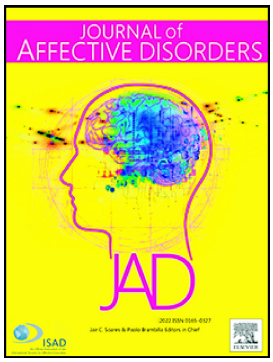

Increased immunological markers in female adolescents with non-suicidal self-injury

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Title: Increased immunological markers in female adolescents with non-suicidal self-injury

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Immunology, Stress, Depression, Childhood trauma, Non-Suicidal Self-injury, Adolescents

Highlights:

- Immunological factors and childhood maltreatment are associated with suicidal behaviour.
- The leukocyte/cortisol ratio reflects a combined score of immunology and social stress.
- In female adolescents with non-suicidal self-injury, the leukocyte/cortisol ratio is increased as compared to healthy controls and correlates with childhood maltreatment scores.

Abstract:

Background: Nonsuicidal self-injury (NSSI) is a prevalent health problem among adolescents and commonly associated with psychological stressors such as childhood maltreatment and comorbid psychiatric disorders (e.g., depression). There is evidence that alterations of immunological markers may occur in the context of both environmental stress and psychopathological development.

Method: Here, we investigated differences in plasma/serum leukocytes, cortisol, c-reactive protein and interleukin-6 in a large sample of female adolescents with NSSI (n=155) and healthy controls (HC, n=42). Further, we assessed correlations between inflammatory markers, depression severity and the severity of childhood maltreatment.

Results: The absolute number of leukocytes and the leukocyte/cortisol ratio (adjusted for body mass index and smoking) were significantly higher in NSSI as compared to HC, whereas interleukin-6 and CRP levels did not differ significantly between groups. Childhood maltreatment scores were significantly correlated with the leukocyte/cortisol ratio and depression severity was significantly correlated with both, absolute leukocyte numbers and the leukocyte/cortisol ratio.

Conclusions: Our results suggest that an immune activation can be detected in female adolescents with NSSI. Depression and childhood maltreatment, which are commonly reported in NSSI, may potentially underlie immune activation and partially explain group differences.

1. Introduction

Non suicidal self-injury (NSSI), defined as the deliberate and intentional destruction of body tissue without suicidal intent, can be found in 17-18% of adolescents (Swannell et al., 2014) and is a major predictor of future suicide attempts (Koenig et al., 2017). Recently, NSSI disorder has been introduced in DSM-5, warranting further study (American Psychiatric Association, 2013). Neurobiological models of NSSI implicate an involvement of the hypothalamic–pituitary–adrenal (HPA) axis (Kaess et al., 2021a). The HPA axis links psychological stress and the immune system via release of glucocorticoids, transgressing the blood-brain barrier (Bellavance and Rivest, 2014). In particular, the HPA axis is activated by proinflammatory cytokines such as interleukin 6 (IL-6) produced by macrophages and, vice versa, the release of cortisol impacts leukocyte homeostasis (Cole, 2008). Specifically, the leukocyte/cortisol ratio has been suggested as a measure for social stress (Cole, 2008). NSSI is commonly associated with a variety of mental disorders including depression and borderline personality disorder (BPD) (Ghinea et al., 2020), and a large proportion of adolescents with NSSI report childhood maltreatment (Kaess et al., 2013). Depression is also well-known for its associations with disturbed HPA axis activity and increased inflammatory markers (Miller and Raison, 2016), but similar biological alterations have been reported in the context of BPD and suicidality (Drews et al., 2019; Kaess et al., 2021b), defined as the sum of all ideations and behaviours that increase the risk of suicide. In addition, several studies have indicated that child maltreatment is associated with higher inflammation markers, such as higher leukocyte numbers, increased C- reactive protein (CRP), and/or higher IL-6 levels (Keaton et al., 2019; Kraynak et al., 2019; Renna et al., 2021). Given that adolescent NSSI is a strong precursor of suicidality, and closely associated with depression, BPD, and childhood maltreatment, it is plausible that altered inflammatory markers can be found among adolescents with NSSI.

In the present study, we investigated CRP, IL-6, absolute leukocyte numbers and the leukocyte/cortisol ratio in adolescent female patients with NSSI and healthy controls (HC). We hypothesized that inflammatory markers would be elevated in patients with NSSI compared to HC, and that we find a positive association between childhood maltreatment, depression and the number of BPD criteria with immune activation.

