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Impulsivity and Saliva Cortisol in Patients with Suicide Attempt and Controls

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Keywords

Suicidality · Suicide attempt · Impulsivity · Cortisol

Abstract

Objectives: The objective of this study was to prove concepts in the characterization of suicidal patients and the possible usefulness of those markers to potentially identify patients with a higher risk for suicidality. **Methods:** Patients with a recent suicide attempt were compared with patients suffering from depression, adjustment disorder, anxiety, or eating disorders without suicidality, healthy controls and remitted patients with a history of at least 1 suicide attempt (≥ 1 year). We analyzed impulsivity (Barratt Impulsivity Scale, BIS) and saliva cortisol concentrations. **Results:** Independently of suicidality and disease state patients display higher BIS scores than healthy controls. Saliva cortisol levels tend to be higher in patients in the acute disease state than in remitted patients and healthy controls. **Conclusions:** Saliva cortisol may be a useful marker that reveals alterations in nonsuicidal patients suffering from depression, adjustment disorder, anxiety, or eating disorders who might be at risk.

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Introduction

About a million people die by suicide every year. This is a “global” mortality rate of 16 per 100,000, or 1 death every 40 s [1]. The suicide rate has appeared to be remarkably stable at this high level worldwide since 1950 [2]; thus, suicide and nonfatal suicidal behavior remain significant public health issues. Prevention is an important strategy to limit the burden of this behavior, and the identification of potential risk factors (state and trait markers) is essential. Although suicidality is an individual problem caused by multiple factors, different personality traits and biological state markers are known to play a critical role in most suicidal patients. The tendency to impulsive behavior is an acknowledged and usually inherent risk factor for later suicidal behavior [3–10]. Cortisol, a highly relevant hormone for adapting to stressful life events, was also found to correlate with suicidality [11–15]. Płocka-Lewandowska et al. [16] investigated cortisol levels in schizophrenic patients at 2 different time points. They have shown that cortisol levels were significantly higher in patients with previous suicide at-

Table 1. In- and exclusion criteria

	Study No. 1	Study No. 2
Inclusion criteria	Suicide attempt ≥ 1 year ago Patients of both genders Age: 18–50 years	Suicide attempt within the last 3 weeks Patients of both genders Age: 18–75 years Patients with affective disorders (major depression, dysthymia, adjustment disorder) Drug-free for a minimum of 2 weeks prior to inclusion (5 weeks for fluoxetine and lithium)
Exclusion criteria	Organic brain diseases Schizophrenia or schizoaffective disorder Acute or chronic somatic conditions Currently depressive episode	Organic brain disease Schizophrenia or schizoaffective disorder Acute or chronic somatic conditions Pregnant or lactating

tempts, and baseline cortisol was higher in the patients who were to make a future attempt [16]. Researchers have reported lower cortisol levels in suicidal patients compared to controls [17], but a hyperactive hypothalamic-pituitary-adrenal (HPA) axis was generally associated with suicidality [18–21]. Van Heeringen et al. [22] revealed that elevated urine cortisol levels correlate significantly with a personality profile characterized by increased novelty seeking and impulsivity in violent suicidal behavior.

The aims of the present study were to analyze the trait-like personality characteristic impulsivity, and to measure the state-dependent biological marker saliva cortisol. Our analyses were done in patients with a recent suicide attempt compared to healthy controls, patients suffering from depression, adjustment disorder, anxiety or eating disorders without suicidality, and patients with a longer history of suicide attempt. The group of patients suffering from depression, adjustment disorder, anxiety, or eating disorders is named as psychiatric patients within the following paragraphs. Characterization of each group could help to delineate patients with a higher risk for suicidality. We assumed that patients with a recent suicide attempt would exhibit higher levels of impulsivity as well as changes in their diurnal cortisol secretion pattern than healthy controls. We were especially interested in detecting any differences between suicide attempters and nonsuicidal controls. This might hint at factors probably differentiating the 2 groups, with relevance for preventive strategies in the clinical context.

