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Smartphone mindfulness meditation training reduces Pro-inflammatory gene expression in stressed adults: A randomized controlled trial

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ABSTRACT

Mindfulness meditation training has been shown to be an effective stress reduction strategy, but less is known about its immunoregulatory impact. In a randomized controlled trial of stressed customer service workers, the present study tested whether a 30-day smartphone-based mindfulness meditation training program (compared to a problem-solving control program) would affect pro-inflammatory gene expression. Both interventions led to reductions in stress levels, but there was no difference in stress reduction between conditions. Consistent with predictions, mindfulness training reduced activity of the pro-inflammatory NF-κB transcription control pathway compared to the active control. These results suggest that mindfulness training may be a particularly effective method for improving immune cell gene expression in stressful work environments.

1. Introduction

Chronic stress is enduring and toxic, activating biological systems that can lead to deleterious effects on physical health. Studies document how chronic stress, or significant adversity, is associated with an increased risk of disease and poorer health (Cohen et al., 2007) in part via activation of the sympathetic nervous system and pro-inflammatory gene expression (Cole, 2019; Heidt et al., 2014; McKim et al., 2018; Powell et al., 2013; Simons et al., 2017). Specifically, stress activates peripheral neurobiological systems, such as the sympathetic nervous system, and leads to changes in cellular signal transduction (Cole, 2014; Slavich and Cole, 2013) and activation of transcription factors such as NF-κB and CREB, which results in increases in up-regulation of pro-inflammatory gene transcription (Cole, 2014). Studies demonstrate that increases in pro-inflammatory gene expression are associated with worse health outcomes (Chiang et al., 2019; Goldwater et al., 2021). Theories suggest that these transcription control pathways are critical to the link between stress and health, and thus present a strong theoretical target for stress management interventions that aim to improve health (Black et al., 2019).

Initial randomized controlled trials (RCTs) of mindfulness training programs show significant promise for fostering stress resilience and improving mental and physical health (Creswell, 2017; Creswell et al., 2019). For example, mindfulness training interventions have been shown to reduce physiological and self-reported stress responses to a laboratory stress task (Hoge et al., 2013; Lindsay et al., 2018b; Nyklíček et al., 2013) and reduce perceived and daily stress (Chin et al., 2018; Roeser et al., 2013). There have been indications that behavioral stress management programs can reduce pro-inflammatory gene expression in lonely older adults (Creswell et al., 2012), breast cancer survivors (Bower et al., 2020), and older adults with sleep disturbances (Black et al., 2015). These previous trials have primarily focused on clinical samples, and most use waitlist control groups. In this study, we conducted the first active control RCT on healthy stressed adults to determine whether mindfulness meditation training exerts similar effects on pro-inflammatory gene expression in the absence of pre-existing disease.

While most of the scientific literature has focused on group mindfulness programs, such as the Mindfulness-Based Stress Reduction program, smartphone mindfulness training programs (e.g., Headspace) offer the substantial benefit of mindfulness training in a personal, portable, scalable, and low-cost format (Lim et al., 2015; Lindsay et al., 2018a; b). Smartphone-based mindfulness training has been shown to reduce stress and depressive symptoms, and increase positive affect (Cavanagh et al., 2013; Economides et al., 2018; Howells et al., 2016;

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Lindsay et al., 2018a; b), but little is known about their impact on stress-related aspects of immune function. In the present work, we examined the effects of a specific smartphone app training program, *Headspace*, on stress and immune cell *gene expression* in a sample of highly stressed customer service workers. The *Headspace* program has been shown to reduce distress and job strain in initial testing (Bostock et al., 2019), and testing in a sample of highly stressed workers offers a unique opportunity to assess the impact of a digital intervention with a population that might not have the time for in-person mindfulness classes. We employed an active treatment control, and both intervention conditions consisted of a daily guided audio lesson for 10–20 min each day for 30 days, with pre-/post-intervention self-reported stress and mRNA analysis of proinflammatory gene expression by the NF-κB family of transcription factors (indicated by promoter-based bioinformatic analyses of genome-wide transcriptional profiling, as in previous research (Cole, 2019). We hypothesized that the mindfulness meditation training group would show greater reductions perceived stress and in pro-inflammatory gene expression compared to our active control condition (ClinicalTrials.gov NCT03803865). Although not a primary target of these analyses, we also examined activity of the Interferon Response Factor (IRF) family of transcription factors that are often regulated inversely to pro-inflammatory signaling pathways (i.e., down-regulated in the context of stress; (Cole, 2019)).

