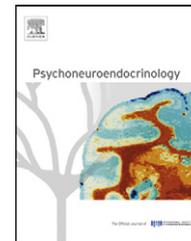




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SHORT COMMUNICATION

Engagement with Cognitively-Based Compassion Training is associated with reduced salivary C-reactive protein from before to after training in foster care program adolescents

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Summary

Background: Children exposed to early life adversity (ELA) have been shown to have elevated circulating concentrations of inflammatory markers that persist into adulthood. Increased inflammation in individuals with ELA is believed to drive the elevated risk for medical and psychiatric illness in the same individuals. This study sought to determine whether Cognitively Based Compassion Training (CBCT) reduced C-reactive protein (CRP) in adolescents in foster care with high rates of ELA, and to evaluate the relationship between CBCT engagement and changes in CRP given prior evidence from our group for an effect of practice on inflammatory markers. It was hypothesized that increasing engagement would be associated with reduced CRP from baseline to the 6-week assessment.

Methods: Seventy-one adolescents in the Georgia foster care system (31 females), aged 13–17, were randomized to either 6 weeks of CBCT or a wait-list condition. State records were used to

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obtain information about each participant's history of trauma and neglect, as well as reason for placement in foster care. Saliva was collected before and again after 6 weeks of CBCT or the wait-list condition. Participants in the CBCT group completed practice diaries as a means of assessing engagement with the CBCT.

Results: No difference between groups was observed in salivary CRP concentrations. Within the CBCT group, practice sessions during the study correlated with reduced CRP from baseline to the 6-week assessment.

Conclusions: Engagement with CBCT may positively impact inflammatory measures relevant to health in adolescents at high risk for poor adult functioning as a result of significant ELA, including individuals placed in foster care. Longer term follow-up will be required to evaluate if these changes are maintained and translate into improved health outcomes.

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1. Introduction

Children exposed to various types of early life adversity (ELA) (e.g. parental loss, physical or sexual abuse, physical and emotional neglect) suffer significantly increased mortality as adults. Although some of this increased mortality comes from suicide, ELA also increases the risk of developing many adult-onset medical and psychiatric conditions associated with increased mortality, including cardiovascular disease and major depression (Felitti et al., 1998; Nanni et al., 2011). Consistent with the contribution of inflammation to the pathophysiology of these conditions (Black, 2003; Haroon et al., 2011), inflammatory activity has been found to be higher in adults with a history of ELA (Danese et al., 2007). Furthermore, maltreatment-related elevation in inflammation levels may already be detected in some children (Danese et al., 2011) and early pharmacological interventions targeting inflammation may be effective in preventing the long-term consequences of ELA (Brenhouse and Andersen, 2011). Taken together, these findings raise the possibility that behavioral interventions known to reduce inflammatory tone, if administered early in life, might protect against – or at least mitigate – the adverse health consequences of ELA.

Previous research by our group has shown that practice of Cognitively-Based Compassion Training (CBCT), a secular, analytical meditation-based program derived from Tibetan Buddhist mind-training (Tibetan *lojong*), is associated with innate immune inflammatory responses to a standardized laboratory psychosocial stressor in medically healthy young adults (Pace et al., 2009, 2010). The goal of CBCT is to challenge unexamined assumptions regarding feelings and actions toward others, with a focus on generating spontaneous empathy and compassion for the self as well as others. Because increased empathy for oneself and others would be expected to enhance prosocial behavior in ways likely to reduce psychosocial stress, our group initially developed CBCT as a behavioral intervention to reduce deleterious behavioral and physiological stress responses (Pace et al., 2009, 2010). In the current study we sought to extend the clinical relevance of these findings by examining whether CBCT would demonstrate anti-inflammatory properties in younger individuals with a history of significant ELA, who are at high risk for developing an inflammatory condition later in life. To accomplish this, we conducted a randomized study to evaluate whether CBCT would reduce salivary concentrations of C-reactive protein (CRP) in a group of highly traumatized adolescents in the Georgia state foster care

system. Based on prior findings of an association between level of engagement with CBCT and reductions in inflammatory biomarkers, in the current study we also examined whether changes in salivary CRP would be associated with amount of practice time in the group randomized to CBCT. Anxiety and depressive symptoms were also assessed to conduct an exploratory analysis of whether changes in CRP were associated with changes in these behavioral constructs. Of note, additional behavioral as well as psychosocial outcomes have been recently published elsewhere (Reddy et al., 2012), and only marginal effects of CBCT were observed for these variables.

