



## Reduced stress and inflammatory responsiveness in experienced meditators compared to a matched healthy control group



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### ABSTRACT

Psychological stress is a major contributor to symptom exacerbation across many chronic inflammatory conditions and can acutely provoke increases in inflammation in healthy individuals. With the rise in rates of inflammation-related medical conditions, evidence for behavioral approaches that reduce stress reactivity is of value. Here, we compare 31 experienced meditators, with an average of approximately 9000 lifetime hours of meditation practice (M age = 51 years) to an age- and sex-matched control group ( $n = 37$ ; M age = 48 years) on measures of stress- and inflammatory responsivity, and measures of psychological health. The Trier Social Stress Test (TSST) was used to induce psychological stress and a neurogenic inflammatory response was produced using topical application of capsaicin cream to forearm skin. Size of the capsaicin-induced flare response and increase in salivary cortisol and alpha amylase were used to quantify the magnitude of inflammatory and stress responses, respectively. Results show that experienced meditators have lower TSST-evoked cortisol ( $62.62 \pm 2.52$  vs.  $70.38 \pm 2.33$ ;  $p < .05$ ) and perceived stress ( $4.18 \pm .41$  vs.  $5.56 \pm .30$ ;  $p < .01$ ), as well as a smaller neurogenic inflammatory response ( $81.55 \pm 4.6$  vs.  $96.76 \pm 4.26$ ;  $p < .05$ ), compared to the control group. Moreover, experienced meditators reported higher levels of psychological factors associated with wellbeing and resilience. These results suggest that the long-term practice of meditation may reduce stress reactivity and could be of therapeutic benefit in chronic inflammatory conditions characterized by neurogenic inflammation.

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### 1. Introduction

Psychological stress is now widely accepted as an important trigger of inflammation and a major contributor to symptoms of chronic inflammatory disease (Pace et al., 2009; Rohleder, 2014; Steptoe et al., 2001; Weik et al., 2008). As such, the impact of behavioral interventions designed to reduce psychological stress, such as meditation training, on inflammatory outcomes has been a growing focus of interest and attention by the scientific community. The overwhelming majority of studies addressing this question have randomly assigned participants to relatively short interventions

(Bower and Irwin, 2015; Gu et al., 2015; Khoury et al., 2015). While this design is considered the gold-standard and has considerable merit, it also has some shortcomings when applied to behavioral interventions, that may be reflected in the mixed results reported in the literature (Black et al., 2015; Malarkey et al., 2013; Morgan et al., 2014; Rosenkranz et al., 2013). First, the ability of these interventions to reliably reduce stress may be highly variable across individuals and/or of small effect size in the early stages of training, perhaps becoming more stable and more easily detectable when the trained skills become more established. Second, the efficacy of any behavioral intervention is predicated upon an individual's engagement with the training and the persistence of practice, unlike in a pharmaceutical trial, where one can be fairly confident that every individual is receiving roughly the same dose. Outside of the laboratory, individuals choose pathways of change that they are most drawn to, or for which they have some aptitude. Choice is a

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strong predictor of adherence to and engagement in an intervention (Lindhiem et al., 2014; Rennie et al., 2007) and effect sizes have been shown to be higher when an intervention is individually initiated, rather than part of a volunteer effort (Brown et al., 2015). Thus, through random assignment, these studies may unintentionally reduce the effect size of the intervention. As a complement to the extant RCTs, the current study was designed to compare individuals with a long-standing and self-initiated practice of meditation to a carefully matched group of healthy, non-meditating community volunteers in stress- and inflammatory responsiveness.

Major advances have been made in the last decade in our understanding of the mechanisms that underlie the relationship between stress and inflammation. However, most of these advances have been focused on the impact of stress on brain-immune pathways that function systemically, whereas very little attention has been paid to pathways through which stress modulates inflammation locally. Though systemic elevations in inflammatory markers are not uncommon in individuals suffering from chronic inflammatory diseases, local inflammatory processes are often more sensitive indicators of disease onset and progression (Bamias et al., 2013; Lotti et al., 2014; Riol-Blanco et al., 2014; Schleich et al., 2014; Ugraş et al., 2011) and the two are not always highly correlated (Davel et al., 2012; Lima et al., 2015; Malinovschi et al., 2013; Schleich et al., 2014; Vernooij et al., 2002). For this reason, we chose capsaicin application to skin as our model to investigate stress responsiveness and local neurogenic inflammation in long-term meditators and community controls.

