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Fingernail Cortisol: A Biological Signal of Lifetime Major Depressive Disorder

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Abstract

Introduction: Elevated levels of the hypothalamic-pituitary-adrenal axis hormone cortisol are a frequently replicated finding in major depressive disorder (MDD). However, the current state of research is inconclusive as to whether hypercortisolism represents a trait- or state-like biological signal of MDD. The aim of the present study was to investigate, for the first time, whether cortisol in fingernails, a highly accessible tissue, could distinguish currently remitted individuals with MDD from healthy controls. A further aim was to identify potential confounders of nail cortisol. ***Methods:*** A total of $N = 100$ individuals from the general population were recruited. A structured clinical interview was administered, which resulted in two groups: $n = 48$ with lifetime MDD and $n = 52$ healthy controls. All participants answered questions on sociodemographic, lifestyle, and psychosocial characteristics. They also grew their nails for 14 days and cut them for the subsequent determination of cortisol. ***Results:*** The groups differed in their nail cortisol concentrations, such that the individuals with lifetime MDD had significantly higher concentrations than the healthy controls ($p = 0.041$). Within the group of individuals with lifetime MDD, the number of experienced episodes was significantly correlated with cortisol ($p = 0.011$). Income emerged as the only significant confounder of cortisol ($p = 0.008$). ***Conclusion:*** Elevated fingernail cortisol appears to be a biological signal of MDD, even in the absence of a current major depressive episode. Its high accessibility and robustness render it a promising methodology for remote research as well as for the integration of biomarkers into clinical research and practice.

Introduction

One of the most frequently replicated biological findings in major depressive disorder (MDD) is elevated levels of the hypothalamic-pituitary-adrenal axis end product cortisol [1]. The presence of hypercortisolism has been found to predict non-responses to psychotherapy [2] and – to some extent – pharmacotherapy [3]. However, whether hypercortisolism is involved in the aetiopathogenesis of MDD or a mere epiphenomenon of stress associated with being chronically ill remains unclear. Indeed, a recent meta-analysis of prospective studies has reported mixed evidence for cortisol as a risk factor for the onset or relapse/recurrence of MDD, with high heterogeneity across studies detected [4].

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One explanation for these discrepant findings may be that all included studies determined cortisol in blood, urine, or saliva. These methodologies, while offering many advantages, also present certain methodological difficulties. The most important drawbacks include invasiveness for blood draws, which may cause anxiety [5], as well as single-time point sampling and/or a lack of adherence to repeated sampling schedules, which make for unreliable estimates of cortisol. In order to address these shortcomings, novel markers of the hypothalamic-pituitary-adrenal axis have been introduced in the past two decades. The most popular alternative to date is hair cortisol, which allows for a retrospective assessment of cumulative cortisol from weeks up to several months [6]. However, one problem inherent in this methodology is that a large proportion of study participants are unable or unwilling to provide hair, e.g., due to insufficient hair or for cultural or aesthetic reasons (e.g., [7, 8]).

It is for this reason that, more recently, fingernail cortisol has attracted the interest of psychoneuroendocrinological researchers [9, 10]. Similar to hair cortisol, cortisol is incorporated into the fingernail plate via passive diffusion from capillary blood [9, 10]. This most likely occurs during keratinisation, and in the nail matrix [9, 10]. Fingernail cortisol bears the advantage of a retrospective assessment of cortisol and is robust against a number of state-like confounders (e.g., time of day). To date, little is known about potential trait-like confounders of fingernail cortisol, and only a handful of studies have investigated it in clinical populations. One study examined fingernail cortisol in individuals with unipolar or bipolar depression [11]. The authors found evidence for elevated cortisol levels in individuals with a current major depressive episode as compared to healthy controls. Interestingly, a second study by the same authors found that, in individuals with bipolar I disorder, elevated levels of nail cortisol were present even in the euthymic state [12]. These findings raise the question of whether elevated fingernail cortisol could also be a biological signal of MDD, even in the absence of a current major depressive episode.

The aim of the present study was thus to examine whether fingernail cortisol, a recently introduced, non-invasive marker of cumulative cortisol, could be used to distinguish individuals with lifetime MDD from healthy controls. As such, the study is only the third investigating fingernail cortisol in affective disorders, the first investigating it in an exclusive MDD sample, and the first to investigate it in the context of lifetime MDD. Based on the literature, it was hypothesised that fingernail cortisol would be elevated in currently remitted individuals with a lifetime MDD as compared to healthy controls. Given the relatively recent introduction of fingernail cortisol, a further aim was to identify potential sociodemographic, lifestyle, nail care, and psychosocial confounders.

