

Reconditioning the Stress Response Reduces the Inflammatory Cytokine IL6:

A Pilot Study

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**ABSTRACT**

**Objective.** To examine if a brief 12-week self-administered CD hypnosis stress reduction intervention can modify self-reported coping and reduce the proinflammatory cytokine IL-6.

**Design:** Eleven subjects were recruited for a 12-week self-administered CD hypnosis stress reduction intervention designed to recondition and minimize subjects' excessive emotional and physical reactions to perceived work and life stressors. **Main Outcome Measures:** Serum cytokine (IL-6), stress response, coping, social support, psychological well-being and health habits. **Results:** Individuals who completed the 12-week intervention revealed a significantly lower IL6 serum level from baseline. Subjects also reported a significant decrease in the use of Negative Appraisal (such as, self-deprecating statements, perfectionism, and catastrophic and pessimistic thinking ) and an improvement in eating/nutritional habits following the intervention. Changes in overall health habits and negative appraisal coping significantly predicted reduction in serum IL-6 in hierarchical regression analyses. **Conclusion:** This pilot study provides evidence that a brief self-administered CD hypnosis stress reduction program can modify serum IL-6 and self-reporting coping in the face of work and life stress. Additional research using a control group will be needed to verify and extend the impact of these findings.

**Keywords:** hypnosis, stress, inflammation, IL-6, cytokines, psychoneuroimmunology, coping

Statement of Confidentiality: The authors are the developers of the hypnosis stress reduction CD and *StressScan* used in this research study

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It is well established that psychological stress can lead to adverse physical and psychological health changes (Graham, Glaser, Loving, Malarkey, Stowell, & Kiecolt-Glaser, 2009). Chronic stress has been clearly associated with systemic inflammation and an overproduction of pro-inflammatory cytokines (Black, 2009; Kiecolt-Glaser, Preacher, K.J., MacCallum, R.C., Atkinson, Malarkey, & Glaser. 2003; Kiecolt-Glaser, Loving, Stowell, Malarkey, Lemeshow, Dickinson, & Glaser 2005). Chronic and high levels of inflammation and its cytokine precursors have been linked to long term morbidity and a variety of acute and chronic conditions including heart disease (Paoletti 2004), autoimmune disorders (Pickup 2004), cancer (Mantovani 2005), and depression (Anisman & Merali 2003). Similarly, inflammation and chronic cytokine production has been shown to be associated with mortality as well in recent studies (Segerstrom & Miller, 2004; Ershler & Keller, 2000).

Only recently, has it become evident that pronounced emotional reactions such as anxiety and fear are directly linked to inflammatory changes in the body as well (Melamed, Shirom, Toker, Berliner & Shapira, 2004; Pitsavos 2005, Von Kanel 2007). Additionally, emotions such as anger, hostility, and loneliness are associated with an escalation of inflammatory activity in the body (Suarez et al 2004; Steptoe 2004). The research data accumulating in the area of inflammation is exciting in that it reveals more precisely the connection between stress and health and how inflammation may be an important mediating variable.

Research conducted on the inflammation stress connection has focused on several key protein indicators with the inflammatory cytokines most frequently investigated including Interleukin 6 (IL-6) and Tumor Necrosis Factor alpha (TNF-a). A growing number of investigations have evaluated different stress modulating interventions and have observed subsequent decrements in inflammatory cytokines including physical activity/exercise

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(Starkweather 2007), music (Conrad, Niess & Jaunch, 2007), relaxation training (Lutgendorf et al. 2000), meditation (Carlson, Speca M., Patel & Goodey , 2003, and online programs (Hanson, Andenber, Theorell & Arnetz , 2005, Weber 2002).

