for 8 weeks) significantly increased striatal dopamine (DA) D_2/D_3 binding potential in methamphetamine users (Robertson et al., 2016), which is likely of considerable import given that long-term methamphetamine use has been previously shown to reduce striatal DA binding (Volkow et al., 2001). Taken together, available data suggest that exercise may reduce methamphetamine use and change brain DA systems.

Importantly, the effects of exercise on cocaine use or craving have not been investigated in humans. However, several reports in rodents show that exercise (i.e., wheel running) reduced cocaine self-administration (Cosgrove et al., 2002; Smith et al., 2008; Zlebnik and Carroll, 2015) and reinstatement of cocaine seeking (Lynch et al., 2010; Ogbonmwan et al., 2015; Thanos et al., 2013). Importantly, rats exposed to 8-weeks running on a treadmill with increasing intensity exhibited reductions in amphetamine-induced DA release (Marques et al., 2008), indicating a potential mechanism of action for this type of intervention.

For this study, we sought to establish for the first time the effects of treadmill exercise on basic fitness measures and objective and subjective measures of cocaine and tobacco use and craving in human volunteers.

2. Methods

The current study was approved by the Baylor College of Medicine institutional review board and the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) Research & Development Committee. Participants were recruited from the Houston area primarily using fliers and newspaper advertisements. Key inclusion criteria were that volunteers be between 21 and 55 years of age, meet DSM criteria for concurrent cocaine- and tobacco-use (cigarette smokers) disorder, be seeking treatment for cocaine use disorder, and have a medical history and brief physical examination demonstrating no clinically significant contraindications for participation in a rigorous exercise program. Participants read and confirmed understanding of the informed consent and were compensated for their time at the conclusion of each week of the study.

Using a between subjects study design, participants were randomized to either running (N=10), walking (N=7) or sitting (N=7; control condition) 3 times per week (30 min per session) for 4 consecutive weeks. The control condition involved sitting passively (for the same period of time) in the laboratory without access to reading materials, mobile phone, or internet, and was based on that used in previous exercise studies in cigarette smokers (Janse Van Rensburg et al., 2009). The 4-week duration of the protocol was chosen for two key reasons. First, this study was designed to mimic the duration and frequency of visits of another protocol completed using this population of individuals (cocaine-dependent smokers) in our lab (Yoon et al., 2013). Second, this protocol was designed with this specific cohort in mind assuming that few of the individuals recruited might be willing to participate in a longer, multi-week (8- or 12-weeks) exercise study (which is a duration commonly used in healthy, non-drug using participants). Distinct groups for runners and walkers were included in this study (rather than just a single moderate intensity "exercise" group) to facilitate an examination of dose response effects of exercise on fitness variables, as well as cocaine- and tobacco-use outcomes.

Participants were not required, nor instructed, to refrain from either tobacco or cocaine use prior to attending any study session. Recent tobacco use was confirmed via breath carbon monoxide (CO) and recent cocaine use was evaluated using a urine toxicology screen (described below). It is important to mention that no participant exhibited signs of acute cocaine intoxication, even those who tested positive for cocaine metabolites in their urine, at the start of any exercise session.

2.1. Bioharness

Remote physiological monitoring of heart rate (HR), respiration, and locomotor activity was accomplished using Bioharness (Zephyr, Annapolis, MD). The validity and reliability of Bioharness measures has been evaluated under controlled laboratory conditions and field-based assessments (Johnstone et al., 2012a, 2012b, 2012c). More recently, studies have begun to examine the clinical and research utility of Bioharness in hospital and exercise settings (Bianchi et al., 2013; Brooks et al., 2013; Kim et al., 2013), and our lab recently demonstrated the usefulness of this device to monitor discreet changes in HR, respiration and body temperature in individuals exposed to an acute dose of cocaine in the laboratory (Yoon et al., 2014). In the current study, Bioharness devices were worn by participants throughout study visits (including specifically throughout the exercise session) so that accurate and detailed exercise profiles could be established.

