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Physiological and behavioral indices of emotion dysregulation as predictors of outcome from cognitive behavioral therapy and acceptance and commitment therapy for anxiety

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ABSTRACT

Background and objectives: Identifying for whom and under what conditions a treatment is most effective is an essential step toward personalized medicine. The current study examined pre-treatment physiological and behavioral variables as predictors and moderators of outcome in a randomized clinical trial comparing cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT) for anxiety disorders.
Methods: Sixty individuals with a DSM-IV defined principal anxiety disorder completed 12 sessions of either CBT or ACT. Baseline physiological and behavioral variables were measured prior to entering treatment. Self-reported anxiety symptoms were assessed at pre-treatment, post-treatment, and 6- and 12-month follow-up from baseline.
Results: Higher pre-treatment heart rate variability was associated with worse outcome across ACT and CBT. ACT outperformed CBT for individuals with high behavioral avoidance. Subjective anxiety levels during laboratory tasks did not predict or moderate treatment outcome.
Limitations: Due to small sample sizes of each disorder, disorder-specific predictors were not tested. Future research should examine these predictors in larger samples and across other outcome variables.
Conclusions: Lower heart rate variability was identified as a prognostic indicator of overall outcome, whereas high behavioral avoidance was identified as a prescriptive indicator of superior outcome from ACT versus CBT. Investigation of pre-treatment physiological and behavioral variables as predictors and moderators of outcome may help guide future treatment-matching efforts.

1. Introduction

The effectiveness of cognitive behavioral therapy (CBT) for the treatment of anxiety disorders is well established (Hofmann & Smits, 2008; Tolin, 2010), and other behavioral treatments, such as acceptance and commitment therapy (ACT; Hayes, Strosahl, & Wilson, 2011), are garnering support (Arch et al., 2012; Craske et al., in press). However, responses vary widely, with some patients achieving long-lasting remission and others remaining symptomatic or experiencing a return of symptoms at follow-up (Arch & Craske, 2009). In an effort to improve outcomes, the National Institutes of Health has called for an increased emphasis on personalized medicine. Identifying both prognostic factors (predictors of overall treatment success), as well as prescriptive factors (moderators of response to different treatments), incrementally improves our capacity to match anxious individuals to the most appropriate treatments (Wolitzky-Taylor, Arch, Rosenfield, & Craske, 2012).

Anxiety disorders are largely characterized by poor regulation of negative emotion (Campbell-Sills & Barlow, 2007; Hofmann, Sawyer, Fang, & Asnaani, 2012), and behavioral treatments for anxiety often target emotion regulation difficulties (Papa, Boland, & Sewell, 2012). In CBT, emotion regulation is addressed through

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cognitive reappraisal, an antecedent-focused emotion regulation strategy used to limit the emotional impact of an event by reframing its meaning or anticipated outcome (Gross, 1998), and exposure, which serves to change expectations and emotional responses associated with feared stimuli (Papa et al., 2012). ACT, a newer behavioral therapy that centers itself within contextual behavioral theory (Hayes et al., 2011), uses mindfulness, acceptance, and cognitive defusion strategies to promote nonjudgmental awareness and increase value-oriented living. These strategies in ACT are thought to reduce the use of maladaptive response-focused emotion regulation strategies (e.g., suppression) by encouraging patients to distance themselves from rigid thoughts, increase contact with the present moment, and reduce experiential avoidance (Hofmann & Asmundson, 2008).

As ACT and CBT both address emotion regulation, pre-treatment levels of emotion dysregulation may provide prognostic or prescriptive information. Emotion dysregulation has been indexed by heightened self-reported negative affect (Lang & McTeague, 2009), heightened amygdala activity in response to threat (Rauch et al., 2000), reduced high-frequency heart rate variability (Friedman & Thayer, 1998; Pittig, Arch, Lam, & Craske, 2013), and avoidance behavior (Chambless & Gracely, 1989). Despite the relevance of each of these indices of emotion dysregulation to the phenomenology of anxiety, only a handful of studies have examined them as predictors of treatment outcome (McClure et al., 2007; Wolitzky-Taylor et al., 2012). Even fewer studies have examined these indices as moderators of outcome from two distinct treatments for anxiety disorders (Meuret, Hofmann, & Rosenfield, 2010; Wolitzky-Taylor et al., 2012).

Increasingly, researchers are examining pre-treatment neural activity as a potential predictor of treatment outcome. Pre-treatment amygdala hyperactivity during complex emotion-processing tasks[1] has been found to predict better outcome from behavioral treatment for generalized anxiety disorder (McClure et al., 2007) and depression (Canli et al., 2005). Assuming that amygdala hyperactivity represents poor emotion regulation (e.g., Schaefer et al., 2002), then one explanation is that individuals with poorly-regulated emotional responses prior to treatment are more likely to benefit from treatment that targets this dysfunction. Thus, physiological and behavioral correlates of amygdala hyperactivity may similarly predict outcome.

High-frequency heart rate variability (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012) and avoidance behavior (Schlund & Cataldo, 2010) have been linked to amygdala activity and therefore may be considered peripheral markers of such activity. Low resting heart rate variability and low heart rate variability in response to stressors are associated with autonomic inflexibility and poor emotion regulation (Appelhans & Luecken, 2006; Hughes & Stoney, 2000; Sahar, Shalev, & Porges, 2001; Thayer & Lane, 2000), as well as increased amygdala activity (Mujica-Parodi et al., 2009) and decreased activity in prefrontal cortex regions responsible for amygdala down-regulation (Lane et al., 2009). Avoidance behavior, an emotion regulation strategy that maintains anxiety and interferes with inhibitory learning (Craske et al., 2008), is also associated with increased amygdala activation during tasks in which individuals avoid or escape an aversive event (e.g., monetary loss; Schlund & Cataldo, 2010; Schlund et al., 2010). Conceivably, these peripheral markers of emotion dysregulation may predict treatment outcome in the same way as amygdala activity. However, the current evidence for their prediction effects is limited.

A number of studies have examined physiological responses *during* treatment as predictors of outcome from behavioral treatments for anxiety. For example, increased heart rate during exposure sessions has been associated with superior treatment outcome for specific phobia (Lang, Melamed, & Hart, 1970), PTSD (Pitman et al., 1996), and claustrophobia (Alpers & Sell, 2008). Some researchers have interpreted these results to signify that elevated autonomic activity indicates activation of the fear structure (bio-informational theory; Lang, Cuthbert, & Bradley, 1998), which allows the fear structure to be modified during treatment (Foa & Kozak, 1998). However, this theory has received inconsistent support (see Craske et al., 2008); several studies indicate no relationship (e.g., Baker et al., 2010; van Minnen & Hagenaars, 2002; Sloan & Telch, 2002) or an inverse relationship (e.g., Telch, Valentiner, Ilai, Petruzzi, & Hehmsoth, 2000) between heart rate reactivity during exposure and subsequent treatment outcome. Moreover, studies examining *pre-treatment* heart rate reactivity as a predictor of outcome are mixed (e.g., Craske, Sanderson, & Barlow, 1987; Kozak, Foa, & Steketee, 1988). One explanation for this inconsistency is that elevated heart rate reflects multiple constructs, including incentive-related activation and active avoidance (Fowles, 1980), and is affected by both sympathetic and parasympathetic activation (Katona, McLean, Dighton, & Guz, 1982). Thus, it is possible that heart rate is too broad of a measure to provide prognostic or prescriptive utility. Instead, heart rate variability, which reflects cardiac parasympathetic activity and is a more reliable measure of emotion regulation (Appelhans & Luecken, 2006; Thayer & Lane, 2000), may provide more consistent and useful results.