Capsaicin is a naturally occurring compound found in hot peppers that imparts their “hotness”. It causes depolarization of predominantly C-fiber type sensory neurons by binding to vanilloid receptors (sub-type 1; TRPV1), leading to a descending impulse or axon reflex. The axon reflex travels down branches of the same sensory nerve, causing neuropeptide release from nearby terminals. When these neuropeptides are released in the skin, they evoke a *neurogenic* inflammatory response, characterized by a “flare response” – the area of redness or *erythema* that extends beyond the area covered by capsaicin, which is caused by nerve-mediated vasodilation (Helme and McKernan, 1985; Holzer, 1988).

We hypothesized that long-term meditators (LTMs) would have a smaller physiological stress response to an acute laboratory stressor and a reduced flare response to capsaicin application. Further, we predicted that the reduction in stress response would account for a significant amount of variance in the size of the flare. Finally, we hypothesized that smaller stress hormone and flare responses would be associated with lower perceived stress and better mental and physical well-being.

## 2. Materials and methods

### 2.1. Participants

Our participants included 37 meditation-naïve participants (MNP; average age  $48.0 \pm 10.4$  years, 25 female) and 31 long-term meditators (LTM; average age  $50.7 \pm 10.1$  years, 17 female). The groups did not differ in socioeconomic status (SES) as measured by the Hollingshead Index of Social Position ( $t(66) = -.56, p = .58$ ) or by family income ( $t(66) = .47, p = .64$ ). Descriptive statistics can be found in Table 1. MNPs were recruited within Madison, WI and the surrounding community using flyers, online advertisements, and advertisements in local media. LTMs were recruited at meditation centers and through related mailing lists, in addition to flyers and advertisements in newspapers. For LTMs, inclusion criteria related to meditation practice included at least three years of vipassana and compassion/loving-kindness meditation, with daily practice of 30 min or more, as well as 3 or more intensive med-

itation retreats lasting 5 or more days. These practices reflect the progression of foundational skills taught in standard MBSR courses, and can thus be viewed in many ways as a long-term, and more in-depth extension of MBSR. Meditation experience criteria were chosen in consultation with meditation teachers and experts, to reflect the minimum experience with personal daily practice and intensive retreat experience, likely to sufficiently distinguish experienced meditators from novices. LTMs had an average of 9081 lifetime hours of meditation practice, ranging from 1439 to 32,612 total hours. Lifetime hours of practice was calculated based on self-reports of the average of their hours of formal (sitting and walking) meditation practice per week, including time spent on meditation retreats, and the total number of years of practice. Participants in either group were excluded if they had used medication for anxiety, depression, or other psychological issues, or had a psychiatric diagnosis in the past year. Participants were also excluded if they had any history of bipolar or schizophrenic disorders, brain damage or seizures.

The task described here was one among a larger set of tasks, including those performed during collection of functional magnetic resonance imaging (fMRI) data, administered during a 24-h lab visit. Sample sizes were constrained by logistical and practical considerations associated with neuroimaging studies. UW-Madison's Health Sciences Institutional Review Board approved the protocol, and all participants provided informed consent and were given monetary compensation for their participation.

### 2.2. Experimental manipulations

Psychological stress was induced using a modified version of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). The stress test consisted of a 5-min impromptu speech, followed by 5 min of mental arithmetic. These tasks were performed standing in front of a microphone before a panel of two (one male, one female) non-supportive and stern-looking judges and a video camera. For the speech task, participants were asked to convince the judges why they are the best candidate for their ideal job. They were given 3 min to prepare their speech after the topic was revealed, but were not allowed to use their notes during the speech. If participants did not speak for the entire 5 min period, they were told that there was time remaining to please continue. This version differs from the original only in that the speech preparation time is 7 min shorter. A local neurogenic inflammatory response was induced in forearm skin of all participants using .5 ml topical capsaicin cream (.1%), applied using a template to standardize coverage area. The capsaicin was applied immediately before participants were escorted to the room where they performed the TSST.

