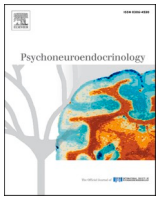
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Good morning or good evening: Daytime and cortisol as modulators of exposure therapy outcomes

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ABSTRACT

Background: Although exposure therapy is considered the gold standard treatment for anxiety disorders, many patients do not respond sufficiently to it. This study investigated the effects of the time of day at which exposure therapy is delivered and endogenous cortisol levels during exposure on treatment success in patients with fear of spiders. It was hypothesized that individuals undergoing exposure therapy in the morning would experience greater symptom reductions compared to those undergoing therapy in the evening, and that higher endogenous cortisol levels would predict greater symptom reductions.

Method: 53 participants with symptoms of spider phobia were recruited to complete a four-hour group-based exposure therapy starting either at 8 a.m. or 5 p.m. in a double-blind design. Symptoms of spider phobia were assessed using the Structured Clinical Interview for DSM-IV. Therapy outcomes were assessed before, one week after therapy and at 3-months' follow-up, using the Spider Phobia Questionnaire (SPQ), the Fear of Spiders Questionnaire (FSQ), and a behavioral approach test (BAT).

Results: Both phobic fear (FSQ: η^2_p=0.70; SPQ: η^2_p=0.59) and avoidance behavior (η^2_p=0.70) significantly improved following exposure therapy. The morning group showed higher cortisol levels than the evening group ($p = 0.036$), however, symptom improvement did not differ between the groups (all $p > 0.05$). Exploratory analyses revealed that a lower cortisol change (AUCi) during individual exposure was associated with greater improvements in phobic fear (FSQ: η^2_p=0.20; SPQ: η^2_p=0.11).

Conclusion: Although daytime was not found to modify exposure therapy treatment success, preliminary evidence points to a potential role of cortisol change, warranting further investigation.

1. Introduction

Anxiety disorders are the most common and impairing mental conditions worldwide (Wu et al., 2025). The recommended gold-standard psychological treatment is cognitive behavioral therapy (CBT), particularly exposure therapy (Bandelow et al., 2015). During exposure therapy, patients are systematically exposed to the feared stimulus while avoidance behavior is prevented, thereby facilitating extinction learning (McNally, 2007). Despite the overall well-documented effectiveness of exposure therapy, up to 50% of patients show no or insufficient improvement (Loerinc et al., 2015). Consequently, there has been an increasing interest in identifying factors that enhance treatment response (Böhnlein et al., 2020).

Hormones may offer a promising approach of optimizing psychological treatment responses (Fischer and Zilcha-Mano, 2022). Cortisol, in particular, has gained considerable interest, as its exogenous administration has been shown to improve treatment success across various anxiety disorders (de Quervain et al., 2011; Soravia et al., 2014). Cortisol, after binding to glucocorticoid and mineralocorticoid receptors that are widely distributed in neuronal regions implicated in the fear circuit (de Quervain et al., 2019; Corcoran and Quirk, 2007), may facilitate extinction learning by enhancing the inhibition of the retrieval of existing memories of the feared stimuli and the consolidation of new, corrective emotionally charged learning during exposure (Merz et al., 2012; de Quervain et al., 2017, 2009).

A systematic review found some evidence suggesting that higher

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endogenous cortisol levels during exposure therapy are associated with greater treatment improvements, however, this could not be confirmed in the meta-analysis (Fischer and Cleare, 2017). Importantly, these findings are based on a relatively small number of studies that substantially differ in design and sample, thereby limiting comparability and thus contributing to the inconclusive findings. Interestingly, cortisol synthesis and secretion follow a pronounced circadian rhythm, characterized by a peak in the morning shortly after awakening (the cortisol awakening response, CAR) and a subsequent decline throughout the day (Kirschbaum and Hellhammer, 2008). This diurnal variation may represent a natural source of cortisol variability with which exposure therapy response may be modulated. Unlike exogenous administration, leveraging these endogenous fluctuations could offer a potentially beneficial and side-effect-free approach of optimizing treatment response.

To date, only three studies have investigated the effects of the time of day at which exposure therapy is conducted on therapeutic outcomes of exposure therapy. Specifically, Lass-Hennemann and Michael (2014) investigated whether randomly assigned participants with spider phobia undergoing a single session of in vivo exposure therapy in the morning (8 a.m.) or in the evening (6 p.m.) differed in their reduction in behavioral avoidance and self-reported phobic fear. The morning group, which also showed higher cortisol levels, exhibited greater reductions in behavioral avoidance, and a trend towards greater reductions in phobic fear, than the evening group, which showed lower cortisol levels. Although the random allocation of participants to different daytime sessions reduced the risk of selection bias (Kunz et al., 2007), the therapists were not blinded to the study hypothesis, which can generally be associated with potential expectation bias (Rosenthal, 2014). Moreover, although cortisol was not directly tested as a moderator of treatment outcome, cortisol levels during the exposure session did differ between the daytime groups, confirming the intended endogenous cortisol differences between groups. In addition, basal cortisol levels were assessed using both hair and saliva samples to characterize participants' long-term and diurnal cortisol activity prior to therapy. Notably, the groups did not differ in basal cortisol levels, further indicating that confounding by pre-existing differences in basal cortisol levels is rather unlikely to have affected the findings. Another study investigated participants with panic disorder and agoraphobia undergoing three in vivo exposure sessions within one week (Meuret et al., 2016). Sessions starting earlier in the day were associated with greater therapeutic gains by the next therapy session, as evident in lower severity of threat misappraisal, avoidance behavior, and panic symptoms, as well as higher perceived control. However, exposure times were not randomly assigned, introducing the possibility of confounding factors that may have differently affected treatment outcomes. Moreover, the study investigated three weekly exposure sessions, meaning cumulative treatment effects or habituation across sessions could not be fully disentangled from time-of-day effects. Critically, other studies failed to observe daytime effects of exposure therapy on treatment outcomes. For instance, Sopp et al. (2024) did not find any effects of daytime (8 a.m. vs. 6 p.m.) of a video-based in virtuo exposure in randomly assigned participants with snake anxiety. Moreover, given the limited sample size statistical power may also have been limited to observe any effects. Taken together, although some evidence points to daytime as involved in exposure therapy outcomes, empirical evidence is still limited, and inconclusive, mostly due to heterogenous study designs.

The present study was therefore designed as a preregistered conceptual replication and extension of Lass-Hennemann and Michael (2014), addressing the same central question, while incorporating several methodological refinements. Specifically, the current study was preregistered, employed a double-blind design, and included a more comprehensive analysis of endogenous cortisol. The following hypothesis was tested: Participants undergoing exposure-based CBT in the morning (8 a.m.) will have a greater reduction in behavioral avoidance and phobic fear than those undergoing exposure-based CBT in the evening (5 p.m.). Exploratory analyses further examined whether average cortisol levels, reactivity (AUCi), total output (AUCg), and response during exposure were associated with reductions in behavioral avoidance and phobic fear. The hypotheses were pre-registered on the Open Science Framework prior to data collection (OSF; osf.io/tfp5n).

2. Methods

This study was part of a larger research project investigating the effects of endogenous hormones during exposure therapy on treatment outcomes. All participants received compensation vouchers for restaurants with a total value of 80 CHF per person. This study protocol was approved by the Ethics Committee of the Kanton Zurich (KEK; 2021–00091). The study was carried out in accordance with the standards of the Declaration of Helsinki.

