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ORIGINAL ARTICLE

Association of arterial hypertension and cognitive impairment in euthymic bipolar disorder

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Abstract

OBJECTIVES: Cognitive impairment in euthymic phase of bipolar disorder has been documented in many studies. Several factors may contribute to such impairment, e.g. sedative medication, thyreopathy. Metabolic syndrome with its components represents another frequent condition found in bipolar disorder exerting probably adverse impact on cognition. Since it is treatable factor and current literature suggests possible connection with cognitive dysfunction, we aimed to explore such associations to identify promising targets of complex treatment.
METHODS: Forty euthymic bipolar patients have been enrolled. Their body and metabolic parameters were measured. Medical history data were collected. Cognition was evaluated using battery of tests. Neuropsychological performance was transformed into neurocognitive composite score. Cognition of subjects was compared dichotomously according to presence or absence of pathological body and metabolic parameters. Correlations of selected parameters and composite score were done.
RESULTS: Low neurocognitive score was found in presence of hypertension, metabolic syndrome, abdominal obesity and hyperglycemia. Only connection of hypertension and cognitive score reached sufficient statistical power. Patients presenting hypertension performed worse in all tested domains of cognition when compared with normal blood pressure group. Subjects using lithium performed substantially worse in cognitive tests. However, in comparison with anticonvulsant group, lithium users had markedly longer disorder history as well as longer duration of thymoprofylaxis. No significant correlation of HDRS score, insulinemia or HOMA-IR was found.
CONCLUSION: Despite relatively small sample size, noticeable association of hypertension and cognitive impairment was revealed. This might indicate possible way of enhancing cognition in bipolar disorder by treating elevated blood pressure.

Abbreviations:

BMI	- Body Mass Index
CPT	- Continuous Performance Test
DS	- Digit Span
HDL	- High Density Lipoprotein
HDRS	- Hamilton Depression Rating Scale
HOMA-IR	- Homeostatic Model Assessment of insulin resistance
ICD 10	- International Classification of Diseases 10th revision
LDL	- Low Density Lipoprotein
RAAS	- Renin-Angiotensin-Aldosteron System
RAVLT	- Rey Auditory Verbal Learning Test
SS	- Spatial Span
TOL	- Tower of London
WCST	- Wisconsin Card Sorting Test
YMRS	- Young Mania Rating Scale

INTRODUCTION

The whole group of bipolar affective disorders constitutes chronic and debilitating disease which is accompanied by cognitive dysfunction even in remission also known as euthymia. Cognitive impairment connected to bipolar disorder has become the focus of research especially in the last fifteen years. Growing interest in this patient population has followed the same study efforts made previously in the field of schizophrenia. Nevertheless, bipolar disorder has lesser impairment than schizophrenia (Bora & Pantelis 2015). Several meta-analyses proved that cognitive dysfunction in bipolar population is affecting almost all domains of cognition in various intensity (Arts *et al.* 2008; Bora *et al.* 2009; Bourne *et al.* 2013; Kurtz & Gerraty 2009; Mann-Wrobel *et al.* 2011; Robinson *et al.* 2006; Torres *et al.* 2007). Cognitive deterioration in euthymia affects executive function, attention, verbal learning and memory (Martinez-Aran *et al.* 2004). This impairment may be at least in part of genetic origin, since very similar disturbance can be found in first degree relatives (Bora *et al.* 2009). Previous hypothesis that cognitive impairment is of a progressive nature has not been confirmed (Strejilevich *et al.* 2015).

General consensus, to how degree pharmacotherapy afflicts cognition in bipolar disorder has not been made yet. Some papers do not detect any difference in cognitive performance between medicated and drug-free patients (Goswami *et al.* 2009). However, none of mood stabilizing drug is free of cognitive side-effects. Proposed mechanisms unfavorably modifying cognition are sedative, extrapyramidal and anticholinergic adverse effect of varying intensity between drugs one from another (Vieta 2009).

Cardio-metabolic disorders represent another group of risk factors potentially harmful to cognitive functioning in bipolar disorder. Investigation undertaken in mentally healthy populations found out that metabolic syndrome is associated with notably worse cognitive performance (Taylor & MacQueen 2007; Yaffe 2007). Vancampfort *et al.* (2013) considered results of studies in bipolar patients from different countries and assessed the prevalence of metabolic syndrome in bipolar disorder as more than thirty percent. Bipolar population is connected with premature death and the most common cause of it is cardio-metabolic disorders (Angst *et al.* 2002). The estimated risk of dying from cardio-vascular disorder is twice the risk in mentally healthy population. Recent Danish study assessed life expectancy in bipolar population twelve to twenty years shorter in comparison with general population.