Several studies have evaluated the effect of hypnosis on modulating inflammatory cytokines. For example, Mawdsley, Jenkins, Macey, Langmead & Rampton (2008) found that hypnosis treatments with ulcerative colitis subjects led to significant decrease in IL-6. Kiecolt-Glaser and her colleagues (Kiecolt-Glaser, Marucha, Atkinson & Glaser, 2001) examined immune dysregulation in 33 medical students who were treated with hypnotic relaxation for acute exam stress. They found that frequent hypnotic-relaxation practice was associated with changes in CD3<sup>+</sup> T and CD4<sup>+</sup> T-lymphocytes, suggesting that their intervention reduced cytokine production associated with acute exam stress. Wood, Burghi, Morrison, Tanavoli & Zadeh (2003) also observed changes in the inflammatory response following brief hypnosis sessions, where levels of Interferon-gamma and Interleukin 2 were significantly decreased in the subjects receiving hypnosis. Finally, stress reduction training using self-hypnosis has also been shown to have a significant impact on natural killer (NK) and CD3<sup>+</sup>CD56<sup>+</sup> in a prospective randomized controlled trial of 48 students designed to help cope with exams (Naito, Laidlaw, Henderson, Frahani, Dwivedi, & Gruzelier, 2003).

Despite the connection between stress, inflammation and illness, only a small percentage of the population actually makes the time to apply stress management principles. Since stress related illnesses constitute a growing segment in healthcare expenditures, it makes intuitive sense to develop stress reduction strategies that would facilitate higher levels of compliance. Therefore, the current pilot study was designed to empirically evaluate a stress reduction strategy that was predicated on simplicity and brevity.

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A strategy such as this would have particular value as a preventative measure in healthy populations. In this investigation, healthy subjects were told to simply listen to a hypnosis stress reduction CD at bedtime and in the early morning. Many clinicians offer hypnosis CDs or tapes for their patients to play between sessions. Although relaxation tapes or CDs have proven effective from subjects' subjective reports, they have not been fully evaluated from the perspective of biochemical measures of inflammation (Laidlaw and Willet, 2002, Costello 1988). This study extends prior research in this area by investigating the impact of hypnosis on inflammatory cytokines using a short-term and self-directed intervention.

The purpose of the current study is to investigate whether the use of a 12-week self-administered hypnosis stress reduction CD can significantly recondition the emotional and physical stress response, as well as, modify self-reported coping and IL-6 in a healthy and normal sample. Based on prior research on the impact of stress reduction on physiological and immune outcomes, two specific hypotheses are presented:

***Hypothesis I:*** Subjects listening to the hypnosis stress reduction CD will experience reductions in serum IL-6.

***Hypothesis II:*** The hypnosis stress reduction CD will result in increased use of positive appraisal, threat minimization and problem focused coping, and decreased use of negative appraisal coping strategies.

## METHOD

### *Participants and Procedure*

#### *Subjects:*

Thirty individuals responded to an email advertisement and a community presentation about participating in a study related to managing stress. Since the study was to focus on healthy individuals, those who were suffering from chronic conditions such as autoimmune disorders, cancer, heart disease, depression, all of which have an inflammatory component, were eliminated. Those taking regular medications that might affect inflammation, such as NSAIDs or statins, were also eliminated. Following the screening, twenty individuals began the study, and six subjects were unable to successfully complete the study due to work commitments or other events that interfered in their ability to listen to the stress reduction CD or complete the blood tests at the scheduled time. Therefore, 14 subjects successfully completed the investigation. Three of these 14 subjects had to ultimately be removed from the study's results. In one case, the subject had developed a cold and flu at the time of the follow up blood test, another had taken Motrin for several days prior to the pre-blood test, and the third had experienced acute significant stress prior to the initial blood test, which unduly elevated her IL-6. The majority of study participants were employed full time (75%) and included 7 women and 4 men. All subjects signed a document of informed consent explaining the purpose of the study and any associated risks.

#### *Measures*

***Emotional Well-Being.*** The measure of emotional well-being in this study was the Psychological Well-being Scale, (StressScan; Nowack, 1994). Psychological Well-Being is

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measured by a 12-item scale assessing overall life satisfaction and absence of psychological distress during the last three months. High scores suggest low overall distress and emotional negativity (i.e., greater satisfaction with one's self, ability to enjoy life, and feeling happy with family, work, interpersonal relationships and achievements. This scale shows high internal consistency reliability (alpha) of .93 and is highly associated with measures of depression, distress and anxiety (Nowack, 1999).