Though existing research is sparse, studies investigating the effects of behavioral treatment on heart rate variability suggest that exposure and mindfulness-based treatments increase heart rate variability. Increases in resting heart rate variability were found following successful CBT for panic disorder (Craske, Lang, Aikins, & Mystkowski, 2005) and PTSD (Garakani et al., 2009), and after mindfulness-based treatment for substance use (Brewer et al., 2009). These findings suggest that low heart rate variability may be targeted by strategies in CBT and ACT. One small study found that individuals who were unresponsive to exposure therapy for flight phobia had higher baseline heart rate variability (Bornas, del Amo, Tortella-Feliu, & Llabrés, 2012), supporting the notion that targeting emotion regulation may be more effective for individuals with low, rather than high, heart rate variability. However, no studies to our knowledge have examined heart rate variability as a predictor or moderator of outcome from CBT or ACT.

Avoidance plays a central role in anxiety disorders and thus may also predict treatment outcomes. Individuals with anxiety disorders discontinue anxiogenic challenges such as voluntary hyperventilation sooner than healthy controls, reflecting greater avoidance of interoceptive sensations (Arch & Craske, 2010). Though particularly evident in panic disorder, avoidance of sensations is observed across multiple anxiety disorders (Arch & Craske, 2010; Chawla & Ostafin, 2007; Roemer, Salters, Raffa, & Orsillo, 2005). CBT targets avoidance of sensations through interoceptive exposure (Craske, 2005), whereas ACT targets avoidance by encouraging clients to “lean into” anxious sensations (Eifert & Forsyth, 2005). Indeed, acceptance training has been found to increase participants' willingness to endure physical sensations brought on by CO_2 inhalation (Eifert & Heffner, 2003; Levitt, Brown, Orsillo, & Barlow, 2004), suggesting that acceptance specifically targets behavioral avoidance of physical sensations. However, no studies to date have investigated whether baseline behavioral avoidance predicts outcome from ACT and CBT.

[1] Conversely, amygdala activity during tasks requiring minimal emotional processing (e.g., viewing rapidly-presented emotional stimuli) was unrelated to treatment outcome in two studies (Bryant et al., 2008; Doehrmann, 2013). As amygdala activation during more complex emotional processing tasks is likely a better index of emotion regulation (e.g., Schaefer et al., 2002), it is therefore emphasized.

The primary goal of this study was to investigate two indices of emotion regulation, heart rate variability and behavioral avoidance, as predictors and moderators of treatment outcome in ACT and CBT for anxiety disorders. Due to limited extant research, our hypotheses were largely exploratory. However, based on the "deficit-matching" model, which theorizes that treatments are most successful when they remediate a particular deficit or weakness (Miller et al., 2005, 2008), we speculated that poorer emotion regulation at pre-treatment would predict a more favorable outcome. Thus, we hypothesized that lower pre-treatment heart rate variability and higher pre-treatment avoidance of interoceptive sensations would predict better outcome. To determine whether these variables predicted who responded better to which treatment, we also evaluated them as moderators of response to ACT and CBT.

2. Materials and methods

2.1. Participants

A total of 121 participants were enrolled in the study. Fifteen participants, blind to their treatment condition, did not complete any treatment sessions, and an additional 31 did not complete treatment, leaving 75 participants who completed all 12 treatment sessions.[2] Attrition did not differ between treatments ($n = 24$ in CBT, $n = 22$ in ACT; $p = .60$). Fifteen of these participants were not included in the current analyses due to missing questionnaire data ($n = 9$ in CBT, $n = 6$ in ACT; $p = .82$), and therefore the final sample included 60 participants ($n = 34$ in CBT, $n = 26$ in ACT).

Participants were eligible for the study if they (a) met *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; American Psychiatric Association, 2000) criteria for one or more anxiety disorders with a Clinician Severity Rating (CSR) ≥ 4 on the Anxiety Disorders Interview Schedule (ADIS-IV; Brown, DiNardo, & Barlow, 1994) and were (b) between 18 and 60 years of age; (c) either medication free or stabilized on medication; (d) not undergoing other behavioral therapies or stabilized on alternative psychotherapies not focused on their anxiety; and (e) English-speaking. Exclusion criteria included (a) active suicidal ideation and/or severe depression (CSR ≥ 6); (b) psychiatric hospitalization within the past five years; (c) serious medical conditions or pregnancy; (d) history of psychotic disorders, bipolar disorder, mental retardation, or organic brain damage, and (e) substance abuse and/or dependence within the past 6 months.

Participants were 46.7% female with a mean age of 35.76 years ($SD = 11.87$) and were 60.0% Caucasian,13.3% Hispanic/Latino, 8.3% Black/African American, 11.7% Asian/Pacific Islander, 1.7% Native American/Alaskan, and 5.0% other race. Panic disorder with or without agoraphobia was the most common principal diagnosis (31.6%), followed by social anxiety disorder (23.3%), generalized anxiety disorder (21.7%), obsessive-compulsive disorder (15.0%), specific phobia (5.0%), and PTSD (3.3%). Participants in ACT and CBT did not differ by gender, age, ethnicity, or frequency of principal diagnosis ($ps > .35$).

2.2. Design

Participants were assessed at pre-treatment (Pre), post-treatment (Post), 6 months (6MFU), and 12 months (12MFU) after Pre. Assessments included administration of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson & Clark, 1991) and a laboratory assessment that included physiological measurement. All moderator variables were collected during the pre-treatment laboratory assessment.

2.3. Pre-treatment laboratory assessment

2.3.1. Baseline

Participants completed a 5-min quiet sitting period at the beginning of the assessment to measure baseline physiological activity.

2.3.2. Relaxation-induced anxiety task

This task was chosen to assess participants' emotion regulation capacity during a focused relaxation induction. Requests to relax can paradoxically induce panic and anxiety symptoms in individuals with panic disorder (e.g., Craske et al., 2005), the most common diagnosis in the current sample. Additionally, though relaxation-induced anxiety is primarily studied in panic disorder, it has also been demonstrated in other anxious samples (e.g., Heide & Borkovec, 1983). Relaxation-induced anxiety is thought to arise from fear of the consequences of having unpleasant sensations or thoughts (e.g., losing control) or fear of the experience of anxiety itself (Heide & Borkovec, 1984), mechanisms which are purportedly targeted in CBT (by reducing maladaptive cognitive appraisals) and ACT (by reducing experiential avoidance). In this task, participants sat in a comfortable, nearly horizontally-reclined chair and were instructed to silently repeat a word ("ah-nam") for an unrevealed duration of 15 min. After 15 min, participants completed a 0–100 anxiety rating (0 = no anxiety at all, 100 = the most severe anxiety).

2.3.3. Hyperventilation task 1

This task was chosen to assess participants' emotion regulation capacity following a biological challenge. Hyperventilation tasks reliably differentiate anxiety disorder patients from healthy controls in terms of reported fear and hyperventilation symptoms (e.g., Rapee, Brown, Antony, & Barlow, 1992). Maladaptive responses to hyperventilation are thought to result from negative interpretations of bodily sensations (e.g., Holloway & McNally, 1987) or fear of experiencing emotions brought on by hyperventilation due to experiential avoidance (e.g., Karekla, Forsyth, & Kelly, 2004). Participants were seated and instructed to breathe rapidly with the pace of a metronome set at 76 beats per minute, with two beats comprising one respiratory cycle (i.e., 38 breaths per minute). Experimenters modeled the hyperventilation breathing, and participants briefly practiced before being asked to hyperventilate for an undisclosed duration of 60 s. After 60 s of hyperventilation, participants completed a 0–100 anxiety rating and sat quietly to recover.

