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ABSTRACT

Background. – Persistent impairment in cognitive function has been described in euthymic individuals with bipolar disorder. Collective work indicates that obesity is associated with reduced cognitive function in otherwise healthy individuals. This sub-group post-hoc analysis preliminarily explores and examines the association between overweight/obesity and cognitive function in euthymic individuals with bipolar disorder.

Methods. – Euthymic adults with DSM-IV-TR-defined bipolar I or II disorder were enrolled. Subjects included in this post-hoc analysis ($n = 67$) were divided into two groups (normal weight, body mass index [BMI] of 18.5–24.9 kg/m^2; overweight/obese, BMI $\geq$ 25.0 kg/m^2). Demographic and clinical information were obtained at screening. At baseline, study participants completed a comprehensive cognitive battery to assess premorbid IQ, verbal learning and memory, attention and psychomotor processing speed, executive function, general intellectual abilities, recollection and habit memory, as well as self-perceptions of cognitive failures.

Results. – BMI was negatively correlated with attention and psychomotor processing speed as measured by the Digit Symbol Substitution Test ($P < 0.01$). Overweight and obese bipolar individuals had a significantly lower score on the Verbal Fluency Test when compared to normal weight subjects ($P < 0.05$). For all other measures of cognitive function, non-significant trends suggesting a negative association with BMI were observed, with the exception of measures of executive function (i.e. Trail Making Test B) and recollection memory (i.e. process-dissociation task).

Conclusion. – Notwithstanding the post-hoc methodology and relatively small sample size, the results of this study suggest a possible negative effect of overweight/obesity on cognitive function in euthymic individuals with bipolar disorder. Taken together, these data provide the impetus for more rigorous evaluation of the mediational role of overweight/obesity (and other medical co-morbidity) on cognitive function in psychiatric populations.

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1. Introduction

Bipolar disorder (BD) has been highly associated with disparate cognitive deficits including attention, psychomotor performance, executive function, verbal fluency, learning, memory and global neurocognitive functioning [2,25–27]. Available evidence also indicates that individuals with BD exhibit cognitive deficits not only during acute mood episodes but also during euthymia [26,27,41,43]. Moreover, a recent meta-analysis reported that euthymic individuals generally had the same level of deficits in memory and learning as an actively symptomatic group [18]. Emerging evidence also indicates that first-degree relatives of probands with BD exhibit a similar pattern of cognitive deficits, providing the bases for hypothesizing that cognitive abnormalities may represent an endophenotypic marker of BD [4,43]. The pertinacity of cognitive deficits in BD is underscored by reports documenting an association between cognitive deficits and psychosocial functioning, workforce performance and interpersonal adjustment [17,32,47].

Emerging evidence also indicates that obesity is associated with reduced cognitive function in otherwise healthy individuals [6,10,11,14,16,19,23,39]. The association between anthropometrics and cognitive deficits is detectable in individuals without obesity-associated co-morbidities (e.g. type 2 diabetes mellitus and hypertension) known to independently affect brain function

[19,20,39]. Most cognitive domains are reported to be adversely affected by excess weight with replicated abnormalities in measures of learning, memory and executive function [10]. A bi-directional relationship between obesity and cognitive function is suggested by studies reporting that individuals with impairment in executive function are more likely to become overweight or obese, perhaps related to disturbances in impulse control, self-monitoring, and goal-directed behaviour [24]. It is further hypothesized that cognitive abnormalities observed in overweight/obese individuals are the expression of abnormalities in brain structure and function [11,16,36].

It has been amply documented that individuals with BD are differentially associated with overweight/obesity and abdominal obesity, and excess weight adversely effects illness presentation, course and outcome; however, to our knowledge, no published study has primarily examined the association between overweight/obesity and cognitive function in adults with BD [15]. Herein, we preliminarily sought to determine whether such an association exists in a well-characterized clinical cohort of euthymic adults with BD I/II.

