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Relation between cigarette smoking and cognitive function in euthymic individuals with bipolar disorder

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ABSTRACT

Background: Individuals with bipolar disorder have higher rates of cigarette smoking and cognitive deficits when compared to the general population. Emerging evidence indicates that both smoking and cognitive deficits are associated with more severe illness presentation and course.
Methods: The data were derived from a study evaluating a novel treatment for cognitive function in bipolar disorder. Smoking status was determined by self-report; cognitive function was evaluated with a comprehensive cognitive battery, which included measures of psychomotor speed, attention, memory, learning and executive function. The relations between smoking status and cognitive measures were evaluated with two independent-samples *t*-test and multiple regression.
Results: The sample comprised forty-three subjects with bipolar disorder (Type I/II). There were no consistent differences in neuropsychological performance between current smokers ($N=16$) and non-smokers ($N=27$) on most tasks. The occurrence of subjective cognitive failures, as measured with the Cognitive Functioning Questionnaire, was non-significantly lower for smokers compared to non-smokers. Lifetime "smoking load" was negatively associated with premorbid intelligence as estimated by the National Adult Reading Test.
Conclusion: This pilot study provides preliminary evidence that cigarette smoking may exert a salutary effect on subjective, but not objective, measures of cognitive function in euthymic bipolar patients. A larger sample size evaluating this hypothesis would be less vulnerable to type II error.

1. Introduction

The prevalence of cigarette smoking has been reported to be significantly higher among psychiatric patients compared to the general population (Hughes et al., 1986). Although smoking rates in the general population have been steadily declining during the past decade, hitherto there is no available compelling evidence that smoking rates are decreasing in psychiatric populations. In the United States, patients with mental illness consume approximately 44% of all cigarettes (Lasser et al., 2000).

Epidemiological and clinical studies indicate that the rates of smoking in individuals with bipolar disorder are greater than the general population (Itkin et al., 2001; Ostacher et al., 2006). In a cross-national survey, 35.3% (Odds ratio [OR]=3.9) and 33.4% (OR=3.5) of individuals with bipolar I and II disorder, respectively, met criteria for nicotine dependence in the prior 12 months (vs. 12.8% in the general population) (Grant et al., 2004). Smoking is a well-established risk factor for cardiovascular, respiratory, and neoplastic disorders, each of which differentially affects the bipolar population (McIntyre et al., 2006). Moreover, smoking status has been reported to be a predictor of suicidality and is associated with psychosis in bipolar disorder (Corvin et al., 2001; Oquendo et al., 2004).

Bipolar symptomatology often includes disturbances in general and specific measures of cognitive function. Cognitive deficits in euthymic bipolar patients have been reported in both treated and untreated populations (as well as unaffected first-degree relatives), indicating that iatrogenic factors are not sufficiently explanatory (Bearden et al., 2001; Macqueen and Young, 2003). Bipolar patients with a more severe illness; as indicated by a greater lifetime duration of illness, higher frequency of prior episodes (notably depression), psychotic symptoms, symptom chronicity, and number of hospitalizations, may have more pronounced cognitive deficits (Bearden et al.,

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2001). Moreover, age-related cognitive decline may be more pronounced in individuals with bipolar disorder when compared to individuals who are unaffected by the condition (Gualtieri and Johnson, 2008). It is not known, however, if the cognitive deficits of the bipolar patient are a consequence of the illness and/or a prodrome to a more progressive disease process.

The neurotransmitter acetylcholine is implicated in arousal, learning and memory. Interventional studies indicate that cholinergic agonists offer memory enhancement effects, conversely, cholinergic antagonists are associated with decrements in memory performance (Levin and Simon, 1998; Levin and Rezvani, 2002). Extant evidence suggests that the central nicotinic acetylcholine receptor (nAChR) mediates the memory enhancing effect of acetylcholine in both normal and neuropsychiatric disease states (Lohr and Flynn, 1992; Foulds et al., 1996; Sacco et al., 2005).

