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Laboratory Induced Cortisol Reactivity Predicts Greater Rates of Treatment Success in Affective Disorders.

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LABORATORY INDUCED CORTISOL REACTIVITY PREDICTS GREATER RATES OF TREATMENT SUCCESS IN AFFECTIVE DISORDERS

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LABORATORY INDUCED CORTISOL REACTIVITY PREDICTS GREATER RATES OF TREATMENT SUCCESS IN AFFECTIVE DISORDERS

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Response rates to first line treatments for affective disorders remain unsatisfactory (Loerinc et al., 2015). Identification of moderators and mediators that can facilitate treatment success is of great scientific and clinical interest. One such candidate could be stress-induced cortisol reactivity. For instance, higher cortisol reactivity to a pretreatment presentation of combat-related stimuli related to significantly worse outcome at post-treatment following 6-sessions of virtual reality exposure therapy in individuals with PTSD (Norrholm et al., 2016). By contrast, greater cortisol reactivity to an acute stressor predicted greater treatment response in not only depressive symptoms (Dieleman et al., 2016) but also anxiety symptoms (Wichmann et al., 2017). Given the varying findings, the aim of present study was to further examine the role of stress-induced cortisol reactivity as a predictor of outcome in individuals undergoing therapy for affective disorders. The sample consisted of 34 participants who underwent a 38-minute intermittent stress induction tasks prior to a 15-session treatment for affective disorders. The stressors included a mental arithmetic task and a fear potentiated startle task. Cortisol was collected at five time points with reactivity being quantified as peak levels during the task minus basal levels of cortisol the evening before the assessment. Using multilevel modeling we examined the associations between cortisol reactivity and slopes of improvement in affective

symptoms (Depression, Anxiety, and Stress Scale). There was a trend toward significance in the interaction between cortisol reactivity and treatment outcome, *b*= -4.21, t(43)= -2.010, p=0.051. That is, high levels of stress-induced cortisol response was related to significantly decreasing slopes across treatment. Literature suggest that higher levels of cortisol during exposure sessions moderate better clinical improvement (Meuret et al., 2015). Moreover, cortisol reactivity assessed during an acute stressor before treatment can also predict treatment outcome in affective disorders (Dieleman et al., 2016; Wichmann et al., 2017) symptoms. The current study also supports that higher levels of cortisol reactivity before treatment predicts better outcomes across affective symptoms.

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This thesis is dedicated to Ashley Roque, my wife and best friend, and my parents Emanuel and Roxana Roque. Thank you for all of your support over the years. Soli Deo Gloria

CHAPTER 1:

INTRODUCTION

1.1 Cortisol and the HPA-Axis

Cortisol is a product of the hypothalamic-pituitary adrenal axis (HPA-axis) and is part of the body's stress response to mobilize. Cortisol has many functions in the body, including assembling and restocking energy stores and containing the immune response (Haglund et al., 2007). Cortisol reactivity is the increase of cortisol during an acute stressor. Cortisol has been discussed as a marker of distress in the stress and emotion regulation literature and investigated for its pathophysiological relationship to affective disorders (Fries et al., 2009; Miller, Chen, & Zhou, 2007; Wichmann et al., 2017; Winiarski et al., 2017). Although cortisol reactivity is a natural part of the endocrine stress response system, dysregulation, defined as either abnormally elevated or reduced levels of cortisol, can be detrimental to long-term health if sustained (Kumari, Shipley, Stafford, and Kivimaki, 2011; Lovallo, 2015).

1.2 Cortisol as a Predictor of Treatment Success

First line treatments for affective disorders remain unsatisfactory (Davidson et al., 2004; Gaynes et al., 2008; Kampman et al., 2002; Loerinc et al., 2015). Therefore, identification of predictors, moderators, and mediators that can facilitate treatment success are of great scientific and clinical interest. Previous research has proposed that anxiety and depression both relate to greater threat sensitivity and lower appetitive motivational systems (Craske et al., 2016; Nelson et al., 2013). Presently, attention is being given to stressed-induced cortisol reactivity as a marker of

threat sensitivity that can influence treatment outcome. Cortisol reactivity is categorized under the negative valence domain, and within there under the construct of acute threat ("fear"), in the Research Domain Criteria Initiative (RDoC) of the National Institute for Mental Health. Dysregulated cortisol reactivity has been associated with depression (Burke et al., 2005; Morris et al., 2014, 2017; Stetler and Miller, 2011; Trueba et al., 2016; Zorn et al., 2017), anxiety (Wichmann et al., 2017; Wintermann, Kirschbaum, & Petrowski, 2016), and stress (Bunea, Szentágotai-Tătar, Miu, 2017; Goldman-Mellor, Hamer, and Steptoe, 2012; Mazurka et al., 2016). Although the direction of cortisol reactivity across studies (hyper-cortisol or hypo-cortisol reactivity) often varies, even within similar presentations of pathology, assessing its impact on treatment can be beneficial. By determining which profiles of cortisol reactivity may best predict treatment, and furthermore examine which treatments best moderates cortisol outcomes, clients may benefit from individualized therapy that reduces the rate of non-response and increase treatment efficacy.

Higher levels, as opposed to higher reactivity, of cortisol during exposure therapy have predicted better treatment outcomes (Meuret et al., 2015; Siegmund et al., 2011). This may be due to its reduction of stimulus-based fear and increased approach behaviors in patients who completed exposure based therapy (Soravia et al., 2006, 2014; de Quervain et al., 2011; Lass-Hannemann and Michael, 2014). In a cross-sectional study on the relationship between emotional arousal and cortisol reactivity to the TSST, Het et al. (2012) also observed a diminished negative emotional arousal for those with elevated cortisol reactivity in a group of healthy participants. Thus higher cortisol reactivity before long term psychosocial interventions may be used a predictor of treatment outcome due to its benefits in therapy and buffering of negative affect in the laboratory. Dieleman and colleagues (2016) observed that greater pre-treatment cortisol reactivity to an acute stressor,

