Original Article

A randomized, double-blind, controlled trial evaluating the effect of intranasal insulin on neurocognitive function in euthymic patients with bipolar disorder

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Background: Neurocognitive deficits are prevalent, persistent, and implicated as mediators of functional impairment in adults with bipolar disorder. Notwithstanding progress in the development of pharmacological treatments for various phases of bipolar disorder, no available treatment has been proven to be reliably efficacious in treating neurocognitive deficits. Emerging evidence indicates that insulin dysregulation may be pertinent to neurocognitive function. In keeping with this view, we tested the hypothesis that intranasal insulin administration would improve measures of neurocognitive performance in euthymic adults with bipolar disorder.

Methods: Sixty-two adults with bipolar I/II disorder (based on the Mini International Neuropsychiatric Interview 5.0) were randomized to adjunctive intranasal insulin 40 IU q.i.d. (n = 34) or placebo (n = 28) for eight weeks. All subjects were prospectively verified to be euthymic on the basis of a total score of ≤ 3 on the seven-item Hamilton Depression Rating Scale (HAMD-7) and ≤ 7 on the 11-item Young Mania Rating Scale (YMRS) for a minimum of 28 consecutive days. Neurocognitive function and outcome was assessed with a neurocognitive battery.

Results: There were no significant between-group differences in mean age of the subjects {i.e., mean age 40 [standard deviation (SD) = 10.15] years in the insulin and 39 [SD = 10.41] in the placebo groups, respectively}. In the insulin group, n = 27 (79.4%) had bipolar I disorder, while n = 7 (21.6%) had bipolar II disorder. In the placebo group, n = 25 (89.3%) had bipolar I disorder, while n = 3 (10.7%) had bipolar II disorder. All subjects received concomitant medications; medications remained stable during study enrollment. A significant improvement versus placebo was noted with intranasal insulin therapy on executive function (i.e., Trail Making Test–Part B). Time effects were significant for most California Verbal Learning Test indices and the Process Dissociation Task–Habit Estimate, suggesting an improved performance from baseline to endpoint with no between-group differences. Intranasal insulin was well tolerated; no subject exhibited hypoglycemia or other safety concerns.

Conclusions: Adjunctive intranasal insulin administration significantly improved a single measure of executive function in bipolar disorder. We were unable to detect between-group differences on other neurocognitive measures, with improvement noted in both groups. Subject phenotyping on the basis of pre-existing neurocognitive deficits and/or genotype [e.g., apolipoprotein E (ApoE)] may possibly identify a more responsive subgroup.

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Bipolar disorder (BD) is a highly prevalent disorder associated with high rates of non-recovery, interepisodic dysfunction, and premature mortality (1). Mania and hypomania are defining features of BD; notwithstanding, neurocognitive deficits are frequently encountered in BD patients and are identified as contributing to psychosocial impairment (2). Neurocognitive impairment in BD is amply documented in symptomatic and euthymic populations (3). Deficits have been reported across all domains of neurocognitive function – for example, verbal learning and memory, attention, executive function, and processing speed (4). Measures of verbal learning and executive function have been the most replicated neurocognitive impairment in BD (3).

Individuals with a more complex BD presentation (e.g., psychotic symptoms) exhibit more pronounced neurocognitive deficits (5). Moreover, neurocognitive deficits are a major factor causing and maintaining psychosocial impairment in BD populations (6). It is hypothesized that the neurocognitive deficits in BD populations are subserved by structural and functional abnormalities in neural structures implicated in memory and other cognitive processes (7). Notwithstanding the pertinence of neurocognitive deficits, no intervention has been established as reliably efficacious.

Converging lines of evidence indicate that insulin and its receptors are critical for neuronal survival and synaptic plasticity (8). The localization of insulin receptors in the hippocampus and medial temporal cortex suggests a role for insulin (and glucose homeostasis) in normal and abnormal memory function (9). Results from animal and human studies indicate that insulin resistance, peripheral hyperinsulinemia, and diabetes mellitus are each associated with deficits across multiple neurocognitive measures (10). Neurocognitive deficits (e.g., verbal fluency) and volumetric changes (e.g., Broca's area 21 and 22) have also been reported to occur in cognitively healthy, non-diabetic elderly men and women (independent of sex effects) as a result of impaired insulin sensitivity (11). Reduced cerebrospinal fluid insulin levels have been reported in patients with Alzheimer's disease (AD), and euglycemic intravenous insulin administration dose-dependently improves memory in AD patients (10). Moreover, insulin dysregulation has been identified as a risk factor for incident mild cognitive impairment (MCI) and AD (12).

Controlled interventional studies in animals, healthy volunteers, and individuals with MCI and AD indicate that intranasal insulin is safe, well tolerated, and associated with improvements in memory performance (13–16). To our knowledge there is no direct evidence indicating that insulin signaling disturbances are salient to cognitive deficits in BD. Extrapolating from preclinical outcomes involving insulin, in addition to interventional studies in healthy controls, as well as individuals with MCI and AD, provided the basis for the present preliminary study hypothesizing that intranasal insulin would enhance hippocampal-dependent neurocognitive function in euthymic individuals with bipolar I/II disorder. We decided to limit enrollment to individuals who were euthymic, primarily to reduce the confound of syndromal affective symptoms affecting cognitive performance. We aimed to reduce the possibility that a pseudo-specific effect would occur wherein insulin intervention and/or placebo may possibly ameliorate both cognitive deficits and affective symptoms, resulting in an inability to dissociate primary effect.

