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Diurnal Profiles of the Endocrine Stress Response in Internet Gaming Disorder

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Stress · Hypothalamus-pituitary-adrenal axis · Cortisol · Amylase · Internet gaming disorder

Abstract
Background: Differences in subjective stress perception and acute response of the hypothalamic-pituitary-adrenal axis have been reported in internet gaming disorder (IGD). The present study aimed to further investigate alterations in diurnal profiles of the endocrine stress response system in IGD compared to healthy controls (HCs). ***Methods:*** The diurnal course of endocrine markers (salivary cortisol and α-amylase) was investigated in a clinical sample of $n = 29$ adolescents with IGD compared to $n = 26$ HC. Further, the effect of unrestricted gaming versus restricted gaming was examined within the IGD group. ***Results:*** No significant differences in salivary cortisol and α-amylase were observed comparing adolescents with IGD and HC. In addition, in the IGD group, there were no significant differences in salivary cortisol and α-amylase between conditions of unrestricted gaming versus restricted gaming. Compared to the HC group, the IGD group showed a significantly higher body mass index. ***Conclusions:*** Our results indicate no alteration in diurnal profiles of the endocrine stress response in IGD.

Introduction

Internet gaming disorder (IGD) shows an estimated prevalence of around 3%–10%, with 2.5-fold higher incidence in men than in women [1, 2]. IGD is associated with elevated subjective stress levels [3], while already a 2-week abstinence from gaming has been shown to reduce the experience of daily stress and IGD symptoms [4]. Theoretical models concerning the development of IGD suggest that predisposing variables, as a reduced inhibitory control and a greater vulnerability to stress, increase the probability of engaging in gaming as a dysfunctional strategy to reduce acute stress [5–7]. However, data

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regarding the neurobiological mechanisms of stress regulation in IGD are scarce [8].

Cortisol and α-amylase are endocrine markers of the two major stress systems: the hypothalamic-pituitary-adrenal (HPA) axis and the autonomous nervous system (ANS) [9–11]. Both hormones demonstrate circadian fluctuations and can be measured in saliva [9]. The diurnal profile of salivary cortisol is characterized by the cortisol awakening response (CAR), which refers to the typical production of cortisol that occurs upon awakening, followed by the diurnal slope, showing a decrease of cortisol throughout the day. Both higher and lower CAR have been associated with stress and poorer mental health outcomes, as well as a flatter diurnal slope [10]. On the other hand, salivary α-amylase levels decrease within the first hour after awakening and then steadily rise during the day, with higher levels associated to chronic stress and greater stress reactivity [9, 12]. Based on current research, no significant sex differences have been consistently observed in the diurnal patterns or acute stress responses of salivary α-amylase [9, 13]. In contrast, sex differences have been documented in the salivary cortisol responses to acute stress [13–15]. Furthermore, in adults, but not in adolescents, the menstrual cycle phase and contraceptive use seem to influence the cortisol response to awakening, social stress and physiological stress [14–16].

Due to the belief that those hormonal differences would make the results incomparable, for decades often only men were included in research. Although it is now understood that both sexes should be included in to provide a comprehensive understanding of physiological responses, in our study we focused only on males due to gender differences in IGD, especially regarding the higher prevalence of IGD compared to females [1, 2, 17].

Recently, we examined the psychological and neurobiological responses to acute stress in young men with IGD, showing no differences in baseline hair cortisol, but a blunted salivary cortisol response to acute stress compared to a group of healthy controls (HCs) [3]. These results suggest that a hyporesponsiveness of the HPA axis to acute stress may be associated with IGD [3, 18]. Similar results were shown in a study that also analyzed salivary α-amylase: participants with internet addiction showed a reduced salivary cortisol response to stress, but no alterations in salivary α-amylase were found [19]. In contrast, another study investigating stress reactivity in problematic internet use did not find a blunted salivary cortisol response to acute stress [20]. Although there is little evidence to date if changes in salivary α-amylase are present in IGD, elevated levels of salivary α-amylase have been observed in various populations experiencing high psychological stress levels, highlighting the relationship between perceived stress and ANS activation [12, 21–23]. Furthermore, some studies found differences in the heart rate variability in IGD, which also indicates a change in the ANS response [24, 25].

