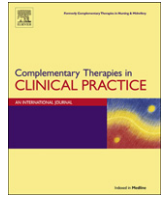


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## Reconditioning the stress response with hypnosis CD reduces the inflammatory cytokine IL-6 and influences resilience: A pilot study

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### ABSTRACT

**Keywords:**  
Resilience  
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Coping

**Aim:** The aim of this investigation was to measure the impact of a self-administered hypnosis intervention on resilience and the inflammatory cytokine IL-6.

**Method:** Over a period of 12 weeks, 11 participants listened to a self-administered hypnosis stress reduction program designed to recondition and improve participants' emotional and physical reactions to perceived work and life stressors. Subjects were administered subjective measures of coping, resilience, and stress tolerance, as well as, IL-6, an objective blood measure of inflammatory activity.

**Results:** After 12 weeks, participants were observed to have a significantly lower IL-6 serum level from baseline. Further, participants reported a significant decrease in the use of negative appraisal coping (such as, self-deprecating statements, perfectionism, and catastrophic and pessimistic thinking), and an improvement in eating/nutritional habits following the intervention. Baseline eating/nutritional habits and threat minimization coping significantly predicted a change in serum IL-6 over the course of the intervention in stepwise hierarchical regression analyses.

**Conclusion:** Pilot study provides support that a brief self-administered CD hypnosis stress reduction program can modify a physiological measure of inflammation (IL-6), and improve coping and resilience in the face of work and life stress.

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### 1. Introduction

It is well established that psychological stress can lead to adverse physical and psychological health changes.<sup>1,2</sup> Chronic stress has been clearly associated with systemic inflammation and an overproduction of pro-inflammatory cytokines.<sup>3–5</sup> 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,<sup>6</sup> autoimmune disorders,<sup>7</sup> cancer,<sup>8</sup> and depression.<sup>9</sup> Similarly, inflammation and chronic cytokine production has been shown to be associated with mortality as well in recent studies.<sup>10</sup>

Further, it has become evident that pronounced emotional reactions such as anxiety and fear are directly linked to inflammatory changes in the body as well.<sup>11,12</sup> Additionally, emotions such as anger, hostility, and loneliness are associated with an escalation of inflammatory activity in the body.<sup>13,14</sup>

More recently, the inflammatory response has been implicated in influencing resilience. Resilience is the ability to effectively cope

and bounce back after being confronted with challenges and adversity.<sup>15</sup> The inflammatory response has been found to elevate the risk of Post-Traumatic Stress Disorder (PTSD).<sup>16</sup> As a result, the inflammatory response has been hypothesized as a mediator of PTSD risk and resilience.<sup>15</sup>

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- $\alpha$ ). A growing number of investigations have evaluated different stress modulating interventions and have observed subsequent decrements in inflammatory cytokines including physical activity/exercise,<sup>17</sup> music,<sup>18</sup> relaxation training,<sup>19</sup> meditation,<sup>20</sup> and online programs.<sup>21,22</sup>

Several studies have evaluated the effect of hypnosis on modulating inflammatory cytokines. For example, Mawdsley, Jenkins, Macey, et al.<sup>23</sup> found that hypnosis treatments with ulcerative colitis participants led to a significant decrease in IL-6. Kiecolt-Glaser and her colleagues<sup>24</sup> examined immune dysregulation in 33 medical students who were treated with hypnotic relaxation for acute examination 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

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cytokine production associated with acute examination stress. Wood, Burghi, Morrison, et al.<sup>25</sup> also observed changes in the inflammatory response following brief hypnosis sessions, where levels of Interferon-gamma and Interleukin-2 were significantly decreased in the participants receiving hypnosis. Finally, stress reduction training using self-hypnosis has also been shown to have a significant impact on natural killer (NK), CD3<sup>+</sup> and CD56<sup>+</sup> in a prospective randomized controlled trial of 48 students designed to help cope with examinations.<sup>26</sup>

Despite the connection between resilience, stress, inflammation, and illness, only a small percentage of the population actually make the time to incorporate stress management principles into their daily habits and lifestyle practices. Since stress related illnesses constitute a growing segment in healthcare expenditures, it makes intuitive and logical sense to develop stress reduction strategies that would facilitate higher levels of compliance. Therefore, the current pilot study was designed to explore the application of an individualized stress reduction strategy predicated on simplicity and brevity.