Methods

Participants

Participants that were included in the study had a DSM-IV diagnosis of bipolar I/II disorder, based on the Mini International Neuropsychiatric Interview (MINI) version 5.0. All eligible subjects were outpatients, identified in the Mood Disorders Psychopharmacology Unit (MDPU), University Health Network (UHN), Toronto, ON, Canada. Subjects were also recruited with the use of media announcements displayed throughout the UHN. Eligible subjects were required to provide written and informed consent. The study was approved by the Research Ethics Board at the UHN, University of Toronto.

All subjects were prospectively verified to be euthymic, defined as a score of ≤ 3 on the seven-item Hamilton Depression Rating Scale (HAMD-7) and ≤ 7 on the 11-item Young Mania Rating Scale (YMRS) (4, 17, 18). Euthymia was established at visit 1 (screening), visit 3 [baseline (i.e., minimum 28 days later)], visit 4 (i.e., seven days post-randomization), and weekly until endpoint. All subjects were permitted to maintain their current medication regimen but were not permitted to initiate or discontinue new pharmacological treatment or initiate manual-based psychotherapy while enrolled in the study.

Exclusion criteria were: (i) other concurrent DSM-IV Axis I/II diagnoses that were a primary focus of clinical concern, (ii) clinically significant untreated medical conditions (e.g., cardiovascular, neurological, gastrointestinal, hematological, renal, hepatic, respiratory, or endocrine illnesses), (iii) history of neurological trauma resulting in loss

of consciousness, (iv) current pregnancy or breast-feeding, history of pregnancy in the last 12 months, or unwillingness or inability to use medically accepted form of contraception, (v) uncorrected hypo/hyperthyroidism (including elevated thyroid-stimulating hormone), (vi) the presence and/or history of diabetes mellitus type I/type II or hypo/hyperglycemia, (vii) electroconvulsive therapy in the preceding six months, (viii) substance or alcohol abuse/dependence in the last three months (meeting DSM-IV criteria), and (ix) body mass index (BMI) $\geq 40 \text{ kg/m}^2$ (19). Individuals who were actively suicidal or evaluated by the clinician as being at suicide risk were also excluded, as well as individuals who could not coordinate intranasal spray administration. Safety measures included the use of the Udvalg for Kliniske Undersogelser (UKU) side-effect rating scale, vital signs, and laboratory measures. Blood glucose measurements were conducted under fasting conditions at screening, baseline, and at each observation point, 30 minutes following the first administration and also at endpoint.

Neurocognitive measures

A neurocognitive battery was administered at baseline (visit 3), one hour after intranasal administration (visit 4), and at endpoint (i.e., visit 12 at week 8). The primary cognitive measures were the California Verbal Learning Test, second edition (CVLT-II) (20) and the Process Dissociation Task (PDT) (21), both of which are recollection memory tasks that are thought to be dependent on the hippocampus and related structures. Secondary outcome measures were the Trail Making Test–Part A (Trails A) (22), the Trail Making Test–Part B (Trails B) (22), the Digit Symbol Substitution Test (DSST) (23), the Controlled Oral Word Association Test (COWAT) {Letter Fluency [Full Analysis Sample (FAS)] and Category Fluency (Animals)} (24), the Visual Backward Masking Test (VBM) (25), the Shipley Institute of Living (SILS)–Abstraction Test (26), the Continuous Visual Memory Test (CVMT) (27), and the Cognitive Failures Questionnaire (CFQ) (28). The National Adult Reading Test-revised (NART-R) was also included to estimate premorbid IQ (29).

Intranasal insulin

Subjects were randomized to receive either adjunctive intranasal insulin or placebo at baseline. All subjects received placebo for the first week. This was done to allow further training of intranasal delivery and to reduce placebo expectancy. For the subsequent eight weeks, patients were randomly assigned to intranasal insulin or placebo. Subjects were trained to coordinate administration of the intervention with inhalation via their nares. Intranasal insulin and placebo were administered four times a day: morning, noon, evening, and at night. Each dose consisted of 0.4 mL insulin [containing 40 IU insulin (Novolin Toronto; Novo Nordisk, Mississauga, ON, Canada)] or vehicle (identical diluents) administered via four puffs of 0.1 mL (two per nostril), amounting to 1.6 mL (160 IU) insulin or placebo per day. There were no stabilizing substances used in the development of intranasal insulin; the device was provided either diluent (i.e., placebo) or diluent + insulin as a spray (i.e., it was not actively aerosolized).

Intranasal insulin was prepared at the UHN pharmacy. Sterility and stability testing was conducted at Mount Sinai Hospital, University of Toronto. The chosen dose of insulin was based on preclinical studies indicating a detectable concentration and effect of intranasal insulin within ten minutes at this dose, as well as prior interventional studies. Intranasal treatment was non-refrigerated and replaced on a weekly basis. Subjects were asked to demonstrate use of the intranasal insulin in the presence of research staff. All subjects were asked to return intranasal bottles at each visit.