Material and Methods

Participants and Recruitment

Data from 2 separate studies were summarized for the purpose of this publication. The first study (No. 1) was carried out in conjunction with a local project (Dresden, Germany) investigating impulsivity, cognitive performance, and cortisol levels in suicide attempters. The second study (No. 2) was conducted within the “German Network on Depression and Suicidality,” which included the investigation of several neurobiological parameters and psychometric tests (for an overview, see Bronisch et al. [23]). Both studies were conducted in parallel at the same time and with identical means of assessing impulsivity and cortisol measurement. Both studies were approved by our local ethics committees. Patients were enrolled after having been admitted to the inpatient ward or after having been referred to the outpatient department. Healthy controls were recruited after responding to a call for study participation in a local bulletin. All patients and healthy controls gave their written consent to participate in the study. All patients and healthy controls were Caucasians of European descent. Diagnoses were based on the MINI (Mini-International Neuropsychiatric Interview) and ICD-10. All diagnostic and treatment information was reviewed by a panel of experienced psychiatrists. For inclusion and exclusion criteria, see Table 1.

Finally, these 2 studies led to 4 different but age- and gender-matched groups (later called groups 1, 2, 3, and 4), which were included in the present study’s analyses. For a detailed overview of these 4 groups, please see Table 2.

Assessment of Impulsivity

The focus of this study was the self-reported impulsivity measured in all groups via the Barratt Impulsivity Scale (BIS [24, 25]), a questionnaire to assess general impulsiveness. It consists of 30 items that consider the multifactorial nature of this behavior. The items are grouped in 6 first-order factors (attention, motor impulsiveness, self-control, cognitive complexity, perseverance, cognitive instability) and 3 second-order factors (attentional impulsiveness, motor impulsiveness, and nonplanning impulsiveness). Each item is scored on a 4-point scale (1: rarely/never; 2: occasionally;

Table 2. Group assignment, age, and diagnoses

	Study No. 1		Study No. 2	
	group 1: SA >1 year (1.4±0.8)	group 2: healthy controls	group 3: SA within the last 3 weeks (13.3 ± 8.5 days)	group 4: psychiatric controls (without SA)
Source of subjects	Impulsivity study Outpatient department Dresden (Germany)	Impulsivity study Local volunteers Dresden (Germany)	Neurobiology study Different German study centers	Neurobiology study Different German study centers
Patients, <i>n</i>	37	42	63	22
Sex	17 males 20 females	19 males 23 females	31 males 32 females	11 males 11 females
Mean age, years				
Males	36.47±7.15	36.44±8.01	39.51±15.59	41.45±12.94
Females	35.84±9.00	37.87±8.50	36.84±13.98	33.90±9.51
Medication	Medication allowed No medication: <i>n</i> = 11 SSRI ± BZ: <i>n</i> = 11 Tricyclic AD ± BZ: <i>n</i> = 4 Neuroleptics ± AD: <i>n</i> = 9 BZ: <i>n</i> = 2	No medication	Drug-free for a minimum of 2 weeks prior to study inclusion (fluoxetine and lithium: 5 weeks)	Drug-free for a minimum of 2 weeks prior to study inclusion (fluoxetine and lithium: 5 weeks)
<i>Diagnoses¹, n</i>				
Major depression	14 (7 male, 7 female)	No diagnoses	35 (15 male, 20 female)	12 (5 male, 7 female)
Dysthymia	0		2 (1 male, 1 female)	3 (3 male, 0 female)
Adjustment disorder	0		14 (8 male, 6 female)	4 (2 male, 2 female)
Agoraphobia	0		1 (0 male, 1 female)	0
Eating disorder	6 (0 male, 6 female)		0	0
PTSD	0		1 (0 male, 1 female)	0
Alcohol abuse	18 (8 male, 9 female)		0	0
Social phobia	0		2 (2 male, 0 female)	0
GAD	24 (7 male, 17 female)		0	1 (0 male, 1 female)

Results are expressed as numbers or as means ± SD. The table shows the main characteristics of each study group; SA, suicide attempt; SSRI, selective serotonin reuptake inhibitor; BZ, benzodiazepine; AD, antidepressant; PTSD, posttraumatic stress disorder; GAD, general anxiety disorder. ¹ Multiple diagnoses were allowed for each patient in groups 1, 3, and 4.

