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Peripheral insulin sensitivity predicting cognitive function in euthymic bipolar disorder patients

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Abstract

Objective. High prevalence of insulin resistance (IR) has been reported in bipolar disorder (BD) patients. Importantly, impaired insulin sensitivity could modulate the course and treatment outcome in BD. Here, we hypothesized that insulin sensitivity could be potentially associated with the neurocognitive trajectory in euthymic BD. We aimed to examine differences in insulin sensitivity and executive function between BD patients and controls.

Methods. Sixty-two patients with BD receiving mood stabilizer treatment and 62 controls, matching age, sex, and body mass index, were recruited in this study. Insulin sensitivity was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). The Wisconsin card-sorting test (WCST) was applied to test participants' ability to shift cognitive set. Group differences were measured and multivariate regression analysis was performed to examine relationships among factors.

Results. The results indicated that the HOMA-IR ($P = .048$) value in the patients with BD were significantly higher than those in controls. With regards to executive function, the BD patients performed significantly poorer than the control subjects ($P < .05$). Moreover, the interaction effect between BD diagnosis and HOMA-IR value on the WCST-preservation errors was significant ($P = .01$), and *post-hoc* analyses showed that the cognitive abilities were worse in the BD patients with a higher IR than in the others groups.

Conclusion. Insulin sensitivity is associated with the neurocognitive performance in euthymic BD patients. Although the underlying mechanisms remain unclear, interventions to improve insulin sensitivity could potentially improve the functional outcome of BD.

Introduction

Neurocognitive performance is an important factor related to the prognosis and functional outcome in patients with bipolar disorder (BD).[1,2] The presence of neurocognitive impairment has been found to be associated with greater disability, and cognitive impairment has been proposed as a marker of neurodegeneration in BD.[3] Neurocognitive impairment has been increasingly recognized as an integral part of the BD phenotype.[4] BD patients have significant cognitive impairment, especially in terms of executive function, attention/working memory, speed/reaction time, and verbal and visual memory.[5] Phases of BD have differential cognitive profiles with regards to executive function.[6] In patients with long-standing BD who are in a euthymic state, persistent neurocognitive difficulties remain.[7,8] One meta-analysis showed that performance in category fluency, mental manipulation, and verbal learning remained significantly impaired in euthymic BD patients.[9] However, there is heterogeneity of neurocognitive function among patients with BD.[10] The proportion of BD patients with significant neurocognitive function impairment is approximately 60%.[11] The decline in neurocognitive abilities over the course of BD seems to be associated with the allostatic load.[12] Factors that affect the neurocognitive trajectory in euthymic BD patients remain unclear.[13,14]

In previous literature, a 30% to 50% prevalence of metabolic syndrome in BD patients was reported, which was higher than that in the general population.[15,16] Other studies indicated that 8% to 17% of BD patients have hyperglycemia and type 2 diabetes, 17% to 36% have a high triglyceride level, 20% to 23% have a low high-density lipoprotein cholesterol level, 36% to 49%

have a large waist circumference, and 29% to 39% have hypertension.[15,17] These metabolic abnormalities, which include abnormalities in glucose and lipid levels, body mass index, and blood pressure, also indicate high risks of cardiovascular diseases and diabetes. High levels of adipokines and hepatokines are also involved in chronic inflammation and are correlated with higher morbidity and mortality.[18,19] In addition, there is growing evidence to suggest that an impaired glucose metabolism moderates the course of the illness and treatment outcomes in BD.[20–23] Insulin resistance (IR), as one of the consequences of the cumulative allostatic load identified through key inflammation, glucose and lipid factors, is known to contribute to neuroprogression in BD.[24,25] The odds of a chronic course of BD and rapid cycling in patients with BD and type 2 diabetes or IR was three times higher than that in euglycemic patients.[23] However, whether peripheral insulin sensitivity represents brain insulin IR and is associated with the neurocognitive trajectory in BD remains unclear.[11,26]

It is important to achieve a better understanding of potential moderators contributing to neurocognitive impairment in BD in order to develop prevention strategies and effective treatments.[4] As metabolic disturbances are associated with neurocognitive deficits, we hypothesized that insulin sensitivity could be potentially associated with neurocognitive trajectory in the euthymic phase of BD.[27] Here, we aimed to measure the differences in insulin sensitivity and executive function between euthymic BD patients and healthy controls, and examined the possible interaction effects of IR on executive function in BD patients.