2. Materials and methods

2.1. Participants and procedure

2.1.1. Participants

Enrolled participants were 100 customer service employees (those who interact with customers daily via phone or in-person interactions) recruited from local companies in the Pittsburgh region for a 30-day randomized controlled trial of a smartphone-based training program for stress management. Participants ranged in age from 18 to 60 (M = 34.03 years, SD = 11.07). 67% identified as female, 30% as male, and 3% as non-binary or genderqueer. 64% of the sample was White, 8% Asian, 18% Black or African American, 7% multi-racial, 3% Other or Not Reported. See Table 1 for baseline characteristics.

Primary analyses are reported using all available data from participants who completed all pre-intervention and post-intervention activities (n = 96). The study design and outcomes described here were preregistered with Clinical Trials identifier NCT03803865. To qualify for the study, the participants had to be fluent in English and between the ages of 18 and 70, and score > 5 on the four-item Perceived Stress Scale (Cohen et al, 1983) adapted for work, reflecting high levels of perceived stress at work. Eligible participants could not be practicing any stress reduction practices—such as meditation, yoga, tai chi—more than twice a week, could not have had any surgeries in the last three months, and were not currently taking any psychiatric medications or prescribed medications that would affect immune or endocrine functioning. Participants were required to own a smartphone (Android or iPhone) to complete the smartphone-based training programs. Participants also completed a neuroimaging scan for the study resulting in additional MRI criteria, which excluded participants at screening if they had non-removable metal in their body or non-MRI safety-approved implants (neuroimaging analyses to be reported elsewhere). See Fig. 1 for a CONSORT flowchart. All participants completed a written informed consent, and the Carnegie Mellon University IRB approved all study procedures.

2.1.2. Study procedure

Participants were prescreened for eligibility by telephone. Eligible participants were enrolled and completed baseline psychosocial questionnaires assessing thoughts, feelings, and individual differences, provided a baseline dried blood spot (DBS) sample, and were oriented to the at-home study assessments and mobile mindfulness training intervention.

Table 1
Baseline characteristics of randomized participants.

	Full Sample (N = 100)	Headspace (N = 50)	Recharge (Control) (N = 50)	Condition Difference Statistic
Characteristic				
Age in years	34.03 (11.07)	35.02 (12.07)	33.08 (10.04)	$F(1,98) = 0.73$
Gender				$\chi^2(3) = 3.26$
Female	67 (67%)	35 (70%)	32 (64%)	
Male	30 (30%)	14 (28%)	16 (32%)	
Non-binary	2 (2%)	0 (0%)	2 (4%)	
Genderqueer	1 (1%)	1 (2%)	0 (0%)	
Race				$\chi^2(4) = 9.24$
American Indian/ Alaska Native	0 (0%)	0 (0%)	0 (0%)	
Asian	8 (8%)	3 (6%)	5 (10%)	
Black/African American	18 (18%)	14 (28%)	4 (8%)	
White/Caucasian	64 (64%)	27 (54%)	37 (74%)	
Bi- or Multi-Racial	7 (7%)	5 (10%)	2 (4%)	
Other/Not Reported	3 (3%)	1 (2%)	2 (4%)	
Ethnicity				
Hispanic or Latino	7 (7%)	5 (10%)	2 (4%)	
Not Hispanic or Latino	93 (93%)	45 (90%)	48 (96%)	
Education Level				$^*\chi^2(5) = 12.84$
High School Diploma	7 (7%)	2 (4%)	5 (10%)	
Technical Training	6 (6%)	2 (4%)	4 (8%)	
Some College	25 (25%)	19 (38%)	6 (12%)	
Bachelor's Degree	39 (39%)	15 (30%)	24 (48%)	
Master's Degree	21 (21%)	10 (20%)	11 (22%)	
MD, PhD, JD, PharmD	2 (2%)	2 (4%)	0 (0%)	

Note: Data are reported as means (SD) or numbers (%).
*Indicating $p < 0.05$.