To our knowledge, the diurnal profiles of the salivary cortisol and α-amylase and the ANS in IGD have not yet been investigated, nor whether those are influenced by the daily gaming time. As the relationship between gaming time and disordered gaming is complex and varying with different diagnostic criteria [26], analyzing the variance of hormonal patterns might help identify thresholds where gaming becomes problematic. Therefore, with the current study, we hope to contribute to a better understanding of the neurobiological mechanisms involved in IGD by investigating whether (i) alterations in diurnal profiles of salivary cortisol and α-amylase are associated with IGD (cross-sectional case-control design); and (ii) whether 1 week of restricted gaming is associated with changes in endocrine profiles compared to unrestricted gaming periods (longitudinal design). We expected higher CAR, flatter salivary cortisol diurnal profile, and higher total salivary α-amylase for the IGD group compared to the HC group. Effects of gaming conditions on endocrine profiles were subject to an exploratory analysis with no a-priori hypothesis concerning the direction of effects.

Methods

Participants

Participants from 15 to 25 years were recruited from the general population of the canton of Bern via public advertisements. In addition, IGD subjects were recruited from the University Hospital of Child and Adolescent Psychiatry and Psychotherapy, Bern. Potential participants were informed about the study and screened for inclusion and exclusion criteria via phone. Due to the greater prevalence of IGD among male youth [1, 17] only male subjects were included. Exclusion criteria were any substance use disorder (excluding nicotine), medication intake affecting the HPA axis, chronic somatic illness, schizophrenia, bipolar affective disorder, and magnetic resonance imaging contraindications since an additional part of the study also included an magnetic resonance imaging scan (not reported here). Other psychiatric comorbid disorders such as, e.g., anxiety,

depression and attention deficit hyperactivity disorder are very common in IGD [27, 28] and were thus not considered as exclusion criteria for the IGD group but for the HC group. Additional exclusion criteria for the HC group were higher online gaming time than the Swiss average (1.5 h/day during the week; 2 h/day on weekends) [29] or more than one IGD criteria according to the research diagnosis of the DSM-5 [30]. The IGD and HC groups were matched for age, smoking status, educational level, and handedness (right, left).

Procedure

Following the diagnostic assessments, participants were instructed to take saliva samples at home from Friday to Sunday, from which cortisol and α-amylase were analyzed. Additionally, participants were asked to respond to daily questions (i.e., ecological momentary assessment; EMA) on a study smartphone (MovisensXS app, Movisens GmbH, Karlsruhe, Germany). After a baseline week (enabling the cross-sectional comparisons of the IGD and the HC group), the IGD group was followed for two more weeks. Participants were instructed to game without restriction for 1 week and to remain as abstinent as possible for the other week. The order of gaming conditions was randomized between participants.

Instruments

Diagnostic Instruments

Basic variables that may influence HPA axis functioning, such as height, weight, regular use of medication, smoking behavior and substance use were obtained. The criteria for the DSM-5 research diagnosis IGD were assessed using a structured clinical interview (DSM-5; [30]). To fulfill diagnostic criteria for IGD, five out of the following nine symptoms need to be fulfilled within the last 12 months: preoccupation, withdrawal, tolerance, unsuccessful control, loss of interest, continuation despite problems, deception, escape negative feelings, and risk opportunities [30]. Additionally the German version of the Video Game Dependency Scale was used (Computerspielabhängigkeitsskala; CSAS; [31]). The CSAS is an 18-item self-report questionnaire with two questions for each of the DSM-5 criteria. Answers are rated on a four-point Likert scale, where a sum of more than 16 points is above average (>89 percentile) and thus indicative for an IGD diagnosis [31]. Comorbid psychiatric disorders were assessed using the Mini-International Neuropsychiatric Interview (MINI; [32]). For participants from 15 to 17 years the adjusted Interview for Children and Adolescents was used (MINI-KID; [33]).