2.1. Participants

The sample consisted of individuals who had registered for exposure therapy for spider phobia at the University's Outpatient Clinic for Cognitive Behavioral Therapy and Behavioral Medicine. Participants recruitment began prior to preregistration of the study (recruitment: May 2021, preregistration: March 2022) and ended February 2025. Participants were contacted by study investigator 1 to be given information about the study. Participants who expressed interest in the study underwent a telephone screening interview to assess eligibility. Recruitment ended before the target sample size was achieved because of time and resource constraints.

Inclusion criteria encompassed women and men between 18 and 65 years, good German language skills, body mass index (BMI) between 18 and 30, and symptoms of spider phobia according to the Structured Clinical Interview for DSM-IV (SCID-IV; Wittchen, Zaudig & Fydrich, 1999). In addition, premenopausal women who had regular menstrual cycles (21–37 days) or were using hormonal contraceptives were included, as well as postmenopausal women.

Participants were excluded if they had medical conditions affecting hormonal balance (e.g., polycystic ovary syndrome, endometriosis, breast cancer, rheumatism, HIV, thyroid disease, diabetes, autoimmune disorders, or multiple sclerosis), lifetime psychotic or bipolar disorders, or current depressive disorders, substance abuse or dependence (past two years), or eating disorders (past five years). Recent use of psychoactive substances (past two months), use of medications or hormones affecting the endocrine system (except hormonal contraceptives), current or planned psychotherapeutic or psychiatric treatment during the study period were also considered exclusion criteria. Women currently pregnant, breastfeeding, or perimenopausal were also excluded, as well as participants who had registered for the present exposure therapy for a second time.

The participant flow chart for the present study is displayed in Fig. 1. The final sample consisted of N = 53 participants, of which n = 21 underwent exposure therapy during the morning (8 a.m.) and n = 32 in the evening (5 p.m.). Although inclusion required clinically relevant spider phobia symptoms rather than a formal diagnosis, all but two participants from the evening group met diagnostic criteria. Both participants reported intense panic responses to spiders but no avoidance or daily impairment and were therefore retained based on clinical judgment.

2.2. Procedure

After successful inclusion, eligible study participants were randomly assigned to either morning or evening session by drawing lots, whereas participants not enrolled in the study were allocated to group capacity and personal preference on their registered day. On dates with too few registered participants to run two groups, one session was selected at random by drawing lots and cancelled, and all patients were combined

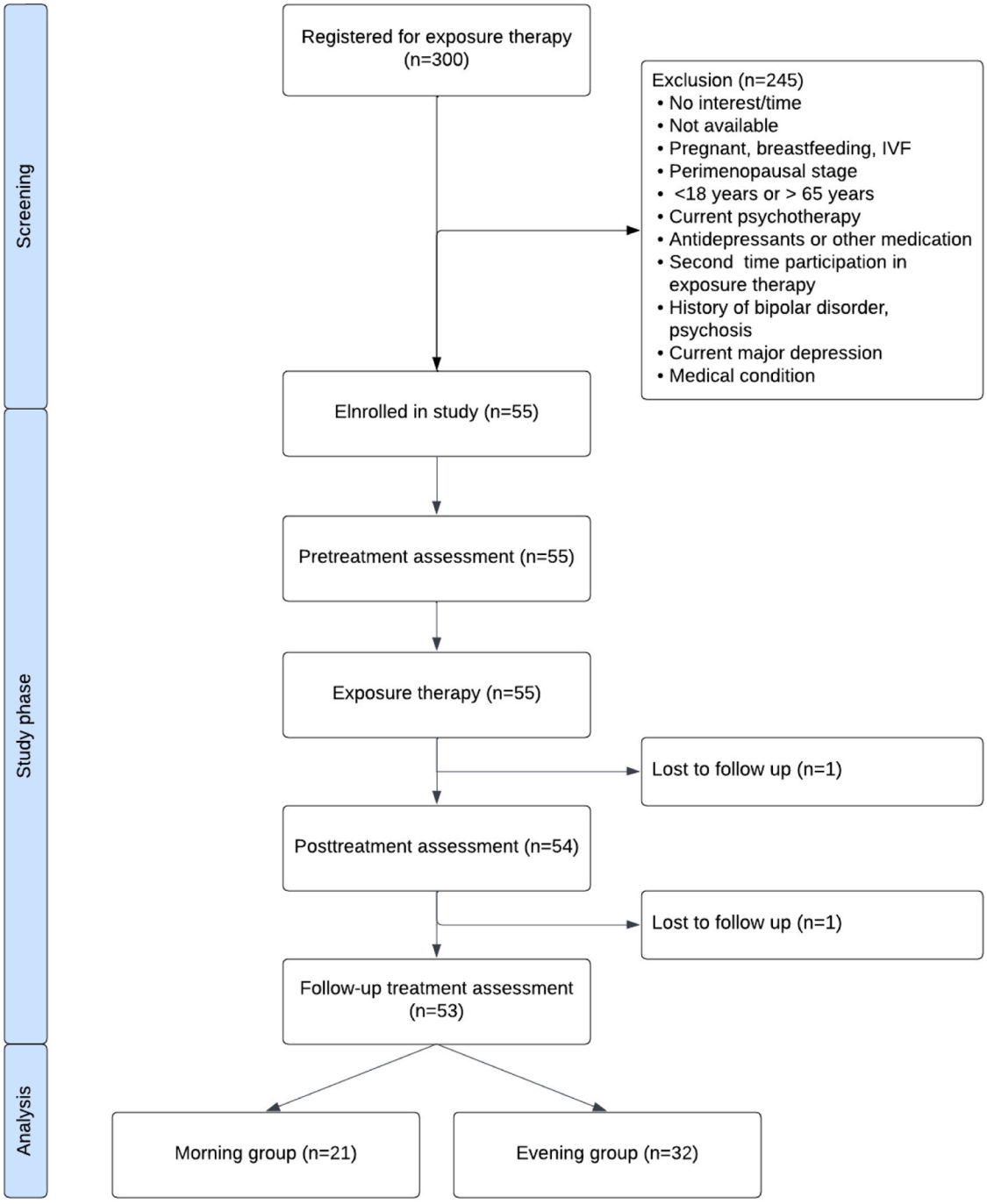


Fig. 1. Participant flow chart.

into the remaining session. Study participation included a total of four appointments, a pretreatment assessment, the exposure therapy, a one-week posttreatment assessment, and a three-month follow-up (Fig. 2). The participants, the clinical psychologists, the study investigators 2 and 3, the biologists, and the biochemical analyst were all blind to the study hypotheses. Specifically, the participants, therapists, and biologists were informed that the study investigated the effects of exposure therapy and a wide range of potentially implicated endogenous hormones and genes, and the session times were presented as given due to room and team availability. No information was provided regarding the comparison between morning and evening groups or the specific hormones under investigation. Investigators responsible for data collection (investigators 2 and 3) were Master's-level students not involved in study design or manuscript preparation and were blinded to study hypotheses and group allocation. The authors involved in study design and preregistration were excluded from delivering exposure therapy or data collection.

