Mindfulness-Based Stress Reduction training reduces loneliness and pro-inflammatory gene expression in older adults: A small randomized controlled trial

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ABSTRACT

Lonely older adults have increased expression of pro-inflammatory genes as well as increased risk for morbidity and mortality. Previous behavioral treatments have attempted to reduce loneliness and its concomitant health risks, but have had limited success. The present study tested whether the 8-week *Mindfulness-Based Stress Reduction* (*MBSR*) program (compared to a *Wait-List* control group) reduces loneliness and downregulates loneliness-related pro-inflammatory gene expression in older adults ($N = 40$). Consistent with study predictions, mixed effect linear models indicated that the *MBSR* program reduced loneliness, compared to small increases in loneliness in the control group (treatment condition × time interaction: $F(1,35) = 7.86$, $p = .008$). Moreover, at baseline, there was an association between reported loneliness and upregulated pro-inflammatory NF-κB-related gene expression in circulating leukocytes, and MBSR downregulated this NF-κB-associated gene expression profile at post-treatment. Finally, there was a trend for MBSR to reduce C Reactive Protein (treatment condition × time interaction: ($F(1,33) = 3.39$, $p = .075$). This work provides an initial indication that MBSR may be a novel treatment approach for reducing loneliness and related pro-inflammatory gene expression in older adults.

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"*Usually* we regard loneliness as an enemy. Heartache is not something we choose to invite in. It's restless and pregnant and hot with the desire to escape and find something or someone to keep us company. When we can rest in the middle [through meditation practice], we begin to have a nonthreatening relationship with loneliness, a relaxing and cooling loneliness that completely turns our usual fearful patterns upside down"

–Pema Chodron (2000), Buddhist nun and teacher

Feeling lonely is a significant risk factor for morbidity and mortality in older adults. For example, lonely older adults have increased risk for cardiovascular disease (Olsen et al., 1991; Thurston and Kubzansky, 2009), Alzheimer's disease (Wilson et al., 2007), and all-cause mortality (Tilvis et al., 2011). Developing effective treatments to reduce loneliness in older adults is thus essential, but previous treatment efforts have had limited success

(Findlay, 2003; Masi et al., 2011). As Pema Chodron suggests above, meditation practice may provide a middle way for reducing one's feelings of loneliness (Chodron, 2000). Loneliness has been described as a state of social distress that arises when there is a discrepancy between one's desired and actual social relationships (Russell et al., 1980; Cacioppo and Hawkley, 2009). Previous mindfulness meditation studies using the standardized 8-week *Mindfulness-Based Stress Reduction* (MBSR) program show that MBSR reduces measures of distress and negative affect in healthy and patient populations (for reviews, Brown et al., 2007; Hölzel et al., 2011) and can improve social relationship functioning in couples (Carson et al., 2004), although no studies have tested whether the MBSR program can reduce loneliness. Our primary aim was thus to test whether MBSR reduces loneliness in a small randomized controlled trial in older adults ($N = 40$).

If the MBSR program reduces loneliness, it offers the intriguing possibility that mindfulness meditation training may also alter gene expression dynamics and protein markers of inflammation (i.e., C Reactive Protein (CRP) and Interleukin-6 (IL-6)) that are implicated in the physical health risks observed in lonely older adults (Cole et al., 2007). Several studies indicate that MBSR may reduce protein biomarkers of inflammation (Carlson et al., 2003,

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2007; Lengacher et al., 2012), and inflammation is known to play a major role in structuring the development and progression of many diseases that drive late-life morbidity and mortality (Finch, 2007). Moreover, recent research shows that immune cells from lonely older adults have increased expression of genes involved in inflammation (Cole et al., 2007, 2011). Bioinformatic analyses of the signaling pathways regulating gene expression suggest that loneliness may activate a biological defensive program mediated by the pro-inflammatory transcription factor, NF-κB, in monocytes (Cole et al., 2007, 2011; Irwin and Cole, 2011; Antoni et al., 2012). Therefore we also tested whether MBSR reduces loneliness-related pro-inflammatory gene expression and circulating protein biomarkers of inflammation (as measured by CRP and IL-6).

Methods

Participants

Randomized participants ($N = 40$) were healthy older adults (age 55–85 years; $M = 65$ SD = 7) recruited via newspaper advertisements from the Los Angeles area, who indicated an interest in learning mindfulness meditation techniques (a self-selected group). The sample was 64% Caucasian, 12% African American, 10% Latino, 7% Asian American, and 5% Other, and was predominantly female (33 women). The trial occurred during October 2007–January 2008. All participants provided written informed consent at the study screening. All study procedures were approved by the UCLA and CMU Institutional Review Boards.