Biological Measures

Saliva samples were collected immediately after awakening (t0), after 10 (t1), 20 (t2), 30 (t3) and 60 (t4) minutes and before bedtime (t5). Participants were instructed not to eat, drink, or brush their teeth 1 h prior to sampling. To record the exact time of sampling participants confirmed each sample via a study smartphone, started a timer during sample taking (60 s) and scanned a barcode on the salivette. After the first measurement in the morning, participants were automatically reminded at the time of t1-t4 to take another saliva sample through a push message on the study smartphone. Participants stored the samples in the refrigerator at home and brought them to the next appointment, where they were frozen and stored at −20°C until further processing and analysis. After thawing, the salivettes were centrifuged at 3,000 rpm for 5 min. Biochemical assays for the analyses of saliva were performed at the laboratory of the Technical University of Dresden, Germany using chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients were below 10%.

Ecological Momentary Assessment

Study participants reported their online gaming time via EMA on the study smartphone. On weekdays, when registering their wake-up and bedtime, participants were asked how long they had played online games since the last survey (answers in hours and minutes). At weekends, the online gaming time was additionally assessed every hour during the day. In the morning participants also rated their sleep quality. Sleep quality was assessed by four questions with answers on a visual analogue scale (0–100), based on the Jenkins Sleep Scale [34]. Questions covered whether last night participants (1) had difficulties to fall asleep, (2) woke up during the night, (3) had problems getting back to sleep, and (4) felt tired/exhausted after waking up.

Actigraphy

Wake-up times were additionally controlled in $n = 35$ participants via an actigraphy device (IGD: $n = 20$ and HC: $n = 15$ HC). For all other participants, wake-up time was verified by a call at the previously fixed wake-up time.

Statistical Analysis

All analyses were performed with the statistical software STATA 17.0 with the significance level set to $\alpha = 0.05$. A power analysis was performed with G-Power 3.0.10 which resulted in a minimum sample size of $n = 25$ per group ($\alpha = 0.05$, power = 0.8).

Cross-Sectional

To test for differences in salivary cortisol and α-amylase between IGD and HC, we applied mixed-effects linear regressions with salivary cortisol and α-amylase as outcome variables and group as a predictor. The hypothesis was tested by calculating the contrast between the two groups. Data were grouped by ID, allowing a random intercept. Eight models with different outcomes were calculated as salivary cortisol and α-amylase can be operationalized in different ways: 1: CAR calculated as area under the curve (AUC) with respect to increase (cortisol at t0; AUCi); 2: CAR calculated as AUC with respect to ground (AUCg); 3: cortisol diurnal slope; 4: cortisol t0 (wake-up level); 5: overall cortisol; 6: α-amylase diurnal slope; 7: α-amylase t0 (wake-up level); 8: overall α-amylase.

For the AUC (model 1 and 2) the salivary cortisol measurements from t0 to t4 were used. The measurements at t4 were linearly interpolated to 60 min using the measurements at t3 and t4. In case of time deviation (>5 min for t1-t3, >15 min for t4), samples were excluded. The diurnal slope (model 3 and 6) was defined as the level at t0 minus level at t5 divided by the time between t0 and t5. In case of missing measurements, the diurnal slope and AUC were not computed. The wake-up level t0 (model 4 and 7) includes the log-transformed measurements at t0. For models 5 and 8, all log-transformed measurements t0-t5 were entered into the model.

