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Post-awakening salivary alpha-amylase as modulator of treatment response in patients with burnout and major depression

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ABSTRACT

Around 50% of patients with major depression do not respond to standard first-line treatments, such as psychotherapy and pharmacotherapy. At the same time, a subgroup exhibits altered functioning of stress-responsive bodily systems, such as the central locus coeruleus/sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Given that these systems impact arousal and cognition, it is possible that this subgroup contributes to the high rates of non-responders. Our aim was to investigate whether sympathetic and HPA axis activity modulate treatment outcomes in patients with stress-related major depression. A total of N = 74 inpatients (median age: 50, 62% male) with signs of burnout who fulfilled diagnostic criteria for major depression were recruited. Saliva samples were collected at awakening as well as 30 and 45 min later. Alpha-amylase activity and cortisol concentrations were determined before patients underwent evidence-based multimodal treatment. Non-responders were defined as patients exhibiting a <50% decrease in depression on the Beck Depression Inventory. Non-responders had significantly higher post-awakening alpha-amylase activity than responders ($p = .025$). In addition, alpha-amylase activity increased significantly over the course of treatment ($p = .004$), irrespective of responder status. Post-awakening cortisol was neither a predictor nor an indicator of treatment response. If future research confirms alpha-amylase activity as a modulator of treatment response, this may indicate a subgroup of patients with major depression which may benefit from augmentative treatments, such as heart rate variability biofeedback and/or cognitive interventions targeting high arousal.

1. Introduction

Both psychotherapy and pharmacotherapy constitute effective treatments for depressive disorders (e.g., Cuijpers et al., 2020) and their combination is recommended for at least moderate levels of depressive episodes (e.g., DGPPN, 2015). However, on average, responses to these therapies are observed in around 50% of patients (Cleare et al., 2015; Cuijpers et al., 2014), suggesting that only half of patients benefit sufficiently from standard first-line treatments. Treatment-resistant depression usually shows a relapsing or chronic progression (Fekadu et al., 2009) and inflicts substantial burden (Johnston et al., 2019). A meta-analysis of studies investigating suicidality in samples with treatment-resistant depression reported rates of almost 0.5 completed and five attempted suicides are reported per 100 patient years (Bergfeld et al., 2018). These findings raise the important question of what mechanisms may underlie treatment non-responses.

One explanation for the low responder rates is the presence of specific subtypes of depression, which may require additional or alternative treatments. A frequent finding in depressed individuals is alterations in stress-responsive systems, such as the central locus coeruleus/sympathetic nervous system as well as the hypothalamic-pituitary-adrenal (HPA) axis. Overall, the literature suggests that at least some individuals with major depressive disorder are characterised by complex alterations in sympathetic functioning, such as a higher activity of the

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salivary enzyme alpha-amylase after awakening (e.g., Bauduin et al., 2018) and an attenuated heart rate upon exposure to psychosocial stress (Schiweck et al., 2019) in comparison to healthy controls. Moreover, a subgroup of individuals with major depressive disorder appears to exhibit comparably elevated HPA axis activity (Stetler and Miller, 2011). Given that these systems are key orchestrators of arousal and cognition, it is conceivable that such alterations may interfere with the degree to which patients benefit from psychological interventions (e.g., Fischer and Ehlert, 2019; Schumacher and Fischer, 2020). Conversely, in view of the key role of the sympathetic nervous system and the HPA axis in governing the stress response, it is also conceivable that positive therapeutic changes will manifest on the biological level.

Along these lines, a handful of studies have investigated whether the main effectors of the sympathetic nervous system, the catecholamines noradrenaline and adrenaline, are related to treatment outcomes in major depression. Whereas the two hormones did not appear to predict outcomes after 12 weeks of group cognitive behavioural therapy (Oei et al., 2010), adrenaline increased in patients responsive to the same treatment (Free et al., 1998). However, the latter finding was not replicated in a follow-up study in inpatients who underwent combined treatment with cognitive behavioural therapy and antidepressants (Dingle et al., 2010). Notably, all of these studies measured the catecholamines in 24 h urine, which mostly reflects tonic sympathetic activity. As such, it remains unclear whether the reactivity of the sympathetic nervous system, which appears to be compromised in major depression (see above), modulates treatment outcomes.

