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Allostatic load index and its clinical correlates at various stages of psychosis

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ABSTRACT

Accumulating evidence indicates systemic biological dysregulations in patients with psychosis that have been conceptualized as the "allostatic load" (AL) index. We aimed to investigate the AL index in 37 subjects at familial high risk of psychosis (FHR—P), 42 first-episode psychosis (FEP) patients, 25 acutely relapsed schizophrenia (SCZ-AR) patients and 42 healthy controls (HCs), taking into account psychopathology and cognitive impairment. The AL index was calculated based on 15 biomarkers (cardiovascular markers, anthropometric measures, inflammatory markers, glucose homeostasis parameters, lipids and steroids). Cognition was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The AL index was significantly higher in patients with psychosis and FHR-P individuals compared to HCs. Patients with FEP and FHR-P individuals had similar AL index. Moreover, the AL index was significantly higher in SCZ-AR patients compared to other groups of participants. Higher AL index was associated with more severe general psychopathology and depressive symptoms, lower scores of attention (total score, digit span and digit coding tasks) and semantic fluency, as well as worse general functioning in patients with psychosis. There was a significant negative correlation between the AL index and the scores of attention (total score and digit coding task) in FHR-P individuals. No significant correlations between the AL index and cognition were found in HCs. Our results indicate that biological dysregulations, captured by the AL index, appear already in FHR-P individuals and progress with psychotic exacerbations. Elevated AL index might contribute to cognitive impairments in FHR-P individuals and patients with psychosis.

1. Introduction

Psychotic disorders represent complex phenotypes with prevalence rates estimated at 3% (Perälä et al., 2007). There are various concepts regarding the mechanisms, underlying the development of psychosis. In the recent years, a growing interest in the role of stress as an important factor in the pathophysiology of psychosis can be observed (Misiak et al., 2017a). Indeed, it has been widely demonstrated that traumatic life events, especially those acting in the childhood, increase susceptibility to psychosis (Beards et al., 2013; Varese et al., 2012). Moreover, there is evidence that stress exposure might trigger psychotic exacerbations in patients with schizophrenia (Nuechterlein et al., 1994). Finally, patients with psychosis might be more likely to utilize maladaptive stress coping strategies (Allott et al., 2015; Corrigan and Toomey, 1995; Stramecki et al., 2019).

There are various biological alterations in patients with psychosis that can be attributed to acute or chronic stress, including low levels of brain-derived neurotrophic factor (BDNF) (Theleritis et al., 2014), hypothalamic-pituitary-adrenal (HPA) axis dysfunction (Berger et al., 2016; Ciufolini et al., 2014; Girshkin et al., 2014), altered DNA methylation profiles (Tomassi and Tosato, 2017) and pro-inflammatory state (Quidé et al., 2018). There is evidence that various stress-related alterations, including elevated levels of salivary cortisol (Carol et al., 2017) and pro-inflammatory cytokines (Zeni-Graiff et al., 2016), blunted cortisol awakening response (Day et al., 2014; Pruessner et al., 2017) appear already in subjects at high risk of psychosis. Moreover, stress response might change with subsequent psychotic exacerbations. Indeed, on the basis of a meta-analysis, our group found elevated levels of dehydroepiandrosterone sulfate (DHEA-S) in patients with first-episode psychosis (FEP) but not in acutely relapsed, multiple-episode schizophrenia patients (Misiak et al., 2018a).

In light of these findings, a need of developing the models that capture various stress-related alterations in patients with psychosis has been highlighted. Accordingly, it has been proposed that the allostatic

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load (AL) concept can be a useful framework to operationalize multisystem alterations related to chronic stress (Misiak et al., 2014). The term "allostasis" describes adaptive mechanisms that are activated in response to a number of external stimuli that include stressful experiences (McEwen and Stellar, 1993). These processes lead to a release of several hormones, neurotransmitters, neurotrophins, oxidative stress markers and pro-inflammatory cytokines. A short-term activation of allostasis enables to maintain homeostasis; however, a chronic activation of these mechanisms exerts systemic detrimental effects (McEwen, 1998). The AL index has been developed to capture various biological responses related to stress exposure. It is a combined score across several physiological measures. It has been found that the AL index predicts various health outcomes, including all-cause mortality (Gallo et al., 2014; Juster et al., 2010).

Elevated AL index in patients with psychotic disorders has been demonstrated by several studies (Berger et al., 2018a; Berger et al., 2018b; Misiak et al., 2018b; Nugent et al., 2015; Savransky et al., 2018). However, only one study investigated the AL index in patients at various stages of psychosis (Berger et al., 2018a). The authors found elevated AL index in patients with first-episode psychosis (FEP) and multiple-episode schizophrenia patients. Only one study investigated the AL index in patients at ultra-high risk of psychosis, showing that the AL index predicted lower social and occupational functioning as well as more severe manic symptoms (Berger et al., 2018b). However, this study did not include a group of healthy controls. Therefore, in our study we aimed to investigate the AL index in individuals at familial high risk of psychosis (FHR—P), FEP patients and acutely relapsed schizophrenia (SCZ-AR) patients compared to healthy controls, taking into account a severity of psychopathological manifestation and cognitive impairment.