which included a mental arithmetic task and a revised version of the social competence interview, predicted greater improvements in reducing depressive symptoms at a 1-year follow-up for children undergoing CBT for anxiety. However, there was not a significant relationship between cortisol reactivity and anxiety symptoms (Dieleman and colleagues, 2016). Similarly, greater cortisol reactivity to the TSST predicted superior treatment outcome after 5 weeks of CBT in those with panic disorder, compared to healthy controls (Wichmann et al., 2017). Notwithstanding, other studies have not observed these effects. Participants who had PTSD with higher cortisol responses to a pretreatment presentation of virtual-reality-based combat stimuli had significantly worse outcomes at post-treatment following 6 sessions of virtual reality exposure therapy for those taking alprazolamor or D-cycloserine (trend only). Cortisol reactivity did not predict treatment response in those within the placebo group. These findings were no longer observed at the 6-month follow up (Norrholm et al., 2016). Overall, these findings suggest that in affective disorders, more so in anxiety than depression, higher levels of stress-induced cortisol reactivity before treatment may predict better treatment improvements. In contrast, minors experiencing externalizing or behavioral difficulties may benefit from a lower cortisol reactivity. Van De Wiel and colleagues (2004) found that children with disruptive behavior disorder who had higher cortisol reactivity to a social stressor before psychosocial treatment, had significantly lesser behavioral problems at a 9-month follow up. The stress induction task was an 80 minute frustration computer program while being evaluated by a virtual competitor. By contrast those who initially had decreasing cortisol reactivity showed lesser improvements (Van De Wiel et al., 2004). Relatedly, children in a parenting intervention study for oppositional defiant disorder or conduct disorder who had higher pre-treatment cortisol reactivity and recovery to a computer based psychosocial stressor (see Schoorl et al., 2016) showed greater improvements in in aggression reduction post treatment and

at 12 months follow-up (Schoorl et al., 2017). However, in adolescents completing Multisystemic Therapy for behavioral problems, greater pre-treatment cortisol reactivity to a math stress task was negatively associated with treatment response (Winiarski et al., 2017). In those with increasing slope of cortisol reactivity, assessed at three timepoints from early in treatment to end of treatment, and a higher cortisol reactivity at the first time point both predicted poorer treatment response. Yet the opposite effect was observed in males who had higher pretreatment cortisol and reductions of cortisol reactivity across the study which was associated with higher likelihood for arrests at post-treatment (Winiarski et al., 2017). Differences in findings may be due to the outcome variable in that Winiarski et al. (2017) used clinician-rated measures and arrest history, while Schoorl et al. (2017) and Van De Wiel et al. (2004) used parent or teacher reports. These findings provide insight to the complexity of cortisol reactivity as a predictor of treatment success and how it varies across development and disorders. Although limited in size, the literature suggest that cortisol arousal may predict better outcomes in internalizing disorders than in externalizing disorders which informed us in the formulation of the hypothesis for the current study, which recruited patients with internalizing difficulties.

1.3 Treatment Effects on Cortisol Reactivity

Moreover, cortisol reactivity could also be changed due to intervention; for example, there is some evidence that cortisol reactivity can be influenced by coping strategies. Abelson et al. (2014) illustrated that cortisol stress reactivity to the TSST was reduced following compassion-oriented instructions. Participants were encouraged to address the speech task (job interview) in an altruistic manner by focusing on being able to help others with the new position (Abelson et al., 2014). Similarly, Salzmann et al. (2018) observed that different writing prompts prior to the Maastricht acute stress test, which is a combination of a cold-pressor task and mental arithmetic,

influenced cortisol reactivity. They found that those who wrote letters designed to either distract or reduce the expectation of stress had lower cortisol reactivity's than those prompted to be grateful in their letter. However, trait optimism moderated these findings in that those with higher optimism across the conditions had lower cortisol reactivity (Salzmann et al., 2018). Furthermore, cortisol reactivity differences post-treatment to a variety of interventions have also been observed. For example, following treatment to a home-based virtual attention bias modification training for anxiety, depression, and stress, pregnant women showed lower cortisol reactivity and perceived anxiety to a TSST compared to those assigned to a placebo training (Dennis-Tiwary et al., 2017). Lower cortisol reactivity to a video stressor following six weeks of virtual reality exposures was observed in DCS versus placebo and alprazolam in treated individuals with PTSD (Rothbaum et al., 2014). Likewise, reductions in cortisol reactivity to acute stressors have also been observed using SSRI for PTSD (Vermetten et al., 2006).

In addition, changes in cortisol reactivity at post treatment have been reported in cognitive behavioral therapy. Compared to wait-list controls Gaab et al. (2003) found that male students receiving 7-hour group cognitive-behavioral stress management training session had significantly lesser cortisol reactivity posttreatment. They also reported less perceived stress and that they could better cope with the stressful task. Hammerfald et al. (2006) who extended the study including both men and women, found women (controlling for the use of oral contraceptives) had smaller decreases in cortisol reactivity than men. Likewise, Storch et al. (2007) demonstrated that a 6-day training in CBT and psychoanalytic methods, which focused on galvanizing resources and increasing action-oriented personal goals using behavioral techniques and role play, was sufficient to reduce cortisol levels to the TSST three months later in treated but not wait-list participants.

Similarly mindfulness and meditation-based interventions may also influence cortisol reactivity. Such interventions promote patients to live in the present moment and approach experiences and thoughts non-judgmentally (Hayes & Feldman, 2004). This is in contrast to CBT based interventions which focus on reducing acute threat sensitivity and negative affect through exposure. Although the current study does not use mindfulness-based intervention strategies, the outcomes from such studies on cortisol reactivity are of great insight for the current hypothesis because they may be examining the same underlying mechanisms of change. The PAT intervention of the current study promotes patients to increase positive affect and wellbeing to improve the appetitive reward system. Similarly, mindfulness practice has been hypothesized to also increase overall positive wellbeing and mood through having greater awareness and less biased processing of life experiences (Brown, Ryan, & Creswell, 2007). For instance, state mindfulness has increased positive affect and also lower day-to-day negative affect in cross-sectional studies (Brown & Ryan, 2003). Likewise, increase in positive affect has also been observed in intervention studies of mindfulness (Bailey et al., 2018; Montero-Marin et al., 2018). Yet, mindfulness interventions do not always increase positive affect (Krägeloh et al., 2018). Therefore, the findings associated with mindfulness based interventions may provide insight to how interventions that increase positive affect and wellbeing affect cortisol reactivity.