2. Methods

2.1. Overview

The data for the present analysis were obtained post-hoc from screening and baseline assessments of euthymic individuals with BD enrolled in a study that primarily aims to evaluate intranasal insulin as a therapeutic intervention for cognitive function. For the purpose of the analysis herein, participants were categorized into normal weight and overweight/obese based on the established criteria of body index mass (BMI) (normal weight, BMI of 18.5–24.9 kg/m^2; overweight/obese, BMI $\geq$ 25.0 kg/m^2) [37].

2.2. Participants

Eligible participants for the principal study (age: 18–60) were euthymic individuals with DSM-IV-TR-defined BD I/II, confirmed by the Mini International Neuropsychiatric Interview (MINI) [1,42]. Euthymia, defined as a score of less or equal to 3 on the 7-item Hamilton Rating Scale for Depression (HAMD-7) and a score of less or equal to 7 on the Young Mania Rating Scale (YMRS) was confirmed at the initial screening and 1 month later at baseline [33,43,48,49]. Subjects were permitted to maintain their medication regimens such as conventional BD pharmacotherapy. No changes in medication were allowed during the study; medications were continued at the time of cognitive assessment. Other inclusion criteria included good physical health verified by a physical exam, provision of informed consent and use of a medically accepted means of contraception for females. Exclusion criteria included other concurrent DSM-IV-defined Axis-I diagnoses clinically significant untreated medical conditions (e.g. cardiovascular, neurological, gastrointestinal, hematological, renal, hepatic, respiratory or endocrine illnesses), uncorrected hypo/hyperthyroidism (including elevated thyroid stimulating hormone), the presence of diabetes mellitus or hypo/hyperglycemia, history of neurological trauma resulting in loss of consciousness, current pregnancy or breastfeeding, or history of pregnancy in the last 12 months, electroconvulsive therapy in the preceding 6 months, substance or alcohol abuse/dependence in the last 3 months (meeting DSM-IV criteria) and BMI greater or equal to 40 kg/m^2 [1].

2.3. Procedures

Participants were largely recruited from referrals to the outpatient Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto and from media announcements at local hospitals in the community. Their eligibility was determined at the initial screening visit wherein their clinical state (i.e. euthymia) and type of BD were confirmed. A physical examination was conducted to exclude those with major medical conditions. After 2 weeks, eligible participants who provided written informed consent and completed the initial assessment were invited to the second screening during which their blood pressure, pulse, height, weight, waist-to-hip ratio and BMI were measured and their blood and urine samples were collected as part of the evaluation. Demographic information and psychiatric history were obtained by direct interview. Prior to the baseline visit (which took place 4 weeks after the initial screening), participants were asked to abstain from alcohol and smoking cigarettes for 48 hours and 30 minutes, respectively, prior to the blood sample collection. At baseline, euthymia was re-verified prior to cognitive testing administered by trained research personnel.

2.4. Cognitive measures

A battery of cognitive tests was administered to assess estimated premorbid IQ (National Adult Reading Test [NART-R] [38]), verbal learning and memory (California Verbal Learning Test [CVLT-II] [12]), attention and psychomotor processing speed (Trail Making Test A [TMT-A] [40] and Digit Symbol Substitution Test [DSST] [46]), executive function (Trail Making Test B [TMT-B] [40] and Verbal Fluency Test [3]), general intellectual abilities (Shipley Abstraction [50]), recollection and habit memory (Process-Dissociation Task [21]), and self-perceptions of cognitive failures (Cognitive Failures Questionnaire [CFQ]) [5]. The cognitive measures that were chosen in this study were based on the primary hypothesis around the efficacy of a cognitive enhancing intervention. The cognitive battery was administered by a trained research coordinator and took approximately 3 hours to administer.