During the 30-day intervention period, participants completed one audio-guided training session each day (10–20 min) and a brief end-of-day daily diary assessing stress, affect, sleep, and workplace perceptions (a text message link was sent an hour before the participant's standard bedtime each day; results will be reported elsewhere). Participants received study reminder texts/emails and phone calls throughout the intervention period and were able to contact study staff to ask questions or resolve technical issues. Participants returned 1 week after completing the smartphone-based audio-guided training intervention for a post-intervention appointment and completed psychosocial questionnaires, an MRI scan and provided a dried blood spot sample. After all outcome measures were collected, participants were informed of the study's primary aims (to test the *Headspace* mindfulness training program) and compensated for their time.

2.2. Interventions

2.2.1. General procedure

Participants were randomly assigned to receive one of two

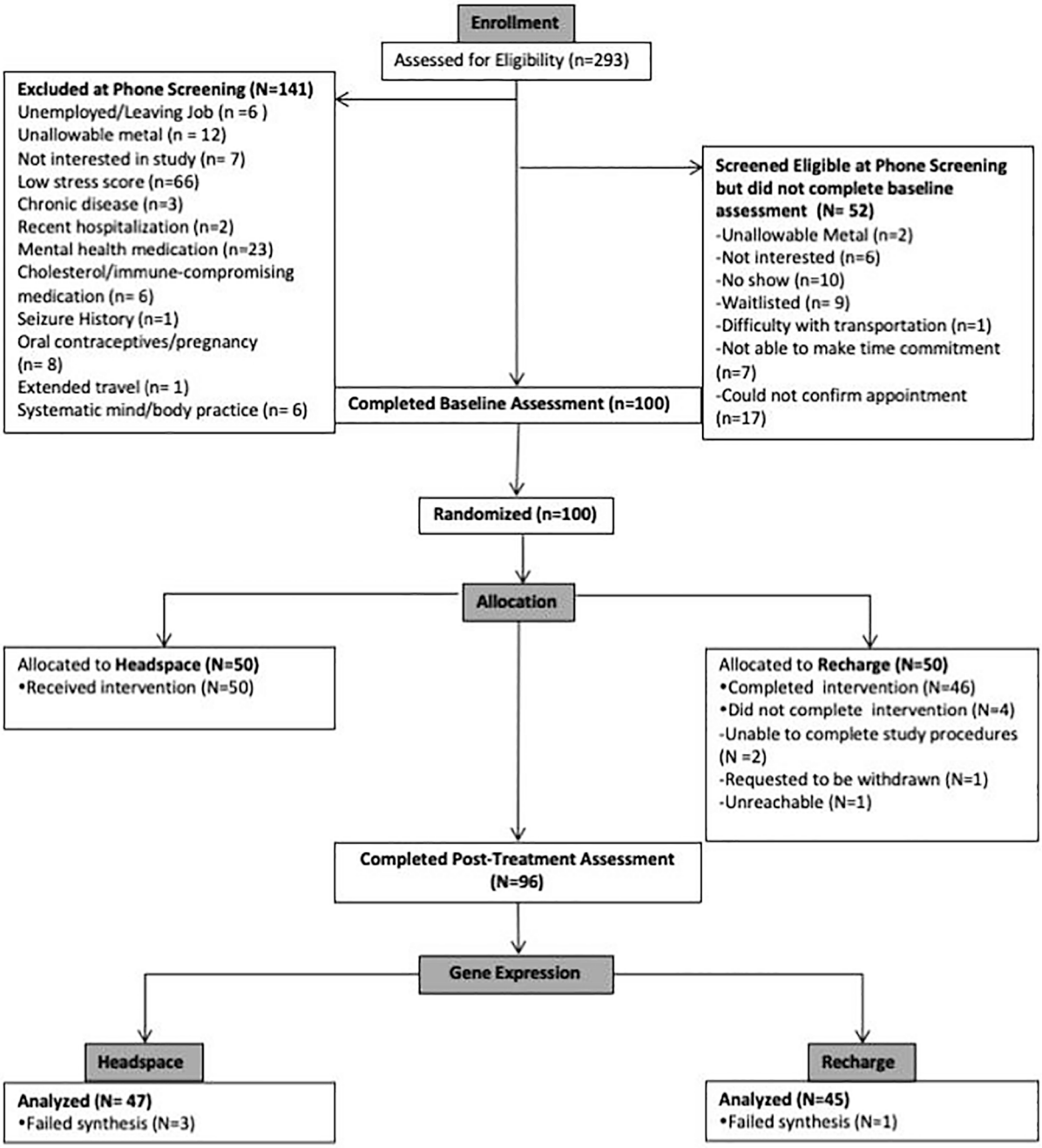

Fig. 1. Consort Flowchart.

smartphone-based interventions: *Headspace* mindfulness training program or *Recharge* control program. The first 10 days consisted of 10-minute daily sessions; the following 10 days increased to 15-minute daily sessions and concluded with 20-minute daily sessions for the final 10 days of the intervention. Participant compliance was monitored to ensure that participants completed one session each day. If participants did not complete a session, a research assistant would contact the participant via telephone, text, or email to remind them to complete one session each day in sequence.

2.2.2. Headspace meditation program

The mindfulness program consisted of the standard base program offered in *Headspace,* "Basics". The *Headspace* program content entailed daily audio sessions in guided mindfulness meditation involving instruction in attention and acceptance, awareness of breathing, and body scanning. The *Headspace* program was intended to increase daily practices in mindfulness meditation.

2.2.3. Recharge control program

The intervention control program was developed in collaboration with *Headspace* and a senior research scientist in the Health and Human Performance Lab at Carnegie Mellon University. Content of the intervention included problem solving strategies, self-reflection and planning, guided imagery, and analytic thinking. All interventions were matched on structure, length, attentional demand, expectancies, and were recorded by the same person as the Headspace content to match for voice.

