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Predictors of Tobacco Abstinence in Outpatient Smokers with Schizophrenia or Bipolar Disorder Treated with Varenicline and Cognitive Behavioral Smoking Cessation Therapy

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Abstract

Background: The estimated mortality gap between those with and without serious mental illness (SMI) is increasing, now estimated at 28 years, which is largely due to smoking-related diseases.

Aims: We sought to identify predictors of 14-day continuous abstinence in stable outpatient smokers with SMI.

Method: Adult smokers with schizophrenia spectrum (n =130) or bipolar disorder (n =23) were enrolled in a 12-week course of varenicline and cognitive-behavioral therapy for smoking cessation.

Results: Independent predictors of abstinence included reduction in withdrawal symptoms prior to the quit day, fewer cigarettes smoked per day at baseline, better baseline attention, remitted alcohol dependence, and lower expectation of peer support to aid quitting.

Conclusions: Interventions that consider these targets may improve smoking cessation outcomes in those with SMI.

Keywords

schizophrenia; nicotine; predictors; smoking cessation; varenicline; abstinence; bipolar

1. INTRODUCTION

Recent estimates indicate that 64–79% of those with schizophrenia spectrum disorders smoke tobacco regularly (Dickerson et al., 2013; Hartz et al., 2014), as do 44–71% of those with bipolar disorder (Dickerson et al., 2013; Hartz et al., 2014; Kreinin et al., 2012), compared to 18% of the general U.S. population (Agaku et al., 2014; Le Cook et al., 2014;

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USDOHAHS, 2004). Moreover, the estimated mortality gap between those with and without schizophrenia spectrum disorders is now estimated to be 28 years, is increasing, and is largely due to diseases that are causally related to tobacco smoking (Olfson et al., 2015). Although pharmacologic smoking cessation aids are effective and well tolerated in this population (Chengappa et al., 2014; Evins et al., 2014; Goff et al., 2005; Heffner et al., 2010; Pachas et al., 2012a; Roberts et al., 2016; Tsoi et al., 2013; Weiner et al., 2011; Williams et al., 2012; Ziedonis et al., 2008), smokers with serious mental illness (SMI) are less likely to receive smoking cessation interventions (Druss et al., 2001; Goff et al., 2005; Heffner & Anthenelli, 2011; Himelhoch & Daumit, 2003; Kupfer, 2005; Prochaska, 2010, 2011; Schroeder & Morris, 2010; Ziedonis et al., 2008) despite often being highly motivated to quit smoking (Addington et al., 1997; Evins et al., 2004).

Among those with psychiatric illness receiving brief behavioral treatment for smoking cessation, varenicline treatment results in superior abstinence rates than placebo, nicotine patch and bupropion (Anthenelli et al., 2016). However, predictors of abstinence with varenicline among smokers with psychiatric illness have not yet been extensively studied, with the exception of a preliminary investigation that identified affective flattening as a negative predictor of abstinence in a modest sample (Dutra et al., 2012). Predictors of abstinence with other smoking cessation pharmacotherapies in this population include cigarettes per day (Culhane et al., 2008), readiness to quit (Chou et al., 2015; Ferron et al., 2012), later age of smoking initiation (Culhane et al., 2008), male gender (Gonzalez-Pinto et al., 2012), and better attention and executive functioning (Culhane et al., 2008; Dolan et al., 2004; Moss et al., 2009; Steinberg et al., 2012). In the general population, predictors of abstinence with varenicline include less severe nicotine dependence (Boudrez et al., 2013), no recent quit attempts (Heffner et al., 2010), and early initiation of abstinence during treatment (Heffner et al., 2010). Identifying characteristics of smokers most likely to quit with varenicline could inform providers who may be hesitant to prescribe to smokers with SMI (Mitchell et al., 2015; Ratschen et al., 2009), thereby increasing access to guideline-concordant smoking cessation treatment.

We sought to identify independent predictors of abstinence in a sample of outpatient smokers with schizophrenia or bipolar disorder treated with 12 weeks of open label varenicline and cognitive-behavioral therapy (CBT). Candidate predictors included factors associated with abstinence in smokers treated with varenicline in the general population (e.g., smoking characteristics, prior quit attempts, and early response to treatment) and in smokers with SMI across different cessation treatments (e.g., gender, cognition), as well as potential novel predictors including smoking environment and physical health.

