Psychoneuroendocrinology (2015) 60, 120—129

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/psyneuen

# Cumulative stress pathophysiology in schizophrenia as indexed by allostatic load

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Received 30 January 2015; received in revised form 10 June 2015; accepted 13 June 2015

**KEYWORDS**
Allostasis;
Cardiovascular;
Psychosis;
Cortisol;
Stress response

**Summary**
*Background:* The etiopathophysiology of schizophrenia has long been linked to stress and the influence of stress is important in all stages of the illness. Previous examinations of perceived stress and acute stress responses may not capture this longitudinal stress pathophysiology. We hypothesized that the cumulative negative effects of stress, indexed by allostatic load (AL), would be elevated in schizophrenia, and that the AL paradigm would be relevant to our understanding of pathophysiology in schizophrenia.
*Methods:* We assessed allostatic load in 30 patients with schizophrenia (SZ; mean age = 33; 17 males) and 20 healthy controls (HC; mean age = 35; 12 males) using 13 cardiovascular, metabolic, neuroendocrine and immune biomarkers. Participants' perceived stress over the past month, functional capacity and psychiatric symptoms were also measured.
*Results:* Controlling for age, SZ had significantly higher AL as compared to HC ($p = 0.007$). Greater AL was present in both early course and chronic SZ, and was associated with reduced functional capacity ($p = 0.006$) and more psychotic symptoms ($p = 0.048$) in SZ. Current level of perceived stress was not significantly elevated in SZ or associated with AL in either group.
*Conclusions:* The higher AL found in SZ may reflect increased bodily ''wear and tear'', possibly caused by more chronic stress exposure or maladaptive responses to stress over time, although additional research is required to differentiate these causes. The higher AL is similarly present in early and chronic SZ, suggesting primary maladaptive stress physiology rather than secondary effects from medications or chronic illness.


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http://dx.doi.org/10.1016/j.psyneuen.2015.06.009
0306-4530/

## 1. Introduction

Schizophrenia is a severe mental illness characterized by hallucinations, delusions, negative symptoms, and often significant cognitive and affective impairment. The disorder generally has onset of psychotic symptoms during late adolescence to early adulthood with lifetime prevalence around 1%. There is considerable heterogeneity in the clinical presentation, course and treatment response (Tandon et al., 2009). Additionally, the neurobiology is varied across patients and may include reduced grey matter volume, alterations in white matter, abnormal neurophysiology, and a range of neurochemical and neuropathological alterations (Keshavan et al., 2008). One of the common findings is the link between stress and the pathophysiology of schizophrenia at all stages of the illness. Prenatal stress increases disease risk (van Os and Selten, 1998) and stressful events precede disease onset (Norman and Malla, 1993). Patients have greater affective reactivity to experimental stress exposure after illness onset (Cohen and Docherty, 2004) and stressful life events precipitate worsening of psychosis (Hultman et al., 1997; Docherty et al., 2009). In addition, both psychological and physiological stress reactivity are associated with psychotic episodes, quality of life, and symptom severity (Garner et al., 2011; Belvederi Murri et al., 2012; Brenner et al., 2011). It has been hypothesized that environmental exposures, including stressful events, induce psychological and/or physiological changes that result in a final common pathway in SZ of altered dopamine neurotransmission and/or cognitive biases (Howes and Kapur, 2009; Myin-Germeys and van Os, 2007; Selten and Cantor-Graae, 2005; Howes et al., 2004). Together, this evidence points to longitudinal associations between stress pathophysiology and schizophrenia. Capturing the longitudinal effect may be needed to guide research and treatment. Previous laboratory paradigms have attempted to link stress to schizophrenia by testing acute physiological stress responses to various behavioral and pharmacological paradigms (Jansen et al., 2000; Marcelis et al., 2004; Breier et al., 1988). Blunted, rather than elevated or prolonged, cortisol responses have been described following acute psychological stress challenges (Elman et al., 1998; Jansen et al., 2000; Jansen et al., 1998). An index of the chronic, cumulative effect of stress responses may be an important complement to the study of acute stress responses in examining the etiological contributions of stress to schizophrenia.