2.2.4. Compliance monitoring

Regardless of condition, participants logged into the Headspace app

on their smartphones for each day's lesson. Based on a pre-assigned voucher code, Headspace sent a list of which lessons were completed each day. We instructed participants to complete their assigned lesson each day, but we considered a lesson complete if they finished the lesson within their 30-day intervention period. Compliance was then calculated as the number of the 30 lessons completed within the 30-day intervention period. When participants did not complete a lesson for two days in a row, a member of our study team would reach out to encourage the participant to complete the assigned lessons.

2.3. Self-Report

Participants completed self-reported measures at baseline and one week post-intervention. Participants also completed a 2-month follow-up on select self-report measures (not perceived stress) and daily diary assessments; results will be presented elsewhere.

2.3.1. Perceived stress

To assess participants perceptions of their stress levels, they were asked to complete the 10-item Perceived Stress Scale (Cohen et al., 1983) at baseline and post-intervention. Participants were asked to report on their feelings of stress over the last month ("In the last month, how often have you felt that you were unable to control the important things in your life?") on a 0 = Never to 4 = Very Often scale, with higher total scores indicating greater perceived stress. Internal reliability was good (Cronbach's $\alpha > 0.86$ at each timepoint). Analyses of change in perceived stress were conducted in two ways using SPSS 26.0 (IBM, Armonk, New York). First, linear mixed models were conducted. LMMs allow all available data to be used, reducing the impact to statistical power from missing data. Time was a repeated measure and modeled using compound symmetry covariance structure. The variables entered into the model (time, condition, and the interaction term) were modeled as fixed effects using restricted maximum likelihood estimation. We additionally explored the simple effect of time on levels of perceived stress within each condition using paired samples t-tests.