2.3.4. Hyperventilation task 2

Following recovery from Hyperventilation 1, participants completed a second hyperventilation task, which followed the same procedure as the first, except that participants were instructed to continue hyperventilating for as long as they were "willing and able to continue" up to an undisclosed 180 s. After the task, participants completed a 0–100 anxiety rating. This task was chosen to measure participant's behavioral avoidance as an index of emotion dysregulation (e.g., Arch & Craske, 2010; Levitt et al., 2004).

[2] Although multiple imputation can be used to estimate missing data, simulation studies suggest that with large amounts of missing data on the dependent variable (10–20%), multiple imputation can inflate standard errors and therefore should not be used (Lane et al., 2009). In the current study, the amount of missing data on the dependent variable was approximately 30%; thus, missing data were not imputed.

2.4. Treatments

Participants received 12 weekly, 1-h individual CBT or ACT therapy sessions by advanced clinical psychology doctoral students or postdoctoral fellows. Therapists followed detailed manuals, and the two treatment conditions were matched on amount of homework and number of sessions devoted to exposure. See Arch et al. (2012) for additional details regarding therapist training and supervision, randomization, and treatment.

2.4.1. Cognitive behavioral therapy (CBT)

CBT followed a manual based on CBT principles relevant across the anxiety disorders, with branching mechanisms that tailored content to individual anxiety disorders (Craske, 2005). Session 1 included psychoeducation, self-monitoring, and a brief assessment in which the patient and therapist decided on the primary focus of treatment (typically the principal anxiety disorder diagnosis). Breathing retraining was emphasized in Sessions 2 and 3, and cognitive therapy techniques (such as cognitive restructuring and behavioral experiments) were emphasized in Sessions 2–4. Exposure (interoceptive, imaginal, and in vivo, as indicated) was introduced in Session 5 and served as the focus for the remainder of treatment. CBT exposures were designed for hypothesis testing and long-term anxiety reduction. Session 12 included a discussion of relapse prevention and planned additional exposures as needed.

2.4.2. Acceptance and commitment therapy (ACT)

ACT followed Eifert and Forsyth's (2005) manual for anxiety disorders. Session 1 included psychoeducation and treatment rationale. Creative hopelessness exercises were emphasized in Session 2, and mindfulness, acceptance, and cognitive defusion were emphasized in Sessions 3–5. Sessions 6–11 continued to hone mindfulness, acceptance, and cognitive defusion skills, and also included values exploration and clarification, with the goal of increasing willingness to engage in valued life activities. In vivo, imaginal, and interoceptive exposures were framed as ways to practice engaging in valued activities while mindfully observing anxiety. Session 12 included a discussion of how to manage obstacles while continuing to move forward.

2.5. Measures

2.5.1. Outcome measure

The Mood and Anxiety Symptom Questionnaire, General Anxiety Subscale (MASQ-GA; Watson & Clark, 1991) was the outcome measure. The MASQ-GA is a subscale of the 90-item MASQ in which participants rate the degree to which they have experienced a number of anxiety symptoms in the past week. This scale was selected as the outcome measure due to its relevance for a heterogeneous anxiety disorders sample. The MASQ-GA shows good convergent and construct validity (Watson et al., 1995), is sensitive to treatment change (e.g., Hides et al., 2010; Wolitzky-Taylor et al., 2012), and had good internal consistency in the current sample (see Wolitzky-Taylor et al., 2012).

2.5.2. Potential pre-treatment moderators

2.5.2.1. High-frequency heart rate variability (HF-HRV). HF-HRV is an index of parasympathetic cardiac control (Thayer & Lane, 2000). HF-HRV was calculated for Baseline, Relaxation, and Hyperventilation 1 Recovery (see below).[3] Measures of cardiovascular recovery (including HRV) after an acute stressor reflect parasympathetic reactivation (Imai et al., 1994) and are related to individual differences in emotion regulation (Tugade, Fredrickson, & Feldman Barrett, 2004).

2.5.2.2. Duration of hyperventilation 2. Duration of voluntary exposure to laboratory stressors is widely used as a standardized measure of avoidance of negative or unpleasant stimuli (e.g. Arch & Craske, 2010; Cioffi & Holloway, 1993). The current study measured avoidance as the amount of time (max 180 s) participants persisted with Hyperventilation 2 (shorter duration = greater avoidance).

2.5.2.3. Subjective anxiety during hyperventilation and relaxation tasks. Participant ratings of their maximum anxiety level (0-100 scale) experienced during Hyperventilation 1, Hyperventilation 2, and Relaxation were also analyzed as potential predictors or moderators of outcome.

2.6. Physiological data recording and processing

Physiological data were collected with the LifeShirt System (VivoMetrics), an ambulatory monitoring device that measures electrocardiography (ECG) and respiration. ECG was continuously recorded at a sampling rate of 250 Hz from two Ag/AgCl electrodes attached under the right clavicle and the lower right rib. An additional Ag/AgCl electrode was attached to the left clavicle and served as ground electrode. Respiration was collected via two embedded sensor bands around the participants' chest and abdomen. R-wave detection, visual inspection of ECG data, and calculation of mean respiratory cycle time was performed with VivoMetrics software.

For HRV measures, cardiac R-wave detection was performed with VivoMetrics software. All intervals were visually inspected and corrected for false or undetected R-waves, movement artifacts, and ectopic beats. HF-HRV was calculated as normative units of the spectral power density of HRV in the high frequency range of 0.15–0.40 Hz (see Camm et al., 1996) with fast Fourier transform (resample rate = 4 Hz, FFT window length = 512) using Kubios software (Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2009). Normative units were calculated as HF-HRV n.u. = 100*(HF absolute power/(total absolute power−very low frequency absolute power)). Here, total power was defined as the total power (area under the curve) over all frequencies for the specified time range and very low frequency power as power in the frequency range of 0–0.003 Hz (Camm et al., 1996). HF-HRV was analyzed for the 5 min baseline period, the 15 min relaxation task, and the 30 s interval immediately following hyperventilation (see Pittig et al., 2013).

2.7. Statistical analyses

For preliminary analyses, multivariate analyses of variance (MANOVA) were conducted to examine baseline differences in MASQ-GA and moderator variables between: 1) included versus excluded participants (due to dropout or missing data), 2) groups (ACT versus CBT), and 3) individuals with a principal diagnosis of panic disorder versus other disorders. For these analyses, baseline MASQ-GA and the moderator variables were included as the dependent variables and inclusion status, group, or presence of principal panic disorder diagnosis was included as the independent variable.