3: often; 4: almost always/always). The total score can be calculated using the different factors. In general, the higher the overall score, the more impulsive someone is.

Cortisol Sampling

Saliva was collected with a Salivette® (Sarstedt, Nümbrecht, Germany), and cortisol levels were determined using a commercial ELISA kit (IBL, Hamburg, Germany). All participants were instructed to insalivate a cotton roll for at least 2 min and to refrain from drinking, eating, smoking, or brushing teeth at least 60 min before sampling. The cotton roll was placed into a sterile plastic insert in a vial and stored at -20 °C until assessments. Saliva was collected as follows: patients from group 1 (suicide attempt ≥1 year) and 2 (healthy controls) were requested to collect saliva in the morning between 8:00 and 9:00 a.m. Group 3 (suicide attempt <3 weeks) and group 4 (psychiatric controls) had 2 collection

times: in the morning around 8 a.m. and in the evening at 7 p.m. Sampling the morning saliva took place at least 1 h after awaking. We did this to circumvent the cortisol-awakening response that takes place during the first 30–45 min after morning awakening [26]. Saliva sampling was not possible in some cases due to an acute psychiatric crisis or xerostomia. In other cases the collected saliva was insufficient for ELISA analysis.

Statistical Procedures

SPSS 23.0 for Windows (SPSS GmbH Software, Munich, Germany) was used for statistical analyses. ANOVAs were calculated, and in case of significance (*p* < 0.05) and whenever appropriate (homogeneity of variance is given), post hoc tests (Bonferroni) were applied. If the homogeneity of variance was not ensured, we carried out another post hoc test (Tamhane T2). The size of the samples available for data analysis varied.

Fig. 1. Overall BIS scores (mean $\pm$ SEM) to assess impulsivity in groups 1–4. SA, suicide attempt.

Fig. 2. Cortisol in morning saliva (mean $\pm$ SEM) in groups 1–4. SA, suicide attempt.

Fig. 3. Cortisol in saliva comparing groups 3 and 4. SA, suicide attempt.

Results

Impulsivity

We observed no significant gender differences in the overall BIS scores (σ 67.86 ± 1.48 ; η 67.12 ± 1.24 ; $F(1, 126) = 0.15$; $p = 0.70$). The BIS score differed significantly among all 4 groups ($F(3, 126) = 12.52$; $p = 0.00$) independently of the patients' gender ($F(3, 126) = 1.13$, $p = 0.338$). Healthy controls (group 2) displayed the lowest BIS scores (59.86 ± 1.59) of all groups. The healthy controls' BIS score was significantly lower than that of the psychiatric patients (69.57 ± 2.50 , $p = 0.006$), those with

a recent suicide attempt (73.73 ± 1.66), or with one more than a year ago (66.79 ± 1.69 , $p = 0.013$). Patients with a recent suicide attempt (<3 weeks) tended to display the highest BIS scores (73.73 ± 1.66), a factor also significantly different compared to patients whose history of suicide attempts was more than a year ago ($p = 0.033$). Figure 1 presents impulsivity within the 4 groups (means $\pm$ SEM).

Morning Cortisol Concentration

As presented in Figure 2 (means $\pm$ SEM) patients acutely suffering from a psychiatric disease (23.33 ± 6.53 ng/mL) or a recently attempted suicide (17.97 ± 3.46 ng/mL) have significantly different morning cortisol levels ($F(3, 118) = 2.85$, $p = 0.041$) than healthy controls (8.16 ± 3.43 ng/mL) and patients who had attempted suicide more than a year ago (7.81 ± 3.62 ng/mL). We were unable to statistically confirm these differences at the group level via pairwise comparisons due to the inhomogeneity of variance, especially in the females' data.