An individualized stress management application would have particular value as a preventative measure in healthy populations. In this investigation, healthy participants were told to simply listen to a brief hypnosis stress reduction CD at bedtime and in the early morning. Relaxation tapes or CDs have proven effective from participants' subjective reports, but have not been fully evaluated from the perspective of biochemical measures of inflammation.<sup>27</sup> 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.

## 2. Hypotheses

The purpose of the current pilot 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, and modify self-reported coping and resilience, and IL-6 in a normally coping and functioning set of participants.

**Hypothesis 1.** *Participants listening to the hypnosis stress reduction CD will experience significant reductions in serum IL-6 from pre-treatment to post treatment.*

**Hypothesis 2.** *The hypnosis stress reduction CD will result in a significantly greater utilization of positive appraisal, threat minimization, problem focused coping, and decreased use of negative appraisal coping strategies from pre-treatment to post-treatment.*

## 3. Method

### 3.1. Participants

The recruitment of subjects was performed over a period of one month. Subjects were recruited from several avenues: an advertisement in a local newspaper, local physicians and therapists, and an email advertisement sent to those who had attended health lectures in the past at the university. The request for subjects emphasized the importance of healthy, as opposed to unhealthy, subjects and that the study was focused on managing stress. Thirty six prospective participants were screened in two main ways. First, they were evaluated on being able to successfully establish eye closure and the hand lowering task on the Harvard Group Scale of Hypnotic Susceptibility.<sup>28</sup> Hypnosis susceptibility was evaluated to assess the participants' ability to respond to a hypnotic intervention. Secondly, since the study was to focus on healthy individuals (normally coping and functioning participants), those who were suffering from chronic conditions such as autoimmune disorders,

cancer, heart disease, depression, all of which can have an inflammatory component, were eliminated. Those taking regular medications that might affect inflammation, such as NSAIDs or statins, were also eliminated. Following the above two screening criteria, 20 individuals began the study. All subjects gave their consent to using their blood and self-report measures for data analysis and future publication, and were assured of complete confidentiality. Five of the 20 participants (after completing their pre blood analysis) were unable to successfully complete the study due to work commitments or other scheduling conflicts. Another subject as a result of the initial blood test was found to have an autoimmune disorder and suffering from gout. As a result, he was excluded from the study. Therefore, 14 normally coping and functioning participants successfully completed the investigation.

Three of these 14 participants had to ultimately be removed from the study's statistical analyses. In one case, the subject had developed a cold and flu at the time of the follow up blood test, another later reported that they had taken the anti-inflammatory over the counter drug (Motrin) for several days prior to the pre-blood test, and the third had experienced acute significant stress immediately prior to the initial blood test (car accident), which resulted in an extreme elevation of her IL-6 level by approximately 3.5 times the average score of all other participants in this pilot study.

The 5 participants who were initially recruited along with the treatment participants but could not participate in the study served as a statistical control group. No significant differences were found between these 5 control participants and the 11 pilot study participants on initial IL-6, stress or coping measures used (all  $p$ 's > 0.05). No post-treatment assessment data was available for this group who were unable to continue in this study.

The majority of the study participants were employed full time (75%), reported no major current psychiatric or current medical conditions they were being treated for, and included 7 women and 4 men with a mean age of 52.4 (S.D. = 7.4). All 11 participants were Caucasian and college educated. Every participant signed a document of informed consent explaining the purpose of the study, any associated risks, and the permission to anonymously use their measures for analysis and publication. It is important to note that the current study does have some inherent power limitations from a statistical perspective.<sup>29</sup> A priori power analysis for correlated  $t$ -tests or regression using a two-tailed option and an alpha of 0.05, with a desired statistical power level of 0.80 and moderate effect size (0.15) would suggest a much higher number of participants (60) to detect changes in inflammation and self-reported subjective coping and lifestyle changes. [Tables 4 and 5](#)

### 3.2. Design and measures

#### 3.2.1. Design

This pilot study utilized a single-case research design with multiple cases as described by Kazdin.<sup>30</sup> In this design, baseline

**Table 1**

Means, standard deviations, and intercorrelations between variables time 1 versus time 2.