2.3.2. Treatment expectancies

To determine how participants viewed the intervention condition they were assigned to, we assessed participants' treatment expectancies at baseline by asking participants to rate how much they believed the stress reduction program they were assigned to would be helpful to them. Items were adapted from the Credibility and Expectancies Questionnaire (Devilly and Borkovec, 2000). Relevant questions included two questions assessing how much benefit they thought they would receive, and two questions assessing how much benefit they felt they would receive. See Supplementary Information for a list of the questions included on this questionnaire. Scores from those four items were averaged such that higher scores indicated greater belief that the program would help the individual reduce their stress.

2.4. Pro-inflammatory gene expression assessment

Gene expression data was assessed in 196 dried blood spots (DBS) collected from 100 study participants during baseline and post-intervention appointments. Research assistants cleaned participants' index finger with alcohol and punctured the middle finger with a disposable sterile lancet. Five drops of blood were collected onto Whatman 903 Protein Saver cards. The DBS samples were covered and left to dry overnight and then stored in a lab freezer at $-70\ ^{\circ}C$ for processing. Dried blood spot samples were shipped on dry ice to the UCLA Social Genomics Core Laboratory for genome-wide transcriptional profiling by RNA sequencing as previously described (Ross et al., 2019a; b). Briefly, total RNA was extracted (Qiagen RNeasy) and polyadenylated RNA was converted to cDNA (Lexogen QuantSeq 3′ FWD with low mass buffer) and sequenced on an Illumina NextSeq instrument (Lexogen Services, GmbH), all following the manufacturers' standard protocols for low-mass samples. Samples *were assayed in a single batch and* yielded an average of 4.6 million sequencing reads, each of which was mapped to the reference human transcriptome using the STAR aligner (95% average mapping rate) (Dobin et al., 2013). The total number of reads for each human gene was normalized to transcripts per million mapped reads, floored at 1 read per million to suppress spurious variability, and $\log_2$ transformed for analysis by linear statistical models as described below. DBS samples yield insufficient RNA for quantification of RNA integrity prior to assay (e.g., by Agilent Bioanalyzer RNA Integrity Number), so this study used standard endpoint quality control metrics for DBS that assess sample validity by testing for the expected cDNA yield (i.e., sufficient for >4 million sequencing reads), expected high rates of read alignment to the human genome sequence (>90%, which does not happen if samples are highly degraded), and a high correlation of gene expression values with the average expression level derived from all other samples (i.e., a correlogram internal consistency metric) (McDade et al., 2016; Ross et al., 2019b). Six samples failed cDNA synthesis *or endpoint quality control screening* and were omitted from subsequent analyses, leaving a total of 184 paired pre- and post-intervention RNA samples for analysis of change over time in 92 individuals. Mixed effect linear models were applied to estimate the magnitude of differential change over time (follow-up – baseline; repeated measure) as a function of study condition (*Headspace* intervention vs. *Recharge* control) either unconditionally (primary intent-to-treat analysis*,* with an analytic model specifying only Group, Time, and Group × Time interaction terms*)* or after additional control for covariates that can affect gene expression profiles, including age, sex, race/ethnicity, and BMI (secondary analysis), and additional control for blood sampling time or measured levels of mRNAs indicating prevalence of major leukocyte subsets (*CD3D, CD3E, CD4, CD8A, CD19, NCAM1/*CD56*, FCGR3A/*CD16*, CD14*), all as in previous research (Cole et al., 2020). Genes showing maximum likelihood point estimates of >50% differential change over time across conditions served as input into TELiS promoter-based bioinformatics analysis of transcription factor activity (Cole et al., 2005), which quantified the prevalence of transcription factor-binding motifs (TFBMs) for the a prori-specified pro-inflammatory transcription factor, NF-κB (assessed by the TRANSFAC position-specific weight matrix, V$NFKB_Q6_01), in core promoter sequences of each differentially expressed gene. To assess specificity, we also examined activity of the IRF family of transcription factors (assessed using the V$IRF_Q6 position-specific weight matrix). Point estimates of differential gene expression served as input for higher-order TELiS analyses because previous research has found this approach to yield more reliable results than gene lists based on p-values or False Discovery Rate q-values (Cole et al., 2003; Fredrickson et al., 2013; Shi et al., 2008; Witten and Tibshirani, 2007). Analyses were performed using 3 different TFBM detection stringencies (TRANSFAC mat_sim values 0.80, 0.90, and 0.95) each computed over 3 different definitions of core promoter scope (−300 bp, −600 bp, and −1000 to +200 bp relative to the RefSeq transcription start site) (Cole et al., 2005). Log_2-transformed TFBM prevalence ratios from the 9 parametric combinations were averaged and statistical significance of that average was derived from a standard error estimated by bootstrap resampling of participant-specific transcript abundance vectors (to account for correlation among genes) (Efron and Tibshirani, 1993).

