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Hypothalamic-pituitary-adrenal axis, childhood adversity and adolescent nonsuicidal self-injury

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ABSTRACT

Background: Whereas childhood adversity (CA) and the hypothalamus-pituitary-adrenal (HPA) axis have been suggested to play a major role in the etiology of non-suicidal self-injury (NSSI), no study has thus far investigated both its associations and interactions with adolescent NSSI.
Method: We investigated CA (antipathy, neglect, physical, psychological, and sexual abuse) and indices of HPA axis activity (salivary and hair cortisol) in a clinical sample of 26 adolescents engaging in NSSI and 26 age- and gender-matched healthy controls (HC). We used standardized interviews for the assessment of CA (CECA), NSSI (SITBI-G), and axis I diagnoses (MINI-KID). Salivary cortisol sampling was surveyed using a monitoring system and instructed via telephone calls.
Results: Adolescents engaging in NSSI exhibited significantly higher cortisol awakening responses compared to HC. No differences were found with respect to the diurnal slope or hair cortisol. In the presence of CA, healthy adolescents showed flatted diurnal cortisol slopes while those engaging in NSSI exhibited significantly steeper ones.
Conclusions: Our findings indicate that adolescents engaging in NSSI may exhibit a stronger cortisol awakening response, potentially in expectation of strain. However, elevated cortisol levels may not be maintained throughout the day, especially among adolescents with a history of CA.

1. Introduction

Non-suicidal self-injury (NSSI) has been defined as the deliberate, direct destruction of body tissue without conscious suicidal intent, such as self-cutting or carving skin, self-burning, self-hitting, biting self or burning skin (Lloyd-Richardson et al., 2007). NSSI has been observed in the context of various mental disorders (Nock et al., 2006) with a worldwide prevalence rate of 17 percent among adolescents (Swannell et al., 2014). Due to its clinical relevance, NSSI has recently been included as a distinct disorder in section 3 of the new DSM-5 (American Psychiatric Association, 2013), making research on its antecedents and correlates even more important.

Previous studies especially highlighted the role of childhood adversity (CA) in the context of adolescent NSSI (Kaess et al., 2013). An invalidating, neglecting or abusive family environment may evoke strong negative emotions in children, which, at the same time, are not tolerated (Linehan, 1993). NSSI might consequently arise as a maladaptive strategy in order to regulate unresolved negative affective states. Kaess et al. (2013) reported strong relations between CA, especially maternal neglect and antipathy, and the engagement in NSSI within a representative clinical sample of adolescents and young adults. While a relationship of NSSI and CA has been established (Gratz et al., 2002), little is known about associations of CA with neurobiological mechanisms in the context of adolescent NSSI. However, environment-biology-relations that specifically arise in the context of NSSI may give key answers to the question why some individuals who experience CA start to self-harm and others don't.

The hypothalamic-pituitary-adrenal (HPA) axis is a major stress response system of the human body. Stressors activate the

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release of corticotropin releasing hormones (CRH) and arginine-vasopressin (AVP) from the hypothalamus, which foster the release of the hormone adrenocorticotropin (ACTH) from the pituitary gland, and consequently the release of *gluco*- and mineralocorticoids from the adrenal cortex. Finally, the glucocorticoid cortisol binds to responding receptors in different brain regions, which in turn inhibits the stress-induced secretion of CRH and AVP (Lupien et al., 2009). Previous research revealed CA to be associated with alterations in HPA axis functioning, and consequently with a higher vulnerability for psychopathologies in adulthood (McCrory et al., 2010). The continuous activation of the HPA axis and the associated releases of glucocorticoids may be particularly critical within the sensitive phase of adolescent development, in which it may alter brain structures that are crucial for emotion regulation (Lupien et al., 2009). However, only few studies have thus far focused on adolescent samples (Bosch et al., 2012; MacMillan et al., 2009). Moreover, the underlying mechanisms are still poorly understood with results of previous studies on relations between CA and HPA axis functioning among adolescents being best described as inconsistent (Trickett et al., 2010). With regard to HPA axis reactivity, Bosch et al. (2012) recently found experiences of adversities before puberty to be associated with increased cortisol after stressful situations, whereas adversities experienced at early adolescence resulted in decreased cortisol. Concerning non-stimulated HPA axis activity, results range from reports on a decreased cortisol awakening response (CAR; e.g., Meinlschmidt and Heim, 2005) to reports on increased morning cortisol levels (e.g., Halligan et al., 2004) after CA. Regarding basal cortisol, elevated hair cortisol levels have been reported in the literature following various forms of childhood adversities among a population-based sample of children (Simmons et al., 2016) and related to sexual abuse among adult patients with trauma-related disorders (Schalinski et al., 2015).