Pretreatment assessment: Around one week prior to exposure therapy, participants were invited to the pretreatment assessment, where written informed consent was obtained, as well as sociodemographic information and medical history. Subsequently, symptoms of spider phobia was assessed using the SCID-IV (Wittchen, Zaudig & Fydrich, 1999), the Fear of Spider Questionnaire (FSQ) and the Spider Phobia Questionnaire (SPQ) were administered, and a Behavioral Avoidance Test (BAT) was conducted. Participants were also informed to refrain from physical activity, alcohol and caffeinated beverages within three hours prior to exposure therapy. At the end of the session, participants received a questionnaire set to assess further psychological variables, which they filled in at home before exposure therapy.

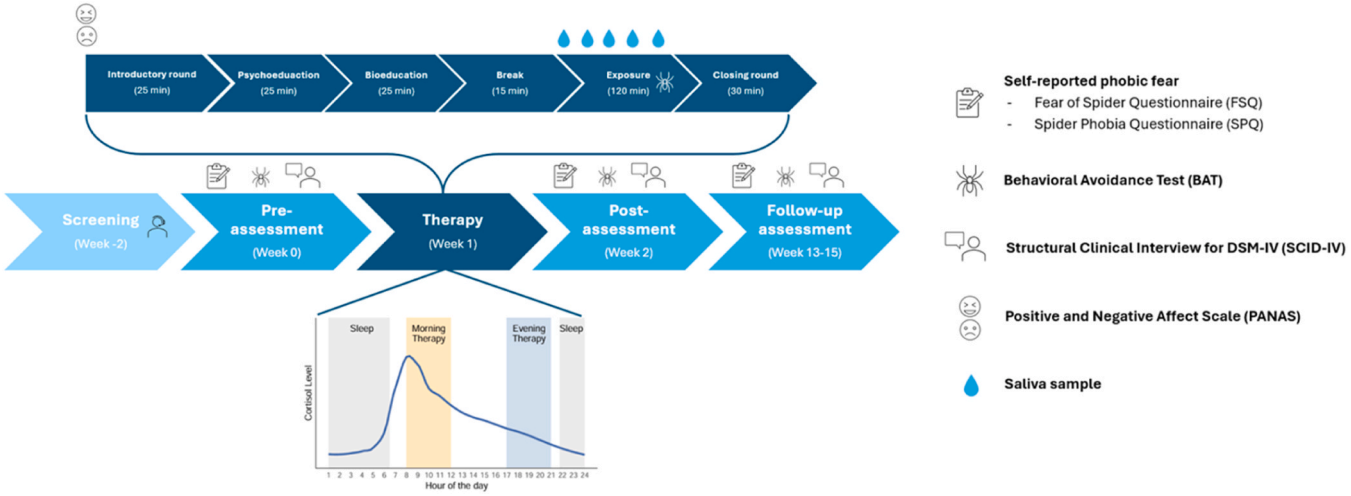


Fig. 2. Study design. **Note.** Schematic representation of the study design and diurnal cortisol rhythm. Study assessment sessions and exposure therapy modules are illustrated alongside the measures assessed at each time point. Cortisol levels peak shortly after waking and decline throughout the day. Grey shading indicates sleep periods, while orange and blue regions represent morning and evening therapy windows, respectively.

Exposure therapy: The exposure therapy consisted of a single four-hour long exposure-based CBT program delivered to a group of ten patients as a routine clinical treatment at the outpatients clinic, starting at 8 a.m. or 5 p.m. Session times were selected to correspond with expected high and low endogenous cortisol concentrations, respectively, aligning with the approach of Lass-Hennemann and Michael (2014). Evening session were scheduled at 5 p.m. rather than 6 p.m. as in Lass-Hennemann and Michael (2014), to ensure sessions concluded at a reasonable time while still capturing the expected a comparable low-cortisol evening window (Miller et al., 2016). The therapy was originally developed in accordance with the one-session treatment approach of the Öst workgroup (Öst, 1996, 1989; Öst et al., 1991), combining gradual exposure and modelling. A total of 30 exposure sessions were conducted, each including ten participants, of whom one to four were enrolled in the study.

Upon arrival, participants handed the completed home questionnaire set to study investigator 3 and completed the Positive and Negative Affect Schedule (PANAS; Krohne et al., 1996). The session started with a 25 min introductory round, in which individual experiences with spiders were exchanged and treatment goals were formulated, followed by a 25 min psychoeducation about fear and anxiety disorders. These therapy elements were guided by two clinical psychologists trained in exposure-based group CBT by licensed clinical psychologists UG and GP. A total of six clinical psychologists (all women) delivered the therapy sessions across both timepoints throughout the study. Within each pair of psychologists guiding a given group, at least one was a licensed psychologist and the other had at least two years of training in CBT. Exposure therapy specific training took place before delivering any therapy sessions, supplemented by intervision before and after each session and by supervision from UG and GP available upon request. Psychologists delivered sessions in both time slots. The psychoeducation was followed by a 25 min bio-education about spiders, delivered by a biologist/curator of a local zoo.

After a break of 15 min, individual exposure began, comprising graded steps of increasing difficulty over 120 min. Throughout, subjective distress (SUDS) was rated repeatedly. Progression to the next step required both a reduction in SUDS of at least 50% from that step's peak and successful completion of the step's behavioral task. In the first step, all participants viewed and touched pictures of spiders guided by clinical psychologists. For subsequent steps, the group was split into two subgroups of around five participants per clinical psychologist, with the biologist rotating between them. Within each subgroup, the therapist first demonstrated each step (modelling); one participant then performed it while the others observed, which continued in turn until all participants completed the step, at which point the subgroup advanced. The steps progressed from touching and holding a dead spider to catching a live spider using a glass and a postcard, repeated with three further spiders of gradually increasing size. All spiders were species indigenous to Switzerland, ranging from approximately 1–5 cm. In contrast to Lass-Hennemann and Michael (2014) and the Öst protocol, participants were not encouraged to touch or hold the live spiders, given that only catching them is relevant for daily functioning. Exposure steps were rated by study investigator 3. The exposure therapy ended with a 30 min closing round.

Posttreatment assessment: The posttreatment assessment took place one week after exposure therapy. The participants underwent once again the SCID-IV, filled in the FSQ and SPQ, and conducted the BAT.

Follow-up treatment assessment: The follow-up treatment assessment took place around 12–14 weeks after exposure therapy, where the same procedures as during the posttreatment assessment were repeated. At the end, however, all participants were fully debriefed about all study hypotheses. Importantly, the pre-, post-, and follow-up treatment assessments were all conducted in the afternoon.

2.3. Measures

2.3.1. Pretreatment

Chronotype was measured via the German version of the Morningness-Eveningness-Questionnaire (MEQ; Horne and Ostberg, 1976), which comprises 19 items that determine whether a person is a morning, neutral or evening type. The MEQ was included in the home questionnaire set.

2.3.2. Pretreatment, posttreatment, and follow-up

Behavioral avoidance was assessed using a behavioral approach test (BAT) with a live 5-cm house spider. The BAT assesses how closely participants are willing to approach the phobic stimuli, thereby providing an objective, in-vivo behavioral measure of avoidance. The BAT followed the established stepwise procedure described by (Öst et al., 1991), which has demonstrated sensitivity to behavioral change in clinically diagnosed sample with spider phobia. The distance of approaching the spider is rated on a 10-point scale: 0 =refuses to enter the test room, 1 =stops 3 m from the container, 2 =stops 2 m from the container, 3 =stops 1 m from the container, 4 =stops close to the windowsill with the container, 5 =touches the container, 6 =removes the lid, 7 =puts a hand in the container, 8 =touches the inside of the

container, 9 =touches the spider with one finger.