Statistical analyses

The full analysis set consisted of all randomized subjects (n = 62) and subjects who completed the full eight weeks of randomized treatment (study completers, n = 43); see Figure 1 for a flow chart giving the reasons for discontinuation. Baseline subject demographic and illness characteristics are shown in Table 1. No prior study had been conducted in BD with intranasal insulin. Sample size was estimated based on effect sizes reported with intranasal insulin in healthy volunteers. Randomization was conducted by the hospital pharmacy. All raters were blind to treatment assignment. Repeated measure analysis of variance (ANOVA) was conducted with a between-subjects factor of treatment (insulin versus placebo) and a within-subjects factor of time (baseline visit 3 versus study endpoint visit 12/week 8). The acute effects of insulin treatment were assessed at visit 4. Primary and secondary neurocognitive measures for subjects that completed the full eight weeks of randomized treatment were included in the analyses and carried out using SPSS software [PASW Statistics 18, SPSS Inc., SPSS (Hong Kong) Ltd, Quarry Bay, Hong Kong]. A Bonferroni correction was conducted to adjust for the effect of multiple comparisons.
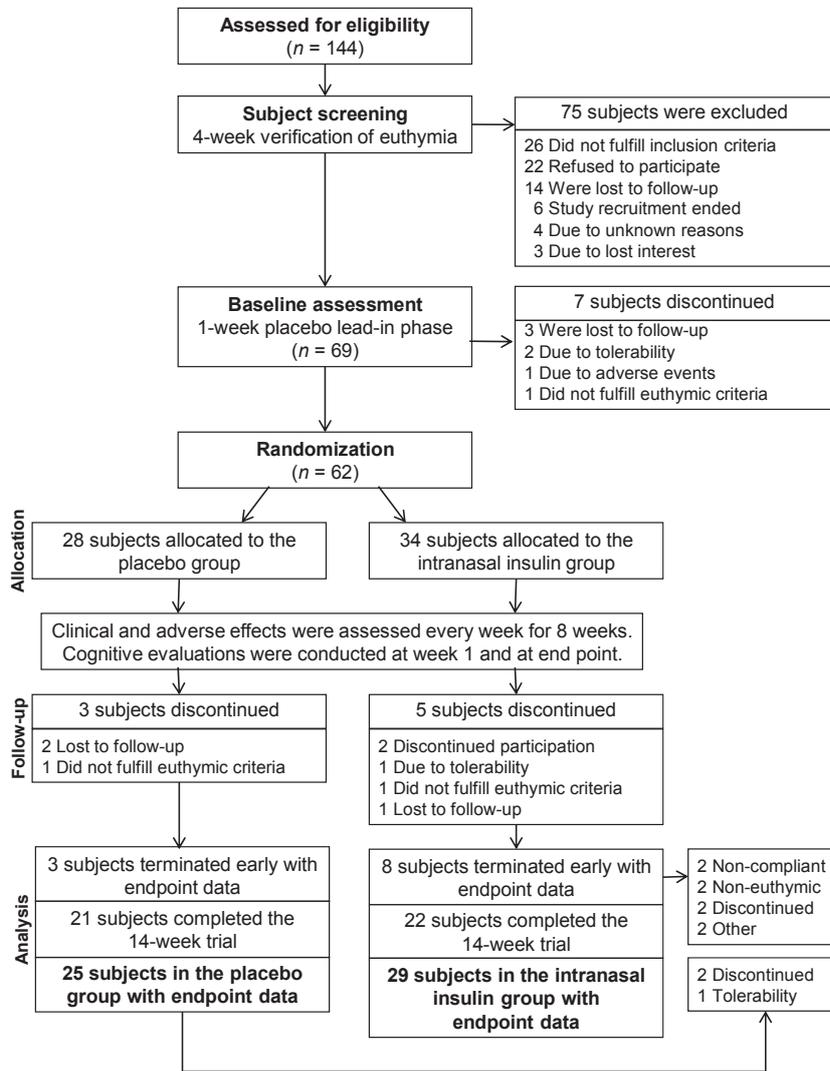
Fig. 1. Intranasal insulin diagram of study course. One subject withdrew consent during follow-up and requested to have all data deleted.

Results

The demographic and clinical characteristics of the sample are presented in Table 1. Of 144 individuals assessed for eligibility, 75 were excluded. The primary reason for exclusion were not fulfilling the inclusion criteria (e.g., symptomatic at the time of assessment). The remaining subjects (i.e., n = 69) were available for baseline assessment and one-week placebo lead-in, of which seven were discontinued, either due to intolerability or lost to follow-up. As a result, 62 subjects were randomized to either intranasal insulin (n = 34) or placebo (n = 28). A similar number of subjects completed the trial in the intranasal group (n = 22) and placebo group (n = 21). The most common reasons for non-completion were non-compliance with the intervention and the emergence of affective symptoms. Two subjects discontinued before study endpoint due to symptom intensification in the intranasal insulin group and did not follow up for repeat cognitive testing. There were no between-group differences in age, gender, or ethnicity distribution. Most of the randomized subjects had bipolar I disorder [n = 27 (insulin); n = 25 (placebo)]. No subjects reported a current or past history of psychotic symptoms. The most frequently prescribed categories of psychotropic medications in both groups were conventional mood stabilizers, atypical antipsychotic agents, antidepressants, hypnotic agents and anxiolytic agents. There were no differences between groups in age of onset of first affective episode or number of lifetime hospitalizations. Most subjects enrolled were overweight (i.e., BMI ≥ 25) prior to treatment assignment.

Table 1. Demographic and clinical characteristics of euthymic bipolar disorder individuals in the intranasal insulin and placebo groups