2.2. Treadmill test

A treadmill test was conducted during screening based on the standard, graded Balke-Ware protocol as described in the 2006 American College of Sports Medicine guidelines. The treadmill test was used primarily for determining maximum and target HR (described in next section) for individuals who were deemed eligible for study enrollment. After resting blood pressure and HR were recorded, participants started walking at a treadmill speed of 2 mph at 0% elevation for 1 min. Treadmill speed was increased 0.5 mph/min with no increase in elevation until treadmill speed was set at 3 mph. After 1 min at speed of 3 mph and 0% elevation, treadmill speed was set at 3.3 mph with 1% elevation. Speed was maintained at 3.3 mph and elevation increased by 1% per minute. Testing was terminated when the participant reached volitional fatigue and could not maintain the pace any longer, or any time the participant expressed desire to stop. After reaching the test termination point the treadmill speed was set back to 2 mph at 0% elevation for a minimum of 3 min for the cool down stage. HR was monitored continuously throughout this session using Bioharness.

2.3. Exercise protocol

All exercise was performed on a NordicTrack Elite 9500 PRO Treadmill and each session was 30-min in duration. HR was monitored using Bioharness on an ongoing basis during exercise. The treadmill speed was adjusted such that participants reached, but did not exceed, target levels. For runners, the target HR was 75% of their maximum HR (MHR) determined by the target HR reserve (THRR) formula. For walkers, the target HR was 25% of their MHR. The THRR formula accounts for individual differences in MHR and individual daily differences in resting HR (RHR). The formula used for runners was $THRR=[(0.75)\times(MHR-RHR)]+RHR$. As a result, the target rate for runners was a consistent 75% of maximum which is considered moderate-vigorous range and thus adequate for a 30 min acute bout of exercise. The goal was to standardize, as much as possible, running among runners and walking among walkers, in an effort to reduce variability among individuals who might be more or less ardent in their exercise participation.

2.4. Assessment of smoking behaviors

Assessment of nicotine dependence was made once during screening using the Fagerstrom Test of Nicotine Dependence (FTND). For this study, tobacco-dependent smokers were defined as those who were currently smoking ≥10 cigarettes/day. Objective measures for tobacco use included once daily measures of breath CO. Subjective measures included twice daily (pre- and post-exercise) self-reports of tobacco craving (using a 100-point visual analog scale: VAS), tobacco use in the previous 24 h (i.e., cigarettes smoked per day, CPD), and once daily measures of the Questionnaire of Smoking Urges (QSU) and the Wisconsin Smoking Withdrawal Scale (WSWS). For the QSU and WSWS, only total scores are reported in the results. Subscale scores for these measures are available upon request.

2.5. Assessment of cocaine use

The objective measure for cocaine use was a once daily measure of urine benzoylecgonine (BE) (Innovacon, Inc., San Diego, CA). Subjective measures included twice daily (pre- and post-exercise) self-reports of cocaine craving (measured using a 100-point VAS) and a once daily self-report (yes vs. no) of cocaine use in the previous 24 h.

2.6. Cognitive behavioral therapy (CBT)

CBT is an evidence-based treatment with strong empirical support that helps patients recognize, avoid, and cope with situations in which they are most likely to abuse drugs. Computerized CBT (CCBT) has been validated for use in cocaine-dependent patients (Carroll et al., 2014). In the current study, all participants received CCBT, which was developed and maintained by HealthSim, Inc. (New York, NY). During each study visit, participants completed a standardized series of CCBT modules specifically designed for the treatment of cocaine addiction. All CCBT information was located on a server maintained by HealthSim Inc., but housed on site.

2.7. Contingency management (CM) and study completion incentives

A platform of CM was used to enhance attendance in this study. CM has been used in stimulant-dependent populations to reward patients for attending consecutive assessment sessions and scheduled follow-up sessions (Carroll and Rounsaville, 2007). The overall total that participants earned if they completed all study visits was $700 USD.

An additional incentive for study participants was that all individuals, regardless of group assignment, received their own new pair of running shoes and socks, running shorts, and a t-shirt. The PI (RD) included the running gear as a way of “ensuring that all participants got off on equal footing”, correctly assuming that these individuals were not likely to have the appropriate gear to ensure the best possible experience while exercising. All participants who completed the protocol were allowed to keep their running equipment with the hope that they might continue to exercise after study completion (though this was not required, nor monitored).