	Time 1		Time 2		Effect size
	Mean	SD	Mean	SD	
1. IL-6	1.01	0.55	0.68	0.21	0.61
2. Stress	17.67	4.09	15.33	1.94	0.57
3. Eating/nutrition	29.0	3.04	31.89	4.04	0.94
4. Positive appraisal	15.44	1.74	16.44	2.29	0.57
5. Negative appraisal	14.00	3.00	12.10	2.08	0.63
6. Threat minimization	14.56	1.74	15.33	1.08	0.45
7. Problem focused coping	16.89	2.02	17.11	1.83	0.48
8. Psychological well-being	41.0	5.83	42.22	4.89	0.21

**Table 2**

Summary of step-wise hierarchical regression analysis for time 1 variables predicting change in IL-6 ( $N = 11$ ).

IL-6				
Variable	<i>B</i>	SE	<i>B</i>	$R^2$ change
Eating/nutrition	−0.08	0.02	−0.79*	63
Threat minimization	−0.11	0.18	−0.66*	0.15

\* $p < 0.01$ .

measures are collected on multiple participants prior to the treatment intervention. Since there is not a control group in this design, all participants receive the treatment intervention.

### 3.2.2. Measures

Psychosocial outcomes used in this study were part of a more comprehensive and validated assessment called StressScan.<sup>31</sup> Description of the development and validation of StressScan and its scales has been previously described.<sup>31,32</sup> StressScan scales have 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 job performance.<sup>33–35</sup> The StressScan includes the following measures: psychological well being,<sup>36</sup> coping style/resilience,<sup>32,34,36</sup> eating/nutrition,<sup>31</sup> and stress.<sup>31–39</sup>

### 3.2.3. Pre testing

All participants completed the above described self-report measures prior to listening to the hypnosis stress CD. All participants were scheduled for morning blood tests at Quest Labs, after fasting for 12 h.

### 3.2.4. Hypnosis intervention

The following week all participants attended an introductory 2-h meeting. In this meeting they were all given an introduction to hypnosis and the hypnosis stress reduction CD program. The introduction entailed acquainting them with hypnosis, such as providing them with some background as to how it's used and how it works, as well as, answering any questions that they might have about the CD hypnosis intervention. The hypnosis stress reduction CD contained two different 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. A 12 week study period was selected based on our clinical observations which have often revealed that significant clinical change with hypnosis CDs typically materializes within 6–2 weeks. No other meetings or interactions were scheduled during the 12-week self-administered hypnosis intervention. In order to strengthen compliance, subjects were told to listen to the CD at least 5 days a week. They were asked to keep a log each evening as a reminder, and then asked to email me each week with their logs. Their logs revealed a strong pattern of consistency.

**Table 3**

Pre and post test measurements (paired sample tests).

Variable	Mean difference	df	<i>t</i>
IL6	0.33	10	2.48*
Stress	2.33	8	1.61
Eating/nutrition	2.89	8	3.93**
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

\* $p < 0.05$ ; \*\* $p < 0.01$ .

**Table 4**

Subject demographics.

Subjects mean age	52.4
Number of subjects	16
Sex	Experimental group (7 women 4 men) Control group (3 women 2 men)
Education	College education and employed
Health	Absence of illness and no medications

The hypnosis stress reduction CD, based on a paradigm for reconditioning the stress response,<sup>2,40</sup> was designed to minimize participants' excessive emotional and physical reactions to perceived work and life stressors while facilitating their coping skills and resilience. The Night CD was 25 min in duration, while the Day CD was 7 min in length. The Day CD was briefer, since it served as a trigger for the suggestions received during the Night CD. Direct resilience suggestions were given to the participants to respond more productively and calmly to unanticipated and anticipated stress. Additional direct resilience suggestions were 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 were given direct suggestions for boosting their sense of control, overall feelings of self-efficacy, self-esteem, and suggestions for reducing catastrophic thinking.