### 2.3. Biological measures

Levels of two salivary stress hormones, cortisol and alpha-amylase (AA), provided measures of the magnitude of the stress response to the TSST. These hormones were chosen as markers of activity in the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, respectively. Participants provided samples of saliva at baseline, before application of capsaicin cream, using salivettes. Subsequent saliva samples were collected immediately after the end of the TSST, as well as every 10 min for the next 40 min, for a total of 6 saliva samples. Salivary cortisol and AA levels were measured by Dr. Nicolas Rohleder at Brandeis University, using standard assay techniques. Cortisol was measured using a commercially available luminescence immunoassay (CLIA; IBL-Hamburg, Hamburg, Germany), and AA was measured using an enzyme-kinetic assay using reagents provided by Roche Diagnostics (Indianapolis, IN, USA) as previously described (Rohleder and Nater, 2009). Intra- and inter-assay coefficients of variation for cor-

**Table 1**  
Descriptive characteristics.

	LTM		MNP		Test statistic	p-Value
	Mean	Standard error	Mean	Standard error		
Age	50.73	1.81	48.05	1.71	−1.07	.29
SES (Hollingshead)	61.90	1.57	60.73	1.41	−.56	.58
SES (Family income)	11.97	.98	12.49	.60	.47	.64
Sex	17 male 14 female		25 male 12 female		1.16	.32
Race	28 White2 Asian1 Multiracial		34 White1 Multiracial2 not provided		4.08	.25
Baseline cortisol	6.32	.46	7.96	.79	1.70	.09
BaselineAlpha amylase	236.90	26.73	213.28	20.42	−.71	.48

tisol were 3.42% and 4.06% and for alpha-amylase were 5.64% and 3.63%.

The size of the capsaicin-induced flare response provided a measure of local neurogenic inflammation (Petersen et al., 1997). The neurogenic nature of the flare response has been demonstrated in studies where it was abolished or greatly attenuated by impairing nerve function (Bjerring and Arendt-Nielsen, 1990; Izumi and Karita, 1992). Digital photographs were taken immediately after the TSST and at subsequent 10-min intervals for 30 min to capture the development of the flare. Software developed in-house was used to detect the outside edge of the flare and calculate its area. Each digital trace was visually inspected for artifacts and errors and corrected when necessary. Differences in image scale were normalized by dividing the flare area by the area of a circular sticker placed on the arm, which was identical for every participant.

#### 2.4. Self-report measures

In addition to the biological measures, a number of questionnaire measures were collected to assess perceived cognitive, emotional, and health-related changes that may be expected as a result of a long-term meditation practice. These measures were also used to explore relations between perceived cognitive, emotional, and health-related function and the biological measures that are the main focus of this report. Questionnaire measures included: Positive and Negative Affect Scale (Watson et al., 1988), Big Five Inventory (BFI; John et al., 2008, 1991), Barratt Impulsivity Scale (BIS; Patton et al., 1995), Dweck Implicit Theory Form (Dweck, 2000), Five Factor Mindfulness Questionnaire (FFMQ; Baer et al., 2008), Interpersonal Reactivity Index (IRI; Davis, 1983), Marlowe–Crowne Social Desirability Scale (MCSD; Crowne and Marlowe, 1960), Medical Symptom Checklist (MSC; Travis, 1977), Ryff's Psychological Wellbeing Scales (PWB; Ryff, 1989), Social Connectedness Scale (SCS; Lee et al., 2001), and Satisfaction With Life Scale (SL; Diener et al., 1985). To assess the perceived stressfulness of the TSST, participants were asked to rate how stressful the experience was on a scale from 1 to 10, where 1 indicates “not stressful at all” and 10 indicates “the most stressful I can imagine”.

#### 2.5. Data analysis

Two computed variables were used to summarize data for both stress hormone responsiveness and inflammation: area under the curve and percentage of maximum increase. Area under the curve (AUC) with respect to ground was calculated as described in Pruessner et al. (2003). Cortisol and AA AUC values were then log-transformed to normalize their distribution. Flare AUC was normally distributed without transformation. Maximum increase in cortisol and AA were calculated by subtracting the baseline value from the highest post-TSST value and dividing by the baseline ((max value – baseline)/baseline) to obtain a percentage of maximum increase from baseline metric. The maximum, or peak, of

the flare response was simply the largest flare area, among the 4 photos.