To our knowledge, three studies evaluating the impact of cardio-metabolic risk factors on cognition in bipolar disorder have been published yet. Yim *et al.* (2012) performed post-hoc analysis of results from study primarily aiming to evaluate intranasal insulin as a therapeutic intervention for cognitive dysfunction. They detected negative correlation of attention and psychomotor processing to BMI in euthymic bipolar subjects. Moreover, overweight and obese bipolar individuals had significantly lower score on the Verbal Fluency Test when compared to normal weight subjects. Depp *et al.* (2014) conducted neuropsychological examination in a group of patients treated for schizophrenia and bipolar disorder. They compared the data with self-reported information concerning height, weight and usage of antihypertensive or antidiabetic medication. The conclusion was that obesity and hypertension treatment are associated with a worse global cognitive ability. Silveira *et al.* (2014) studied a group of young patients at ages 16–35 recently recovered from their first episode of mania. Subjects were evaluated using a battery of neuropsychological tests and their Body Mass Index was calculated. They found no correlations between cognitive domains and BMI within the patient group.

Our study aimed to explore potential relationships between cardio-metabolic factors clustered in metabolic syndrome and neurocognitive abilities in a cross-sectional study design. The second aim is to detect possible cognitive side-effect of currently used mood stabilizers.

MATERIAL & METHODS

Subjects

Participants in this study were recruited from outpatient service of Psychiatry Department in University Hospital Hradec Kralove. Study was approved by the local ethics committee. Each participant signed informed consent. Patients with history of dementia, stroke or other organic brain disorder that might exert cognitive dysfunction were not enrolled. Only subjects diagnosed bipolar affective disorder currently in remission according to ICD 10 (1992) diagnostic criteria for research were enrolled. Remission was also defined as score below 6 points on YMRS (Young *et al.* 1978) and below 9 points on HDRS (Hamilton 1960). Eligible patients were men and women aged eighteen or older and using lithium, carbamazepine or valproic acid.

Participants using combination of above mentioned medication were not accepted for the study. Concomitant use of other psychopharmacotherapy was allowed. Patients treated for thyreopathy were enrolled only under condition of adequate endocrinology care. History of current thymoprofylaxis usage duration, bipolar disorder history and number of hospital inpatient treatments due to bipolar disorder was obtained from patients' medical records.

Body and metabolic parameter evaluation

Physical measurements were made including height, weight, waist circumference and blood pressure. BMI was calculated. Blood sample was taken and levels of total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, fasting glucose and fasting insulin were examined. For the purpose of judging the parameter as pathological or not, criteria of metabolic syndrome published in NCEP ATP III Final Report were applied (National Cholesterol Education Program Expert Panel on Detection & Treatment of High Blood Cholesterol in 2002). Total cholesterol (less than 5.18 mmol/l, i.e. less than 200 mg/dL in conventional units) and LDL cholesterol (less than 3.34 mmol/l, i.e. less than 129 mg/dL) were evaluated according to criteria valid in University Hospital Hradec Kralove and appropriate to classification published in NCEP ATP III Executive Summary (Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) 2001). Insulin resistance was calculated using levels of fasting insulin and fasting glucose in accordance with HOMA-IR (Matthews *et al.* 1985).

Neurocognitive evaluation

Neuropsychological tests covering the most often impaired domains of cognition in bipolar disorder were chosen. To assess the global cognitive ability of our patients, we constructed a neurocognitive composite score using T scores of neuropsychological tests stated below. Patients' neuropsychological performance in tests was transformed into neurocognitive composite score.

- Here we list the employed neuropsychological methods and cite the normative data sources:
- Rey Auditory Verbal Learning Test is a test of verbal learning and memory (Preiss 2002)
- Subtests Spatial Span and Digit Span from Wechsler Memory Scale-III are measures of short-time memory and attention (Wechsler 1999)
- Continuous Performance Test II examines sustained attention (Conners 2004)
- Tower of London DX is a test of executive function, psychomotor speed and attention (Culbertson & Zillmer 2005)
- Wisconsin Card Sorting Test is a method addressing executive function (Heaton *et al.* 1993)

Statistics

Analyses were performed using Statistica (StatSoft, USA). Dichotomous comparison of groups was done to evaluate possible detrimental effect of pathological body and metabolic parameters on cognition. Subjects were divided into two groups according to presence or absence of pathological parameter. Same dichotomous assessment was applied to ascertain the influence of thymostabilizing medication type on neurocognition, body and metabolic parameters. Correlations of neurocognitive composite score and selected parameters were computed. We used Shapiro-Wilk's W test for normality testing. Logarithmic transformation of insulinemia values was used to correct distribution and enable statistical evaluation. In case of normal distribution, t-test for independent samples and Pearson product-moment correlation coefficient were calculated. In other variable distributions, Mann-Whitney U test for dichotomous comparisons and Spearman's rank correlation coefficient were computed. Power analysis was calculated using Cohen's d.