Phobic fear was assessed via the German version of both the Fear of Spiders Questionnaire (FSQ; Rinck et al., 2002) and the Spider Phobia Questionnaire (SPQ; Rinck et al., 2002). The FSQ measures the severity of phobic fear by means of 18 items rated on a 7-point Likert scale ("0 =does not apply to me at all" to "6 =fully applies to me"), scoring up to 108 points in total, with higher scores indicating greater phobic fear. The SPQ measures phobic fear by means of 43 items that are answered by checking either "yes" or "no", scoring up to 33 points, with higher scores indicating greater fear. The FSQ and SPQ were selected to provide complementary assessments of spider fear. The SPQ assesses one behavioral factor (e.g., avoidance and help-seeking) and two cognitive factors (e.g., vigilance and internal preoccupation) using a binary yes/no response format with no specified time frame (Watts and Sharrock, 1984). The FSQ was developed to complement the SPQ by capturing a broader range of fear-related dimensions, including cognitive, behavioral, physiological, negative attitudes, and fear of harm, with a Likert-scale response format anchored to the present moment (i.e., "now"; Szymanski and O'Donohue, 1995).

2.3.3. Exposure therapy

Exposure steps were scored as follows: 0 =watching pictures of spiders, 1 =touching pictures of spiders, 2 =watching dead spiders, 3 =touching dead spiders, 4 =putting the hand in the container that contains the small spider, 5 = touching the small spider, 6 =catching the small spider using a postcard and plastic cup, 7 =putting the hand in the container that contains the large spider, 8 =touching the large spider, 9 =catching the large spider using a postcard and plastic cup.

2.4. Hormonal assessment

A total of five saliva samples were collected during the individual exposure (at the beginning, +30 min, +60 min, +90 min, +120 min) using SaliCaps (IBL, Hamburg, Germany). The samples were stored at −20°C up until to biochemical analysis, which was conducted at the biochemical laboratory of the Institute of Psychology at the University of Zurich. Cortisol was assessed in all five samples by means of commercially available luminescence immunoassays (IBL, Hamburg, Germany). The intra- and inter-assay variance of these kits was < 10%.

Cortisol output (area under the curve with respect to ground; AUCg) and change (the area under the curve with respect to increase; AUCi) during individual exposure were both calculated using the trapezoidal method (Pruessner et al., 2003). Calculations were based on cortisol measurements obtained at 0, 30, 60, 90, and 120 min relative to the start of individual exposure. This phase began approximately 90 min after the start of the overall therapy session. Cortisol responder status was defined following recommendations by Miller et al. (2013). Participants were classified as responders if cortisol increased by at least 1.5 nmol/L from the first assessment prior to start of individual exposure to the person's peak, and as nonresponders if the increase fell below this threshold.

2.5. Statistical analysis

Appropriate statistical tests, encompassing independent samples *t*-test or Fisher's exact test, were applied to assess differences in sample characteristics between the morning and evening group, based on data type and distribution assumptions. A linear mixed-effects repeated-measures analysis of variance (ANOVA) was used to investigate changes in cortisol levels during exposure therapy with daytime (morning vs. evening) as a categorical between-subjects factor, assessment time (start of exposure, +30 min, +60 min, +90 min, +120 min) as a categorical within-subjects factor, and a random intercept for participant. The statistical analyses regarding our study aims were divided into primary analyses, based on preregistered hypotheses and statistical methods, and secondary, exploratory analyses, reflecting analyses not specified a priori.

Primary analyses: For the first hypothesis, linear mixed-effects repeated-measures ANOVAs were again used to examine changes in behavioral avoidance (BAT) and phobic fear (FSQ and SPQ), with daytime specified as a categorical between-subjects factor, assessment time (T1: pretreatment, T2: posttreatment, T3: follow-up) fitted as a categorical within-subjects factor, and a random intercept for participant. The Type III ANOVA-based F-tests with Satterthwaite-approximated degrees of freedom were used to evaluate fixed effects. Significant main and interaction effects were followed up using planned contrasts based on estimated marginal means. For significant main effects, pairwise comparisons examined differences between factor levels. For significant interaction effects, planned within-group contrasts tested changes from pre- to posttreatment assessment and from pre- to follow-up treatment assessment, and between-group contrasts compared these change scores across groups. Chronotype was included as a covariate to account for individual differences in participants' daytime preferences in a second exploratory step, as this was not preregistered.

Exploratory analyses: Additional exploratory analyses were conducted using median split groups of mean cortisol levels during exposure, cortisol output (AUCg) and reactivity (AUCi) during individual exposure, as well as cortisol responder status, as between-subjects factors. Moreover, exploratory Spearman rank correlations examined the association between cortisol measures (mean levels, AUCg, and AUCi) and delta changes in behavioral avoidance and phobic fear from pre- to posttreatment assessment and from pre- to follow-up treatment assessment.

All analyses were corrected for multiple testing using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995) and were conducted in R (version 4.5.1).

2.6. A priori power analysis

An a priori power analysis using G*Power (Faul et al., 2007) indicated that a sample size of N = 60 participants (α=0.05, power=80%) would be required to detect a moderate effect size, as inferred from Lass-Hennemann and Michael (2014), of the interaction between time and daytime groups in a mixed ANOVA. The preregistration targeted a larger sample size (N = 120) because the study was aimed to test additional hypotheses and outcomes beyond those examined in the present manuscript.

3. Results

3.1. Sample characteristics

Sample characteristics are displayed in Table 1. The morning group showed significantly higher pretreatment phobic fear (SPQ) than the evening group and comprised a greater proportion of individuals classified as cortisol responders compared to the evening group. No further significant group differences were observed

3.2. Cortisol during exposure therapy

Fig. 3 shows the trajectory of cortisol levels during exposure therapy according to daytime group status. Cortisol levels were found to significantly differ between the daytime groups ($F(1, 52) = 4.64$, $p = 0.035$, $\eta^2 = 0.08$). Post-hoc tests revealed that the morning group (M=2.8, SE=0.5) showed overall higher cortisol levels overall than the evening group (M=1.4, SE=0.3, estimate=-1.4, SE=0.63, $t = -2.15$, $p = 0.036$). However, cortisol levels did not change during the exposure therapy ($F(4, 194) = 0.31$, $p = 0.865$, $\eta^2 = 0.006$), and there was no evidence that this pattern differed between daytime groups ($F(4, 194) = 0.31$, $p = 0.525$, $\eta^2 = 0.02$).

Table 1
Sample characteristics.