Methods

Subject enrollment and measurement of psychopathology

All participants provided written informed consent to their participation in the trial, and the National Cheng Kung University Hospital Institutional Review Board reviewed and approved the study protocol prior to patient enrollment. Eligible participants were aged between 18 and 70 years. Patients diagnosed with BD according to the DSM 5 criteria who were receiving mood stabilizer treatment, including valproic acid (VPA) (n = 21, 33.9%), VPA + antipsychotics (n = 19, 30.6%), lithium + antipsychotics (n = 12, 19.4%), antipsychotics (n = 10, 16.1%), were enrolled consecutively. Patient psychopathology was evaluated using the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS). The HDRS and YMRS scores were not higher than 8 in all of the participants. Patients were excluded if they had (i) a diagnosis of organic mood disorder, (ii) a mood disorder not otherwise specified, (iii) received more than one course of electroconvulsive therapy (ECT) or undergone ECT within the last 6 months, (iv) cerebrovascular disease, (v) neurodegenerative disorders, or (vi) macrovascular disorders. We also recruited 62 controls, matching age, sex, and body mass index, from the community after exclusion of individuals with mental illnesses by a senior psychiatrist using the Chinese version of the Mini International Neuropsychiatry Interview. To avoid confounding factors interfering with the IR and cognitive function, all of the control meeting the following criteria were excluded through chart reviews and patient-reported questionnaires: (i) a serious surgical condition or physical illness including all chronic diseases, heart disease, stroke, kidney dialysis, transplant, etc., (ii) cerebrovascular disease, (iii) neurodegenerative disorders, (iv) macrovascular disorders.

Diagnosis of IR and type 2 diabetes mellitus (T2DM)

Tests of fasting plasma glucose (FPG) and fasting serum insulin (FSI) levels was performed in all patients and analyzed in a single laboratory using the same assay to eliminate variability. If the FPG level was elevated (>7 mmol/L), the test was repeated on another day to confirm the diagnosis of T2DM. If the diagnosis of T2DM was equivocal (repeated test was not >7 mmol/L, or initial FPG level was between 5.7 and 6.9 mmol/L), then a 2-h 75 g oral glucose tolerance test was performed. Glucose intolerance (GI) was defined as a FPG level < 7.0 mmol/L, and a glucose level >7.8 and <11.1 mmol/L measured 2 h after ingestion of 75 g of glucose. A diagnosis of T2DM was made if the 2-h glucose level was >11.1 mmol/L, irrespective of the FPG level. These are standard diagnostic procedures for T2DM. In patients who did not meet the laboratory criteria for T2DM or GI, IR was estimated using the homeostatic model assessment-IR (HOMA-IR) equation (HOMA-IR = FPG (mmol/L) × FSI (U/mL)/22.5), and participants were classified into groups with and without IR according to a cut-off point of 2.6. HOMA-IR ≥ 2.6 is a suitable cutoff point of HOMA-IR value for diagnosis of metabolic syndrome, abdominal obesity, fasting hyperglycemia, hypertriglyceridemia, low-HDL, and greater cardiovascular risk.[28–32] Furthermore, an observational study has revealed that subjects with HOMA-IR ≥ 2.6 had larger odds of cognitive dysfunction.[28] The participants with IR and GI were combined into a single group for the analyses. Among all of the subjects (BD and controls), there were only two BD patients having T2DM in the study.

Wisconsin card-sorting test (WCST)

The WCST was conducted by an experienced clinical neuropsychologist. There were 64 cards in the test. All definitions of indices were as described in the WCST manual.[33] Using a computerized version of the WCST, the patients were required to match response cards to four stimulus cards along one of three dimensions (color, form, or number) on the basis of sign feedback (correct or incorrect). The subjects were not given any information about the dimensions. After sorting a series of 10 cards in one category, the subject was asked to sort the cards again in a different category. The indexes of preservative errors and completed categories were used to assess performance in the WCST.[34]

Statistical analyses

SPSS Statistics 20.0 (SPSS Inc., Chicago, IL) was used for all of the analyses. The results were considered significant at $P < .05$ (two-tailed). Chi-square tests or independent *t*-tests were conducted to examine group (patients with BD vs controls) differences in demographic characteristics, HDRS score, YMRS score, IR, and WCST score. Because educational year was significantly different between groups, multivariate regression analysis, controlling educational year, was used to test the interaction effects between groups in IR and the WCST score.