RESULTS

Subjects

Our study group comprised of forty patients, twenty five females and fifteen males, who were examined between the years 2008 and 2013. Average age value was 55.4 years (SD 14.34) and 15.12 years (SD 3.22) of education. Mean length of bipolar disorder history was 23.75 years (SD 12.65). Mean number of hospital inpatient treatments due to bipolar disorder was 4.45 (SD 2.98). Metabolic syndrome was found in 37.5% patients and several other parameters reached unfavorably high frequency. 75% of subjects had BMI above 25 points, 60% had hypertension, 52.5% had abdominal obesity (pathological waist circumference) and pathological cholesterol was present in one half of the patients. Frequencies of all parameters are listed in Table 1. Twenty patients were medicated with lithium, sixteen with valproic acid and four patients were using carbamazepine. Neurocognitive composite score for the whole bipolar group was 44.616 (SD 5.21), which in comparison with T score of 50 in normative data, suggests significant ($p<0.001$) cognitive dysfunction.

Dichotomous comparison

Patients exhibiting hypertension performed significantly worse in neuropsychological testing ($p=0.003$) (Figure 1). Considerably inferior cognitive performance was also found in presence of metabolic syndrome ($p=0.011$), abdominal obesity ($p=0.039$) and hyperglycemia ($p=0.027$). Other body and metabolic parameters were not connected with significantly lower neurocognitive composite score (Table 1). Lithium users (T=42.863) versus anticonvulsant users (T=46.370) demonstrated substantially lower cognitive performance (t=2.237; $p=0.031$; df=38). Further

Tab. 1. Neurocognitive composite score T values and parameter frequency in groups of patients with pathological and normal body/metabolic parameter. t-test for independent samples.

	Pathological / Present % (No. of patients)	Normal / Not present % (No. of patients)	t-value	*p*-value	
Waist circumference	**43.015** 52.5% (21)	**46.386** 47.5% (19)	–2.137	0.039	df=38
BMI	43.844 75% (30)	46.934 25% (10)	–1.662	0.105	df=38
Blood pressure	**42.668** 60% (24)	**47.539** 40% (16)	–3.231	0.003	df=38
Total cholesterol	43.925 50% (20)	45.308 50% (20)	–0.837	0.408	df=38
LDL cholesterol	46.349 32.5% (13)	43.782 67.5% (27)	1.483	0.146	df=38
HDL cholesterol	43.244 32.5% (13)	45.277 67.5% (27)	–1.162	0.253	df=38
Triglycerides	44.983 32.5% (13)	43.856 67.5% (27)	0.636	0.528	df=38
Fasting glucose	**45.582** 22.5% (9)	**41.289** 77.5% (31)	2.294	0.027	df=38
Thyreopathy	45.289 25% (10)	42.599 75% (30)	1.434	0.160	df=38
Metabolic syndrome	**41.985** 37.5% (15)	**46.195** 62.5% (25)	–2.663	0.011	df=38

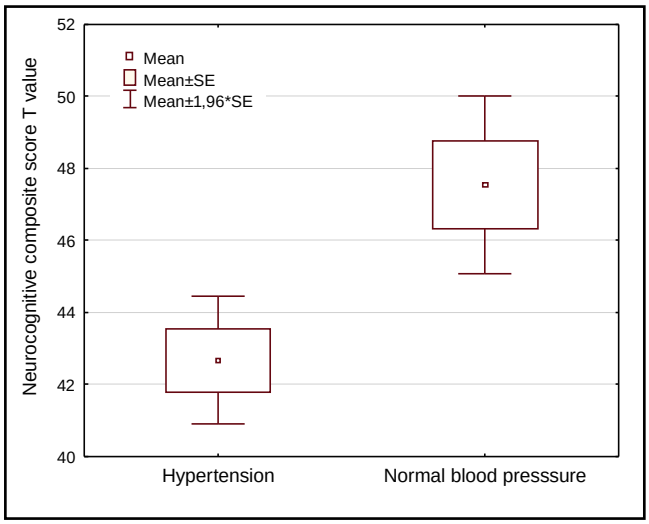

Fig. 1. Neurocognitive composite score in relation to normal and pathological blood pressure. t-test for independent samples. t=–3.231; *p*=0.003; df=38.