Regarding cortisol, a more extensive evidence base attests to cortisol as a predictor of psychotherapy and antidepressant responses (see Fischer et al., 2017a; Fischer et al., 2017b for meta-analyses). More specifically, higher levels of cortisol have been found to predict worse treatment outcomes, indicating that the greater the pre-treatment changes in the HPA axis, the less likely patients are to benefit from standard first-line treatments. Furthermore, there is preliminary evidence that cortisol can decrease over the course of (combined) psychotherapeutic and pharmacological treatments (Fischer and Zilcha-Mano, 2022; Laufer et al., 2018). However, no studies to date have investigated whether these decreases are related to treatment response, hence not allowing us to answer the question of whether they reflect naturally occurring fluctuations or therapeutic changes.

Taken together, there is preliminary evidence to suggest that, at least in a subgroup of patients with major depression, cognitive behavioural therapy and antidepressants are capable of reversing previously observed alterations in stress-responsive bodily systems. Furthermore, it appears that the more pronounced these alterations are pre-treatment, the worse the subsequent outcome will be. The aim of the present study was therefore to investigate, for the first time, whether robust indicators of sympathetic and HPA axis functioning could be used to distinguish non-responders from responders to an inpatient treatment combining cognitive behavioural therapy and pharmacotherapy, with additional interventions such as relaxation and sport (for a detailed description of the treatment programme see Hochstrasser et al., 2008). To this end, post-awakening levels of salivary alpha-amylase, a surrogate marker of sympathetic activity (Nater and Rohleder, 2009), and cortisol were determined before and after patients with a stress-related episode of major depression, that is, patients reporting both signs of burnout and fulfilling diagnostic criteria for a major depressive episode, underwent an evidence-based multimodal inpatient treatment. Burnout is considered as a syndrome related to work stress (Hallsten et al., 2011; Leiter and Maslach, 1999; Maslach, 1976) In the ICD-11, which will be implemented by 2022, burnout is considered as a work related qualifying disorder (WHO, 2019).

Based on the literature, we expected that a) the higher the post-awakening alpha-amylase activity and b) the higher the post-awakening cortisol concentration, the more likely a patient would be considered a treatment non-responder. Moreover, we assumed that c) post-awakening alpha-amylase activity and cortisol concentrations would decrease over the course of treatment, and that d) these changes would be related to whether a patient was considered a treatment responder vs. a non-responder.

2. Methods

2.1. Sample and protocol

This study was part of a larger project on a specialised multimodal treatment for inpatients with burnout (see e.g., Elkuch et al., 2010; Haberthur et al., 2009; Pallich et al., 2020; Pallich et al., 2021). The project used a naturalistic observational design. For the present analysis, the following eligibility criteria were applied: 1) inpatient admission due to any number of self-reported signs of burnout as specified in the ICD-10 (WHO, 1992), 2) a current major depressive episode according to the standardised clinical interview Mini-DIPS (Margraf, 2013), 3) no dementia, substance abuse, psychotic symptoms, suicidal ideation, or eating disorders, as assessed by a psychiatrist/clinical psychologist, and 4) no intake of corticosteroids. All patients underwent a standardised inpatient treatment for burnout and major depression (see next section). In addition, patients were instructed on how to collect saliva samples over the course of two consecutive days. The measurement time points were upon awakening, +30 min, and +45 min, and all patients provided samples at the beginning of treatment (within the first week of entering the clinic) as well as in the final week of the treatment (i.e., in the week before leaving the clinic). Importantly, all patients completed a sampling diary and only those who adhered to the sampling schedule (i.e., no more than 5 min deviations; Stalder et al., 2016) were included in the statistical analyses. The final sample size was N = 74. Although the sample size was not specifically calculated for the purpose of the present study, the number of recruited individuals is higher than in previous research on catecholamines/cortisol measured before/after psychotherapy or combined treatments in major depression (Dingle et al., 2010; Fischer et al., 2017a, 2017b; Free et al., 1998; Laufer et al., 2018; Oei et al., 2010) and was large enough to detect medium-sized effects regarding the comparison of non-responders vs. responders ($\alpha = 0.05$, $1\text{-}\beta = 0.80$).

The study protocol was approved by the Ethics Committee of the Canton of Berne and written informed consent was obtained from all participants.

2.2. Specialised inpatient treatment

A detailed description of the specialised multimodal inpatient treatment has been provided elsewhere (Hochstrasser et al., 2008). In brief, the programme was composed of two 50 min sessions of individual and two 90 min sessions of group cognitive behavioural therapy per week. Furthermore, the patients were given the opportunity to participate in relaxation training, meditation sessions, massages, body therapies, sports, physiotherapy, and interventions of complementary medicine. Pharmacotherapy was applied in accordance with European Guidelines (Hochstrasser et al., 2016b; Hochstrasser et al., 2016a).