### 3.2.5. Post-testing

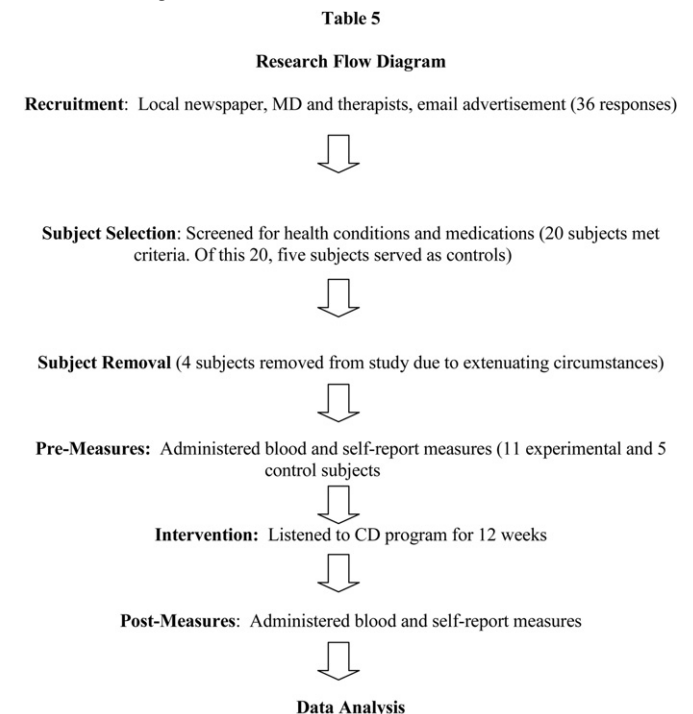
At the end of 3 months, all participants completed the same self-report inventories they had taken prior to the study. Additionally, a follow-up morning blood test was drawn at Quest Labs after a 12-h fast.

## 4. Results

Descriptive statistics for pre-treatment time 1 and post-treatment time 2 for the main study variables are presented in

**Table 5**

Research flow diagram.



**Table 1.** Consistent with **Hypothesis 1**, IL-6 significantly decreased (mean difference was .334,  $t(10) = .03$ ) across the intervention from pre-treatment to post-treatment (**Table 3**). A comparison was also made between the 11 participants' post treatment IL-6 measures that had completed the study to the IL-6 pre-treatment measures of the 5 participants who were unable to complete the study due to work commitments. These 5 participants served as a convenient quasi-experimental control to the 11 participants who completed the treatment. Results from a one-way ANOVA were conducted and demonstrated that the mean post-treatment IL-6 scores of the 11 study participants were lower than the pre-treatment mean IL-6 scores of the 5 controls ( $F(1, 15) = 4.50, p = 0.05$ ). To control for the underpowered and unequal  $n$ 's in the first analysis, a second ANOVA was conducted with a random sample of 5 pilot study participants to compare against the 5 control participants. Again, no significant differences in initial IL-6 scores were observed ( $F(5,10) = 0.30, p = 0.59$ ).

To test **Hypothesis 2**, separate paired  $t$ -tests were run on each of the four unique coping style scales used in this study (**Table 3**). Only the change in scores from time 1 to time 2 for IL-6, eating/nutrition, and negative appraisal coping were significant (all,  $p$ 's < .01). The experiment-wise error rate for these calculations is .19 which is the probability of making at least one Type I error when performing the whole set of comparisons. In general, the experiment-wise error rate increases as the number of comparisons, and particularly post hoc comparisons, are made. Some researchers suggest that special adjustments are not necessary<sup>41</sup> and that all significant results should be reported, with each result allowed to stand on its own to be refuted or confirmed by other researchers in future studies. Others<sup>42</sup> suggest using methods, such as Bonferroni's correction method for post hoc comparisons to ensure a family-wise type II error rate that is no greater than alpha once all the comparisons are made. Additionally, no reduction in self-reported work/life stress or increase in overall psychological well-being was observed (all  $p$ 's > 0.05). Stepwise hierarchical regression analyses revealed that both baseline eating/nutrition and threat minimization coping proved to be significant in predicting change in IL-6 measures (**Table 2**). Therefore, **hypothesis 2** was partially supported with the hypnotherapy intervention leading to less self-reported use of perfectionist, self-blaming, catastrophic, self-defeating cognitions, or greater resilience in the face of work and life stressors.

## 5. Discussion

The results of this pilot study suggest that listening to a self-administered hypnosis stress reduction CD program for 3 months may be associated with increased resilient coping style changes (negative appraisal), self-reported improvements in eating and nutritional habits, as well as a significant decrease in pro-inflammatory cytokine production (IL-6) in normal participants. It further suggests that a self-administered hypnosis stress reduction program may reduce the use of self-critical, self-blaming, catastrophic, and perfectionist thinking by decreasing participants' reliance on negative appraisal coping and strengthening their resilience to everyday life and work stressors. Anecdotal observations from the study's participants were very consistent with these findings, with many of the participants reporting that when they experienced stressful situations in their lives that they felt less affected and concerned by the stressful event. Other participants also indicated that they felt less physically affected when they encountered stress in their lives. The stress reduction also appeared to facilitate healthy lifestyle practices as evidenced by the significant change in eating/nutrition habits.