Methods

2.1 Participants

Patients with NSSI (aged 12 to 17 years) were recruited from the outpatient clinic for risk-taking and self-harm behaviour ("Ambulanz für Risikoverhalten und Selbstschädigung (AtR!Sk)") at the Department of Child and Adolescent Psychiatry, University Hospital Heidelberg, Germany. Following an initial diagnostic assessment, patients were invited to participate in the nested AtR!Sk-Bio cohort, which is an ongoing study aiming at identifying biological correlates of adolescent risk-taking and self-harming behaviour. The Ethics Committee of the Faculty of Medicine, University of Heidelberg, approved the scientific evaluation of AtR!Sk (IRB approval number S-449/2013) and the add-on neurobiological assessments (IRB approval number S-514/2015). Recruitment for AtR!Sk-Bio took place within six weeks after the diagnostic assessment. Age matched female HC were recruited via public advertisements and underwent an adapted form of the diagnostic assessment used in AtR!Sk. Exclusion criteria for patients and HC were acute psychosis, pregnancy, neurological, endocrinological or cardiovascular primary diseases, or lacking speech comprehension. Additional exclusion criteria for the HC group were lifetime self-harming behaviour, lifetime psychological or psychiatric treatment, or any current psychiatric disorder. For the present analyses, only female patients, aged 12-17 years, fulfilling the criteria for NSSI disorder, defined as incidents of NSSI on five or more days during the last 12 months according to the DSM-5 (American Psychiatric Association, 2013), were included. All participants and their caregivers provided informed and written consent to participate in the study.

2.2. Psychopathology assessment

NSSI was measured using the German version of the Self-Injurious Thoughts and Behaviours Interview (SITBI-G) (Fischer et al., 2014), a semi-structured interview for the detailed assessment of self-injurious thoughts and behaviours that was slightly modified to meet DSM-5 criteria for NSSI. The SITBI-G shows good psychometric properties. BPD symptoms were assessed using the respective part of the German version of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (Münster, 1999), with items showing good internal consistency (Cronbach's $\alpha = 0.83$). In addition, patients underwent the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (Sheehan et al., 2010), a

short semi-structured interview designed to assess common axis I psychiatric disorders in children and adolescents aged 6–19 years. The Depression Inventory for Children and Adolescents (DIKJ) (Stiensmeier-Pelster J et al., 2000) was used to measure self-reported depressive symptoms. The DIKJ consists of 26 items and is based on DSM-IV criteria for depression, having excellent psychometric properties. Further, all participants completed the German translation of the Childhood Experiences of Care and Abuse questionnaire (CECA.Q) (Kaess et al., 2011), showing good psychometric properties. The CECA.Q items were taken directly from the interview version and adapted, covering modules for parental care (antipathy and neglect), physical abuse and sexual abuse. To assess maltreatment severity, we created a dimensional trauma score using four modules of the CECA.Q, showing moderate to excellent internal consistency (Cronbach's α between 0.60 and 0.92). Following dichotomization of each variable, a mean score ranging from 0 (no maltreatment) to 1 (multiple types of maltreatment) was generated for each participant. Finally, a variable "maltreatment" was created representing the mean of antipathy, neglect, physical abuse and sexual abuse [(sexual abuse + antipathy + neglect + physical abuse)/4)]. Further, smoking behaviour during last month was assessed and categorized [0 = "0 cigarettes", 1 = <1 cigarettes , 2 = "1-2 cigarettes" , 3 = "3-5 cigarettes" ,4 = "6-10 cigarettes", 5 = "11-20 cigarettes" , 6 = ">20 cigarettes"] and body-mass index (BMI in kg/m²) was acquired as previous studies showed associations between smoking (Koarai et al., 2012) and BMI (de Heredia et al., 2012) with inflammatory markers.

2.3. Peripheral immunological markers

Samples of fasting peripheral blood were collected from patients and healthy controls between 8:30 a.m. and 9:00 a.m. to control for diurnal variation in hormone levels (van der Venne et al., 2021). Blood samples were subsequently sent to the central laboratories of the Heidelberg University Hospital for further analyses. Probes were centrifugated for 10 min at 3900 U/min on a Hettich centrifuge and automatically analyzed via an APTIO automation system (Siemens Healthineers Germany, siemens-healthineers.com). Leucocytes were measured by flow cytometry (ADVIA2120®, Siemens Healthineers) in EDTA blood. CRP was defined in Li-heparin-plasma using an ADVIA XPT® chemistry device (Siemens Healthineers). IL-6 was measured in serum by chemiluminescence immunoassay (CLIA) via IMMULITE® 2000 XPI analyzer (Siemens). Cortisol was assessed in serum by CLIA via CENTAUR XPT® (Siemens Healthineers).

