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Abstract

Background

Cognitive impairment contributes to deterioration in social, family and work functioning in Bipolar Disorder (BD). Cognitive deficits are present not only during, but also outside of mood episodes. Insulin resistance (IR) impairs cognitive functioning and is frequent in participants with BD. Thus, we hypothesized that IR might contribute to cognitive deficits in remitted BD participants.

Methods

We acquired biochemical (fasting insulin, glucose, lipids) cognitive (California Verbal Learning Test, Digit Span) measures from 100 euthymic participants with BD type I or II. IR was diagnosed using HOMA-IR.

Results

BD participants with IR displayed worse composite verbal memory score (-0.38 vs 0.17; $F(1, 8.23)=17.90$; $p = 0.003$), while composite working memory scores were comparable in patients with or without IR (-0.20 vs 0.07; $F(1, 6.05)=1.64$; $p = 0.25$). Insulin resistance remained significantly associated with composite verbal memory scores ($F(1, 47.99)=9.82$, p

= 0.003) even when we controlled for levels of lipids. The association between IR and verbal memory was not confounded by exposure to antipsychotics, which were not associated with worse cognitive performance (F(1, 2.07)=5.95, p = 0.13).

Limitations

The main limitation is the cross-sectional design, which does not allow us to rule out reverse causation.

Conclusions

We demonstrated that among remitted BD participants without diabetes mellitus, IR was significantly associated with verbal memory performance, even when we controlled for other relevant metabolic or treatment variables. These findings raise the possibility that early detection and treatment of IR, which is reversible, could possibly improve cognitive functioning in at least some BD participants.

Keywords

Bipolar disorder

Insulin resistance

Verbal

Memory

Cognitive function

1. Introduction

Bipolar Disorders (BD) affect millions of people worldwide. Even outside of acute episodes, patients with BD often experience deterioration in social, family and work functioning, which is often related to cognitive impairment.

Acute symptoms of mood episodes impair cognitive functions. However, several studies and meta-analyses have highlighted that cognitive deficits, especially in verbal and working memory, processing speed and executive functions (Bourne et al., 2013; Robinson et al., 2006) persist during euthymia. These cognitive deficits contribute to poor occupational outcomes, even more than residual symptoms (Tse et al., 2014). Consequently, a recent report from the International Society for Bipolar Disorders stressed the need for routine evaluation of cognitive functions in patients remitted from a mood episode (Miskowiak et al., 2018).

Nevertheless, our options for treating this key obstacle to functional recovery are limited. Current medications target the acute symptoms of illness, but they do not improve and may even worsen the cognitive functions. Consequently, it is necessary to better understand the factors that contribute to cognitive impairment in BD. If we can identify risk factors for

cognitive impairment, perhaps we would be able to develop new treatments specifically targeting cognition.

Patients with BD are more at risk for diabetes, insulin-resistance (IR) and metabolic syndrome than the general population (De Hert et al., 2011; Vancampfort et al., 2013). This could be related to shared genetic factors, symptoms of illness, lifestyle issues, poor access to care, or the use of antipsychotic medications. Regardless of the reasons for this comorbidity, we need to better understand the contribution of metabolic alterations to neuropsychiatric outcomes.

Patients with IR display cognitive impairments similar to those found in major psychiatric disorders. IR has been associated with impaired verbal memory and fluency, processing speed and executive functions (Kullmann et al., 2016), reduced hippocampal volume (Hajek et al., 2014; Ursache et al., 2012), and with a higher risk for developing dementia in old age (Gudala et al., 2013; Norton et al., 2014). This is not surprising, as insulin receptors are abundantly distributed throughout the brain, and insulin binding to its receptors not only produces numerous metabolic effects but also plays a promoting role in synaptic transmission and neuronal survival/growth (Ott et al., 2012).

Considering the high prevalence of IR/metabolic syndrome in BD and the similarity between cognitive impairments in both conditions, it is possible that some of the cognitive changes in BD may be related to the presence of comorbid metabolic alterations. Perhaps the fact that only some patients with BD suffer from these comorbidities could also help explain why only some patients with BD show cognitive impairments. To test this hypothesis, we measured IR and cognitive functioning in euthymic patients with BD.

2. Methods

2.1. Patients

This multicenter study was conducted in the outpatient clinics of University hospitals in Milan (Italy), Turin (Italy), and Prague (Czech Republic), between February 2017 and October 2018.