For our moderator and predictor analyses, we chose a repeated measures multi-level model (MLM), implemented using the xtmixed command in Stata 12.1, which is consistent with recent statistical approaches for assessing moderators of treatment outcomes (e.g., Craske et al., in press; Wolitzky-Taylor et al., 2012). Pre MASQ-GA score was included as a covariate, and the Post, 6MFU,

[3] Heart rate during Baseline, Relaxation, and Hyperventilation 1 Recovery was also calculated but yielded inconsistent results. As heart rate (compared to HRV) has weaker theoretical and empirical links with emotion regulation constructs, we chose to report only HRV findings here.

and 12MFU MASQ-GA scores were levels of the repeated measures independent variable (Time); thus, only those participants who completed a Post assessment were included in the analyses. Pre MASQ-GA was included as a covariate rather than a level of the repeated measures independent variable in order to minimize the variance in outcomes and more fully equate groups on baseline levels of the outcome variable (Tabachnick & Fidell, 2007). The intercept represented MASQ-GA at Post and was included as a random effect. The variance/covariance structure of the Level 1 residuals was modeled as independent with one common variance estimated and covariances set to zero. Models using an independent variance/covariance structure did not significantly differ from those with exchangeable or autoregressive structures when compared using likelihood ratio tests.

Between subjects variables consisted of Group (CBT or ACT), Pre MASQ-GA, and moderators. Respiratory cycle time was covaried in HRV analyses to account for the potential influence of respiration on HRV (Berntson et al., 1997). For task-related HRV analyses, we included baseline HRV as a covariate.

Since a moderator might interact with Group or Time, we included both of these interactions, (Group × moderator; Time × moderator) as well as the three-way interaction (Group × Time × moderator) in each analysis. Further, because relationships between group and moderator variables are often non-linear (e.g., Wolitzky-Taylor et al., 2012), we included quadratic terms for the moderator and its interaction with Group and Time in the model (i.e., moderator,^{2} Group × moderator,^{2} Time × moderator,^{2} and Group × Time × moderator^2). When there was no significant quadratic relationship between the moderator and outcome, the quadratic term was dropped from the model. Similarly, when Time did not significantly interact with the moderator and Group, Time interaction terms were dropped.

Models were examined for outliers and fit, and outliers (3 *SD*) were replaced with the next higher value on two occasions (Winsor method; Guttman, 1973). On one occasion, an outlier had particularly strong influence that could not be corrected using the Winsor method. To avoid drawing conclusions based on the influence of one participant, this data point was removed. Less than 1% of the data were modified or eliminated during outlier correction.

For significant findings, effect sizes were calculated using the "multilevel tools" (mlt) package in Stata 12.1 (Mohring & Schmidt, 2012), which computes effect sizes according to the Snijders & Bosker (1994) method. Between-subject effects (R^2_2) are reported as the proportion of the between-subject variance accounted for by the effect. The effect size of Time (R^2_1) is reported as the proportion of within-subject variance accounted for by Time.

Significant Group × moderator interaction effects were followed by 1) tests of Group differences at "low" (1 *SD* below the mean) and "high" (1 *SD* above the mean) values of the moderator variable, and 2) tests of simple effects of the moderator *within* each Group. Significant interactions with Time were followed by tests of the simple effects of the moderator on outcome at each time point, followed by contrasts (Bonferroni-corrected for multiple comparisons) at the mean value of the moderator and ± 1 *SD*.

3. Results

Descriptive data for potential moderator variables are reported in Table 1. Descriptive statistics of the dependent variable (MASQ-GA) across assessment periods are reported in Table 2.

3.1. Preliminary analyses

No significant differences existed between included versus excluded participants on baseline MASQ-GA and moderator variables ($p = .99$). Among participants included in the moderator analyses, there were no significant differences between ACT versus CBT ($p = .60$) or between individuals with a principal diagnosis of panic disorder versus other disorders ($p = .66$) on baseline MASQ-GA and moderator variables. Baseline MASQ-GA did not significantly correlate with any potential moderator variables ($ps > .13$).

Table 1
Means (standard deviations) of potential predictors and moderators at pre-treatment between groups.

	CBT ($n = 34$)	ACT ($n = 26$)
HF-HRV (*SD*)		
Baseline	29.61 (12.50)	33.29 (12.94)
Hyperventilation 1 Recovery	16.29 (11.90)	27.04 (21.29)
Relaxation	32.48 (14.46)	38.88 (16.01)
Duration (in seconds) of Hyperventilation 2 (*SD*)	129.53 (62.48)	132.72 (59.21)
0–100 Anxiety Level (*SD*)		
Hyperventilation 1	41.64 (22.64)	33.64 (26.63)
Hyperventilation 2	45.10 (26.04)	41.10 (27.21)
Relaxation	23.00 (27.04)	22.68 (26.62)

CBT = cognitive behavioral therapy; ACT = acceptance and commitment therapy; HF-HRV = normalized high-frequency heart rate variability.

3.2. Treatment outcome

To assess the efficacy of the treatments and examine whether participants in one group improved more than the other, we investigated changes in MASQ-GA over time using a repeated measures multi-level model. We included main effects of Group (CBT or ACT) and Time and the Group × Time interaction. For this analysis only, all 4 levels of Time (Pre, Post, 6MFU, and 12MFU) were used in order to replicate the approach used for previous treatment outcome analyses in the current sample (Arch et al., 2012; Wolitzky-Taylor et al., 2012).

Significant effects of Time at Post ($z = -3.95$, $p < .001$), 6MFU ($z = -4.45$, $p < .001$), and 12MFU ($z = -3.78$, $p < .001$) indicated a reduction in MASQ-GA from Pre to Post, 6MFU, and 12MFU. There was no effect of Group or Group × Time ($ps > .10$), indicating that both groups improved at comparable rates.

3.3. Moderators and predictors

The term "outcome" in the following results refers to MASQ-GA across Post, 6MFU, and 12MFU time points (unless otherwise stated), controlling for MASQ-GA at Pre.

3.3.1. Heart rate variability (HRV)

Baseline HRV predicted outcome in a nonlinear manner that did not differ by group ($z = 3.48$, $p = .001$, $R^2_2 = .26$; Fig. 1a), such that individuals with high HRV (+1 *SD*) scored .56 *SD* (4.01 points) greater on the MASQ-GA across time points compared to those with mean HRV and .43 *SD* (3.08 points) greater on the MASQ-GA than those with low HRV (−1 *SD*).

Table 2
Means (standard deviations) across groups and assessment points on MASQ-GA.

Assessment	CBT	ACT
Pre-Treatment	26.99 (7.63)	30.06 (7.79)
Post-Treatment	22.46 (7.87)	23.34 (7.38)
6-Month Follow-Up	20.67 (5.20)	21.86 (7.74)
12-Month Follow-Up	20.94 (6.48)	25.03 (8.09)

MASQ-GA = Mood and Anxiety Symptom Questionnaire, General Anxiety Subscale.