Results

We recruited 62 euthymic BD patients, 32 (51.6%) of whom had BD I, and 62 age, sex, and body mass index matched control subjects. The demographic characteristics are shown in Table 1. The BD patients also had a lower educational year, higher YMRS score, and higher HOMA-IR. However, the frequency of IR,

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Table 1. Demographic Characteristics of the Euthymic BD Patients and the Control Subjects

	BD (n = 62) Mean ± SD	Control (n = 62) Mean ± SD	Statistics t/χ^2	*P*-value	*P*, Controlling Educational Year
Gender, male, n (%)	24 (38.7)	24 (38.7)	—	—	
Age (years)	35.87 ± 12.67	34.16 ± 12.04	0.77	.443	.612
Educational year	14.93 ± 2.12	16.19 ± 2.77	−2.80	.006	—
HDRS	1.60 ± 2.07	1.77 ± 1.53	−0.54	.588	.424
YMRS	0.65 ± 1.15	0.00 ± 0.00	4.43	<.001	<.001
Body mass index (kg/m^2)	26.41 ± 4.97	25.19 ± 5.41	1.30	.195	.223
Insulin (uIU/mL)	16.16 ± 12.16	12.79 ± 7.02	1.89	.062	.074
Glucose (mg/dL)	93.52 ± 20.86	90.44 ± 10.06	1.05	.297	.399
HOMA-IR	3.89 ± 3.48	2.90 ± 1.72	2.00	.048	.056
HOMA-IR ≥2.6, n (%))	33 (53.2)	28 (45.2)	0.81	.369	
WCST_ preservative errors	12.31 ± 9.80	8.37 ± 5.74	2.73	.007	.049
WCST_ completed categories	2.73 ± 1.66	3.53 ± 1.42	−2.90	.004	.074

Abbreviations: BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale; HOMA-IR, homeostasis model assessment of insulin resistance; WCST, Wisconsin card-sorting test; YMRS, Young Mania Rating Scale.

Table 2. Performance of the Euthymic BD Patients and the Control Subjects in the Neuropsychological Functional Tests, Subgrouped by HOMA-IR

	BD (N = 62)		Control (N = 62)		*P*-Value[a]			*P*-Value[b]		
	Non-IR (n = 29)	IR (n = 33)	Non-IR (n = 34)	IR (n = 28)	Group Effect	IR Effect	Group*IR Effect	Group Effect	IR Effect	Group*IR Effect
WCST										
Preservative errors	9.45 ± 6.36	14.82 ± 11.56	8.71 ± 5.83	7.96 ± 5.71	.062	.097	.010*	.073	.277	.009*
Completed categories	3.07 ± 1.67	2.42 ± 1.62	3.65 ± 1.35	3.39 ± 1.52	.099	.075	.179	.127	.405	.137

Abbreviations: BD, bipolar disorder; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance (HOMA-IR ≥ 2.6); WCST, Wisconsin card-sorting test.
[a]Educational year was controlled.
[b]Educational year and body mass index were controlled.
*$P < .05$.

defined as HOMA-IR ≥ 2.6, was no significantly different in the BD patients than in the controls (53.2% vs 45.2%, $P = .369$). Moreover, performance in the WCST-preservation errors (12.31 ± 9.80 vs 8.37 ± 5.74, $P = .007$) and WCST-completed categories (2.73 ± 1.66 vs 3.53 ± 1.42, $P = .004$) was poorer in the BD patients as compared with the controls (Table 1). The results were similar even after adjustment for educational years (Table 1).

When considering stratification of IR, we further subgrouped patients according to a cut-off point for HOMA-IR. The results showed that there was a significant interaction effect between BD diagnosis and IR in the WCST-preservation errors ($F = 6.80$, $P = .010$) (Table 2). The *post-hoc* analyses showed that the cognitive abilities were worse in the BD patients with a higher IR than in the other groups (Figure 1).

Discussion

The results here again showed significant differences in insulin sensitivity and executive function between BD patients and healthy controls. Moreover, the results demonstrated that insulin sensitivity was associated with neurocognitive performance in euthymic BD patients. Importantly, insulin sensitivity impairment significantly aggravates the impaired executive function of cognitive set shifting (ie, perseverative errors in WCST) in BD patients. The neurocognitive trajectory in BD is highly variable and the progression of cognitive decline is not a general rule in BD.[10] Factors reflecting differences in illness severity but not the clinical subtypes might explain observed variation.[35,36] Before, a cohort study showed BD patients who have a greater number of manic or hypomanic episodes may present significant neuroprogression.[13] And the impact of pharmacological treatments upon cognitive function is inconclusive.[37] Here we demonstrated IR could be a testable and potentially modifiable factor for early screening and intervention that prevent neuroprogression advance in BD.[38]

IR as one of the consequences of the cumulative allostatic load identified through key inflammation, glucose and lipid factors. Therefore, BD patients, especially those with IR, might have a higher C reactive protein (CRP) level that associated with greater impairments in neurocognitive function and altered brain functional connectivity.[39,40] In addition, levels of inflammatory biomarkers, such as peripheral CRP, has also been considered to help stratifying the outcomes in treating mood disorders.[41] In BD, the peripheral CRP level is elevated prominently during the manic state, but is still moderately elevated during the depressive and euthymic states[42], In this study, we have compared the CRP