2.4 Statistical Analysis

First, group differences of CRP, IL-6 and leukocytes were analysed between NSSI and HC. Due to detection limits of CRP and IL-6, group differences were estimated as follows: Bootstrapped 0.8-quantile regression with group as predictor was used on the sum score of CRP and IL-6 (Eilers et al., 2012; Uh et al., 2008) with 1000 repetitions. To ensure comparability between the two inflammatory markers, values were normalized by the mean of the top 15% values to a unitless measure. Thus the "inflammation score" represents [(normalized IL-6 + normalized CRP) + its minimum]. As a result, values at or below the detection limit are 0, and elevated inflammation scores are positive. For leukocytes, ordinary least square regression was used on the log-transformed data and on the log-transformed ratio of leukocytes/cortisol (Suarez et al., 2015) with group as predictor. All models were adjusted when group differences were detected (e.g., smoking). Additionally, we included BMI as a covariate, as BMI correlates with inflammatory markers (de Heredia et al., 2012). Further, partial correlations (partial rank correlations) between inflammatory markers and individual clinical outcomes were calculated across groups in order to estimate the correlation between depression/trauma/number of BPD criteria and inflammatory markers, excluding the effects of the adjustment variables BMI and smoking. Deliberate tissue damage might have the potential to increase neutrophil leukocytes within a short time frame after the injury (Kim et al., 2008). To evaluate the role of tissue damage on immunological parameters Pearson's correlations were calculated between the frequency of self-injury within the last week before measurement between IL-6, CRP, leukocytes, cortisol and the inflammation score.

Group comparisons of sample characteristics were done using t-tests or Mann-Whitney-U tests. The significance level was set to $\alpha = 0.05$. All analyses were performed using STATA 16.1 (StataCorp LLC, College Station, TX, USA).

2. Results

3.1 Sample description

In total, 155 female patients with NSSI and 42 female HC were included in the study (Table 1). No statistical differences were detected in age and BMI between groups. However, significantly more NSSI patients were smokers. NSSI patients showed significantly higher maltreatment and depression scores and fulfilled more BPD criteria. Among NSSI patients, 35.5% had a history of at least one suicide attempt within the last year. An elevated inflammation score was detected in 29.2% of NSSI patients and 13.5% of HC. Absolute numbers of leukocytes, leukocyte/cortisol ratio, CRP and IL-6 levels are shown in Table 1.

---------- include Table 1 about here ----------

3.2.Group differences of inflammatory markers

When comparing NSSI with HC, significantly higher leukocyte numbers (p=0.014) and a significantly higher leukocyte/cortisol ratio (p=0.019) was detected in NSSI patients (Table 2A). However, the "inflammation score", was not significantly different when comparing NSSI with HC, indicating that IL-6 and CRP levels were not significantly higher in individuals with NSSI (p=0.222). No significant correlations were detected between frequency of self-injury within the last week before measurement and IL-6 (r=-0.068, p=0.438, n=134), CRP (r=-0.017, p=0.839, n=146), leukocytes (r=-0.063, p=0.455, n=143) and cortisol (r=0.033, p=0.695, n=142), as well as the inflammation score (r=-0.079, p=0.430, n=130).

Associations between inflammatory markers and psychopathology

The maltreatment score significantly and positively correlated with the leukocyte/cortisol ratio (p=0.047), indicating an association between higher trauma exposition and higher inflammation within the total sample (Table 2B). Further, the depression score significantly and positively correlated with number of leukocytes (p=0.022) and the leucocyte/cortisol ratio (p=0.026). No significant association was detected with the number of BPD criteria (leukocytes p=0.8, leucocyte/cortisol ratio p=0.4).

---------- include Table 2 about here ----------

4. Discussion

Our findings of higher absolute numbers of peripheral leukocytes and a higher leukocyte/cortisol ratio in NSSI as compared to HC suggests a proinflammatory process in female adolescents with NSSI. Further, depression scores correlated significantly with both, number of leukocytes and the leukocyte/cortisol ratio supporting the notion that affective symptomatology may underlie increased inflammatory markers in patients with NSSI. Most importantly, our study shows a significant association between childhood maltreatment scores and the leukocyte/cortisol ratio, reflecting a combined score of immunological and stress markers

4.1. Group effect of leukocytes

To date, several studies demonstrated an immune activation in suicide attempters in adult populations (Keaton et al., 2019; Miller and Raison, 2016). Higher leukocyte expression has been specifically suggested as a peripheral biomarker for suicidal behaviour (Velasco et al., 2020). Importantly, there is evidence that proinflammatory markers negatively influence cognitive (Kindler et al., 2019) and emotional functions, thereby potentially impacting suicidal behaviour (Brundin et al., 2017). For example, one recent study reported that peripheral proinflammatory markers were negatively related to functional connectivity between the prefrontal cortex and the amygdala, suggesting a decoupling of prefrontal inhibition on limbic functioning (Kraynak et al., 2019). Importantly, previous studies showed that leukocytes may induce analgesic mediators that antagonise pain (Rittner and Brack, 2007) and therefore could be implicated in reduced pain sensitivity as reported in patients with NSSI (Cummins et al., 2021; van der Venne et al., 2021). To the best of our knowledge our study is the first to show increased number of leukocytes can be detected as early as in adolescence in patients with NSSI and thus in a sample at high risk for future suicide attempts.