2. MATERIAL AND METHODS

The study was approved by the institutional review boards at all study sites and by an independent data and safety monitoring board. Participants provided written informed consent and demonstrated understanding of study procedures via a written test of competency to consent.

2.1 Participants

Two hundred and four participants were enrolled in the parent trial (Evins et al., 2014) involving a 12-week, open-label trial of varenicline and weekly group CBT for smoking cessation (NCT00621777). Participants were stable adult outpatient daily smokers with a DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder, enrolled from 10 community mental health centers in six states. Participants were eligible to enroll who smoked ≥ 10 cigarettes per day, had expired carbon monoxide (CO) >9 parts per million (ppm), were on a stable, clinically determined antipsychotic or mood stabilizing medication for at least one month before enrollment, and willing to take varenicline and set a quit date within four weeks of enrollment. Current or recent suicidality or homicidality, hospitalization for suicidality in the prior 12 months, a major depressive episode in the prior six months, an active substance use disorder, or unstable medical illness were exclusionary. Analyses only included the 153 participants (75% of participants in parent project) who had withdrawal scores within two weeks of the quit date, as change in withdrawal was evaluated as a predictor of abstinence.

2.2 Intervention

The 12-week intervention (Pachas et al., 2012) was open label varenicline 0.5 mg once daily for three days, 0.5 mg twice daily for four days, then 1 mg twice daily for 11 weeks, along with weekly one-hour manualized group CBT for smokers with SMI (Cather et al., 2013). Participants began study medication at baseline and set a quit date between study weeks four and five.

Fourteen-day point prevalence abstinence at study week 12 was the outcome of interest and was defined as self-reported 7-day continuous abstinence at study week 12, biochemically verified by semi-quantitative urine cotinine (Accutest NicAlert Urine Screen, Jant Pharmaceuticals) and self-reported 7-day continuous abstinence at study week 11, biochemically verified by expired CO <9 ppm. Expired CO was assessed at all study visits and CO <9 ppm was the *a priori* CO concentration cutoff for biochemical confirmation of self-reported abstinence at week 12 if cotinine data were missing (Hughes et al., 2003; Evins et al., 2014). Participants who discontinued the study before week 12 ($n=39$) were considered to be non-abstinent for the analyses (Hajek et al., 2013).

2.3 Candidate Predictors (Table 2)

2.3.1 Cognitive performance.—Participants were administered three measures of neurocognition at baseline, which yielded over 25 variables. A principal component analysis (PCA) was conducted for variable reduction, as in prior studies with this population (Kern et al., 2006). Orthogonal rotation produced five factors with eigenvalues >1 : vigilance, memory, speed of processing, accuracy, and reaction time variability (Table 1). Resultant factors were included as candidate abstinence predictors.

2.3.2 Patient characteristics.—Age, gender, race, marital status, history self-reported lifetime alcohol dependence, education, and estimated full-scale IQ (Wechsler Test of Adult Reading, WTAR (Wechsler, 2001)) were assessed at baseline. Prior analyses from this

sample indicated no difference in abstinence rates by primary diagnosis, and therefore diagnosis was not considered as a candidate predictor (Evins et al., 2014).

2.3.3 Treatment characteristics.—Participants' antipsychotic treatment regimen was assessed at baseline by a clinician. Clozapine versus non-clozapine antipsychotic treatment was examined as a potential predictor of abstinence, as other studies have found clozapine treatment to improve substance use outcomes in general and smoking cessation outcomes in particular compared to other antipsychotic agents (George et al., 1995; McEvoy et al., 1995).

2.3.4 Smoking characteristics.—Expired CO concentration at baseline (Bedfont Smokerlyzer, Kent, England), age of smoking initiation, years smoked, number of cigarettes smoked per day, percent change in number of cigarettes smoked per day from baseline to quit day, severity of nicotine dependence (total score on the Fagerstrom Test for Nicotine Dependence, FTND (Fagerstrom, 2012)), percent change in nicotine withdrawal symptom rating scale total score from baseline to quit day (Wisconsin Smoking Withdrawal Scale, WSWs (Welsch et al., 1999)), smoking expectancies (total score on the Tiffany Questionnaire of Smoking Urges, TQSU (Tiffany & Drobes, 1991)), self-reported motivation to quit smoking, and number of lifetime quit attempts were assessed for each participant.