Characteristic	Insulin (n = 34)	Placebo (n = 28)	p-value
Age, years [mean (SD)]	40.76 (10.15)	39.29 (10.41)	0.575
Gender, n (%)			
Female	15 (44.12)	14 (50.00)	0.644
Male	19 (55.88)	14 (50.00)	
Ethnicity, n (%)			
White	32 (94.12)	27 (96.43)	0.653
Black	0 (0)	0 (0)	
Asian	1 (2.94)	1 (3.57)	
Other	1 (2.94)	0 (0)	
Education, years (from Grade 1) [mean (SD)][a]	16.61 (3.77)	16.18 (2.55)	0.630
Type of bipolar disorder, n (%)			
Bipolar I disorder	27 (79.41)	25 (89.29)	0.293
Bipolar II disorder	7 (20.59)	3 (10.71)	
Current medications, n (%)			
Antidepressants	15 (44.12)	14 (50.00)	0.644
Anxiolytic ∕ hypnotic agents	27 (79.41)	10 (35.71)	0.465
Mood stabilizers	18 (52.94)	20 (71.43)	0.233
Atypical antipsychotic agents	0 (0)	19 (67.86)	0.050
Psychostimulants	5 (14.71)	3 (10.71)	0.310
Hormonal	10 (28.41)	7 (25.00)	0.597
Other	–	10 (35.71)	
Age at onset of first depressive episode [mean (SD)][b]	19.52 (9.90)	16.17 (5.42)	0.142
Age at first treatment for depression [mean (SD)][c]	28.60 (10.24)	26.60 (10.56)	0.480
No. of lifetime depressive episodes, [mean (SD)][d]	8.86 (9.82)	12.50 (15.22)	0.388
No. of lifetime hospitalizations for depression [mean (SD)][e]	1.19 (2.40)	0.88 (1.33)	0.562
Age at onset of first hypo∕manic episode [mean (SD)][f]	24.57 (10.23)	21.33 (7.03)	0.197
Age at first treatment for hypo∕mania [mean (SD)][g]	33.41 (10.12)	27.27 (12.45)	0.043[k]
No. of lifetime manic episodes [mean (SD)][h]	7.86 (11.88)	9.47 (13.87)	0.699
No. of lifetime hospitalizations for mania [mean (SD)][i]	0.87 (1.17)	0.89 (1.53)	0.951
Body mass index, mean (SD)[j]	27.85 (6.21)	29.61 (5.20)	0.243
HAMD-7 score [mean (SD)]			
Week 4	1.21 (1.55)	0.96 (1.20)	0.896
Week 0	1.62 (1.63)	1.32 (1.52)	
YMRS score (mean (SD)]			
Week 4	0.71 (1.36)	0.86 (1.43)	0.891
Week 0	1.53 (1.74)	1.57 (1.93)	
NART-R full-scale IQ	114.26 (7.70)	111.78 (7.57)	0.210
NART-R verbal IQ	113.26 (8.78)	110.42 (8.64)	0.210
NART-R performance IQ	112.11 (4.14)	110.78 (4.08)	0.210

HAMD-7 = Hamilton Depression Rating Scale (7 items); NART-R: National Adult Reading Test-revised; SD = standard deviation; YMRS = Young Mania Rating Scale.
[a]Sample size varies according to availability of data (placebo: n = 25; insulin: n = 33).
[b]Sample size varies according to availability of data (placebo: n = 24; insulin: n = 31).
[c]Sample size varies according to availability of data (placebo: n = 25; insulin: n = 30).
[d]Sample size varies according to availability of data (placebo: n = 14; insulin: n = 22).
[e]Sample size varies according to availability of data (placebo: n = 25; insulin: n = 31).
[f]Sample size varies according to availability of data (placebo: n = 24; insulin: n = 28).
[g]Sample size varies according to availability of data (placebo: n = 26; insulin: n = 32).
[h]Sample size varies according to availability of data (placebo: n = 17; insulin: n = 22).
[i]Sample size varies according to availability of data (placebo: n = 27; insulin: n = 30).
[j]Sample size varies according to availability of data (placebo: n = 27; insulin: n = 34).
[k]Indicates statistical significance at $\alpha < 0.05$.

The test performance results are presented in Tables 2–4. The results of the primary outcome measures for insulin and placebo treatment groups are shown in Table 2 (CVLT-II and PDT). Time effects were significant for most CVLT-II indices and the PDT habit estimate, indicating that the performance improved between baseline and endpoint for these measures (i.e., presence of practice effects). However, the absence of significant time × treatment interactions for any of the measures indicated that both groups improved equally and thus no therapeutic benefit related to insulin treatment.

Table 3 shows the secondary neurocognitive measures results (Trails A and B, DSST, SILS–Abstraction Test, VBM, CVMT) for insulin and

Table 2. Primary neurocognitive measure results for the insulin and placebo groups

	Insulin[a]		Placebo[b]		Time effect	Treatment effect	Time × treatment interaction
	Baseline[c] [mean (SD)]	Endpoint[d] [mean (SD)]	Baseline[c] [mean (SD)]	Endpoint[d] [mean (SD)]	p-value	p-value	p-value
CVLT Trial 1	7.76 (2.89)	9.81 (2.64)	7.95 (2.89)	9.77 (2.72)	< 0.001	0.92	0.73
CVLT Trial 5	12.05 (2.85)	13.91 (2.55)	13.09 (2.22)	14.09 (2.39)	< 0.001	0.39	0.17
CVLT immediate free-recall total (Trials 1–5)	52.95 (12.05)	62.19 (12.34)	54.27 (12.45)	63.27 (11.19)	< 0.001	0.73	0.91
CVLT List B	6.76 (2.21)	6.29 (2.57)	6.95 (2.59)	7.00 (2.41)	0.46	0.51	0.37
CVLT Short-delay free-recall	10.48 (3.53)	13.00 (3.36)	10.36 (4.10)	13.14 (3.92)	< 0.001	0.99	0.77
CVLT Short-delay cued-recall	11.67 (3.21)	13.71 (2.74)	12.18 (2.79)	13.36 (3.37)	< 0.001	0.92	0.23
CVLT Long-delay free-recall	10.86 (3.85)	12.67 (3.83)	11.64 (3.66)	13.14 (3.37)	< 0.001	0.57	0.58
CVLT Long-delay cued-recall	11.62 (3.41)	13.29 (3.62)	12.00 (3.31)	13.45 (2.87)	< 0.001	0.77	0.77
CVLT total intrusions	4.00 (3.92)	2.33 (2.13)	4.55 (4.26)	3.41 (4.44)	< 0.05	0.40	0.69
CVLT total repetitions	7.52 (7.20)	8.47 (7.18)	6.95 (7.21)	8.31 (6.70)	0.18	0.86	0.81
PDT recollection	0.32 (0.15)	0.33 (0.12)	0.36 (0.18)	0.40 (2.00)	0.43	0.31	0.61
PDT habit estimate	0.59 (0.11)	0.57 (0.06)	0.60 (0.09)	0.54 (0.12)	< 0.05	0.31	0.71