Outpatients with diagnosis of BD type I or II (verified by SCID-I) in euthymic phase of the disorder consecutively admitted to the study centers were asked to participate. To be enrolled, patients had to be in euthymic state (HAM-d-17 ≤ 7; YMRS ≤ 5; CGI-BP ≤ 3) and free from significant mood symptoms at least two months before the index visit. Psychiatrists administered the diagnostic interview and rating scales.

Patients were excluded if they had dementia, borderline personality disorder, diabetes mellitus or current alcohol/substance use disorder. Other comorbid psychiatric disorders were allowed.

Study procedures were explained in detail, and patients were asked to read and sign an informed consent. The study was conducted according to the Declaration of Helsinki and approved by the Independent Ethics Committee of participating centers.

2.2. Study procedures

During the study visit, a blood draw measuring basal insulin, glucose, total cholesterol, HDL cholesterol and triglycerides (TGC) was performed in fasting condition. The samples were

analyzed in hospital laboratories using standard methods of clinical biochemistry. We also collected anthropometric measures (weight, height). Patients were then asked to undergo assessment by psychiatrist and cognitive testing within one month from the blood sampling. During the interview we systematically assessed for the following socio-demographic and clinical variables, including age, gender, education, marital and occupational status, diagnosis, age at onset, number of previous episodes, pharmacological treatment. Participants underwent neuropsychological testing, which consisted of the California Verbal Learning Test (CVLT) and the Digit Span forward and backward (DS).

The CVLT is a test of verbal learning, recall (encoding and retrieval) and recognition of the learned content. A list of 16 words (belonging to four semantic categories) is read five times, and the patient has to recall the words in the list after each trial (trials 1–5). After the fifth trial, an interference list is read and the patient is asked to recall it. A short delayed recall test is conducted immediately after recalling the interference list, where the participant is asked to recall the words in the first list of words (trial 6). Cues are then provided for the four semantic categories to facilitate recall (trial 7). After 20 min in which the participants performed the DS, a long delayed recall test was presented (trial 8). Cues were again provided for the four semantic categories to facilitate recall (trial 9). Finally, a yes-no recognition list consisting of 44 words was read to the patient, who had to correctly retrieve the 16 words (recognition).

The DS is a test evaluating auditory attention and working memory. In the DS a sequence of digits is read aloud at a rate of one digit per second, and the participant must repeat the sequence. The sequences start at a length of two digits, and two sequences of each length are read out. The sequence length increases by one digit as long as the participant recalls correctly at least one sequence of the same length. In the DS forward, the patient must recall the sequence in the same order that was read by the experimenter; in the DS backward, the patient must recall the sequence in the reverse order.

IR was estimated with the homeostatic model assessment of insulin resistance (HOMA-IR = [fasting plasma insulin (mU/L) x fasting plasma glucose (mmol/L)]/22.5). The HOMA-IR correlates well with estimates using the euglycaemic clamp method and it is a well-accepted measure of IR (Pillinger et al., 2017; Wallace et al., 2004).

The HOMA scores used as cutoff to define IR vary across studies, ranging from 1.7 to 3.875 (Tang et al., 2015). Nevertheless, the World Health Organization (WHO) defines IR as a value equal or greater than the 75th percentile value for non-diabetic subjects (Alberti and Zimmet, 1998). As all subjects in our study were non-diabetic, we employed the WHO definition and diagnosed IR in those with a HOMA-IR score ≥ 3.5, corresponding to the 75th percentile in HOMA scores in our sample.

2.3. Statistical analyses

We used standard descriptive statistics to document the socio-demographic and clinical characteristics of the sample.

To limit the number of comparisons and thus to preserve statistical power, we converted the cognitive measures to z-scores and calculated composite scores separately for verbal and working memory, according to a previously published method (Bruehl et al., 2010; Laws et al.,

2017). The verbal memory composite scores were calculated from CVLT subtests, which were available in all participants, including trials 1–5, trial 6, and trial 8 (total recall, short-delayed recall, long-delayed recall).

Verbal and working memory composite scores were then calculated as follows:

- composite verbal memory score = (trials 1–5 z-score + trial 6 z-score + trial 8 z-score) / 3
- composite working memory score = (DS forward z-score + DS backward z-score) / 2

These composite verbal and working memory scores were separately entered as dependent variables into a general linear model with IR (yes, no) as predictor, age as covariate and center as a random factor.