Variable	Full sample (n = 53)		Morning group (n = 21)		Evening group (n = 32)		Statistics, *p*-value
	n(%)	M(SD)	n(%)	M(SD)	n(%)	M(SD)	
Age (years)		30.3 (8.5)		28.0 (7.7)		31.7 (8.8)	$t = 1.59$, $p = 0.11$
Gender							Fisher's test, $p = 0.99$
Women	50 (94.4)		20 (95.2)		30 (90.7)		
Men	3 (5.6)		1 (4.8)		2 (6.3)		
Chronotype (MEQ)							Fisher's test, $p = 0.10$
Definitely morning type	1 (1.9)		0 (0)		1 (3.1)		
Moderately morning type	12 (22.6)		3 (14.3)		9 (28.1)		
Neither type	27 (50.9)		15 (71.4)		12 (37.5)		
Moderately evening type	12 (22.6)		3 (14.3)		9 (28.1)		
Definitely evening type	0 (0)		0 (0)		0 (0)		
Exposure steps		6.5 (2.3)		6.4 (2.1)		6.5 (2.4)	$t = 0.06$, $p = 0.95$
Cortisol							
Average[a] (nmol/L)		1.8 (2.3)		2.5 (2.9)		1.4 (1.6)	$t = -1.59$, $p = 0.12$
AUCg		234 (290)		363(392)		161(183)	$t = -2.05$, $p = 0.05$
AUCi		-12.3 (365)		9.35(549)		-24.5(213)	$t = -0.25$, $p = 0.80$
Responders	9 (16.9)		7 (33.3)		2 (6.3)		Fisher's test, $p = 0.006$
Pretreatment behavioral avoidance (BAT)		3.4 (2.1)		2.8 (2.4)		3.85 (1.9)	$t = 1.61$, $p = 0.11$
Pretreatment phobic fear							
Fear of Spiders Questionnaire (FSQ)		73.9 (18.4)		78.5 (15.1)		70.9 (19.6)	$t = -1.58$, $p = 0.12$
Spider Phobia Questionnaire (SPQ)		22.8 (4.9)		25.0 (3.1)		21.3 (5.3)	$t = -3.20$, $p = 0.002$

Note. [a]Mean cortsiol levels during exposure therapy. AUCg; Area Under the Curve with respect to ground, AUCi; Area Under the Curve with respect to increase.

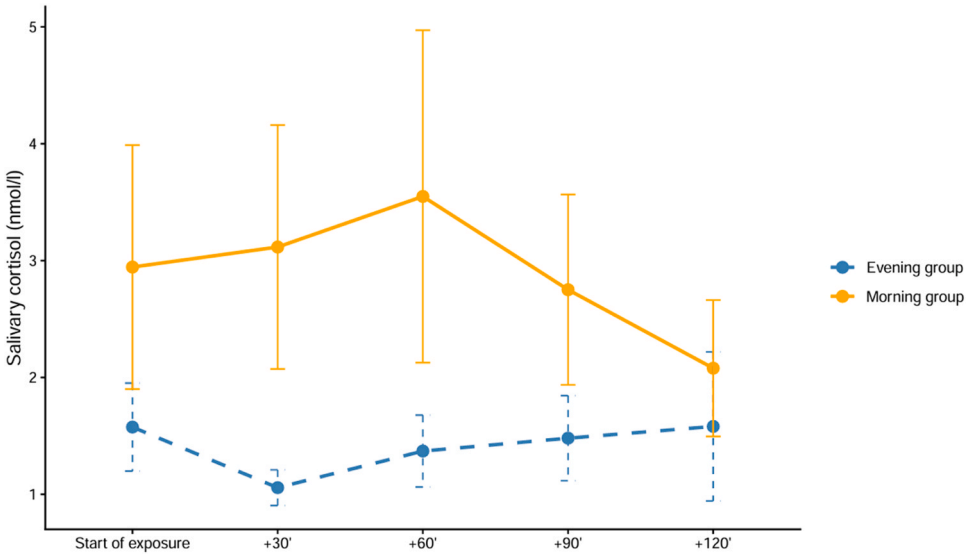


Fig. 3. Changes in salivary cortisol during exposure in the morning and evening groups. **Note.** Mean salivary cortisol levels (± standard error) across exposure therapy sessions for the morning and evening groups. Time points represent repeated assessments during exposure.

3.3. Behavioral avoidance

Daytime: Fig. 4A displays the trajectories for behavioral avoidance for the daytime groups. As expected, behavioral avoidance significantly improved following exposure therapy ($F(2, 102) = 116.77$, $p < 0.001$, $\eta^2_p = 0.70$), from both pre- to posttreatment (estimate=-2.66, SE=0.21, $t = -12.29$, $p < 0.001$) and pre- to follow-up treatment assessment (estimate=-3.03, SE=0.21, $t = -14.00$, $p < 0.001$). The daytime groups differed in their overall behavioral avoidance ($F(1, 51) = 5.65$, $p < 0.021$, $\eta^2_p = 0.10$). Post-hoc tests revealed greater behavioral avoidance in the morning than the evening group across all time points (estimate=1.27, SE=0.53, t = 2.37, $p = 0.021$). However, contrary to expectation, there were no significant group differences in terms of behavioral avoidance improvement over time ($F(2, 102) = 0.59$, $p = 0.553$, $\eta^2_p = 0.01$). These results withstand correction for multiple testing and remained consistent after accounting for chronotype in exploratory analyses.

Exploratory cortisol analyses: Neither mean cortisol levels nor cortisol output (AUCg) or reactivity (AUCi) during individual exposure were correlated with behavioral avoidance changes (see Table 2). Further exploratory analyses using median split groups revealed no significant main or interaction effects for mean cortisol levels, cortisol output (AUCg) or reactivity (AUCi; all $p > 0.05$). However, a trend emerged for the cortisol response group to differ in their overall behavioral avoidance ($F(1, 48) = 3.83$, $p = 0.055$, $\eta^2_p = 0.07$). Post hoc test revealed a trend for overall higher behavioral avoidance among nonresponders than among responders (estimate=1.36, df=0.69, $t = 1.95$, $p = 0.055$). However, there were no significant group differences in terms of behavioral avoidance improvement over time between responders and non-responders ($F(2, 96) = 0.66$, $p = 0.514$, $\eta^2_p = 0.01$).

3.4. Self-reported phobic fear

Daytime: Fig. 4B-C displays the trajectories of phobic fear (both FSQ

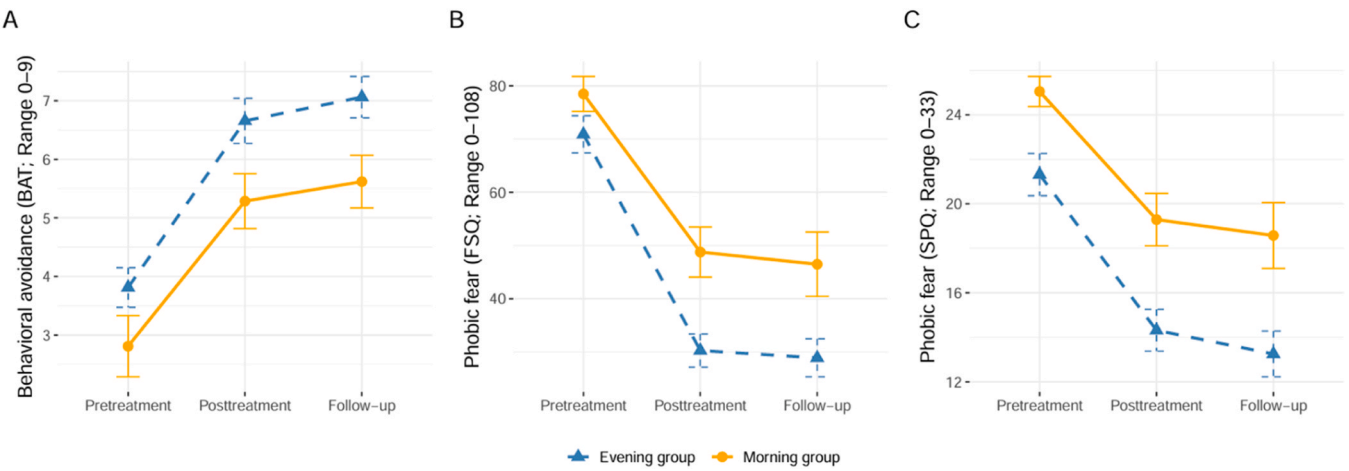


Fig. 4. Unadjusted behavioral avoidance and phobic fear over time according to daytime group status. **Note.** Higher BAT values indicate less behavioral avoidance towards a spider. Higher FSQ and SPQ values indicate less phobic fear towards a spider.

