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Cognitive behavioral therapy, mindfulness, and cortisol habituation: A randomized controlled trial

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ABSTRACT

Background: Hypothalamic-pituitary-adrenocortical (HPA) axis dysregulation is associated with disease and may be indexed by poor cortisol habituation (i.e., a failure to show decreased responding with repeated stressor exposure). Thus, stress management training that can enhance HPA axis habituation may benefit health. To date, the effects of Mindfulness Based Stress Reduction (MBSR) and Cognitive Behavioral Therapy (CBT) interventions on HPA axis habituation remain untested. To test the effects of MBSR and CBT on HPA axis habituation, the present study used a parallel arm randomized controlled trial.

Methods: Healthy adults reporting moderate-to-high stress (n = 138) were randomly assigned to a 6-week MBSR intervention, a 6-week CBT intervention, or Waitlist control group. Post-intervention, participants completed a social-evaluative performance stressor during each of two laboratory visits scheduled 48-h apart. Salivary cortisol was collected pre-stressor, and 25, 35, and 60 min post-stressor onset during each visit. Final analyses included 86 participants who completed procedures up to the first laboratory visit.

Results: Relative to the control condition, both MBSR and CBT groups showed greater cortisol habituation. The MBSR group exhibited marginally greater habituation than the Waitlist group in cortisol samples corresponding to the recovery time points (35 and 60 min post-stressor onset). In contrast, the CBT group showed greater habituation than the Waitlist across all sampling timepoints collected (pre-stressor, 25, 35, and 60 min post-stressor onset). Yet, the CBT group also demonstrated elevated pre-stressor cortisol during the first visit.

Conclusions: Results suggest that MBSR and CBT interventions promote greater HPA axis habituation relative to no training, but do not reduce overall cortisol output (i.e., across both visits). Observed differences between CBT and MBSR training in relation to cortisol habituation are discussed.

1. Introduction

Stress is widely acknowledged as a factor that predisposes individuals for disease and aggravates the state of both psychiatric (Burke et al., 2005; Caspi et al., 2003; Mantella et al., 2008) and non-psychiatric illness (Hocking Schuler and O'Brien, 1997; Lovallo, 2015; Rosmond, 2003). A major link between stressors and illness lies in the potentially damaging effects of biological stress responses (McEwen, 1998a). Episodes of acute stress can activate peripheral stress response cascades like the hypothalamic-pituitary-adrenocortical (HPA) axis, resulting in the release of primary stress mediators which, in turn, influence the functioning of various biological processes. Over time, stress may lead to dysregulated HPA axis functioning and cortisol secretion and thus promote varied disease states. For example, excessive cortisol may increase the risk of developing infectious diseases (Glaser and Kiecolt-Glaser, 2005), whereas insufficient cortisol secretion may promote inflammation (Edwards et al., 2011).

Related, some prototypical stress response profiles are thought to be indicative of a dysregulated HPA axis. For example, the magnitude of cortisol stress responses may be too large or too small (i.e., suggesting heightened reactivity or non-reactivity), or cortisol levels may take too long to return to pre-stressor levels after the stressor has ended (i.e., indicating delayed recovery; McEwen, 2004; McEwen, 1998b). Moreover, cortisol production can be dysregulated in the context of repeated

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Table 1
Characteristics of the final sample by condition.

Characteristic	Full sample (N = 86)	MBSR (N = 31)	CBT (N = 34)	Waitlist (N = 21)	Condition comparison statistics
Age (years)	24.31 (7.88)	26.61 (9.51)	23.65 (7.21)	22.00 (5.25)	$F(2,83) = 2.42$
Sex					$X^2(2, N = 86) = 1.17$
Male	24 (27.9%)	9 (29.0%)	11 (32.4%)	4 (19.0%)	
Female	62 (72.1%)	22 (71.0%)	23 (67.6%)	17 (81.0%)	
Race					$X^2(10, N = 86) = 8.65$
Asian	7 (8.2%)	4 (13.4%)	3 (8.8%)	0 (0.0%)	
Black/African American	2 (2.4%)	1 (3.3%)	0 (0.0%)	1 (4.8%)	
White/Caucasian	71 (83.5%)	22 (73.4%)	30 (88.2%)	19 (90.4%)	
Multiracial	2 (2.4%)	1 (3.3%)	0 (0.0%)	1 (4.8%)	
Middle Eastern	2 (2.4%)	1 (3.3%)	1 (3.0%)	0 (0.0%)	
Other	1 (1.1%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	
Ethnicity					$X^2(2, N = 83) = 7.42^*$
Hispanic or Latino	4 (4.8%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	
Not Hispanic or Latino	79 (95.2%)	26 (86.7%)	33 (100%)	20 (100%)	
Education Level					$X^2(10, N = 86) = 15.72$
High School	7 (8.1%)	3 (9.7%)	2 (5.9%)	2 9.5%)	
Some College (no degree)	41 (47.7%)	10 (32.3%)	17 (50.0%)	14 (66.7%)	
Junior College	4 (4.6%)	2 (6.4%)	1 2.9%)	1 (4.8%)	
Bachelor's degree	11 (12.8%)	4 (12.9%)	4 (11.8%)	3 (14.3%)	
Some graduate school (no degree)	6 (7.0%)	1 (3.2%)	5 (14.7%)	0 (0.0%)	
Master's or doctoral degree	17 (19.8%)	11 (35.5%)	5 (14.7%)	1 (4.8%)	
BMI	25.58 (6.26)	24.88 (5.63)	24.94 (4.96)	27.57 (8.47)	$F(2,81) = 1.429$
Visit 1					
Caffeine consumption (cups)	1.20 (1.20)	1.25 (1.36)	1.10 (1.14)	1.26 (1.06)	$F(2,82) = 0.162$
Alcohol consumption (drinks)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	$F(2,81) = 0.000$
Tobacco consumption (cigarettes)	0.13 (1.10)	0.00 (0.00)	0.34 (1.771)	0.00 (0.00)	$F(2,80) = 0.956$
Physical activity (h)	2.31 (1.99)	2.02 (1.47)	2.60 (2.42)	2.23 (1.99)	$F(2,50) = .446$
Visit 2					
Caffeine consumption (cups)	1.12 (1.32)	1.08 (1.45)	1.00 (1.32)	1.39 (1.13)	$F(2,79) = 0.549$
Alcohol consumption (drinks)	0.01 (0.111)	0.03 (0.183)	0.00 (0.00)	0.00 (0.00)	$F(2,78) = 0.847$
Tobacco consumption (cigarettes)	0.17 (1.24)	0.07 (0.36)	0.34 (1.94)	0.05 (0.22)	$F(2,78) = 0.495$
Physical activity (h)	2.41 (2.16)	2.48 (1.94)	2.63 (2.77)	1.96 (2.16)	$F(2,50) = 0.386$
Time interval (days)					
End of intervention to visit 1	21.2 (12.10)	20.3 (12.50)	22.0 (11.86)	NA	$t(63) = .555$
Visit 1 to Visit 2	2.4 (2.29)	2.0 (0.00)	2.7 (3.40)	2.5 (1.61)	$F(2,79) = 0.738$
Visit 1 (hours since midnight)					
Wake time	7.67 (1.38)	7.59 (1.40)	7.82 (1.52)	7.55 (1.09)	$F(2,82) = 0.32$
Laboratory visit start time	16.98 (1.60)	17.09 (1.52)	16.63 (1.76)	17.36 (1.40)	$F(2,84) = 1.445$
Visit 2 (hours since midnight)					
Wake time	7.82 (1.65)	7.42 (1.75)	8.04 (1.61)	8.05 (1.50)	$F(2,78) = 1.349$
Laboratory visit start time	16.97 (1.59)	17.19 (1.49)	16.51 (1.75)	17.43 (1.59)	$F(2,79) = 2.523$
Intervention adherence[a]	4.43 (1.79)	4.19 (1.93)	4.64 (1.66)	NA	$F(1,63) = 1.037$

