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Course of symptom change during anxiety treatment: Reductions in anxiety and depression in patients completing the Coordinated Anxiety Learning and Management Program

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Abstract

When treating anxious patients with co-occurring depression, research demonstrates that both types of symptoms independently improve. The current analyses examined how reductions in anxiety and depression may be interrelated both during treatment, as well as over time following treatment. Participants were 503 individuals with one or more DSM-IV anxiety disorders who completed a collaborative care anxiety management program. Anxiety and depression were assessed at each treatment session (i.e., session by session data) and also at 6, 12, and 18-month post-baseline assessments (i.e., long-term outcomes data). Mediation analysis examined changes in symptoms in session by session data and long-term outcomes data. Anxiety and depression

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changed reciprocally in session by session data; change in anxiety mediated change in depression to a greater extent than vice versa. In the long-term outcomes data, change in anxiety mediated change in depression. However, the reverse mediation model of the long-term outcomes period revealed that accounting for changes in depression altered the effect of time on anxiety. Thus, temporal change during active treatment may share similarities with those related to maintaining gains after treatment, although differences arose in the reverse mediation models. Limitations of the methodology and implications of anxiety treatment for depression outcomes are discussed.

Keywords

Treatment; Mediation; Anxiety; Depression; CBT

1. Introduction

Anxiety is a common and disabling problem in the general population. Epidemiological studies indicate that anxiety disorders are among the most prevalent of mental health disorders, with almost 30 percent of individuals in the US being affected in their lifetimes (Kessler et al., 2005). Anxiety disorders are associated with significant distress, functional impairment, and reduced quality of life (Rapaport et al., 2005; Olatunji et al., 2007; Beard et al., 2010). Moreover, costs associated with anxiety are significant, making identification and treatment of anxiety disorders a significant public health issue (DuPont et al., 1996).

Anxiety is not treated in isolation, however. Depression and anxiety co-occur at high rates (e.g., Mineka et al., 1998; Kaufman and Charney, 2000; Brown et al., 2001), and the presence of comorbid depression detrimentally impacts course, chronicity, and relapse rates in anxious patients (Bruce et al., 2005; van Balkom et al., 2008). Given the high co-occurrence of these disorders, understanding the reciprocal interactions of these two categories of symptoms during treatment is highly relevant. For example, level of depression could adversely affect adherence with treatment components, including homework-based aspects that require substantial motivation and effort to complete (e.g., Telch, 1988, although empirical data about the effect of comorbid depression on anxiety treatment is mixed; see for example Emmrich et al., 2012). Conversely, anxiety treatments contain aspects of therapy that are likely to reduce depression symptoms or alter shared vulnerability factors such as negative affect (e.g., treatments that require exposure increase behavioral activation). Thus, understanding the interplay of anxiety and depression in the context of treatment and maintenance of gains is a critical part of understanding how interventions might operate within anxious patients.

Empirical data suggest that both depression and anxiety typically respond to evidence-based treatment. Although individuals with comorbid depression and anxiety may initially present with greater symptom severity, both cognitive behavioral therapy (CBT) and pharmacotherapy appear to decrease distress broadly, including reductions in both disorder-specific symptoms and comorbid symptoms (e.g., Rudolph et al., 1998; Mennin and Heimberg, 2000; Russell et al., 2001; Persons et al., 2003; Norton et al., 2004; Joorman et al., 2005; Kring et al., 2007; Allen et al., 2010; Tourian et al., 2010). The reason for this

broad response, however, is unknown. For example, depression may remit once anxiety symptoms become more manageable, allowing for re-engagement with natural reinforcers in the environment that boost mood. Alternatively, treatments may alter anxiety and depression simultaneously, possibly by operating on higher order constructs such as neuroticism or negative affect that convey vulnerability to emotional disorders (e.g. Brown and Barlow, 2009).

In the interest of addressing the question of treatment mediators, to date three studies specifically examined how changes in anxiety affect depression and vice versa during the course of anxiety interventions. In the first, Moscovitch and colleagues (2005) modeled change in a cognitive behavioral therapy (CBT) program for social anxiety disorder (SAD). Results indicated that changes in anxiety preceded changes in depressive symptoms during treatment. This finding was replicated in a second study in patients with SAD examining changes in symptoms as a result of medication treatment (Dempsey et al., 2009). Aderka and colleagues (2011) later extended this methodological approach to a sample of youths receiving Prolonged Exposure for posttraumatic stress disorder (PTSD). Consistent with the prior two studies, changes in posttraumatic stress symptoms mediated changes in depression.

These trials provide excellent insight into change processes within these specific disorders and treatments but, as noted by the authors, a number of limitations exist. First, these studies are limited to individuals with SAD and PTSD and their respective, disorder-specific treatments, limiting generalizability to other disorders. In addition, the studies exclusively examined symptom changes during the course of treatment. The present set of analyses sought to expand upon this work in a number of ways. We extended the approach of these prior studies to a more diverse set of anxious patients. Participants in this study were a large group of individuals diagnosed with one or more anxiety disorders taking part in the Coordinated Anxiety Learning and Management (CALM) program (Roy-Byrne et al., 2010). CALM is unique in that participants were recruited from and treated in primary care settings and provided with transdiagnostic treatment that could include both CBT and/or medication. Moreover, multiple assessment time points allowed for observation of change both over each weekly treatment session (i.e., session by session data) and over a post-treatment period utilizing assessment data obtained 6, 12, and 18 months post-baseline (i.e., long-term outcomes data). These multiple assessment points permitted examination of temporal precedence in the mediation models. We hypothesized that, consistent with prior studies, anxiety would mediate changes in depression during the active portion of treatment. Given the paucity of data on long-term change, we treated models predicting change in anxiety and depression after acute treatment as exploratory without *a priori* predictions.

2. Methods

2.1. Participants

Participants were individuals participating in a randomized controlled effectiveness trial comparing the CALM intervention to usual care (UC; clinicaltrials.gov Identifier NCT00347269; for a detailed description of the study see Roy-Byrne et al., 2010 and Craske et al., 2011). All individuals met diagnostic criteria for at least one of the following anxiety disorders, which are commonly reported in primary care settings: panic disorder (PD), SAD,

generalized anxiety disorder (GAD), or PTSD. Participants could meet diagnostic criteria for more than one anxiety disorder. These individuals were recruited through primary care physicians in 17 primary care clinics from four U.S. cities (Seattle, WA, San Diego, CA, Los Angeles, CA, Little Rock, AR). Potential participants were referred from primary care providers at these clinic locations based on the presence of suspected anxiety as determined by a brief anxiety screener administered within the primary care office. Final eligibility was determined by a study clinician. All procedures were approved by the Institutional Review Board at each institution.