Methods

Participants

Online advertisements for a study on stress and depression were posted on the website of the Freie Universität Berlin and on social media. Furthermore, study flyers were distributed across university campuses and supermarkets. Exclusion criteria were left-handedness, pregnancy or breastfeeding, a current major depressive episode, physical illnesses, intake of medication, and recreational drug use within the last 6 months, as we wanted to eliminate any major confounding influences of these variables on fingernail cortisol concentrations. Moreover, the participants were required not to have changed their smoking habits or any intake of hormonal contraceptives within the last 6 months. Applying these eligibility criteria resulted in a sample of $N = 100$ individuals. The study protocol was approved by the ethics committee of the Freie Universität Berlin.

Procedures

After completion of a preliminary online screening, which assessed the presence of childhood trauma ([13]; see also below), an appointment for a telephone interview was scheduled. During this interview, eligibility was assessed, and the participants received further information about the study purpose and procedures. Concretely, they received instructions to cut their nails and to regrow them for 14 days, until a subsequent in-person study appointment. During the in-person study appointment, the participants were interviewed by means of the Structured Clinical Interview for DSM-5 (SCID-5-CV; [14]), to assess the presence of lifetime MDD. The participants then filled out additional questionnaires and were instructed to once again cut their fingernails (see below). The appointment was conducted on the premises of the Freie Universität Berlin until February 2020. Due to the COVID-19 pandemic, all following appointments were conducted remotely, via telephone.

Questionnaires

Information on depression severity was collected by means of the depression module of the Patient Health Questionnaire, and validated cut-off scores were used to ensure that none of the participants had a current major depressive episode (PHQ-9; [15]). Sociodemographic, lifestyle, and nail care information was collected via standardised forms. This included data on age, sex, household income (six categories from below 1,000 EUR to over 3,000 EUR), BMI, smoking, use of hormonal contraceptives, daily handwashing frequency, and use of nail varnish. Regarding psychosocial variables, critical life events in the past 6 months were assessed by means of the Life Experiences Survey (LES; [16]), and childhood trauma was assessed by the short form of the Childhood Trauma Questionnaire (CTQ; [17]). Chronic stress was assessed regarding the 4–7 month period before the in-person study appointment and by the screening

version of the Trier Inventory for the Assessment of Chronic Stress (SSCS; [18]). This was done to capture the period presumably reflected in the sampled fingernails.

Fingernail Cortisol

After having cut and regrown their nails for 14 days (see above), the participants were instructed to once again cut the nail of all ten digits as short as possible. These samples were subsequently inserted in zipper bags and stored at room temperature and protected from sunlight until shipment to the biochemical laboratory of the Institute of Psychology at the University of Zurich. For cortisol extraction, the nail clippings were put in 15-mL falcon tubes, washed with 2.5 mL isopropanol, and dried overnight. Subsequently, the samples were weighed and ground, and 10 mg of the powder was mixed with 1,800 μL of methanol and incubated overnight. The samples were then centrifuged, and 1,000 μL of the extract was evaporated with nitrogen. Lastly, 400 μL of phosphate buffer was added to the residue, and 50 μL of the sample was analysed using luminescence assays (IBL, Hamburg, Germany).

Statistical Analyses

All data were visually inspected, and $n = 2$ outliers (one in each group) above three standard deviations were removed. This resulted in a final sample size of $N = 98$ participants. Data were then tested for normal distribution using the Kolmogorov-Smirnov test. As a result of this, nail cortisol concentrations were log-transformed. The two groups were first compared regarding sociodemographic, lifestyle, nail care, and psychosocial variables using Mann-Whitney and χ^2 tests. Next, correlations between the same variables and nail cortisol were calculated using Spearman's rank correlations. Finally, a univariate ANCOVA was conducted to compare the two groups with respect to their nail cortisol concentrations, with age, sex, and any other potentially relevant confounders of fingernail cortisol included as covariates. The statistical significance was set at $\alpha = 0.05$. All analyses were conducted in SPSS 25.

Results

Participant Characteristics

The median age of the $N = 98$ participants was 27.5 (interquartile range, IQR: 9.3), and 81% of the sample identified as women (see also Table 1). Approximately two thirds of the sample had a household income of less than 2,000 EUR per month. The median BMI was 22.3 (4.3), 20% of the sample were smokers, and 18% used hormonal contraception. The median handwashing frequency per day was 7 (5), and 30% of the sample used nail varnish. The mean number of life events in the past 6 months was 4 (4), the mean level of chronic stress during the 3-month period was 14.5 (16.5), and the mean level of childhood trauma as assessed was 36 (14).