Table 1
Demographic and drug use information for all study participants. Data reflect Mean ± S.D. for the 3 treatment groups.

		Groups			Stats	
		Runners N=10	**Walkers N=7**	**Sitters N=7**	X^2	***p***
Gender	Male	9	5	5	1.2	0.54
	Female	1	2	2		
Race	Black	5	5	6	3.2	0.20
	White	5	1	1		
Other					**F**	***p***
	Age (yr)	43.4 ± 7.4	45.6 ± 1.6	45.7 ± 5.2	0.47	0.64
	Edu (yr)	13.5 ± 2.3	13.0 ± 1.3	11.4 ± 2.1	2.21	0.13
Cocaine	Years	18.6 ± 7.9	18.9 ± 9.3	22.0 ± 8.3	0.38	0.69
	Last 30 days	14.7 ± 8.2	15.7 ± 9.2	15.8 ± 7.5	0.05	0.95
	Grams/day	1.8 ± 1.0	1.4 ± 0.9	1.7 ± 0.9	0.38	0.69
Nicotine	# Smokers	9/10	7/7	6/7		
	Years	24.6 ± 9.5	28.7 ± 9.6	26.9 ± 10.6	0.32	0.73
	Cigs/day	11.9 ± 10.6	11.5 ± 6.9	13.7 ± 7.8	0.12	0.89
	FTND	3.3 ± 2.6	4.7 ± 3.1	5.7 ± 2.1	1.7	0.021

2.8. Statistical analyses

Key outcome measures for this study included changes in fitness measures (e.g., resting HR and body weight), changes in self-reported craving for cocaine and tobacco, changes in withdrawal from tobacco, and changes in cocaine urine toxicology and breath CO.

Within session data (e.g., craving, resting HR) was calculated as change from baseline and compared among groups using ANOVA. Time-course data within sessions (e.g., HR, respiration and locomotor activity) were evaluated using repeated measures ANOVA (with time in minutes being the repeated measure). To evaluate changes between groups for categorical variables (yes vs. no outcomes; i.e., BE urines, self-report cocaine use) data were summed across the week 4 period and compared among groups using one-way ANOVA. For BE urines and self-report cocaine use, the data were evaluated using intent-to-treat analyses such that missing data were presumed to be positive for urines and affirmative for self-report of cocaine use. To evaluate changes between groups for continuous variables (i.e., weight, resting HR, QSU, CPD, and cocaine craving) data were normalized comparing outcomes from week 4 (mean of Days 10, 11 and 12) minus the result from screening, and the result was compared among groups using one-way ANOVA. For cocaine craving, a majority (>50%) of screening data were not available because of a computer error storing those files, so the normalized data reflect comparing outcomes from week 4 (mean of Days 10, 11 and 12) minus the result from Day 1.

Given the small group sizes, an exploratory analysis was conducted combining runners and walkers and renaming these as an “exercise” group, which was then statistically compared to sitters.