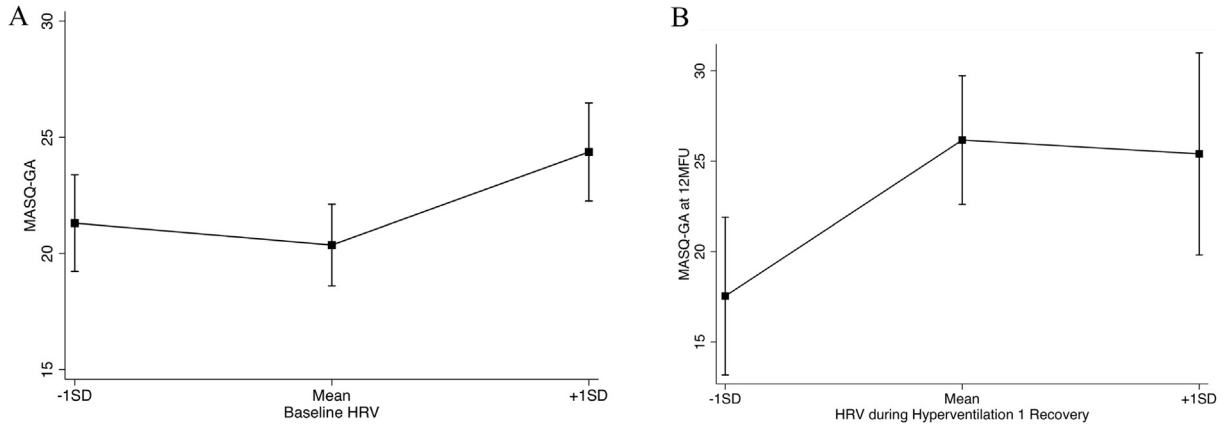

Fig. 1. Pre-treatment heart rate variability (HRV) as a predictor of outcome. (A) Prediction by Baseline HRV. (B) 12MFU Prediction by HRV Recovery from Hyperventilation 1. MASQ-GA = Mood and Anxiety Symptom Questionnaire, General Anxiety Subscale; 12MFU = 12-month follow-up.

The interaction between Time and the quadratic term of HRV during Recovery predicted outcome similarly across groups ($z = -3.19$, $p = .001$, $R^2_1 = .08$, $R^2_2 = .06$). Recovery HRV was a significant predictor of 12MFU outcome only ($b = .31$, CI = .06 to .56, $p = .01$; Fig. 1b), with low Recovery HRV (−1 *SD*) predicting better outcome than mean Recovery HRV ($\psi = 8.63$, Bonferroni-corrected $p = .02$) and marginally better outcome than high (+1 *SD*) Recovery HRV ($\psi = 7.86$, Bonferroni-corrected $p = .17$) at 12MFU.

HRV during Relaxation did not significantly predict or moderate outcome (*p*s > .17).

3.3.2. *Duration of hyperventilation 2*

A significant Group × Hyperventilation 2 Duration interaction ($z = 2.72$, $p = .01$, $R^2_2 = .07$; see Fig. 2) indicated that individuals who demonstrated greater behavioral avoidance (shorter duration) had better outcomes in ACT than CBT (significant effect at −1 *SD*; $b = -5.04$, CI = −9.85 to −.22; $p = .04$). Group differences at the mean and max (180 s) of Hyperventilation 2 Duration were non-significant (*p*s > .09). Longer duration of Hyperventilation 2 was associated with better outcome within CBT ($b = -.03$, CI = −.06 to −.003; $p = .03$) and worse outcome within ACT ($b = .04$, CI = −.002 to .08; $p = .06$).

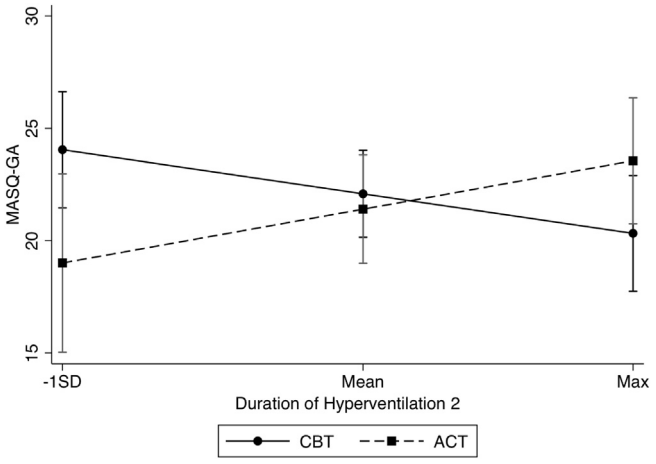

Fig. 2. Moderation by Pre-treatment Hyperventilation 2 Duration (180 s max); MASQ-GA = Mood and Anxiety Symptom Questionnaire, General Anxiety Subscale; CBT = cognitive behavioral therapy; ACT = acceptance and commitment therapy.

3.3.3. *Subjective anxiety*

Subjective anxiety during Hyperventilation 1, Hyperventilation 2, and Relaxation did not predict or moderate outcome (*p*s > .07).

4. Discussion

This study offers evidence of pre-treatment physiological and behavioral indicators of outcome from ACT and CBT for anxiety disorders. Heart rate variability was an overall predictor of outcome, whereas behavioral avoidance emerged as a moderator. Low and mean baseline heart rate variability were associated with better outcome overall, as was low heart rate variability during hyperventilation recovery. In terms of moderator effects, ACT outperformed CBT for individuals with greater behavioral avoidance of hyperventilation. Subjective levels of anxiety during laboratory tasks did not predict or moderate outcome. These findings demonstrate that pre-treatment physiological and behavioral variables are important targets for guiding future treatment-matching efforts.

In support of our hypothesis, individuals with low baseline heart rate variability showed better outcomes across both ACT and CBT than individuals with high baseline heart rate variability. Similarly, low heart rate variability during hyperventilation recovery predicted better long-term outcome than higher heart rate variability. These results provide preliminary evidence that ACT and CBT may be more potent for individuals with lower heart rate variability and are consistent with the finding that higher baseline heart rate variability predicted poorer outcome from exposure treatment for flight phobia (Bornas et al., 2012). Thus, strategies in ACT and CBT that focus on emotion regulation may better target individuals with this deficit in biologically-linked emotion regulation (Appelhans & Luecken, 2006). Conversely, individuals with higher heart rate variability at pre-treatment may benefit less from such approaches due to ceiling effects.

Behavioral avoidance of voluntary hyperventilation moderated treatment outcome. Whereas we had expected that individuals with greater avoidance of interoceptive sensations would have better treatment outcome overall (due to greater room for improvement and targeting of avoidance behaviors in both treatments), our data indicated that individuals with greater avoidance at baseline improved more in ACT than CBT. In fact, within the CBT group, individuals who endured the hyperventilation task longer had better outcomes than those who stopped early, whereas within the ACT group, the opposite trend emerged. These findings suggest that ACT may work better for those who are highly avoidant of

sensations at baseline, whereas CBT may work better for those who are already more willing to engage in stressful tasks.

Notably, these behavioral results contrast with some recent findings that higher *self-reported* experiential avoidance predicts better outcome from CBT than ACT (Wolitzky-Taylor et al., 2012; Niles et al., under review). However, this research is mixed; pre-treatment self-reported experiential avoidance predicted better outcome from ACT in a study comparing ACT and systematic desensitization for math anxiety (Zettle, 2003). One potential explanation for this discrepancy is that self-report measures intend to assess trait levels of experiential avoidance, even though experiential avoidance is highly context-dependent (Karekla et al., 2004). In addition, experiential avoidance takes many forms (e.g., thought suppression, escape behavior; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996), and thus it is possible that behavioral versus subjective measurements of avoidance tap into different domains. While CBT may better target broad, trait-like experiential avoidance, our current results suggest that ACT's emphasis on willingness and "leaning into" sensations may be particularly well-suited for individuals with high levels of behavioral avoidance of physical sensations.