3. Results

3.1. Baseline analyses

There were no baseline differences between randomized groups in age or gender; however, there were condition differences on race and education (see Table 1), with those randomized to the *Recharge* (control) condition more likely to be White and have completed college. 96% of randomized participants completed the study, but Participants in the *Recharge* condition were more likely to drop out of the study (see

Table 2
Adherence, treatment expectancies, and pre-intervention stress of randomized participants.

Characteristic	Full Sample (N = 100)	Headspace (N = 50)	Recharge (Control) (N = 50)	Condition Difference Statistic
Intervention Dropouts	4 (4%)	0 (0%)	4 (8%)	t(98) = 2.06*
Intervention Compliance (sessions)	0.97 (0.07)	0.97 (0.06)	0.97 (0.08)	$F(1,95) = 0.00$
Treatment Expectancies	5.33 (1.78)	5.35 (1.81)	5.32 (1.70)	$F(1,98) = 0.01$
Pre-Intervention Stress (PSS 4-item)	7.57 (2.10)	7.40 (2.10)	7.74 (2.10)	$F(1,99) = 2.89$
Post-Intervention Daily Diary Compliance	0.88 (0.12)	0.86 (0.14)	0.89 (0.11)	$F(1,95) = 0.90$

Note: Data are reported as means (SD) or numbers (%). Intervention Dropouts is reported as number of dropouts at the completion of the intervention period. * Indicates ps > 0.05.

Table 2). Participants in both *Headspace* and *Recharge* groups were adherent to the training programs (97% adherence) and daily diary assessment (88% compliance), with no condition differences in adherence. Additionally, there were no baseline condition differences on the 4-item perceived stress screening measure; all participants began the study with a high degree of perceived work stress (see Table 1). Finally, participants reported a moderate degree of expectancy that the stress reduction program would work ($M = 5.33$ out of 9), and there were no condition differences in treatment expectancy.

3.2. Intervention effects on Self-Reported perceived stress

In the *Headspace* condition, paired-sample t-tests showed a decrease in perceived stress from baseline ($M = 21.64$, $SD = 5.21$) to post-intervention ($M = 17.16$, $SD = 4.73$), $t(49) = 6.20$, $p < 0.001$, *Cohen's d = 0.877*. In the *Recharge* control condition, participants showed a similar decrease in perceived stress from baseline ($M = 18.96$, $SD = 5.71$) to post-intervention ($M = 13.41$, $SD = 6.20$), $t(45) = 5.86$, $p < 0.001$, *Cohen's d = 0.864*. However, mixed effects linear models did not demonstrate any significant differential change in perceived stress by condition, $F(1, 96.19) = 1.048$, $p = 0.308$, *Cohen's d = 0.183*.

