Letter to the Editor

Elevated allostatic load index is associated with working memory deficits in first-episode psychosis

Dear Editor,

Cognitive impairment represents one of core characteristics of schizophrenia psychopathology. Chronic stress might impact cognition via various mechanisms (Marin et al., 2011). According to the allostatic load (AL) concept, processes that are activated in response to stress are adaptive in a short-term perspective and enable to maintain homeostasis (McEwen and Wingfield, 2003). These processes have been termed 'allostasis'. The AL refers to detrimental effects of chronic stress exposure that appear due to over-activation of allostatic mechanisms. The AL index is a collective measure of systemic dysregulations associated with chronic stress. Several studies have provided evidence of elevated AL index in patients with schizophrenia (Berger et al., 2018; Chiappelli et al., 2017; Misiak et al., 2018; Nugent et al., 2015; Savransky et al., 2017). Additionally, it has been reported that elevated AL index might be related to lower fornix connectivity (Savransky et al., 2017) and gray matter loss (Chiappelli et al., 2017). Therefore, we investigated whether increased AL index contributes to cognitive impairment observed in first-episode psychosis (FEP).

A detailed description of our study can be found elsewhere (Misiak et al., 2018). The current sample included 40 FEP patients and 35 controls. The study was approved by the Ethics Committee of Wroclaw Medical University (Poland) and all participants were consented. The patients met the DSM-IV criteria for schizophrenia-spectrum disorders. Diagnoses were validated using the Operational Criteria for Psychotic Illness (OPCRIT) checklist. Controls with a negative present, past and family history of psychotic and affective disorders were recruited through advertisements. They had never been treated due to any psychiatric disorders. The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) was used to examine cognitive performance (Randolph et al., 1998). The RBANS consists of several tasks grouped into the following domains: immediate memory, visuospatial/constructional functions, language, attention and delayed memory. The AL index was calculated as described previously (Berger et al., 2018; Misiak et al., 2018), based on the following parameters: blood pressure, body mass index, waist-to-hip ratio, as well as serum levels of low- and high-density lipoproteins, triglycerides, total cholesterol, glucose, insulin, albumin, fibrinogen, high-sensitivity C-reactive protein, cortisol and dehydroepiandrosterone sulfate.

Bivariate comparisons were performed using the Mann-Whitney U tests or independent samples t-tests (depending on data distribution) and the χ^2 test (categorical variables). Correlations were assessed using the Spearman rank correlation coefficients. Due to multiple bivariate tests, the Benjamini-Hochberg correction was applied. After this correction, bivariate differences and correlations were considered statistically significant if p-value was ≤0.011 (false discovery rate set at 25%). Differences or correlations that remained significant after the Benjamini-Hochberg correction were further tested using the Analysis of Co-Variance (ANCOVA) or linear regression analysis (the level of significance set at 0.05). Education level, chlorpromazine equivalent dosage (CPZeq) and cigarette smoking status were included as covariates. All analyses were performed using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, Illinois, USA).

Both groups were matched for age, sex and parental education (Table 1). However, there were significantly more cigarette smokers and individuals with lower number of years of education in the group of patients. Patients with FEP scored significantly lower on all RBANS domains and single tasks, except for picture naming task. As expected they had significantly higher AL index. After co-varying for potential confounders, FEP patients had significantly higher AL index and significantly lower scores on almost all RBANSS cognitive domains, except for visuospatial/constructional abilities (Supplementary table 1). Regarding single RBANS tasks, ANCOVA revealed significant effects of group (FEP vs. controls) on the following tasks: list learning, story memory, figure copy, line orientation, semantic fluency, digit span, digit coding, list recall, story memory, figure recall and global cognition (Supplementary table 1). There was a strong and significant negative correlation between the AL index and the score of digit span in FEP patients ($r = -0.599$, $p < 0.001$) but not in controls ($r = 0.111$, $p = 0.511$) (Supplementary table 2). This correlation was also significant in linear regression analysis ($B = -1.271$, $t = -4.601$, $p < 0.001$) after adjustment for the number of education years ($B = -0.174$, $t = -1.259$, $p = 0.216$), CPZeq ($B = -0.002$, $t = -1.068$, $p = 0.293$) and cigarette smoking ($B = 0.190$, $t = 0.288$, $p = 0.775$). In turn, a negative correlation between the AL index and the list recall score was significant only in controls ($r = -0.472$, $p = 0.007$). This correlation appeared to be significant in linear regression analysis ($B = -0.900$, $t = -2.951$, $p = 0.006$) after controlling for the effects of education ($B = 0.045$, $t = 0.364$, $p = 0.719$) and cigarette smoking ($B = -0.060$, $t = -0.070$, $p = 0.945$).

We confirmed significantly higher AL index in FEP patients after adjustment for potential confounders. A higher AL index was strongly associated with lower scores of digit span task, measuring working memory, in FEP patients. Working memory is defined as "the ability to keep in mind an event that has just occurred, or bring to mind information for long-term storage, and use this representational knowledge to regulate behaviour, thought and emotion" (Arnsten, 2009). Working memory deficits are widely observed in patients with schizophrenia. Prefrontal cortex that is responsible for working memory contains a high density of glucocorticoid receptors and there is mounting evidence that chronic stress might impact performance of this cognitive domain

Table 1
General characteristics of FEP patients and controls.