***Lifestyle Habits.*** A global measure of health habits and separate scales of eating/nutrition, exercise/physical activity, sleep/rest and preventive practices was measured using StressScan (Nowack, 1994; Nowack, 2008). Descriptions of the development and validation of StressScan and its scales have been described by Nowack (1994). The StressScan has been associated with diverse health and productivity outcomes in both cross sectional and longitudinal studies including immune response, job burnout, depression, absenteeism, physical illness, anxiety, job satisfaction, organizational commitment and performance (Nowack, 2000; Beasley, Thompson & Davidson 2003; Sharpley & Yardley, 1999; Sharpley & Yardley, 1999).

***Coping Style.*** Coping style in this study was assessed by a 20-item scale (StressScan; Nowack, 1994) which assesses four trait coping responses to work and life stressors and challenges. Respondents are asked how they typically use these four techniques to cope with work, family and personal stressors. The four coping style scales include: 1) Positive Appraisal (realistically emphasizing the positive side of stressful situations through self-talk and cognitively minimizing the importance of the stressor); 2) Negative Appraisal (self-deprecating statements, perfectionism, and catastrophic and pessimistic thinking); 3) Threat Minimization (actively acknowledging and moving ahead without dwelling excessively on the stressor and using humor to

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put things in the proper perspective and 4) Problem-Focused Coping (proactive attempts to modify one's behavior or the environment).

High scores on these independent scales suggest frequent use of these coping styles. These coping scales have shown internal consistency reliabilities ranging from .68 to .79 in previous studies. In both cross sectional and prospective studies, each of these coping scales have been associated with diverse outcomes such as physical illness, job burnout, absenteeism, and depression (Giesser, 2005; Nowack, 1989).

***Social Support.*** Social support is measured using an 18-item scale separately assessing the availability, utility, and satisfaction with five separate support groups available to the respondent including co-workers, supervisor/boss, family, friends, and significant others (Nowack, 1999). An overall Social Support score is calculated across all five of these groups. This scale has demonstrated an internal consistency reliability (alpha) of .83. High scores on this scale suggest that an individual perceives the availability of social resources at work and home, seeks them out when required and reports a level of satisfaction with the type of support they received (e.g., emotional, informational, instructional, etc.).

***Stress.*** Self-reported stress in this study was assessed by a 6-item Stress scale (StressScan; Nowack, 1994) which provides a global index of the appraisal of stress (hassles) over a three-month period. The Stress scale has demonstrated an internal consistency reliability (alpha) of .68 and has shown to be associated with immune response (Schwartz et al., 1993), job burnout (Nowack 1987; 1991), absenteeism (Greene & Nowack, 1996; Nowack, 1994a) and physical illness (Nowack, 1990). This scale also seems to be sensitive to changes in specific interventions designed to teach stress management skills to those with a chronic illness (Giesser et al., 2005).

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This finding has important implications in light of several recent studies indicating the impact of stress management interventions on major chronic conditions and illness (Nowack, 2000).

***Pre Testing:*** All subjects completed the above described self-report measures prior to listening to the hypnosis stress CD. All subjects were scheduled for morning blood tests at Quest Labs, after fasting for twelve hours.

***Intervention:*** The following week all subjects attended an introductory 2-hour meeting. In this meeting they were all given an introduction to hypnosis and the hypnosis stress reduction CD program. The stress reduction CD contained two hypnosis tracks, one to be played prior to sleep at night time and the other to be played in the morning. Each subject was instructed to listen to both tracks once each day for the duration of the 12-week study. No other meetings or interactions were scheduled during the 12-week self-administered hypnosis intervention.

The hypnosis stress reduction CD, based on a paradigm for reconditioning the stress response (Schoen, 2001), was designed to minimize subjects' excessive emotional and physical reactions to perceived work and life stressors. Participants are given suggestions to respond more productively and calmly to unanticipated and anticipated stress. Suggestions are also given to listeners to help them in reappraising stressful situations in a more positive and productive manner. To further facilitate reductions in perceived stress, listeners are given suggestions for boosting their sense of control, overall feelings of self-efficacy, self esteem, and suggestions for reducing catastrophic thinking.