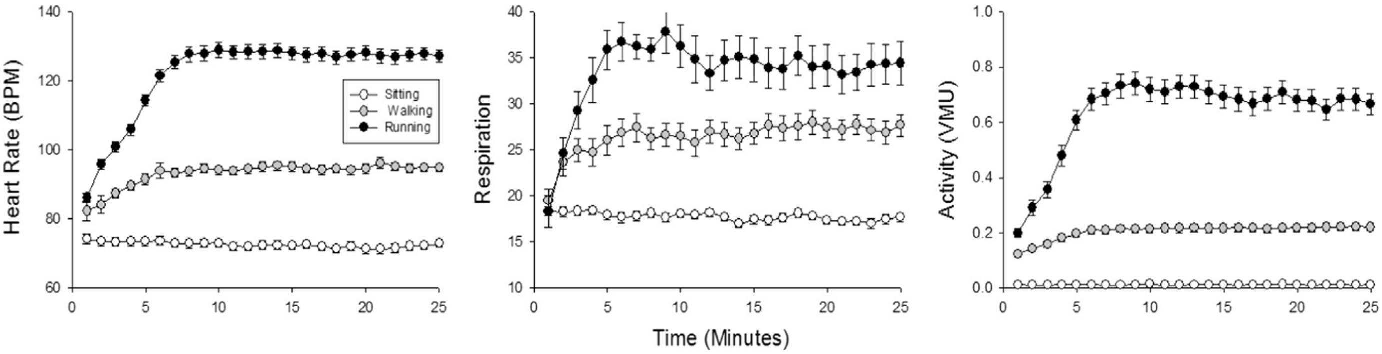

Fig. 1. Within individual sessions, exercise increased heart rate, respiration and locomotor activity. Data reflect Mean ± S.E.M. for the 3 treatment groups.