2.3. Psychological measures

Comorbidity with other mental disorders was established using the Mini-DIPS, a standardised clinical interview (Margraf, 2013). Depressive symptoms were assessed using the German version of the Beck Depression Inventory (Hautzinger et al., 1994), which was administered at the beginning and the end of treatment. Patients exhibiting a reduction in depressive symptoms of <50% were considered treatment non-responders.

2.4. Biological measures

The saliva samples were collected in Salivettes (Sarstedt, Sevelen,

Switzerland) and were subsequently stored at − 20 °C until biochemical analyses. The biochemical analyses were conducted at the biochemical laboratory of the Institute of Psychology, University of Zurich. Thawed saliva samples were centrifuged and analysed using reagents from Roche (Basel, Switzerland) for alpha-amylase and immunoassays from IBL (Hamburg, Germany) for cortisol. The intra- and inter-assay variation of these assays is less than 10%.

2.5. Statistical analysis

All data were tested for normal distribution and alpha-amylase and cortisol concentrations were subsequently log-transformed. To obtain an index of post-awakening alpha-amylase activity and cortisol secretion, areas under the curve with respect to the ground (AUC) were calculated (Pruessner et al., 2003). First, Mann-Whitney U tests and Chi-squared tests were computed to investigate whether treatment non-responders and responders differed regarding pre-treatment symptom severity, the intake of antidepressants and antipsychotics, and the duration of treatment. Second, univariate ANOVAs were conducted to test whether treatment non-responders and responders differed regarding their pre-treatment alpha-amylase and cortisol. In this model, pre-treatment symptom severity, the intake of antidepressants and antipsychotics, the duration of treatment, age, sex, and BMI were included as covariates (a priori specification). Next, a repeated measures ANOVA was conducted to examine whether alpha-amylase and cortisol changed over the course of treatment and whether this was dependent on non-responder vs. responder status. All analyses were performed in SPSS 25 and the alpha error was set at 5%.

3. Results

3.1. Patient characteristics

All characteristics of the N = 74 patients are displayed in Table 1. The patients were mostly middle aged, of average weight, and around two thirds were male. The median score on the BDI was 23.5, indicating moderate levels of depression in most patients. Comorbidity with other mental disorders was relatively low, with the most frequent diagnoses being specific phobias (16%), panic disorder (8%), and generalised anxiety disorder (3%). Over half of the patients (60%) took antidepressants, and around a quarter took antipsychotics (26%).

The median treatment duration was 51 days (minimum: 24 days, maximum: 93 days). Of the entire sample, 71% were treatment responders and 29% were non-responders. Treatment non-responders and responders did not differ in age (U = 379.00, p = .174) or BMI (U = 353.500, p = .510), pre-treatment depression severity (U = 378.00, p = .138), intake of antidepressants (X^2 = 1.40, p = .237) or antipsychotics (X^2 = 0.02, p = .895), or in treatment duration (U = 364.00, p = .096). However, women were more frequently represented in the non-responder category (X^2 = 5.15, p = .023).

Table 1
Pre-treatment characteristics of patients (N = 74). Descriptive statistics are given as median and interquartile range or absolute and relative frequencies.

	Descriptive statistics
Age (years)	50 (14)
Sex	
Female	28 (38%)
Male	45 (62%)
Body Mass Index (BMI; kg/m^2)	25 (5)
Depression severity (BDI)	23.5 (8.5)
Diagnoses (Mini-DIPS)	
Specific phobia	12 (16%)
Social anxiety disorder	1 (1%)
Panic disorder	6 (8%)
Generalised anxiety disorder	2 (3%)
Obsessive-compulsive disorder	1 (1%)
Post-traumatic stress disorder	1 (1%)
Other	13 (18%)
Medication	
Antidepressants	44 (60%)
Antipsychotics	19 (26%)
Anxiolytics*	64 (87%)
Hypnotics*	59 (80%)
Other	6 (8%)

BDI = Beck Depression Inventory (theoretical score range 0–63), *pro re nata.

3.2. Alpha-amylase and cortisol as predictors of treatment response

Treatment non-responders had significantly higher pre-treatment alpha-amylase activity post awakening as compared to responders (F(1, 47) = 5.35, p = .025, partial eta^2 = 0.102; see also Fig. 1). By contrast, pre-treatment post-awakening cortisol concentrations did not distinguish non-responders from responders (F(1, 47)<0.01, p = .989; see Fig. 2).