Several studies have described the cognitive enhancing effects of acute nicotine administration in healthy volunteers and psychiatric populations (Jacobsen et al., 2004; Potter and Newhouse, 2008; Barr et al., 2008). To our knowledge, no published studies have primarily evaluated the relationship between nicotine and cognitive function in bipolar disorder. Consequently, the primary aim of this pilot investigation was to explore the association between cigarette smoking and cognitive function in bipolar disorder. We hypothesized that cigarette smoking would exert a salutary effect on measure of cognitive function. The impetus for this analysis was further provided by clinical observation and empirical evidence of pro-cognitive effects of smoking in the schizophrenic population and recent evidence suggesting a relationship between smoking status and severity of bipolar illness (Ostacher et al., 2006).

2. Methods

2.1. Subjects and procedures

This investigation was conducted at the Mood Disorders Psychopharmacology Unit (MDPU), University Health Network, University of Toronto. The MDPU is an academic outpatient specialty research program providing clinical service to adults (18–65 years) seeking evaluation and treatment for major depressive disorder and bipolar disorder.

The data for this analysis was procured from the baseline visit of an ongoing study evaluating a novel therapy for cognitive function (i.e. intranasal insulin) in euthymic patients with bipolar disorder. Inclusion criteria for the principal study were: (1) euthymic individuals with DSM-IV-defined bipolar I or II disorder verified using the DSM-IV Mini International Neuropsychiatric Interview (MINI); (2) age 18–55; (3) use of adequate contraception for females; (4) provision of informed consent and; (5) treatment with conventional pharmacotherapy and psychosocial treatment for bipolar disorder. Exclusion criteria were (1) other concurrent Axis-I diagnoses (DSM-IV criteria); (2) clinically significant medical comorbidity; (3) history of neurological trauma resulting in loss of consciousness; (4) drug or alcohol abuse/dependence within the previous 3 months; (5) current pregnancy or lactation, or history of pregnancy within the last 12 months; (6) uncorrected hypo- or hyperthyroidism, including elevated thyroid stimulating hormone; (7) hyper- and hypoglycemia or diabetes mellitus; (8) electroconvulsive therapy in the preceding 6 months and; (9) body mass index (BMI) >40 kg/m^2.

Euthymia was defined as the absence of depressive, hypomanic/manic or mixed symptoms for a minimum of 4 weeks. The absence of symptoms was operationalized as a Hamilton Rating Scale for Depression 7 item (HAMD-7) total score of <3 and a Young Mania Rating Scale (YMRS) total score of <7 at screening and after 28 days of prospective observation. The HAMD-7 has been validated in both primary and tertiary-care and is capable of evaluating symptomatic severity of depression, establishing and comparing the efficacy of antidepressant intervention, and determining when symptomatic remission has occurred (McIntyre et al., 2002; McIntyre et al., 2005).

Smoking history was assessed by self-report at screening. A lifetime smoker was defined as an individual who reported a history of cigarette smoking without regard to duration. A current smoker was an individual who smoked either daily or occasionally at the time of survey. A current non-smoker was defined as an individual who had not consumed any cigarettes in the six months preceding the time of survey.

Current and lifetime substance abuse and dependence as well as lifetime anxiety disorders were assessed using the DSM-IV MINI. Blood and toxicology screens were conducted as part of the evaluation and were used to corroborate information obtained through the structured interview. Demographic information and psychiatric history were obtained by direct interview.

2.2. Cognitive measures

Subjects were administered the following cognitive measures by trained research assistants.

2.2.1. The National Adult Reading Test (NART)

The test requires subjects to read out loud a set of 61 words which are irregular in terms of their grapheme–phoneme correspondences (Bright et al., 2002). The responses are individually scored as correct or incorrect, according to their pronunciation. Verbal performance and Full Scale IQ scores derived from NART-based equations were used to estimate premorbid intellect (Bright et al., 2002).

2.2.2. California Verbal Learning Test (CVLT)

A list of 16 semantically-related shopping items is presented orally in five successive trials. The test format provides assessment of short- and long-term (20-minute) delayed and cued recall, verbal learning strategies, and response discrimination (Delis et al., 1988). The CVLT raw scores were converted to standard scores corrected for age and gender.

2.2.3. Continuous Visual Memory Test (CVMT)

A set of ambiguous designs is digitally presented on a black computer screen one at a time. The participants are asked to indicate whether the figure is 'new' (not previously seen), or 'old' (previously seen). Scores on the number of hits, the number of false alarms, d-prime (a measure of memory discriminability), and the total number of correct response were computed (Banos et al., 2001).