	FEP ($n = 40$)	Controls ($n = 35$)	p
Age, years	27.6 ± 7.4	25.5 ± 6.7	0.119
Sex, males (%)	21 (52.5)	14 (40.0)	0.279
Education, years	13.6 ± 2.5	15.3 ± 2.4	**0.002**
Paternal education, higher (%)	11 (27.5)	11 (31.4)	0.709
Maternal education, higher (%)	15 (37.5)	14 (40.0)	0.824
Cigarette smokers, n (%)	15 (37.5)	4 (11.4)	**0.010**
AL index	2.4 ± 1.1	1.6 ± 0.9	**0.002**
Immediate memory	42.5 ± 8.4	51.0 ± 11.2	**<0.001**
List learning	26.1 ± 5.4	32.8 ± 4.5	**<0.001**
Story memory	16.4 ± 3.9	19.9 ± 2.8	**<0.001**
Visuospatial/constructional functions	34.6 ± 5.3	36.9 ± 7.1	**0.003**
Figure copy	18.6 ± 2.4	19.8 ± 0.4	**0.007**
Line orientation	16.0 ± 3.9	18.3 ± 2.3	**0.011**
Language	28.2 ± 6.2	34.3 ± 9.2	**<0.001**
Picture naming	9.3 ± 0.9	9.8 ± 0.3	0.167
Semantic fluency	19.0 ± 5.8	25.5 ± 6.8	**<0.001**
Attention	55.0 ± 12.3	67.0 ± 15.5	**<0.001**
Digit span	10.2 ± 2.3	14.2 ± 2.4	**<0.001**
Digit coding	44.8 ± 11.2	54.9 ± 8.7	**<0.001**
Delayed memory	46.8 ± 7.8	55.1 ± 10.9	**<0.001**
List recall	5.5 ± 2.4	7.8 ± 1.7	**<0.001**
List recognition	18.5 ± 2.0	19.9 ± 0.2	**<0.001**
Story memory	8.1 ± 2.5	10.9 ± 1.3	**<0.001**
Figure recall	14.6 ± 3.9	18.1 ± 2.1	**<0.001**
Global cognition	207.3 ± 31.7	252.1 ± 20.8	**<0.001**
SOFAS	52.5 ± 14.2	99.0 ± 3.4	**<0.001**
GAF	54.5 ± 17.9	–	–
PANSS – positive symptoms	13.0 ± 5.2	–	–
PANSS – negative symptoms	18.4 ± 8.5	–	–
PANSS – general psychopathology	30.0 ± 8.8	–	–
SAPS	14.3 ± 14.1	–	–
SANS	30.1 ± 24.1	–	–
HDRS	9.3 ± 9.2	–	–
YMRS	2.1 ± 5.1	–	–
CPZeq, mg/day	310.1 ± 186.7	–	–

Significant differences after Benjamini-Hochberg correction ($p ≤ 0.011$) were marked with bold characters.
Abbreviations: AL – allostatic load, CPZeq – chlorpromazine equivalent dosage, FEP – first-episode psychosis, GAF – the General Assessment of Functioning, HDRS – the Hamilton Depression Rating Scale, PANSS – the Positive and Negative Syndrome Scale, SAPS – the Scale for Assessment of Positive Symptoms, SANS – the Scale for Assessment of Negative Symptoms, SOFAS - the Social and Occupational Assessment of Functioning, YMRS – the Young Mania Rating Scale.

([Lupien and McEwen, 1997](#)). Our findings are also in agreement with a previous study showing a negative correlation between the AL index and cortical volume ([Chiappelli et al., 2017](#)). Interestingly, we observed a moderate but significant association between the AL index and list recall task, measuring delayed verbal memory, only in controls. Our study has also certain limitations that should be taken into account and include low sample size, potential medication effects and a cross-sectional design.

In summary, the AL might serve as a potential mechanism of working memory impairments in FEP. Differential associations between the AL index and cognition indicate that various cognitive domains might be vulnerable to the effects of enduring stress in FEP patients and healthy individuals. More studies with neuroimaging data, addressing these correlations in larger samples, are needed.

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Contributors

Study design: BM, recruitment and assessment of psychopathology: BM, JAB, PP, FS, MJ, PP, KW, MW, AM, assessment of cognition: KK and AS, measurement of biochemical markers: OL, data analysis: BM, manuscript writing: BM, PP, AS, LS, JS.

Conflict of interest

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.09.003.

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Błażej Misiak
Department of Genetics, Wroclaw Medical University, Marcinkowskiego 1 Street, 50-368 Wroclaw, Poland
Corresponding author.
E-mail address: blazej_misiak@interia.pl.

Kamila Kotowicz
Department of Psychiatry, Wroclaw Medical University, Pasteura 10 Street, 50-367 Wroclaw, Poland

Olga Loska
Department of Forensic Medicine, Wroclaw Medical University, Mikulicza-Radeckiego 4 Street, 50-345 Wroclaw, Poland
4th Military Clinical Hospital, Laboratory Diagnostics Unit, Weigla 5 Street, 50-981 Wroclaw, Poland

Filip Stramecki
Jan Aleksander Beszłej
Department of Psychiatry, Wroclaw Medical University, Pasteura 10 Street, 50-367 Wroclaw, Poland

Jerzy Samochowiec
Department of Psychiatry, Pomeranian Medical University, Broniewskiego 26 Street, 71-460 Szczecin, Poland

Agnieszka Samochowiec

Institute of Psychology, Department of Clinical Psychology, University of Szczecin, Krakowska 69 Street, 71-017 Szczecin, Poland

Marcin Jabłoński
Piotr Podwalski
Katarzyna Waszczuk
Michał Wroński
Anna Michalczyk

Department of Psychiatry, Pomeranian Medical University, Broniewskiego 26 Street, 71-460 Szczecin, Poland

Leszek Sagan

Department of Neurosurgery, Pomeranian Medical University, Unii Lubelskiej 1 Street, 71-252 Szczecin, Poland

Patryk Piotrowski

Department of Psychiatry, Wroclaw Medical University, Pasteura 10 Street, 50-367 Wroclaw, Poland

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