Analysis of covariance (ANCOVA) was used, with age and sex as covariates, to test for group differences in stress hormone responsiveness. T-tests were used to identify group differences in inflammation and self-report variables. Hierarchical regressions were used to test for associations between stress hormone responsiveness variables and inflammation variables. In these models, inflammation (e.g. flare AUC) was the dependent variable. Age, sex, perceived stressfulness of the TSST, and group were entered on the first step and stress hormone responsivity (e.g. cortisol AUC) was entered on the second step. Hierarchical regressions were also used to test for associations between stress hormone and self-report variables, including reported meditation practice. In these models, self-report variables were the dependent variables, age and sex were entered on the first step and stress hormone variables (e.g. cortisol AUC) were entered on the second step. Finally, Pearson's correlations were used to test the relationship between self-report and inflammation measures. To ensure that the assumptions of our models were not violated, we inspected residual plots of our data for outliers and heteroscedasticity, Normal QQ plots to test normality, and we used Cook's D and leverage metrics to evaluate the presence of influential outliers in our regression and ANCOVA analyses. In addition, we estimated variance inflation factors to assess any possible collinearity in models with multiple regressors. All analyses were carried out using SPSS and R software.

### 3. Results

The outcome of analyses testing for group differences in biological variables showed a significant effect of group on both cortisol AUC ( $F(1, 59) = 5.03, p = .029$ ), after controlling for the effects of age and sex, and flare peak<sup>1</sup> ( $t(64) = 2.41, p = .019$ ), such that LTMs had a significantly smaller cortisol AUC and flare peak (Fig. 1). In addition, LTM's rating of the perceived stressfulness of the TSST was significantly lower than that of the MNP group ( $t(64) = 2.75, p = .008$ ). Significant group differences were not observed in the maximum increase in cortisol, flare AUC, alpha amylase AUC or the maximum increase in alpha amylase (see Table 2 for means and standard errors).

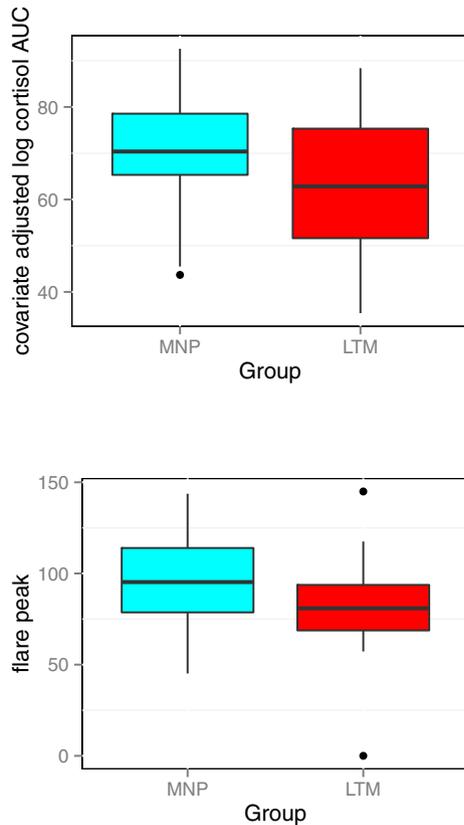
The *t*-tests revealed higher levels of self-reported openness (BFI;  $t(66) = -3.39, p = .001$ ) and mindfulness (total FFMQ;  $t(66) = -5.37, p < .001$ )<sup>2</sup> in LTMs compared to MNPs. In addition, LTMs scored significantly higher on the Dweck Implicit Theory Form relative to the MNP group ( $t(66) = -4.13, p < .001$ ), indicating greater endorsement by LTMs of the belief that people can change, in contrast to the belief that who a person is, is mostly fixed. There were no variables

<sup>1</sup> Age and sex were not included as covariates for flare variables because they were not significant in models where they were included. In the ANCOVA model with these covariates included, the effect for a group difference in peak flare was also significant ( $F(1, 62) = 4.52, p = .038$ ).