[a] Total number of intervention sessions attended.
* $p < .05$.

exposure to the same or similar stressors. HPA axis activation rapidly declines with repeated exposure to the same stressor, such that the majority of prior work reports a significant decline as soon as the second exposure (e.g., Kudielka et al., 2006; Schommer et al., 2003; Wust et al., 2000). This pattern of decline in cortisol response magnitude with repeated exposure tends to be observed in most individuals (Wüst et al., 2005), and non-habituation is associated with indicators of poor health (e.g., exhaustion; Kudielka et al., 2006) and disease (e.g., depression; Morris and Rao, 2014). As such, HPA axis habituation to repeated stress may be indicative of normative HPA axis function.

To reduce the negative effects of stress on health, researchers have developed and tested numerous stress reduction interventions. Among these are Mindfulness Based Stress Reduction (MBSR) and Cognitive Behavioral Therapy (CBT) (Creswell, 2017; Hofmann et al., 2012). MBSR interventions, which include training in various meditation practices, focus on applying mindfulness to daily life by attending to bodily sensations, thoughts and emotions with awareness and acceptance (Kabat-Zinn, 1982). In contrast, CBT interventions focus, in part, on modifying maladaptive cognitions and behaviors to reduce emotional distress by teaching progressive muscle relaxation, cognitive restructuring, behavioral activation, and emotional regulation (Cully and Teten, 2008). Both MBSR and CBT are considered to be generally effective in the context of a variety of stress-related outcomes (Grossman et al., 2004; Hofmann et al., 2012), such as reducing anxiety in college populations (Regehr et al., 2013).

To date, the impact of MBSR and CBT on HPA axis functioning in response to novel or repeated stressors is unclear. For example, a randomized controlled trial found that cortisol reactivity to a social-evaluative speech and mental arithmetic task did not differ pre-to post-intervention between participants assigned to an MBSR or Waitlist condition (Nyklíček et al., 2013). Similarly, a study examining a sample of socially-anxious individuals found that cortisol responses to a social-evaluative speech task did not differ pre- to post-treatment in either a CBT or MBSR intervention (Faucher et al., 2016). In contrast, participants randomized to a 14-day mindfulness smartphone intervention (focused on teaching both mindful awareness and acceptance) had lower cortisol reactivity (i.e., stress-induced increases of lower magnitude) than participants assigned to a control condition focusing on general coping strategies (Lindsay et al., 2018). With regards to CBT, two randomized controlled trials found that participants assigned to cognitive behavioral stress management displayed lower cortisol reactivity than participants assigned to a Waitlist control (Gaab et al., 2003; Hammerfald et al., 2006). Yet, in contrast, a brief cognitive reappraisal manipulation (a primary training component of CBT) has been found to lead to greater cortisol reactivity than a control condition (Denson et al., 2014). In sum, the literature linking MBSR and CBT to

HPA axis responses to novel stressors is growing but the findings are mixed. Further, to the authors' knowledge, the effect of MBSR or CBT on cortisol habituation to repeated stressors administered post-treatment has yet to be examined.

A test of the effect of MBSR and CBT on cortisol responses using a repeated acute stress paradigm may reveal unique and perhaps more subtle influences of these stress interventions on HPA axis function. Because HPA axis habituation is regulated by neural and peripheral feedback mechanisms, as well as learning and memory processes regarding prior exposures to stressors (Grissom and Bhatnagar, 2009), examining intervention effects on habituation may reveal unique information about dysregulation of adaptive stress-responsive systems that cannot be observed with one stressor exposure. Consistent with this view, prior work suggests that repeated stressor exposure paradigms are better suited to examine the effect of stable individual differences on the HPA axis relative to single stressor exposure (Kirschbaum et al., 1995).

In sum, testing the effect of MBSR and CBT on cortisol habituation is novel and may be methodologically advantageous. The present study evaluated the effects of 6-week MBSR, 6-week CBT, and Waitlist control conditions on cortisol responses to acute social-evaluative stress. The effects of MBSR and CBT on habituation across two post-intervention stressor sessions, delivered 48-h apart, were compared to the responses of Waitlist controls. We hypothesized that participants assigned to the MBSR and CBT interventions would show greater habituation (i.e., a greater decrease in cortisol responses from the first to the second stressor) than participants assigned to the Waitlist condition. The present study also compared the effect of MBSR versus CBT on cortisol habituation to evaluate the relative utility of these interventions.

2. Material and method

2.1. Participants

Enrolled participants were 138 healthy adults recruited from Ohio University using fliers posted on campus and emails sent to faculty, staff, and students that advertised a "Stress Reduction Intervention Study". See Table 1 for sociodemographic characteristics of the final sample. Participants were ineligible if they: (1) had previously completed an MBSR or CBT program, (2) were pregnant, (3) used steroid medication, (4) reported a major psychiatric or endocrine disorder, (5) generally did not wake up by 10:00 AM on a weekday, (6) were not available in the evening, (7) were a member of the psychology department or (8) were under 18 or over 50 years of age. These eligibility criteria were used to minimize the impact of factors that can influence HPA axis functioning. In addition, the sample was restricted to individuals who reported moderate to high stress during the past month. This criterion was included to maximize the potential effectiveness of stress reduction interventions, which are hypothesized to be most evident in high stress burden populations (Creswell and Lindsay, 2014). For the sake of brevity in our screening survey, we developed and implemented a one-item measure: "How would you rate your average level of stress during the past month?" where 1 = little or no stress and 10 = a great deal of stress, similar to what is used in the annual Stress in America™ survey (American Psychological Association, 2018). Individuals with scores at or above 4 were considered eligible. In the most recent Stress in America™ survey, a score of 3.9 or higher was considered to be "generally unhealthy" by a nationally representative sample of U.S. adults (American Psychological Association, 2018).