2. Methods

2.1. Participants

Seventy-one adolescents (mean age = 14.7 [SD = 1.14]; 56% female) in the Georgia foster care system were evenly randomized (by a list of random numbers, generated by computer) to either 6 weeks of CBCT or a 6 weeks wait-list control condition during late August 2010. All participants were free of medical illness including cancer, cardiovascular disease, diabetes, and autoimmune disorders. Participants were also free of schizophrenia, bipolar I disorder, eating disorders, and major depression severe enough to require hospitalization, as determined by psychiatric examination. Participants taking medications known to influence immune and endocrine functioning including corticosteroids and non-steroidal anti-inflammatory compounds were excluded. Case managers for each participant provided informed written consent and participants provided informed written assent. The study was approved by the Institutional Review Board at the Georgia Department of Public Health.

2.2. Overview of study procedures

The 6-week CBCT program employed in this study generally followed procedures outlined previously (Pace et al., 2009). Children randomized to the CBCT group attended 1-h long classes twice a week for 6 weeks, for a total of 12 classes. As in our previous studies (Pace et al., 2009, 2010), CBCT class sessions combined teaching, discussion, and CBCT meditation practice. Our previous experience with teaching CBCT in children suggested that foster care adolescents would likely benefit from several targeted changes in the way CBCT is typically delivered to adults. Specifically, we adapted our

approach to include more dynamic and interactive pedagogical presentations of program material, such as plays, games and storytelling. Rather than concluding each class session with a 20–30 min meditation period which adolescents and children find difficult to tolerate, we began each class with a short meditation and concluded each class with a slightly longer guided meditation practice. As in our earlier studies, adolescents were given a meditation compact disk to guide at-home practice and encouraged to practice 30 min per day outside of class meetings.

Saliva was collected immediately upon awakening in the morning both before and after the 6-week CBCT or wait-list control conditions using synthetic swab Salivettes (51.1534.500, Sarstedt, Nümbrecht, Germany). As opposed to passive drooling which can take up to 15 min (Strazdins et al., 2005), the Salivette permits rapid, standardized saliva collection in the home setting. The synthetic swab was used to obviate the possibility of plant hormone contamination and analyte binding with natural cotton swabs (Shirtcliff et al., 2001). Participants were instructed to hold the synthetic swab in their mouth for exactly 1 min. Foster parents were instructed to store sealed saliva samples in a home freezer before courier transport to the lab on dry ice. Samples were then stored at -20°C until assay. Concentrations of CRP in saliva were measured with an enzyme immunoassay (Salimetrics, State College, PA). Intra- and inter-assay coefficients of variation for this assay were 2.40% and

4.18%, respectively. Of note, salivary CRP concentrations determined with this assay have been shown to correlate with plasma CRP concentrations (Ouellet-Morin et al., 2011).

Participants in the CBCT group were asked to complete a practice diary on a daily basis. These diaries prompted participants to report whether or not they had practiced CBCT (at home or in class), and if so how many times they had practiced and for how many minutes. When they failed to complete these diaries, they were asked at the next class session how often they had practiced in the last week. Symptoms of depression and anxiety were measured before and after CBCT or wait-list control conditions by self-report assessment using the Quick Inventory of Depressive Symptomatology (QIDS) and State-Trait Anxiety Inventory (STAI). As noted above, additional self-report assessments of behavioral as well as psychosocial variables have been recently reported in a parallel article (Reddy et al., 2012). State records provided information in each participant's history of trauma and neglect, as well as reason for placement in foster care. Study completers were considered as those participants who completed pre- and post-intervention assessments of salivary CRP and depressive/anxiety symptoms.