2. Material and methods

2.1. Participants and measures

Initial results of our study of FEP patients and healthy controls were reported in previous publications (Misiak et al., 2018b, 2018c). These publications also include a detailed study protocol. Participants were 42 FEP inpatients (16 with schizophrenia, 14 with schizophreniform disorder, 5 with brief psychotic disorder, 6 with schizoaffective disorder and 1 with delusional disorder), 25 SCZ-AR inpatients and 42 healthy controls. The group of FHR-P individuals included 37 participants who were the healthy offspring of schizophrenia patients and had never been medicated due to mental disorders. All participants were non-consanguineous. Healthy controls represented 42 subjects who were enrolled through advertisements. They had a negative family history of psychotic and affective disorders. Parental education was recorded for all participants as a proxy measure of socioeconomic status (Aarø et al., 2009). All participants were recruited at two clinical sites - Department and Clinic of Psychiatry (Wroclaw Medical University, Wroclaw, Poland) and Department and Clinic of Psychiatry (Pomeranian Medical University, Szczecin, Poland). Our study protocol was approved by the Ethics Committee at Wroclaw Medical University (Wroclaw, Poland). A written informed consent was obtained from all patients and healthy controls. Participants were diagnosed based on the DSM-IV criteria using the Operational Criteria for Psychotic Illness (OPCRIT) checklist (McGuffin, 1991). Patients with FEP were included with treatment duration was no longer than 30 days.

Psychopathological manifestation and general functioning were assessed using the following measures: 1) the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); 2) the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960); 3) the Young Mania Rating Scale (Young et al., 2011); 4) the Global Assessment of Functioning (GAF) (Hall, 1995) and 5) the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992). The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) was administered to examine cognitive performance (Randolph et al., 1998). The RBANS consists of several tests grouped into the following index scores: immediate memory (list learning and story memory), visuospatial/constructional functions (figure copy and line orientation), attention (digit span and coding) and delayed memory (list recall, list recognition, story memory and figure recall). Self-appraisal of stress exposure over the preceding month was assessed using the Perceived Stress Scale (PSS) (Cohen et al., 1983). Lifetime exposure to stressful situations was evaluated using the List of Threatening Experiences (LTE) (Brugha and Cragg, 1990). A severity of nicotine dependence was recorded using the Fagerström Test for Nicotine Dependence (FTND) (Pomerleau et al., 1989).

The AL index was computed based on a previously reported protocol (Berger et al., 2018a; Bizik et al., 2013; Chen et al., 2012; Misiak et al., 2018b) and included the following biomarkers: systolic and diastolic blood pressure (SBP and DBP), body mass index (BMI) and waist-to-hip ratio (WHR), high-sensitivity C-reactive protein (hsCRP), fibrinogen, albumin, fasting glucose and insulin, total cholesterol, low- and high-density lipoproteins (LDL and HDL) and triglycerides, cortisol as well as DHEA-S. Scores of specific biological dysregulations were calculated according to the distribution in the sample of healthy controls. Blood samples were collected after overnight fasting between 7 a.m. and 9 a.m.. All biochemical parameters were determined in serum samples. Weight and height were measured wearing light clothing and no shoes, using a balance beam scale with stadiometer. Waist circumference was recorded at the midpoint between the lower margin of the last palpable ribs and the top of the iliac crest. In turn, hip circumference was measured as the distance around the largest part of the buttocks.

2.2. Statistical analysis

The χ^2 test was used for assessment of group differences in categorical variables. In case of non-normal distribution (examined using the Kolmogorov-Smirnov test), between-group differences in continuous variables were tested using the Mann-Whitney *U* test or the Kruskal-Walis test. Otherwise, *t*-test or one-way analysis of variance (ANOVA) were used. The Spearman's rank correlation coefficients were used to evaluate bivariate correlations. The Benjamini-Hochberg correction (the false discovery rate set at 25%) was used due to multiple bivariate tests. After this correction, bivariate correlations and comparisons were considered statistically significant if the p-value was ≤0.036. Correlations that were significant after the Benjamini-Hochberg correction were further tested using the linear regression analysis. Age, the number of years in education, chlorpromazine equivalent dosage (CPZeq) and cigarette smoking status were added as independent variables. The variance inflation factor (VIF) was calculated to assess multicollinearity. The analysis of co-variance (ANCOVA) was used to test the effects of diagnostic groups (FEP, SCZ-AR, FHR-P and healthy controls) on the AL index after co-varying for age, sex, cigarette smoking status CPZeq. In case of non-normal distribution of dependent variables, logarithmic or square root transformations were performed before the ANCOVA and linear regression analyses. The level of significance was set at 0.05 in the ANCOVA and linear regression analyses. All analyses were performed using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, Illinois, USA).

3. Results

Sample characteristics were shown in Table 1. There were significant between-group differences in age, cigarette smoking status, the number of years in education, the FTND score, scores of all cognitive domains and single RBANS tasks, the LTE score and the SOFAS score. Illness duration and CPZeq were significantly higher in the group of SCZ-AR patients compared to FEP patients. Moreover, patients with SCZ-AR had significantly higher scores of negative symptoms and general psychopathology than FEP patients.

