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Childhood abuse and depression in adulthood: The mediating role of allostatic load

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ABSTRACT

Background: Traumatic experiences during childhood are considered a major risk factor for depression in adulthood. Childhood trauma may induce physiological dysregulation with long-term effects of increased allostatic load until adulthood, which may lead to depression. Thus, our aim was to investigate whether allostatic load – which represents a multi-system measure of physiological dysregulation – mediates the association between childhood trauma and adult depression.

Methods: The study sample consisted of 324 depressed inpatients participating in the Munich Antidepressant Response Signature (MARS) project and 261 mentally healthy control participants. The mediation analysis using a case-control approach included childhood trauma, i.e., physical and sexual abuse, as predictor variables and an allostatic load index comprised of 12 stress-related biomarkers as mediator. Age and sex were included as covariates.

Results: Mediation analyses revealed that the influence of physical abuse, but not sexual abuse, during childhood on depression in adulthood was mediated by allostatic load. This effect was moderated by age: particularly young (18–42 years) and middle-aged (43–54 years) adults with a history of physical abuse during childhood exhibited high allostatic load, which in turn was associated with increased rates of depression, but this was not the case for older participants (55–81 years).

Conclusions: Results support the theoretical assumption of allostatic load mediating the effect of physical abuse during childhood on depression in adulthood. This predominantly holds for younger participants, while depression in older participants was independent of physical abuse and allostatic load. The effect of sexual abuse on depression, however, was not mediated by allostatic load. Identifying allostatic load biomarkers prospectively in the developmental course of depression is an important target for future research.

1. Introduction

"Many abused children cling to the hope that growing up will bring escape and freedom" (Herman, 1997 p. 110). Contrary to these expectations, research has shown that adverse experiences during childhood play a major role in the etiology and development of mental disorders in adulthood (Gillespie and Nemeroff, 2005). Epidemiological data suggest that childhood adversities, including physical abuse, sexual abuse, and interpersonal loss, predict the incidence of up to 32% of psychiatric disorders in adulthood (Green et al., 2010; Kessler et al., 1997). Robust associations have been found for childhood adversities and depression (Kessler, 1997; Widom et al., 2007): adults who have been traumatized during childhood exhibit a higher lifetime prevalence of major depression (Macmillan et al., 2001) and an unfavorable course of illness including poor treatment outcome (Nanni et al., 2012). Identifying neurobiological processes involved in this pathway may, therefore, help find both appropriate prevention strategies and novel treatments for depression.

The most prominent neurobiological systems that primarily respond to stress are the sympathetic-adrenal-medullary (SAM) axis and the

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hypothalamic-pituitary-adrenal (HPA) axis. Through secretion of catecholamines and glucocorticoids, SAM and HPA axis provide the body's energy that is necessary to successfully respond to stress. While these adaptive processes are generally beneficial in the short term, chronic or inappropriate adaptation – caused by repeated or long-term exposure to stress – may have detrimental effects on the organism; this is labelled "allostatic load" (AL) (McEwen and Stellar, 1993). For instance, Heim et al. (2000) demonstrated that women who experienced physical or sexual abuse during childhood exhibited elevated parameters in both, HPA and SAM axis system in adulthood. Those hormonal agents that are released from the SAM and HPA axes are referred to as "primary mediators" of AL (Mc Ewen and Seeman, 1999). In response to the primary mediators, interconnected biological systems such as the immune, metabolic and cardiovascular systems are modulated (McEwen, 2006) which are called "secondary outcomes" also contributing to AL when overactivated. The extent of AL is quantified by measuring alterations in these physiological systems. Seeman et al. (1997) initially operationalized the measurement of AL using a count-based algorithm that represents the number of biomarkers for which participants exhibit levels above or below a certain threshold.

AL in those physiological systems is expected to impact brain plasticity in specific brain regions like the hippocampus, amygdala and prefrontal cortex (Mc Ewen and Gianaros, 2011), which in turn are implicated in the vulnerability of stress-related mental disorders like depression (e.g., Campbell et al., 2004). Thus, AL is assumed to contribute to increased vulnerability for mood disorders (McEwen, 2003). Following this concept, traumatic experiences during childhood are supposed to induce significant biological changes that become manifest in terms of allostatic overload in adulthood and thus affect physical and mental health in later life (Danese and McEwen, 2012; McEwen, 2000).