3.3. Effects on Pro-inflammatory gene expression

Unconditional intention-to-treat mixed effect linear model analyses of peripheral blood mRNA samples analyses identified 1027 gene transcripts that differed by >50% between groups in the magnitude of change in average expression level from baseline to post-intervention follow-up (854 relatively down-regulated in the *Headspace* group and 173 relatively down-regulated in *Recharge* group; Dataset S1). Promoter-based bioinformatics analysis of these genes indicated reduced activity of the pro-inflammatory NF-κB transcription control pathway in *Headspace* intervention participants compared to *Recharge* controls (Fig. 2; 0.62-fold relative prevalence of NF-κB-binding motifs in promoters of genes up-regulated in *Headspace* relative to *Recharge*; −0.689 $\log_2$-motif ratio ± SE 0.241, $p = 0.0047$; Cohen's d = −0.298). Similar results emerged in conditional (covariate-adjusted) analyses controlling for demographic influences on gene expression (age, sex, race/ethnicity, and BMI; 0.66-fold; −0.602 ± 0.247, $p = 0.0155$; Cohen's d = −0.254) and additionally controlling for blood sampling time (0.60-fold; −0.728 ± 0.242, $p = 0.0030$; Cohen's d = −0.314) or mRNA indicators of major leukocyte subset prevalence (0.72-fold; −0.472 ± 0.206, $p = 0.0228$; Cohen's d = −0.239). By contrast, parallel analyses of the innate antiviral IRF transcription control pathway showed no significant differential change in *Headspace* intervention participants compared to *Recharge* controls in either unconditional (unadjusted) analyses (0.97-fold; −0.043 ± 0.202, p =.8330; Cohen's d = −0.022) or in analyses controlling for demographic factors (1.14-fold; 0.186 ± 0.176, p = 0.2919; Cohen's d = 0.110) and additionally controlling for blood sampling time (0.86-fold; −0.222 ± 0.140, p = 0.1140; Cohen's d = −0.165) or leukocyte subset prevalence (0.88-fold; −0.189 ± 0.181, p = 0.2954; Cohen's d = −0.109).

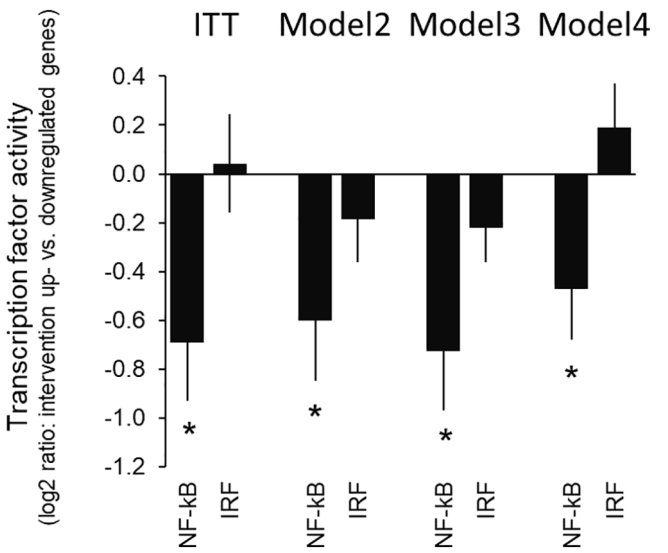

Fig. 2. Intervention effect on pro-inflammatory and antiviral gene expression.

4. Discussion

This study identified a significant reduction in pro-inflammatory *gene expression* in peripheral blood cells samples from a sample of highly stressed call center workers who were randomly assigned to 30 days of a digital mindfulness training intervention vs. a parallel control digital intervention. These results were independent of demographic characteristics and changes in the prevalence of major leukocyte subsets in circulating blood, and they were specific to the NF-κB pro-inflammatory signaling pathway, as no significant changes were observed in activity of the IRF transcription control pathway involved in Type I interferon responses. Interestingly, both intervention conditions led to reductions in perceived stress, but only the mindfulness training intervention led to reductions in inflammatory gene expression. This is the first RCT to examine the effects of smartphone app-based mindfulness training on immune cell gene expression. Results suggest that this more accessible mindfulness training delivery mode can impact stress biology in stressed workers, highlighting the potential translational benefit of digital mind–body training programs.