In total, 1004 primary care patients were randomized between June 1, 2006 and April 1, 2008. Our aims were to examine the process of change in the CALM intervention so only those participants randomized to CALM (N = 503) were included. Eligible participants were between the ages of 18 and 75, met diagnostic criteria for one or more of the target anxiety disorders, and scored 8 or greater on the Overall Anxiety Severity and Impairment Scale (OASIS; Campbell-Sills et al., 2009), indicating clinically meaningful distress and impairment. Exclusion criteria included presence of life-threatening medical conditions, significant cognitive impairment, active suicidality, Bipolar I disorder, current substance use disorders (except alcohol abuse and marijuana abuse), current enrollment in a CBT program, and inability to speak either English or Spanish.

2.2. Intervention

The CALM intervention allowed participants to select their preferred treatment modality: CBT, medication, or a combination of the two interventions (approximately 35%, 9%, and 56% of the sample, respectively). Within each of these treatment modalities, the representation of each of the disorders was similar (CBT: GAD 42.3%, PD 25.2%, PTSD 10.8%, SAD 21.7%; medication: GAD 42.9%, PD 25.0%, PTSD 8.3%, SAD 23.8%; combined: GAD 41.9%, PD 25.0, PTSD 9.1% , SAD 24.3%) and overall a majority of the sample (N = 308) met criteria for more than one anxiety disorder. Across treatment modalities, participants completed approximately nine sessions (M = 8.70, SD = 4.6). The CBT program was administered by a trained Anxiety Clinical Specialist (ACS), who was a social worker, nurse, or masters- or doctoral-level psychologist trained to deliver the intervention (see Rose et al., 2011 for a comprehensive description of training of ACS staff on CBT delivery). Participants attended intervention sessions until they achieved clinical remission (an OASIS score less than 5, described below), declined further services, or needed additional care not addressed by this treatment protocol. Components of the CBT program included five generic modules of anxiety treatment (self-monitoring, psychoeducation, exposure fear-hierarchy building, breathing retraining, and relapse prevention), three disorder-specific modules addressing exposure to internal and external cues and cognitive restructuring that were tailored to specific anxiety concerns, and an optional depression module[i] (for a detailed review of treatment components, see Craske et al., 2009). These components were presented in a computer-guided format that guided the clinician as well as the patient; the ACS and patient together reviewed the material and

[i]The depression module was used relatively infrequently during the trial, with only 15 participants receiving a total of 28 sessions that included depression-focused modules. No differences in findings were observed when models were analyzed without these participants.

completed exercises. Content of the modules included text summarizing the goals and summaries for the session, homework review, presentation of new skills and in-session practice (including via video presentations), and presentation of homework for the next session. Participants were provided with printouts of session materials to enhance understanding. The program prompted the ACS to engage in specific treatment tasks (e.g., in-vivo skill demonstration, summarizing material). Participants with more than one type of anxiety disorder completed activities for the disorder they considered most distressing and/or disabling.

Participants who selected medication management were prescribed these medications by the primary care provider in collaboration with the local study psychiatrist. A medication algorithm was used based on first-line use of selective serotonin reuptake inhibitor or serotonin noradrenalin reuptake inhibitory antidepressants. Individuals considered to be non- or sub-optimal responders to medication (i.e., failure to reach clinical recovery criteria, defined as an OASIS score less than five, with an adequate trial of the first-line medication approach) were provided with a medication change or were given another antidepressant or adjunctive benzodiazepine treatment as per previously established medication management guidelines (Roy-Byrne et al., 2009). For patients given medication, the ACS provided adherence monitoring, as well as counseling on sleep hygiene, alcohol and caffeine reduction, and behavioral activation[ii].

2.3. Assessments

2.3.1. Diagnostic status—To determine diagnostic status and initial eligibility, the ACS staff administered the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). ACS staff were trained on MINI administration, including completing didactic presentations and mock assessments with reliability assessment on eight mock MINI assessments (results indicated a 94% match; Zbonzinek et al., 2012). MINI assessments conducted for the study were reviewed in detail with a trained diagnostician (either a study psychologist or psychiatrist) to confirm diagnostic accuracy.

2.3.2. Demographic variables—Following the MINI –based eligibility assessments, participants were contacted via telephone by the RAND Corporation to complete further assessments. The initial telephone interview included sociodemographic questions such as age and ethnicity/race. Further details on all assessments given during this telephone interview can be found in Roy-Byrne et al. (2010).

2.3.3. Symptom assessments—All participants received assessments of anxiety and depressive symptoms during the active phase of treatment (i.e., session by session data) as well as over a post-treatment period utilizing assessment data obtained 6, 12, and 18 months post-baseline (i.e., long-term outcomes data). However, the specific measures collected for the session by session data and the long-term outcomes data differed, as did the time intervals at which data was collected. Session by session data consisted of symptom

[ii]Because participants across different CALM treatment types could engage in a differential number of sessions, all analyses were re-conducted using the number of sessions attended as a covariate. Results revealed virtually identical results and are thus not reported here, but are available from the first author upon request.

measures tracked at each treatment session by the ACS; data from these measures were used by the clinician to monitor patient progress (including when the therapeutic goal had been reached and the individual could terminate therapy sessions, as noted above). Because these measures were collected at treatment visits, scales were selected that were brief and could be easily administered with minimal patient and ACS burden (see below for description of measures). In contrast, long-term outcomes data measures were designated as the primary outcomes for the clinical trial from which these data were obtained. These measures were obtained by RAND interviewers at 6, 12, and 18 month post-baseline assessments. These assessments were longer and more comprehensive both because of the need for thorough data on symptomology and because the separate assessment session conducted outside of treatment sessions allowed for significantly more time to complete measures.