2.2.4. Trail Making Test (TMT)

TMT is a visuomotor task that consists of two parts: TMT-A and TMT-B (Drane et al., 2002). TMT-A is a simple visual-scanning task that requires one to draw a line connecting consecutive numbers from 1 to 25. TMT-B adds a dimension of "cognitive flexibility" by requiring one to draw a line connecting numbers and letters in alternating sequence. Time to completion scores for parts A and B were used to examine aspects of attention and executive function, respectively (Drane et al., 2002).

2.2.5. Digit Symbol Substitution Test (DSST)

Digit Symbol Substitution is a subtest from the Wechsler Adult Intelligence Scale that measures attention and psychomotor speed (Robinson et al., 2006). The subjects substitute randomly distributed digits with the corresponding symbols within 90 s. The total number of correctly identified symbols was converted to standard scores corrected for age and gender.

2.2.6. Verbal fluency test

The Verbal fluency consists of two parts: letter fluency (i.e. FAS) and category fluency (i.e. animal). The subjects are required to generate as many words as possible that begin with the letter or that belong to the particular category within 60 and 90 s, respectively. The total number

of correctly named words was used to evaluate frontal executive function (Brucki and Rocha, 2004).

2.2.7. Shipley Abstraction

Shipley Abstraction is a subtest from the Shipley Institute of Living Scale, which provides an estimate of general intellectual abilities (Fadardi and Cox, 2006). This subtest consists of 20 questions in which sequences of numbers, letters, or words with the final element in each sequence omitted. The Abstraction subtest relies heavily on abstract thinking and cognitive flexibility (Fadardi and Cox, 2006). The total number of correct responses was used.

2.2.8. Cognitive Functioning Questionnaire

The Cognitive Functioning Questionnaire (CFQ) is a self-rating instrument designed to assess cognitive failures in perception, memory, and action experienced in every-day life situations during the last six months (Keizer et al., 2003). It consists of 25 items which are rated for their frequency of occurrence from 0 to 4 (4=very often). The total score ranges 0–100, with higher scores indicating more cognitive failures.

2.3. Statistical analysis

All data were analyzed with SPSS version 16.0 (SPSS, Chicago, IL, USA). Gender, ethnicity, and concomitant medication received were compared between current smokers and non-smokers using χ^2 tests. Age, body mass index, and mean scores on cognitive measures were compared between the two groups using two independent-samples *t*-tests. Multiple linear regressions were performed to examine the association between lifetime "smoking load" and scores on cognitive measures. "Smoking load" was computed by multiplying the average number of cigarettes smoked by the number of years smoked. Logistic regression was performed to examine the association between lifetime smoking history and illness severity.

3. Results

A total of 43 euthymic individuals with bipolar disorder were evaluated. The demographic and clinical characteristics are presented in Table 1. Current smokers were, on average, seven years younger than non-smokers; however both groups were similar in sex, weight, and ethnicity. Sixteen subjects were current (and chronic) smokers, smoking at least 10 cigarettes per day for the past year. No between-group differences were noted in most classes of concomitant medication with the exception of "non-psychotropic agents" (e.g. hormones, gastrointestinal drugs) wherein a higher rate of usage was noted in the non-smokers ($p=0.001$). All subjects were medically healthy.

Table 1
Demographic and clinical characteristics of current smokers and non-smokers

Characteristic	Smokers ($n=16$)	Nonsmokers ($n=27$)	Analysis		
			Test result	*Df*	*p*
Gender (*n*, %)					
Male	9 (56.3)	15 (55.6)	$\chi^2=0.002$	1	0.965
Female	7 (43.7)	12 (44.4)			
Age (years) (*m*, SD)	34.8 (8.10)	42.2 (9.73)	$t=2.536$	41	0.015
Ethnicity (*n*, %)					
White	13 (81.3)	25 (92.6)	$\chi^2=3.541$	3	0.316
Black	0 (0.0)	1 (3.7)			
Asian	2 (12.5)	1 (3.7)			
Other	1 (6.2)	0 (0.0)			
Body mass index (*m*, SD)	26.7 (5.1)	29.0 (5.2)	$t=1.399$	41	0.169
Concomitant medication (*n*, %)[a]					
Mood stabilizer	13 (81.3)	25 (92.6)	$\chi^2=1.258$	1	0.262
Antipsychotic	7 (43.8)	12 (44.4)	$\chi^2=0.002$	1	0.965
Antidepressant	7 (43.8)	17 (63.0)	$\chi^2=1.504$	1	0.220
Anxiolytic/hypnotic	5 (31.3)	10 (37.0)	$\chi^2=0.148$	1	0.700
Non-psychotropic agents	1 (6.3)	15 (55.6)	$\chi^2=10.435$	1	0.001

[a] The numbers of subject in each medication category are not mutually exclusive as majority of subjects received polypharmacy.