Taken together, our findings demonstrate some support for the "deficit-matching" hypothesis (e.g., Miller et al., 2005); that is, emotion regulation deficits predict better outcome because interventions can target these deficits. Low heart rate variability - an index of emotion dysregulation - predicted better outcome, which is consistent with neuroimaging studies of pre-treatment amygdala hyperactivation as a positive predictor of outcome (e.g., McClure et al., 2007). These findings suggest that behavioral treatments for anxiety serve to "correct" biologically-linked deficits in emotion dysregulation rather than enhance or capitalize on individuals' prior emotion regulation capacities (e.g., Rude & Rehm, 1991). In addition, the treatment-specific effects of behavioral avoidance suggest that this emotion regulation deficit is uniquely addressed in ACT. Though CBT purports to address behavioral avoidance of sensations through interoceptive exposure, it is possible that highly behaviorally avoidant individuals first need training in how to participate or engage in interoceptive exposures, such as through willingness and acceptance strategies in ACT.

Should these results be replicated across different samples and indices of change, preliminary prognostic and prescriptive recommendations can be drawn. Individuals with lower baseline and/or recovery heart rate variability at pre-treatment may be particularly well suited for behavioral treatment for anxiety, whether it be CBT or ACT. Individuals with greater avoidance of an anxiety-inducing task at pre-treatment may improve more in ACT than CBT. Conversely, those with less behavioral avoidance of an anxiety-inducing task may be better suited for CBT.

Despite these novel findings, this study has several limitations. First, the small sample size of each principal disorder precluded disorder-specific analyses. However, the inclusion of all anxiety disorders is consistent with a transdiagnostic approach to anxiety disorder treatment (Barlow, Allen, & Choate, 2004). Second, our ECG sampling rate (250 Hz) was below the current recommendation for HRV analysis (Hejjel & Roth, 2004), though researchers have suggested that 250 Hz is sufficient for analysis of ECG for human adults (see Berntson et al., 1997). Third, because this was the first study to examine these factors as predictors and moderators of treatment outcome, variables were investigated individually. To gain a more comprehensive and nuanced understanding, it will be important for future studies to investigate how physiological, behavioral, and other variables may interact to predict outcome. Finally, though the statistical approach we used reduced the number of tests needed to examine the effects of these variables across time points, a large number of analyses were performed, thus risking the possibility of Type I error.

This study provides preliminary evidence that pre-treatment physiological and behavioral variables predict and moderate outcome from ACT and CBT for anxiety disorders. If further research supports our initial findings, these readily measurable factors have the potential to provide researchers and clinicians with informative and objective measures for guiding treatment selection.

References

Alpers, G. W., & Sell, R. (2008). And yet they correlate: psychophysiological activation predicts self-report outcomes of exposure therapy in claustrophobia. *Journal of Anxiety Disorders, 22*(7), 1101–1109. http://dx.doi.org/10.1016/j.janxdis.2007.11.009.

Appelhans, B. M., & Luecken, L. J. (2006). Heart rate variability as an index of regulated emotional responding. *Review of general psychology, 10*(3), 229.

Arch, J. J., & Craske, M. G. (2009). First line treatment: a critical appraisal of cognitive behavioral therapy developments and alternatives. *Psychiatric Clinics of North America, 32*, 525–547.

Arch, J. J., & Craske, M. G. (2010). Laboratory stressors in clinically anxious and non-anxious individuals: the moderating role of mindfulness. *Behaviour Research and Therapy, 48*(6), 495–505. http://dx.doi.org/10.1016/j.brat.2010.02.005.

Arch, J. J., Eifert, G. H., Davies, C., Vilardaga, J. C. P., Rose, R. D., & Craske, M. G. (2012). Randomized clinical trial of cognitive behavioral therapy (CBT) versus acceptance and commitment therapy (ACT) for mixed anxiety disorders. *Journal of Consulting and Clinical Psychology*. http://dx.doi.org/10.1037/a0028310.

Baker, A., Mystkowksi, J., Culver, N., Yi, R., Mortazavi, A., & Craske, M. G. (2010). Does habituation matter? Emotional processing theory and exposure therapy for acrophobia. *Behaviour Research and Therapy, 48*, 1139–1143.

Barlow, D. H., Allen, L. B., & Choate, M. L. (2004). Toward a unified treatment for emotional disorders. *Behavior Therapy, 35*(2), 205–230. http://dx.doi.org/10.1016/S0005-7894(04)80036-4.

Berntson, G. G., Thomas Bigger, J., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., et al. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology, 34*(6), 623–648. http://dx.doi.org/10.1111/j.1469-8986.1997.tb02140.x.

Bornas, X., del Amo, A. R., Tortella-Feliu, M., & Llabrés, J. (2012). Heart rate variability profiles and exposure therapy treatment outcome in flight phobia. *Applied Psychophysiology and Biofeedback, 37*(1), 53–62.

Brewer, J. A., Sinha, R., Chen, J. A., Michalsen, R. N., Babuscio, T. A., Nich, C., et al. (2009). Mindfulness training and stress reactivity in substance abuse: results from a randomized, controlled stage I pilot study. *Substance Abuse, 30*(4), 306–317. http://dx.doi.org/10.1080/08897070903250241.

Brown, T. A., DiNardo, P. A., & Barlow, D. H. (1994). *Anxiety disorders interview schedule for DSM - IV: Adult Version*. Oxford University Press.

Bryant, R. A., Felmingham, K., Kemp, A., Das, P., Hughes, G., Peduto, A., et al. (2008). Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. *Psychological Medicine, 38*(04), 555–561. http://dx.doi.org/10.1017/S0033291707002231.

Camm, A. J., Malik, M., Bigger, J. T., Breithardt, G., Cerutti, S., Cohen, R. J., et al. (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation, 93*(5), 1043–1065.

Campbell-Sills, L., & Barlow, D. H. (2007). Incorporating emotion regulation into conceptualizations and treatments of anxiety and mood disorders. In *Handbook of emotion regulation* (pp. 542–559). New York, NY, US: Guilford Press.

Canli, T., Cooney, R. E., Goldin, P., Shah, M., Sivers, H., Thomason, M. E., et al. (2005). Amygdala reactivity to emotional faces predicts improvement in major depression. *Neuro Report: For Rapid Communication of Neuroscience Research, 16*(12), 1267–1270. http://dx.doi.org/10.1097/01.wnr.0000174407.09515.cc.

Chambless, D. L., & Gracely, E. J. (1989). Fear of fear and the anxiety disorders. *Cognitive Therapy and Research, 13*(1), 9–20. http://dx.doi.org/10.1007/BF01178486.

Chawla, N., & Ostafin, B. (2007). Experiential avoidance as a functional dimensional approach to psychopathology: an empirical review. *Journal of Clinical Psychology, 63*(9), 871–890. http://dx.doi.org/10.1002/jclp.20400.

Cioffi, D., & Holloway, J. (1993). Delayed costs of suppressed pain. *Journal of Personality and Social Psychology, 64*(2), 274–282.

Craske, M. G. (2005). *Cognitive-behavioral treatment of anxiety disorders*. Unpublished manuscript.

Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy, 46*(1), 5–27. http://dx.doi.org/10.1016/j.brat.2007.10.003.

Craske, M. G., Lang, A. J., Aikins, D., & Mystkowski, J. L. (2005). Cognitive behavioral therapy for nocturnal panic. *Behavior Therapy, 36*(1), 43–54. http://dx.doi.org/10.1016/S0005-7894(05)80053-X.

Craske, M. G., Niles, A. N., Burklund, L. J., Wolitzky-Taylor, K. B., Plumb, J. C., Arch, J. J., et al. (2014). Randomized controlled trial of cognitive behavioral therapy and acceptance and commitment therapy for social anxiety disorder: outcomes and moderators. *Journal of Consulting and Clinical Psychology* (in press).