2.3.3.1. Session-by-session symptom data: Patients were administered the OASIS (Campbell-Sills et al., 2005) to assess anxiety symptoms. The OASIS is a five-item measure of disorder-nonspecific anxiety and avoidance symptoms with established psychometric properties (Campbell-Sills et al., 2005; Norman et al., 2006). Depression was measured using a three-item version of the Patient Health Questionnaire (PHQ; Kroenke et al., 2001). The nine-item PHQ, as well as abbreviated versions such as the two-item PHQ have well established psychometric properties (Kroenke et al., 2001; Kroenke et al., 2003). The three-item version of the PHQ (PHQ-3) was used due to the need for a very brief measure that could be administered by ACS staff at regular intervals, and contained the items from the PHQ-8 assessing depressed mood, lack of interest, and low energy/fatigue. Because these assessments were given during individual sessions and thus varied by the number of sessions attended by a particular patient, the number of assessment points varied. For the purposes of the present analyses, data from sessions 1- 20 were used, as few individuals attended more than 20 sessions.

2.3.3.2. Long-term outcomes data: Assessment of symptoms after treatment was conducted via telephone appointment by the RAND group at 6, 12, and 18 months post-baseline (see Roy-Byrne et al., 2010, for a more thorough description of the use of these assessments for the primary trial outcomes). Anxiety symptom severity was assessed using 12 items that comprise the anxiety and somatization subscales of the 18-item Brief Symptom Inventory (BSI-18; we will refer to the subset used in this project as the BSI-12; Derogatis and Savitz, 2000). Depression was measured using the Patient Health Questionnaire-8 (PHQ-8, the Patient Health Questinnaire-9 excluding the suicide item; Kroenke et al., 2001).

2.4. Analytic strategy

This data set formed a multilevel structure with repeated measures collected over time nested within participants. Thus, the lower level (Level 1) data consisted of the repeated measure of anxiety and depression collected session by session and over the long-term outcomes period. The upper level (Level 2) units were the individual participants. Given this data structure, a hierarchical linear modeling framework was utilized using SPSS software version 18.0. Advantages of this analytic approach include effective handling of missing data and varying numbers of observations across participants (Kenny et al., 2003; Maxwell & Delaney, 2004).

Assessment of mediation involved determining whether or not a potentially mediating variable partially or fully accounts for the relationship between two other variables (i.e., the independent variable and outcome). Traditional procedures for determining mediation according to Baron and Kenny (1986) require each of the following: first, the predictor variable must be related to the mediator (path a). Second, the predictor variable must be related to the outcome of interest (path c). Third, when the predictor and mediator variables are simultaneously modeled to predict the outcome, the mediator must be significantly associated with the outcome. Finally, the relationship between the predictor and the outcome must be reduced when the mediator and the predictor are both included in the model predicting the outcome variable. Although recent research suggests that all four conditions need not be met in order to demonstrate statistically significant mediation, results from these four steps adapted for multilevel data are included to allow for comparisons with other studies and to increase clarity of the results (see MacKinnon et al., 2007, and MacKinnon et al., 2000, for updated reviews of conceptualization and calculation of mediated effects).

In the case of longitudinal data, this mediation approach can be adapted for multilevel data structures to assess potential mediation of the effect between time and the outcomes of interest, in this case anxiety and depression. This type of analysis is also referred to as lower level mediation (Kenny et al., 2003; Bauer et al., 2006). We followed the guidelines established by Kenny et al., (2003) and Bauer et al., (2006) to test a total of four models. First, we examined two models of the session by session data (OASIS and PHQ-3). We modeled mediation in the predicted direction, such that changes in anxiety mediated changes in depression over time (i.e., primary anxiety reduction model). We then created a reverse mediation model, where changes in depression predicted changes in anxiety over time (i.e., primary depression reduction model). Second, we replicated this approach for the long-term outcomes data using the BSI-12 and PHQ-8. In all analyses, we “lagged” the mediator variable, examining whether changes in the mediator at time *t* accounted for change in the outcome of interest at time *t+1*, to assess temporal precedence of the mediated effect (see for example Aderka et al., 2011). As a supplementary analysis, we also conducted each of our mediation models including type of treatment (CBT, medication, or both) as a covariate to determine the potential impact of modality on mediation patterns. Because the conclusions that can be drawn from this analysis are limited (due to self-selection rather than randomization) and the results were extremely similar, results from all analyses are presented in Table 2 but we comment only on primary analysis throughout the manuscript.

To determine the significance of potential mediated effects, we utilized the PRODCLIN program (distribution of the PRODuct Confidence Limits for Indirect effects; MacKinnon et al., 2007) to obtain confidence intervals for the direct effect. This program requires the user to input information on the a and b coefficeints, as well standard error information, and utilizes this information to obtain confidence limits on the indirect effect using the distribution of the product method (downloaded from www.psychonomic.org/archive as described in MacKinnon et al., 2007). We calculated the percent mediation for each model using the equation described by Kenny and colleagues (2003) to quantify the magnitude of mediated effects.

3. Results

3.1. Demographic and clinical variables

Demographic and socioeconomic data on participants are presented in Table 1. Clinical variables, including anxiety and depression severity, are also presented in this table. Full details on clinical data can be found in Roy-Byrne et al. (2010).[iii]

3.2. Mediational analyses: Session by session data

The results of each mediational model are presented graphically in Figs. 1 and 2. Tables 2 and 3 present complete statistical results for each of these models. We began by examining changes in session by session data in the primary anxiety reduction mediation model (i.e., change in anxiety mediating change in depression). As noted in the table and graph, the model regressing depression on time indicated that depression symptoms significantly ameliorated during treatment ($B = -0.23$, $p < 0.001$, path c). Regressing anxiety on time also indicated that anxiety decreased over the course of treatment ($B = -0.63$, $p < 0.001$; path a). When entering time and anxiety simultaneously to predict depression, anxiety ($B = 0.13$, $p < 0.001$; path b) and time both predicted depression ($B = -0.14$, $p < 0.001$; path c'). The magnitude of the relationship between time and depression was decreased suggesting a mediated effect. Results from the Prodclin program were consistent with this conclusion, as the confidence intervals for the indirect effect did not cross zero (95% CI [−0.10, −0.07]). Moreover, anxiety symptoms accounted for 39.1% of the effect of time on depression symptoms.

Next, the primary depression reduction mediation model was examined (see Figure 2 and Table 3). When regressing anxiety on time and depression, the effect of time on anxiety remained significant ($B = -0.48$, $p < 0.001$; path c') but was slightly attenuated relative to the model excluding depression. There was again evidence of multilevel mediation, 95% CI [−0.10, −0.06]. Depression symptoms accounted for relatively less of the total effect of time on anxiety (18.6%) compared to the first model.