***Post-Testing:*** At the end of three-months, all subjects completed the same self-report inventories they had taken prior to the study. Additionally, a follow-up morning blood test was drawn at Quest Labs after a 12-hour fast.

## RESULTS

Descriptive statistics for time 1 and time 2 for the main study variables are presented in Table 1. Consistent with Hypothesis 1, IL-6 significantly decreased (mean difference was .334,  $t(10) = .03$ ) across the intervention.

A hierarchical regression analysis was used to identify the predictors of IL-6. The analysis was completed at two steps, and an overall significant model emerged ( $F(2, 15) = 9.89$ ,  $p < .01$ ; predicting 54.2% (Adj.  $R^2$ ) of the variance in the criterion variable. Age was entered in the first step but did not significantly contribute to the prediction of IL-6. Overall health habit changes significantly contributed in the first step 30.1% ( $F_{\text{change}}(1, 14) = 7.45$ ,  $p = .016$ ) followed by change in negative appraisal coping which significantly increased the predicted variable by 24.1% ( $F_{\text{change}}(1, 13) = 8.39$ ,  $p = .012$ ).

To test Hypothesis 2, paired t-tests were run on each of the four unique coping style scales used in this study. Only the change in scores from time 1 to time 2 for negative appraisal coping were significant ( $t = -1.50$ ,  $p < .01$ ). Change in threat minimization, positive appraisal and problem focused coping were all insignificant, all  $p$ 's  $> .05$ . So, hypothesis 2 was partially supported with the hypnotherapy intervention leading to less self-reported use of perfectionist, self-blaming, and catastrophic and self-defeating cognitions in the face of work and life stressors.

Additional paired-sample t-tests were run on the other variables collected in this study. The only scale that showed a significant change from time 1 to time 2 was self-reported eating and nutritional habits ( $t = -3.931$ ,  $p < .01$ ). No significant differences were found in the Overall Health Habits scale which was not surprising in light of the non-significant changes in the

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majority of its subscales, including physical activity/exercise, rest/sleep, and preventive practices (all  $p$ 's > .05). Additionally, no reduction in self-reported work/life stress or increase in overall happiness/psychological well-being was observed (all  $p$ 's > .05).

### DISCUSSION

This pilot study demonstrates that listening to self-administered hypnosis stress reduction CD program for three months is associated with self-reported coping style changes (Negative Appraisal), self reported improvements in eating and nutritional habits, as well as, a significant decrease in proinflammatory cytokine production (IL-6). These findings suggest that a self-administered hypnosis stress reduction program reduces the use of self-critical, self-blaming, catastrophic and perfectionist thinking as evidenced by the significant reduction in the use of *Negative Appraisal Coping* in this study. Individuals who perceive work and life stress with greater use of Negative Appraisal Coping tend to report greater stress, job burnout, anxiety and depression (Nowack, 1994; Geisser et al., 2008).

Prior research has shown that hypnosis can successfully change the use of cognitive coping strategies and appraisal processes (Ter Kuike, Sinhoven, Linseen & Van Houwelingen, 1996). Hypnosis can also lead to a decrease in anxious thoughts and pessimism, and improvements in self-esteem (Lioffi & White, 2001). In light of the stress reduction hypnotic intervention used in this study, the finding of a significant change in cognitive coping (negative appraisal) is not surprising. Subjects who cognitively react more modestly to stress are more likely to reveal a lowered physiological reactivity and concomitant systemic inflammation. Self-reported changes in health habits may be reflective of hypnotic suggestions aimed at coping skills, self esteem, and self efficacy, which in turn were facilitative of enhanced health behaviors such as eating and nutrition. This is consistent with a previous investigation which found self-

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efficacy leading to improvements in adults' lifestyle practices and health behaviors (Grembowski, Patrick, Durham, Beresford, Kay & Hecht, 1993).

It is possible that that subjects' hypnotically induced sense of self-efficacy led to a greater sense of empowerment and conscientiousness about adopting healthy stress coping behaviors. Prior research has shown that conscientious-related traits are typically negatively correlated to all risky health related behaviors while positively related to all health enhanced behaviors (Bogg & Roberts, 2004).