Table 2
Effects of cigarette smoking on cognitive measures

Variables	Smokers ($n=16$)	Non-smokers ($n=27$)	*p* value
	M (SD)	*M* (SD)	
Premorbid IQ			
NART Estimated Verbal IQ	111.90 (12.81)	112.65 (8.48)	0.49
NART Estimated Performance IQ	111.47 (6.05)	112.27 (3.76)	0.09
NART Estimated Full Scale IQ	113.08 (11.23)	113.73 (7.44)	0.48
Shipley Abstraction Total Correct	13.13 (4.41)	14.30 (3.85)	0.37
Learning and memory			
CVLT			
Trial 1 free recall correct	0.09 (1.33)	0.70 (1.30)	0.15
Trial 2 free recall correct	0.13 (1.10)	0.44 (1.04)	0.35
Trial 3 free recall correct	−0.06 (1.18)	0.39 (1.05)	0.20
Trial 4 free recall correct	0.13 (1.34)	0.20 (1.09)	0.83
Trial 5 free recall correct	−0.06 (1.21)	0.19 (1.00)	0.47
Trials 1–5 free recall total correct	52.81 (14.24)	56.70 (11.85)	0.34
Short delay free recall	−0.25 (1.40)	−0.02 (1.23)	0.57
Short delay cued recall	−0.25 (1.14)	0.11 (1.15)	0.33
Long delay free recall	−0.20 (1.40)	0.13 (1.35)	0.46
Long delay cued recall	−0.33 (1.32)	0.07 (1.13)	0.30
Total intrusions	0.10 (1.15)	0.15 (0.96)	0.89
Total repetitions	−0.17 (0.67)	0.20 (1.05)	0.23
Long-delay yes/no recognition hits	−0.60 (1.56)	−0.44 (1.41)	0.74
Long-delay yes/no recognition false-positives	0.50 (1.48)	−0.22 (0.71)	0.038*
CVMT			
Hits	37.38 (2.39)	35.89 (4.89)	0.26
False alarms	19.38 (5.54)	17.96 (6.20)	0.46
d-prime	1.67 (0.40)	1.86 (0.99)	0.47
Total score	72.00 (5.62)	71.96 (6.35)	0.98
Attention and psychomotor speed			
Trail Making Test A	32.83 (7.13)	31.83 (9.30)	0.77
Digit Symbol Total Correct	10.00 (3.35)	10.07 (2.00)	0.93
Executive function			
Trail Making Test B	86.94 (36.71)	73.44 (34.67)	0.33
Verbal fluency			
Letter F	12.36 (4.70)	14.24 (4.66)	0.25
Letter A	12.79 (4.23)	12.33 (6.13)	0.81
Letter S	14.79 (4.30)	14.71 (4.71)	0.96
Animals	24.23 (5.73)	24.38 (5.05)	0.94
Total	64.50 (15.65)	65.71 (16.83)	0.83
Subjective measure			
CFQ	49.94 (13.88)	62.63 (12.97)	0.004**

The asterisks denote statistical significance $P<0.05$; CFQ= Cognitive Functioning Questionnaire; CVLT= California Verbal Learning Test; CVMT= Continuous Visual Memory Test; NART= The National Adult Reading Test.

Table 2 presents the mean scores on the cognitive measures of the current smokers and non-smokers. Statistical analyses demonstrated that smokers had a significantly lower CFQ total score compared with non-smokers ($p=0.01$). However, the between-group difference in CFQ total score did not reach statistical significance at the level of 0.001 after Bonferroni correction. There were no significant differences in favour of current smokers when compared to non-smokers in the performance on the NART, Shipley Abstraction, CVLT, CVMT, DSST, verbal fluency and TMT. A significant, negative trend in NART Full Scale IQ with increasing smoking load was observed ($p=0.026$). This effect remained significant when age was used as a covariate ($p=0.025$).