All models were controlled for body mass index (BMI), age, smoking (number of cigarettes smoked in the past 30 days), sleep quality (sum score of the visual analog scales) and weekday (=Friday) versus weekend (=Saturday/Sunday). Control variables were chosen as the endocrine stress response seems to differ with overweight [35], age [36], nicotine use [37], and sleep behavior [38].

Longitudinal

To test for differences in salivary cortisol and α-amylase between the gaming conditions in the IGD group, the same eight mixed-effects linear regressions as described above were applied, with condition (baseline, unrestricted gaming, restricted gaming) instead of group as a predictor. The hypothesis was tested calculating the contrast between unrestricted gaming versus restricted gaming.

Results

The sample included $n = 55$ male youth between 15 and 25 years (mean age IGD = 19.8 years; mean age HC = 20.7 years), consisting of $n = 29$ participants with IGD (5–9 DSM-5 IGD criteria within the last 12 months) and $n = 26$ matched HC (0–1 DSM-5 IGD criteria) [30]. Five participants ($n = 5$) of the $n = 29$ participants (17.24%) with IGD met the criteria for attention deficit hyperactivity disorder, agoraphobia or generalized anxiety disorder according to the MINI(-KID) screening. A significantly higher BMI was found in the IGD group (mean BMI 24.4 kg/m^2) compared to the HC group (mean BMI 21.8 kg/m^2). Detailed descriptions of the study sample are provided in supplementary Table A (for all online suppl. material, see https://doi.org/10.1159/000541292). Due to insufficient compliance with saliva sampling, $n = 3$ participants of the IGD group had to be excluded from statistical analysis, resulting in $n = 26$ participants with IGD and $n = 26$ HC.

During the baseline week wake-up time, controlled via actigraphy, deviated from the first sampling by ≥15 min in 6.98% of all controlled samples for the HC and in 1.70% of all controlled samples for the IGD group. Wake-up time sample deviation ≥15 min was observed in the unrestricted gaming week in 17.86% of all controlled samples and in the restricted gaming week in 11.86% of all controlled samples.

Mean online gaming time during the baseline week was 0.8 h/day on weekdays and 0.5 h/day on weekends in the HC group. In the IGD group mean online gaming time was 3.3 h/day on weekdays and 5.3 h/day on weekends (see online suppl. Table A). Comparing saliva samples taken during the baseline week of the IGD and HC group (hypothesis 1), no group differences were found in the AUCi and AUCg of cortisol, cortisol and α-amylase diurnal slope, cortisol and α-amylase at t0 and overall cortisol and α-amylase. Results are presented in Table 1. Controlling for BMI, age, smoking, sleep quality, and weekday/weekend revealed no confounding effects.

During restricted gaming mean online gaming time was 0.1 h/day on weekdays and weekends. During unrestricted gaming mean online gaming time was 2.9 h/day on weekdays and 4.9 h/day on weekends (see online suppl. Table B). Comparing the unrestricted and restricted gaming conditions in the IGD group (hypothesis 2), no significant differences were found in the AUCi and AUCg of cortisol, cortisol and α-amylase diurnal slope, cortisol and α-amylase at t0 and overall cortisol and α-amylase (see Table 2). Controlling for BMI, age, smoking, sleep quality, and weekday/weekend revealed no confounding effects.

Discussion

To the best of our knowledge, this is the first study to examine diurnal profiles of the endocrine stress response, measured by salivary cortisol and α-amylase, in individuals with IGD. In contrast to our hypotheses, we did

Table 1. Comparison of endocrine markers between groups (IGD vs. HC)