No significant correlations were found between the frequency of self-injury within the last week before measurement and immunological parameters. Therefore, we believe that the increased leukocyte numbers in NSSI patients reported in our paper are not solely caused by tissue damage and consecutive wound healing among patients.

4.2. Group effect of IL-6 & CRP

Whereas suicidality has also been associated with increased IL-6 and CRP levels in adult populations (Black and Miller, 2015; Keaton et al., 2019; Miola et al., 2021), we did not detect higher IL-6/CRP levels in young, female NSSI patients as compared to HC. Next to age effects, this discrepancy might be caused by the fact that adult studies generally include patients after suicide attempts in the course of severe mental disorders which clearly differs from our NSSI cohort. Further, the number of borderline criteria were not significantly associated with immune markers, suggesting independence from a full diagnosis of BPD.

4.3. Group effect of the leukocyte/cortisol ratio and association with maltreatment

Exposure to stress due to aversive live events results in glucocorticoid receptor resistance that causes a failure to downregulate inflammatory response (Cohen et al., 2012). This finding links psychological trauma with immune system activation. NSSI is influenced by various stressors and is associated with increased prevalence for childhood maltreatment and an attenuated cortisol stress response (Kaess et al., 2021a, 2012). Indeed, maltreatment scores were significantly higher in our NSSI sample as compared to HC (Giinea et al., 2021). Thus, in the present study a higher leukocyte/cortisol ratio in NSSI may reflect an immune activation due to increased social stress and consecutively deregulated glucocorticoid metabolism as consequence of maltreatment. In support of the latter, our study shows that childhood maltreatment correlated positively with the leukocyte/cortisol ratio in adolescents. While the exact pathophysiological mechanisms have yet to be defined, trauma induces chronic immune activation that influences brain development and function (Danese and Lewis, 2017).

4.4. Association of inflammatory markers with depression

A well-replicated finding in depression in adults are increased proinflammatory cytokines, CRP and leukocyte levels (Miller and Raison, 2016). Immune activation affects neurotransmitters like dopamine, serotonin and may increase neurotoxic kynurenine pathway metabolites (Kindler et al., 2019), all of which are involved in the pathogenesis of depressive symptoms and suicidality (Brundin et al., 2017; Miller and Raison, 2016). Here, we found a significant correlation between depression scores and leukocytes and the leukocyte/cortisol ratio, which matches well with previous literature.

5. Limitation

Limitations of our study concern the restricted number of peripheral proinflammatory biomarkers analyzed, that however are comparable with previous studies (Keaton et al., 2019; Kraynak et al., 2019; Renna et al., 2021). Importantly, we have adjusted for smoking and BMI, both potential confounders of immunological markers (de Heredia et al., 2012; Koarai et al., 2012). Further, our sample consisted of young, physically healthy and exclusively female patients, reducing the influence of somatic disorders and sex hormones on immunological parameters. Larger longitudinal studies will have to clarify whether maltreatment and inflammation have a common pathway or independently influence suicidal behaviour.

6. Conclusion

Summing up, the findings of our study integrate well with a previously proposed model on the pathophysiology of suicidal behaviour (Courtet et al., 2016): Childhood maltreatment may cause chronic stress inducing an inflammatory cascade that deregulates the HPA axis leading to aberrations in neurotransmitters such as serotonin and consecutively depressive symptoms finally ending in NSSI and often subsequent suicidal behaviour. Inflammatory biomarkers such as the leukocyte/cortisol ratio might have the potential to predict suicidality.