Procedure

To determine eligibility, interested participants were phone screened and invited for an in-person evaluation. To qualify for the study, participants had to be English-speaking, not currently practicing any mind–body therapies more than once per week (e.g., meditation, yoga), non-smokers, mentally and physically healthy for the last three months, and not currently taking medications that affect immune, cardiovascular, endocrine, or psychiatric functioning. Participants also completed fMRI tasks (described in a separate report), and additional MRI criteria excluded participants at screening if they were left handed, had any non-removable metal (dental fillings okay) or non-MRI safety approved implants, or weighed more than 300 lbs. Participants were also excluded if they had cognitive impairment (<23 on the Mini-Mental State Examination) (Folstein, 1975). Participants were compensated up to $200 for participating in this study (part of this compensation was for the fMRI-related study activities).

If participants were eligible, they were asked to complete a number of study measures, which included a questionnaire assessing loneliness and a blood sample (see Measures). Participants were then randomized to either the 8-week Mindfulness-Based Stress Reduction (MBSR) program or a Wait-List (WL) control condition using a computerized number generator. MBSR is a standardized and manualized 8-week mindfulness meditation intervention (Kabat-Zinn, 1990) that has been used widely in behavioral medicine research. MBSR was administered by one of three trained clinicians over three cohorts, and consisted of eight weekly 120-min group sessions, a day-long retreat in the sixth or seventh week, and 30-min of daily home mindfulness practice. Our trained clinicians had co-taught previous MBSR programs together and all maintained a daily mindfulness meditation practice. During each group session, an instructor lead participants in guided mindfulness meditation exercises, mindful yoga and stretching, and group discussions with the intent to foster mindful awareness of one's moment-to-moment experience. The daylong 7-h retreat during week six or seven of the MBSR intervention focused on integrating and elaborating on the exercises learned during the course. Finally, MBSR participants were asked to participate in 30 min of daily home mindfulness practice six days a week during the program. After the 8-week period, all participants returned to complete the same measures as those administered at baseline, including the loneliness questionnaire and another blood sample by blinded study staff. Participants in the WL condition were asked not to participate in any new behavioral health programs during the waiting-period and received the MBSR program after completing the primary dependent measures in the study.

Measures and data analytic approach

MBSR class attendance was recorded by a hypothesis-blind staff member, and participants were asked to complete daily home practice logs indicating how many minutes they practiced each day during the 8-week MBSR program.

Mindfulness Skills

The 39-item *Kentucky Inventory of Mindfulness Skills* (KIMS) was administered at baseline and post-treatment as a manipulation check, to assess whether MBSR program increases self-reported use of Mindfulness Skills (anchored by 0 = never true to 5 = always true) (Baer et al., 2004). These skills include *observing* one's experience (sample item: "I notice when my moods begin to change"; baseline study $\alpha = .86$), *describing* (sample item: "I'm good at finding words to describe my feelings"; baseline study $\alpha = .87$), *acting with awareness* (sample item: "When I do things, my mind wanders and I am easily distracted (reverse-scored)"; baseline study $\alpha = .80$), and *acceptance* (sample item: "I tell myself I shouldn't be feeling the way I'm feeling (reverse-scored) (baseline study $\alpha = .85$). A composite measure of Mindfulness Skills was created by summing all items, and higher scores indicate greater mindfulness.

Loneliness

The composite *UCLA-R Loneliness Scale* (Russell et al., 1980) was administered at baseline and post-treatment, and consists of 20 items measuring general feelings of loneliness (sample item: "I lack companionship"; anchored 1(never) to 4 (often); baseline study $\alpha = .92$). Higher scores indicate greater loneliness.

Following intent-to-treat principles, mixed effect linear models (MLMs) tested for treatment condition (MBSR vs. WL) × time (baseline vs. post-treatment) interactions on Mindfulness Skills and loneliness using SPSS 19.0 (IBM, Armonk, New York). Treatment Condition and Time were modeled as fixed effects.

Gene expression profiling and pro-inflammatory protein analysis

Participants provided 10 ml of blood at baseline and post-treatment. Genome-wide transcriptional profiling was carried out as previously described (Cole et al., 2010, 2011). Briefly, peripheral blood mononuclear cells (PBMC) were isolated by density gradient centrifugation and total RNA was extracted (RNeasy; Qiagen, Valencia, CA), tested for suitable mass (Nanodrop ND1000) and integrity (Agilent Bioanalyzer), and converted to fluorescent cRNA for hybridization to human HT-12 BeadChips (Illumina, San Diego, CA) following the manufacturer's standard protocol in the UCLA Southern California Genotyping Consortium Core Laboratory. Quantile normalized gene expression values were transformed to $\log_2$ for genome-wide general linear model analysis. Initial cross-sectional analyses examined baseline data collected prior to randomization in order to determine whether these samples showed the same associations previously observed between individual differences in loneliness and (1) bioinformatic indications of increased pro-inflammatory NF-κB transcription factor activity, and (2) increased monocyte-mediated gene expression (Cole et al.,