2.3.5 Smoking environment.—At baseline, participants reported the number of people who smoked in their households (other than self), percent of closest friends who smoked, supportive others' desire for the participant to quit smoking (on a 10-point visual analogue scale), and perceived helpfulness of supportive others to aid a quit attempt (on a 10-point visual analogue scale).

2.3.6 Psychopathology.—At baseline, participants answered a self-report questionnaire on trait impulsivity (total score on the Barrett Impulsiveness Scale, BIS (Patton et al., 1995)), as well as staff-administered interviews on psychiatric symptoms (total score on the Brief Psychiatric Rating Scale, BPRS (Overall & Gorham, 1962)), and severity of negative symptoms (total score on the Schedule for Assessment of Negative Symptoms, SANS (Andreasen, 1983)).

2.3.7 Physical health.—Participants' 10-year cardiovascular risk (Framingham score (D'Agostino et al., 2008)) and body mass index (BMI) were calculated at baseline.

2.4 Statistical Analysis

Alphas of $p = 0.05$ were required for forward-selection multivariable logistic regression model entry. Available case-wise analysis was used when evaluating each variable (Little & Rubin, 2014). Alphas of $p = 0.05$ were significant. Model performance was examined with area under the receiver operating curve (AUC) and a five-fold cross-validated AUC was used to evaluate the sensitivity of the final model (Chuang, et al., 2007; Guyon & Elisseeff, 2003; Stone, 1977).

3. RESULTS

One hundred and fifty-three adult smokers with schizophrenia spectrum or bipolar disorder completed at least 3 weeks of the intervention and 49.7% achieved at least 14 days biochemically-verified continuous abstinence at week 12 (Abstinent: $M=42.4$ days abstinent, $SD=18.9$ and CO $M=1.2$ ppm, $SD=1.6$; Non-Abstinent: $M=1.4$ days abstinent, $SD=2.8$ and CO $M=12.7$ ppm, $SD=12.1$; $p<0.0001$). Sample demographics are shown in Table 2 by abstinence status. The 153 participants included in analyses did not differ from the 49 excluded participants on demographic, clinical or smoking related variables (p -values >0.09), except included participants had more education ($M=12.6$ years, $SD=2.4$) than excluded participants ($M=11.5$ years, $SD=3.0$; $p = 0.008$). The mean CO at week 12 for those considered to have met criteria for abstinence was 1.2 ppm ($SD=1.6$) as compared to 12.7 ppm ($SD = 12.1$) in the non-abstinent group.

Univariate predictors of abstinence ($p \leq 0.10$) included: ever married, prior alcohol dependence, fewer cigarettes smoked per day at baseline, greater reduction in withdrawal prior to quitting, lower expectation of peer support to aid quitting, more severe psychiatric symptoms (BPRS), and superior estimates of vigilance, memory, and reaction time variability (Table 2).

Predictors of abstinence in the multivariable model were prior alcohol dependence, number of cigarettes per day, improvement in withdrawal prior to quitting, less expectation of peer support to aid quitting, and better vigilance and less reaction time variability (Table 3). The AUC was 0.77 and was 0.74 after cross-validation indicating sufficient discriminative strength (Rice & Harris, 2005) and a large effect size.

In exploratory analyses, we replaced the withdrawal scale total score in the multivariable model with each of the seven subscales separately (Welsch et al., 1999). Only change in the 'craving' subscale was associated with abstinence ($p=0.03$; all other p -values >0.09).

4. DISCUSSION

This is the first study to evaluate the association between multiple participant characteristics and tobacco abstinence among smokers with schizophrenia spectrum and bipolar disorders treated with varenicline and CBT. Reduction in withdrawal prior to the quit date, smoking fewer cigarettes per day at baseline, better baseline attentional performance, past alcohol dependence, and anticipating *less* support from others in their environment during a cessation attempt were all associated with end of treatment abstinence.