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This study provides some limited evidence for how a physiological outcome of stress (IL-6) may in fact be mediated by alterations in cognitive appraisal of work and life events. In the present investigation a reduced inflammatory response was associated with a reduction in negative appraisal over the 12-week period, while there was no relationship with other aspects of cognitive coping (e.g., positive self-talk, problem focused coping or threat minimization strategies). This finding suggests that lower systemic inflammation may in fact be a result of reductions in self blaming, and negative, catastrophic, and perfectionistic thinking — all of which are characteristic of individuals who score lower on the Negative Appraisal coping scale (Nowack, 1990).

A growing body of evidence has established the involvement of inflammation in a variety of illnesses and diseases. This study focused on the proinflammatory cytokine interleukin-6 (IL-

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6) which is involved in arthritis, osteoporosis, Alzheimer's disease, Type II diabetes, some cancers, cardiovascular disease, and cognitive decline (Kiecolt-Glaser, 2009). Of great importance is that anxiety, depression, and negative affect have been found to be significant factors in contributing to the production of pro-inflammatory cytokines (Kiecolt-Glaser et al., 2005). Self-directed stress management interventions like the one used in this study would appear to be one approach to help moderate the impact of acute and chronic stressors on pro-inflammatory processes that are associated with physical health and well-being.

Self-directed and Internet based interventions have shown utility for a variety of health conditions and behaviors (Tate, Finkelstein, Khavjou, & Gustafson, 2009). For example, effect sizes reported in meta-analytic studies of Internet interventions are consistently larger than those found in the control groups, and typically range from -0.01 to 0.75 (Tate et al., 2009). These findings add support for the cost effectiveness and efficacy of self-directed interventions for facilitating changes in physical and psychological health. Even if self-directed programs are found to be slightly less effective than traditional intervention modalities, the cost effectiveness and simplicity of this type of intervention can still play an important role in facilitating health changes. Ultimately, additional research will be needed to determine the cost effectiveness of such self-directed and web-based interventions compared to traditional therapy modalities.

As Kiecolt-Glaser argues that given the interaction between stress, depression, diet and immune function that diverse and multilayered interventions may be the most effective in improving individuals management of stress (Kiecolt-Glaser, 2009). Future research will be required to validate our finding of enhanced health habits and determine whether these types of hypnotic suggestions are also correlated with other preventive lifestyle practices and behaviors.

### *Limitations*

Despite finding support for the two hypotheses detailed within this study, there are several inherent limitations to this study. First, the pilot study design was not able to utilize a control group where participants could be randomly assigned to a control and treatment group. Without a control group and randomization, generalization of results beyond the scope of the current study are limited. Interestingly, there was not a significant difference between subjects' pre-test and post-test self-reported overall work/life stress scores. Since decrements in IL-6 are correlated with reduced stress levels in prior research (e.g., Kiecolt-Glaser et al., 2005), it is somewhat unclear as to the exact mechanism in which the intervention led to changes in these serum levels beyond changes in cognitive coping strategies. It is possible that the self-reported stress measures employed in this study were not sensitive enough to detect changes in a normal and healthy population. Additionally, it is not possible to determine whether the reductions in inflammation, although statistically significant, are clinically meaningful and confer some increased resistance to actual illness and disease over time. Future longitudinal research, using both physical and psychological health measures, should be planned to explore the clinical significance of IL-6 reductions with diverse physical and psychological health outcomes.

Another limitation was the small sample size which may have also lowered the probability of finding differences in perceived stress levels, in that the effect size might have been too small to be significant. With a larger sample size, the difference in perceived stress levels might have been more obvious given the brief measure used in this study has been shown to be a reliable measure of work/life stress (Nowack, 1990). Yet despite the small sample size,

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the effect sizes for the other self-reported measures and serum IL-6 levels were much more evident.