scrutiny unveiled noticeably longer thymoprofylaxis usage duration in lithium users, 582.5 months, versus anticonvulsant, 237.5 months, users (U=27.500; Z=–4.666; $p<0.001$). Patients on lithium had also markedly longer bipolar disorder history, 495.5 months, when compared to anticonvulsant, 324.5 months, group (U=114.5; Z=–2.313; $p=0.021$). Post-hoc effect size analysis showed insignificant results in case of metabolic syndrome (d=0.74) and abdominal obesity (d=0.55) impact on neurocognitive composite score. Nevertheless, testing arterial hypertension and cognitive impairment association reached robust effect size (d=0.87). Subjects manifesting hypertension ended up significantly worse in all tested domains of cognition versus subjects with normal blood pressure (Figure 2). Lithium and anticonvulsant users neither differed in metabolic and body parameters nor in HOMA index or metabolic syndrome occurrence.

Correlations

Several significant correlations were found. As expected, number of education years correlated with composite neurocognitive score positively, Pearson correlation (r=0.375; $p=0.017$), whereas duration of bipolar disorder measured by number of months correlated with above mentioned score negatively, Pearson correlation (r=–0.446; $p<0.01$). Correlations of fasting insulin, HOMA index, HDRS score and number of hospital inpatient treatments due to bipolar disorder with neurocognitive composite score did not reach significance. Thymoprofylaxis usage duration correlated with neurocognitive score negatively, Spearman correlation (r=–0.409; $p<0.01$), nevertheless all other calculated correlations with body and metabolic parameters resulted non-significantly.

DISCUSSION

The strength of our study lies in the direct measuring of cognitive function together with body and metabolic parameters at the same time. Previous studies used only BMI assessment or self-reported information concerning height, weight and usage of medication. We replicated some findings from previous research relating obesity and hypertension to worse global cognitive abilities (Depp *et al.* 2014). What is interesting is that similar reports were published from investigations in schizophrenia samples. Friedman *et al.* (2010) found an association between hypertension and memory impairment. Goughari *et al.* (2015) revealed linkage of verbal fluency and verbal memory to hypertension. There are several ways that hypertension could affect cognition. The first mechanism is vascular by growing amount of atherosclerosis in central nervous system and thus exerting ischemia of brain tissue resulting in cognitive dysfunction (Taylor & MacQueen 2007). The second mechanism is an increased activation of brain RAAS bringing neuronal damage. Several studies have described that lowering blood pressure by RAAS receptor blockers ameliorates dementia and cognitive impairment (Yagi *et al.* 2013; Hajjar *et al.* 2013), which may look promising for bipolar patients with the manifest cognitive impairment together with hypertension.

Our study design has several limitations. Evaluation lacked control group of mentally healthy individuals matching the bipolar group with similar body and metabolic parameters. That's a limiting condition when attempting to exactly measure the impact of pathological body and metabolic measures on cognition. Bipolar disorder itself constitutes an independent cognition impairing factor and usage of normative data solely may bring biases, because it's not clear, how large are the proportions of metabolic pathology and bipolar disorder preexistence in overall cognitive performance of studied subjects. We didn't collect patient information regarding the time of pathological body and metabolic factors onset. So we were not able to draw any statement concerning precedence or antecedence of those factors to bipolar disorder and its accompanying cognitive dysfunction. Relatively small sample size ensured sufficient statistical power only for comparison of hypertension to neurocognitive composite score. In that case, significant connection of metabolic syndrome, abdominal obesity and hyperglycemia to inferior neurocognitive performance has limited generalizability. Our groups average age of 55.4 years assigns the sample into the category of late middle age, where the first symptoms of physiological decrease of cognition might occur. Thus age of our group might bias classifying cognitive dysfunction associated only with