2.2. Procedure

2.2.1. Recruitment and randomization

Individuals interested in enrolling completed an online survey assessing eligibility criteria. Eligible individuals were contacted to participate in group information sessions where they were told they would be assigned to one of two interventions (i.e., the MBSR or CBT group) or a Waitlist control condition, and the general content of both intervention programs was described. After consent was obtained by the study coordinator and primary investigators, participants completed a packet of questionnaires and were then randomly assigned and informed in person by the study coordinator about their assigned group. Participants were recruited and enrolled in four cohorts between August 2016 and January 2018. At each recruitment wave, participants were randomly allocated to conditions with a blocked randomization scheme where block size was determined by the number of individuals in each cohort (size of block ranged from 5–20). At the beginning of the trial (Cohort 1), block random assignment was performed with a 1:1:1 allocation ratio for enrolled participants. At subsequent cohort enrollments (Cohorts 2–4), the allocation ratios were adjusted for differential attrition in study groups to achieve approximate balance in the number of participants who attended at least one intervention group session for each of the two intervention conditions. Intervention assignments were written on appointment cards and concealed from both the researchers and participants until the assignments were made. The study coordinator generated the random allocation sequence by physically shuffling appointment cards marked with study conditions.

2.2.2. Follow up survey and laboratory visits

Following the 6-week intervention, or 6 weeks on the Waitlist, participants were emailed a link to an online follow-up survey and asked to complete the survey as soon as possible and before attending their first follow-up study visit. Subsequently, participants came into the laboratory on two separate occasions that were scheduled 48 h apart. Both study visits followed the same format, and all visits occurred between 2:00 PM and 8:30 PM to minimize variation in diurnal cortisol (see Fig. 1 for a timeline of these laboratory visits). At the beginning of each visit, seven electrodes were placed on participant's neck and torso to measure electrocardiography and impedance cardiography (not included in the present manuscript). Next, participants completed health behavior questionnaires and rested for 10 min (during which emotionally neutral readings were provided). Then, participants completed another set of questionnaires and provided saliva samples. Next, participants completed the Trier Social Stress Test (TSST; Kirschbaum et al., 1993; discussed below) followed by an Implicit Association Task (Greenwald et al., 1998) pertaining to associations between the concept of self and shame (not included in the present manuscript). This was followed by more questionnaires (during which saliva was collected)

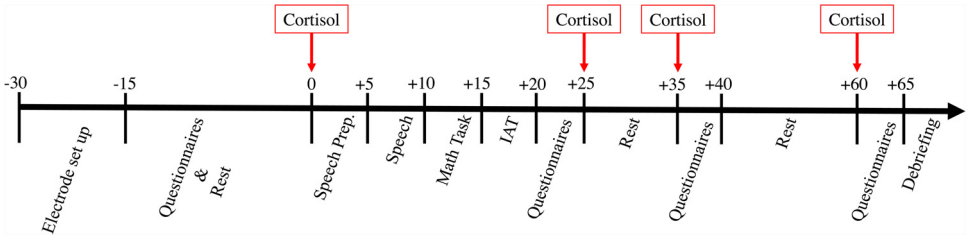

Fig. 1. Laboratory visits timeline. Numbers shown on the timeline correspond to minutes from stressor onset. Speech Prep. refers to the speech preparation portion of the Trier Social Stress Test. IAT refers to the Implicit Association Task.

and another 10-min rest period (during which potentially distracting material was removed). Then, participants completed another set of questionnaires (during which saliva was collected) and a 20-min rest period during which participants were provided with emotionally neutral reading. A final set of questionnaires was then administered, and the last saliva sample was collected. At the end of the first visit, researchers confirmed participants' next appointments. At the end of the second visit, participants were debriefed and thanked for their participation. Participants earned up to $70 for completing all procedures ($20 for the pre-intervention survey + $20 per visit + $10 bonus for completing both visits). Enrollment and laboratory visits took place in Ohio University facilities. All procedures were approved by the Ohio University Institutional Review Board. The present study was registered as a clinical trial on ClinicalTrials.gov (identifier #: NCT02894229). Study methods were not altered after the trial had begun.

2.3. Materials

2.3.1. MBSR group

A 6-week version of MBSR (Klatt et al., 2008; Lengacher et al., 2009) was developed and administered using established guidelines derived from standardized treatment manuals (Kabat-Zinn, 1990; Kabat-Zinn and Santorelli, 1999). Participants met weekly as a group for six consecutive weeks for 2 h each week. The groups were facilitated by two trained masters and/or doctoral-level clinicians. All facilitators were trained in the MBSR and CBT protocols by a licensed clinical psychologist with extensive experience with both interventions. All study therapists received multiple hours of training on the interventions, with weekly supervision during the course of the study. Each group session followed a standardized manual and contained didactic information about mindfulness, instruction on mindfulness meditation practices (e.g., body scan, sitting meditation, yoga), and group discussion related to in-class practices and homework. Participants were asked to engage in various formal (e.g., body scan) and informal (e.g., mindful daily activity) meditation practices daily for 45–60 min during the 6-week program. Participants were provided with audio recordings of mindfulness practices and handouts covering various topics to aid in home practice.

2.3.2. CBT group

The 6-week CBT group program developed for the present study followed empirically-supported CBT approaches for reducing stress (e.g., Cully and Teten, 2008). Participants met as a group weekly for six consecutive weeks for a period of 2 h each week. Groups were facilitated by two trained masters and/or doctoral-level clinicians. Each group session followed a standardized manual and contained didactic information on stress, instruction on various CBT approaches to reducing stress (i.e., progressive muscle relaxation, healthy sleep habits, increasing positively reinforcing activities, cognitive restructuring, interpersonal assertiveness, and emotion regulation), and discussion of course material and homework assignments. Throughout the 6-week protocol participants were asked to engage in 45–60 min of homework daily related to the topics discussed in each class (e.g., practice progressive muscle relaxation; engage in identified pleasurable activities).

2.3.3. Waitlist

Participants assigned to the Waitlist control condition received no intervention prior to completing the laboratory visits, but all had the option of completing a CBT intervention at the end of the study.

2.3.4. Trier social stress test

Acute stress at each post-intervention laboratory visit was induced using the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), which is known to reliably elicit acute cortisol responses (Dickerson and Kemeny, 2004). Specifically, participants were given 5 min to prepare a speech pertaining to a hypothetical job interview, and then were asked to give their speech in front of an evaluative panel (i.e., two research assistants wearing white lab coats, trained to maintain stoic expressions) for 5 min. Next participants completed a 5-min mental arithmetic task in front of the evaluative panel. Instructions for the speech portion of TSST were identical between visit 1 and visit 2, whereas instructions for the mental arithmetic task varied (visit 1: count backwards by 13 s starting at 1022; visit 2: count backwards by 17 s starting at 1039).

2.4. Measures

2.4.1. Salivary cortisol

Saliva was sampled using Salivettes (Sarstedt, Inc., Newton, N.C.) on four occasions (pre-stressor, 25, 35, 60 min post-stressor onset) during each laboratory visit to measure levels of salivary cortisol. To collect saliva, a research assistant instructed participants to drop the swab in their mouth without touching it with their hands, saturate it with saliva for up to 3 min, and replace the roll in the Salivette using their lips. Samples were stored at −20 °C and later centrifuged and assayed at Ohio University using standard enzyme-linked immunoassay procedures (Salimetrics, LLC, State College, PA). All samples were assayed in duplicate and averaged. The assay had a sensitivity of < 0.007 μg/dL, and inter-assay coefficients of variation were less than 11.0% and intra-assay coefficients of variation were less than 7.0%.