Craske, M. G., Sanderson, W. C., & Barlow, D. H. (1987). How do desynchronous response systems relate to the treatment of agoraphobia: a follow-up evaluation. *Behaviour Research and Therapy, 25*(2), 117–122. http://dx.doi.org/10.1016/0005-7967(87)90082-9.

Doehrmann, O., Ghosh, S. S., Polli, F. E., Reynolds, G. O., Horn, F., Keshavan, A., et al. (2013). Predicting treatment response in social anxiety disorder from functional magnetic resonance imaging. *JAMA Psychiatry, 70*(1), 87–97. http://dx.doi.org/10.1001/2013.jamapsychiatry.5.

Eifert, G. H., & Forsyth, J. P. (2005). *Acceptance and commitment therapy for anxiety disorders: A practitioner's treatment guide to using mindfulness, acceptance, and values-based behavior change*. New Harbinger Publications.

Eifert, G. H., & Heffner, M. (2003). The effects of acceptance versus control contexts on avoidance of panic-related symptoms. *Journal of Behavior Therapy and Experimental Psychiatry, 34*(3–4), 293–312. http://dx.doi.org/10.1016/j.jbtep.2003.11.001.

Foa, E. B., & Kozak, M. J. (1998). Clinical applications of bioinformational theory: understanding anxiety and its treatment. *Behavior Therapy, 29*(4), 675–690.

Fowles, D. C. (1980). The three arousal model: Implications of Gray's two-factor learning theory for heart rate, electrodermal activity, and psychopathy. *Psychophysiology, 17*(2), 87–104. http://dx.doi.org/10.1111/j.1469-8986.1980.tb00117.x.

Friedman, B. H., & Thayer, J. F. (1998). Autonomic balance revisited: panic anxiety and heart rate variability. *Journal of Psychosomatic Research, 44*(1), 133–151. http://dx.doi.org/10.1016/S0022-3999(97)00202-X.

Garakani, A., Martinez, J. M., Aaronson, C. J., Voustianiouk, A., Kaufmann, H., & Gorman, J. M. (2009). Effect of medication and psychotherapy on heart rate variability in panic disorder. *Depression and Anxiety, 26*(3), 251–258. http://dx.doi.org/10.1002/da.20533.

Gross, J. J. (1998). Antecedent-and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology, 74*(1), 224.

Guttman, I. (1973). Premium and protection of several procedures for dealing with outliers when sample sizes are moderate to large. *Technometrics, 15*(2), 385–404. http://dx.doi.org/10.2307/1266997.

Hayes, S. C., Strosahl, K., & Wilson, K. G. (2011). *Acceptance and commitment therapy*. Guilford Press.

Hayes, S. C., Wilson, K. G., Gifford, E. V., Follette, V. M., & Strosahl, K. (1996). Experiential avoidance and behavioral disorders: a functional dimensional approach to diagnosis and treatment. *Journal of Consulting and Clinical Psychology, 64*(6), 1152.

Heide, F. J., & Borkovec, T. D. (1983). Relaxation-induced anxiety: paradoxical anxiety enhancement due to relaxation training. *Journal of Consulting and Clinical Psychology, 51*(2), 171–182. http://dx.doi.org/10.1037/0022-006X.51.2.171.

Heide, F. J., & Borkovec, T. D. (1984). Relaxation-induced anxiety: mechanisms and theoretical implications. *Behaviour Research and Therapy, 22*(1), 1–12.

Hejjel, L., & Roth, E. (2004). What is the adequate sampling interval of the ECG signal for heart rate variability analysis in the time domain? *Physiological Measurement, 25*(6), 1405. http://dx.doi.org/10.1088/0967-3334/25/6/006.

Hides, L., Carroll, S., Catania, L., Cotton, S. M., Baker, A., Scaffidi, A., et al. (2010). Outcomes of an integrated cognitive behaviour therapy (CBT) treatment program for co-occurring depression and substance misuse in young people. *Journal of Affective Disorders, 121*(1–2), 169–174. http://dx.doi.org/10.1016/j.jad.2009.06.002.

Hofmann, S. G., & Asmundson, G. J. (2008). Acceptance and mindfulness-based therapy: new wave or old hat? *Clinical Psychology Review, 28*(1), 1–16.

Hofmann, S. G., Sawyer, A. T., Fang, A., & Asnaani, A. (2012). Emotion Dysregulation Model of Mood and Anxiety Disorders. *Depression and Anxiety, 29*(5), 409–416.

Hofmann, S. G., & Smits, J. A. J. (2008). Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *The Journal of Clinical Psychiatry, 69*(4), 621–632.

Holloway, W., & McNally, R. J. (1987). Effects of anxiety sensitivity on the response to hyperventilation. *Journal of Abnormal Psychology, 96*(4), 330.

Hughes, J. W., & Stoney, C. M. (2000). Depressed mood is related to high-frequency heart rate variability during stressors. *Psychosomatic Medicine, 62*(6), 796–803.

Imai, K., Sato, H., Hori, M., Kusuoka, H., Ozaki, H., Yokoyama, H., et al. (1994). Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *Journal of the American College of Cardiology, 24*(6), 1529–1535. http://dx.doi.org/10.1016/0735-1097(94)90150-3.

Karekla, M., Forsyth, J. P., & Kelly, M. M. (2004). Emotional avoidance and panicogenic responding to a biological challenge procedure. *Behavior Therapy, 35*(4), 725–746.

Katona, P. G., McLean, M., Dighton, D. H., & Guz, A. (1982). Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest. *Journal of Applied Physiology, 52*(6), 1652–1657.

Kozak, M. J., Foa, E. B., & Steketee, G. (1988). Process and outcome of exposure treatment with obsessive-compulsives: psychophysiological indicators of emotional processing. *Behavior Therapy, 19*(2), 157–169. http://dx.doi.org/10.1016/S0005-7894(88)80039-X.

Lane, R. D., McRae, K., Reiman, E. M., Chen, K., Ahern, G. L., & Thayer, J. F. (2009). Neural correlates of heart rate variability during emotion. *NeuroImage, 44*(1), 213–222. http://dx.doi.org/10.1016/j.neuroimage.2008.07.056.

Lang, P. J., Cuthbert, B. N., & Bradley, M. M. (1998). Measuring emotion in therapy: imagery, activation, and feeling. *Behavior Therapy, 29*(4), 655–674.

Lang, P. J., & McTeague, L. M. (2009). The anxiety disorder spectrum. *Anxiety, Stress, and Coping, 22*(1), 5–25. http://dx.doi.org/10.1080/10615800802478247.

Lang, P. J., Melamed, B. G., & Hart, J. (1970). A psychophysiological analysis of fear modification using an automated desensitization procedure. *Journal of Abnormal Psychology, 76*, 229–234.

Levitt, J. T., Brown, T. A., Orsillo, S. M., & Barlow, D. H. (2004). The effects of acceptance versus suppression of emotion on subjective and psychophysiological response to carbon dioxide challenge in patients with panic disorder. *Behavior Therapy, 35*(4), 747–766. http://dx.doi.org/10.1016/S0005-7894(04)80018-2.

McClure, E. B., Adler, A., Monk, C. S., Cameron, J., Smith, S., Nelson, E. E., et al. (2007). fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology, 191*(1), 97–105. http://dx.doi.org/10.1007/s00213-006-0542-9.