The two groups did not differ regarding their age, sex, income, BMI, smoking status, intake of hormonal contraceptives, handwashing frequency, or use of nail varnish (all $p > 0.110$). However, individuals with lifetime MDD had a higher current depression severity (U = 1,684.5, $p < 0.001$), reported more critical life events (U = 1,546, $p = 0.013$), had higher levels of chronic stress (U = 1,643.5, $p = 0.002$), and higher levels of childhood trauma (U = 1,569, $p = 0.008$).

Nail Cortisol Concentrations

Fingernail cortisol was not found to be related to any of the lifestyle, nail care, or psychosocial characteristics (all $p > 0.100$). Among the sociodemographic characteristics, the only significant confounder of fingernail was household income ($r_s = 0.27$, $p = 0.008$). The subsequent analysis was thus controlled for income.

As evident from Figure 1, the two groups significantly differed in fingernail cortisol, such that individuals with lifetime MDD had higher concentrations than healthy controls (1.42 [1.33] vs. 1.19 [0.94]; F [1, 93] = 4.297, $p = 0.041$, partial eta$^2 = 0.044$). Moreover, within the group of individuals with lifetime MDD, the number of past major depressive episodes was significantly associated with fingernail cortisol concentrations ($r_s = -0.37$, $p = 0.011$).

Discussion

The main aim of this study was to investigate whether elevated fingernail cortisol is a biological signal of lifetime MDD. Given the recent introduction of this methodology, a second aim was to identify potential sociodemographic, lifestyle, and psychosocial confounders of fingernail cortisol. We found significantly enhanced fingernail cortisol concentrations in individuals with lifetime MDD in comparison to healthy controls. Income emerged as the only significant determinant of fingernail cortisol.

The main finding of the present study is in line with an extensive literature attesting to elevated HPA axis activity in MDD [1]. It adds to previous research investigating salivary cortisol in currently unmedicated individuals with lifetime MDD [19–21], which also suggests that increased cortisol may be a trait rather than a state-like marker of MDD. It complements previous studies, which have attempted to establish cortisol as a predictor of the onset and progression of MDD [4]. It aligns well with a previous study in individuals with bipolar I disorder, which also found that cortisol was elevated even in the absence of a current major depressive episode [12]. Interestingly, within the group of individuals with

Table 1. Sociodemographic, lifestyle, nail care, and psychosocial characteristics of individuals with lifetime MDD (n = 47) and healthy controls (n = 51)

	MDD	Healthy controls
Age, years	27 (8)	28 (11)
Sex (female), *n* (%)	41 (87)	38 (75)
Household income, *n* (%)		
Below 1,000 EUR	21 (45)	18 (35)
1,000 EUR to 1,500 EUR	10 (21)	15 (29)
1,500 EUR to 2,000 EUR	6 (13)	9 (18)
2,000 EUR to 2,500 EUR	6 (13)	3 (6)
2,500 EUR to 3,000 EUR	1 (2)	0 (0)
Over 3,000 EUR	3 (6)	6 (12)
Body mass index, kg/m^2	22.3 (4.9)	22.5 (4.3)
Smoking (yes), *n* (%)	8 (17)	12 (24)
Hormonal contraceptives (yes), *n* (%)	6 (13)	12 (24)
Handwashing frequency (per day)	6 (5)	7 (6)
Nail varnish (yes), *n* (%)	16 (34)	13 (26)
Depression severity (PHQ-9)[a]	6 (5)	3 (3)
Life events (past 6 months; LES)[b]	5 (6)	3 (4)
Chronic stress (3 months; SSCS)[c]	19 (17)	12 (14)
Childhood trauma (CTQ)[d]	39 (17)	34 (11)

PHQ-9, depression module of the Patient Health Questionnaire (9 items rated by frequency of occurrence; theoretical score range from 0 to 27). LES, Life Experiences Survey (42 items rated by occurrence, theoretical score range from 0 to 42). SSCS, screening scale of the Trier Inventory for the Assessment of Chronic Stress (12 items rated by frequency of occurrence; theoretical score range from 0 to 48). CTQ, Childhood Trauma Questionnaire (25 items rated by frequency of occurrence; theoretical score range from 25 to 125). Medians and interquartile ranges and absolute and relative frequencies are presented. Group comparisons were conducted using Mann-Whitney and χ^2 tests. [a]Individuals with lifetime MDD had significantly higher levels of depression than healthy controls ($p < 0.001$). [b]Individuals with lifetime MDD had significantly more critical life events than healthy controls ($p = 0.013$). [c]Individuals with lifetime MDD had significantly higher levels of chronic stress than healthy controls ($p = 0.002$). [d]Individuals with lifetime MDD had significantly higher levels of childhood trauma than healthy controls ($p = 0.008$).

lifetime MDD, the number of major depressive episodes was negatively associated with fingernail cortisol levels. One potential explanation for this seemingly contradictory finding is the notion of cortisol *increasing* in the initial stages of chronic stress but *decreasing* to below the statistical average as stress levels persist [22], which could be the case in MDD with several recurring episodes. The fact that this was a relatively young sample fits in well with this notion, but prospective research is warranted to confirm this hypothesis.