Table 1
General characteristics of participants.

	FEP (n = 42)	SCZ-AR (n = 25)	FHR-P (n = 37)	HCs (n = 42)	p
Age, years	27.7 ± 7.3	42.8 ± 13.8	36.9 ± 11.0	27.8 ± 8.4	<**0.001**
Sex, M/F (%)	21/21 (50.0/50.0)	14/11 (56.0/44.0)	12/25 (32.4/67.6)	16/26 (38.1/61.9)	0.199
Education, years	13.6 ± 2.4	13.1 ± 3.1	15.5 ± 3.6	15.7 ± 2.5	<**0.001**
Paternal education, higher/other than higher (%)	11/31 (26.2/73.8)	3/22 (12.0/88.0)	4/33 (10.8/89.2)	12/30 (28.6/71.4)	0.125
Maternal education, higher/other than higher (%)	16/26 (38.1/61.9)	5/20 (20.0/80.0)	7/30 (18.9/81.1)	15/27 (35.7/64.3)	0.148
Cigarette smoking, yes/no (%)	15/27 (35.7/64.3)	15/10 (60.0/40.0)	6/31 (16.2/83.8)	4/38 (10.5/89.5)	<**0.001**
FTND	1.5 ± 2.5	3.8 ± 3.9	0.7 ± 1.8	1.0 ± 5.0	<**0.001**
LTE	4.9 ± 2.5	5.9 ± 1.9	4.2 ± 1.9	3.4 ± 2.3	<**0.001**
PSS-10	23.6 ± 6.4	22.7 ± 6.7	23.4 ± 4.3	22.0 ± 3.8	0.543
Illness duration, weeks	42.9 ± 85.7	718.7 ± 563.4	–	–	<**0.001**
CPZeq, mg/day	309.6 ± 183.4	470.5 ± 208.8	–	–	<**0.001**
PANSS-P	12.8 ± 5.1	15.0 ± 4.6	–	–	0.065
PANSS-N	18.1 ± 8.5	23.4 ± 9.7	–	–	**0.026**
PANSS-G	30.0 ± 8.7	36.1 ± 10.4	–	–	**0.019**
HDRS	9.1 ± 9.0	8.8 ± 6.7	–	–	0.710
YMRS	2.0 ± 5.0	2.1 ± 3.8	–	–	0.851
SOFAS	52.8 ± 14.3	42.0 ± 12.2	92.8 ± 9.5	98.7 ± 3.5	<**0.001**
GAF	54.6 ± 17.5	38.6 ± 11.2	–	–	<**0.001**
Immediate memory					
Total score	42.6 ± 8.2	32.2 ± 13.3	50.0 ± 6.5	52.2 ± 6.4	<**0.001**
List learning	26.3 ± 5.4	21.4 ± 6.1	31.2 ± 5.1	32.7 ± 4.2	<**0.001**
Story memory	16.3 ± 4.0	13.7 ± 4.5	18.8 ± 3.0	19.5 ± 4.0	<**0.001**
Visuospatial/constructional functions domain:					
Total score	34.8 ± 5.3	28.7 ± 10.7	36.6 ± 3.9	38.2 ± 2.2	<**0.001**
Figure copy	18.7 ± 2.4	17.2 ± 4.0	19.2 ± 1.2	19.9 ± 0.3	<**0.001**
Line orientation	16.1 ± 3.9	14.1 ± 4.6	17.4 ± 3.5	18.4 ± 2.1	<**0.001**
Language					
Total score	28.3 ± 6.1	23.7 ± 9.2	32.5 ± 6.2	34.5 ± 6.4	<**0.001**
Picture naming	9.2 ± 0.8	9.4 ± 0.7	9.6 ± 1.2	9.8 ± 0.4	**0.003**
Semantic fluency	19.0 ± 5.7	16.4 ± 5.6	22.9 ± 6.1	24.7 ± 6.4	<**0.001**
Attention					
Total score	54.7 ± 12.2	34.7 ± 16.1	62.8 ± 13.7	69.9 ± 9.6	<**0.001**
Digit span	9.9 ± 2.5	8.7 ± 2.5	10.2 ± 2.3	11.0 ± 2.6	**0.036**
Digit coding	44.8 ± 11.0	29.1 ± 12.8	52.6 ± 13.0	58.9 ± 8.5	<**0.001**
Delayed memory domain					
Total score	46.8 ± 7.6	35.8 ± 14.1	51.9 ± 5.5	56.3 ± 4.4	<**0.001**
List recall	5.6 ± 2.3	4.0 ± 2.5	7.3 ± 2.3	7.9 ± 1.7	<**0.001**
List recognition	18.6 ± 2.0	18.1 ± 1.8	19.2 ± 1.9	19.9 ± 0.3	<**0.001**
Story memory	8.1 ± 2.5	6.7 ± 2.7	9.8 ± 2.5	10.4 ± 2.0	<**0.001**
Figure recall	14.4 ± 3.9	10.3 ± 4.7	15.7 ± 2.9	18.1 ± 2.0	<**0.001**
Global cognition	207.2 ± 30.9	161.8 ± 47.4	233.9 ± 26.2	251.3 ± 19.7	<**0.001**