3.3. Mediational analyses: Long-term outcomes data

Mediational models of long-term outcomes data are presented in Figs. 3 and 4 and Tables 4 and 5. Changes in anxiety and depression 6-, 12-, and 18-month post-baseline assessments were modeled first in the predicted direction with the primary anxiety reduction mediation model. Depression symptoms did not significantly decrease over time when modeled in the regression equation ($B = -0.17$, $p = 0.51$, path c). Anxiety symptoms, however, did decrease ($B = -0.90$, $p < 0.01$, path a). When controlling for anxiety, the relationship between time and depression was reduced ($B = 0.06$, $p = 0.86$, path c'). In this model, anxiety remained a significant predictor of depression ($B = 0.37$, $p < 0.001$, path b). Mediation was indicated both by the change in the pathway between time and depression symptoms (−0.17 versus 0.06), as well as from the results of the Prodclin program (95% CI [−0.59, −0.10]). Anxiety

[iii]The presence of comorbid depression did not moderate the effect of treatment overall. Full details regarding this issue are presented in Campbell-Sills et al. (in press).

symptoms fully accounted for the effect of time on depression symptoms during this time frame.

The primary depression reduction mediation model was then examined (see Figure 3 and Table 4). The overall effect of time on anxiety was minimal ($B = -0.01$, $p = 0.99$, path c), indicating that participants demonstrated little change in the latter part of the long-term outcomes period. Results from the analysis predicting anxiety from time and depression indicated that including depression in the model reversed the direction and increased the magnitude of the effect of time on anxiety ($B = 0.46$, $p = 0.29$, path c'), such that accounting for early change in depression led to a positive relationship between time and anxiety that did not reach the level of statistical significance. The test of this indirect path indicated this was statistically significant 95% CI [−0.81, −0.23].

4. Discussion

Evaluating symptom reduction during the course of and after anxiety treatment may provide critical insights into the temporal course of change, and may ultimately improve the efficacy and personalization of treatment. The present analyses sought to determine the relationship between amelioration of anxiety and depression in the anxiety-focused CALM intervention delivered to patients recruited from primary care. Specifically, the first aim of the present analyses was to examine how anxiety and depression reciprocally change during treatment, using session by session symptom data. As hypothesized, change in anxiety mediated change in depression during the active phase of treatment. When comparing percent mediation, change in anxiety mediated a greater portion of change in depression than vice versa, although changes in anxiety and depression were reciprocal to some extent. Thus, there was both a direct effect of time on depression as well as an indirect effect through anxiety when examining session by session data. Data suggests that as individuals become less anxious they become less depressed, but also that individuals experienced reductions in depression that was not fully accounted for by changes in anxiety.

We also explored changes in anxiety and depression symptoms from long-term outcomes data collected at 6-, 12-, and 18-month post-baseline assessments. Results suggested that the change in the long-term outcomes data was similar to the session by session data, such that change in anxiety mediated subsequent change in depression. Change in anxiety symptoms occurred primarily early after the acute intervention (i.e., between 6- and 12-month post-baseline assessments). However, when examining the reverse mediation model interpretation of the findings was complicated by a reversal of the time-anxiety relationship once preceding change in depression was included. A number of conclusions arise from this data. First, subsequent change in depression primarily occurred for individuals whose anxiety improved. The reverse model did not support the competing hypothesis that change in depression reciprocally mediates subsequent change in anxiety. Instead, these analyses indicated that controlling for preceding change in depression altered the relationship between time and anxiety; those with greater reductions in depression later became more anxious and vice versa, although the effect of time on anxiety did not reach the level of statistical significance.

Findings from the session by session data are consistent with prior literature examining the course of change in anxiety and depression during completion of anxiety treatment. Consistent with earlier work on transdiagnostic protocols for anxiety, results revealed reductions in anxiety over time and support the use of broadly-targeted interventions for reducing psychiatric distress (e.g., Farchione et al., 2012). Also in line with earlier research, anxiety reduction appears to account for depression reductions over time, although these effects are somewhat reciprocal (Moscovitch et al., 2005; Dempsey et al., 2009; Aderka et al., 2011). The reciprocal influences suggest that some aspects of treatment may target shared components of anxiety and depression. Temperament variables are one possible shared aspect of anxiety and depression that could account for disorder onset/maintenance and symptom overlap, which might also account for reciprocal change over time (e.g., Brown, 2007). For example, to the extent that neuroticism or negative affect is shared across anxiety and depression and therapeutically malleable, this may have been one factor mediating reciprocal symptom reduction over time (e.g., Brown and Barlow, 2007). It is also possible that the observed effect was driven by the inclusion of the optional depression module. To address this possibility, data analyses were conducted excluding individuals who received any depression-specific modules. Results remained similar, indicating that this hypothesis is not likely to account for the findings. However, it appears that a greater portion of depressive symptom change is mediated by anxiety reduction, suggesting that reductions in anxiety drove subsequent changes in depression.

These findings suggest some degree of specificity to anxiety, such that change in anxiety accounts for reduction in depression. How this latter effect on depression occurs is an empirical question, although hypotheses posed to date include increases in engagement with positive activities or social interactions that results from reduced anxiety and avoidance (e.g., Moscovitch et al., 2005; Aderka et al., 2011). Alternatively, cognitive changes as a result of learning during anxiety reduction techniques may lead to depression reductions by increasing self-efficacy or perceptions of control (e.g., learning to rationally challenge thoughts about feared outcomes may also lead to modifying depressogenic beliefs about the self as incompetent or unlikable). The consistency of the current findings with earlier work suggests that effects generalize to multiple anxiety disorders. In addition, the generalizability of these effects appears to apply to empirically supported treatments more broadly than specific interventions tested in prior studies. It is important to note that the present analyses do not disentangle CALM program treatment effects with other effects (e.g., spontaneous remission, non-specific treatment effects), given that all models were conducted within participants receiving the intervention, so specific inferences about the effects of the CALM intervention cannot be made. Determining the mechanisms by which these effects are observed is one direction for future research in this area.