To explore the extent to which the individual subtests contributed to the association between IR and cognitive performance, we repeated equivalent models, but with raw scores from individual subtests as the dependent variables and calculated eta squared as the measure of effect size.

We also explored associations between individual biochemical, clinical, demographic predictors and individual composite cognitive scores, while controlling for age and site. Variables, which were significantly associated with cognitive performance were then included in a model together with IR.

All analyses were performed using IBM SPSS 20.0 software (Armonk, NY).

3. Results

We recruited 111 euthymic BD participants. Eleven patients were excluded from the final sample: 5 had current alcohol or substance abuse, 4 had borderline personality disorder comorbidity, 2 had type 2 diabetes mellitus. Thus, we analysed data from 100 euthymic BD participants.

51% of participants in the whole sample were females, mean age was 45.2 ± 13.3 years, age at onset 25.8 ± 8.7 years and 56.7% had bipolar disorder type I. Mean BMI was 26.5 ± 5.4 kg/m2, and mean HOMA-IR was 2.9 ± 4.0.

Patients with IR were older and less educated than patients without IR. Age of onset of BD was higher in patients with IR. BMI and TGC levels were greater in patients with IR. Patients with IR were more frequently treated with mood stabilizers, while exposure to antipsychotics (aripiprazole, olanzapine, quetiapine) did not differ between the two groups Socio-demographic and clinical v variables are shown in Table 1.

3.1. Cognitive functions in ir

When controlling for age and center, participants with IR displayed worse composite verbal memory score (−0.38 vs 0.17; F(1, 8.23)=17.90; p = 0.003, partial eta squared=0.69). Among the individual subtests, short delayed free recall showed the largest effect size (partial eta squared=0.73), whereas CVLT long delayed free recall showed the lowest effect size (partial eta squared=0.48) for differences between those with and without IR (Table 2).

3.2. Exploratory analyses

Composite verbal memory scores were nominally associated with TGC (Beta=−0.21, t(92)=−2.02, p<0.05), HDL (Beta=0.20, t(91)=2.13, p = 0.04), but not with total cholesterol (Beta=−0.03, t(85)=−0.26, p = 0.80), BMI (Beta=0.02, t(83)=0.21, p = 0.84), exposure to antipsychotics (F(1, 2.07)=5.95, p = 0.13) or mood stabilisers (F(1,1.03)=0.10, p = 0.80), or years of education (Beta=0.08, t(61)=0.70, p = 0.49). In the model, which controlled for age, site, TGC and HDL, IR remained significantly associated with composite verbal memory scores (F(1, 47.99)=9.82, p = 0.003), whereas the association between TGC or HDL and composite memory scores became non-significant (F(1,82)=0.07, p = 0.79; F(1,82)=3.52, p = 0.06, respectively).

Composite working memory scores were nominally associated with years of education (Beta=0.37, t(59)=3.05, p = 0.004), but not with HDL (Beta=0.14, t(82)=1.31, p = 0.19), TGC (Beta=−0.21, t(83)=−1.86, p = 0.07), total cholesterol (Beta=0.03, t(76)=0.25, p = 0.80), BMI (Beta=0.07, t(75)=0.63, p = 0.53), exposure to antipsychotics (F(1,2)=0.28, p = 0.65) or mood stabilizers (F(1,1)=0.004, p = 0.96). The association between IR and composite working memory scores remained non-significant (F(1, 47.75)=3.43, p = 0.07), even when we controlled for site, age and years of education.

4. Discussion

Here, for the first time, we report that among BD participants IR was associated with worse cognitive functioning, especially verbal memory. No other biochemical or anthropometric measures, including total cholesterol, HDL, TGC, BMI, were associated with verbal or working memory performance either individually (BMI) or when analyzed jointly with IR (HDL, TGC). Importantly, the association between IR and verbal memory was not confounded by exposure to antipsychotics, which were not associated with worse cognitive performance.

Similar association between IR and verbal memory was recently documented in schizophrenia (Wijtenburg et al., 2019). Our study is also in keeping with previous cross sectional as well as prospective reports documenting the negative association between IR and cognitive functioning in participants without psychiatric disorders. For example, participants with hyperinsulinemia showed declarative memory impairments and greater cognitive decline over a 6-year follow-up (Young et al., 2006). Bruehl and colleagues showed worse performance in declarative memory and executive functions in participants with versus without IR (Bruehl et al., 2010). In a larger study of cognitively normal adults, higher HOMA-IR was associated with poorer performance on measures of verbal episodic memory, executive function and global cognition (Laws et al., 2017).