Model	Model fit	Contrast	SE	95% CI	*p* value
1: CAR AUCi	$\chi^2(6) = 7.02$, $p = 0.32$	68.01	46.47	−23.06, 159.09	0.14
2: CAR AUCg	$\chi^2(6) = 5.24$, $p = 0.51$	59.64	51.42	−41.14, 160.41	0.25
3: Cortisol diurnal slope	$\chi^2(6) = 0.99$, $p = 0.99$	−0.02	0.05	−0.11, 0.08	0.73
4: Cortisol t0	$\chi^2(6) = 0.93$, $p = 0.99$	−0.04	0.15	−0.33, 0.25	0.79
5: Overall cortisol	$\chi^2(6) = 3.46$, $p = 0.75$	0.10	0.14	−0.16, 0.37	0.45
6: α-amylase diurnal slope	$\chi^2(6) = 6.02$, $p = 0.42$	−1.28	1.58	−4.37, 1.81	0.42
7: α-amylase t0	$\chi^2(6) = 8.58$, $p = 0.20$	−0.41	0.27	−0.94, 0.12	0.13
8: Overall α-amylase	$\chi^2(6) = 19.27$, $p = 0.004$	−0.009	0.26	−0.51, 0.49	0.97

IGD, internet gaming disorder; HC, healthy control; SE, standard error; CI, confidence interval; CAR, cortisol awakening response; AUCi, area under the curve with respect to increase, quantified in [(nmol/L)×min]; AUCg, area under the curve with respect to ground, quantified in [(nmol/L)×min]; cortisol diurnal slope, quantified in [(nmol/L)/h]; overall cortisol and cortisol t0 are quantified in log-transformed nmol/L; α-amylase slope is quantified in [(U/mL)/h]; overall α-amylase and α-amylase t0 are quantified in log-transformed U/mL.

Table 2. Comparison of endocrine markers between conditions (unrestricted vs. restricted gaming) in the IGD group

Model	Model Fit	Contrast	SE	95% CI	*p* value
1: CAR AUCi	$\chi^2(7) = 7.92$, $p = 0.34$	19.77	32.24	−43.41, 82.95	0.54
2: CAR AUCg	$\chi^2(7) = 3.33$, $p = 0.85$	−29.51	34.68	−97.48, 38.45	0.40
3: Cortisol diurnal slope	$\chi^2(7) = 10.40$, $p = 0.17$	−0.08	0.04	−0.17, 0.00	0.06
4: Cortisol t0	$\chi^2(7) = 8.15$, $p = 0.32$	−0.15	0.10	−0.36, 0.05	0.15
5: Overall cortisol	$\chi^2(7) = 3.87$, $p = 0.79$	−0.07	0.08	−0.23, 0.09	0.39
6: α-amylase diurnal slope	$\chi^2(7) = 5.85$, $p = 0.56$	−0.67	1.19	−3.01, 1.66	0.57
7: α-amylase t0	$\chi^2(7) = 17.14$, $p = 0.02$	−0.13	0.12	−0.36, 0.10	0.27
8: Overall α-amylase	$\chi^2(7) = 13.12$, $p = 0.07$	−0.03	0.05	−0.13, 0.07	0.51

IGD, internet gaming disorder; SE, standard error; CI, confidence interval; CAR, cortisol awakening response; AUCi, area under the curve with respect to increase, quantified in [(nmol/L)×min]; AUCg, area under the curve with respect to ground, quantified in [(nmol/L)×min]; cortisol diurnal slope, quantified in [(nmol/L)/h]; overall cortisol and cortisol t0 are quantified in log-transformed nmol/L; α-amylase slope is quantified in [(U/mL)/h]; overall α-amylase and α-amylase t0 are quantified in log-transformed U/mL.

neither find alterations in the IGD group compared to the HC group, nor changes of diurnal profiles between unrestricted versus restricted gaming conditions. However, a significantly higher BMI was found in the IGD group.

Earlier studies did not find differences in baseline levels of hair cortisol but a blunted salivary cortisol response to induced stress [3, 18, 19]. Since HPA axis reactivity to acute stress differs from the response to chronic stress [39], our finding may support the assumption that only an altered acute stress response is implicated in the pathophysiology of IGD.