The characteristics associated with mindfulness may be beneficial in the face of life stressors and even acute stressors in the laboratory, as there has been some literature to support this hypothesis. Higher levels of trait mindfulness (Brown et al., 2012) and more lifetime meditation (Rosenkranz et al., 2016) were associated with reduced cortisol reactivity to the TSST. By contrast higher trait level of mindfulness related to greater cortisol response to a stressful social evaluative speech task, compared to those who were low in this trait and were non-responders (Manigault,

2018). Mindfulness treatment interventions also influence cortisol reactivity. Tang et al. (2007) observed an increase in positive mood and a decrease in cortisol reactivity to an acute math stressor after a 5-day integrative body-mind training. Moreover, Lindsay et al. (2018) conducted a dismantling study to better understand how a 15-lesson smartphone-based mindfulness intervention may buffer biological stress reactivity indices. They found that the facets of monitoring and acceptance combined reduced cortisol reactivity to a modified TSST at the end of treatment, compared to a solely monitoring or control condition in stressed adults.

Nevertheless, many more studies have found no moderation of cortisol reactivity due to mindfulness. Arch et al. (2014) demonstrated that women who listened to a 10-minute self-compassion training for four days had a lower salivary alpha amylase (SAA) area under the curve increase to the TSST and lower state anxiety than those in two control conditions. There were no significant effects for cortisol response, which the authors hypothesized may be due to the intervention reducing the sympathetic system specifically, rather than the HPA-axis. Similarly, Nyklíc̆ek et al. (2013) found no differences in cortisol reactivity to a modified TSST before or after an 8-week mindfulness-based stress reduction therapy compared to waitlist-controls; while Creswell and colleagues (2014) found that a 3-day mindfulness-based intervention increased cortisol reactivity to the TSST at the end of treatment when compared to a cognitive training control program for healthy participants. Despite decreases in self-reported stress reactivity in the mindfulness condition, low pre-treatment mindfulness was associated with higher cortisol reactivity during the TSST in the intervention group (Creswell et al., 2014). Moreover, participants that completed compassion meditation over 6 weeks did not affect cortisol response TSST after treatment compared to a health discussion group (Pace et al., 2009). The only effect seen was a reduction in distress mood state and interleukin (IL)-6, which is a marker for stress-induced

immune response, for those high in meditation. In a follow-up study examining whether physiological indices and behavioral responses before treatment affected engagement in the same medication practice, Pace et al. (2010) found no association between any of the indices examined in the first study and meditation practice with a group of healthy adults. Similarly, in an 8-week mindfulness-based stress reduction group treatment, a significant reduction in ACTH AUC levels, but not cortisol AUC levels, was examined in response to the TSST at the end of treatment for the MBSR group when compared to a stress management education control group for patients with generalized anxiety disorder (Hoge et al., 2018). The authors hypothesized that the delay in cortisol diffusion in the blood may have led to the differences in the perplexing findings. Nevertheless, in a note to the editor, Ranjita (2018) noted that differences in cortisol and ACTH may be due to gender differences. In a cross sectional study examining 8 weeks of daily mindfulness exercises over an audio tape, Basso et al. (2019) did not find differences in cortisol reactivity to the TSST when compared to a control group who listened to podcast. The mindfulness group did report lower self-report anxiety to the social stressor (Basso et al., 2019). One article has observed changes in cortisol over treatment using multiple assessment timepoints. In a previously addressed study on externalizing behaviors, Winiarski et al. (2017) found that as cortisol reactivity to an acute stressor decreased across treatment in males, there was a higher likelihood they would be arrested compared to women (Winiarski et al., 2017).

Taken together, pre-treatment cortisol reactivity to acute laboratory stressors may produce differential response patters across treatment. In affective disorders, specifically-anxiety related disorders, it appears that hypo-cortisol reactivity to an acute stressor administered before therapy predicts worse treatment gains. In contrast, for externalizing or behavioral difficulties, hyper-cortisol reactivity to a stressor is detrimental to treatment outcome in the majority of studies. As

previously delineated, cortisol reactivity to acute stressors is a natural response. Within the context of therapy, biophysiological arousal in the form of typical or elevated cortisol reactivity may help patients with affective disorders become more engaged and have more salient therapeutic experiences. Moreover, different forms of interventions appear to moderate cortisol reactivity to acute stress post-treatment. Specifically, CBT therapies provide more consistent evidence for reduced cortisol reactivity to acute stressors at post-treatment when compared to control groups than mindfulness-based interventions. Although the current study does not use mindfulness based interventions strategies, the current treatment may be targeting similar mechanism of change in increasing positive affect and the appetitive reward system.

Current conclusions on the role of cortisol as a prognostic or prescriptive index of treatment success are restricted due to a number of methodological shortcomings. Those include the limited number of studies on cortisol reactivity to an acute stressor before and after therapy. Although there are various studies examining the change in cortisol after treatment when compared to a control group, the majority did not collect pre-treatment cortisol reactivity to compare to the post-treatment session. Therefore, one cannot truly assess whether an individual's cortisol reactivity has been modified without evaluating it before treatment. Instead they based their findings on a healthy control group and it is possible that their sample already had similar cortisol reactivity profiles before treatment. Due to this, it is crucial to assess changes within the participant's on their cortisol reactivity to acute stressors over time. Moreover, replication and extension are needed for understanding what psychosocial interventions most influence the cortisol reactivity to stress. While most studies examine one form of therapy, few compare the results to other interventions. Therefore, in order to help further the field, it is crucial to examine both treatments that target the reduction of acute threat and treatments that increase reward

sensitivity in the same study in order to clarify how they may be differentially affecting the underlying mechanisms of psychopathology.

Consequently, the aims of this study were 4-fold: 1) to examine the impact of pretreatment cortisol reactivity to stressful laboratory tasks on outcome for treatment of affective disorders; 2) to evaluate whether pretreatment cortisol response moderates the outcome to two different types of interventions differently; 3) to examine whether cortisol reactivity changes following treatment and the degree to which change is related to symptom changes; and 4) to examine whether the different forms of treatment moderate pre-to-post cortisol reactivity slope distinctly. Based on prior research, it is hypothesized that greater cortisol reactivity before treatment will be beneficial to treatment outcome. Likewise, higher cortisol reactivity before treatment will predict better treatment outcomes for those in NAT rather than PAT because the treatment was specifically formulated to reduce threat sensitivity. Since there is limited research previously examining changes in cortisol reactivity cross-treatment within participants, the third and fourth aims will be exploratory and specific directions of change will not be hypothesized.