Abbreviations: CPZeq – chlorpromazine equivalent dosage, FEP – first-episode psychosis patients, FHR-P – individuals at familial high risk of psychosis, FTND – the Fagerström Test for Nicotine Dependence, GAF – the Global Assessment of Functioning, HCs – healthy controls, HDRS – the Hamilton Depression Rating Scale, LTE – the List of Threatening Experiences, PANSS-G - the Positive and Negative Syndrome Scale (subscale of general psychopathology), PANSS-N - the Positive and Negative Syndrome Scale (subscale of negative symptoms), PANSS-P – the Positive and Negative Syndrome Scale (subscale of positive symptoms), PSS – the Perceived Stress Scale, SCZ-AR – acutely relapsed schizophrenia patients, SOFAS – the Social and Occupational Assessment of Functioning, YMRS – the Young Mania Rating Scale.
Significant differences after the Benjamini-Hochberg correction (p ≤ 0.036) were marked with bold characters.

There were significant between-group differences in the level of AL index (Fig. 1). Bivariate comparisons revealed significantly higher AL index in FEP patients, SCZ-AR patients and FHR-P individuals compared to healthy controls. The AL index was significantly higher in SCZ-AR patients compared to FEP patients and FHR-P individuals. In turn, the difference in the AL index between FEP patients and FHR-P individuals was not significant. The ANCOVA revealed that differences in the AL index remained significant ($F = 7.99$, $p < 0.001$) after co-varying for age ($F = 25.7$, $p < 0.001$), sex ($F = 2.00$, $p = 0.160$), CPZeq ($F = 2.58$, $p = 0.110$) and cigarette smoking status ($F = 0.04$, $p = 0.836$). Analysis of single biomarkers demonstrated significant between-group differences in SBP and WHR as well as the levels of hsCRP, albumin, glucose, insulin, HDL, triglycerides, cortisol and DHEA-S (Table 2).

Correlations between the AL index and clinical variables were shown in Table 3. In patients with psychosis, higher AL index was associated with worse performance of visuospatial/constructional functions, language, attention and global cognition. Moreover, higher AL index was related to significantly lower scores on single RBANS tasks, including figure copy, line orientation, semantic fluency, digit span, digit coding and figure recall in patients with psychosis. Psychosis patients with higher AL index had significantly higher scores of HDRS and the PANSS general psychopathology subscale, as well as significantly lower GAF scores. There were also significant negative correlations between the AL index and performance of visuospatial/constructional functions (total score, figure copy and line orientation), attention (total score and digit coding) and global cognition in FHR-P individuals. In healthy controls, higher AL index was associated with lower scores of single tasks measuring delayed memory, including list recall and story memory. Linear regression analysis revealed that the associations between the AL index and the scores of semantic fluency, attention (total score, digit span and digit coding), the GAF score, the HDRS score as well as the PANSS general psychopathology score remained significant after controlling for age, the number of years in education, CPZeq and cigarette smoking status in patients with psychosis (Table 4). In FHR-P individuals, the correlations between the AL index and attention performance (total score and digit coding) also remained significant in linear regression analysis. However, the association between the AL index and list recall as well as story memory appeared to be non-significant in healthy controls after controlling for potential confounding factors.

4. Discussion

Results of our study imply that systemic biological dysregulations, captured by the AL index, appear in patients with psychosis and FHR-

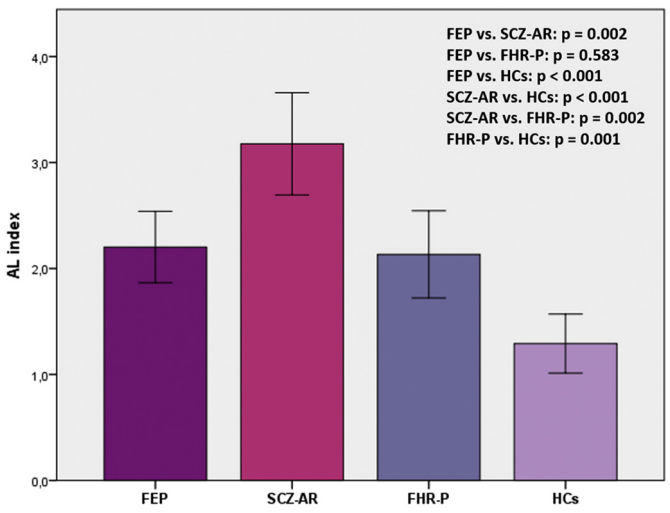

Fig. 1. Mean AL index in FEP patients, SCZ-AR patients, FHR-P individuals and HCs (error bars represent 95%CI).

Table 2
The levels of biomarkers integrated in the allostatic load index.