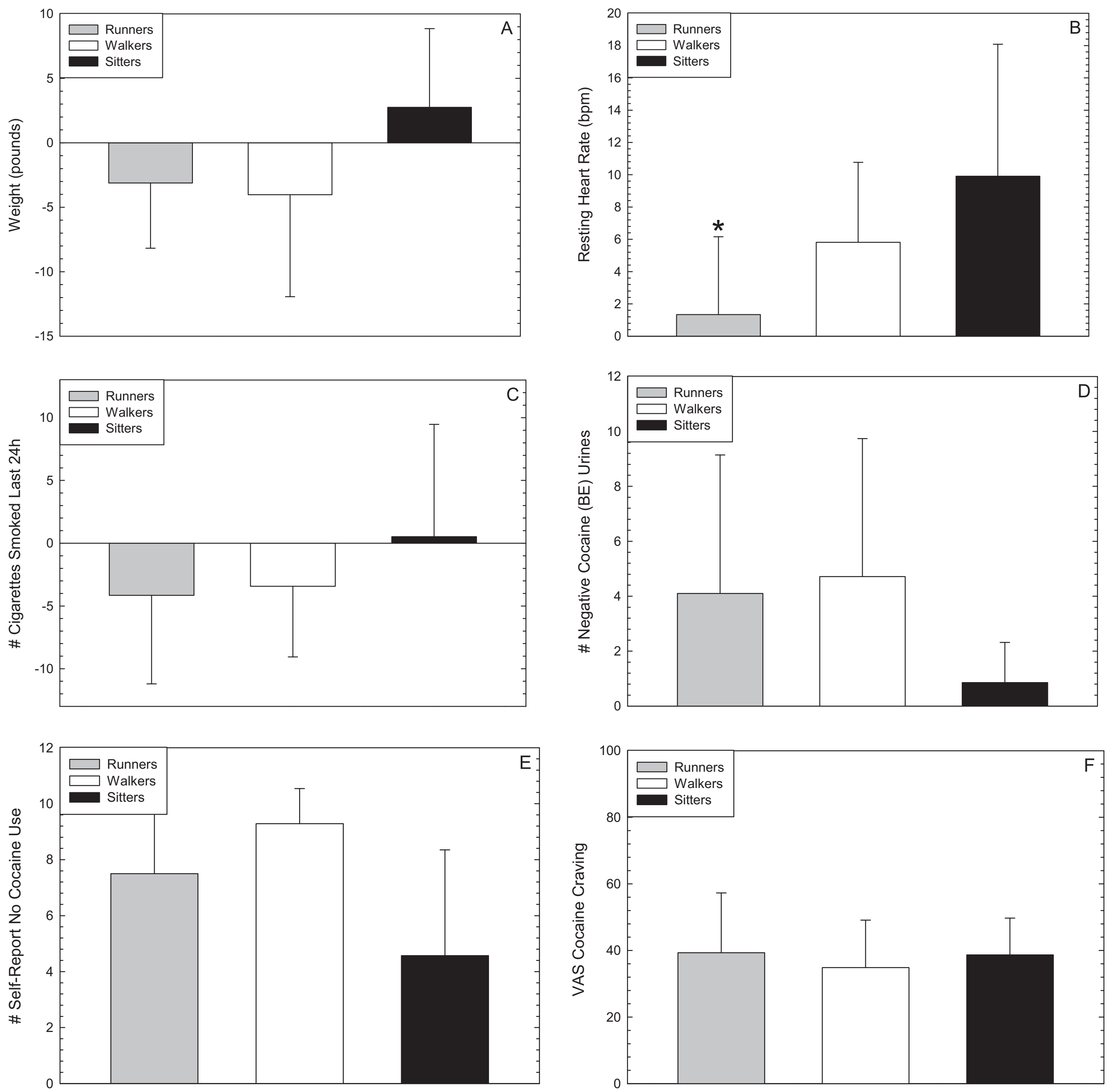

Fig. 2. Key outcomes among three groups for fitness measures (body weight and resting HR), tobacco use (cigarettes smoked in the last 24 h), and cocaine use and craving (# of negative BE urines, # self-report of no cocaine use in the last 24 h and VAS cocaine craving).

Table 2
Data for drug use and craving outcomes for each of the 12 study days is provided. Data reflect Mean ± S.D. Outcomes reflect cigarettes smoked in the last 24 h, percent individuals with negative cocaine (BE) urines [note that percentages are used since group sample sizes were distinct], percent who self-reported no cocaine use in the previous 24 h, and VAS cocaine craving prior to each exercise session.

Session →		1	2	3	4	5	6	7	8	9	10	11	12
Cigs Last 24 h	**Run**	14.2 ± 10.6	12.0 ± 13.8	14.6 ± 9.0	12.5 ± 10.2	13.7 ± 12.3	10.8 ± 7.9	10.6 ± 6.6	12.8 ± 9.7	10.9 ± 7.1	12.2 ± 12.2	13.1 ± 8.2	9.4 ± 8.9
	Walk	9.1 ± 8.0	8.4 ± 8.0	7.3 ± 7.5	9.3 ± 11.1	7.1 ± 5.5	8.0 ± 8.9	5.7 ± 5.4	4.6 ± 4.2	6.1 ± 6.7	6.4 ± 6.5	6.7 ± 4.5	6.1 ± 3.0
	Sit	8.9 ± 7.9	13.4 ± 7.4	13.9 ± 6.8	11.1 ± 7.3	11.4 ± 8.4	12.4 ± 9.5	12.6 ± 7.3	12.0 ± 7.2	11.6 ± 7.7	13.3 ± 8.5	10.1 ± 6.9	10.7 ± 8.9
% Neg Cocaine Urines	**Run**	40	40	30	40	30	40	40	30	30	30	30	30
	Walk	43	29	43	57	29	43	29	57	29	43	43	29
	Sit	14	14	14	14	0	0	0	29	14	0	0	0
%Self-Rep No Use Cocaine	**Run**	60	40	50	60	70	60	70	60	80	60	60	80
	Walk	57	57	71	100	71	100	71	100	86	71	71	71
	Sit	57	29	29	29	15	43	43	29	43	57	29	43
Cocaine Craving	**Run**	41.7 ± 33.7	28.3 ± 29.4	34.4 ± 37.5	35.6 ± 35.7	33.3 ± 39.7	25.6 ± 33.2	25.6 ± 43.3	33.3 ± 34.6	27.8 ± 41.5	28.9 ± 37.2	34.4 ± 41.3	26.7 ± 42.1
	Walk	49.3 ± 26.5	37.1 ± 19.8	22.1 ± 23.8	25.7 ± 17.2	28.6 ± 32.4	20.0 ± 14.1	20.7 ± 28.6	20.7 ± 23.9	13.6 ± 13.1	14.3 ± 25.7	27.9 ± 36.3	21.4 ± 29.1
	Sit	41.4 ± 26.7	32.9 ± 35.0	42.9 ± 32.0	41.4 ± 35.3	38.6 ± 39.8	35.7 ± 40.8	34.3 ± 29.4	44.3 ± 39.1	45.7 ± 39.1	34.3 ± 41.2	32.9 ± 40.7	40.0 ± 41.6

All data analytic strategies described above were used for these outputs as well.

Data are reported as percentages or mean ± S.D., and statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographics and smoking characteristics

There were no significant differences in demographic or drug use variables among runners, walkers and sitters. On average, participants were Black (71%), male (80%), ~45 years of age, and reported frequent use of cocaine (15+ days each month) and moderate levels of cigarette smoking (~½ pack per day) (Table 1).