Among the verbal memory subtests, total and short delay free recall were most sensitive to IR. This pattern of verbal memory alterations among euthymic BD participants with IR was generally in keeping with the patterns of alterations in euthymic/subsyndromal BD participants (Cardoso et al., 2016; Chepenik et al., 2012; Martínez-Arán et al., 2004; Sumiyoshi et al., 2017; Vasconcelos-Moreno et al., 2016). In addition, among the CVLT subtests, total immediate recall is most strongly associated with lower hippocampal volumes in BD (Chepenik et al., 2012). In our previous study on an unrelated sample, we reported lower hippocampal volumes in BD participants with relative to those without IR (Hajek et al., 2014).

We did not find association between IR and working memory. This observation is in line with a previous study, where the effects of IR on declarative memory were three times higher than the effects of IR on working memory (Bruehl et al., 2010). This is very much in keeping with the effect sizes for verbal (partial eta squared=0.69) and working memory (partial eta squared=0.21) in our study.

The effects of IR on brain function are not surprising. Insulin acts not only peripherally but also on the brain: it is actively transported through the blood-brain barrier and binds to its receptors, which are widely distributed throughout the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, and septum (Kullmann et al., 2016). In rodent studies, insulin signaling in the hippocampus has been shown to promote cell survival and synaptic plasticity (Banks et al., 2012). The mechanisms underlying the connection between IR and cognition could include withdrawal of trophic factors, inhibition of insulin-responsive gene expression and impaired mitochondrial energy metabolism, which causes oxidative stress through increased production of reactive oxygen species (Andreazza et al., 2010; Brietzke et al., 2011; de la Monte, 2009; Kroner, 2009). In addition, insulin signaling appears to increase NMDA-mediated glutamatergic transmission in hippocampus, thus enhancing processes of long-term potentiation (Ferrario and Reagan, 2018). In a recent rodent study, high-fat diet-induced IR led to excess of palmitic acid deposition in hippocampus, causing impairment in long-term potentiation through reduced glutamatergic synaptic currents (Spinelli et al., 2017).

These mechanisms contribute to explain why both type 2 diabetes and IR are associated with specific cognitive impairment in memory, processing speed and executive functions (Moheet et al., 2015) and with reduced hippocampal volume (Hajek et al., 2016, 2014; Ursache et al., 2012).

Metabolic syndrome, which is often characterized by IR, and diabetes are frequent in BD. Yet, the screening for diabetes in BD is insufficient and IR is not monitored at all. Even a well-done routine assessment for diabetes may thus overlook the presence of IR, which typically presents with normal glucose levels. Yet, this factor appears to be associated with cognitive impairment and could contribute to poor psychiatric and brain outcomes (Calkin et al., 2015; Hajek et al., 2014). Also, in this study, IR was more strongly associated with cognitive performance than the more traditional measures, which are recommended for screening in psychiatry, i.e. cholesterol, triglycerides, BMI. In line with previous research (Hajek et al., 2016), our findings put more emphasis on clinical screening of insulin metabolism in BD.

The confirmation of the effect of IR on verbal memory in BD could pave the way for new interventions. Firstly, a lifestyle intervention, including regular physical exercise and dietary modifications, which may reverse IR might also positively affect cognition. In addition, several studies have investigated the effects on cognition of pharmacological interventions addressing brain IR. Administration of insulin in healthy subjects positively affects memory. In a first such study, a high dose of intravenous insulin was more effective than a low dose in acutely improving the ability of remembering word lists (Kern et al., 2001). In a subsequent study conducted on healthy subjects before and after 8 weeks of intranasal insulin treatment, delayed recall of words was enhanced, yet immediate recall, non-declarative memory and selective attention were not affected by insulin administration (Benedict et al., 2004). There is also a growing evidence that several insulin-sensitizers such as rosiglitazone, liraglutide, and to some extent metformin independently improve cognitive function in mice models (Hansen et al., 2015; Patel et al., 2016; Ying et al., 2014). Liraglutide also improved memory and executive functions in individuals with mood disorders and, interestingly, the effect was moderated by baseline HOMA-IR scores (Mansur et al., 2017).