Biomarker	FEP	SCZ-AR	FHR-P	HCs	p
Cardiovascular markers					
SBP (mmHg)	120.2 ± 11.2	127.8 ± 8.3	123.6 ± 9.2	118.9 ± 8.7	**0.001**
DBP (mmHg)	75.4 ± 7.6	80.0 ± 6.8	76.2 ± 8.3	74.6 ± 7.2	0.049
Anthropometric measures					
BMI (kg/m^2)	23.7 ± 3.7	26.2 ± 4.2	24.3 ± 4.1	24.0 ± 3.5	0.072
WHR	0.85 ± 0.10	0.90 ± 0.09	0.84 ± 0.11	0.81 ± 0.08	**0.003**
Inflammatory markers					
hsCRP (mg/l)	1.2 ± 1.9	3.4 ± 3.3	0.9 ± 0.9	1.4 ± 2.4	**0.006**
fibrinogen (g/l)	2.5 ± 0.7	3.0 ± 1.0	2.7 ± 0.6	2.5 ± 0.6	0.104
albumin (g/dl)	4.2 ± 0.3	4.2 ± 0.3	4.3 ± 0.2	4.4 ± 0.2	**0.001**
Glucose homeostasis					
Glucose (mg/dl)	89.2 ± 19.3	91.4 ± 11.2	93.2 ± 18.1	83.4 ± 10.9	**0.010**
Insulin (uIU/ml)	22.7 ± 22.3	15.9 ± 13.5	10.9 ± 6.3	11.3 ± 5.3	**0.019**
Lipids					
Cholesterol (mg/dl)	177.1 ± 31.6	191.0 ± 47.7	187.6 ± 38.7	177.1 ± 27.4	0.257
LDL (mg/dl)	103.8 ± 28.0	117.7 ± 46.1	109.1 ± 36.4	102.8 ± 31.9	0.606
HDL (mg/dl)	48.4 ± 16.7	44.1 ± 11.1	60.8 ± 13.3	61.5 ± 15.3	<**0.001**
Triglycerides (mg/dl)	123.4 ± 58.3	146.4 ± 54.7	88.2 ± 41.0	80.4 ± 31.0	<**0.001**
Steroids					
Cortisol (nmol/l)	334.2 ± 74.6	443.8 ± 146.7	325.0 ± 158.9	255.4 ± 66.4	<**0.001**
DHEA-S (μg/dl)	338.2 ± 112.3	366.9 ± 175.0	250.6 ± 114.9	318.6 ± 136.9	**0.006**

Abbreviations: BMI – body mass index, DBP – diastolic blood pressure, DHEA-S – dehydroepiandrosterone sulfate, FEP – first-episode psychosis patients, FHR-P – individuals at familial high risk of psychosis, HCs – healthy controls, HDL – high density lipoproteins, hsCRP – high sensitivity C-reactive protein, LDL – low density lipoproteins, SBP – systolic blood pressure, SCZ-AR – acutely relapsed schizophrenia patients, WHR – waist-to-hip ratio.
Significant differences after the Benjamini-Hochberg correction ($p \leq 0.036$) were marked with bold characters.

P individuals. The AL index was significantly higher in SCZ-AR patients compared to other groups of participants. Interestingly, FEP patients and FHR-P individuals had similar levels of the AL index. These findings are in line with previous studies demonstrating elevated AL index in FEP patients and multiple-episode schizophrenia patients (Berger et al., 2018a; Chiappelli et al., 2017; Nugent et al., 2015; Savransky et al., 2018, 2017).

To our knowledge, elevated AL index in FHR-P individuals has not been documented so far. Similar levels of the AL index in FHR-P individuals and FEP patients support the hypothesis that enhanced emotional reactivity to stress might be associated with psychosis susceptibility (Aiello et al., 2012). Indeed, there are studies showing that relatives of patients with psychosis present higher levels of emotional reactivity to daily stressors (Lataster et al., 2010), higher diurnal cortisol levels and heightened cortisol response to stress (Collip et al., 2011), pituitary enlargement (Mondelli et al., 2008) and hippocampal volume reductions (Boos et al., 2007). Several lines of evidence also indicate that interactions between variation in genes regulating the HPA axis and stressful experiences impact a risk of psychosis (Misiak et al., 2017b). It is also important to note that the levels of DHEA-S were very low in FHR-P individuals compared to other subgroups of participants. However, the mechanisms underlying this observation remain unknown and require additional studies with more comprehensive clinical assessment.

Significantly higher levels of the AL index in SCZ-AR patients compared to FEP patients, FHR-P individuals and healthy controls might be explained by accumulating exposure to environmental factors, including stressful experiences, poor dietary habits, cigarette smoking and medication effects. There is convincing evidence that cardiovascular risk is significantly higher in chronic schizophrenia patients than in FEP patients (Mitchell et al., 2013). It has also been demonstrated that patients with multiple-episode schizophrenia patients might prefer slightly different stress coping styles than those with FEP (Kommescher et al., 2017). In the analysis of data from FEP patients, we have previously reported that lower preference of active coping styles contributes to elevated AL index (Misiak et al., 2018b). In both groups of patients, we found that a higher AL index was related to lower level of global functioning and more severe depressive symptoms. These findings are in agreement with other studies examining the AL index in psychosis (Berger et al., 2018a; Nugent et al., 2015). Moreover, higher AL index predicted worse social and occupational functioning in a longitudinal study of individuals at ultra-high risk of psychosis (Berger et al., 2018b). Moreover, elevated AL index has been demonstrated in patients with depression (Kobrosly et al., 2014; Rodriquez et al., 2018; Scheuer et al., 2018).