2.4.2. Covariate measures

Salivary cortisol is known to follow a diurnal pattern where levels fluctuate rapidly following awakening, and decrease in the afternoon (Chida and Steptoe, 2009). Additionally, numerous studies have noted sex difference in cortisol responses to acute stress (e.g., Stephens et al., 2016). As such, biological sex, wake time, and the time at which each laboratory visit began were considered as potential covariates. Wake time was self-reported, whereas time at which the experiment began was recorded by research assistants. Both wake time and time at which the experiment began were recoded as hours since midnight (where greater values indicate later times).

Other covariates considered included age, race, ethnicity, education, caffeine consumption, alcohol consumption, tobacco consumption, physical activity, and body mass index (BMI). Participants self-reported age, race (coded as 1 = White; 0 = non-White for analyses), ethnicity (coded as 1 = Hispanic/Latino; 0 = not Hispanic/Latino), and education as part of questionnaires completed during the consenting session. Participants self-reported caffeine consumption (# of cups of coffee/tea and other caffeinated beverages), alcohol consumption (# of alcoholic drinks consumed), physical activity (total duration of physical activity prior to the visit) during each laboratory visit. Participants' height and weight were measured at the end of the first laboratory visit to calculate BMI ($703 \times$ weight (lbs)/[height (in)]^2).

2.4.3. Intervention attendance

At the beginning of each weekly meeting of the MBSR and CBT interventions participants were asked to write down their names on a sign-in sheet. The total number of sessions attended by participants ranged from 0 to 6. As shown on Table 1, mean attendance did not differ between the MBSR and CBT interventions (MBSR: 4.19 ± 1.93; CBT: 4.64 ± 1.66).

2.5. Analytic plan

2.5.1. Study completion

Primary analyses are reported on data from 86 participants who completed procedures up to the first laboratory visit (see Fig. 2 for CONSORT flow chart). Study condition assignment did not predict the likelihood of withdrawing from the experiment prior to the first laboratory visit ($X^2_{LR}(2, N = 138) = 2.69$, $p = .26$). Additionally, individuals who withdrew prior to the first laboratory visit did not differ

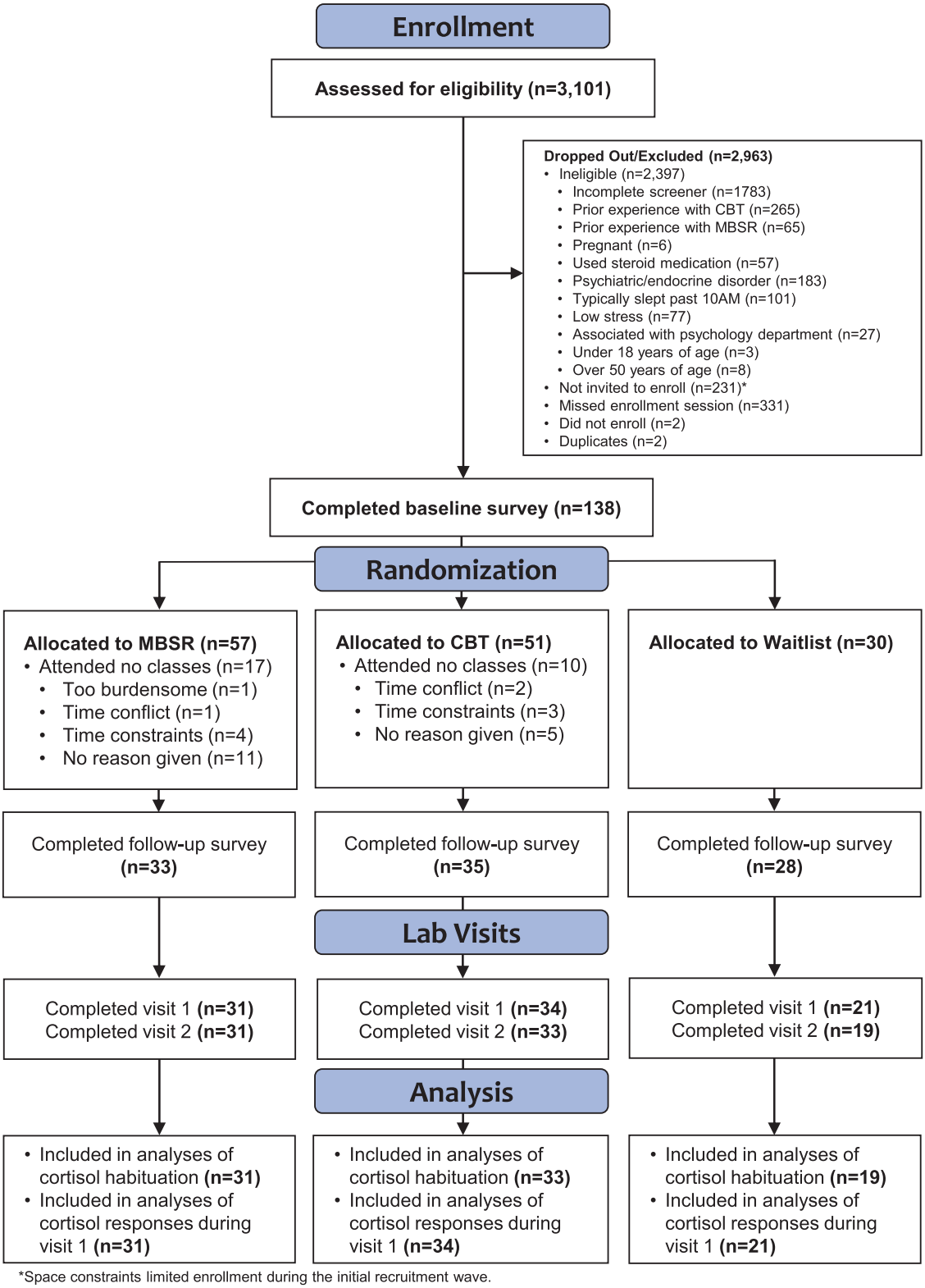

Fig. 2. CONSORT flow chart.

from individuals who attended the first visit on the basis of age, sex, education, race, stress or ethnicity (all *ps* > .05). Analyses were performed after all data were collected.

2.5.2. Treatment of missing and outlying data

A total of 676 saliva samples were collected. Of this number, one sample did not contain enough saliva to be assayed, and four samples were below assay threshold. Of the remaining 671 valid cortisol samples, four samples fell below three standard deviations from the mean. Excluding these four samples from primary analyses had no influence on the conclusions of the present study. As such, all valid sample values were retained in final analyses.