CVLT = California Verbal Learning Test; PDT = Process Dissociation Task; SD = standard deviation.
[a]CVLT: n = 21; PDT: n = 15.
[b]CVLT: n = 22; PDT: n = 15.
[c]Visit 3.
[d]Visit 12.

Table 3. Secondary neurocognitive measure results for the insulin and placebo groups

	Insulin[a]		Placebo[b]		Time effect	Treatment effect	Time × treatment interaction
	Baseline[c] [mean (SD)]	Endpoint[d] [mean (SD)]	Baseline[c] [mean (SD)]	Endpoint[d] [mean (SD)]	p-value	p-value	p-value
Trails A	37.30 (16.69)	31.82 (19.30)	34.69 (12.07)	30.78 (10.08)	< 0.05	0.66	0.70
Trails B	85.81 (47.18)	66.72 (41.39)	72.56 (22.77)	66.59 (20.42)	< 0.01	0.52	<0.05
DSST score	55.00 (10.21)	54.70 (10.99)	52.05 (10.42)	54.73 (12.45)	0.29	0.65	0.18
Digit Symbol Recall	5.70 (2.00)	6.40 (2.23)	6.18 (2.34)	6.41 (2.68)	0.08	0.72	0.36
SILS–Abstraction Test	14.29 (3.88)	15.86 (2.93)	14.05 (3.58)	14.91 (2.89)	< 0.01	0.54	0.34
CVMT total	71.19 (8.21)	74.81 (8.70)	70.59 (6.49)	77.00 (7.13)	< 0.001	0.70	0.23
COWAT–Letter Fluency (FAS)	41.19 (10.66)	40.95 (9.92)	39.18 (15.10)	41.91 (14.69)	0.18	0.89	0.11
COWAT–Category Fluency (Animals)	23.49 (5.26)	25.14 (4.56)	23.86 (7.64)	25.18 (6.75)	0.10	0.90	0.84
COWAT total score	64.67 (22.02)	66.09 (11.51)	63.71 (22.02)	66.90 (20.36)	0.12	0.99	0.54
CFQ	60.14 (14.58)	54.48 (15.21)	57.36 (16.56)	50.05 (16.77)	< 0.001	0.42	0.66
VBM (mean time 14)	618.34 (250.08)	538.31 (179.71)	634.34 (250.08)	614.95 (293.20)	< 0.05	0.60	0.20
VBM (mean time 29)	537.17 (233.17)	495.76 (184.89)	588.26 (248.53)	550.66 (215.56)	0.09	0.50	0.93
VBM (mean time 43)	507.59 (185.54)	472.08 (173.32)	529.61 (216.59)	500.98 (181.29)	0.07	0.71	0.84
VBM (mean time 57)	508.61 (242.53)	444.96 (158.28)	524.75 (231.86)	487.89 (199.48)	< 0.05	0.69	0.58
VBM (mean time 86)	455.66 (203.11)	409.25 (140.92)	469.16 (203.76)	409.25 (140.92)	< 0.05	0.80	0.92
VBM (mean time 114)	415.51 (185.14)	365.02 (131.06)	437.82 (176.72)	402.06 (159.87)	< 0.05	0.60	0.70
VBM (errors 14)	28.58 (18.66)	21.48 (13.63)	31.00 (20.37)	26.84 (20.00)	< 0.05	0.55	0.51
VBM (errors 29)	18.76 (21.03)	10.43 (10.92)	22.67 (20.99)	18.64 (19.84)	< 0.01	0.36	0.29
VBM (errors 43)	14.15 (17.83)	6.71 (8.84)	19.12 (20.54)	13.48 (18.32)	< 0.01	0.33	0.63
VBM (errors 57)	10.42 (17.97)	4.18 (6.90)	13.99 (20.25)	10.06 (18.77)	< 0.01	0.43	0.52
VBM (errors 86)	7.44 (13.87)	3.12 (5.76)	10.79 (18.79)	8.09 (18.41)	< 0.05	0.45	0.56
VBM (errors 114)	5.35 (12.72)	2.84 (5.59)	9.32 (17.22)	7.98 (17.20)	0.19	0.37	0.69

CFQ = Cognitive Functioning Questionnaire; COWAT = Controlled Oral Word Association Test; CVMT = Continuous Visual Memory Test; DSST = Digit Symbol Substitution Test; SD = standard deviation; Trails A = Trails Making Test–Part A; SILS = Shipley Institute of Living Scale–Abstraction Test; Trails B = Trails Making Test–Part B; VBM = Visual Backward Masking.
[a]CFQ: n = 21; VBM: n = 14.
[b]CFQ: n = 22; VBM: n = 17.
[c]Visit 3.
[d]Visit 12.