CHAPTER 2:

METHOD

2.1 Participants

Participants were recruited from the Dallas-Fort Worth (n=21) and Los Angeles (n=13) metroplexes for a treatment study comparing two forms of treatment, which emphasized either increasing positive mood and the appetitive motivational system (Positive Affect Treatment, PAT, n=19) or decreasing negative mood and the threat sensitivity system (Negative Affect Treatment, NAT, n=13; n=2 missing; Craske et al., in press). Inclusion was based on having elevated scores on any of the DASS-21 subscales. This included either a score ≥ 11 on depression, ≥ 6 on anxiety, or a ≥ 10 on stress. To screen for clinical impairment, participants had to score at least a five or higher on any of the three Sheehan Disability subscales (Sheehan, Harnett-Sheehan & Raj, 1996). In addition, participants had to be between the ages of 18 to 65, stable on any medications, English speaking, and willing (suggested) to not begin any other psychosocial or pharmacological treatment until after their 6-month follow-up assessment. Exclusion criteria for the study included: serious medical conditions that would interfere with the psychophysiological assessment, such as severe asthma, chronic obstructive pulmonary disease, etc., active suicidal ideation or self-harm, previous suicide attempt, substance abuse/ dependence, psychosis, bipolar disorder, and intellectual disability. The overarching goal of the treatment study was to identify biologically based moderators of treatment response. Thus, patients completed a pre-post psychophysiological assessment with different task that assessed acute threat sensitivity and reward sensitivity. Moreover, treatment outcome was assessed as changes

in these biologically based indices from before to after treatment. A total of 56 participants completed the psychophysiological assessments before treatment. Out of those who completed the pre-psychophysiological assessment, only 34 participants were included in the current analysis because of missing data within the key variables of interest. There were 616 missing cortisol assessments out of 1092 (56.41%) due to non-completion or dry samples. Those who had missing data did not differ from those with full data on any of the baseline demographic information. There was significantly more missing data on the outcome variable, DASS Total scores, at UCLA than at SMU, $\chi^2(1)= 6.79$, p=.010. Participants were predominantly female (n=23), white (n=18), and on psychotropic medication (n=22). The participants DASS total score was in the moderate-to-severe range, 30.87 (SD=13.49) at pretreatment. For a full description of the sample demographics, refer to table1 in appendix A below.

2.2 Procedure

Eligible participants completed two 3-hr comprehensive laboratory assessments one week apart prior to and following treatment to examine how psychophysiological indices may influence treatment and similarly whether treatment would moderate these factors. Part of the testing battery were two consecutive intermittent stress tasks. The first was an 11-minute mental arithmetic task (Vögele and Steptoe, 1992). Participants had to add and subtract single and double digit numbers on a computer screen consecutively for 3 minutes while listening to background noises through in-ear headphones. The second task was a fear-potentiated startle (FPS) task, which involved the repetition of eight "safe" and "danger" sequences on a computer screen. Participants were instructed that delivery of an aversive stimulus (muscle contraction of the arm) may occur only in the late part of danger conditions leading to a muscle contraction of the bicep (Craske et al., 2012; Grillon, Ameli, Foot, & Davis, 1993). This stressor lasted

approximately 25 minutes during which participants received one bicep stimulation. Unlike standard laboratory-induced stressor tasks that assess cortisol reactivity, including the TSST which are less than 15-minutes long (Kirschbaum, Pirke, Hellhammer, 1993), the current combined stress task was 55 minutes of intermittent stress. Salivary cortisol was collected at four times during the stress task (before the math task, before the FPS tasks, and two after the stressor to assess the peak cortisol) in addition to evening and morning before (awakening and +30 min) the cortisol session. The assessment was repeated following the 15-week intervention of NAT or PAT.

2.3 Measures

Depression Anxiety and Stress Scale. The primary outcome measure was the Depression Anxiety and Stress Scale (DASS, Brown, Chorpita, Korotitsch, & Barlow, 1997). The DASS is a 21-item measure that examined current depressive, anxiety and stress symptoms. It has adequate psychometric properties, including an alpha of 0.97 (Page, Hooke & Morrison, 2007). Participants completed this measure before treatment, at every session of treatment, and after treatment.

Cortisol. Cortisol was collected using Salivettes® tubes with cotton swabs. Participants placed the swab in their cheek for two minutes while making a chewing motion to capture saliva. Samples were stored in freezers and spun at 1600xg for 3 minutes to obtain saliva. For analysis liquid chromatography–mass spectrometry was used and cortisol was calculated as ng/ml and converted to nmol/L, The limit of quantification for the assay was 0.17 nmol/L.

Treatment for Affective Disorders.

The Treatment for Affect Disorders (TAD) is a 15-week randomized control trial where participants are assigned to either the Negative Affect Condition (NAT) or a Positive Affect Condition (PAT). The study aimed to examine the effects of NAT and PAT on positive and negative affect. Although the trial primarily focused on examining change in anhedonia, it also accepted patients with a wide variety of clinical presentations, including depression, anxiety and stress.

Both treatment arms consisted of three modules that addressed patients' behaviors, cognitions, and physiological arousal. In NAT, the goal of treatment was to reduce negative emotions and modify threat sensitivity. Within treatment, participants completed typical cognitive behavioral intervention strategies. During session 1, participants were provided psychoeducation and rationale about negative affect and exposures. Between sessions 2-7 participants completed exposures in-session and at-home which were on their fear hierarchy. After completing these exposures, sessions 8-10 encompassed different facets of cognitive restructuring, which included identifying biases and completing worksheets that targeted how to have more rational thought patterns. Lastly, they completed Capnometry-Assisted Respiratory Training (CART) and relapse prevention from sessions 11-15.

The first session in PAT provided participants with psychoeducation about positive emotions and positive event scheduling (augmented behavioral activation training). During sessions 2-7, they completed behavioral activation for homework and used the session to complete an imaginal recounting of positive events they completed outside of session. Between sessions 8-10, therapists helped clients attend to positive aspects in their life, which focused on increasing reward sensitivity. This was accomplished by identifying positive qualities of events in their daily

lives, anticipating the potential of positive events in their future, and taking ownership of their positive moments. Lastly, in sessions 11-15, participants reviewed relapse prevention and completed meditation activities that fostered loving kindness, increased generosity, and nurtured appreciative joy to help cultivate positive emotions about their lives.