Baseline characteristics of the sample were compared using *t*-tests for continuous variables and Chi-Square for categorical variables (Table 1). Salivary CRP concentrations, QIDS and STAI scores from the pre- and post-assessments were

Table 1 Baseline characteristics of 55 participants who were both randomized to Cognitively Based Compassion Training (CBCT) or the wait-list control condition, and who completed the entire study protocol (i.e. completed pre and post study assessments).

Characteristic	CBCT group	Wait list group
Number of participants	29	26
Females/males	13/16	11/15
Race	African American 75.86% Caucasian 17.24% Multiracial 6.89%	African American 76.92% Caucasian 7.69% Multiracial 7.69% Asian 7.69%
Hispanic/non-Hispanic	93.10% non-Hispanic	100% non-Hispanic
Mean age (SD)	14.55 (1.21)	14.96 (1.0)
BMI (SD)	23.62 (5.97)	23.46 (5.84)
Number of psychiatric medications ^b	0.71 (0.9)	0.72 (1.06)
Number of psychiatric diagnoses ^b	1.79 (1.06)	1.68 (1.36)
Reasons for DFCS ^a intervention ^b	Neglect 29.63% Physical abuse 29.62% Sexual abuse 18.52% Inadequate housing/supervision 18.52% Absence of legal guardian 11.11% Abandonment/rejection 14.81% Inability to manage child's behavior 11.11%	Neglect 52.0% Physical abuse 20.0% Sexual abuse 4.0% Inadequate housing/supervision 16.0% Absence of legal guardian 12.0% Abandonment/rejection 20.0% Inability to manage child's behavior 12.0%
Total number of placements within the last 5 years (SD) ^b	4.86 (3.95)	4.05 (3.03)
Length of current placement in months (SD) ^b	10.45 (9.45)	11.95 (17.72)
State Trait Anxiety Inventory	17.17 (7.39)	21.12 (8.90)
Quick inventory of depressive symptoms	10.59 (5.66)	10.08 (6.67)
Salivary C-reactive protein concentration (ng/ml) (mean, SD)	27.03 (47.73)	24.24 (48.73)

^a Georgia Department of Human Services, Division of Child and Family Services.

^b Data obtained from state records.

compared between groups using 2-way analysis of variance (ANOVA) for mixed measures, as well as a change score from the before to after the study (i.e. delta CRP, QIDS, or STAI). Effect sizes were also examined. Relationships between amount of practice time during the study and change in salivary CRP from pre to post-assessment (delta CRP) was analyzed using Spearman correlations, given non-normal distribution of delta CRP data.

3. Results

Seventy-one adolescents (31 females) met entry criteria and were allocated to either the CBCT group ($n = 37$) or the wait-list control group ($n = 34$). Sixteen children did not complete the full study protocol and were excluded from the analyses because of failure to complete home saliva sampling procedures and/or self-report assessments, or because of causing disruptions during CBCT group instruction (see [Supplementary Fig. 1](#)). Children who failed to complete the full study protocol did not differ from those who did in terms age, sex, BMI, and depressive or anxiety symptom scores (data not shown). Furthermore, no differences were found between participants who completed the study who were allocated to the CBCT group or wait list group in terms of age, sex, and baseline CRP, BMI, QIDS scores, or STAI scores ([Table 1](#)). Of note, baseline CRP was not correlated with BMI. Across all participants, a strong correlation was found between baseline and post study CRP concentrations ($r_s = 0.82$, $p < 0.001$, $N = 55$), highlighting the overall within subject stability of this marker regardless of study group assignment.

No main effects of group ($F[1,53] = 0.03$, $p = 0.86$, $\eta_p^2 = 0.001$) or time ($F[1,53] = 2.0E^6$, $p = 0.99$, $\eta_p^2 = 4.0E^8$) were found for salivary CRP, nor was a group \times time interaction evident ($F[1,53] = 0.022$, $p = 0.88$, $\eta_p^2 = 0.0004$). However, among children in the CBCT group with complete practice time data ($n = 26$), reductions in morning salivary CRP concentrations across the 6-week study period were associated with the number of CBCT practice sessions during the study ($r_s = -0.58$, $p = 0.002$, $n = 26$) ([Fig. 1](#)).