Meuret, A. E., Hofmann, S. G., & Rosenfield, D. (2010). Catastrophic appraisal and perceived control as moderators of treatment response in panic disorder. *International Journal of Cognitive Therapy, 3*, 262–277. http://dx.doi.org/10.1521/ijct.2010.3.3.262.

Miller, I. W., Keitner, G. I., Ryan, C. E., Solomon, D. A., Cardemil, E. V., & Beevers, C. G. (2005). Treatment matching in the posthospital care of depressed patients. *The American Journal of Psychiatry, 162*(11), 2131–2138. http://dx.doi.org/10.1176/appi.ajp.162.11.2131.

Miller, I. W., Keitner, G. I., Ryan, C. E., Uebelacker, L. A., Johnson, S. L., & Solomon, D. A. (2008). Family treatment for bipolar disorder: family impairment by treatment interactions. *The Journal of Clinical Psychiatry, 69*(5), 732.

van Minnen, A., & Hagenaars, M. (2002). Fear activation and habituation patterns as early process predictors of response to prolonged exposure treatment in PTSD. *Journal of Traumatic Stress, 15*(5), 359–367.

Mohring, K., & Schmidt, A. (2012). *Multilevel tools, Stata Users Group*.

Mujica-Parodi, L. R., Korgaonkar, M., Ravindranath, B., Greenberg, T., Tomasi, D., Wagshul, M., et al. (2009). Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. *Human Brain Mapping, 30*(1), 47–58. http://dx.doi.org/10.1002/hbm.20483.

Papa, A., Boland, M., & Sewell, M. T. (2012). Emotion regulation and CBT. In W. O'Donohue, & J. E. Fisher (Eds.), *Cognitive behavior Therapy: Core principles for practice*. Hoboken, New Jersey: John Wiley & Sons, Inc.http://dx.doi.org/10.1002/9781118470886.ch11

Pitman, R. K., Orr, S. P., Altman, B., Longpre, R. E., Poiré, R. E., Macklin, M. L., et al. (1996). Emotional processing and outcome of imaginal flooding therapy in Vietnam veterans with chronic posttraumatic stress disorder. *Comprehensive Psychiatry, 37*(6), 409–418.

Pittig, A., Arch, J. J., Lam, C. W. R., & Craske, M. G. (2013). Heart rate and heart rate variability in panic, social anxiety, obsessive-compulsive, and generalized anxiety disorders at baseline and in response to relaxation and hyperventilation. *International Journal of Psychophysiology, 87*(1), 19. http://dx.doi.org/10.1016/j.ijpsycho.2012.10.012.

Rapee, R. M., Brown, T. A., Antony, M. M., & Barlow, D. H. (1992). Response to hyperventilation and inhalation of 5.5% carbon dioxide-enriched air across the DSM- III—R anxiety disorders. *Journal of Abnormal Psychology, 101*(3), 538.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., et al. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry, 47*(9), 769–776. http://dx.doi.org/10.1016/S0006-3223(00)00828-3.

Roemer, L., Salters, K., Raffa, S. D., & Orsillo, S. M. (2005). Fear and avoidance of internal experiences in GAD: preliminary tests of a conceptual model. *Cognitive Therapy and Research, 29*(1), 71–88. http://dx.doi.org/10.1007/s10608-005-1650-2.

Rude, S. S., & Rehm, L. P. (1991). Response to treatments for depression: the role of initial status on targeted cognitive and behavioral skills. *Clinical Psychology Review, 11*(5), 493–514. http://dx.doi.org/10.1016/0272-7358(91)90001-B.

Sahar, T., Shalev, A. Y., & Porges, S. W. (2001). Vagal modulation of responses to mental challenge in posttraumatic stress disorder. *Biological Psychiatry, 49*(7), 637–643. http://dx.doi.org/10.1016/S0006-3223(00)01045-3.

Schaefer, S. M., Jackson, D. C., Davidson, R. J., Aguirre, G. K., Kimberg, D. Y., & Thompson-Schill, S. L. (2002). Modulation of amygdalar activity by the conscious regulation of negative emotion. *Journal of Cognitive Neuroscience, 14*(6), 913–921. http://dx.doi.org/10.1162/089892902760191135.

Schlund, M. W., & Cataldo, M. F. (2010). Amygdala involvement in human avoidance, escape and approach behavior. *NeuroImage, 53*(2), 769–776. http://dx.doi.org/10.1016/j.neuroimage.2010.06.058.

Schlund, M. W., Siegle, G. J., Ladouceur, C. D., Silk, J. S., Cataldo, M. F., Forbes, E. E., et al. (2010). Nothing to fear? Neural systems supporting avoidance behavior in healthy youths. *NeuroImage, 52*(2), 710–719. http://dx.doi.org/10.1016/j.neuroimage.2010.04.244.

Sloan, T., & Telch, M. J. (2002). The effects of safety-seeking behavior and guided threat reappraisal on fear reduction during exposure: an experimental investigation. *Behaviour Research and Therapy, 40*(3), 235–251.

Tabachnick, B. G., & Fidell, L. S. (2007). *Using multivariate statistics*. Pearson Education, Limited.

Tarvainen, M. P., Niskanen, J. P., Lipponen, J. A., Ranta-Aho, P. O., & Karjalainen, P. A. (2009). Kubios HRV—a software for advanced heart rate variability analysis. In *4th European Conference of the International Federation for Medical and Biological Engineering* (pp. 1022–1025). Berlin Heidelberg: Springer.

Telch, M. J., Valentiner, D. P., Ilai, D., Petruzzi, D., & Hehmsoth, M. (2000). The facilitative effects of heart-rate feedback in the emotional processing of claustrophobic fear. *Behaviour Research and Therapy, 38*(4), 373–387.

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J., III, & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for

heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews, 36*(2), 747–756. http://dx.doi.org/10.1016/j.neubiorev.2011.11.009.

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders, 61*(3), 201–216.

Tolin, D. F. (2010). Is cognitive-behavioral therapy more effective than other therapies? A meta-analytic review. *Clinical Psychology Review, 30*(6), 710–720. http://dx.doi.org/10.1016/j.cpr.2010.05.003.

Tugade, M. M., Fredrickson, B. L., & Feldman Barrett, L. (2004). Psychological resilience and positive emotional granularity: examining the benefits of positive emotions on coping and health. *Journal of Personality, 72*(6), 1161–1190. http://dx.doi.org/10.1111/j.1467-6494.2004.00294.x.

Watson, D., & Clark, L. A. (1991). *The mood and anxiety symptom questionnaire*. Unpublished manuscript. Iowa City: University of Iowa, Depart- ment of Psychology.

Watson, D., Weber, K., Assenheimer, J. S., Clark, L. A., Strauss, M. E., & McCormick, R. A. (1995). Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. *Journal of Abnormal Psychology, 104*(1), 3–14. http://dx.doi.org/10.1037/0021-843X.104.1.3.

Wolitzky-Taylor, K. B., Arch, J. J., Rosenfield, D., & Craske, M. G. (2012). Moderators and non-specific predictors of treatment outcome for anxiety disorders: a comparison of cognitive behavioral therapy to acceptance and commitment therapy. *Journal of Consulting and Clinical Psychology, 80*(5), 786–799. http://dx.doi.org/10.1037/a0029418.

Zettle, R. D. (2003). Acceptance and commitment therapy vs. systematic desensitization in treatment of mathematics anxiety. *The Psychological Record, 53*(2), 197–215.