Repeating the analyses without patients on antipsychotics reduced the sample size by a quarter and rendered the previously significant finding regarding alpha-amylase insignificant (F(1, 34) = 1.19, p = .283).

3.3. Alpha-amylase and cortisol as indicators of treatment response

Regarding post-awakening alpha-amylase activity, a significant overall increase was observed from pre-to post-treatment (time effect: F(1, 39) = 9.13, p = .004, partial eta^2 = 0.190). However, this increase did not differ between treatment non-responders and treatment responders (time by group effect: F(1, 39) = 0.68, p = .416). No changes in post-awakening cortisol were apparent (time effect: F(1, 38) = 0.44, p = .512; time by group effect: F(1, 38)<0.01, p = .973).

Repeating the analyses without patients on antipsychotics reduced the sample size by a quarter. The previously significant finding regarding alpha-amylase remained significant (time effect: F(1, 27) = 7.92, p = .009).

4. Discussion

The present study yielded three main findings. First, in inpatients with self-reported signs of burnout and major depression, the higher the pre-treatment alpha-amylase activity, the more likely patients were to exhibit insufficient responses to evidence-based multimodal treatment. Second, while alpha-amylase activity increased over the course of treatment, this was independent of non-responder vs. responder status. Third, post-awakening cortisol concentrations were neither a predictor nor an indicator of treatment response.

Our first finding is novel insofar as the present study is the first to examine alpha-amylase, an indicator of sympathetic activity, as a modulator of treatment response in patients with depression. Moreover, it contradicts the null-finding reported in an earlier study which tested 24 h urinary noradrenaline, adrenaline, and other catecholamines as predictors of outcomes after twelve weeks of group cognitive behavioural therapy (Oei et al., 2010). The most likely explanation for this discrepancy is that the previous study used a combined index of catecholamines as independent variable and divided patients into low vs. high catecholamine excreting individuals based on standard deviations. This approach may have masked any potential effects of individual hormones, such as noradrenaline and may have neglected additional information available from continuous hormonal levels. Our finding also resonates well with the literature on salivary alpha-amylase in major depressive disorder, which suggests comparably enhanced alpha-amylase activity after awakening (Bauduin et al., 2018). Given that the central locus coeruleus/sympathetic nervous system is a crucial orchestrator of the stress response (e.g., Goddard et al., 2010), an enhanced sympathetic activity after awakening may indicate a specific subgroup of patients with a high degree of psychosocial stress. This

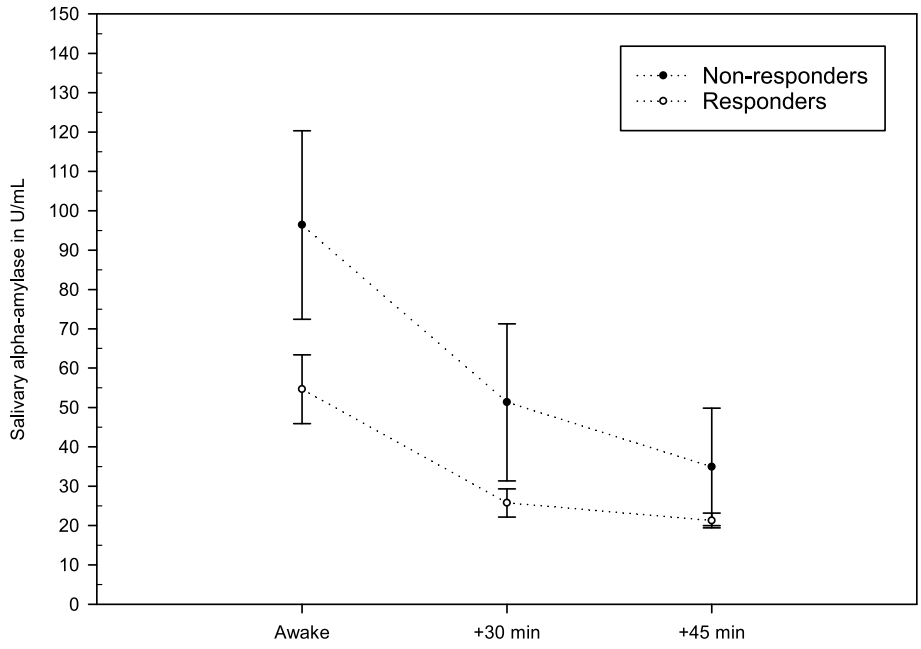

Fig. 1. Alpha-amylase activity in treatment non-responders vs. responders (Beck Depression Inventory). Bars represent means and standard errors. Non-responders had significantly higher pre-treatment alpha-amylase activity post awakening when compared to responders.