2.4 Data Analytic Overview

Data were analyzed using multilevel models (MLMs) to examine the changes of cortisol over time as well as the slopes of improvement in treatment. Additionally, it is the recommended approach for analyzing clinical trials (Hamer & Simpson, 2009). Since the raw data of cortisol samples was not naturally distributed, it was logarithmically transformed prior to analysis. The analysis controlled for different aspects that are known to affect cortisol, including age, race, gender, medication usage, and time of day the samples were taken. Demographic variables that did not significantly predict outcomes in the analysis were dropped in able to conserve degrees of freedom. This analysis allowed the inclusion of all individuals regardless of missing data, and will treat the missing data as missing at random (MAR). MLM provides unbiased estimates of the growth curve parameters when data are MAR. We examined whether participants with missing data differed from those with complete data on any demographic or baseline level of the study variables. We then performed pattern mixture modeling to investigate whether growth curve parameters differed for those with missing data compared with those with complete data. Moreover, we followed the Aiken and West (1991) method centering to use the whole sample to estimate the growth curve at specific levels of predictor variables like cortisol reactivity.

The association between cortisol reactivity and treatment benefits.

The primary aim of the study was to examine whether cortisol reactivity to an acute stressor before treatment predicts better treatment outcomes. Higher cortisol reactivity to the intermittent stress task at pre-treatment was hypothesized to predict lower slopes of change during treatment. Multi-level modeling was used to assess how changes in cortisol over the experimental paradigm related to slopes of change over the 15 treatment time points (DASS). Cortisol reactivity was quantified as peak cortisol during the stress tasks minus basal level of cortisol the evening prior. Basal cortisol the evening prior was used as the baseline variable due to stressful laboratory session effects on the in-session baseline samples. These in session samples may have been elevated due to being in an experimental condition. Therefore, the evening before sample was used as a baseline to capture the reactivity of participants to stress. We assessed the best growth curve model for the data was logarithmic and subsequently the error covariance matrix for the model that best fit the data was Toeplitz. Due to the use of Toeplitz error covariance matrix, none of the random effects were able to converge in the model and were left out. In addition to the previously listed variables that will be controlled, we also controlled for baseline levels of DASS Total scores in the *hypothesis 1*.

Therefore, the MLM for hypothesis 1 was:

$$Y_{ij} = b0 + b1*Cortisol_i + b2*Time_{ij} + b3*Cortisol_i*Time_{ij} + b4*Medication_i +$$

$$b5*\ Medication_i\ *Time_{ij} + b6\ *Pre\text{-}TreatmentY_i + \varepsilon_{ij}$$

Y_{ij} is the outcome measure (e.g., DASS-Total) for participant i at assessment j. $Cortisol_i$ is the cortisol reactivity for participant i. $Time_{ij}$ is the log of time for participant i at assessment j and was scaled so that the regression coefficient (slope) for time reflected the total change from session 1 through follow-up. $Pre\text{-}TreatmentY_i$ is the pre-treatment value of the outcome measure for

participant i. Time was centered at the post-assessment. Since pre-treatment levels of outcome were used as a predictor of the growth curve, the growth curve was modeled from session 1 through follow-up assessment (outcomes were assessed at the beginning of each session).

Hypothesis 2 predicted that higher cortisol reactivity would predict better treatment outcomes for those in NAT rather than PAT. The condition the participant was randomized into was added to the MLM model in hypothesis one. The best growth curve model for the data was logarithmic and subsequently the error covariance matrix for the model that best fit the data was Toeplitz.

Changes in cortisol reactivity before and after treatment.

The secondary aim of the study was to examine whether improvements due to psychosocial intervention influences cortisol reactivity assessed before and after treatment. Hypothesis three did not have a specific direction of cortisol reactivity changing due to treatment improvements over the 15 weeks. Changes in cortisol over time were assessed by measuring differences in cortisol reactivity (computed as peak stressor task level minus basal evening level) across two different time points (before treatment, at the end of treatment). Moreover, because cortisol reactivity was conceptualized using evening basal levels, a secondary analysis with evening change was also completed to confirm that changes in cortisol reactivity were not due to changes in basal levels. The predictor of treatment success in the subsequent analysis was the predicted OLS intercept of the post treatment DASS Total score. The best growth curve model for the data was Linear and subsequently the error covariance matrix for the model that best fit the data was Scaled Identity.

$$Y_{ij} = b0 + b1*Outcome_i + b2*Time_{ij} + b3*Outcome_i*Time_{ij} + b4*Gender + \varepsilon_{ij}$$

The last hypothesis investigated whether treatment differences between NAT and PAT moderated changes in cortisol reactivity independently. To asses this aim, we examined whether there are differences between the groups on cortisol reactivity from pre-treatment to post-treatment by interacting the condition by time by DASS variables in the same model as hypotheses 3. The best growth curve model for the data was Linear and subsequently the error covariance matrix for the model that best fit the data was Scaled Identity.

CHAPTER 3:

RESULTS

Pre-treatment Patient Characteristics

Participants reported having moderate-to-severe levels of DASS Total score, 30.5(SD=13.6), severe levels of DASS Depression 10.88 (SD=6.01), severe DASS Anxiety 8.03 (SD=5.54), and moderate DASS Stress 11.58 (SD=11.58). As stated above, due to the varying findings on pretreatment cortisol reactivity for individual psychopathology, the total score of the DASS was used for the treatment outcome analysis. Missing data analysis found that the main study variables were not missing completely at random using Little's MCAR Test, $\chi^2(69)= 1466.025$, $p< 0.001$. In completing a pattern mixture modeling to assess whether the growth curve is significantly different for those with missing data, the model fit was significantly better fit than the one without it for cortisol $\chi^2(8)= 59.011$, $p<.001$ and DASS total scores, $\chi^2(8)= 45.951$, $p<.001$. However, the missing data did not predict different growth curve slopes in the analysis and were therefore removed to conserve degrees of freedom.