3.2. Bioharness outputs, exercise intensity and fitness measures

The exercise program was very well tolerated with >90% retention rate and no treatment-related adverse events. All participants (100%) achieved their individually calculated target HR for all exercise sessions (*data not shown*, but implicit from Fig. 1), which provides evidence of adherence to the exercise "prescription" (or group) to which they were assigned.

Several metrics indicated clear distinctions among groups during individual exercise sessions, including mean distance covered (1.89 ± 0.30, 1.19 ± 0.36, 0 ± 0 miles, for runners, walkers and sitters respectively; $F_{2,21}=97.5$, $p<0.0001$) and calories burned (274.4 ± 104.2, 134.6 ± 27.8,*46 ± 0; $F_{2,21}=32.2$, $p<0.0001$). *Value for calories burned for sitters presumed from published standards (Harvard_Health, 2015).

Remote physiological monitoring via Bioharness during sessions showed that the groups also differed according to mean maximum HR, respiration, and locomotor activity (Fig. 1). Specifically, for HR, repeated measures ANOVA reveal a main effect of Group ($F_{2,145}=403.1$, $p<0.0001$), Time ($F_{2,24}=90.8$, $p<0.0001$), and a Group × Time interaction ($F_{2,48}=52.2$, $p<0.0001$). For respiration, repeated measures ANOVA reveal a main effect of Group ($F_{2,107}=75.6$, $p<0.0001$), Time ($F_{2,24}=11.0$, $p<0.0001$), and a Group × Time interaction ($F_{2,48}=5.7$, $p<0.0001$). For locomotor activity, repeated measures ANOVA reveal a main effect of Group ($F_{2,145}=293.5$, $p<0.0001$), Time ($F_{2,24}=57.0$, $p<0.0001$), and a Group × Time interaction ($F_{2,48}=35.5$, $p<0.0001$).

Comparing across groups, exercise improved fitness measures including a non-significant reduction in body weight ($F_{2,20}=2.4$, $p=0.11$) (Fig. 2A) and a significant reduction in resting HR ($F_{2,20}=3.9$, $p=0.035$) (Fig. 2B). Post-hoc tests confirmed significant differences for resting HR between runners vs. sitters ($p=0.01$).

3.3. Effects of exercise on tobacco craving and use

Exercise did not significantly alter QSU total scores (−7.1 ± 7.1, −20.5 ± 14.9, −10.7 ± 15.2; $F_{2,20}=2.4$, $p=0.12$) and did not change CPD ($F_{2,20}=0.88$, $p=0.43$) (Fig. 2C).

In addition, exercise resulted in non-significant reductions in current craving for tobacco (VAS scale of 100) (−11.3 ± 9.5, −20.2 ± 9.9, +1.4 ± 5.5; $F_{2,21}=1.5$, $p=0.25$), but did not affect WSWS total scores (−0.14 ± 0.2, −0.29 ± 0.3, −0.42 ± 0.2; $F_{2,19}=0.37$, $p=0.69$).

3.4. Effects of exercise on cocaine craving and use

Within-session changes (post-exercise minus pre-exercise) included most notably non-significant reductions in craving for cocaine (VAS scale of 100) (−7.9 ± 3.3, −6.9 ± 3.3, −0.06 ± 1.8; $F_{2,21}=1.8$, $p=0.18$).