Data on the neurobiology of NSSI are rare, and little is known about specific neurobiological factors which may either predispose to or co-occur with NSSI (Westlund Schreiner et al., 2015). Clinical experience and empirical evidence show that NSSI often occurs in reaction to stressful situations (Pagano et al., 2004), and therefore might arise from a particular vulnerability to stress or might even be understood as regulatory coping strategy regarding exaggerated emotional stress reactions. Therefore, the HPA axis is likely to play a major role in the context of NSSI. Kaess et al. (2012) found alterations in the neurobiological stress response among adolescents engaging in NSSI, reflected in an attenuated cortisol response to a social stress test compared to healthy controls. Beauchaine et al. (2015) revealed associations between NSSI and decreased post-dexamethasone cortisol. These preliminary results seem to fit previous research on the impact of CA on HPA axis functioning (MacMillan et al., 2009), but data on non-stimulated HPA axis functioning in NSSI are lacking. However, there are several reasons to believe that variations of cortisol secretion during the day may also be altered among adolescents engaging in NSSI. First, previous research found NSSI to be related to experiences of psychological distress (Richmond et al., 2015). These experiences may predispose adolescents engaging in NSSI to expectations of strain, which have been associated with an increased cortisol secretion after awakening (Hall et al., 2010). Moreover, previous research revealed stress experiences to be associated with flatter diurnal slopes (Ly et al., 2015). Second, NSSI has been discussed as a strategy to temporarily relief from negative affectivity (Westlund Schreiner et al., 2015) with individuals engaging in NSSI showing generally higher levels of neuroticism (Mullins-Sweatt et al., 2013). Neuroticism, specifically the facet of anger, has in turn been associated with increased cortisol secretion after awakening (Adam, 2006). Third, Westlund Schreiner et al. (2015) stressed the need for research on alterations in basic arousal systems among individuals engaging in NSSI, arguing that those persons may suffer from sleep difficulties which may impair daily functioning.

Finally, it has been argued that relations between CA and HPA axis activity depend on clinical symptoms (Strüber et al., 2014). Previous research discussed the possibility that CA would result in a hypoactivity of the HPA axis in the context of externalizing problems, such as antisocial behavior (Susman, 2006), whereas interactions between CA and internalizing problems, such as depressive symptoms, may result in a hyperactivity of the HPA axis (Heim et al., 2004). Cicchetti et al. (2010) further revealed that children who have been physically or sexually abused during the first 5 years of life showed an attenuated diurnal slope in cortisol only if they showed a large extend of internalizing symptoms. To our knowledge, no study has yet investigated whether engagement in NSSI moderates relations between CA and diurnal cortisol secretion.

In our study, we aim at investigating several indices of non-stimulated HPA axis functioning (CAR, diurnal slope, hair cortisol levels) in adolescents engaging in NSSI compared to a healthy control group (HC). We further examine relations between CA (antipathy, neglect, psychological, physical, sexual abuse) and HPA axis indices for both groups. Finally, we test whether associations between CA and HPA axis indices differ between adolescents engaging in NSSI and the HC. The outlined considerations led us to formulate the following hypotheses: First, that adolescents engaging in NSSI show alterations in HPA axis functioning compared to age- and gender-matched HC. Second, that CA is associated with elevated baseline HPA axis activity (hair cortisol) and altered diurnal HPA axis activity (salivary cortisol). Third, that the relationship between CA and HPA axis functioning is moderated by NSSI.

2. Method

2.1. Participants and recruitment

Adolescents engaging in NSSI were consecutively recruited from our specialized outpatient clinic for adolescent risk-taking and self-harm behavior (AtR!Sk; "Ambulanz für Risikoverhalten & Selbstschädigung") as well as our inpatient units at the Clinic of Child and Adolescent Psychiatry, University Hospital Heidelberg, Germany. Participants from the HC group were recruited via public advertisement. Adolescents with acute psychotic symptoms, acute suicidality, poor knowledge of the German language, pregnancy, being on glucocorticoid medication or having endocrine disorders were not included (Stalder et al., 2016). Our study was approved by the institutional ethics committee of the Medical Faculty, University of Heidelberg and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed and written consent was obtained from participants and their parents/caregivers.

Our sample consists of 26 adolescents aged between 14 and 18 years who had engaged in NSSI at least 5 times during the last 6 months (24 females; M_{age} = 16.28 years; SD_{age} = 1.28) and 26 age-, gender- and school type-matched HC who had neither received any psychiatric diagnosis, nor undergone any psychiatric treatment or engaged in NSSI (HC; 24 females; M_{age} = 16.22 years; SD_{age} = 1.11). In the NSSI group, frequency of NSSI was on average 112 times during the last year (SD = 101.6) and 10.5 times during the last month (SD = 20.0). The most common forms of NSSI were deliberate cutting (100%), followed by manipulating wounds (69.2%), scratching (57.7%), hitting one's body (50%) and biting (46.2%). Twenty-two adolescents (84.6%) in the NSSI group reported that they had already attempted suicide at least once during lifetime. On average, adolescents in the NSSI group met the criteria for 2.81 axis I diagnoses (*SD* = 1.52), and fulfilled 4.38 (SD = 2.17) diagnos-