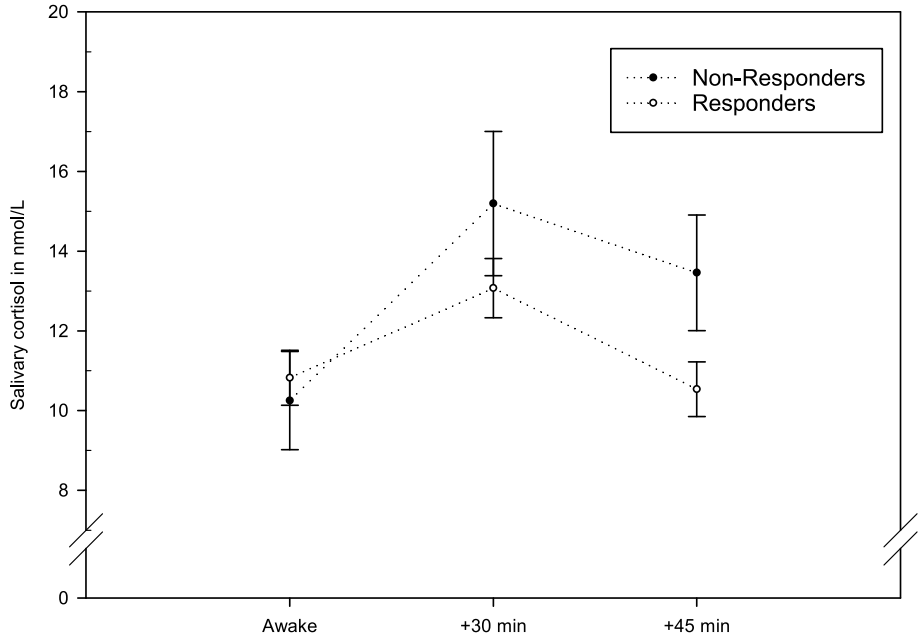

Fig. 2. Cortisol concentrations in treatment non-responders vs. responders (Beck Depression Inventory). Bars represent means and standard errors. Non-responders and responders did not differ in their pre-treatment post awakening cortisol concentrations.

notion aligns well with the fact that the patients in the present sample reported signs of burnout, a syndrome related to work stress.

Our second finding was a significant increase in post-awakening alpha-amylase activity over the course of treatment, which was unrelated to non-responder vs. responder status. Again, the present study is the first to use this parameter as a potential indicator of therapeutic change in depression. This findings corresponds to one previous study, which employed repeated measures of catecholamines over the course of combined pharmacotherapy and psychotherapy, and failed to detect any different trajectories in catecholamines between treatment non-responders and responders (Dingle et al., 2010). Longitudinal research has repeatedly demonstrated that salivary alpha-amylase activity is subject to substantial intra-individual variation (e.g., Skoluda et al., 2017). Although little is known about the reasons for the medium- or long-term variation of salivary alpha-amylase, it is conceivable that environmental changes, such as those related to seasons, or changes in diet or physical activity are contributing factors (see Rohleder and Nater, 2009 for a review of confounders of salivary alpha-amylase). Given that, in the present study, the observed increases were unrelated to treatment response, they are thus more likely to be attributable to environmental/lifestyle factors rather than to constitute an antecedent or consequence of improvements in depressive symptoms.

Our third finding is that, in our sample of patients with self-reported signs of burnout and major depression, cortisol was neither a predictor

nor an indicator of therapeutic change. This is in contrast to the findings of two meta-analyses, which reported unfavourable treatment outcomes in patients with major depression when pre-treatment cortisol was high (Fischer et al., 2017a, 2017b). Moreover, it conflicts with some findings of decreases in the stress hormone over the course of combined treatments in depression, although these are tentative (Fischer and Zilcha-Mano, 2022; Laufer et al., 2018). Importantly, the vast majority of the previous studies obtained measures of cortisol in blood and either at rest or after challenge with dexamethasone, a synthetic analogue of cortisol which inhibits HPA axis activity. The present study is the first to utilise repeated measurement of cortisol in response to a natural challenge (i.e., awakening) as a prognostic factor for responses to combined pharmacological and psychological treatment. Similarly, only one previous study to date has used post-awakening cortisol as an indicator of therapeutic change, yielding a null-finding (Taylor et al., 2009). It is thus possible that only specific aspects of HPA axis functioning (e.g., negative feedback sensitivity) are related to the degree to which patients benefit from therapy or that highly standardised tests, such as the dexamethasone suppression test, may be better suited to discriminate non-responders and responders. Alternatively, the present study may have been under-powered to detect any small effects of post-awakening cortisol on treatment response.