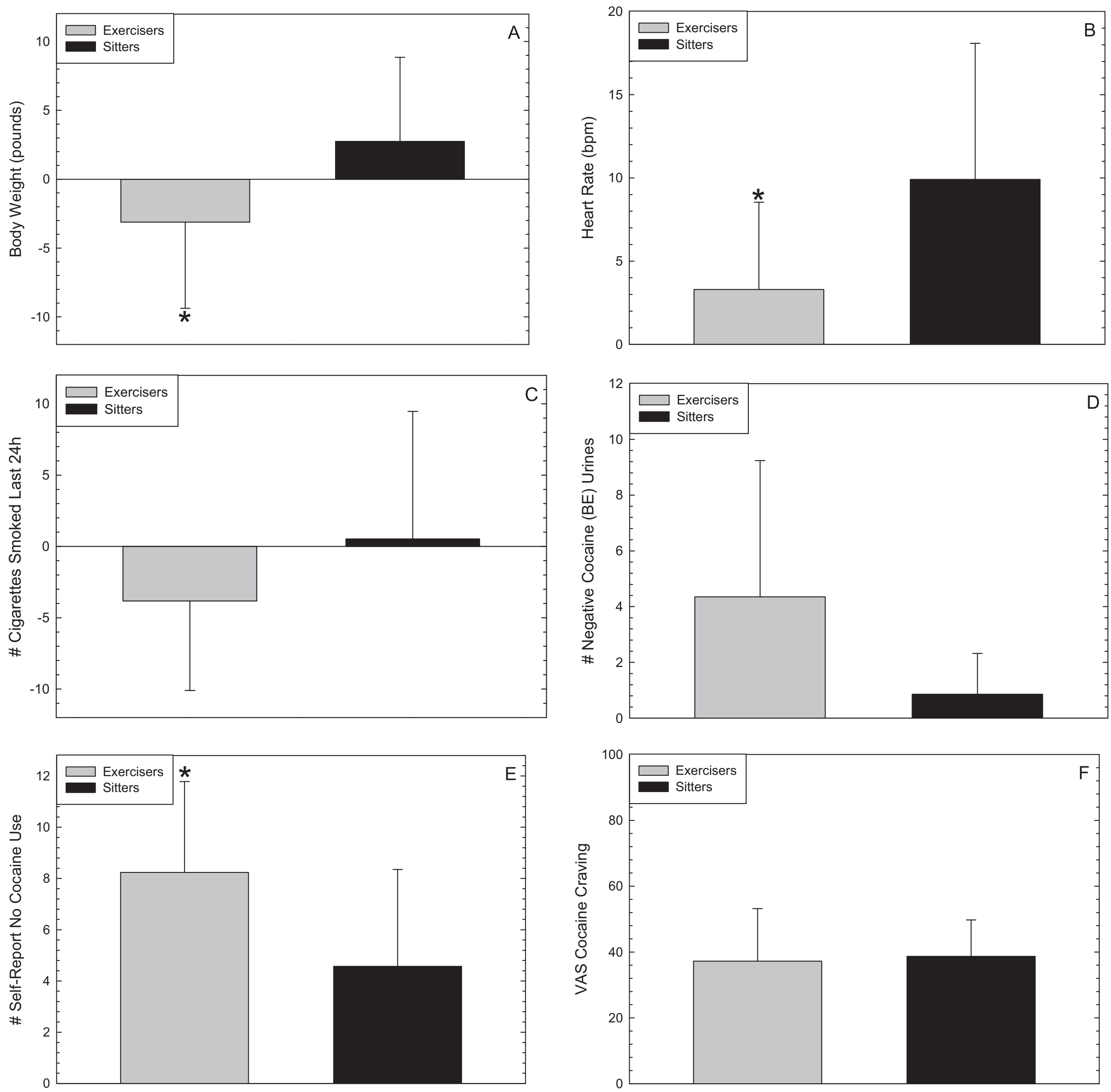

Fig. 3. Key outcomes between two groups for fitness measures (body weight and resting heart rate), tobacco use (cigarettes smoked in the last 24 h), and cocaine use and craving (# of negative BE urines, # self-report of no cocaine use in the last 24 h and VAS cocaine craving).

Though not statistically significant, exercise improved abstinence from cocaine (number of negative BE urines out of 12) ($F_{2,21}=1.7$, $p=0.21$) (Fig. 2D), increased self-reports of no cocaine use in last 24 h (number of days out of 12) ($F_{2,21}=3.1$, $p=0.07$) (Fig. 2E), and did not significantly change craving for cocaine ($F_{2,21}=0.19$, $p=0.83$) (Fig. 2F).

3.5. *Time course of effects for drug use and craving*

The data for drug use and craving outcomes for each of the 12 study days is provided in Table 2.