Table 2
Exploratory Spearman correlation results for behavioral avoidance and self-reported phobic fear.

Cortisol	Behavioral avoidance (BAT)		Phobic fear (FSQ)		Phobic fear (SPQ)	
	Pre- to post	Pre- to FU	Pre- to post	Pre- to FU	Pre- to post	Pre- to FU
Mean	0.02	-0.12	-0.03	0.02	-0.11	-0.08
AUCi	-0.12	-0.17	**0.46***	**0.54***	**0.39***	**0.47***
AUCg	-0.08	-0.06	-0.01	0.06	-0.03	-0.01

Note. Significant results are bolded. *Significant after correction for multiple testing.

and SPQ) relative to daytime group status. As expected, phobic fear assessed with the FSQ significantly improved following exposure therapy ($F(2, 102) = 122.48$, $p < 0.001$, $\eta^2_p = 0.71$), from pre- to posttreatment assessment (estimate=-35.15, SE=2.66, t = -13.19, $p < 0.001$) and from pre- to follow-up treatment assessment (estimate=-36.98, SE=2.66, t = -13.88, $p < 0.001$). Overall phobic fear also differed between daytime groups ($F(1, 51) = 9.07$, $p < 0.004$, $\eta^2_p = 0.15$). Post-hoc tests revealed greater phobic fear in the morning than the evening group across all time points (estimate=14.6, SE=4.83, t = 3.01, $p = 0.004$). Furthermore, a trend emerged indicating that phobic fear improvement differed between groups ($F(2, 102) = 2.56$, $p = 0.081$, $\eta^2_p = 0.05$). Although the evening group showed a greater improvement (both from pre- to posttreatment assessment and from pre- to follow-up treatment assessment), planned contrasts were all non-significant (all $p > 0.05$).

Similarly, phobic fear assessed with the SPQ significantly improved following exposure therapy ($F(2, 102) = 72.78$, $p < 0.001$, $\eta^2_p = 0.59$). This improvement was again evident from both pre- to posttreatment assessment (estimate=-6.38, SE=0.65, t = -9.70, $p < 0.001$) and pre- to follow-up treatment assessment (estimate=-7.26, SE=0.65, t = -11.05, $p < 0.001$). Overall phobic fear likewise differed between the daytime groups ($F(1, 51) = 12.46$, $p < 0.001$, $\eta^2_p = 0.20$), with greater phobic fear in the morning than the evening group across all time points (estimate=4.68, SE=1.32, t=3.53, $p < 0.001$). However, improvement in phobic fear did not differ between daytime groups ($F(2, 102) = 0.80$, $p = 0.450$, $\eta^2_p = 0.02$). These results withstood correction for multiple testing and remained consistent after accounting for chronotype in a secondary exploratory step.

Exploratory cortisol analyses: Contrary to expectation, mean cortisol levels during exposure were not correlated with changes in phobic fear, as measured by both the FSQ and the SPQ (see Table 2), and the same was true for cortisol output (AUCg). However, after correction for multiple testing, exploratory analyses found moderate to large correlations between cortisol change (AUCi) and changes in phobic fear (FSQ and SPQ) for both pre- to posttreatment assessment and pre- to follow-up treatment assessment (see Table 2).

Further exploratory analyses investigating median split groups did not find any significant main or interaction effects for mean cortisol levels or cortisol output (AUCg), for either the FSQ or the SPQ. However, a significant interaction emerged between median split groups of cortisol change (AUCi) and time for both FSQ ($F(2, 96) = 12.12$, $p < 0.001$, $\eta^2_p = 0.20$, Fig. 5A) and SPQ ($F(2, 96) = 90.20$, $p < 0.001$, $\eta^2_p = 0.11$, Fig. 5B), indicating that improvement in phobic fear differed between the groups. Post-hoc tests revealed a greater improvement in phobic fear following exposure therapy in the group with lower cortisol change (low AUCi) than those with higher cortisol change (high AUCi) from pre- to posttreatment assessment (FSQ: estimate=-16.56, SE=4.97, t = -3.32, $p < 0.002$; SPQ: estimate=-3.28, SE=1.24, t = -2.64, $p = 0.018$) and from pre- to follow-up treatment assessment (FSQ: estimate=-23.92, SE=4.97, t = -4.80, $p < 0.001$; SPQ: estimate=-4.04, SE=1.24, t = -3.26, $p = 0.004$). Exploratory follow-up sensitivity analyses were conducted by categorizing participants according to cortisol change (AUCi), distinguishing between increases (AUCi > 0) and decreases (AUCi ≤ 0). The significance, direction, and magnitude of the results remained unchanged, indicating that participants with cortisol decreases during exposure showed greater improvement compared to those with increases.

Additional exploratory analyses among cortisol responders and nonresponders revealed a significant interaction between response group and time for both FSQ ($F(2, 96) = 10.10$, $p < 0.001$, $\eta^2_p = 0.17$, Fig. 5C) and SPQ ($F(2, 96) = 5.91$, $p = 0.003$, $\eta^2_p = 0.11$, Fig. 5D), indicating phobic fear improvement differences between the groups (Figure 6). Post-hoc tests revealed a greater improvement in phobic fear following exposure therapy in nonresponders than responders from pre- to posttreatment assessment (FSQ: estimate=-19.42, SE=6.59, t = -2.94, $p < 0.008$; but not for SPQ: estimate=-2.68, SE=1.61, t = -1.65, $p = 0.100$) and from pre- to follow-up treatment assessment (FSQ: estimate=-29.07, SE=6.59, t = -4.41, $p < 0.001$; SPQ: estimate=-5.55, SE=1.61, t = -3.43, p=0.002).

3.5. Sensitivity analysis

As an exploratory post hoc sensitivity analysis, all models were re-run excluding the three male participants in light of established gender differences in hypothalamic-pituitary-adrenal axis (HPA) activity and cortisol secretion (Fries et al., 2009; Uhart et al., 2006). The pattern of results remained unchanged.