In contrast, the pattern of change observed following the active treatment phase has not yet been documented in the existing literature. Like the session by session data, it appears that over the long-term outcomes period changes in depression continued to occur via preceding changes in anxiety severity. The active therapy components were removed during this time, meaning that any continued therapy-related activities were purely patient-driven. Presuming that treatment was effective in increasing anxiety-reducing behavioral change, patients may have been participating in activities that operate to directly on anxiety, but also have an

impact on depression as described in the session by session data. However, the pattern of the reverse mediation model was unexpected. The relationships indicated that changes in anxiety were not significant over the long-term outcomes period for those who experience early reductions in depression, although the pattern of means suggested a slight increase in severity. Because this study is the first to examine change over this time period, this data should be replicated in future work. Nonetheless, results suggest that the pattern of change during the long-term outcome phase did not directly mirror those in the acute phase of treatment; in long-term outcomes data it was not the case that anxiety ameliorated because individuals experience depression reductions. A number of hypotheses for this observed effect could be proposed. For example, it may be that when individuals experience relief from their depressive symptoms, they may more readily notice or be more markedly impaired by anxiety symptoms. Level of anxious arousal could play a role in this process, as the symptoms associated with greater arousal levels might be more prominent once vegetative symptoms of depression remit. Alternatively, another variable may account for these effects. Indeed, the observed increased magnitude of the c' path in this model is consistent with the presence of a "suppressor" variable in the mediation model that would account for variance in the time-anxiety relationship (e.g. MacKinnon et al., 2000). For example, when individuals are less depressed they may be more behaviorally activated, and thus more likely to confront situations that may provoke anxiety (e.g., in the context of more active participation in occupational or social activities), which may lead to a greater experience of anxiety that is reflected in the assessments. Initial severity may play a role, such that those with more severe symptoms might show greater reductions during treatment but also be more likely to relapse after sessions end. Given the paucity of data on this issue, future research is needed to more fully explore how change processes unfold over longer durations of time.

From a clinical perspective, results highlight the importance of managing both anxiety and depression symptoms during treatment to facilitate continued improvement after the active phase of treatment concludes. Specifically, beneficial effects on depression may occur if anxiety continues to improve after completion of treatment sessions. Conversely, if an individual is not equipped with skills for managing and continuing to reduce anxiety skills, they may fail to continue achieving gains or potentially be at risk for increasing depressive symptoms. From the perspective of personalizing patient care, findings indicate that treatment for anxiety has utility in patients presenting with anxiety and co-occuring depression, and that providing these patients with treatment components targeting anxiety relapse prevention before termination of care may improve long-term outcomes for both types of symptoms.

A number of limitations warrant consideration in interpreting these findings. The methodology of the study design imposed certain limitations on the assessment and treatment of patients. First, patients received different combinations of CBT, medications, or both depending on their individual needs. Although this feature is a strength in regard to personalization of treatment and generalizability of findings, the data cannot speak to which intervention components contributed to the pattern observed and in what way, nor the mechanisms of treatment in a more stringent manualized CBT protocol. Also, after completion of the CALM program patients may have completed additional treatment. Thus,

the long-term outcomes data interpretation must be qualified by the fact that patients may have completed additional treatment[iv]. Reasons for termination were not collected for the subset of participants who discontinued treatment before symptom amerlioration, and it is unclear how their reasons for terminating may have influenced the mediation patterns (e.g., those with lower functioning may have been unable to complete treatment requirement, and may have demonstrated unique patterns of symptom change). The assessments provided during sessions were necessarily brief, resulting in different assessments used for the session by session data analyses and the long-term outcomes data analyses. Measures (i.e., the OASIS and BSI, PHQ-8 and PHQ-3) are designed to tap very similar putative constructs. However, the measures do have unique features that may have accounted for the observed differences in patterns between the session by session and long-term outcomes models. Because items vary to some extent across measures, differences in mediation models observed across the session-by-session and long-term outcomes data could be accounted for by differential symptoms being tapped in the measures. Although the OASIS and BSI-12 both aimed to tap anxiety symptoms, the BSI-12 includes items assessing of somatic anxiety while the OASIS includes items assessing anxiety-related avoidance. As one illustration, is it possible that reduced depression during the long-term outcomes period would be more likely to impact somatic symptoms, as would be captured by the BSI, but that the mediation pattern would more closely resemeble the session by sessiond data if avoidance symptoms were measured. Similarly, although data suggests that items from the PHQ-9 load on a single factor in diverse primary care samples (i.e., Huang et al., 2005), reductions in anxiety may have particularly impacted the symptoms captured by the PHQ3 (i.e., mood, interest, and energy symptoms). Thus, it may be the case that change in depression impacts reduction of the specific *type* of anxiety symptoms measured – or vice versa - and that these different facets of anxiety may lead to diverging models without necessarily indicating that the relationships between constructs differed across the time periods. The time period between assessments differed in the models, so it is possible that differential effects across session by session and long-term outcomes models were attributed to differential lag between assessments. Using consistent assessment (in measurement type and time period) would strengthen confidence in these results, disentangling whether the differential patterns of relationships in the session by session data and the long-term outcomes data is due to measurement change or true differences in the relationships between anxiety and depression over time. In addition, we utilized a time lag of one visit to be consistent with prior studies (e.g., Moscovitch et al., 2005), but further research would be need to draw conclusions regarding differential change over longer time lags (or the optimal time span to assesse these changes). Future studies might consider a more comprehensive model, including consistent symptom measurements over time and higher-order constructs (including assessment of potential moderators of relationships), in conjunction with more complex modeling of temporal paths of these variables using crossed-lagged or autoregressive modeling, to further delineate the nature of relationships between observed changes. Addressing moderators is a particularly important area for future research to understand how these proceses of change may depend on individual characteristics. Finally, generalizability of the

[iv]Data were re-analyzed using the CALM intervention modality and the presence or absence of additional treatment post-CALM as a factor. The pattern of results was nearly identical, suggesting that these variables were not primary factors driving the observed pattern of effects.

present sample is limited given the selection of participants into a clinical trial using inclusion and exclusion criteria. Although these criteria were designed to be relatively broad, future studies examining more diverse samples (and other types of CBT protocols, including other transdiagnostic programs) are warranted.

In summary, results from the present study suggest that during weekly treatment session for anxiety, changes in anxiety mediate changes in depression, while the reverse is true for the long-term outcomes period. This suggests that anxiety treatment operates on depression both through anxiety reduction but also directly, potentially through treatment components that target shared aspects of anxiety and depression. In addition, findings highlight the importance of continued anxiety reduction for the maintenance and continued improvement of treatment-related gains in depression. Findings are partially consistent with prior work in this area, but expand prior literature in this area by examining change during long-term outcomes.