Table 4. Acute neurocognitive measure results for the insulin and placebo groups

	Insulin[a]		Placebo[b]		Time effect	Treatment effect	Time × treatment interaction
	Baseline/Visit 3 [mean (SD)]	Visit 4 [mean (SD)]	Baseline/Visit 3 [mean (SD)]	Visit 4 [mean (SD)]	p-value	p-value	p-value
Trails A	37.30 (16.69)	35.35 (16.80)	34.69 (12.07)	29.13 (6.13)	< 0.01	0.32	0.35
Trails B	98.08 (78.09)	84.06 (94.82)	72.56 (22.77)	70.25 (30.08)	0.10	0.30	0.23
DSST score	55.00 (10.21)	52.85 (12.16)	52.05 (10.42)	52.55 (12.61)	0.48	0.63	0.26
Digit Symbol Recall	5.70 (2.00)	6.15 (2.25)	6.18 (2.34)	6.86 (2.23)	< 0.05	0.34	0.68
VBM (mean time 14)	618.34 (250.08)	531.07 (180.43)	634.34 (250.08)	588.68 (225.35)	< 0.01	0.59	0.54
VBM (mean time 29)	537.17 (233.17)	479.79 (167.32)	588.26 (248.53)	540.48 (178.97)	< 0.01	0.42	0.95
VBM (mean time 43)	507.59 (185.54)	455.39 (168.34)	529.61 (216.59)	505.82 (192.34)	< 0.01	0.56	0.47
VBM (mean time 57)	508.61 (242.53)	436.09 (169.46)	524.75 (231.86)	489.20 (204.40)	< 0.01	0.61	0.47
VBM (mean time 86)	455.66 (203.11)	396.99 (137.79)	469.16 (203.76)	438.54 (167.11)	< 0.01	0.62	0.55
VBM (mean time 114)	415.51 (185.14)	352.79 (131.34)	437.82 (176.72)	406.77 (169.68)	< 0.01	0.48	0.45
VBM (errors 14)	28.58 (18.66)	24.86 (18.94)	31.00 (20.37)	24.87 (17.49)	< 0.05	0.78	0.50
VBM (errors 29)	18.76 (21.03)	15.20 (14.14)	22.67 (20.99)	14.20 (16.51)	< 0.05	0.76	0.27
VBM (errors 43)	14.15 (17.83)	11.19 (13.82)	19.12 (20.54)	11.21 (12.66)	< 0.05	0.61	0.32
VBM (errors 57)	10.42 (17.97)	8.19 (15.61)	13.99 (20.25)	6.78 (11.83)	0.06	0.79	0.26
VBM (errors 86)	7.44 (13.87)	6.25 (9.45)	10.79 (18.79)	4.96 (8.26)	0.17	0.76	0.35
VBM (errors 114)	5.35 (12.72)	4.32 (9.71)	9.32 (17.22)	3.92 (7.91)	0.14	0.61	0.29

DSST = Digit Symbol Substitution Test; SD = standard deviation; Trails A = Trails Making Test–Part A; Trails B = Trails Making Test–Part B; VBM = Visual Backward Masking.
[a]DSST: n = 21; VBM: n = 14.
[b]DSST: n = 22; VBM: n = 17.

placebo groups. Time effects were significant for most of these measures, again suggesting improved performance between baseline and endpoint related to practice effects. A significant treatment × time interaction was found for Trails B, indicating improved performance of the Trails B following insulin treatment as compared to placebo at endpoint (p < 0.05) (see Table 3). There were no differences between the intranasal insulin and placebo groups prior to the endpoint evaluation. The Trails B is a neurocognitive measure evaluating subjects' ability to switch their attention as a proxy for executive function and consists of 25 circles containing both numbers and letters; participants complete this neurocognitive measure by alternating between numerical and alphabetical sequences, starting with '1', which is connected to 'A', then connecting to '2', which is connected to 'B', and so forth. The Trails B outcome was corrected for multiple testing and was also covaried for baseline performance. Notwithstanding, the overall effect, as measured by Trails B, would be considered modest at best.

Table 4 shows the neurocognitive results one hour after intranasal insulin or placebo on visit 4 (acute effects). Time effects were significant for most of these measures, indicating that performance improved between baseline and visit 4; however, the absence of any significant time ×

treatment interactions indicated that both groups improved equally. Results for primary and secondary efficacy measures did not differ in the completers or the full analysis set. It should be noted that none of the cognitive measures worsened at any testing time point in either group.

No subject exhibited hypoglycemia during study enrollment at any time point of observation. The most commonly reported adverse events in the intranasal insulin treatment group were intranasal irritation (13.6%), anxiety (4.9%), and nose bleed (2.9%). The most commonly reported adverse events in the placebo group were nasal irritation (21.0%), increased appetite (3.6%), and light-headedness (2.4%). The most common adverse events leading to treatment discontinuation were headache in the insulin treated group (n = 1) and symptomatic worsening in the placebo group (n = 1).

Discussion

Intranasal insulin significantly improved a measure of executive function (Trails B) in adults with BD. The Trails B evaluates executive function, of which the dorsolateral prefrontal cortex is a neuroanatomical correlate, suggesting regional effects of insulin administration (30). Subjects enrolled and randomized in this experiment generally exhibited

improvement with both intranasal insulin and placebo on most primary and secondary neurocognitive measures, which is suggestive of a practice effect. Notwithstanding, it cannot be excluded that some individuals may experience symptom worsening with intranasal insulin as two subjects in the intranasal insulin group discontinued prematurely owing to symptom intensification. However, the degree of symptom intensification was mild as these individuals had subsyndromal affective symptomatology.