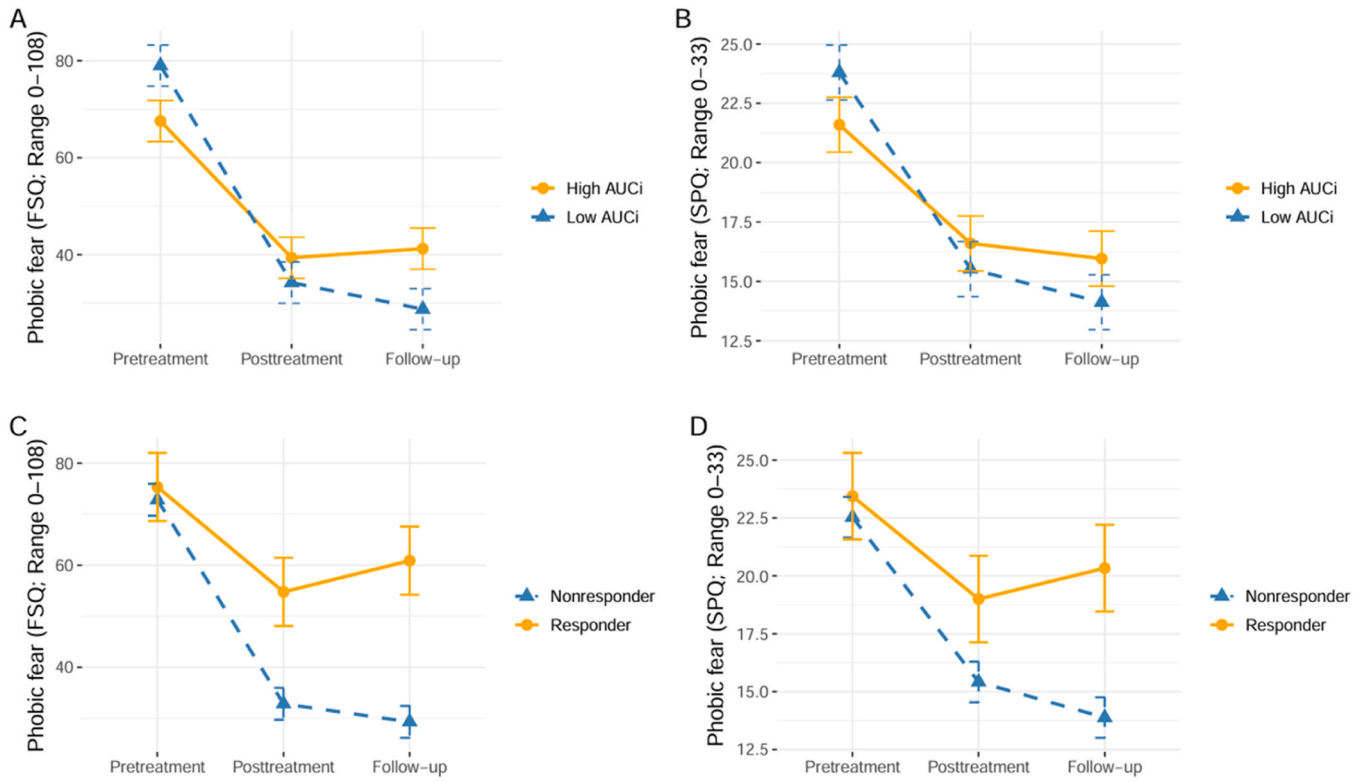


Fig. 5. Unadjusted phobic fear over time according to cortisol change and response groups. **Note.** Panels A-B present median split groups based on cortisol AUCi, whereas Panels C-D present cortisol responder and nonresponder groups according to Miller et al. (2013). AUCi reflects cortisol change during individual exposure relative to first measurement prior to starting individual exposure, with positive values indicating increases and negative values indicating decreases over time.

4. Discussion

This study aimed to replicate and extend Lass-Hennemann and Michael (2014) investigation of time-of-day of exposure therapy (8 a.m. or 5 p.m.) and endogenous cortisol during exposure as potential modulators of treatment outcomes. As expected, exposure therapy was highly effective and cortisol levels were higher in the morning than evening group and remained stable throughout exposure. However, contrary to expectation, the daytime groups did not differ in their symptom improvement. Nevertheless, exploratory analyses revealed that lower cortisol change during individual exposure, as reflected by lower cortisol AUCi and categorization as a cortisol nonresponder during individual exposure, was associated with greater improvement in phobic fear.

A single session of exposure therapy resulted in large reductions of both phobic fear and avoidance behavior, aligning with previous findings (Lass-Hennemann and Michael, 2014). Contrary to expectations, however, symptom improvement did not differ between morning and evening groups. This contrasts previous findings in spider phobia reported by Lass-Hennemann and Michael (2014), who found greater symptom improvements for those undergoing exposure therapy in the morning. Several methodological differences may account for this discrepancy. First, therapists in the previous study were not blinded to the study hypothesis, whereas the present study employed a double-blind design, thereby reducing expectancy effects. Second, the sample investigated by Lass-Hennemann and Michael (2014) consisted solely of women taking oral contraceptives, while our sample comprised both men and women with either natural cycles or hormonal contraceptive use. Third, although both studies scheduled morning sessions at 8 a.m., individual exposure to spiders in the present study did not begin until approximately 10 a.m., a time point at which cortisol levels likely have already substantially declined following awakening (Miller et al., 2016). Although we were able to observe higher cortisol levels in the morning than evening group, morning cortisol levels in the present study were substantially lower than in the previous study (Lass-Hennemann and Michael, 2014). This is further supported by a study by Meuret et al. (2016), indicating that earlier morning exposure sessions were associated with increased therapeutic improvement in participants with panic disorder and agoraphobia. Earlier sessions were further associated with higher cortisol levels, which in turn were associated with greater therapeutic improvement by the next therapy session. Moreover, a greater CAR on the exposure day was associated with greater treatment improvements, although the effect of potential confounders can not be ruled out (Meuret et al., 2015). However, all exposure sessions in the present study were conducted on weekends, when the CAR is typically reduced compared to weekdays (Kunz-Ebrecht et al., 2004). The expected effects may have therefore only been observable immediately after awakening, when endogenous cortisol reaches its peak. As the individual exposure began somewhat later in the morning, this window may not have been captured. Future studies could address this by scheduling individual exposure very shortly after awakening, and preferably on weekdays. Nevertheless, the absence of time-of-day differences in the present study is in line with more recent findings in snake anxiety following in virtuo exposure (Sopp et al., 2024), suggesting that the effect of session timing during the day on treatment efficacy may potentially be less robust than previously assumed.

Moreover, although overall treatment effects were comparably strong to Lass-Hennemann and Michael (2014), rendering it unlikely that methodological differences in treatment procedure and therapists substantially affected overall efficacy, differences in the group-based, multi-component delivery format and in therapist behavior and exposure procedure itself may still have contributed to the divergent daytime outcomes. In particular, participants in the present study were not required to touch or hold the spiders but only to catch them, representing a lower exposure intensity than in Lass-Hennemann and Michael

(2014). However, given the limited sample size, non-significant daytime findings should overall be interpreted with caution, as they may reflect insufficient statistical power rather than a true absence of effects, highlighting the need for replication in larger samples.

Although mean cortisol levels and cortisol output (AUCg) during exposure were not associated with treatment improvements, exploratory analyses revealed that a lower cortisol change (AUCi) and classification as a cortisol nonresponder during individual exposure predicted greater improvements in phobic fear (both SPQ and FSQ). At first glance, this finding appears counterintuitive, as cortisol increases during stress are typically considered adaptive (McEwen, 2007), and have been hypothesized to enhance exposure-based treatment responses (Fischer and Cleare, 2017). Indeed, randomized controlled trials have shown that administration of exogenous cortisol prior to exposure enhances fear reduction in specific phobia, which has been attributed to reduced fear-memory retrieval during exposure and enhanced consolidation of extinction memory (de Quervain et al., 2011; Soravia et al., 2014, 2006). Endogenous cortisol has likewise been implicated in supporting fear extinction, by suppressing retrieval of phobic-specific memories and enhancing the consolidation of new, non-fearful experiences with the phobic stimulus (Bentz et al., 2010). However, while studies of exogenous cortisol have observed relatively consistent findings (de Quervain et al., 2011; Soravia et al., 2014, 2006), those investigating endogenous cortisol have been more mixed (Meuret et al., 2016, 2015; Sopp et al., 2024; Zuj et al., 2017), suggesting a more complex relationship.