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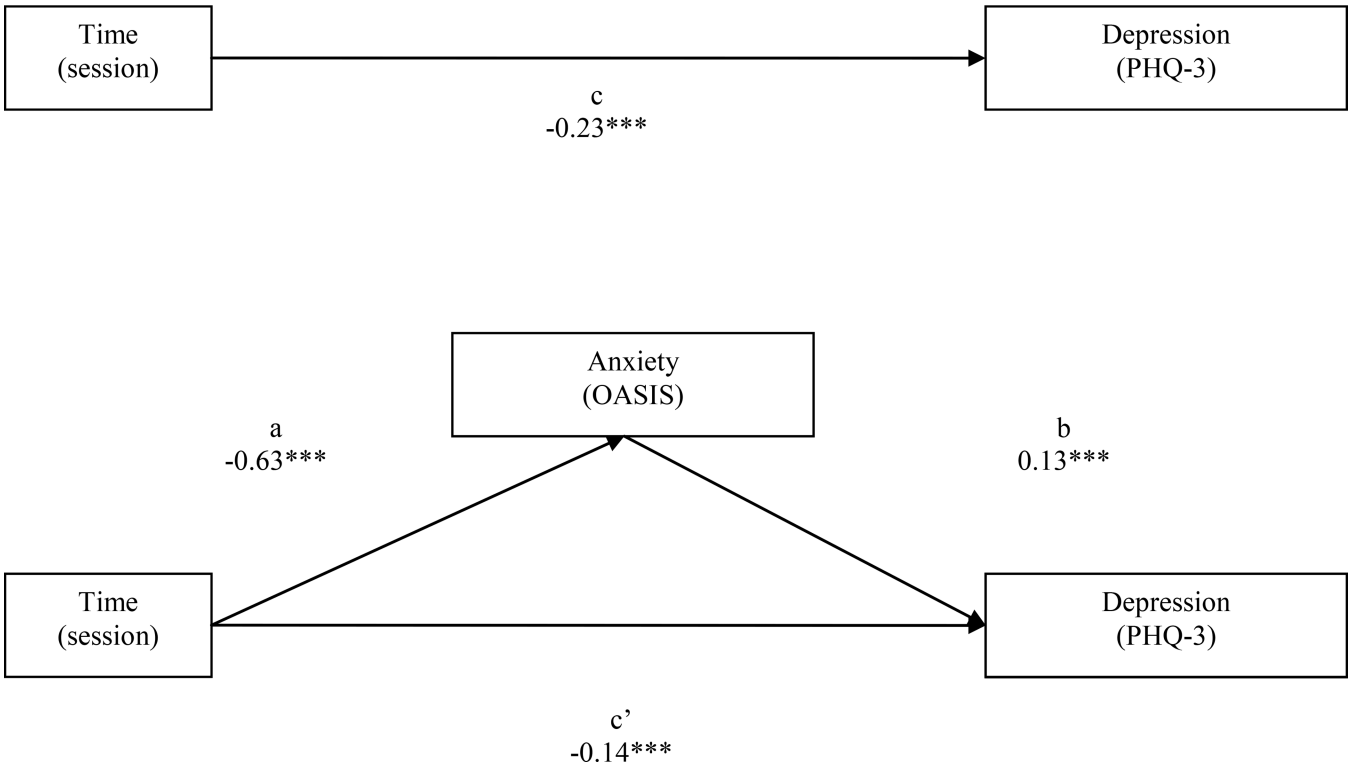

Figure 1.

Results of the hypothesized mediation model with the effect of time on change in depression mediated by change in anxiety (session by session data). ***$p < .001$, **$p < .01$, * $p < .05$

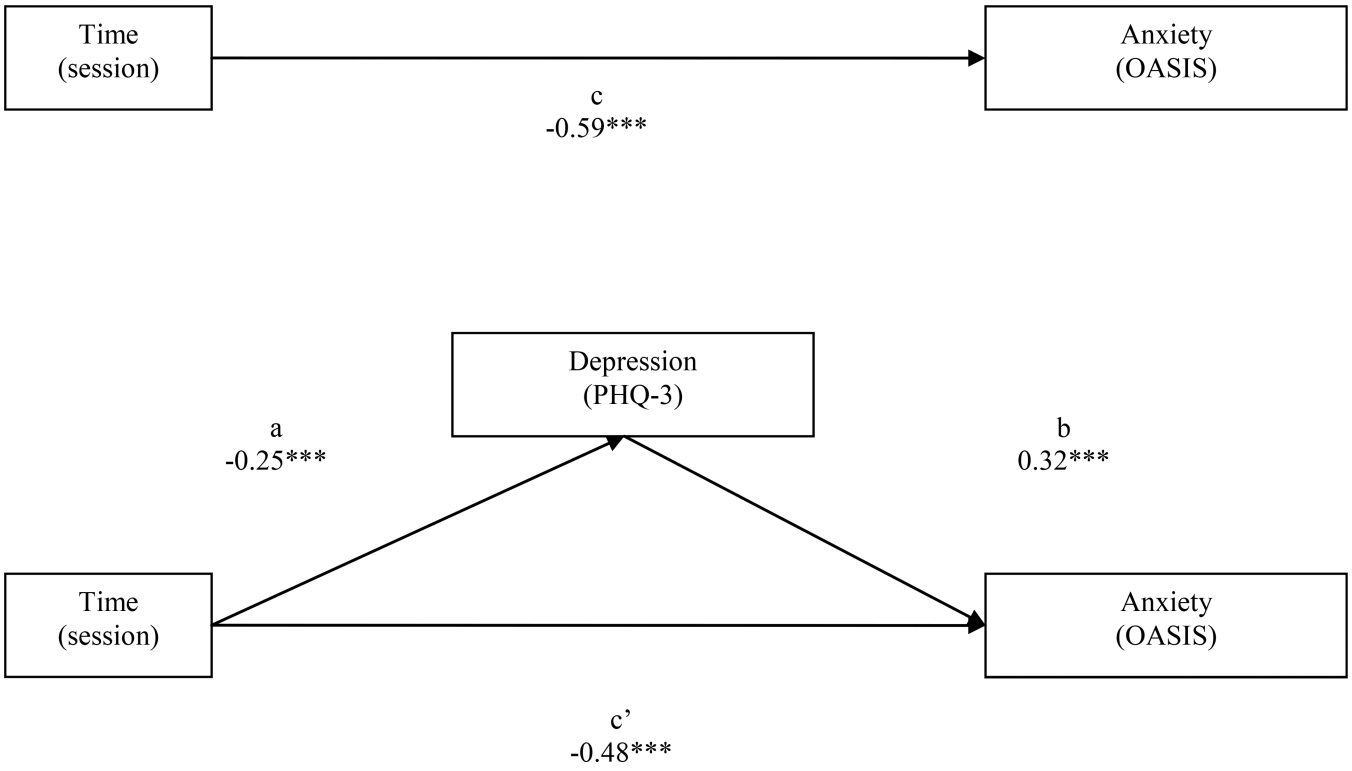

Figure 2.