The biological concept of allostatic load incorporates several elements of stress pathophysiology in one comprehensive model. The term ''allostasis'' refers to how an organism accommodates to a stressor by adjusting homeostatic set points to maintain internal stability (McEwen, 2004). These adaptive mechanisms operate through primary mediators including hormones of the hypothalamic—pituitary—adrenal (HPA) axis, catecholamines, neurotransmitters, and immune responses (McEwen and Wingfield, 2003). The brain is the central mediator of these accommodations to stressors, thus they can be influenced by appraisal, learning, memory and coping (Sterling and Eyer, 1988; Ganzel et al., 2010; McEwen and Gianaros, 2010). While allostasis mechanisms are adaptive in the short-term, they can lead to an elevated allostatic state in which there is an imbalance of the primary mediators. The cumulative effect of an elevated allostatic state is termed allostatic load (AL), which refers to the wear and tear the body experiences after having to respond to and make accommodations in light of stress (McEwen, 2002). The core emotional regions of the brain are theorized to initiate allostatic accommodation, and Ganzel et al. (2010) have demonstrated that these neural systems are some of the first to display AL wear and tear. Furthermore, there are theorized to exist time periods of increased sensitivity to environmental experience, during which the stress response itself could be changed in qualitative or quantitative ways (Ganzel and Morris, 2011), a concept perhaps linking findings on prenatal stress, early adversity and childhood trauma in the etiology of schizophrenia.

The AL index is traditionally operationalized as the sum of dysregulated neuroendocrine, immune, metabolic and cardiovascular biomarkers (Seeman et al., 1997) reflecting a multisystemic view of the physiological toll that is placed on the body for adaptation. The AL model has mostly been utilized to predict worse health outcomes, including development of cardiovascular disease, declines in physical and cognitive functioning and greater mortality risk (Seeman et al., 2001; Seeman et al., 2004). Additionally, AL has been examined in relation to greater cumulative risk, including physical (i.e. crowding), psychosocial (i.e. maternal separation) and personal (i.e. poverty) risk exposures (Danese and McEwen, 2012; Evans and Kim, 2012; Evans, 2003). The first operationalization of AL was performed using the MacArthur Studies of Successful Aging (Seeman et al., 2001; Seeman et al., 2004). They quantified AL through a series of 10 biomarkers; *systolic* and *diastolic blood pressure* are indices of cardiovascular activity; *waist—hip-ratio* reflects levels of metabolism and adipose tissue deposition; *serum high density lipoprotein (HDL)* and *total cholesterol* are related to the development of atherosclerosis; *glycosylated hemoglobin* measures long-term glucose metabolism; *serum dihydroepiandrosterone sulfate (DHEA-S)* is a functional HPA axis antagonist; *overnight urinary cortisol* excretion is a measure of 12-h HPA axis activity; and *overnight urinary noradrenalin* and *adrenalin* index 12 h sympathetic nervous system activity (McEwen, 2000). Subsequent studies have employed additional biomarkers, including *resting heart rate* to index cardiovascular activity, *BMI* to index metabolism and adipose tissue deposition, and *C-reactive protein* for assessing overall immune status [see (Juster et al., 2010) for a review]. We therefore also included these measures especially as prior research has documented elevated pulse rates (Lake et al., 1980; Van Kammen and Kelley, 1991), BMI, and a pro-inflammatory state (Ostermann et al., 2013) in SZ. AL is most commonly quantified by summing the number of parameters for which persons fall into the ''highest'' risk quartile (Seeman et al., 1997).

In psychiatry, AL has been investigated in bipolar disorder (Vieta et al., 2013; Kapczinski et al., 2008), depression (McEwen, 2004), PTSD (McFarlane, 2010) and their comorbid physical health conditions (McIntyre et al., 2007; Bizik et al., 2013). The AL paradigm is proposed as a relevant model for explaining the course of these illnesses, reflecting predispositions and then effects of repeated stress on the brain across biological mechanisms that contribute to psychiatric and somatic outcomes. AL could be instrumental to our understanding of how early life stress alters the stress response system as well as how cumulative stress