These very preliminary results cohere with extant evidence documenting a cognitive enhancing effect of intranasal insulin in healthy volunteers as well as in individuals with MCI and AD (13, 14). The effect of intranasal insulin in MCI and AD is moderated by genotype status ([i.e., apolipoprotein E (ApoE)]. For example, interventional studies with intranasal insulin in MCI and AD indicate that insulin administration facilitates recall on measures of verbal memory in memory-impaired ApoE4 adults but did not improve memory performance in ApoE4+ subjects (14). We did not stratify subjects in the present study on the basis of genotype. It could be hypothesized that genotype status may identify a subpopulation of BD adults who are particularly responsive to intranasal insulin treatment.

A separate methodological issue that may have affected treatment outcome is the impact of residual affective symptoms in our *euthymic* BD subjects as well as the effects of baseline cognitive impairment. A recently published study evaluating the procognitive effects of pramipexole in BD failed to detect an effect on the primary outcome measure: change from baseline to week 8 on a neurocognitive battery. A subsequent analysis, however, revealed that BD individuals who were euthymic and/or exhibiting higher levels of baseline cognitive impairment demonstrated improvement with pramipexole treatment. This observation underscores the possibility that heterogeneous, baseline mood states as well as cognitive performance may alter assay sensitivity in interventional trials evaluating cognitive enhancing strategies (31).

Inferences and interpretations from this study need to be considered within the context of methodological limitations. The major limitation was that we did not stratify patients prior to treatment assignment on the basis of pre-existing neurocognitive deficits or genotype status. It could be hypothesized that the effect size of intranasal insulin may be greater in individuals demonstrating more pronounced pretreatment neurocognitive deficits. Moreover, the present study allowed for the inclusion of individuals with either bipolar I or bipolar II disorder. Available evidence does not allow a definitive conclusion as to whether one subgroup is differentially affected by neurocognitive deficits (3, 32). Moreover, it was curious that, notwithstanding the use of randomization, no subjects assigned to adjunctive insulin therapy were taking atypical antipsychotic treatment, yet 19 subjects (67.9%) assigned to adjunctive placebo were receiving atypical antipsychotic agents. Moreover, the percentage of individuals in the insulin-treated group (79.4%) who were receiving anxiolytic/hypnotic agents was significantly higher than in the placebo-treated group (35.7%). There is no clear reason available to us why this asymmetric distribution occurred. Available evidence indicates that the effect of atypical antipsychotic agents on neurocognitive performance appears to be mixed, and as such this would need to be an additional factor to be considered when interpreting the data (33). The possibility cannot be excluded that the differential use of anxiolytic/hypnotic agents may have affected the primary and secondary outcome.

It could be hypothesized that a more rapidly acting insulin analog (i.e., insulin aspart) may possess a greater therapeutic effect, as has been suggested elsewhere (34). Moreover, the dose of insulin chosen in the present study (i.e., 40 IU q.i.d.) may have been insufficient to realize the full therapeutic potential of intranasal insulin. Three separate lines of evidence provided the basis for selecting the dosing in the present study. Firstly, 40 IU q.i.d. has been demonstrated to deliver a detectable increase in insulin concentrations in the cerebrospinal fluid within ten minutes of administration, with peak levels achieved in 30 minutes (35). Secondly, within 60 minutes of administration, this dosing of insulin has been demonstrated to induce changes in auditory-evoked potentials compared to placebo (13). Thirdly, controlled studies in subjects with MCI and AD indicated that 40 IU q.i.d. was capable of improving memory performance (15). The response characteristics in elderly subjects with dementia may be different to those in subjects with BD, as the former subpopulation may be susceptible to both insulin deficiency and insulin resistance (i.e., type 3 diabetes mellitus) (36). Although we hypothesized that insulin disturbances in BD may also contribute to neurocognitive impairment, the characteristics of insulin deficiency may not be identical to those of AD and, as such, may require differential dosing.

All subjects in the present study received intranasal insulin or placebo as an adjunct to their conventional pharmacological treatments. We are of the view that discontinuing all psychotropic

medication in the BD population would be unethical. We are uncertain whether or not the allowance of psychotropic medications moderated the response to treatment. We did not allow for any medication adjustments during enrollment in the clinical trial. It could be hypothesized that some treatments may have moderated response to intranasal insulin therapy. For example, available evidence indicates that commonly employed agents in the treatment of BD (e.g., lithium, anticonvulsants, atypical antipsychotic agents, benzodiazepines) may negatively affect disparate measures of neurocognitive performance, with most lines of evidence reporting adverse effects (37). However, the cognitive deficits in BD cannot be fully explained by the use of psychotropic medication (38).

Notwithstanding these limitations, the strength of the study lies in the deliberate attempt to identify a well-characterized and euthymic group based on prospective evaluation. The emphasis on euthymia was purposeful in order not to confound the treatment effect with the presence of manic or depressive symptomatology.

In conclusion, the present study indicates that intranasal insulin is safe, well tolerated, and effective on a measure of executive function. We were unable to detect between-group differences on other neurocognitive measures, with improvement noted in both groups. Future interventional studies with intranasal insulin (and other treatments that target insulin signaling) should consider subject stratification on the basis of pretreatment neurocognitive deficits. In addition, the effect of other metabolic treatments (e.g., aerobic exercise, dietary modification, and weight loss (i.e., bariatric surgery) on neurocognitive performance are current research vistas in BD.