2.5.3. Measures of habituation

To test primary hypotheses, we examined the effect of study condition and laboratory visit on (1) cortisol values across sampling time points (to infer habituation effects with respect to total cortisol output), (2) cortisol values corresponding to each sampling occasion (to infer habituation effects with respect to each sampling occasion), and (3) the cortisol response curvilinearity (to infer habituation effects with respect the shape of cortisol responses). A change in total cortisol levels from the first to the second visit to can be used to infer a global, time-independent, measure of habituation, consistent with prior work examining a change in Area Under the Curve relative to ground (AUCg; Wüst et al., 2005). A change in cortisol values from the first to the second visit corresponding to a specific timepoint can be used to examine what specific timepoints (e.g., pre-stressor levels) may be driving differences in overall cortisol exposure, thus providing a more nuanced (time-dependent) measure of habituation. Finally, cortisol response curvilinearity can be used to infer how repeated stress exposure influences the overall shape of response trajectories irrespective of total cortisol levels. Modeling cortisol values across visits was preferred over computing AUCg for each visit because this approach can handle partially missing data while providing conceptually similar insight. Nevertheless, to ease comparison with prior work (e.g., Boyle et al., 2016; Thoma et al., 2017), we also report tests of study condition and visit on cortisol AUCg and cortisol reactivity scores in Supplementary files.

2.5.4. Modeling cortisol trajectories and intercepts

Maximum likelihood mixed linear models were used to model temporal changes in salivary cortisol using SAS 9.4/STAT 13.1 (SAS Institute Inc., Cary, N.C). Cortisol levels were log-transformed prior to analyses to render level 1 residuals normally distributed. To model cortisol responses during the first *or* the second visit, 2-level multilevel models were used where sampling occasions (sampling occasion-level) were nested within individuals (individual-level). In contrast, when testing changes from the first to the second visit (i.e., habituation patterns), a 3-level multilevel model was used where sampling occasions (sampling occasion-level) were nested within visits (visit-level) and visits were nested within individuals (individual-level). In models used to predict cortisol intercepts (e.g., pre-stressor sample) and growth trajectories, the linear (time) and quadratic (time^2) slopes relating time (in hours; centered on pre-stressor samples) to cortisol levels were entered as fixed effects. In contrast, time slopes were omitted from models estimating total cortisol output. The two-level multilevel models included random individual-level intercepts, whereas the 3-level multilevel models included random visit-level and individual-level intercepts. Laboratory visit (centered on the first visit) was entered as a fixed effect in 3-level models. Tests of study conditions included all assigned participants regardless of non-adherence (i.e., intervention attendance), consistent with an intent-to-treat approach. Mixed model equations used to predict salivary cortisol are presented in Supplementary files.

2.5.5. Evaluation of random assignment success

The success of random assignment was evaluated by comparing study conditions on the basis of demographics and variables pertaining to the protocol (e.g., laboratory visit start time). Random assignment was also evaluated on the basis of self-report measures of stress (Perceived Stress Scale; Cohen et al., 1983; Trier Inventory for Chronic Stress; Schulz et al., 2004), mindfulness (Five Facet Mindfulness Questionnaire; Baer et al., 2006), depressed mood (Center for Epidemiologic Studies Depression scale; Radloff, 1977), anxiety (State-Trait Anxiety Inventory; Speilberger et al., 1970), and general coping strategies (Brief Cope Inventory; Carver, 1997). These analyses are included in Supplementary files.

2.6. Power considerations

Previous research and cost considerations shaped sample size decisions, rather than formal power analyses prior to data collection. Specifically, previous work on social-evaluative threat suggests that 30+ participants per cell is sufficient to observe cortisol stress reactivity and recovery (Dickerson et al., 2008). Additionally, research on cortisol habituation has detected moderate effects with sample sizes as low as $N = 25$ (Kudielka et al., 2006). The current study has a notably larger sample size ($N_{enrolled} = 138$; $N_{final} = 86$). Enrollment for the trial ended after the minimum number of participants ($N = 30$) were *enrolled* in each of study conditions (MBSR = 57; CBT = 51; Waitlist = 30).

3. Results

3.1. Preliminary analyses

3.1.1. Evaluation of random assignment

As shown on Table 1, participants assigned to MBSR, CBT, or the Waitlist condition did not differ with regards to age, sex, race, education, BMI, or caffeine consumption, alcohol consumption, tobacco consumption and physical activity preceding each laboratory visit. However, the MBSR condition included a greater proportion of participants reporting “Hispanic or Latino” ethnicity ($n = 4$) than the CBT and Waitlist conditions (both groups $n = 0$). Participants assigned to the MBSR, CBT, or the Waitlist conditions did not differ with regards to days elapsed between the first and second laboratory visit, wake time, or laboratory visit start time (for either the first or the second visit). Finally, participants assigned to the MBSR or CBT conditions did not differ with regards to total attendance or days elapsed between the end of the intervention and the first laboratory visit.

3.1.2. Modeling temporal changes in cortisol

Across laboratory visits and study groups, mixed linear models revealed a significant effect of time and time^2 ($F(1, 483) = 21.63$, $p < .001$, and $F(1, 483) = 46.35$, $p < .001$), indicating that salivary cortisol levels increased to a peak, then declined. Including the effect of laboratory visit in this model revealed a non-significant visit × time^2 interaction ($F(1,481) = 1.70$, $p = .19$), indicating that the curvilinearity of cortisol responses did not differ from the first to the second laboratory visit. Follow-up tests revealed that linear cortisol trajectories were more positive on the first relative to the second visit pre-stressor ($F(1,481) = 5.04$, $p = .025$) and 25 min post-stressor onset ($F(1,481) = 11.41$, $p < .001$). However, the linear slope of cortisol trajectories did not differ between visits for samples collected 35 and 60 min post-stressor onset. Additionally, across the three study conditions, cortisol levels were significantly greater 25, 35, and 60 min post-stressor onset during the first visit relative to the second ($F(1,81) = 13.53$, $p < .001$, $F(1,81) = 19.78$, $p < .001$, and $F(1,81) = 16.28$, $p < .001$, respectively), but did not differ between visits pre-stressor ($F(1,81) = 0.78$, $p = .38$).

3.2. Tests of covariate measures

3.2.1. Sex

Sex interacted with linear and quadratic slopes relating time to cortisol levels ($F(1,477) = 3.14$ $p = .076$, and $F(1,477) = 7.82$ $p = .005$, respectively), suggesting that males showed more curvilinear (i.e., peaked) responses than females, across laboratory visits. Furthermore, males showed greater pre-stressor cortisol levels than females across laboratory visits ($F(1,477) = 6.30$ $p = .012$). However, the interactions of time × visit × sex as well as the interaction of time^2 × visit × sex were non-significant ($F(1,477) = 0.13$ $p = .72$, and $F(1,477) = 0.41$ $p = .52$, respectively), which indicates that the sex differences were consistent between visit 1 and visit 2.

3.2.2. Wake time

Wake time was negatively associated with pre-stressor cortisol levels across study visits ($F(1,468) = 6.17$, $p = .013$), such that later wake times predicted lower pre-stressor cortisol levels. However, the interactions of time^2 × wake time, visit × wake time, time × visit × wake time, or time^2 × visit × wake time were all non-significant (all $ps > .34$), indicating that wake time was unrelated to the shape of cortisol responses across visits or changes in the shape of cortisol responses from visit 1 to visit 2. Furthermore, wake time was not associated with the difference in cortisol levels from the first to the second visit 25, 35, or 60 min post-stressor onset (all $ps > .12$).