Recent empirical evidence indeed suggests that individuals who experienced abuse or neglect during childhood exhibited higher AL in adulthood compared to individuals without a history of childhood abuse or neglect (Horan and Widom, 2015). While this result was restricted to females, longitudinal population-based data of a cohort aged 54 years and older suggest that physiological dysregulation operationalized in terms of AL is predicted by perceived chronic strain only in men. (Glei et al., 2013). Another longitudinal study suggests cumulative risk exposure during childhood preceding high AL in early adolescence, but only if maternal responsiveness was low (Evans et al., 2007). Although several studies point to an association between childhood trauma and AL, the results are often sex-specific. Moreover, according to Cohen's classification of effect sizes (Cohen, 1977), those results are only of small (Glei et al., 2013; Horan and Widom, 2015) or medium effect size (Evans et al., 2007). Additionally, a few studies did not find a link between adverse childhood experiences and AL in adulthood (Hellhammer et al., 2004; Rogosch et al., 2011).

AL is influenced by age because several stress parameters increase with increasing age, resulting in an age-accumulated AL index (e.g., Crimmins et al., 2003). Moreover, AL was associated with various adverse health outcomes in higher age, including mortality (Seeman et al., 2004, 2001), physical (Seeman et al., 2001), and cognitive functioning (Karlamangla et al., 2002).

Considering the effect of AL on depressive symptomatology, positive and negative findings have been reported. Two studies have shown that AL is related to concurrent depressive symptomatology in the elderly (Juster et al., 2011a; Kobrosly et al., 2014). The sample sizes of the two studies were relatively small, and secondary stress-related outcomes like immune or metabolic parameters were not considered in their AL indices. Nevertheless, the observed results reached medium effect size. Additionally, AL in healthy elderly was found to be predictive of future depressive symptoms during a follow-up interval of up to three years (Goldman et al., 2006; Juster et al., 2011a). While these effect sizes were only small, no effects between AL and depressive symptoms were found after six years (Juster et al., 2011a). Moreover, recent evidence suggests that higher AL is associated with burnout symptoms in healthy adults (Hintsa et al., 2014), although these results were of small effect size. This might partly be attributed to the composition of AL because only secondary stress-related parameters were considered. Nevertheless, the link between AL and burnout has further been supported by Juster et al. (2011b). By using 15 AL biomarkers including primary stress mediators like cortisol and other parameters across all important categories, their results reached medium effect size. However, other studies have found only single parameters like waist-hip-ratio but not the combined AL index to be predictive of depression (Rogosch et al., 2011) or found no association at all (Hellhammer et al., 2004).

In sum, most of the studies point towards an association of AL and depression, while a few studies did not detect this association. A similar pattern of results has been obtained for the link between childhood trauma and AL. Because of these inconsistent results the current study examined in a large case-control study of 585 participants whether childhood trauma is related to AL in adulthood and if AL in adulthood is related to depression. By addressing these questions, the present study attempts to overcome the following limitations of previous research:

First, prior studies focused almost exclusively on the effects of concurrent or chronic stress on AL rather than on the influence of childhood abuse. There exists only one study to date investigating long-term consequences of childhood abuse on AL in adulthood (Horan and Widom, 2015). To carefully and validly estimate the long-term consequences of stress on AL, we assessed traumatic experiences that occurred during childhood, focusing on physical and sexual abuse.

Second, most of the studies investigated the influence of AL on depressive symptomatology in population-based samples without psychiatric assessments, which does not allow drawing conclusions about the impact of AL on clinically relevant levels of depression. To clearly establish to what degree AL is associated with diagnosed depression, we used a case-control design comparing a large group of depressed patients with an equally large group of healthy controls.

Third, research on AL mostly included small numbers of biomarkers, thus restricting the external validity of these results. Moreover, some previous studies did not include primary mediators like cortisol, but rather used secondary outcomes like metabolic or immune parameters. To obtain a more comprehensive view, we included 12 biomarkers reflecting the most important stress parameters ranging from primary mediators reflected by neuroendocrine markers over secondary outcomes including anthropometric condition, cardiovascular activity, metabolic regulation, and immune system activity.

Importantly, it has been proposed that childhood trauma might lead to increased vulnerability for depression by accumulating AL (McEwen, 2000). However, this hypothesis has never been examined directly by testing for statistical mediation. Thus, based on this vulnerability model, the main aim of the present study was to extend previous research by investigating whether AL mediates the association between childhood trauma and acute depression. Because AL is influenced by age (Crimmins et al., 2003), age was included as a moderator in a supplementary analysis. To assess the role of potential confounders of AL in the context of acute depression, we further examined the influence of antidepressant medication, smoking and psychiatric diagnosis on AL in an exploratory analysis.

2. Material and methods

2.1. Participants

The study was part of the multi-center Munich Antidepressant Response Signature (MARS) project and was comprised of 324 inpatients (165 men, 159 women) diagnosed with depression and receiving antidepressant treatment. This naturalistic MARS project aimed at identifying biomarkers to facilitate determining subgroups of patients who have a common pathology and to predict antidepressant treatment response (Hennings et al., 2009). Patients were recruited at the Max Planck Institute of Psychiatry (MPI-P) in Munich and at five