A number of strengths of the present study can be noted. First, no previous research has investigated the role of salivary alpha-amylase as a modulator of treatment response in major depression. As this is a non-invasive, low-cost marker of a key pathophysiological system in this disorder, our results are highly relevant for clinical practice. Second, as we examined a homogenous sample of patients with major depression, and one that presented with a low degree of comorbidity, it is relatively unlikely that any other mental illnesses influenced our biological markers (Chrousos, 2009). Third, salivary alpha-amylase and cortisol were repeatedly assessed over the course of two days, resulting in reliable estimates of alpha-amylase activity and cortisol concentrations. Finally, very little research has investigated responses to combined psychological and pharmacological treatments, which represent the guideline-recommended choice for individuals with moderate to severe depression.

Nevertheless, some limitations of the study need to be mentioned. First and foremost, our study did not include a healthy control group. Therefore, it remains unknown whether our sample of patients had altered salivary alpha-amylase activity at baseline, although prior research suggests that this may well have been the case (Bauduin et al., 2018). Second, given that this was a secondary analysis of a larger project and that we controlled for a number of important confounders, our sample size is small and may have been too small to detect any small effects of cortisol on treatment outcomes. Third, the study was conducted in a clinic specialising in the treatment of burnout, which means that our findings may not generalise to other forms of major depression. Finally, apart from treatment duration, no measures of other factors (e.g., the number of unstandardised treatment components, such as massages, medication dosage, or changes in physical activity or diet over the course of the treatment) that could have influenced our biological measures were obtained. This means that it remains unclear which aspects of the inpatient stay were less effective for high-amylase individuals. However, previous research has shown that biomarkers are predictive of both stand-alone psychotherapy and pharmacotherapy responses and our study complements these findings by showing that they may also serve as prognostic factors in naturalistic scenarios in which multimodal treatments are administered.

In sum, the present study demonstrated for the first time that, in patients with self-reported signs of burnout who fulfil diagnostic criteria for major depression, higher levels of salivary alpha-amylase are associated with poorer outcomes after combined pharmacological and psychotherapeutic treatment. Given that high sympathetic activity is often accompanied by high levels of arousal and agitation, this may point to a subgroup of patients with major depression who could benefit from complementary interventions. On the one hand, reducing sympathetic overdrive in the morning by augmenting conventional treatment modalities with heart rate variability biofeedback training could help these individuals to achieve better outcomes (see e.g., Caldwell and Steffen, 2018). On the other hand, adding interventions that are capable of minimising anxiety upon awakening (e.g., exposure-based or meta-cognitive strategies targeting worrying) may increase the degree to which patients are able to benefit from treatment. Further research replicating and extending our findings in larger samples is necessary to make further progress in improving treatment for depression.

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Author statement

GP, MgH, RLM and BH contributed to the conception and design of the study; GP prepared the study and collected the data. GP and RLM prepared the data. SF and RLM performed the statistical analysis and interpreted the data. SF wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Contributing authors

GP, MgH, RLM and BH contributed to the conception and design of the study; GP prepared the study, collected the data and prepared the data. SF and RLM performed the statistical analysis and interpreted the data. SF wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Declaration of competing interest

GP and BH were employed at the Burnout ward of the Private Hospital Meiringen.

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References

Bauduin, S., van Noorden, M.S., van der Werff, S.J.A., de Leeuw, M., van Hemert, A.M., van der Wee, N.J.A., Giltay, E.J., 2018. Elevated salivary alpha-amylase levels at awakening in patients with depression. Psychoneuroendocrinology 97, 69–77.

Bergfeld, I.O., Mantione, M., Figee, M., Schuurman, P.R., Lok, A., Denys, D., 2018. Treatment-resistant depression and suicidality. J. Affect. Disord. 235, 362–367.