Tables

Table 1

Sample characteristics

	NSSI (N = 155, 78.7%)		**HC (N = 42, 21.3%)**		**Total (N = 197, 100%)**		**Group comparisons**
Female (n; %)	155	100.00	42	100.00	197	100.00	-
Suicide attempt (past 12m) (n; %)	55	35.48	-	-	-	-	-
Age (m; sd)	14.98	1.50	14.74	1.21	14.9[illegible]	1.44	t(195) = 0.97, p = 0.3357
BMI (m; sd)	21.39	4.01	20.20	2.73	21.15	3.81	U = 2583.0, p = 0.1162
Smoking (m; sd)	1.59	1.93	0.33	0.8[illegible]	1.32	1.83	U = 2095.0, p = 0.0001*
Trauma (m; sd)	0.36	0.30	0.02	0.0[illegible]	0.28	0.30	U = 1027.5, p < 0.0001*
Depression (m; sd)	30.16	9.03	6.54	5.30	24.72	12.98	U = 133.0, p < 0.0001*
# BPD (m; sd)	3.50	2.01	0.07	0.34	2.77	2.28	U= 118.5, p < 0.0001*
Elevated inflammation score (n; %)	38	29.23	5	13.51	43	25.75	-
Leukocytes absolute [1/nl] (m; sd) (median; iqr) (skewness; kurtosis)	6.76 6.24 1.96	2.09 2.29 9.00	5.73 5.56 0.33	1.54 2.05 2.54	6.53 6.18 1.83	2.03 2.35 9.03	-
Leuk/Cort Ratio [ml/nl*ng] (m; sd) (median; iqr) (skewness; kurtosis)	0.05 0.04 3.23	0.03 0.02 19.43	0.04 0.03 1.61	0.01 0.01 5.64	0.05 0.04 3.44	0.03 0.02 22.07	-
CRP [mg/l] (m; sd) (median; iqr)	3.12 2.00	4.99 0.00	2.05 2.00	0.34 0.00	2.89 2.00	4.43 0.00	-

(skewness; kurtosis)	7.21	61.52	6.17	39.02	8.18	78.75	
IL-6 [pg/ml] (m; sd)	2.77	3.29	2.20	0.89	2.65	2.95	-
(median; iqr)	2.00	0.00	2.00	0.00	2.00	0.00	
(skewness; kurtosis)	6.95	58.93	5.41	31.51	7.70	72.74	

NSSI: Patients with non-suicidal self-injury, HC: healthy controls, inflammation score represents [(normalized Interleukin-6 + normalized C-reactive protein) + its minimum)], n: absolute numbers, %: percentage, m: mean, sd: standard deviation, iqr: interquartile range, age in years, BMI body mass index in kg/m², Smoking during last month: number of cigarettes categorized by [0 = "0 cigarettes", 1 = <1 cigarettes , 2 = "1-2 cigarettes" , 3 = "3-5 cigarettes" , 4 = "6-10 cigarettes", 5= "11-20 cigarettes", 6 = ">20 cigarettes"], Trauma (measured with Childhood Experiences of Care and Abuse questionnaire), Depression (measured with Depression Inventory for Children and Adolescents), # BPD number of borderline criteria. Leukocytes absolute in number per nanolitre (l/nl), Leukocyte/Cortisol ratio (Leuk/Cort ratio) in millilitre/nanolitre*nanogram (ml/nl*ng), CRP in milligram per litre (mg/l), Interleukin 6 (IL-6) in picogram per millilitre (pg/ml), Group comparisons: t-test or Mann-Whitney-U test. * significant at $p<0.05$, two sided.

Table 2

Group differences of inflammatory markers between HC and NSSI and correlations between inflammatory markers and trauma, depression or BPD criteria

A)	**Group difference (HC vs NSSI)**			**B)**	**Trauma**		**Depression**		**# BPD**	
	coef	t(df)	p-value		Part. Rank corr.	p-value	Part. Rank corr.	p-value	Part. Rank corr.	p-value
Leuko	-0.129	-2.48(176)	**0.014***		0.083	0.292	0.122	**0.022***	0.018	0.812
Leuko/Cort	-0.219	-2.36(170)	**0.019***		0.160	**0.047***	0.180	**0.026***	0.064	0.403

A) Group differences healthy controls (HC) vs patients with non-suicidal self-injury (NSSI): Negative coefficients (coef) indicate higher inflammation scores in NSSI. Leuko = absolute number of leukocytes. Leuko/Cort = leukocyte/cortisol ratio.

B) Partial correlations between inflammation markers and trauma score (Trauma), depression score (Depression) and number of borderline personality disorder criteria (# BPD). t test value, df degrees of freedom, * significant at $p<0.05$, two sided.

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Authorship contributor statement

Jochen Kindler analysed the data and wrote the manuscript, Stefan Lerch analysed the data, Julian Koenig and Franz Resch designed the study and revised the manuscript and Michael Kaess as principal investigator was responsible for funding and design of the study, was directing the analysis of data and drafting of the manuscript.

Declaration of interest

None of the authors have financial or personal relationships with other people or organizations that could influence their work.

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