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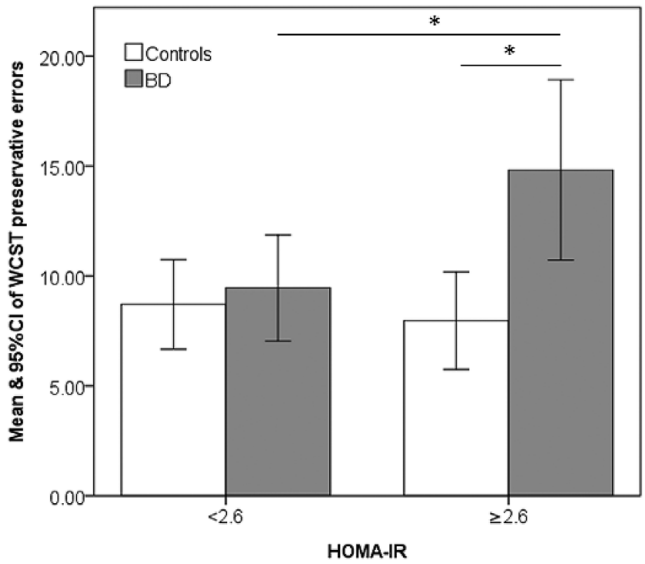

Figure 1. Post-hoc analyses of WCST preservative errors and HOMA-IR in the euthymic bipolar disorder patients and controls. Abbreviations: WCST, Wisconsin card-sorting test; HOMA-IR, homeostasis model assessment of insulin resistance; BD, bipolar disorder. *$P < .05$.

levels between groups, however, the difference was not significant although the CRP levels were significantly associated with HOMA-IR in both groups (Supplementary Table 6). Moreover, the interaction effect between BD diagnosis and CRP levels on the WCST-preservation errors was not significant.

IR could contribute to neuroprogression through blood–brain barrier (BBB) leakage and pro-inflammatory cytokines activating in brain.[43] Before, an image study had found increased BBB dysfunction in BD subject with IR. The extensive BBB leakage is associated with worse neuropsychiatric status (including more frequent of chronic illness episodes, greater severity of depression, and socio/occupational dysfunction) and with metabolic dysregulation (including higher body mass indices, increased risk of cardiovascular disease, advanced heart age, and higher levels of IR) in BD patients.[44] Systemic insulin sensitivity might also indicate the degree of insulin sensitivity in the brain.[45] Importantly, brain IR is related to a greater amyloid burden post-mortem and increased deposition within areas affected by early Alzheimer's disease (AD).[46,47] In addition, brain IR is known to contribute to a poorer memory performance and beta amyloid deposition in brain regions affected by AD.[48,49] Importantly, patients with BD have been associated with future risk of dementia.[50,51] Moreover, clear independent roles of BD and IR in the risk of dementia have been demonstrated.[52] Future studies are warranted to understand the detail mechanisms of the role IR in neuroprogression in BD patients.

Taken together, the results indicated that IR might play a key role in cognitive deficit in BD.[53] Therefore, medications or therapies approved for treating IR may help to treat mood and neurocognitive symptoms in BD.[54] Several anti-hyperglycemic agents have been observed to have effects on depressive symptoms and cognitive decline, and this efficacy is probably the result of action on shared brain targets between the two conditions.[41] These medications include subcutaneous insulin, intranasal insulin, metformin, and liraglutide. Other promising brain stimulating, behavioral, and chronotherapeutic approaches are currently being investigated.[55,56]

Although the data were presented carefully, this study has certain limitations. The first limitation is the relatively small sample size of the BD patients and controls. The second limitation is that the BD patients received different kinds of mood stabilizer treatment, which might influence the status of insulin homeostasis and neurocognitive function in different degrees. In the current study, in order to decrease the confounding factor, all of the BD patients received the same treatment at least for 3 months. Further study is needed to clarify whether insulin sensitivity could be a useful clinical indicator for monitoring neurocognitive function in BD patients.

Conclusions

In summary, our study suggested that insulin sensitivity is associated with the neurocognitive performance in euthymic BD patients. Although the underlying mechanisms remain unclear, interventions to improve insulin sensitivity could potentially improve the functional outcome of BD. The course of BD is highly variable, with a subset of patients presenting with a progressive course associated with brain changes and functional impairment.[57] Further study about enhancing brain insulin signaling would be beneficial for the treatment of metabolic and cognitive deficits in BD.

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Supplementary Materials. To view supplementary material for this article, please visit http://doi.org/10.1017/S1092852921000158.

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