Caldwell, Y.T., Steffen, P.R., 2018. Adding HRV biofeedback to psychotherapy increases heart rate variability and improves the treatment of major depressive disorder. Int. J. Psychophysiol. : Off. J. Int. Organ. Psychophysiol. 131, 96–101.

Chrousos, G.P., 2009. Stress and disorders of the stress system. Nat. Rev. Endocrinol. 5 (7), 374–381.

Cleare, A., Pariante, C.M., Young, A.H., Anderson, I.M., Christmas, D., Cowen, P.J., Dickens, C., Ferrier, I.N., Geddes, J., Gilbody, S., Haddad, P.M., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R.H., Ramchandani, P., Scott, J., Taylor, D., Uher, R., Members of the Consensus M, 2015. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J. Psychopharmacol. 29 (5), 459–525.

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S.D., van Straten, A., 2014. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. J. Affect. Disord. 159, 118–126.

Cuijpers, P., Noma, H., Karyotaki, E., Vinkers, C.H., Cipriani, A., Furukawa, T.A., 2020. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatr. : Off. J. World Psychiatr. Assoc. 19 (1), 92–107.

DGPPN, B., KBV, AWMF (Hrsg.) für die Leitliniengruppe Unipolare Depression, 2015. S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression – Langfassung, 2. Auflage. Version 5.

Dingle, G.A., Oei, T.P., Young, R.M., 2010. Mechanisms of change in negative thinking and urinary monoamines in depressed patients during acute treatment with group cognitive behavior therapy and antidepressant medication. Psychiatr. Res. 175 (1–2), 82–88.

Elkuch, F.M., Haberthur, A.K., Hochstrasser, B., grosse Holtforth, M., Soyka, M., 2010. Langzeiteffekte einer stationären Burnouttherapie – eine Nachbefragung. Verhaltensther. Verhaltensmed. 31 (1), 4–18.

Fekadu, A., Wooderson, S.C., Markopoulo, K., Donaldson, C., Papadopoulos, A., Cleare, A.J., 2009. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. J. Affect. Disord. 116 (1–2), 4–11.

Fischer, S., Ehlert, U., 2019. Psychoneuroendocrinology and clinical psychology. Clin. Psychol. Eur. 1 (2).

Fischer, S., Macare, C., Cleare, A.J., 2017a. Hypothalamic-pituitary-adrenal (HPA) axis functioning as predictor of antidepressant response-Meta-analysis. Neurosci. Biobehav. Rev. 83, 200–211.

Fischer, S., Strawbridge, R., Vives, A.H., Cleare, A.J., 2017b. Cortisol as a predictor of psychological therapy response in depressive disorders: systematic review and meta-analysis. Br. J. Psychiatr. : J. Ment. Sci. 210 (2), 105–109.

Fischer, S., Zilcha-Mano, S., 2022. Why does psychotherapy work and for whom? Hormonal answers. Biomedicines 10 (6).

Free, M.L., Oei, T.P., Appleton, C., 1998. Biological and psychological processes in recovery from depression during cognitive therapy. J. Behav. Ther. Exp. Psychiatr. 29 (3), 213–226.

Goddard, A.W., Ball, S.G., Martinez, J., Robinson, M.J., Yang, C.R., Russell, J.M., Shekhar, A., 2010. Current perspectives of the roles of the central norepinephrine system in anxiety and depression. Depress. Anxiety 27 (4), 339–350.

Haberthur, A.K., Elkuch, F.M., Holtforth, M.G., Hochstrasser, B., Soyka, M., 2009. Characterization of patients discharged from inpatient treatment for burnout: use of psychological characteristics to identify aftercare needs. J. Clin. Psychol. 65 (10), 1039–1055.

Hallsten, L., Voss, M., Stark, S., Josephson, M., 2011. Job burnout and job wornout as risk factors for long-term sickness. Absence Work 38 (2), 181–192.

Hautzinger, M., Bailer, M., Worall, H., Keller, F., 1994. Beck- Depressions-Inventar (BDI): Bearbeitung der deutschen Ausgabe. Testhandbuch. Hans Huber, Bern.

Hochstrasser, B., Brühlmann, T., Cattapan, K., Hättenschwieler, J., Holsboer-Trachlser, E., Kawohl, W., Schulze, B., Schaufeli, W.B., Seifritz, E., Zemp, A., Keck, M.E., 2016b. Therapieempfehlungen des Schweizer Expertennetzwerks für Burnout - burnout-Behandlung Teil 2: praktische Empfehlungen. Swiss Med. Forum 16 (26–27), 561–566.