Results of the reverse mediation model with the effect of time on change in anxiety mediated by change in depression (session by session data). ***$p < .001$, **$p < .01$, * $p < .05$

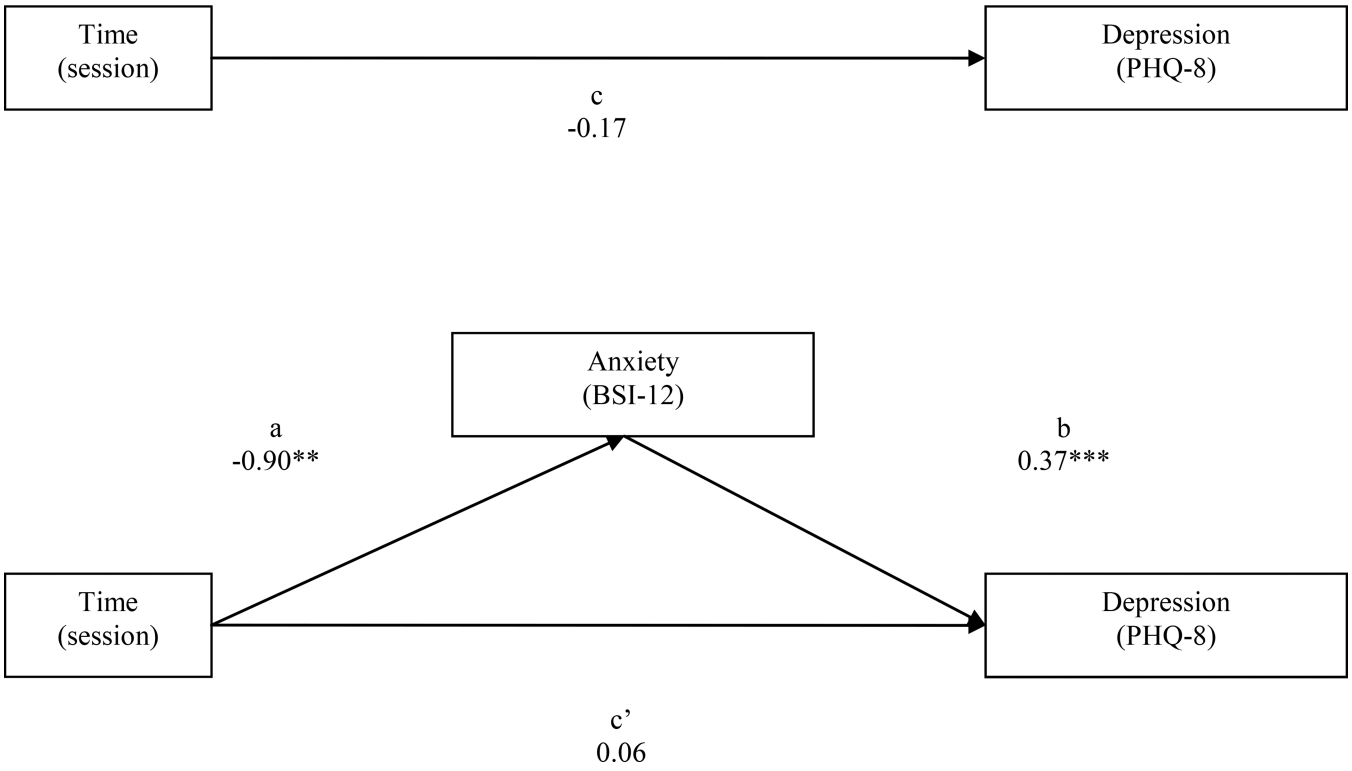

Figure 3.

Results of the hypothesized mediation model with the effect of time on change in depression mediated by change in anxiety (long-term outcomes data). ***$p < .001$, **$p < .01$, * $p < .05$