Exposure therapy, despite subjective increases in distress, is typically not associated with HPA activation, as previous findings indicate that cortisol levels often remain relatively stable in exposure-based treatments across anxiety disorders (Kellner et al., 2012; Lass-Hennemann and Michael, 2014). Likewise, we did not observe a systematic cortisol increase during exposure, suggesting that cortisol increases during individual exposure may potentially reflect an atypical or maladaptive stress response to exposure, which may interfere with efficient inhibitory learning processes. Supporting this interpretation, several studies have reported negative associations between cortisol and treatment outcomes. For instance, elevated endogenous in-session cortisol during exposure for social anxiety disorder was associated with reduced symptom improvement, indicating that elevated neuroendocrine signaling may impair exposure therapy responses (Kuhlman et al., 2020). Another study by Norrholm et al. (2016) investigated whether psychophysiological responses and cortisol reactivity during confrontation with combat-related virtual reality (VR) scenes predict symptom improvements of posttraumatic stress disorder (PTSD) in combat veterans. While greater psychophysiological reactivity (e.g., skin conductance, heart rate) predicted greater symptom improvements, the opposite was observed for cortisol reactivity (difference between cortisol 15 min after VR scenes and baseline cortisol). Together, these findings suggest that elevated endogenous cortisol reactivity during exposure may potentially reflect an excessively strong biological stress response that may interfere with processing of corrective learning. This may be particularly relevant in anxiety disorders, which are characterized by hyperreactivity of the neuronal fear circuitry alongside deficits in regulatory prefrontal control and fear inhibition (Liberzon et al., 2015). Successful exposure therapy may therefore require emotional engagement without excessive endogenous neuroendocrine stress activation. However, empirical evidence remains limited and inconclusive, as opposing associations between cortisol reactivity and exposure-based treatment outcomes have also been observed (Zuj et al., 2017). Importantly, the studies differ substantially in their designs, populations, and outcome measures, which limit direct comparability. Moreover, given the limited sample size and thus limited statistical power, these contradictory findings should be interpreted cautiously, as small samples can inflate effect sizes and increase the risk of false positives. Further research is therefore needed to clarify the role of endogenous cortisol reactivity and change in exposure-based treatment outcomes.

Cortisol-dependent effects were primarily observed on self-reported phobic fear, whereas no significant effects emerged for behavioral avoidance, contrasting with previous findings (Lass-Hennemann and Michael, 2014). This discrepancy may reflect several possibilities: a true absence of behavioral effects, insufficient sensitivity of the BAT scale to detect subtle avoidance differences, or limited statistical power given the small sample size. Among the self-report measures, findings were also more consistent for the FSQ than the SPQ, which may reflect the FSQ's greater sensitivity to change because of the Likert-scale response format and present-focused time frame compared with the SPQ's binary format and unspecified time frame (Szymanski and O'Donohue, 1995). The divergence between the two measures may therefore reflect their differing sensitivity and the distinct aspects of spider fear assess, rather than inconsistency in the underlying construct.

A key strength of the present study is that it constitutes a preregistered conceptual replication and extension of Lass-Hennemann and Michael (2014). Specifically, the present study employed a double-blind design, which minimized expectancy effects and potential bias from both participants and investigators, thereby enhancing internal validity. The inclusion of both a one week post-, and a 3-month follow-up assessment further allowed for the examination of both immediate and sustained effects of exposure therapy. An additional strength lies in the well-characterized sample, with stringent inclusion and exclusion criteria, which likely enhanced internal validity by reducing heterogeneity and limiting potential confounding influences.

However, several limitations should be considered. First, the relatively small and unbalanced sample size limited statistical power, particularly for daytime effects and cortisol responder effects. Consequently, the study was primarily sensitive to larger daytime effects, highlighting the importance of interpreting null findings with caution and the need for further replication. Notably, because participants were allocated by simple randomization (drawing lots), rather than a block or stratified procedure, equal group sizes were not guaranteed. Second, the sample comprised both women and men, despite evidence of gender differences in avoidance behavior in individuals with specific phobias (Graham et al., 2020) and cortisol reactivity (Liu et al., 2017). Although exploratory sensitivity analyses excluding the three male participants did not change the pattern of results, replication in larger samples and further investigation of potential gender differences is warranted. Moreover, several factors may have influenced the interpretation of the present findings by differing between morning and evening groups. One is the higher pretreatment SPQ scores in the morning group. In addition, sleep during the night before exposure therapy and attention during exposure therapy were not assessed, leaving a further, unmeasured source of potential confounding between the two groups. Moreover, given that SUDS were only assessed orally during exposure, they could not be modeled quantitatively in relation to the cortisol concentration curves, and therefore no conclusions can be drawn as to whether they have been affected by SUDS. Moreover, given that the initial saliva sample was collected at the onset of the individual exposure phase, the AUCi should be interpreted as the change in cortisol across individual exposure rather than as reactivity relative to a resting baseline. In addition, because no basal cortisol levels were assessed on non-therapy days, the session cortisol trajectories could not be compared against a control condition and can therefore not be unambiguously distinguished from the expected diurnal decline. Finally, full blinding cannot be guaranteed, as the possibility that participants or team members independently sought out the preregistration or otherwise inferred the study hypotheses cannot be excluded.

5. Conclusion

Although leveraging endogenous circadian cortisol fluctuations for exposure therapy would represent a promising, easily implementable, and side-effects free approach to enhance therapeutic response, the present findings do not support its application. Nevertheless, our exploratory findings provide preliminary evidence that lower cortisol

change during individual exposure may be associated with greater phobic fear improvements. Whether endogenous cortisol change during individual exposure is meaningfully related to treatment response, potentially serving as a biomarker to distinguish between individuals who are more or less likely to benefit from exposure-based interventions, warrants investigation in larger studies. Overall, these findings highlight the complexity of neuroendocrine effects on exposure-based learning and underscore the need for further research to clarify the role of daytime and cortisol.

CRediT authorship contribution statement

Gianna Zorzini: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Patricia Ritter:** Writing – review & editing, Investigation, Data curation. **Gianandrea Pallich:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Ursula Galli:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Ulrike Ehlert:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Susanne Fischer:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study included organ or tissue donors. This study includes human biological material and consent was obtained by donors, or their next of kin or legal representatives, for use in this study and for publication of the article. The samples used in this research were not sourced from executed prisoners or prisoners of conscience.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was conducted in accordance with Declaration of Helsinki. This study was approved by the Ethics Committee of the Kanton Zurich. (Approval No. 2021–00091)

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Susanne Fischer reports financial support was provided by Schweizerische Gesellschaft für kognitive Verhaltenstherapie (SGVT). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Our local regulations require that the participants' data in clinical studies is only shared for research purposes and only with additional informed consent, which is why they will only be shared upon reasonable request.

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