This study has the following strengths – inclusion of participants in euthymic state, the use of well-established criteria for diagnosing IR, assessment of relevant cognitive functions, and the consistency of results across different centers. However, several relevant limitations should also be acknowledged. Firstly, only a prospective study could confirm the direction of the association between IR and verbal memory. Thus, we cannot rule out reverse causation, whereas impaired memory causes IR. In addition, without a control group, we cannot test for interactions between BD and IR in their effects on cognitive functioning. Comparison with a control group could help disentangle the effects of IR from those of BD on memory function. Regardless of whether this is an independent effect of only IR or an interaction between BD and IR, our data suggest that the presence of IR is an important factor, which could explain some of the variation in cognition in patients with BD. The sample size was primarily targeting differences in verbal memory and could have been underpowered to detect the association between IR and working memory. Since the studied population is at high risk for metabolic issues the chosen HOMA-IR cutoff might have underestimated IR in our study group. While HOMA-IR is the easiest and most frequently employed method to measure insulin resistance, future validation with gold-standard measurements of insulin sensitivity would provide deeper insight into the association between insulin signaling and cognition in BD. Finally, the study was carried out in three centers in different countries, where patient characteristics might have varied. However, we controlled for effects of site in statistical analyses.

In conclusion, we demonstrated that among BD participants without diabetes mellitus, IR was significantly associated with verbal memory performance, even when we controlled for other relevant metabolic or treatment variables. IR was more strongly associated with cognitive alterations than any of the traditional metabolic markers, including BMI, cholesterol, HDL, TGC. This is highly clinically relevant, as IR is currently not screened for. Our findings raise the possibility that early detection and treatment of IR, which is reversible, might improve cognitive functioning in some BD participants.

Author contributions

Drs. Salvi and Hajek conceived and designed the study. Drs. Di Salvo, Korcakova, Torriero, Aragno, Kolenic and Ungrmanova collected the data. dr. Salvi and Hajek analysed the data. dr. Salvi wrote the first draft of the manuscript. dr. Hajek contributed in drafting the manuscript in its final form. Prof Maina and Prof. Mencacci provided with insightful comments and reviewed the manuscript. All authors read and approved the manuscript.

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Declarations of Competing Interest

None

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	IR	No IR	Partial eta squares
CVLT scores			
CVLT total recall (trial 1–5)	42.2 (9.7)	50.0 (11.6)	0.688
CVLT short delayed free recall (trial 6)	9.6 (2.3)	11.1 (3.0)	0.727
CVLT long delayed free recall (trial 8)	9.0 (3.0)	10.6 (3.2)	0.478
DS scores			
DS Forward	6.4 (1.4)	6.5 (1.4)	0.002
DS Backward	4.3 (1.4)	5.0 (1.4)	0.502

Table 2

Exploratory analyses of association between IR and individual cognitive subt-ests.

	IR *N* = 24	No IR *N* = 71	*P*
Sex (female), n (%)	10 (41.7)	37 (52.1)	0.38
Age (years), mean ± *sd*	**49.2 ± 9.3**	**43.7 ± 14.3**	**0.04**
Education (years), mean ± *sd*	**12.9 ± 3.3**	**14.9 ± 2.7**	**<0.01**
BD type I, n (%)	13 (54.2)	46 (66.7)	0.27
Age of onset (years), mean ± *sd*	**29.3 ± 10.3**	**24.5 ± 7.5**	**0.05**
Duration of illness (years), mean ± *sd*	19.9 ± 14.4	19.3 ± 13.4	0.87
N. of manic episodes, mean ± *sd*	4.8 ± 4.3	3.9 ± 3.7	0.33
N. of depressive episodes, mean ± *sd*	4.6 ± 3.9	4.8 ± 4.7	0.66
At least one lifetime suicide attempt, n (%)	4 (16.7)	20 (29)	0.23
BMI, mean ± *sd*	**29.3 (5.5)**	**25.9 (5.1)**	**<0.01**
Triglycerides, mmol/l	**3.3 (2.1)**	**1.8 (1.0)**	**<0.01**
HDL cholesterol, mmol/l	1.3 (0.5)	1.4 (0.4)	0.21
Total cholesterol, mmol/l	4.7 (1.3)	4.8 (1.0)	0.55
Psychotropic medication, n (%) *Antipsychotics* ***Mood stabilizers*** *Antidepressants*	18 (75) **24 (100)** 7 (29.2)	39 (57.4) **56 (82.4)** 9 (13.2)	0.13 **0.03** 0.08

Table 1

Socio-demographic/clinical characteristics of patients with and without IR