2.5. Statistical analyses

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL). Since the variables presented normal distribution, parametric tests were chosen. Demographic and clinical characteristics of normal weight subjects and overweight/obese subjects were compared using Chi-square tests for categorical variables and independent samples t-tests for continuous variables. Correlations between BMI and measures of cognitive performance were generated using Pearson's correlation tests. Performance on cognitive tests was compared between the two groups using independent samples t-tests. Statistical significance was set at $P < 0.05$. In order to examine the main effect of obesity on cognitive function, multivariate analyses of covariance (MANCOVA's) were conducted on test performance in three different cognitive domains: verbal learning and memory (measured by CVLT), attention and psychomotor processing speed (measured by TMT-A and DSST), and executive function (measured by TMT-B and Verbal Fluency Test). The independent variable in each analysis included BMI groups (normal vs. overweight/obese). Variables such as age and the number of years of education counted from Grade 1 were included in each model as covariates, which showed a significant association with dependent variables based on Pearson's correlation tests ($P < 0.05$). Binary logistic regression was performed to assess the association between the dichotomous dependent variable, BMI group, and predictor variables such as age and the total number of correct responses on the Shipley Abstraction subtest.

3. Results

3.1. Sample characteristics

A total of 67 euthymic individuals with BD were included in the analysis. 71.6% ($n = 48$) of the sample were overweight or obese. Demographic and clinical characteristics are presented in Table 1 (the subjects removed did not differ in demographic or clinical parameters from the 60 who were analyzed). There were no significant differences between normal and overweight/obese groups in demography, except for sex wherein a higher proportion of males were observed in the overweight/obese group than expected. The two groups did not differ in clinical characteristics including illness severity, age at the first mood episode, the number of lifetime mood episodes and the number of lifetime hospitalizations for depression/mania. Moreover, current smoking status and family history of mental illness did not differ significantly between the two groups (data not shown). All subjects received conventional pharmacological treatment for bipolar disorder. There were no significant differences between groups in the number or type of medications. Metabolic syndrome components were exclusion criteria, and as such, there were no differences in lipid or cholesterol profiles or markers of insulin resistance. Also, the results remained unchanged after adjusting for the effects of gender.

3.2. Correlation between BMI and measures of cognitive test performance

BMI was significantly and negatively correlated with scores on the Digit Symbol Substitution Test ($r = -0.320$, $P < 0.01$). For most of the analyses, a trend was observed in the hypothesized direction wherein BMI was negatively correlated with various cognitive measures.

3.3. Performance on cognitive tests by normal weight and overweight/obese individuals with BD

Group mean performance and statistical comparisons for all cognitive measures are summarized in Table 2. Subjects who were overweight or obese had a significantly lower score on the Verbal Fluency Test compared to those who were normal weight ($P = 0.013$). No significant differences in performance on any other cognitive measures were detected between the two groups.

3.4. Main effect of obesity on cognitive domains

Table 3 presents the main effect of obesity on cognitive test performance. Results from MANCOVA analyses did not yield any significant main effect of obesity on cognitive function domains (verbal learning and memory; attention and psychomo-

Table 1
Demographic and clinical characteristics of normal weight and overweight/obese euthymic individuals with bipolar disorder (BD).

Characteristic	Normal weight ($n = 19$)	Overweight/Obese weight ($n = 48$)	P value
Sex (n, %)			0.008[c]
Female	14 (73.7)	18 (37.5)	
Male	5 (26.3)	30 (62.5)	
Age (mean, SD)	36.68 (10.36)	41.48 (9.90)	0.082
Ethnicity (n, %)			0.099
White	17 (89.5)	45 (93.8)	
Black	1 (5.3)	0 (0)	
Asian	0 (0)	3 (6.2)	
Other	1 (5.3)	0 (0)	
Number of years of education counted from Grade 1 (mean, SD) (N: 16, O: 44)[a]	16.78 (2.61)	15.73 (3.00)	0.220
Type of BD (n, %)			0.776
BD I	16 (84.2)	39 (81.2)	
BD II	3 (15.8)	9 (18.8)	
Current medication (n)[b]			
Antidepressants	11	20	0.230
Sleep medication	5	11	0.769
Anxiolytic	5	13	0.949
Anticonvulsants	15	38	0.984
Antipsychotic	11	30	0.727
Hormonal	5	8	0.368
Age at first depressive episode (mean, SD) (N = 18, O = 42)[a]	17.22 (5.91)	19.50 (9.78)	0.363
Age at first manic episode (mean, SD) (N = 17, O = 38)[a]	22.65 (6.10)	24.08 (10.72)	0.610
Number of lifetime depressive episodes (n, SD) (N = 13, O = 28)[a]	6.23 (8.10)	10.32 (8.65)	0.159
Number of lifetime manic episodes (n, SD) (N = 13, O = 28)[a]	6.46 (9.56)	7.00 (9.32)	0.865
Number of lifetime hospitalizations for depression (n, SD) (N = 18, O = 42)[a]	0.72 (1.13)	1.19 (2.02)	0.360
Number of lifetime hospitalizations for mania (n, SD) (N = 17, O = 43)[a]	0.71 (0.92)	0.81 (1.22)	0.743