Pretreatment Cortisol Reactivity Predicting Treatment Outcome

In line with Aim 1, hypothesis 1, higher pre-treatment cortisol reactivity was related to decreasing slopes of change in DASS total scores at post treatment, *b*= -4.21, t(43)= -2.010, p=0.051. Although not fully significant, there were noteworthy differences between those who had higher and lower cortisol reactivity on slopes of change in DASS scores. Those with average, b=

-2.27, t(42)=-3.03, p=0.004, and higher (centered at 1SD above the mean), b= -3.64, t(33)=-3.81, p=0.001, cortisol reactivity had significantly decreasing slopes of DASS Total score across treatment. In contrast, those with lower cortisol reactivity (1SD below the mean) did not have significantly decreasing slopes of DASS total score, b= -0.91, t(53)=-0.86, p=0.396 (Figure 1). Nevertheless, these results were moderated by significant differences in rates of improvement between those on and off medications, in that those who were taking medications had significantly smaller DASS Total scores at post treatment, b= -7.389, t(56)= -2.020, p=0.048. For those without medication and lower in cortisol reactivity, treatment slopes became significant b= -4.92, t(44)=-3.45, p=0.001. Cortisol reactivity changes were not different for participants who were of minority backgrounds, b= 3.16, t(28)= 0.32, p=0.751. This was also examined for all other subsequent analysis. Therefore, the variable for race was dropped to conserve degrees of freedom.

Pretreatment cortisol reactivity moderating treatment outcome for NAT and PAT

In contrast to our aim 1, hypothesis 2, that cortisol reactivity would predict better treatment outcomes in NAT treatment, the type of treatment did not differentially affect the relationship between cortisol reactivity and slopes of change, b=0.25, t(67)=0.05, p=0.962. Those in the negative affect treatment did not show different improvements compared to those in the positive affect treatment in slopes of change of DASS Total score.

Treatment Modifying Cortisol Reactivity from Pre-Treatment to Post-Treatment

Cortisol Reactivity did not significantly change from pre to post treatment b=-0.020, t(36)=-0.081, p= 0.936. Moreover, DASS Total scores slope at post-treatment were not related to cortisol reactivity changes from before to after treatment, b=0.034, t(36)=0.632, p= 0.531. Therefore, the variable for race was dropped to conserve degrees of freedom. Similarly, there was

also no changes in evening basal levels of cortisol from before to after treatment, b= -0.166, t(40)= -0.955, p=0.345, or due to change changes in treatment, b= 0.012, t(40)= 0.328, p=0.745. degrees of freedom

Treatment Condition as a Moderator of the Effects of Treatment on Cortisol Reactivity

In addition to seeing whether cortisol reactivity changes as a result of treatment, we also investigated whether the two different forms of treatment would relate differently influence such change. Treatment condition did not moderate changes in cortisol reactivity, b=-0.15, t(32)= -1.33 , p=0.20. Likewise, treatment condition did moderate the relationship between DASS treatment outcome and evening basal cortisol changes, b= 0.042, t(36)= 0.548, p= 0.587.

CHAPTER 4:

DISCUSSION

The current study investigated whether cortisol reactivity to a series of laboratory induced intermittent stress tasks were a predictor of treatment success, and whether such success were moderated by treatment condition. We furthermore investigated whether cortisol reactivity changes from before to after treatment would be related to improvements in affective symptoms and treatment condition. As hypothesized, cortisol reactivity nearly significantly predicted treatment outcome in that those with higher cortisol reactivity had significantly greater decreases in affective symptoms over treatment. In contrast, no significant improvements were observed in those with low cortisol reactivity. Yet, no changes in cortisol reactivity to treatment were observed and the relationship between cortisol reactivity and treatment outcome was not moderated by treatment condition.

The result that greater cortisol reactivity predicts better treatment outcome are noteworthy because they provide evidence that cortisol reactivity before treatment may be conceptualized as a threat sensitivity biological marker in predicting who benefits most from psychotherapeutic intervention. This outcome has been supported in the literature in not only depressive symptoms (Dieleman et al., 2016) but also anxiety symptoms (Wichmann et al., 2017). In both of these studies, higher cortisol reactivity was beneficial to treatment outcome. Since both depression and anxiety are highly comorbid, the current study used a combined

symptoms score and was able to provide evidence that cortisol reactivity may be a marker for affective symptoms more generally. The finding that higher cortisol reactivity is beneficial to treatment outcome advances the literature because it provides a different framework on conceptualizing cortisol. In the behavioral medicine literature, prolonged and elevated cortisol levels have been associated with negative health outcomes. For example, elevated evening cortisol can be detrimental to cardiovascular health (Kumari, Shipley, Stafford, and Kivimaki, 2011). However, the acute activation of cortisol within a stress paradigm assesses a different biological stress system that is unique from the diurnal patterns observed throughout the day. Thus, acute cortisol arousal may provide different implications on intervention. Although there have been previous studies examining how cortisol reactivity can be changed using intervention studies, which only have a post treatment cortisol assessment, these studies operate under the premise that higher cortisol reactivity should be buffered. Yet, according to treatment outcome literature, acute cortisol stress reactivity may be advantageous. One proposed hypothesis as to why this may occur is that those with more severe and prolonged symptoms may have a habitualized HPA-axis due to continued overactivation and allostatic load (Dieleman et al., 2006; McEwan, 2000). This is also observed in the effects that early life stress has on cortisol. Goldman-Mellor, Hamer, and Steptoe (2012) found that adults who not only had early life stressors, but also consistent psychological distress had blunted cortisol responses to cognitive challenges compared to individuals who either had no early life stress or lower levels of consistent psychological distress. Therefore, increasing the cortisol reactivity response when enrolled in therapy may be more beneficial to treatment. More research on the activation of the HPA-axis to acute stressors and its relationship with long-term psychological functioning is of

vital concern because it may be detrimental to continue trying to reduce biological indices that are a natural response.

Likewise, the mechanisms of how cortisol reactivity may be influencing treatment outcome is still unclear. Cortisol reactivity may predict better outcomes when in conjunction with other within-treatment factors as is observed in D-cycloserine where those with successful exposures (Smits et al., 2013) and greater homework compliance (Olatunji et al., 2015) have better treatment outcomes. One mechanism by which cortisol reactivity may have its boosting effect is through its influence on extinction learning. Within the treatment outcome literature, higher cortisol within treatment exposures predict better treatment success through improvements in extinction learning. Meuret et al. (2015) observed that higher cortisol levels during exposures for panic disorder and agoraphobia enhanced extinction learning and predicted lower avoidance behavior, lower threat appraisal, and higher perceived control. Siegmund et al., (2011) also found better treatment outcome for those with higher levels of cortisol during exposures. However, cortisol reactivity may also be an independent factor predicting treatment outcome as is seen in the buffering effects of cortisol on stress (Rao et al., 2012) and the onset or continuation of trauma related memories (Aerni et al., 2004; Zohar et al., 2011).