3.2.3. Laboratory visit start time

Laboratory visit start time was significantly associated with linear cortisol slopes and pre-stressor levels across visits ($F(1, 476) = 7.45$, $p = .006$, and $F(1, 476) = 11.29$, $p < .001$, respectively), indicating that individuals who arrived for sessions later in the day showed less positive linear slopes and lower cortisol levels prior to the stressor. Laboratory visit start time was also marginally associated with the quadratic effect of time across laboratory visits ($F(1,476) = 3.05$, $p = .081$) such that individuals who came in the laboratory at later times trended toward less peaked responses across both visits. Nonetheless, the interactions of visit × laboratory start time, time × visit × laboratory start time, or time^2 × visit × laboratory start time were all non-significant (all $ps > .30$), indicating that visit start time was unrelated to changes in the shape of cortisol responses from visit 1 to visit 2. Furthermore, laboratory visit start time was not associated with the difference in cortisol levels from the first to the second visit pre-stressor, 25, 35, or 60 min post-stressor onset (all $ps > .19$).

3.2.4. Excluded covariates

Age, race, ethnicity, caffeine consumption, alcohol consumption, tobacco consumption, physical activity, and BMI were all unrelated to cortisol responses trajectories (i.e., time and time^2), intercepts, or visit × trajectories and visit × intercept interactions (all $ps > .12$). As such, race, age, ethnicity, caffeine consumption, alcohol consumption, tobacco consumption, physical activity, and BMI were not retained as covariates in final analyses.

3.3. Tests of study conditions

Given that sex, wake time, and laboratory visit start time were all found to be associated with cortisol responses, test of primary hypotheses were conducted while controlling for these variables. Consistent with primary hypotheses, tests of habituation (i.e., changes in cortisol responses from the first to the second visit) are presented first. To provide a frame of reference for habituation effects and to allow for comparison with prior studies, condition effects were also compared in the context of the first and second study visit separately and are presented after habituation results.

3.3.1. Habituation

A plot of estimated mean cortisol levels as a function of visit and study condition is presented in Fig. 3. Study condition and visit interacted to predict total cortisol levels ($F(2,489) = 3.95$, $p = .019$), such that total cortisol levels significantly decreased in the CBT condition relative to the Waitlist ($t(489) = 2.79$, $p = .005$), but did not differ between MBSR and Waitlist ($t(489) = 1.42$, $p = .15$), or CBT and MBSR ($t(489) = 1.51$, $p = .13$). Study conditions and visit interacted to predict cortisol intercepts pre-stressor, 25, 35 and 60 min post stressor onset ($F(2,451) = 5.01$, $p = .007$, $F(2,451) = 3.16$, $p = .043$, $F(2,451) = 3.24$, $p = .040$, and $F(2,451) = 2.49$, $p = .083$, respectively). Follow up tests revealed that participants assigned to CBT displayed a significantly greater decrease in cortisol levels collected pre-stressor, 25, 35, and 60 min post-stressor from the first to the second visit relative to participants assigned to the Waitlist condition ($t(451) = 2.54$, $p = .011$, $t(451) = 2.51$, $p = .012$, $t(451) = 2.51$, $p = .012$, and $t(451) = 2.15$, $p = .031$, respectively). Similarly, participants assigned to the MBSR condition showed a marginally greater decrease in cortisol levels collected 35 and 60 min post-stressor onset from the first to the second visit than participants assigned to Waitlist conditions ($t(451) = 1.88$, $p = .060$, and $t(451) = 1.79$, $p = .074$, respectively). Contrasting CBT and MBSR, participants assigned to the CBT condition showed a greater decrease in pre-stressor cortisol from the first to the second visit relative to participants assigned to MBSR ($t(451) = 2.77$, $p = .005$). Finally, study condition interacted with study visit and time (centered at 25 min post stressor onset; $F(2, 451) = 3.11$, $p = .045$), such that the decrease in linear slopes relating time to cortisol levels from the first to the second visit was significantly greater among MBSR versus CBT participants ($t(451) = 2.39$, $p = .017$) and marginally greater among MBSR versus Waitlist participants ($t(451) = 1.70$, $p = .088$), but non-significant among CBT versus Waitlist participants ($t(451) = .40$, $p = .68$). However, the interaction of study condition × visit × time^2 was non-significant ($F(2, 451) = 0.45$, $p = .63$), suggesting that study condition assignment was not associated with a change in the curvilinearity of cortisol responses from the first to the second laboratory visit.

3.3.2. First laboratory visit

During the first laboratory visit, total cortisol levels were significantly larger in the CBT and MBSR groups relative to the Waitlist group ($t(489) = 2.76$, $p = .005$ and $t(489) = 2.55$, $p = .011$, respectively). In contrast, the CBT and MBSR groups did not differ with respect to total cortisol during the first visit ($p = .81$). Study condition also predicted intercepts corresponding to samples obtained pre-stressor, 25, 35 and 60 min post stressor onset ($F(2,232) = 5.88$, $p = .003$, $F(2,232) = 3.85$, $p = .022$, $F(2,232) = 4.33$, $p = .014$, and $F(2,232) = 4.65$, $p = .010$, respectively). Follow up tests revealed that participants assigned to the CBT condition had significantly greater pre-stressor cortisol levels than participants assigned to the MBSR ($t(232) = 2.18$, $p = .030$) and Waitlist ($t(232) = 3.33$, $p = .001$) conditions. In contrast, participants assigned to the MBSR and Waitlist conditions had similar pre-stressor cortisol levels during the first visit ($t(232) = 1.42$, $p = .15$). Furthermore, participants assigned to the CBT and MBSR condition showed greater cortisol levels than waitlisted participants 25, 35 and 60 min post stressor onset (CBT: $t(232) = 2.45$, $p = .014$, $t(232) = 2.31$, $p = .02$, $t(232) = 2.42$, $p = .016$; MBSR: $t(232) = 2.53$, $p = .012$, $t(232) = 2.86$, $p = .004$, $t(232) = 2.96$, $p = .003$, respectively); no other comparisons of intercepts were significant.

3.3.3. Second laboratory visit

During the second laboratory visit, total cortisol levels did not differ between study conditions (all ps > .13). There was also no significant interaction of time^2 × condition ($F(1, 219) = 0.70$, $p = .49$), time × condition ($F(1, 219) = 1.21$, $p = .30$), or any significant tests of intercepts (pre-stressor: $F(1, 219) = 2.14$, $p = .13$; 25 min: $F(1, 219) = 2.20$, $p = .11$; 35 min: $F(1, 219) = 2.38$, $p = .10$; 60 min: $F(1, 219) = 2.15$, $p = .11$).