Interestingly, we found some similarities in the correlations between the AL index and performance of the attention domain in patients with psychosis and FHR-P individuals after controlling for potential confounding factors. More specifically, higher AL index was associated with worse performance of attention (correlations with the total score and the scores of single tasks - digit span and digit coding) and semantic fluency in patients with psychosis. In FHR-P individuals, higher AL index was related to lower scores of attention and digit coding. No significant correlations between the AL index and cognition were found in healthy controls. At this point, it should be noted that a significant impairment of digit coding, which measures attention and processing speed, has been well-documented in patients with schizophrenia (Dickinson et al., 2007). Prospective and longitudinal studies have shown that cognitive deficit measured by this task appears already in at-risk individuals and is present in FEP patients as well as chronic schizophrenia patients, with a very modest positive response to treatment (Dickinson et al., 2007; Hill et al., 2004; Verdoux et al., 1995). Similarly, impairments of working memory (measured by the digit span task), have been widely observed in patients with schizophrenia (Bokat and Goldberg, 2003; Forbes et al., 2009) and their unaffected relatives (Sitskoorn et al., 2004; Zhang et al., 2016). These cognitive deficits (worse performance of semantic fluency, digit coding and digit span tasks) have been associated with impairments of the prefrontal gray matter in patients with schizophrenia (Kubota et al., 2005; Sanfilipo et al., 2002; Van Snellenberg et al., 2016). Prefrontal cortex contains a high density of glucocorticoid and adrenergic receptors, being a target for chronic stress (Arnsten, 2009; Lupien and McEwen, 1997). Notably, chronic stress has been found to cause debranching and shrinkage of dendrites within the prefrontal cortex (Radley et al., 2004). The correlation between a higher AL index and cortical thinning has been observed in patients with schizophrenia (Chiappelli et al., 2017) and non-clinical adults (Ottino-González et al., 2017). Elevated AL index in patients with psychosis and FHR-P together with correlations between the AL index and cognitive impairment in both groups suggest that these physiological dysregulations might be attributed to genetic backgrounds. Interestingly, it has been found that genetic variability associated with psychosis risk can also influence cognitive performance with respect to verbal-numerical reasoning, reaction time and general cognitive function (Smeland, et al., 2017). Moreover, interactions between variation in the *FKBP5* gene and a history of traumatic events, might influence both psychosis risk and cognitive performance (Green et al., 2015; Misiak et al., 2017b). A lack of significant correlations between the AL index and cognition in healthy controls might suggest that certain factors might protect cognitive performance against deleterious effects of multisystem biological dysregulations. Moreover, according to the AL concept, short-term activation of allostasis might enable adaptation to stress. Therefore, detrimental effects of low AL index on cognitive performance cannot be observed in healthy controls.

It is important to note that we found no significant correlations between the AL index and the measures of stress (the LTE and the PSS).

Table 3
Correlations between the AL index and the measures of clinical manifestation.

	Psychosis (FEP and SCZ-AR)	FHR-P	HCs
Immediate memory			
Total score	r = −0.213, p = 0.087	r = −0.108, p = 0.523	r = −0.234, p = 0.157
List learning	r = −0.245, p = 0.051	r = −0.074, p = 0.662	r = −0.222, p = 0.181
Story memory	r = −0.181, p = 0.153	r = −0.132, p = 0.436	r = −0.085, p = 0.614
Visuospatial/constructional functions			
Total score	**r = −0.368, p = 0.002**	**r = −0.470, p = 0.003**	r = 0.078, p = 0.641
Figure copy	**r = −0.291, p = 0.020**	**r = −0.366, p = 0.026**	r = 0.018, p = 0.916
Line orientation	**r = −0.375, p = 0.002**	**r = −0.360, p = 0.029**	r = 0.101, p = 0.545
Language			
Total score	**r = −0.322, p = 0.008**	r = −0.005, p = 0.975	r = −0.158, p = 0.342
Picture naming	r = −0.028, p = 0.828	r = −0.058, p = 0.735	r = 0.036, p = 0.829
Semantic fluency	**r = −0.362, p = 0.003**	r = −0.022, p = 0.899	r = −0.174, p = 0.296
Attention			
Total score	**r = −0.340, p = 0.005**	**r = −0.495, p = 0.002**	r = −0.056, p = 0.736
Digit span	**r = −0.372, p = 0.002**	r = −0.123, p = 0.470	r = 0.058, p = 0.728
Digit coding	**r = −0.336, p = 0.007**	**r = −0.501, p = 0.002**	r = −0.055, p = 0.741
Delayed memory			
Total score	r = −0.227, p = 0.067	r = −0.262, p = 0.118	r = −0.287, p = 0.080
List recall	r = −0.172, p = 0.174	r = −0.236, p = 0.159	**r = −0.365, p = 0.024**
List recognition	r = −0.170, p = 0.179	r = −0.150, p = 0.377	r = 0.116, p = 0.488
Story memory	r = −0.096, p = 0.451	r = −0.163, p = 0.335	**r = −0.356, p = 0.028**
Figure recall	**r = −0.266, p = 0.034**	r = −0.223, p = 0.185	r = −0.080, p = 0.634
Global cognition	**r = −0.330, p = 0.007**	**r = −0.372, p = 0.023**	r = −0.232, p = 0.161
LTE	r = 0.045, p = 0.724	r = 0.212, p = 0.215	r = 0.188, p = 0.246
PSS-10	r = 0.144, p = 0.251	r = −0.159, p = 0.354	r = −0.035, p = 0.828
SOFAS	r = −0.215, p = 0.086	r = −0.011, p = 0.950	r = −0.225, p = 0.151
GAF	**r = −0.261, p = 0.036**	–	–
PANSS-P	r = 0.200, p = 0.111	–	–
PANSS-N	r = 0.197, p = 0.117	–	–
PANSS-G	**r = 0.310, p = 0.012**	–	–
HDRS	**r = 0.335, p = 0.006**	–	–
YMRS	r = −0.159, p = 0.206	–	–