QIDS scores decreased across the study period in all participants (baseline: 10.33 [SEM = 0.83]; 6-week

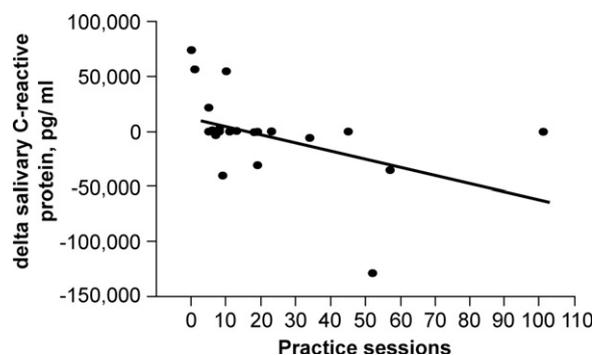


Figure 1 Cognitively Based Compassion Training (CBCT) practice sessions over the 6-week program were negatively associated with the change in salivary C-reactive protein (CRP) concentrations from before to after CBCT in adolescents in foster care ($r_s = -0.58$, $p = 0.002$). Saliva was collected in the home setting immediately after waking and analyzed for concentrations of CRP.

follow-up: 8.26 [SEM = 0.97]; $F[1,53] = 8.36$, $p = 0.01$, $\eta_p^2 = 0.14$), but no group main effect ($F[1,53] = 0.006$, $p = 0.94$, $\eta_p^2 = 1.0E^4$) or group \times time interaction ($F[1,53] = 0.28$, $p = 0.60$, $\eta_p^2 = 0.005$) was observed. STAI scores did not change as a function of time ($F[1,53] = 0.41$, $p = 0.53$, $\eta_p^2 = 0.008$), however, across the 6-week study period (i.e. both before and after the intervention) STAI total scores tended to be lower in the CBCT group (16.76 [SEM = 1.39]) compared to the control group (20.78 [SEM = 1.47]) ($F[1,53] = 3.96$, $p = 0.052$, $\eta_p^2 = 0.07$). Within the CBCT group, practice sessions across the 6-week period were not correlated with baseline or post CBCT QIDS or STAI scores, and no correlations were observed between changes in QIDS or STAI scores and changes in salivary CRP. Finally, controlling for change in STAI or QIDS scores did not significantly change the association between number of CBCT practice sessions and reductions in salivary CRP concentrations during the study.

4. Discussion

Findings from the current study suggest that engagement with CBCT may buffer the detrimental effects of ELA on inflammation in a group of adolescents placed in foster care. Consistent with previous studies of the effects of CBCT on inflammatory biomarkers (Pace et al., 2009, 2010), no main effect of group assignment was observed in the current study. This lack of a group effect highlights the fact that mere exposure to CBCT in a class setting does not appear to be sufficient to induce health-relevant changes in immune functioning. **Rather, it is the degree of engagement with the practice – and perhaps the act of practicing itself – that appears to be influencing inflammation levels.**

The association of greater number of practice sessions with reduced CRP was not accounted for by changes in either anxiety or depression features. This is of interest given a large database linking depression and anxiety to increased plasma concentrations of inflammatory biomarkers, including CRP. However, because elevated CRP levels predict the future development of depression and, conversely, interventions that reduce inflammation have antidepressant and/or anti-anxiety properties (Haroon et al., 2011), a longer follow-up period might have demonstrated that the effects of practice time extended beyond reductions in CRP and to improvements in behavioral symptoms.

The mechanisms by which the practice of CBCT may reduce peripheral inflammation are unknown. However, given that both interpersonal conflict/social isolation and stress exposure/perception have been associated with increased inflammation (Black, 2003; Cole et al., 2007; Kiecolt-Glaser et al., 2005), it is possible that practicing CBCT attenuates inflammation by reducing these aversive states. In this regard, it is interesting that the practice of CBCT had no effect on self-reported depressive or anxiety symptoms as well as a much wider array of psychosocial measures reported separately including callousness, unemotionality, loving kindness, compassion, joy, and acceptance toward self and others (Reddy et al., 2012). However, marginal effects were noted between CBCT practice in the last 3 weeks of the program and improved hopefulness, and a trend for decreased anxiety (please see Reddy et al., 2012).