3.3.4. Adherence

To evaluate the effect of intervention adherence on cortisol habituation, the interaction of adherence (i.e., group session attendance) and laboratory visit was tested for participants assigned to MBSR and CBT separately. When restricting analyses to participants assigned to the MBSR intervention, the interaction of adherence × visit × time^2 and the interaction of adherence × visit × time were both non-significant ($F(1,149) = 1.47$, $p = .22$, and $F(1,149) = 2.24$, $p = .13$, respectively), suggesting that intervention adherence did not moderate the degree to which cortisol levels decreased from visit 1 to visit 2. Similarly, when restricting analyses to participants assigned to the CBT intervention, the interaction of adherence × visit × time^2 and the

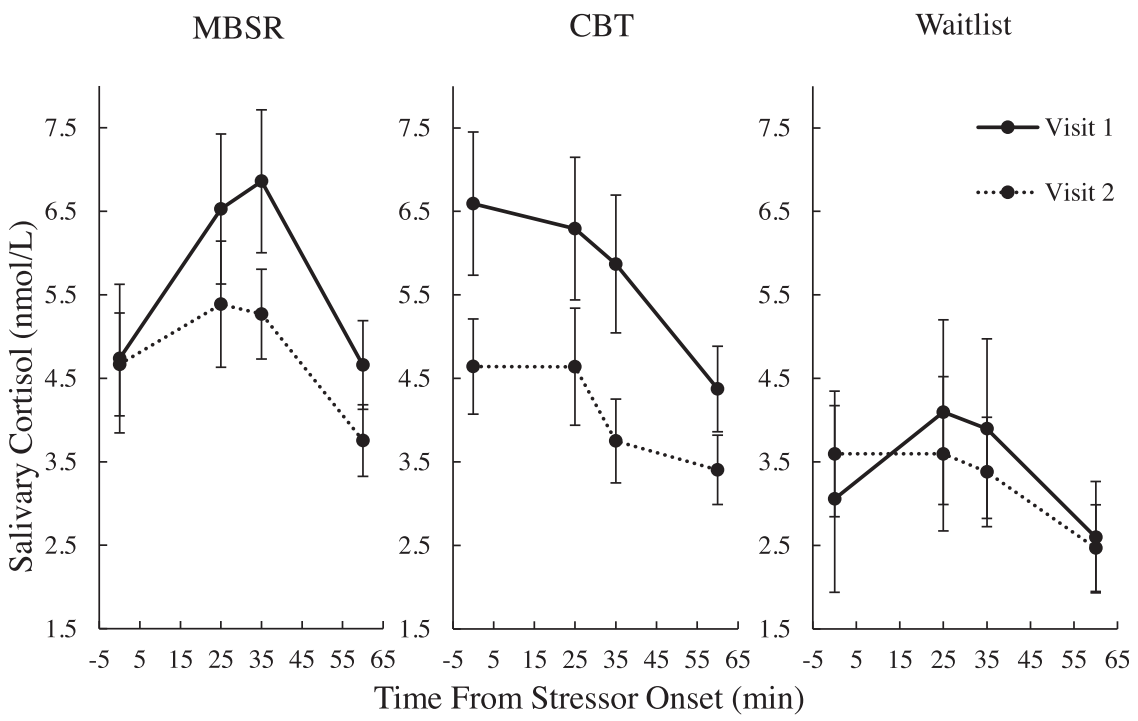

Fig. 3. Salivary cortisol as a function of time from stressor onset, laboratory visit, and study condition (MBSR = Mindfulness Based Stress Reduction; CBT = Cognitive Behavioral Therapy). Data shown are estimated mean values for each sampling occasion, laboratory visit, and study condition. Consistent with analyses, means estimates were adjusted for biological sex, wake time, and experiment start time. Error bars shown are standard errors of mean estimates.

interaction of adherence × visit × time were both non-significant ($F(1,170) = 0.64$, $p = .42$, and $F(1,170) = 0.23$, $p = .63$, respectively) suggesting that intervention adherence did not moderate the degree to which cortisol levels decreased from visit 1 to visit 2.

4. Discussion

The primary aim of the present study was to evaluate the effect of MBSR and CBT interventions on HPA axis habituation to repeated acute stressors. Overall, our results showed that both MBSR and CBT displayed response profiles consistent with habituation (where participants in both interventions showed greater total cortisol than the Waitlist during the first but not the second TSST). Further, MBSR showed a more time-dependent profile of habituation than the CBT condition. More specifically, participants in the MBSR group exhibited decreases in cortisol samples corresponding to the recovery time points (35 and 60 min post-stressor onset) but no decreases in cortisol pre-stressor. In contrast, in the CBT group, cortisol levels decreased from the first to second visit across all sampling timepoints collected (pre-stressor, 25, 35, and 60 min post-stressor onset). Yet, the CBT group also displayed elevated pre-stressor cortisol during the first visit.

To the authors' knowledge, this study is the first to test the effects of either a CBT or MBSR intervention on HPA axis habituation to repeated acute stress. Habituation, or decrements in stress responding to a repeated stressor are thought to reflect adaptation as it is metabolically costly to repeatedly induce HPA axis activation to non-harmful stressors (Grissom and Bhatnagar, 2009). Failure to habituate may be one pathway leading to overexposure of stress mediators (i.e., relatively large magnitude of HPA axis activation in response to repeated exposures to the same stressful stimuli), consistent with the allostatic load model of stress (McEwen, 1998b). However, failure to habituate following a relatively small HPA axis stress response magnitude (to the first stressor) may not necessarily lead to greater exposure to stress mediators over time, and yet may still be an indicator of HPA axis dysregulation. Indeed, complex neural and peripheral feedback mechanisms regulate HPA axis functioning and cortisol output, including sensory and affective inputs, and learning and memory processes (Grissom and Bhatnagar, 2009). Impairments in these regulatory processes may contribute to negative mental and physical health outcomes over time (but may not lead to excessive cortisol output over time). Posttraumatic stress disorder (PTSD) is one such example in which a failure to adapt to environmental stimuli (e.g., fear- or trauma-related stimuli) co-occurs with low overall cortisol output (for review, see Yehuda and Seckl, 2011). The present habituation effects of stress interventions were driven by greater cortisol exposure to the first TSST (consistent with prior work examining habituation patterns; Wüst et al., 2005), and therefore suggest that any potential long-term health benefits of these stress interventions are unlikely to rely on reducing cortisol exposure.

Follow-up contrasts further revealed that, although the overall response trajectory or reactivity did not differ between groups and across visits, there were group differences at specific timepoints between the first and second stressor exposure. Relative to the Waitlist group, participants assigned to CBT exhibited a greater decrease in cortisol from the first to the second visit at all timepoints measured (i.e., pre-stressor, 25, 35 and 60 min post-stressor onset). In contrast, participants assigned to the MBSR condition displayed marginally greater decreases in salivary cortisol from the first to the second laboratory visits (relative to the Waitlist group) only for cortisol samples corresponding to recovery timepoints (i.e., 35 and 60 min post-stressor onset). Prior work suggests that cortisol responses typically peak 20–30 min post-stressor onset, begin to recover after 30 min, and often fully return to pre-stressor levels 60 min post-stressor onset (Dickerson and Kemeny, 2004). Thus, both cognitive behavioral and mindfulness-based stress reduction trainings may derive positive health effects by promoting greater habituation in cortisol recovery from repeated stressor exposure. Alternatively, contrasts of the Waitlist control condition and stress interventions could be driven by the non-habituation/non-response pattern exhibited by the Waitlist condition. Presently, it is unclear why waitlisted participants did not show a prototypical habituation pattern. Restricting the present sample to moderately/highly stressed individuals may have contributed to this finding, as prior work reports

that greater self-reported exhaustion is associated with lower cortisol habituation (Kudielka et al., 2006). Alternatively, it is possible that non-habituation patterns exhibited by the Waitlist group were the result of random assignment failure. Replication will be necessary to test this possibility.