This study replicates prior reports of an association between smoking fewer cigarettes per day at baseline (Kale et al., 2015; Vangeli et al., 2011) in smokers without major psychiatric illness and superior baseline attentional performance in smokers with schizophrenia spectrum disorders (Culhane et al., 2008). A novel finding in this study was that reduction in withdrawal prior to the quit date was associated with abstinence. Varenicline has been reported to ameliorate craving in smokers with and without schizophrenia (Rollema et al., 2007; Smith et al., 2016), and this may be an important early marker of treatment efficacy in smokers with SMI. There may be clinical benefit to monitoring withdrawal symptom relief

in the first weeks of treatment so that treatment can be modified for those whose nicotine withdrawal symptoms in general or urge to smoke in particular remains high.

Consistent with prior work (Culhane et al., 2008), baseline vigilance and hit reaction time variability, components of attention assessed with a continuous performance task, predicted end of treatment abstinence. Sustained attention is mediated by the basal forebrain cholinergic system, which is impacted by nicotine administration and withdrawal (Levin et al., 2006). Smokers with poorer attention at baseline may be more likely to continue smoking to relieve baseline cognitive deficits, and varenicline may both improve baseline attention and attenuate any withdrawal-emergent attentional impairment (Liu et al., 2011; Roh et al., 2014; Wing et al., 2013). Additionally, individuals with better attention may be better able to attend to and learn cessation skills taught in CBT (Fals-Stewart & Lam, 2010), and to more efficiently engage in goal-directed behavior change (Loughead et al., 2015; Patterson et al., 2010), particularly during times of craving or cue-exposure (Heatherton & Wagner, 2011; Kemps et al., 2008; Sayette & Hufford, 1994). Interventions that improve cognitive deficits may improve smoking cessation outcomes, particularly among smokers with schizophrenia whose cognitive deficits represent a core component of the disease.

Prior alcohol dependence was positively associated with attainment of abstinence with varenicline in this population. Although current alcohol and substance use disorders have been reported to decrease rates of successful tobacco abstinence (Gonzalez-Pinto et al., 2012; Humfleet et al., 1999b; Hurt et al., 1994; Hymowitz et al., 1997), those with a past history of an alcohol use disorder have been reported to be as likely to quit smoking as those with no such prior history (Breslau et al., 1996; Humfleet et al., 1999a). Those who have recovered from other substance use disorders may benefit from relevant skills learned to attain such sobriety, such as alternative coping responses to stress and avoidance of triggers.

Finally, it was unexpected that anticipation of *less* support from others in the environment during a cessation attempt would be associated with abstinence. It is reasonable to postulate that overestimating the magnitude of support from people in the environment may decrease the probability of attaining abstinence, particularly for those with major psychiatric illness for whom current smokers commonly comprise a majority of those in one's social network. Eighty-three percent of smokers in this study lived with a smoker. Significant reliance on support to quit from current smokers may undermine a cessation attempt through multiple pathways, such as increasing time spent in social environments with smokers, an established risk factor for failure to quit and/or relapse (Chang et al., 2006; Kleinjan et al., 2009; Roberts et al., 2015). It may be beneficial to directly assess the smoking environment to help foster realistic appraisals of support for smoking cessation from social networks.

The major limitation in this study is the lack of a control group without which we are unable to identify whether the identified predictors of abstinence are specific to varenicline, and are able to conclude only that these variables are predictors of abstinence in the context of varenicline treatment. A low smoking cessation rate of approximately 4% has consistently been reported in those with schizophrenia spectrum disorders with behavioral treatment and placebo, and pharmacotherapy for smoking cessation consistently increases the odds of quitting by 3–6 fold in smokers with schizophrenia and bipolar disorder (Chengappa et al.,

2014; Culhane et al., 2008; Evins et al., 2005; Evins et al., 2007; Evins et al., 2016; Roberts et al., 2016; Tsoi et al., 2013; Williams et al., 2013). Thus, a control group was not included because pharmacotherapy is likely to have a much larger effect on abstinence than other predictors, particularly in this population. As pharmacotherapy is recommended by clinical practice guidelines for smokers with schizophrenia (Buchanan et al., 2010; Evins & Cather, 2015), this study may be clinically useful as a report of predictors of abstinence in smokers with schizophrenia spectrum and bipolar disorders in the setting of recommended pharmacotherapy and behavioral support. Additionally, these findings may not generalize to those who do not remain in treatment for at least three weeks, are psychiatrically or medically unstable, or have other active substance use disorders. As the bipolar cohort in this study was small ($n = 20$), predictors of abstinence were not examined separately by primary diagnosis. Similarly, because of limitations due to low power for subgroup analyses, this study did not control for potential differences across recruitment sites. Finally, other studies identify additional aspects of neurocognition including executive functioning as important predictors of abstinence in this population (Dolan et al., 2004; Moss et al., 2009), which we were unable to evaluate given the limited executive function battery employed.