Moreover, no associations were observed between changes in any self-report variable and CRP. While this might suggest that the impact of CBCT on CRP was independent of any effects on emotional/social variables, it is also quite possible that our adolescent study participants were unreliable reporters of their own internal states. Along these lines, it is noteworthy that prior studies have found poor levels of agreement between adult informants and young patients in regards to the emotional/behavioral functioning of these patients (Kraemer et al., 2003). Moreover, as in the current report, a prior study of CBCT in young adults found no effect of practice time on any self reported behavioral variable when these measures were collected "at rest". However, a strong association between practice time and reductions in self-reported negative emotionality was observed when participants were "placed under load" as a result of undergoing a standardized laboratory psychosocial stressor (Pace et al., 2009, 2010). This raises several intriguing possibilities. It may be that behavioral effects of CBCT relevant to inflammation are only apparent under adverse psychosocial situations, or that such situations improve the accuracy of self-reported emotions in adolescents and young adults, or both. If so, we may have observed inflammation-relevant effects on emotional/behavioral functioning in the current study had we administered some type of psychosocial stressor prior to and upon completion of CBCT. Unfortunately, for ethical reasons this was not feasible in the highly traumatized population of adolescents.

Like other populations subjected to significant ELA, foster children are at increased risk for medical and psychiatric disorders (Ringeisen et al., 2008) in which inflammatory pathways are known to contribute to disease pathogenesis (Black, 2003).

Several limitations of the current study are worth noting. First, we measured CRP in saliva instead of blood. Despite the fact that CRP concentrations in saliva have been shown to correlate with CRP concentrations in serum (Ouellet-Morin et al., 2011), assessment of circulating CRP would have permitted a more direct comparison of current findings with already published studies. The current study is also limited by not having conducted longitudinal follow-up to evaluate whether ongoing CBCT practice would be required to maintain the reductions in CRP levels that we observed immediately after training. A third limitation is that because study participants were free from serious medical and psychiatric illnesses, results cannot be generalized to more impaired adolescents in state custody who might be unable to engage in CBCT or who might derive even greater benefit from it than did the participants studied here. Fourth, the current study utilized a wait list control instead of an active control condition, raising the possibility that the anti-inflammatory effect of engaging with CBCT might not have derived from the specific practice of CBCT but rather from other more non-specific factors captured by the practice time. Finally, the current study is limited by a small sample size and corresponding limited statistical power. Given this, the association between CBCT practice time and delta CRP should be replicated, given that a few extreme cases at the low end of CBCT practice sessions, as well as one participant with a marked change in salivary CRP from before to after the intervention may have disproportionately contributed to the association between CBCT practice time and reductions in salivary CRP.

Nonetheless it should be noted that these cases fell along the regression line for the correlation of the group as a whole, and removing these individuals only slightly reduced the size of the correlation between practice time and reductions in CRP.

In summary, findings from the current study suggest that CBCT may hold promise as a preventive, or disease-modifying, behavioral intervention in foster children, and by extension, to other populations of young people with experiences of ELA. Given the short nature of our study, longer-term follow-up will be required to determine if CBCT-related reductions in inflammatory tone are durable across time and translate into improved health outcomes in this population.

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Conflict of interest statement

All of the authors have no conflict of interest to declare related to this study and its findings.

Acknowledgments

T.W.W.P. and C.L.R. wrote the original manuscript version. S.D.R. and A.D. revised the manuscript. A.D. assisted with study design and data interpretation. L.T.N., B.O. and B.D. provided CBCT program instruction and reviewed the manuscript. S.P.C. conducted statistical analyses and reviewed the manuscript. L.W.C. and S.D.R. oversaw participant screening and self-report assessments and reviewed the manuscript. All authors had access to the study data. Data in the current report were presented at the Compassion Meditation Conference, October 18, 2010 at Emory University, Atlanta, GA, USA. We would like to thank Commissioner B.J. Walker, Mr. Lamar Smith, Mr. Primos Cobb, and Ms. Allison Williams for their invaluable assistance with this project.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.psyneuen.2012.05.019>.

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