Although CBT training uniquely predicted decreased cortisol levels from the first to the second visit for all sampling timepoints, it is important to note that participants assigned to CBT training did not display a prototypically curvilinear response to the first TSST (i.e., where cortisol levels progressively increase, peak, then decrease). Instead participants assigned to CBT showed elevated pre-stressor cortisol levels and a decrease from pre-stressor levels to expected peak during the first laboratory visit. In contrast, participants assigned to MBSR displayed a more normative, peaked, response to the first TSST (as shown on Fig. 3). Consistent with these observations, tests of linear slopes at 25 min post-stressor revealed that participants assigned to MBSR displayed a greater change in the slope of cortisol responses from the first the second visit relative to participants assigned to CBT. While these analyses could suggest that MBSR led to a more normative cortisol habituation pattern (i.e., where the initial visit is marked by a peaked response and the second visit is relatively less peaked) than CBT, one should note that this finding appears to be driven by pre-stressor cortisol difference during the initial visit. Despite taking precautions to control for sex, wake time, and laboratory session start time, participants in the CBT condition still exhibited elevated pre-stressor cortisol levels during the first visit. We considered multiple possible explanations for this finding. First, as with any randomized controlled trial, it is possible that random assignment failed. However, we observed no significant group differences on any measured variable of relevance (with the exception of Hispanic/Latino ethnicity, which was too small of a group to probe further). Alternatively, participants assigned to CBT may have failed to display a cortisol response to the first TSST because of some aspect of CBT training. While prior tests of the effect of CBT training on cortisol responses to acute stress report that CBT decreases cortisol reactivity relative to control conditions (Gaab et al., 2003; Hammerfald et al., 2006), other work found that a brief cognitive reappraisal manipulation (an important training component of CBT) led to greater cortisol reactivity compared to a control condition (Denson et al., 2014). Moreover, other work suggests that prompting the use of cognitive coping strategies during the hour preceding the TSST leads to greater pre-stressor cortisol levels relative to standard TSST instructions (Abelson et al., 2014). Thus, participants who tried to reappraise the upcoming laboratory visit could have displayed an anticipatory cortisol response resulting in elevated pre-stressor cortisol levels during the first visit. The pattern of cortisol response exhibited by the CBT group during visit 1 is consistent with anticipatory response profiles identified in prior work (e.g., Engert et al., 2013). Nevertheless, this possibility cannot be verified because the present study was not designed to detect anticipatory cortisol responses with repeated pre-stressor sampling. Future studies could address this limitation by measuring cortisol levels before participants arrive in the laboratory or at multiple time points during an extended pre-stressor period and asking participants to self-report their appraisals of the laboratory visit or stressor.

Finally, the finding that MBSR training led to greater cortisol responses (i.e., greater cortisol levels 25, 35, and 60 min post-stressor onset) than waitlisted participants during the first study visit adds to a mixed literature. Prior tests of the effect of mindfulness interventions suggests that mindfulness training either decreases (Lindsay et al., 2018) or has no effect (Faucher et al., 2016; Nyklíček et al., 2013) on the magnitude of acute cortisol responses. The present results contrast these findings by suggesting that mindfulness training increases cortisol reactivity to acute stress relative to no training. Nevertheless, our results are consistent with some tests of the effects of brief mindfulness manipulations and trait mindfulness on cortisol responses to acute stress (e.g., Creswell et al., 2014; Manigault et al., 2018). Creswell et al. (2014) proposed that implementation of mindfulness skills during an initial stressor may be more effortful (i.e., greater active coping) and may therefore heighten cortisol responses. Additionally, Monitor and Acceptance Theory (Lindsay and Creswell, 2017) posits that mindfulness training can lead to increased stress reactivity when mindful awareness (i.e., the tendency to attend to present moment experiences) is taught but mindful acceptance (i.e., an attitude of acceptance and non-judgment toward present moment experiences) is not. Future research could ask participants to self-report mindful awareness and acceptance throughout their training to address this possibility.

Strengths of the present study include the use of standardized stress interventions, use of a stress habituation paradigm, inclusion of a Waitlist control, and collection of eight cortisol samples per participant. Furthermore, the present analytical approach allowed for comparison of cortisol trajectories as well as individual intercepts and instantaneous slopes, thus more precisely indicating at what time point reduction in cortisol levels occurred from the first to the second visit. Nevertheless, the present study also had important limitations. Cortisol samples were not collected prior to participants entering the laboratory. As such, the presence of an anticipatory stress response could not be determined. Another potential limitation is that we recruited stressed individuals based on responses to a single item and then used a cutoff score of ≥ 4. This cutoff is consistent with self-reported "unhealthy" stress levels in recent national survey data (American Psychological Association, 2018), but was not derived from traditional scale validation. Importantly, examination of participant scores on the Perceived Stress Scale (see Supplementary files) supports the notion that this approach was successful in recruiting individuals with moderate to high levels of stress on this well-validated measure (for comparisons with national U.S. samples, see Cohen and Janicki-Deverts, 2012). We also found that intervention adherence did not moderate habituation patterns for participants assigned to either MBSR or CBT. Testing for moderation of habituation patterns by adherence within each stress intervention conditions limited our analyses to a relatively small subset of participants and thus likely limited statistical power. Similarly, other tests may have been underpowered and future studies would likely benefit from using a larger sample size. Using stratified sampling to ensure pre-treatment group equivalence (e.g., with regards to ethnicity) should also be considered in future studies. Finally, replicating the present study in other populations (e.g., clinical samples, older adults) may be warranted to evaluate generalizability.

5. Conclusions

The present study compared the effects of MBSR and CBT stress reduction interventions on HPA axis habituation to repeated acute stress to a Waitlist control condition. Both MBSR and CBT training led to greater cortisol habituation relative to no training, but did not reduce overall cortisol output (i.e., across both visits). Furthermore, the effect of MBSR was limited to post-stressor samples whereas CBT led to greater habituation across all samples collected. Contributing to these differences, CBT training led to flat cortisol responses to the first TSST with elevated pre-stressor cortisol levels whereas MBSR training led to more peaked responses during initial stress exposure with pre-stressor cortisol levels comparable with those of waitlisted participants. Thus, MBSR training may lead to a more normative pattern of cortisol habituation than CBT training. More research is needed to replicate current findings and to elucidate the potential benefits of improved HPA axis habituation to repeated stress.

Conflicts of interest and source of funding

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Supplementary files

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