In a logistic regression model with history of smoking as the dependent variable, no differences between the two groups were found with respect to age at onset, number of lifetime depressive episodes, number of lifetime hospitalizations for depression, number of lifetime hypomanic and/or manic episodes and number of lifetime hospitalizations for hypomania and/or mania (data not shown). Moreover, the relative risks for comorbid anxiety, suicidal behaviour

and alcohol/substance use did not differ significantly between the two groups (data not shown).

4. Discussion

To our knowledge, the pilot study herein is the first to evaluate the relation between smoking status and cognitive function in euthymic patients with bipolar disorder. The occurrence of subjective cognitive failures, as measured with CFQ total score, was lower for patients who were smokers compared to non-smokers. However, this outcome did not remain significant after correcting for multiple comparisons. Regression analysis indicated that smoking load was inversely associated with premorbid IQ as estimated by the NART.

Ostacher et al. (2006) reported that a lifetime history of smoking was associated with an early age at onset of depressive and manic episodes, lower Global Assessment of Functioning (GAF) scores, higher Clinical Global Impressions-Bipolar Disorder (CGI-BD) scores, increased anxiety, alcohol and substance use comorbidity, and a higher lifetime history of suicide attempts in a sample of bipolar individuals (n=399) (Ostacher et al., 2006). In the relatively small sample herein, euthymic individuals with bipolar disorder with a current and/or past history of smoking did not differ from the non-smoking sample in any indices of illness severity.

The role of the central cholinergic system on attention and learning is well-established. The nAChRs are widely distributed throughout the central nervous system including brain regions subserving cognitive functions (e.g. hippocampus and frontal cortex) (Warburton, 1992). Alterations in the central signaling of acetylcholine are hypothesized to be a critical neurochemical abnormality in Alzheimer's disease, a condition characterized by progressive memory deficits (Jones et al., 2006). Nicotine facilitates the release of acetylcholine and acts as an agonist at the nAChRs. Pre-clinical studies indicate that the administration of nicotinic agonists improves measures of attention and working memory performance (Levin and Rezvani, 2002). Similar findings are also documented in non-psychiatric populations (Foulds et al., 1996). These observations are hypothesized to be related to an increase in ventral tegmental dopaminergic neuron burst activity (Iversen, 1996; Knott et al., 1999). Moreover, functional imaging studies have reported that nicotine administration alters regional brain activities, notably in the anterior cingulate and thalamus, both of which are implicated in attention and arousal (Lawrence et al., 2002; Kumari et al., 2003).

Several clinical studies have reported beneficial cognitive effects of nicotine treatment in schizophrenic subjects. For example, nicotine patch treatment has been demonstrated to improve measures of working memory and attention and increase regional brain activation in smoking-deprived schizophrenic subjects (Jacobsen et al., 2004). This effect was not observed in smokers without psychiatric illnesses, which suggests a differential neurobiological substrate in psychotic subjects. Preliminary results also indicate that the use of adjunctive oral acetylcholinesterase inhibitor has been demonstrated to improve dimensions of cognitive function (Stip et al., 2005; Chouinard et al., 2007).

There are several methodological limitations to the inference and interpretation of the results of this investigation. The primary limitation of this study is the small sample size. Other limitations are: the study was a post-hoc analysis of data obtained during execution of a separate primary study; the subjects were recruited at a tertiary care centre, and were not representative of patients in other settings; smoking status was determined by self-report and was not verified by biomarkers the type of cigarette and nicotine content were variable throughout the subject sample; subjects were asked not to smoke within 30 min of testing eviscerating any possibility of evaluating the immediate effect of smoking on cognitive performance; and details of medication regimens were not controlled in the analysis.

Despite these limitations, an important strength is the inclusion of bipolar individuals who were prospectively verified to be euthymic. Our main objective was to initiate discussion, provide perspective, and enumerate methodological factors that may alter a putative association between cigarette smoking and cognitive function in bipolar disorder. Smoking rates are increased in the bipolar population and comprise a risk factor for myriad medical disorders. Cognitive deficits are also prevalent; they persist between episodes and contribute to functional impairment. An adequately powered study that precisely evaluates putative associations between smoking and cognitive function may possibly illuminate pathophysiological mechanisms and suggest novel therapeutic avenues for cognitive enhancement in bipolar disorder.

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