As mentioned above, cognitive behavioral therapies have been most efficacious in reducing elevated threat sensitivity in control group studies of cortisol reactivity. Since the positive affect treatment was created to increase appetitive motivational system, and not target threat sensitivity directly, it was expected that the negative affect treatment will be more likely to moderate cortisol reactivity. However, we did not find moderation of cortisol reactivity in response to treatment condition. This may be because the NAT treatment modules did not directly address how to cope with acute stressors. Instead, patients engaged in feared activities

over multiple weeks of exposure, were told to not avoid their fears, and used cognitive restructuring strategies to decrease psychosocial distress. Similarly, the purpose of the breathing training (CART) modules of the NAT treatment were to normalize carbon dioxide levels in those with panic symptoms and not as a relaxation training as observed in prior behavioral interventions (Gaab et al., 2003; Hoge et al., 2018). Yet, there is evidence that interventions that do not have an explicit relaxation intervention can also buffer cortisol reactivity as was seen in Dennis-Tiwary and colleagues (2017) who used a home attention bias modification training. Therefore, future research on interventions may be able to distinguish necessary components that target acute endocrinological threat sensitivity by completing a dismantling study. These results may provide fine-tuned and personalized interventions for those whose cortisol reactivity may be overactive and producing a negative treatment effect as is seen in externalizing disorders (Winiarski et al., 2017).

4.1 Strengths and Limitations

A primary limitation in the current study is that the intermittent stress task provided to participants may not have been salient enough to increase cortisol levels. This was seen in how cortisol reactivity to the task was significantly decreasing across the laboratory assessment time points. Recent articles have found that cortisol reactivity is consistently elicited in laboratory studies when the task has a social evaluative component and is unpredictable (Dickerson, Kemeny, 2004; Skoluda et al., 2015). Therefore, since the two intermittent stress tasks in the study did not have an explicit social evaluative component, it may not have been optimal to induce cortisol reactivity. Another possibility is that the sample was actually hypo-reactive due to their clinical impairments. Previous findings have found a cortisol hypo-reactivity in depression (Burke et al., 2005; Zorn et al., 2017) and anxiety (Wichmann et al., 2017). Yet, there

are also studies that observe a hyper-reactive response in depression (Morris et al., 2017; Trueba et al., 2016) and anxiety (Abelson et al., 2007). Future studies should enlist a control group of healthy participants to confirm that the intermittent stressor truly elicits a cortisol response and the hypo-reactivity is a valid response. Previous literature has also examined a novelty effect of cortisol in laboratory studies in that participants have elevated cortisol due to being in a new and exhilarating environment (McEwen, 2000). This many times causes cortisol reactivity to not be as prominent because they are elevated throughout the session regardless of stressor. However, a strength of this study is that participant's completed the cortisol reactivity measures on the second day of assessment. They would have been acclimated to the environment and the cortisol reactivity response may have been more accurate than if it was assessed on the first day.

The findings in this study may not be able to be extrapolated to specific subpopulations of primarily anxiety or depression disorder patients due to the fact that the sample was trans-diagnostic. However, this is a strength of the study because the reality is that in epidemiological studies it is observed that patients have many comorbid anxiety and depressive disorders. Moreover, within the study, we used a self-report measure of psychopathology symptoms across the different treatment timepoints, which was the depression anxiety and stress scale. Using a single rater and self-report measures may not fully capture all the nuances of clinical changes that occurred; and at times, may also inflate greater treatment responses than having multiple raters, including clinician measures (Loerinc et al., 2015). Nonetheless, the use of psychophysiological measures, like cortisol reactivity, as predictors of change are more objective in nature and reduced the overlap of shared method variance.

A strength of our study is that the laboratory stressor was manualized which provided structure and controlled for cortisol collection factors not often adhered to in naturalistic

stressors. In addition, although the current study controlled for gender, time of day the cortisol samples were taken, and other demographic information; there were still limitations in that we did not control for female reproductive influences and other factors like smoking, caffeine, alcohol, and circadian rhythm. Moreover, since we had a small sample size due to missing data of participants who completed the psychophysiological study, we may not have the ability to generalize the results. Nevertheless, the use of MLM has been shown to provide unbiased estimates of regression coefficients within studies with small sample sizes and even with large amounts of missing data. Future studies should enroll a larger cohort to complete treatment outcome studies that have psychophysiological components to understand the effect it had on underlying mechanisms.

In conclusion, the results of this study provide evidence that cortisol reactivity to acute stressors may be used as a threat sensitivity biomarker for treatment outcome in affective disorders. We did not find a moderating effect of treatment modality; however, larger scale studies must be conducted to better understand which treatments modalities may best optimize this biological response and capitalize on its benefits.

APPENDIX

Table 1. Baseline Demographics and Characteristics

Characteristics	Values[a]
Age, mean (SD),[b]	36.27 (14.24)
Female sex	23 (67.6)
Race/Ethnicity[b]	
White	18 (52.9)
Asian	4 (11.8)
African American	2 (5.9)
Hispanic/ Latino White	3 (8.8)
Hispanic/ Latino Non-white	5(14.7)
Other	1 (2.9)
Marital Status[b]	
Married	9 (26.5)
Single, in a relationship	6 (17.6)
Single, not in relationship	12 (35.3)
Other	5 (14.71)
Employed full or part time[b]	21 (61.76)
Education Level[b]	
Less than high school	1 (2.9)
High school diploma/GED	4 (11.8)
Some college/2/4 year degree	9 (26.5)
Graduate degree	11 (32.4)
Income[b]	
<10,000– 30,000	8 (23.53)
30,001 – 50,000	4 (11.76)
50,001 – 70,000	6 (17.65)
70,001 – 100,000	7 (20.59)
>100,000	6 (17.65)
Medications	
Antidepressants	13 (38.2)
Benzodiazepines	5 (14.7)
Sleep	1(2.9)
Non-psychiatric	14(41.2)
Stimulants	2(5.9)
Unknown	1(2.9)
DASS Total Scores	30.87(13.49)
DASS Depression	11.15 (5.94)
DASS Anxiety	8.00 (5.48)
DASS Stress	11.72 (4.74)