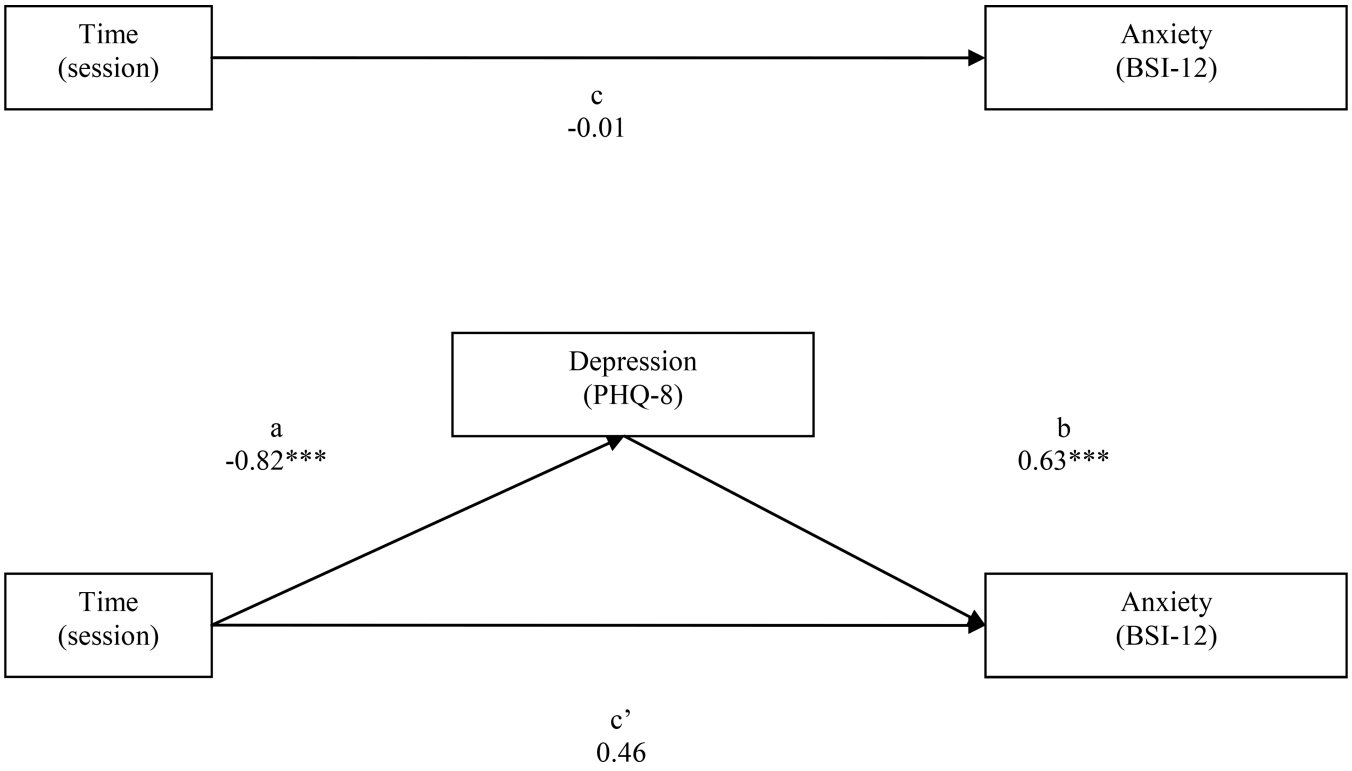

Figure 4.

Results of the reverse mediation model with the effect of time on change in anxiety mediated by change in depression (long-term outcomes data). ***$p < .001$, **$p < .01$, * $p < .05$

Table 1

Demographic and Clinical Variables

Variable	Descriptive data
Mean Age (SD)	43.3 (13.2)
Gender (% female)	71.3
Race/Ethnicity (N per category)	
Hispanic	104 (20.7)
Black	51 (10.1)
White	279 (55.5)
Other	69 (13.7)
Education (N per category)	
< 12 years	29 (5.8)
12 years	78 (15.5)
> 12 years	396 (78.7)
Diagnosis (N)	
PD	235
SAD	210
GAD	390
PTSD	92
MDD	648
Dysthymia	45
OASIS Mean (SD)	
Baseline score	10.5 (3.6)
Score at session 20	7.9 (3.0)
BSI Mean (SD)	
6 month score	9.0 (8.4)
12 month score	7.9 (8.0)
18 month score	7.9 (8.4)
PHQ3 Mean (SD)	
Baseline score	4.8 (2.5)
Score at session 20	2.6 (1.9)
PHQ-8 Mean (SD)	
6 month score	7.5 (6.0)
12 month score	6.5 (6.1)
18 month score	6.3 (5.9)

Table 2

Summary of Multilevel Regression Analyses for Mediational Model with [a] and without [b]treatment type as a covariate (session by session data)

Step	Path	Predictor	Outcome	*B*	SE *B*	t	p
1a	C	Time	Depression	−0.23	0.01	−16.77	< .001
1b	C	Time	Depression	−0.23	0.01	−16.89	< .001
2a	A	Time	Anxiety	−0.63	0.03	−25.22	< .001
2b	A	Time	Anxiety	−0.63	0.02	−25.27	< .001
3a	B	Anxiety	Depression	0.13	0.01	11.30	< .001
	C'	Time	Depression	−0.14	0.01	−11.71	< .001
3b	B	Anxiety	Depression	0.13	0.01	11.05	< .001
	C'	Time	Depression	−0.15	0.01	−11.96	< .001

Table 3

Summary of Multilevel Regression Analyses for Reverse Mediational Model with [a] and without [b]treatment type as a covariate (session by session data)

Step	Path	Predictor	Outcome	*B*	SE *B*	t	p
1a	C	Time	Anxiety	−0.59	0.03	−22.63	< .001
1b	C	Time	Anxiety	−0.59	0.03	−22.61	< .001
2a	A	Time	Depression	−0.25	0.01	−18.43	< .001
2b	A	Time	Depression	−0.25	0.01	−18.54	< .001
3a	B	Depression	Anxiety	0.32	0.03	10.61	< .001
	C'	Time	Anxiety	−0.48	0.02	−19.85	< .001
3b	B	Depression	Anxiety	0.32	0.03	10.48	< .001
	C’	Time	Anxiety	−0.48	0.02	−19.94	< .001

Table 4

Summary of Multilevel Regression Analyses for Mediational Model with [a] and without [b]treatment type as a covariate (long-term outcomes data)

Step	Path	Predictor	Outcome	*B*	SE *B*	t	p
1a	C	Time	Depression	−0.17	0.26	−.66	.51
1b	C	Time	Depression	−0.05	0.27	−.17	.86
2a	A	Time	Anxiety	−0.90	0.33	−2.76	<.01
2b	A	Time	Anxiety	−0.88	0.34	−2.63	< .01
3a	B	Anxiety	Depression	0.37	0.03	11.95	<.001
	C'	Time	Depression	0.06	0.32	0.17	.86
3b	B	Anxiety	Depression	0.35	0.02	14.46	< .001
	C’	Time	Depression	0.17	0.32	0.52	.60

Table 5

Summary of Multilevel Regression Analyses for Reverse Mediational Model with [a] and without [b]treatment type as a covariate (long-term outcomes data)

Step	Path	Predictor	Outcome	*B*	SE *B*	t	p
1a	C	Time	Anxiety	−0.01	0.35	−0.02	.99
1b	C	Time	Anxiety	0.05	0.36	0.15	.88
2a	A	Time	Depression	−0.82	0.23	−3.50	< .01
2b	A	Time	Depression	−0.78	0.24	−3.24	.001
3a	B	Depression	Anxiety	0.63	0.04	14.25	< .001
	C'	Time	Anxiety	0.46	0.43	1.06	.29
3b	B	Depression	Anxiety	0.58	0.05	12.38	< .001
	C’	Time	Anxiety	0.47	0.43	1.10	.27