This assumption is supported by a study that found no differences between baseline salivary cortisol of recreational and pathological gamblers, but a hypoactive HPA axis response in pathological gamblers while gambling [40]. Also, in another study, adults with pathological gambling and nicotine dependency showed a blunted salivary cortisol response to induced stress [41]. This blunted response may play a role in the addiction process, as stimuli no longer elicit the previous level of rewarding stress-related arousal [42]. In contrast, another study of adult male pathological gamblers

found a negative correlation between baseline salivary cortisol and the duration of pathological gambling, but no blunted salivary cortisol response to induced stress [43].

To our knowledge, there have been no studies to date on IGD or pathological gambling regarding α-amylase. While Tsumara et al. [19] (2022) showed no alterations of salivary α-amylase to stress in participants with internet addiction, a study on social media use showed an a salivary cortisol and α-amylase increase in depressed adolescents compared to healthy subjects after social media use [44]. As literature on IGD and the endocrine stress response is scarce, particularly with regard to α-amylase, further studies are needed for clarification [8].

A main strength of this study is the rigorous and controlled assessment of diurnal endocrine profiles (e.g., by using wake-up time by actigraphy or registration of the sampling time on the study smartphones). Due to the presence of few comorbid disorders in the IGD group, the results cannot be solely attributed to IGD, but, as IGD often co-occurs with other psychiatric disorders, our study sample is representative [27, 28]. However, some limitations of the study should be mentioned, such as the relatively small sample size and the patient selection from only the canton of Berne, Switzerland. Additionally, a selection bias due to a convenience sample should be considered. Because this sample consisted only of male adolescents, the results of our study cannot be generalized to female adolescents. An investigation with a relatively large sample size (363 children and 344 adolescents) found sex being a determinant of the stress response, with females showing a higher salivary cortisol and heart rate reactivity [14]. In one study, there was also evidence of a gender-specific influence on the association between stress and IGD, finding that male gamers with high levels of stress were at a greater risk of IGD than female gamers [45]. Given these findings, it is crucial to consider how our results can be applied to female adolescents. Gender differences in the clinical presentation of IGD further suggest that females with IGD exhibit different symptoms and comorbidities, underscoring the need for gender-specific research [46, 47]. Including females in future studies will provide a more comprehensive understanding of IGD and ensure that interventions are effective for both sexes.

During the restricted gaming week, the reported low gaming time appears low considering the DSM-5 criterion for IGD "Unsuccessful attempts to reduce or stop playing" [30]. On the one hand, this may show good adherence to the study protocol, on the other hand it raises the question of a social-desirability bias and whether the diagnostic criteria differentiated sufficiently accurate between engaged and pathological involvement in gaming [48]. The regular saliva sampling, EMA and wearing of the actigraphy device may also have contributed to a change in the gaming behavior by reminding the participants of being in a study design.

Conclusions

We found no alterations in diurnal profiles of salivary cortisol and α-amylase between male adolescents with IGD and HC. Whether the adolescents with IGD played without restriction or remained abstinent from online gaming also had no significant influence on the endocrine parameters. This suggests that there are no alterations in the diurnal profiles of the endocrine stress response system in IGD.

Statement of Ethics

The study was approved by the Local Ethics Committee (Kantonale Ethikkommision KEK, Biomedizinische Ethikkommission Bern, ID 2018-01604) and was carried out in accordance with the Declaration of Helsinki [49]. Study participants and, in case of minors, their legal guardians, signed written informed consent. All participants received vouchers for local shops as compensation for study participation (cross-sectional design 60 CHF; longitudinal design 90 CHF). Additionally, adolescents who were diagnosed with IGD were informed about treatment options.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.K. and P.K.: writing – original draft (A.K. and P.K. equal contribution, shared first authorship); J.K.: resources, writing – review and editing, investigation, data curation, and writing – review and editing; S.L: formal analysis and writing – review and editing; M.C: supervision and writing – review and editing; M.K: conceptualization, supervision, methodology, and writing – review and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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