[a]Data are presented as number (percentage) of patients unless otherwise indicated
[b]Indicates missing responses (age=1, race=1, employed=4, income=3, marital status=2,education level=1)

Figure 1. Scatter Plot of Cortisol

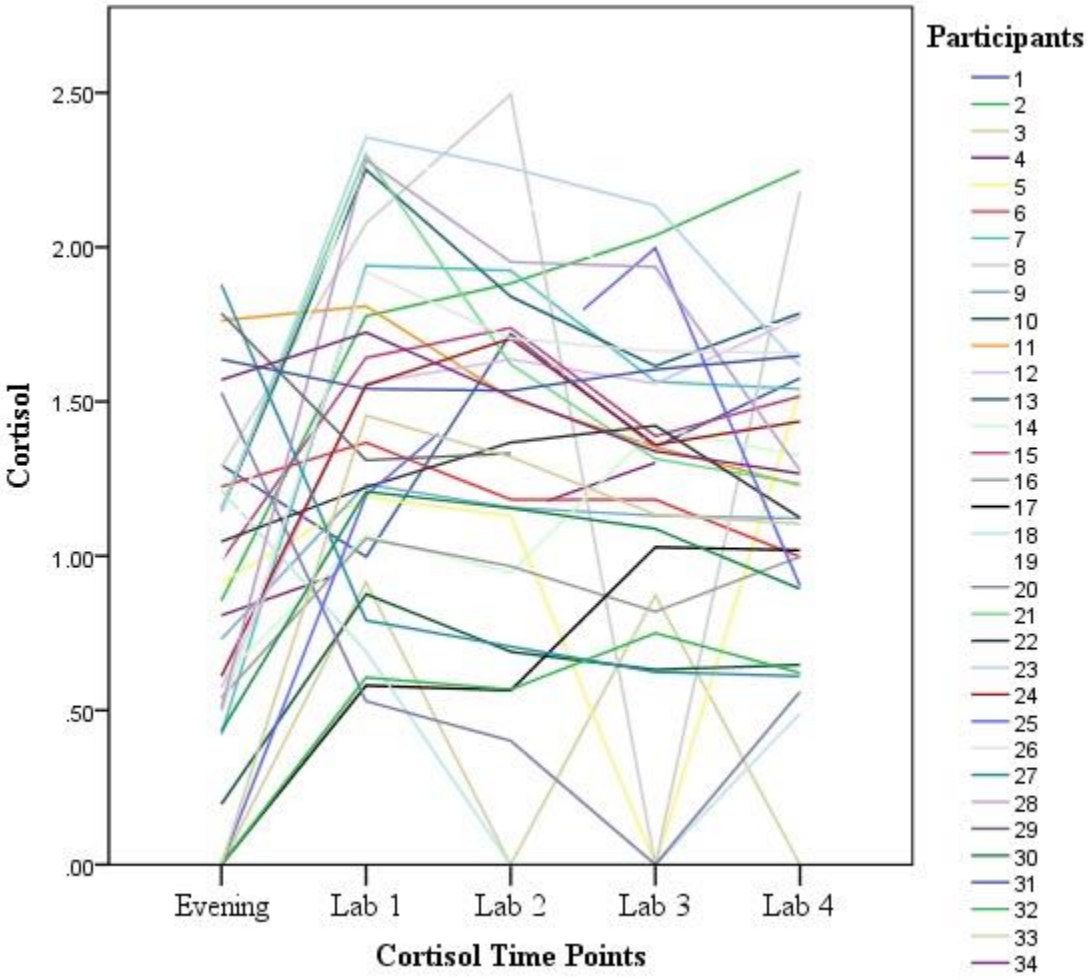
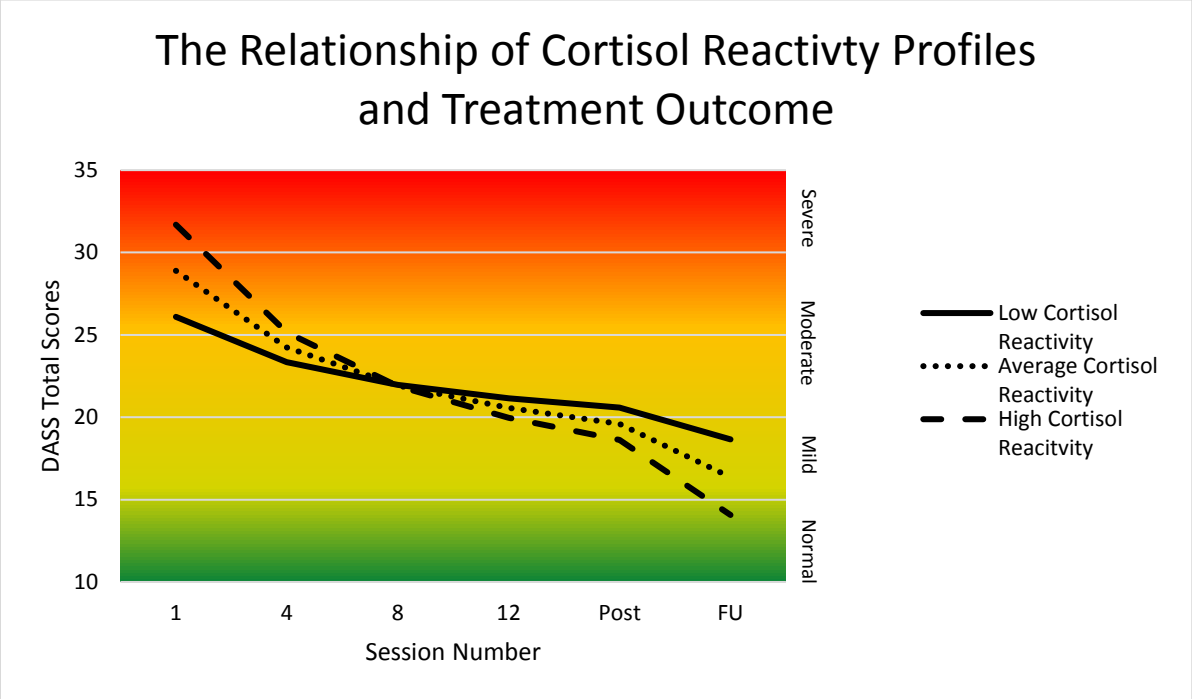


Figure 2. Higher cortisol reactivity before treatment is significantly related to lower slopes of DASS Total score over time.



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