5. CONCLUSIONS

Smoking remains an epidemic among those with SMI, responsible for large and still growing disparities in life expectancy between those with and without SMI. To improve smoking cessation rates in this population, and reduce these disparities, it is important to understand factors associated with cessation success. These results indicate that for smokers with schizophrenia and bipolar disorders who attempt to quit smoking with varenicline and behavioral support, interventions are needed to improve outcomes in sub-groups who smoke more heavily, do not report significantly reduced craving with treatment, have poorer attention, have not previously learned skills to cope with addiction, and who have unrealistic expectations of support from others for quitting. Future studies should consider whether the predictors identified in this study generalize to other guideline concordant smoking cessation treatments in this population.

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Table 1.

Loadings of cognitive performance dependent variables on principal factors

	Components				
	1: Vigilance	2: Memory	3: Speed of Processing	4: Accuracy	5: Reaction Time Variability
CPT 2-digit correct hits	0.820				
CPT 3-digit correct hits	0.863				
CPT 4-digit correct hits	0.789				
CPT Shapes correct hits	0.853				
CPT 2-digit correct hits error				0.414	
CPT 3-digit correct hits error				0.693	
CPT 4-digit correct hits error				0.858	
CPT Shapes correct hits error				0.772	
CPT 2-digit reaction time mean			0.796		
CPT 3-digit reaction time mean			0.802		
CPT 4-digit reaction time mean			0.866		
CPT Shapes reaction time mean			0.858		
CPT 2-digit reaction time SD					0.599
CPT 3-digit reaction time SD					0.647
CPT 4-digit reaction time SD					0.761
CPT Shapes reaction time SD					0.635
CPT 2-digit D'	0.774				
CPT 3-digit D'	0.785				
CPT 4-digit D'	0.671				
CPT Shapes D'	0.730				
WMS scaled score		0.505			
BVMT encoding		0.906			
BVMT total learning		0.946			
BVMT delayed recall		0.902			
BVMT response bias		0.550			

Note: Loadings are rotated orthogonal solutions from the pattern matrix between cognitive variables and retained components.

Table 2.

Univariate comparison of candidate predictors at baseline by 12-week abstinence status

	Abstinent (n=76)	Non-Abstinent (n=77)	p-value
<u>Patient Characteristics</u>			
Age	48.2(10.4)	46.8 (10.0)	0.38
Sex, male	n = 49 (64.5%)	n = 46 (59.7%)	0.55
Race, White [†]	n = 57 (75.0%)	n = 56 (72.7%)	0.75
Hispanic ethnicity	n = 1 (1.4%)	n = 3 (4.0%)	0.32
Never married	n = 46 (60.5%)	n = 57 (74.0%)	0.08
Prior alcohol dependence diagnosis	n = 38 (50.0%)	n = 28 (36.4%)	0.09
Highest grade completed	12.8 (2.2)	12.4 (2.5)	0.23
Estimated IQ	97.9 (11.4)	95.6(12.6)	0.23
<u>Illness/Treatment Characteristics</u>			
Clozapine ^x	n = 14 (18.9%)	n = 12 (15.6%)	0.64
<u>Smokina Characteristics</u>			
Expired CO (ppm)	21.4 (14.6)	24.0 (14.4)	0.28
Age at smoking initiation	17.1 (5.2)	18.3 (6.6)	0.19
Years smoked	28.9(12.7)	26.5 (12.0)	0.24
Cigarettes per day	20.8 (12.4)	24.9 (11.8)	0.04
Change in cigarettes per day from baseline to quit day, %	62.0% (46.7)	52.2% (40.3)	0.22
FTND total score	6.0 (1.7)	6.4 (1.7)	0.19
Change in withdrawal from baseline to quit day, %	-15.0% (20.5)	-4.9% (21.0)	0.005
TQSU total score	24.4 (4.5)	24.7 (4.9)	0.72
Motivation to quit (1-10)	8.8 (1.4)	8.9 (1.3)	0.63
Number of lifetime quit attempts	4.5 (6.5)	7.2 (18.0)	0.26
<u>Smokina Environment</u>			
Smokers in household, %	83.0% (27.0)	81.8% (26.5)	0.79
Closest friends who smoke			
Less than half	n = 28 (36.8%)	n = 31 (40.3%)	0.66
Half or more	n = 48 (63.2%)	n = 46 (59.7%)	
Others' desire for participant to quit (1,Not at all to 10, Very much)	8.1 (2.5)	8.1 (2.6)	0.87
Others' helpfulness to aid quitting (1,Not at all to 10, Very much)	6.7 (3.1)	7.7 (2.9)	0.04
<u>PsychoDatholoav</u>			
BIS total score	66.0 (9.6)	67.6 (10.3)	0.34
BPRS total score ^{††}	53.1 (13.4)	49.5 (13.1)	0.10
SANS total score	45.9 (18.5)	46.3 (17.4)	0.90
<u>Physical Functioning</u>			
Framingham score	0.2 (0.1)	0.1 (0.1)	0.35
BMI	32.0 (7.0)	31.4 (6.5)	0.62
<u>Coanitive Performance</u>			
Component 1 (Vigilance)	0.2 (0.9)	-0.1 (1.0)	0.02