Hochstrasser, B., B, T., Cattapan, K., Hättenschwieler, J., Holsboer-Trachsler, E., Kawohl, W., Seifritz, E., Schaufeli, W.B., Zemp, A., Keck, M.E., 2016a. Therapieempfehlungen des Schweizer Expertennetzwerks für Burnout - burnout-Behandlung Teil1: Grundlagen. Swiss Med. Forum 16 (25), 538–541.

Hochstrasser, B., Von Bardeleben, U., Ruckstuhl, L., Soyka, M., 2008. Therapie des Burnout-theoretischer Hintergrund, Klinik und Darstellung eines stationären multimodalen Behandlungskonzeptes. Nervenheilkunde 27, 11–24.

Johnston, K.M., Powell, L.C., Anderson, I.M., Szabo, S., Cline, S., 2019. The burden of treatment-resistant depression: a systematic review of the economic and quality of life literature. J. Affect. Disord. 242, 195–210.

Laufer, S., Engel, S., Knaevelsrud, C., Schumacher, S., 2018. Cortisol and alpha-amylase assessment in psychotherapeutic intervention studies: a systematic review. Neurosci. Biobehav. Rev. 95, 235–262.

Leiter, M.P., Maslach, C., 1999. Six areas of worklife:a model of the organizational context of burnout. J. Health Hum. Serv. Admin. JHHSA 472–489.

Margraf, J., 2013. Mini-DIPS: Diagnostisches Kurz-Interview bei psychischen Störungen. Springer.

Maslach, C., 1976. Burned-out. Hum. Behav. 5, 16–22.

Nater, U.M., Rohleder, N., 2009. Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: current state of research. Psychoneuroendocrinology 34 (4), 486–496.

Oei, T.P., Dingle, G.A., McCarthy, M., 2010. Urinary catecholamine levels and response to group cognitive behaviour therapy in depression. Behav. Cognit. Psychother. 38 (4), 479–483.

Pallich, G., Blattler, L., Gomez Penedo, J.M., Grosse Holtforth, M., Hochstrasser, B., 2020. Emotional competence predicts outcome of an inpatient treatment program for burnout. J. Affect. Disord. 274, 949–954.

Pallich, G., grosse Holtforth, M., Hochstrasser, B., 2021. Burnout subtypes: psychological characteristics, standardized diagnoses and symptoms course to identify aftercare need. Clin. Psychol. Eur. 3 (3), e3819.

Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28 (7), 916–931.

Rohleder, N., Nater, U.M., 2009. Determinants of salivary alpha-amylase in humans and methodological considerations. Psychoneuroendocrinology 34 (4), 469–485.

Schiweck, C., Piette, D., Berckmans, D., Claes, S., Vrieze, E., 2019. Heart rate and high frequency heart rate variability during stress as biomarker for clinical depression. A systematic review. Psychol. Med. 49 (2), 200–211.

Schumacher, S., Fischer, S., 2020. What can biological markers do for behavior therapy? Verhaltenstherapie 30 (1), 5–7.

Skoluda, N., La Marca, R., Gollwitzer, M., Muller, A., Limm, H., Marten-Mittag, B., Gundel, H., Angerer, P., Nater, U.M., 2017. Long-term stability of diurnal salivary cortisol and alpha-amylase secretion patterns. Physiol. Behav. 175, 1–8.

Stalder, T., Kirschbaum, C., Kudielka, B.M., Adam, E.K., Pruessner, J.C., Wust, S., Dockray, S., Smyth, N., Evans, P., Hellhammer, D.H., Miller, R., Wetherell, M.A., Lupien, S.J., Clow, A., 2016. Assessment of the cortisol awakening response: expert consensus guidelines. Psychoneuroendocrinology 63, 414–432.

Stetler, C., Miller, G.E., 2011. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom. Med. 73 (2), 114–126.

Taylor, C.B., Conrad, A., Wilhelm, F.H., Strachowski, D., Khaylis, A., Neri, E., Giese-Davis, J., Roth, W.T., Cooke, J.P., Kraemer, H., Spiegel, D., 2009. Does improving mood in depressed patients alter factors that may affect cardiovascular disease risk? J. Psychiatr. Res. 43 (16), 1246–1252.

WHO, 1992. The ICD-10 Classification of Mental and Behavioural Disorders - Clinical Descriptions and Diagnostic Guidelines. World Health Organization, Geneva.

WHO, W.H.O., 2019. https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/129180281.