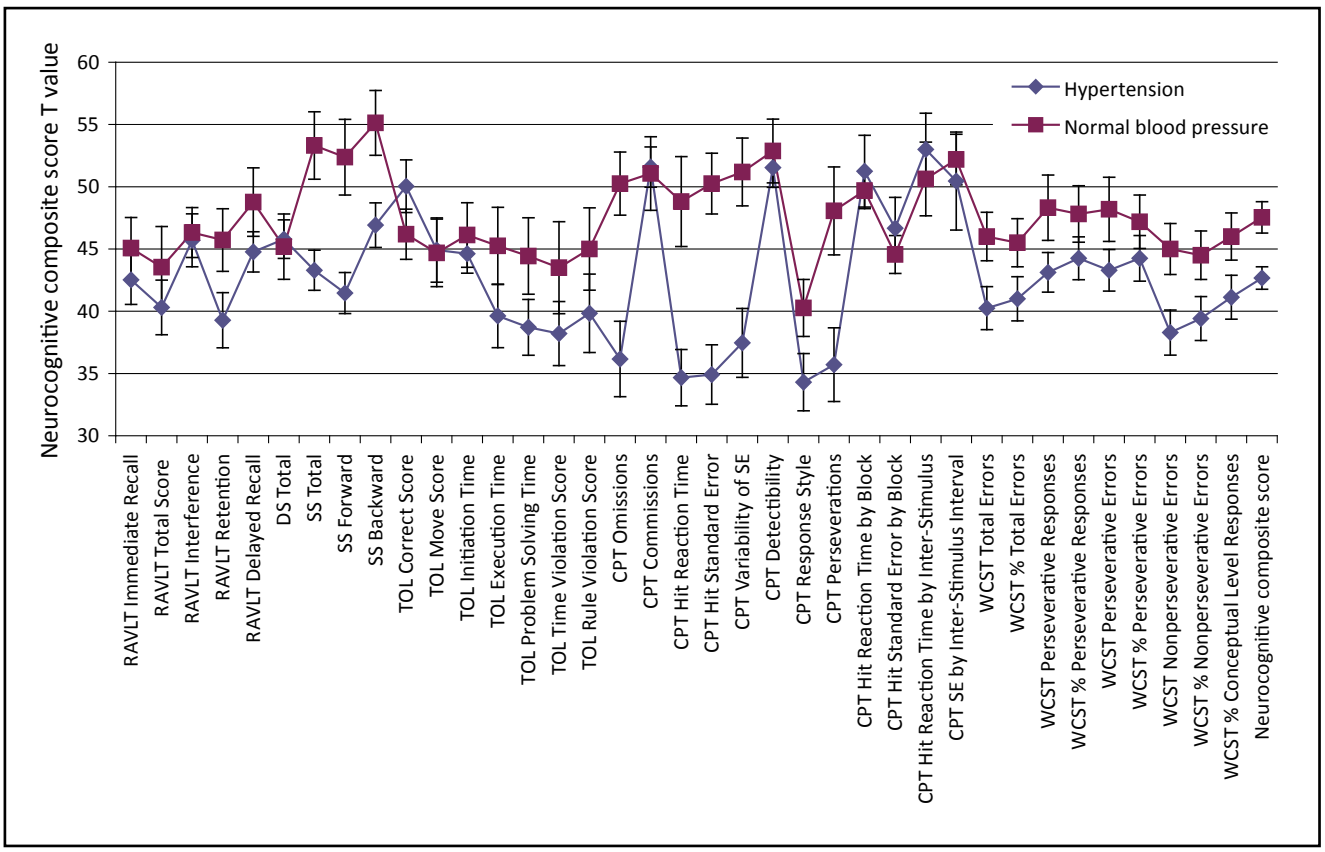

Fig. 2. Differences in neurocognitive profile of groups in relation to normal and pathological blood pressure. t-test for independent samples.

bipolar disorder or metabolic syndrome. In our study group, lithium usage appeared to be in association with low cognitive performance. However, the lithium group was linked with apparently longer thymoprofylaxis usage duration and longer bipolar disorder history, when compared to anticonvulsant group. Such contrast between lithium and anticonvulsant groups does not allow conclusive statements regarding medication type and disorder length impact on cognition. Cross-sectional study design also limits designating hypertension as an independent factor connected with cognitive dysfunction. Longitudinal studies are needed to prove whether such connection would remain or not.

CONCLUSION

This study showed significant association of hypertension and global cognitive dysfunction in euthymic bipolar disorder. Collected data did not permit to establish direction of causality between hypertension and cognitive impairment. Nevertheless, lowering blood pressure may represent hypothetic but promising way of ameliorating such impairment. We found an inferior cognitive performance in lithium group when in comparison to anticonvulsant group. Unfortunately, considerably longer bipolar disorder history and usage duration of lithium did not allow us to make any statements concerning association of cognition and medication. A larger study sample is necessary to clarify cognitive side effects of medication.

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