	Abstinent (n=76)	Non-Abstinent (n=77)	p-value
Component 2 (Memory)	0.2 (1.0)	-0.1 (1.0)	0.10
Component 3 (Speed of Processing)	0.1 (1.0)	-.001 (0.9)	0.56
Component 4 (Error Rate)	-0.05 (1.0)	0.004 (0.9)	0.74
Component 5 (Reaction Time)	-0.2 (0.9)	0.2 (1.0)	0.03

Note: Group differences in categorical variables were tested with chi-square tests and when expected cell count is less than 5, group differences were tested with Fisher's exact. Group differences in continuous variables were evaluated with unbalanced one-way ANOVA. All values are means and standard deviations unless otherwise noted.

BIS, Barrett Impulsiveness Scale; BMI, Body Mass Index; BPRS, Brief Psychiatric Rating Scale; CO, Carbon monoxide; FTND, Fagerstrom Test for Nicotine Dependence; SANS, Schedule for Assessment of Negative Symptoms; TQSU, Tiffany Questionnaire of Smoking Urges; WSWs, Wisconsin Smoking Withdrawal Scale; WTAR, Wechsler Test of Adult Reading.

[†] Race (White) was correlated with IQ ($r=0.39$, $p<0.001$).

[×] Clozapine was associated with race ($r=0.23$, $p<0.01$), younger age of smoking initiation ($r=-0.20$, $p=0.01$), and lower perception of others' desire for participant to quit ($r=-0.23$, $p<0.01$).

^{††} BPRS was correlated with more prior quitting attempts ($r=0.19$, $p=0.02$), greater Framingham cardiac risk ($r=0.24$, $p<0.01$), younger age of smoking initiation ($r=-0.21$, $p=0.01$), more years of regular smoking ($r=0.25$, $p<0.01$), older age ($r=0.2$, $p=0.01$), higher BIS score ($r=0.40$, $p<0.001$), and higher SANS score ($r=0.41$, $p<0.001$).

Table 3.

Independent Predictors of 14-day Smoking Abstinence in Multivariable Analysis

Factor	Effect (Beta)	Odds Ratio	95% CI	p-value
<u>Background Characteristics</u>				
Prior alcohol dependence	1.07	2.91	1.33, 6.39	0.008
<u>Smoking Characteristics</u>				
Cigarettes per day	−0.03	0.97	0.94, 0.99	0.04
Change in withdrawal from baseline to quit day	−2.92	0.05	0.01, 0.38	0.004
<u>Smoking Environment</u>				
Others' helpfulness to aid quitting	−0.20	0.82	0.71, 0.93	0.003
<u>Cognitive Performance</u>				
Vigilance	0.52	1.68	1.13, 2.5	0.01
Reaction time variability	−0.40	0.67	0.46, 0.98	0.04