Abbreviations: CPZeq – chlorpromazine equivalent dosage, FEP – first-episode psychosis patients, FHR-P – individuals at familial high risk of psychosis, GAF – the Global Assessment of Functioning, HCs – healthy controls, HDRS – the Hamilton Depression Rating Scale, LTE – the List of Threatening Experiences, PANSS-G - the Positive and Negative Syndrome Scale (subscale of general psychopathology), PANSS-N - the Positive and Negative Syndrome Scale (subscale of negative symptoms), PANSS-P – the Positive and Negative Syndrome Scale (subscale of positive symptoms), PSS – the Perceived Stress Scale, SCZ-AR – acutely relapsed schizophrenia patients, SOFAS – the Social and Occupational Assessment of Functioning, YMRS – the Young Mania Rating Scale.
Significant correlations after the Benjamini-Hochberg correction were marked with bold characters ($p \leq 0.038$).

These negative findings might be attributed to characteristics of both tools. Indeed, the PSS measures exposure to stress over the preceding month. In turn, the AL index captures systemic dysregulations related to chronic stress. A recent study by Nugent et al. (2015) also failed to detect a significant correlation between the AL index and the score of PSS in patients with schizophrenia. Regarding the LTE, it should be noted that this tool records a limited number of specific stressors without timing of exposure. Indeed, timing of exposure has been found to impact the association between traumatic events and psychosis risk (Schalinski et al., 2019; Schalinski and Teicher, 2015). A history of childhood trauma, a known risk factor of psychosis, has been associated with a number of stress-related biological dysregulations (Misiak et al., 2017a). On the other site, it might be hypothesized that elevated AL in patients with psychosis and FHR-P individuals does not appear as a consequence of psychological stress but represents a cumulative biological dysregulation attributable to psychosis liability. It cannot also be excluded that caregiving burden, not assessed in our study, contributed to elevated AL index in FHR-P individuals. Indeed, a recent study demonstrated elevated AL index in caregivers of patients with Alzheimer's disease (Roepke et al., 2011).

Results of our study should be interpreted after considering certain limitations. Firstly, our sample was small, especially when considering specific subgroups of participants. Secondly, there were significant between-group differences in age. However, differences in the AL index between specific subgroups of participants remained significant after adjustment for potential confounders that included age. Moreover, age differences are difficult to be excluded in studies of patients with psychosis at various stages of illness. Another limitation is that the vast majority of patients were not drug-naïve and thus medication effects should be taken into account. However, in our study we controlled for the effects of cumulative dosage of antipsychotics. It should also be noted that the use of LTE provides a limited insight into stressful experiences and thus addressing the effects of lifetime stressors on the AL index in psychosis requires additional studies. Additionally, we did not use any measures of subclinical symptoms and caregiving burden in FHR-P individuals. It cannot also be excluded that our findings simply represent dysregulations associated with stress related to experiencing acute psychosis. Finally, a cross-sectional study design does not allow to establish direction of causality.

In summary, findings from our study point to the hypothesis that familial risk of psychosis is associated with systemic biological dysregulations that are similar to those observed in FEP patients. Multisystem dysregulations, measured by the AL index, might progress with subsequent psychotic exacerbations. Our results also indicate that biological alterations, captured by the AL index, might contribute to cognitive impairment observed in FHR-P individuals and patients with psychosis, creating potential targets for pro-cognitive treatment strategies. In addition, the development of interventions aimed at reducing the AL might improve somatic health status of patients with psychosis. Another future direction for this field would be to investigate the impact of childhood traumatic events on the AL index in individuals at clinical high risk of psychosis, taking into account the timing of exposure.

Table 4
Linear regression analysis testing for the association between the AL index and clinical measures after adjustment for potential confounding factors.