In general, females (19.77 ± 3.17 ng/mL) also differed significantly ($F(1, 118) = 5.98$, $p = 0.016$) from males (8.87 ± 3.13 ng/mL), an effect that interacts slightly with the group affiliation ($F(3, 118) = 2.54$; $p = 0.06$).

Diurnal Cortisol Rhythm

As shown in Figure 3 (means $\pm$ SEM) only complete data were included in our data analysis (that is, morning and evening cortisol levels available per patient). The time of the day significantly influenced ($F(1, 100) = 4.80$; $p = 0.031$) the cortisol levels in patients who had attempted suicide (group 3). Morning cortisol levels (13.80 ± 4.14

ng/mL) were significantly higher than the evening levels (4.05 ± 1.62 ng/mL). In patients acutely suffering from a psychiatric disease, morning (12.5 ± 7.39) and evening levels (12.36 ± 6.31) did not differ ($F(1, 36) = 0.000$; $p = 0.988$).

Discussion

Personality traits tend to be inherent, and they make attractive targets for suicidality research and the development of prevention strategies (for an overview, see Brezo et al. [27]). Impulsivity is a target known to be involved in suicidality. Psychiatric patients exhibit generally greater impulsivity than controls [28, 29], and impulsivity is considered as a trait that characterizes individuals at high risk for suicide attempts regardless of the psychiatric diagnosis [30].

We detected the lowest overall impulsivity levels in our healthy controls. All our patients, independently of acute illness, remission phase, with or without acute suicidality, displayed significantly higher overall impulsivity (BIS score). This fact associates impulsivity with psychiatric illness independently of the acute disease state and therefore reinforces high impulsivity as personal characteristic (trait marker) in psychiatric patients [28, 29]. We identified the highest impulsivity in patients who had attempted suicide (in most cases, several days before study inclusion); a significant difference from the psychiatric patients in remission and from those whose suicide attempt had taken place at least a year ago. We conclude that besides generally higher impulsivity in psychiatric patients, there must be other internal or environmental factors that enhance self-rated impulsivity and are associated with an acute suicidal act. Impulsivity is therefore a key personality trait for diagnostic purposes, as well as a probable target for psychotherapy in the prevention of further suicide attempts.

Although very useful, appraising complex personality traits such as self-rated impulsivity is a complex and demanding endeavor requiring personal resources and time. Moreover, it cannot be generally applied to every patient. Markers that are obtainable rapidly and easily are also needed. Measuring cortisol in saliva is just such a comparatively easy method. Cortisol is a steroid hormone whose saliva concentration reflects precisely the concentration of free cortisol in plasma [31–34]. Its production in the adrenal cortex and its diurnal secretion are rhythmic and controlled by the pituitary gland. Morning levels tend to be higher than evening levels [35]. Cortisol secre-

tion peaks within the first 45 min after awakening and then fall slightly during the day [26]. We found marked group differences in morning plateau cortisol levels. We observed a general trend toward higher cortisol levels in acute psychiatric patients regardless of whether they were suicidal or not, although the variance was high and mainly caused by the patient's sex. The females in particular displayed higher cortisol levels than the men in these 2 groups (3 and 4). There is evidence that cortisol concentrations are influenced by the menstrual cycle and that cortisol responsiveness following a psychosocial stressor is significantly higher during the follicular phase [36]. Since we had not considered the menstrual cycle, we can only speculate that that phase might also have influenced the cortisol level in the female patients in acute stress from their disease and previous suicide attempt. In general, stress per se is a crucial generating factor in major depression [37], and most of the patients we analyzed suffer from acute major depression. Thus, the higher cortisol levels we observed are perhaps more likely associated with an altered stress-regulating system, i.e., the HPA axis, with concomitant higher basal cortisol levels or greater stress sensitivity. It is also discussed that different types of depression have different effects on the HPA system. A study by Lamers et al. [38] investigated whether biological parameters such as cortisol may be influenced by the subtype of depression. They found a lower cortisol and lower diurnal cortisol slope in atypical depression compared with melancholic depression. They indicated that atypical depression is a distinct phenomenon.