Previous research has linked mindfulness training and physical health, demonstrating improvements in stress-related diseases like irritable bowel syndrome, clinical colds, and posttraumatic stress disorder (Creswell et al., 2019). Plausible biological mechanisms include alterations in peripheral sympathetic nervous system and hypothalamic–pituitaryadrenal axis responses to stress. Indeed, work in the area of social stress effects on pro-inflammatory gene expression indicates that the sympathetic nervous system can up-regulate pro-inflammatory gene transcription and may contribute to inflammatory disease (Heidt et al., 2014; Powell et al., 2013). The present results demonstrate that a well-established stress-reduction intervention, mindfulness training, can exert the opposite effect, and may thus have health-enhancing benefits.

While most of the scientific literature has focused on group mindfulness programs, smartphone app-based mindfulness programs offer training benefits in a more flexible format (Lim et al., 2015; Lindsay

et al., 2018b; in press) making them especially accessible for vulnerable populations (low income, rural, stressed individuals). Demonstrating that an app-based mindfulness training program can down-regulated pro-inflammatory *gene expression* highlights the importance of future work on whether digital stress-reduction programs might have important physical health benefits. As stress levels rise (Cohen and Janicki-Deverts, 2012), identifying effective interventions that can impact a biological marker of stress-related disease risk has wide ranging implications for mitigating chronic health conditions.

Work stress might be a particularly interesting area of focus for stress reduction interventions. As the COVID-19 pandemic continued, significant attention was drawn to essential workers, working parents and other employees that might have significant work stress burdens. Work stress has been linked to risk of diabetes (Li et al., 2013) and negative associations with autonomic nervous system health (Jarczok et al., 2020), highlighting the impact that one's employment conditions can have on health. However, relatively little work has examined the impact of stress reduction programs on stressed employee's health. This is the first RCT to demonstrate that mindfulness training can alter biomarkers of physical health in stressed employees. Because the intervention focused on an accessible intervention format that could be deployed across an array of demographic groups, there are wide ranging implications for populations that have historically been unable to participate in stress reduction interventions due to time or financial constraints.

There are a few limitations in this study that underscore important future directions for work in this area. First, while our sample was diverse, screened for high stress burdens and had a high degree of compliance from participants, it is possible that the employees with the greatest stress levels did not enroll in the study. Thus, it will be important to continue work in this area with larger samples that recruit those with the highest stress burdens—those participants might struggle more with compliance or interest, and future work can determine if the benefits extend to those participants. Indeed, because the research team encouraged intervention compliance (and achieved 97% compliance), real-world conditions might make for more inconsistent engagement with the intervention content, yielding less successful outcomes. Second, because this study utilized dried blood spots for gene expression data collection, results do not include other biomarkers of immune health, including circulating pro-inflammatory cytokines. Thus, we can only assess intervention-related changes on one aspect of immune system biology (pro-inflammatory gene expression) in the present data. Third, this study was designed and powered to assess a pre-specified biological hypothesis regarding change in pro-inflammatory gene expression (NCT03803865). Stress reduction interventions may well impact other gene regulatory pathways besides the pro-inflammatory NF-κB system assessed here, and future studies using larger samples will be required to support well-powered exploratory/discovery analyses identifying additional pathways. Finally, it will be important for future research to engage in long-term follow-ups that investigate whether changing pro-inflammatory gene expression outcomes after an intervention has associated health improvements.

The present work is consistent with previous research suggesting that mindfulness training can down-regulate the pro-inflammatory NF-κB transcription control pathway (Creswell et al., 2012), but does so with an active control group in an RCT using a mobile phone-based intervention format. Furthermore, this reduction in pro-inflammatory *gene expression* emerged in a sample of highly diverse customer service employees with significant stress burdens, a population with known risk for poorer health outcomes (Eddy et al., 2017; Jarczok et al., 2020; Li et al., 2013). These results offer a potential mechanistic pathway by which mindfulness training could potentially help support health in stressed workers, and it will be important for future studies to further explore the long-term benefits associated with these changes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.04.003.

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