Although screening on underlying medical conditions was used, it was entirely self-report so it is possible that more clinical conditions, infections or other diseases unknown to the subjects might have affected both baseline and follow-up serum IL-6. Unfortunately, no other medical information other than self-report was available for the subjects of this pilot study. Finally, since no control group was available for this pilot study, it is not possible to conclusively suggest that the hypnosis intervention alone resulted in the changes observed in the dependent variables in this study.

### *Implications and future directions*

The results of the present study are suggestive of some short-term beneficial effects from just a 12-week self-administered hypnosis intervention developed to cope more effectively with work and life stress. Future studies may want to evaluate when is the best time to listen to a stress reduction CD. In this study, subjects were instructed to listen to the CD at bedtime and in the morning. It is possible, that there may be differences between these listening times, with one being superior to the other (e.g., such as at bedtime). It would also be useful to compare the benefits derived from subjects experiencing hypnosis directly from an experienced practitioner to those delivered on a CD program like the current study. Since the CD hypnosis is more expedient and inexpensive, it would be very edifying to learn that CD hypnosis is comparable to a therapist administered hypnotic intervention. Furthermore, verification of usage patterns of the hypnosis CD may contribute with knowledge about how self-administered interventions could be improved.

## CONCLUSIONS

The two hypothesis of this study were supported, providing evidence that a self administered stress reduction hypnosis CD program can recondition the stress response and lead to decreases in IL-6 and in self reported improvements in cognitive appraisal coping and health behaviors in the face of work and life stress. Despite some design limitations, this pilot provides some promising evidence that a self-administered stress reduction program that is simplistic and time efficient can be a clinically effective tool for modifying the stress response. Further, this investigation adds to the body of knowledge accumulating regarding self-help interventions. As the delivery of health care increasingly demands evidenced based interventions, this study provides further evidence that hypnosis CDs are a viable option for creating subjective and objective (biochemical) changes in our clients. This pilot study also corroborates the observation found in the clinical setting where patients can report no improvements in their subjective stress levels, yet experience significant improvements in other areas of their lives, such as physical symptoms and improved life choices. Since there is such a low adherence to stress management strategies, a self-administered stress reduction program such as this may offer a solution to those who are reluctant to devote time to stress reduction methods. Finally, this research provides a useful model to replicate using a control group to extend and expand upon the findings of this initial pilot study.

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Table 1

*Means, standard deviations, and intercorrelations between variables*

	Time 1 Mean	SD	Time 2 Mean	SD
1. IL-6	1.01	.55	68	.21
2. Stress	17.67	4.09	15.33	1.94
3. Health Habits	93.67	10.97	98.44	10.69
4. Exercise	12.11	3.02	11.55	3.47
5. Eating/Nutrition	29.0	3.04	31.89	4.04
6. Positive Appraisal	15.44	1.74	16.44	2.29
7. Negative Appraisal	14.00	3.00	12.10	2.08
8. Threat Minimization	14.56	1.74	15.33	1.08
9. Problem Focused Coping	16.89	2.02	17.11	1.83
10. Social Support	50.33	4.92	51.44	6.44
11. Psychological Well-Being	41.0	5.83	42.22	4.89

*Note.* Correlation tables are available from the authors upon request

\*\*  $p < .01$  level (2-tailed).

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Table 2

*Summary of Hierarchical Regression Analysis for Variables Predicting IL-6 (N = 9)*

Variable	IL-6			
	<i>B</i>	SE	B	R <sup>2</sup>
Change in Health Habits	-.025	.007	-.66*	.35
Change in Negative Appraisal	-.082	.028	-.51*	.26

\* $p < .05$ . \*

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Table 3

*Paired Sample Tests*

Variable	Mean Difference	df	<i>t</i>
IL6	.33	10	2.48*
Stress	2.33	8	1.61
Health Habits	4.78	8	1.88
Eating	2.89	8	3.93**
Social Support	1.11	8	1.61
Positive Appraisal	1.00	8	1.50
Negative Appraisal	1.89	8	3.09**
Threat Minimization	0.78	8	1.36
Problem Focused Coping	0.38	8	0.38
Psychological Well Being	0.22	8	0.75
Anxiety	1.87	8	1.87

\* $p < .05$ ; \*\*  $p < .01$