Group	Clinical variable	AL index	Age	The number of years in education	CPZeq	Cigarette smoking
Psychosis	Visuospatial constructional functions:					
	Total score	B = −0.55, p = 0.558	**B = −0.23, p = 0.015**	**B = 0.88, p = 0.031**	B = 0.005, p = 0.310	B = 1.38, p = 0.531
	Figure copy	B = −0.10, p = 0.780	**B = −0.08, p = 0.027**	B = 0.29, p = 0.065	B = 0.001, p = 0.604	B = 0.75, p = 0.388
	Line orientation	B = −0.88, p = 0.081	B = −0.07, p = 0.142	B = 0.37, p = 0.075	B < 0.001, p = 0.991	B = 0.27, p = 0.812
	Language:					
	Total score	B = −0.73, p = 0.385	B = −0.16, p = 0.064	**B = 0.82, p = 0.025**	**B = 0.009, p = 0.034**	B = −1.39, p = 0.481
	Semantic fluency	**B = −0.63, p = 0.020**	B = −0.10, p = 0.130	B = 1.09, p = 0.088	B = 0.005, p = 0.106	B = −1.70, p = 0.251
	Attention:					
	Total score	**B = −2.24, p = 0.002**	**B = −0.80, p < 0.001**	B = 0.66, p = 0.686	B = −0.001, p = 0.933	B = 3.61, p = 0.352
	Digit span	**B = −0.65, p = 0.040**	B = −0.03, p = 0.321	B = 0.12, p = 0.334	B = 0.001, p = 0.735	B = 0.474, p = 0.508
	Digit coding	**B = −1.82, p = 0.002**	**B = −0.67, p < 0.001**	B = 0.75, p = 0.574	B = −0.006, p = 0.352	B = 2.48, p = 0.423
	Delayed memory:					
	Figure recall	B = −0.47, p = 0.405	B = −0.07, p = 0.237	B = 0.28, p = 0.246	B = −0.002, p = 0.521	B = 0.23, p = 0.863
	Global cognition	B = 0.35, p = 0.940	**B = −1.65, p = 0.001**	**B = 6.14, p = 0.003**	B = 0.001, p = 0.969	B = 6.48, p = 0.558
	GAF	**B = −3.33, p = 0.031**	B = −0.25, p = 0.221	B = 1.39, p = 0.116	B = 0.004, p = 0.674	B = 4.46, p = 0.357
	PANSS-G	**B = 2.66, p = 0.018**	B = 0.10, p = 0.347	B = −0.77, p = 0.104	B = −0.004, p = 0.431	B = −4.85, p = 0.065
	HDRS	**B = 2.87, p = 0.003**	B = −0.13, p = 0.155	B = 0.39, p = 0.332	B = −0.006, p = 0.196	B = 0.21, p = 0.924
FHR-P	Visuospatial constructional functions:					
	Total score	B = −1.20, p = 0.058	B = 0.08, p = 0.303	B = −0.08, p = 0.655	–	B = −1.92, p = 0.280
	Figure copy	B = −0.41, p = 0.056	B = −0.008, p = 0.720	B = −0.07, p = 0.189	–	B = −0.93, p = 0.085
	Line orientation	B = −1.24, p = 0.050	B = 0.08, p = 0.222	B = −0.008, p = 0.960	–	B = −0.98, p = 0.549
	Attention:					
	Total score	**B = −3.94, p = 0.014**	B = −0.44, p = 0.062	B = −0.28, p = 0.611	–	B = −5.32, p = 0.335
	Digit coding	**B = −3.53, p = 0.010**	B = −0.43, p = 0.053	B = −0.12, p = 0.824	–	B = −0.99, p = 0.328
	Global cognition	B = −6.87, p = 0.123	B = −0.60, p = 0.201	B = 0.27, p = 0.812	–	B = −17.15, p = 0.131
HCs	Delayed memory:					
	List recall	B = −0.67, p = 0.051	B = −0.02, p = 0.610	B = 0.105, p = 0.440	–	B = −0.032, p = 0.974
	Story memory	B = −0.12, p = 0.705	**B = −0.18, p < 0.001**	B = 0.17, p = 0.221	–	B = 0.576, p = 0.553

Abbreviations: AL index – the allostatic load index, CPZeq – chlorpromazine equivalent dosage, FHR-P – individuals at familial high risk of psychosis, GAF – the Global Assessment of Functioning, HCs – healthy controls, HDRS – the Hamilton Depression Rating Scale, PANSS-G - the Positive and Negative Syndrome Scale (subscale of general psychopathology).
Significant correlations ($p < 0.05$) were marked with bold characters.
VIF ≤ 1.90.

These studies are needed to explore whether our observations are attributable to the effects of psychological stress or represent biological alterations related to psychosis liability. A consensus statement regarding operationalization of the AL index is also required to allow comparability of results from various studies. Moreover, longitudinal studies are needed to establish direction of causality in the relationship between the AL and psychosis.

Contributors

Study design: BM and PP, recruitment and assessment of psychopathology: PP, JAB, BM and BTD assessment of cognition: KK, PP and SK, data analysis: BM, manuscript writing: PP, BM, JS and JR.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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