[a] N: the number of subjects in normal weight group; O: the number of subjects in overweight/obese group.
[b] The majority of subjects received polypharmacy.
[c] Statistically significant ($P < 0.05$).

Table 2
Performance on cognitive measures by normal weight and overweight/obese euthymic individuals with BD.

Cognitive domains	Normal weight ($n = 19$)	Overweight/obese ($n = 48$)	P value
Cognitive measures	Mean (SD)	Mean (SD)	
Premorbid IQ			0.672
NART estimated full scale IQ	113.10 (9.23)	112.14 (8.08)	
Verbal learning and memory			
CVLT			
Trials 1–5 free recall total correct	56.74 (11.48)	54.33 (12.05)	0.459
Short-delay free recall	11.16 (3.70)	10.56 (3.68)	0.553
Short-delay cued recall	12.32 (3.15)	11.86 (2.82)	0.543
Long-delay free recall	11.79 (3.54)	11.43 (3.46)	0.702
Long-delay cued recall	12.26 (3.14)	12.02 (3.10)	0.776
Attention and psychomotor processing speed			
Trail Making Test A	32.12 (14.76)	32.94 (10.10)	0.798
(N = 18, O = 47)[a]			
Digit Symbol Substitution Test	58.68 (11.80)	53.38 (11.26)	0.091
Executive function			
Trail Making Test B	72.56 (26.89)	74.21 (35.42)	0.859
(N = 18, O = 47)[a]			
Verbal Fluency Test	70.06 (19.50)	59.29 (13.87)	0.013[b]
General intellectual abilities			
Shipley Abstraction subtest	14.11 (3.23)	13.90 (4.01)	0.840
Memory deficits			
HABCON			
Recollection memory	0.36 (0.12)	0.34 (0.18)	0.778
(N = 14, O = 33)[a]			
Habit memory	0.57 (0.11)	0.59 (0.11)	0.515
(N = 13, O = 33)[a]			
Subjective measure			
Cognitive Failures Questionnaire	54.74 (15.20)	57.46 (16.45)	0.535

[a] N: the number of subjects in normal weight group; O: the number of subjects in overweight/obese group.
[b] Statistically significant ($P < 0.05$).

Table 3
Main effect of obesity on cognitive domain.

Cognitive domain (cognitive measures used)	Number of subjects included in the model (n)	df	Pillai's F	P value
Verbal learning and memory (CVLT)	59	3, 53	0.399	0.754
Attention and psychomotor processing speed (TMT-A, DSST)	58	2, 53	0.548	0.582
Executive function (TMT-B, Verbal Fluency Test)	57	2, 52	1.991	0.393

Table 4
Binary logistic regression model of independent variables predicting obesity in subjects ($n = 60$).

Predictor	Odds Ratio (OR)	95% CI for OR	P value
Age	1.045	0.986–1.107	0.136
Total correct responses on Shipley Abstraction	1.022	0.871–1.199	0.788

tor speed; and executive function) after accounting for the confounders.

3.5. Predictor of obesity in euthymic individuals with BD

The sample size included in the regression analysis was 60 subjects (outliers and missing data excluded from the analysis) (Table 4). Statistical analyses demonstrated that both age and the score of the Shipley Abstraction subtest were not significant predictors of obesity in euthymic individuals with BD.