Prior research has shown that hypnosis can successfully change the use of cognitive coping strategies and appraisal processes.<sup>43</sup> Hypnosis can also lead to a decrease in anxious thoughts and pessimism, and improvements in self-esteem.<sup>44</sup> In light of the stress reduction hypnotic intervention used in this study, the finding of a significant change in cognitive coping (negative appraisal) and the finding that baseline threat minimization coping is predictive of IL-6 change in the regression is not surprising. Participants 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-efficacy leading to improvements in adults' lifestyle practices and health behaviors.<sup>45</sup>

It would be reasonable to wonder if relaxation, as opposed to hypnosis, was the operative agent in creating results in the study. Although relaxation is often a side effect of hypnosis, the reverse is not true. Relaxation alone would be unlikely of creating the significant changes in negative appraisal, threat minimization, and eating habits. Secondly, specific hypnotic suggestions were given to influence these reactions and prior research has found that hypnosis is effective in this manner.<sup>43</sup>

It is possible that participants' hypnotically induced sense of self-efficacy led to a greater sense of empowerment and conscientiousness about adopting healthy stress coping behaviors. Certainly the ability to successfully manage stress effectively has been found to be an effective and important intervention.<sup>46</sup> 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.<sup>47</sup>

This pilot study provides some insight as to 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 pilot study a reduced inflammatory response was associated with a significant reduction in self-reported negative appraisal over the 12-week period. This finding suggests that lower systemic inflammation may be a direct result of hypnotically induced reductions in self-blame, and negative and perfectionistic thinking, all of which are characteristic of individuals who score lower on the negative appraisal coping scale. This finding was consistent with several of the study's participants who reported using less catastrophic negative appraisals while in the course of their daily work and life challenges. Relatively few investigations have examined positive psychosocial functioning and its relationship to inflammatory markers. Our study is one of the first to explore the possibility that inflammation, as measured by IL-6, can be modified by a short-term self-directed hypnosis intervention. Self-directed stress management interventions like the one used in this study may be both a self-directed and clinician supported therapy strategy to help moderate the impact of acute and chronic stressors on pro-inflammatory processes that are associated with physical health, resilience, and well-being.

Self-directed and Internet based interventions have shown utility for a variety of health conditions and behaviors such as physical activity and stress reduction.<sup>48–50</sup> 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  $0.75$ .<sup>48</sup> 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.

### 5.1. Limitations

Despite finding preliminary support for the two hypotheses detailed within this study, there are several inherent limitations to this pilot study. Without randomized control groups (e.g., non-hypnosis stress management CD and non-intervention CD) and post-treatment measures, generalization of results beyond the scope of the current pilot study are limited.

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 in this study. Yet despite the small sample size, the effect sizes for the other self-reported measures and serum IL-6 levels were much more evident (Table 1).

### 6. Conclusions

The results of this pilot study with normally coping and functioning adults provide some limited support for a self-administered stress reduction hypnosis program's potential for reconditioning the stress response and a resilience to everyday stressors. Participants' objective measures revealed a decrement in IL-6, and improvements in subjective measures of cognitive appraisal coping in the face of work and life stress. As previous investigations have observed, reducing the inflammatory response may in fact be a mediating variable in boosting resilience. This pilot study provides some promising suggestive evidence that a self-administered stress reduction program that is simplistic and time efficient may be a clinically effective tool for modifying the stress response and boosting resilience. Although this self-administered program is not meant to be a replacement for one on one therapeutic hypnosis sessions, it may offer an alternative to those patients who cannot afford private sessions or the distance to receiving treatment is too formidable. Further, 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 or resistant to devote time to stress reduction methods.<sup>51</sup> The findings of this study may have particular value with respect to the growing trend of patients seeking evidence based interventions. Additionally, the management of stress and its damaging effects on healthy individuals via inflammatory channels is of increasing significance. A simple self-help approach that requires very little effort that positively influences health and inflammation may offer a first line solution to patients, particularly those who are averse to more traditional behavioral approaches or have limited resources. Although this study was conducted on healthy subjects, it is very likely that individuals with greater health concerns, and higher inflammatory loads may actually benefit more. Finally, this pilot study provides a useful model to replicate for future research using a randomized control group on individuals who are more inflammatory compromised, such as autoimmune disorders and heart patients.

### Conflict of interest statement

No financial support was received for this study.

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