3.6. *Exploratory analyses comparing exercisers vs. sitters*

Comparing between groups, exercise improved fitness measures including a significant reduction in body weight ($F_{1,22}=4.4$, $p=0.048$) (Fig. 3A) and a significant reduction in resting HR ($F_{1,22}=5.5$, $p=0.029$) (Fig. 3B). Post-hoc tests confirmed significant differences between exercisers vs. sitters for body weight ($p=0.048$) and resting HR ($p=0.03$).

Exercise did not significantly change CPD ($F_{1,21}=1.8$, $p=0.19$) (Fig. 3C), but resulted in non-significant improvements in abstinence from cocaine ($F_{1,22}=3.4$, $p=0.08$) (Fig. 3D) and significantly increased self-reports of no cocaine use in last 24 h ($F_{1,22}=5.1$, $p=0.03$) (Fig. 3E). Post-hoc tests confirmed significant differences between exercisers vs. sitters for self-reports of no cocaine use in last 24 h ($p=0.03$). Finally, there were no significant changes in craving for cocaine ($F_{1,21}=0.15$, $p=0.70$) (Fig. 3F).

4. Discussion

To our knowledge, this is the first study to evaluate the effects of a multi-week exercise program in individuals with concurrent cocaine and tobacco-use disorder. The data clearly show significant improvements in basic fitness measures and several indices reveal non-significant reductions in cocaine use and craving, though reductions in tobacco use and craving were not as robust. Of note was the effect of exercise in this study on resting HR. Resting HR has been shown to predict longevity is also an important marker of outcome in cardiovascular disease, including heart failure.

The data in the current report appear to coincide with recent research showing that exercise reduced methamphetamine use (Rawson et al., 2015) as well as craving in methamphetamine users (Wang et al., 2015). In addition, exercise significantly increased striatal DA D2/D3 binding potential in methamphetamine users (Robertson et al., 2016), and these data imply that exercise training may ameliorate dopaminergic deficits.

The neurobiological means by which exercise may have altered cocaine use and craving were not investigated in this study. Available evidence in rodents (Marques et al., 2008) and humans (Fisher et al., 2013; Robertson et al., 2016) suggests changes to DA systems as one potential mechanism of action. Other research indicates that aerobic exercise in rodents reduces cocaine seeking behavior and these changes are accompanied by alterations in neuronal signaling in the prefrontal cortex (assessed by pERK western blot analysis) (Lynch et al., 2010).

The current study design addressed the previously identified limitation of “lack of measures of exercise adherence” of most exercise trials (Ussher et al., 2012) since all exercise occurred in the presence of trained research staff and a wireless device provided quantitative data of exercise engagement (including duration and intensity) for all sessions. Of interest, despite marked statistical differences between runners and walkers for distance covered, calories burned, and maximum HR and respiration, there were few instances where running proved more effective than walking for reducing cocaine use or craving. If anything, additional clarity of potential benefits of this intervention was gained using an exploratory analysis combining walkers and runners into a single exercise group and comparing those outcomes against sitters.

Despite these encouraging outcomes, it is important to concede some limitations. This was a preliminary trial with a small sample size, so our power to detect statistically significant effects on cocaine and tobacco use and craving outcomes was limited. In particular, the small sample size prevents a complete understanding of differences between the walking and running conditions. Also, the small sample sizes did not allow us to correlate change in fitness with changes in drug use or craving. Another limitation is that the majority of participants were male, so the effects of gender could not be evaluated, but certainly warrant careful consideration especially given what is known from animal models (Sanchez et al., 2014; Zlebnik et al., 2014). In this study, participants were not required, nor instructed, to refrain from either tobacco or cocaine use prior to attending any study session. It is feasible, therefore, that variability in pre-session cocaine/cigarette exposure influenced some outcomes (e.g., HR and craving) and this should also be considered a potential limitation. Lastly, in the report by Rawson et al. (2015), the best outcomes were shown for the subset of individuals who used drug less frequently every month. Given our small sample size, it was not possible to conduct a similar analysis of data according to recent drug use. Notwithstanding the limitations, the data from this study provide preliminary evidence for the efficacy of exercise for improving fitness and reducing cocaine use.

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