Disclosures

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References

1. McIntyre RS, Konarski JZ. Bipolar disorder: a national health concern. CNS Spectr 2004; 9 (Suppl. 12): 6–15.
2. MacQueen GM, Young LT, Galway TM, Joffe RT. Backward masking task performance in stable, euthymic out-patients with bipolar disorder. Psychol Med 2001; 31: 1269–1277.
3. Yatham LN, Torres IJ, Malhi GS et al. The International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC). Bipolar Disord 2010; 12: 351–363.
4. Thompson JM, Gallagher P, Hughes JH et al. Neurocognitive impairment in euthymic patients with bipolar affective disorder. Br J Psychiatry 2005; 186: 32–40.
5. Martinez-Aran A, Vieta E, Colom F et al. Cognitive dysfunctions in bipolar disorder: evidence of neuropsychological disturbances. Psychother Psychosom 2000; 69: 2–18.
6. Bowie CR, Depp C, McGrath JA et al. Prediction of real-world functional disability in chronic mental disorders: a comparison of schizophrenia and bipolar disorder. Am J Psychiatry 2010; 167: 1116–1124.
7. Lyoo IK, Sung YH, Dager SR et al. Regional cerebral cortical thinning in bipolar disorder. Bipolar Disord 2006; 8: 65–74.
8. van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. Prog Neurobiol 2006; 79: 205–221.
9. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004; 3: 169–178.
10. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res 2007; 4: 147–152.
11. Benedict C, Brooks SJ, Kullberg J et al. Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly. Diabetes Care 2012; 35: 488–494.
12. Watson GS, Craft S. Insulin resistance, inflammation, and cognition in Alzheimer's disease: lessons for multiple sclerosis. J Neurol Sci 2006; 245: 21–33.
13. Benedict C, Hallschmid M, Hatke A et al. Intranasal insulin improves memory in humans. Psychoneuroendocrinology 2004; 29: 1326–1334.
14. Reger MA, Watson GS, Frey WH et al. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. Neurobiol Aging 2006; 27: 451–458.
15. Reger MA, Watson GS, Green PS et al. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. J Alzheimers Dis 2008; 13: 323–331.
16. Schiöth HB, Craft S, Brooks SJ, Frey WH 2nd, Benedict C. Brain insulin signaling and Alzheimer's disease: current evidence and future directions. Mol Neurobiol 2011; doi:10.1007/s12035-011-8229-6.

17. Yatham LN, Kennedy SH, O'Donovan C et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disord 2005; 7 (Suppl. 3): 5–69.

18. McIntyre RS, Konarski JZ, Mancini DA et al. Measuring the severity of depression and remission in primary care: validation of the HAMD-7 scale. CMAJ 2005; 173: 1327–1334.

19. American Psychiatric Association Task Force on DSM–IV. Diagnostic and statistical manual of mental disorders DSM–IV–TR. 4th ed., text revision ed. Washington, DC: American Psychiatric Association, 2000.

20. Jacoby LL. Invariance in automatic influences of memory: toward a user's guide for the process-dissociation procedure. J Exp Psychol Learn Mem Cogn 1998; 24: 3–26.

21. Delis DC, Freeland J, Kramer JH, Kaplan E. Integrating clinical assessment with cognitive neuroscience: construct validation of the California Verbal Learning Test. J Consult Clin Psychol 1988; 56: 123–130.

22. Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills 1958; 8: 271–276.

23. Wechsler D. Wechsler Adult Intelligence Scale: WAIS-III. Manual. San Antonio: The Psychological Corporation, 1997.

24. Benton AL, Hamsher K. Multilingual Aphasia Examination. Iowa City: University of Iowa, 1976.

25. MacQueen GM, Grof P, Alda M, Marriott M, Young LT, Duffy A. A pilot study of visual backward masking performance among affected versus unaffected offspring of parents with bipolar disorder. Bipolar Disord 2004; 6: 374–378.

26. Zachary RA. Shipley Institute of Living Scale: Revised Manual. Los Angeles: Western Psychological Services, 2000.

27. Trahan DE, Larrabee GJ. Continuous Visual Memory Test: Professional Manual. Odessa: Psychological Assessment Resources, 1988.

28. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol 1982; 21: 1–16.

29. Nelson HE, Willison JR. The Revised National Adult Reading Test—Test Manual. Windsor, England: NFER-Nelson, 1991.

30. Millan MJ, Agid Y, Brune M et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov 2012; 11: 141–168.

31. Burdick KE, Braga RJ, Nnadi CU, Shaya Y, Stearns WH, Malhotra AK. Placebo-controlled adjunctive trial of pramipexole in patients with bipolar disorder: targeting cognitive dysfunction. J Clin Psychiatry 2012; 73: 103–112.

32. Bora E, Yücel M, Pantelis C, Berk M. Meta-analytic review of neurocognition in bipolar II disorder. Acta Psychiatr Scand 2011; 123: 165–174.

33. MacQueen G, Young T. Cognitive effects of atypical antipsychotics: focus on bipolar spectrum disorders. Bipolar Disord 2003; 5 (Suppl. 2): 53–61.

34. Benedict C, Hallschmid M, Schmitz K et al. Intranasal insulin improves memory in humans: superiority of insulin aspart. Neuropsychopharmacology 2007; 32: 239–243.

35. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci 2002; 5: 514–516.

36. de la Monte SM, Tong M, Lester-Coll N, Plater M Jr, Wands JR. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. J Alzheimers Dis 2006; 10: 89–109.

37. Savitz JB, van der Merwe L, Stein DJ, Solms M, Ramesar RS. Neuropsychological task performance in bipolar spectrum illness: genetics, alcohol abuse, medication and childhood trauma. Bipolar Disord 2008; 10: 479–494.

38. Goswami U, Sharma A, Varma A et al. The neurocognitive performance of drug-free and medicated euthymic bipolar patients do not differ. Acta Psychiatr Scand 2009; 120: 456–463.