4. Discussion

To our knowledge, the analysis herein is the first attempt to assess whether overweight/obesity was associated with decrements in cognitive function in euthymic individuals with BD. A high proportion of the participants in this study were overweight or obese (71.6%), as has been previously reported in bipolar populations [31,34,35]. Possible factors contributing to obesity in BD include lifestyle, medication exposure, neuroendocrine and neurotransmitter dysfunctions, genetic predisposition and co-morbid conditions such as binge-eating disorder [30,31,34,35]. Our data were unable to determine whether obesity occurred prior to the onset of BD or as a consequence of multi-episode/chronic illness and treatment.

In keeping with the view that increased body weight is negatively correlated with cognitive function in non-psychiatric samples, a trend was observed wherein BMI was inversely related to cognitive test performance in euthymic individuals with BD [19]. Moreover, in a separate study evaluating euthymic individuals, BMI was negatively correlated with the Global Assessment of

Functioning (GAF) [8] (the GAF has been positively correlated with cognitive test performance in separate studies [27,28]). Based on these previous findings, it may be inferred that BMI contributes to decreased cognitive functioning in euthymic individuals with BD.

It is well established that impairments in executive function are apparent in mixed populations of individuals with BD as well as obese individuals without psychiatric disorders [7,10,16,19, 22,26,27,28,41,45]. It could be hypothesized that obesity and BD are associated with common central nervous system structural and/ or functional changes in brain regions that subserve cognitive functioning. For example, frontal cortical regions that mediate executive function are hypometabolic in depressed individuals; similarly, overweight/obese individuals manifest reduced metabolic activity, as well as atrophy, in several cortical and subcortical structures [13,41,44]. Moreover, the interrelationship between obesity and mood disorders may be due to a pathophysiological nexus that includes abnormalities in hypothalamus-pituitary-adrenal axis function, inflammatory and metabolic systems, disruption of brain circuitry, all of which are potential mediators of cognitive function [9,10,28,43]. Further structural and functional investigations, as well as the establishment of mechanisms mediating cognitive deficits in obesity and BD, are required before a firm conclusion can be drawn.

Several methodological deficiencies limit inferences and interpretations that can be made from these data. First, this study was a sub-group post-hoc analysis that was not designed a priori to address the association of cognition with overweight/obesity. Secondly, the sample size was relatively small, increasing the possibility of type II error. Thirdly, the sample was comprised of individuals enrolled in a clinical trial at a university-based health science centre, limiting generalizability to other patient populations. Fourthly, there was no attempt to "enrich" the sample for individuals who have cognitive deficits. As a result, considerable heterogeneity in cognitive profiles was observed, which may have also decreased the likelihood of detecting an association [22] Fifthly, we did not have detailed information regarding the duration of overweight/obesity. Studies in non-psychiatric populations indicate that the adverse effect of overweight/obesity may be duration-dependent [19]. The inclusion of individuals with past psychiatric co-morbidity was permitted, as was psychiatric medicine, introducing additional confounds [28,29]. Finally, the obese individuals in this study did not have co-morbid hypertension, diabetes mellitus or cardiovascular disease. It is not known if our study results are representative of most other obese individuals who have obesity-associated co-morbidity.

Taken together, this preliminary analysis is intended to be hypothesis-generating rather than confirming. It is our objective to provide the impetus for more refined evaluation of the mediational/moderational role of overweight/obesity on cognitive function in bipolar (and other psychiatric) populations. Hitherto, over-weight/obesity and other medical co-morbidity pertinent to cognitive function (e.g. diabetes mellitus) have not been systematically evaluated as variables possibly pertinent to cognitive function in psychiatric populations. Future studies should also consider whether weight loss strategies in BD offer a salutary effect on cognitive function in addition to other benefits on physical health. Moreover, although we did not find a difference between bipolar I and bipolar II populations, a sufficiently powered study should attempt to enroll both bipolar I and bipolar II populations, as cognitive deficits are prominent in both groups.

Disclosure of interest

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