Medication prior to study inclusion was very limited; in particular, selective serotonin reuptake inhibitors that indirectly regulate the HPA axis [39] were not allowed. We can effectively rule out the possibility that the different cortisol levels in psychiatric patients with or without suicidality compared to healthy controls and remitted patients were influenced by medication.

We also analyzed the cortisol day profile in acute psychiatric patients with or without a suicide attempt to more specifically characterize these groups and elucidate a marker that might differentiate these two groups. We detected a consistent cortisol profile, that is, high morning cortisol levels and low ones in the evening, in acute psychiatric patients who had attempted suicide within the 3 weeks before study inclusion. In contrast, cortisol levels were diminished in the acute psychiatric patients. We assume that patients with a suicide attempt within 3 weeks prior to the cortisol measurement were still in acute stress, and some of them may still be at risk to attempt suicide. The sensitivity of the HPA stress response system may be

particularly compromised in individuals who have made a recent suicide attempt. This was also shown in a study by O'Connor et al. [40] who investigated 3 different groups: individuals who had previously made a suicide attempt, individuals who had thought about suicide (suicide ideators), and control participants. They measured cortisol levels throughout participants who completed the Maastricht Acute Stress Test. Participants who had made a previous suicide attempt exhibited significantly lower aggregate cortisol levels during the Maastricht Acute Stress Test compared to participants in the control group; suicide ideators were intermediate to both groups.

Limitations

The present study has methodological strengths and shortcomings. Investigations in the field of suicidality are rare, and the availability of patient data shortly after a suicide attempt is the exception rather than the rule. It is the strength of this study that we had access to a nearly homogeneous pool of patients regarding their main diagnoses (major depression). On the other hand, one group consisted of patients with other diagnoses such as alcohol abuse or eating disorders; thus, we could not exclude influences on the HPA system and therefore limits of our findings.

Medications were extremely limited, thus, our results were not skewed. The percentages of males and females were nearly equal; however, the menstrual phase in women should be incorporated in future studies. We were able to recruit a sufficient number of study subjects; however, the patients' data were not always complete for different reasons.

The absence of a cortisol profile for all 4 groups is another limitation. Groups 1 and 2 had only a cortisol measurement in the morning whereas groups 3 and 4 had 2 sampling times.

Saliva sampling was not always possible (or the attempt failed) because of xerostomia, for instance. Cortisol levels are also affected by smoking [41–43]. We did not take smoking habits into account in this study, but it should be in future studies. Finally, whether suicidality, impulsivity, depression, and others are useful tools to classify patients in neurobiological research remains to be proven.

Conclusion

In summary, psychiatric patients are characterized by high impulsivity, especially those who had attempted suicide shortly before study inclusion. Saliva cortisol con-

centrations tend to be higher only in those psychiatric patients acutely suffering from affective disorders (depression and adjustment). The diurnal cortisol profile is striking in patients who are acutely ill but without suicidality. Our data lead us to suggest that high impulsivity is a characteristic personality trait marker in psychiatric patients even after remission. Saliva cortisol levels are easy to obtain and suitable to differentiate patients in an acute psychiatric crisis. Further investigation is needed to reveal those patients within this patient group who are at particular risk for a suicide attempt, and we recommend analysis of the diurnal saliva cortisol profile as a worthwhile parameter.

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Disclosure Statement

The authors have no competing interests to declare.

Author Contributions

U.L. carried out the research and prepared the manuscript. L.G. contributed significantly to the acquisition of data, did the data analysis, and was substantially involved in writing the manuscript. B.R. contributed significantly to the acquisition of data and provided guidance on the analysis. M.B. helped to draft the manuscript. T.B. made a substantial contribution to the study's conception and design, and was involved in drafting the manuscript and revising it critically for important intellectual and statistical content. All authors read and approved the final manuscript.

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