Our study presents a number of strengths. It adds to the small literature on fingernail cortisol and is the first study to investigate this novel marker in the context of lifetime MDD. Second, our participants were physically healthy and free of any medication, hence enhancing the reliability of our biological measurements. Third, and related to this, our sample was large enough to investigate and control for a number of potentially important confounders of fingernail cortisol. However, a number of limitations also deserve mention.

Limitations

First, the high proportion of women in the present sample somewhat limits the generalisability of our findings to men. However, women are more frequently affected by MDD, and, as such, the sample is reflective of this clinical population. Second, previous episodes of MDD were assessed retrospectively, which could have introduced memory bias. Further, prospective research relying on robust markers of cortisol is warranted to further investigate its aetiopathogenetic role in MDD. Third, research on fingernail cortisol is still in its infancy [9, 10]. Although, as shown in the present study, it appears to be fairly robust against the influence of

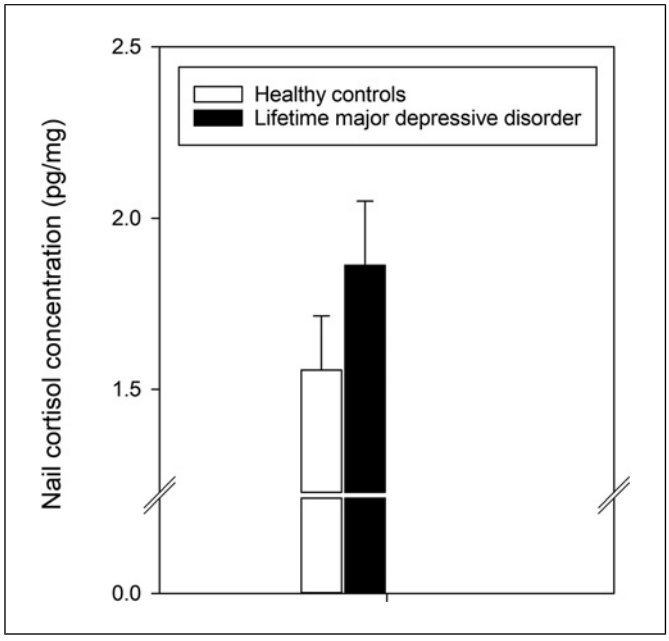

Fig. 1. Fingernail cortisol concentrations in individuals with lifetime major depressive disorder (MDD) (n = 47) and healthy controls (n = 51). Lifetime MDD was assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID-5-CV). Bars represent mean values and standard errors. A group comparison indicated a significant difference (p = 0.041).

state- and trait-like confounders, the route by which cortisol is incorporated into the nail tissue remains unclear. Again, prospective studies mapping psychological states onto repeated measures of nail cortisol while adjusting for individual growth rates will be crucial in further establishing this biological hypothalamic-pituitary-adrenal axis marker. Finally, chronic stress was assessed retrospectively in the present study, which could explain why there was no association with fingernail cortisol concentrations. Researchers specifically interested in whether fingernail cortisol may be a potential marker of chronic stress are advised to employ prospective study designs with time-lagged assessments of stress and fingernail cortisol to answer this research question.

Conclusion

In sum, this study provides initial evidence for elevated concentrations of fingernail cortisol as a biological signal of lifetime MDD. Given that there is preliminary evidence for cortisol levels to decrease as a result of psychotherapy [23, 24], it would be highly interesting for future studies to compare and contrast individuals with lifetime MDD with versus without a history of psychotherapeutic treatment and to find out whether the extent of cortisol "normalisation" during treatment might protect against future major depressive episodes. The study also shows that fingernail cortisol is not only robust against the influence of state-like confounders (e.g., time of day, day of the week), but also appears unchanged in relation to age, sex, smoking, or nail treatments. The abundant availability of nail tissue, which allows for sampling in diverse populations (e.g., very young/older individuals, individuals of different cultural backgrounds), highlights its promise as a vehicle for researchers interested in collecting information on the pathophysiology of stress-related disorders, including MDD.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Freie Universität Berlin (016/2019). Written informed consent was obtained from all participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.S. and S.F. conceived the study. S.L. acquired the data. S.F. analysed and interpreted the data. S.S., S.L., and S.F. drafted the article and revised it critically for important intellectual content. All authors approved the final version of the article.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author.

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