<sup>2</sup> All subscales of the FFMQ were significantly higher in LTMs compared to MNP.

**Table 2**  
Descriptive statistics for stress hormone and inflammation variables, reported for each group separately. Stress hormone means were adjusted for age and sex covariates.

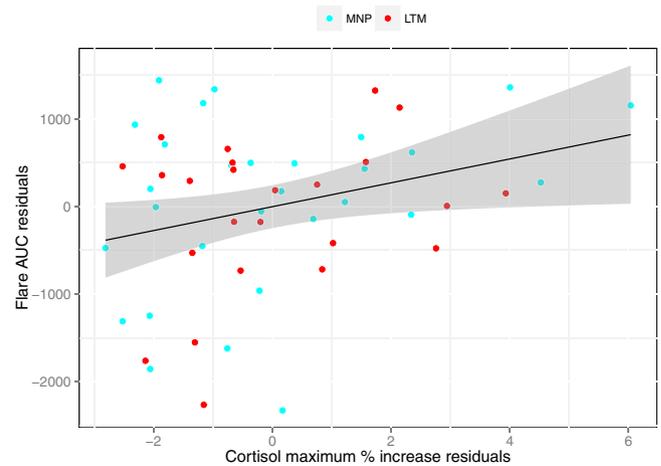
DV	LTM		MNP		Mean difference	95% CI	Cohen's d
	Mean	Standard error	Mean	Standard error			
Cortisol log AUC (covariate adjusted)	62.62	2.52	70.38	2.33	7.76	.84 to 14.68	.57
Cortisol percentage of maximum increase (covariate adjusted)	2.44	.42	2.69	.40	.24	−.92 to 1.41	.12
Alpha amylase log AUC (covariate adjusted)	151.18	3.16	149.33	2.91	1.85	−6.82 to 10.52	.11
Alpha amylase percentage of maximum increase (covariate adjusted)	.88	.22	1.02	.21	.14	−.47 to .74	.12
Flare AUC	2649.70	172.69	3103.65	192.21	453.95	−74.52 to 982.42	.43
Flare peak	81.55	4.60	96.76	4.26	15.21	2.61 to 27.8	.60
TSST stress rating (1–10 scale)	4.18	.41	5.56	.30	1.37	.38 to 2.37	.68



**Fig. 1.** Group difference in covariate (age & sex) adjusted mean log cortisol AUC (top;  $F(1, 59) = 5.03, p = .029$ ) and flare peak (bottom;  $t(64) = 2.41, p = .019$ ). Note that with removal of the one extreme low and one extreme high value in flare peak in the LTM group, the group difference remains significant ( $t(62) = 2.58, p = .012$ ).

on which the MNP group scored significantly higher than the LTM group. In total, 39 *t*-tests were conducted on self-report composite scales and their subscales. Therefore, after correcting for multiple comparisons,  $p < .0013$  is necessary to reach statistical significance for these tests. Several additional self-report indices showed a group difference at an uncorrected  $p < .05$ , including greater social connectedness reported by the LTM group ( $t(66) = -2.36, p < .05$ ). For a complete picture of the self-report data, results for all 39 tests can be found in Supplementary information Table 1.

The outcome of regression analyses, that tested relationships between stress hormone and inflammatory responses, showed that the maximum increase in cortisol in response to the TSST accounted for a significant portion of unique variance in flare AUC ( $\beta = .28, sr = .26, p = .039$ ), above and beyond that attributed to age, sex, perceived stress rating, and group indicating that a higher increase in cortisol is associated with a larger flare response (Fig. 2). Analogous models, where maximum increase in cortisol is replaced with AUC or flare AUC is replaced with flare peak, yield consistent results, though not statistically significant (see Table 3). Neither alpha amy-



**Fig. 2.** Residual variance in maximum percent increase in cortisol (*x*-axis) and flare AUC response (*y*-axis) with variance accounted for by age, sex, perceived stressfulness of TSST, and group removed ( $\beta = .28, sr = .26, p = .039$ ). Red = LTM, blue = MNP. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lase AUC nor maximum increase accounted for a significant portion of unique variance in either flare variable, above and beyond that accounted for by age, sex, and perceived stress. Number of hours of meditation practice was not related to stress hormone or inflammatory responses.

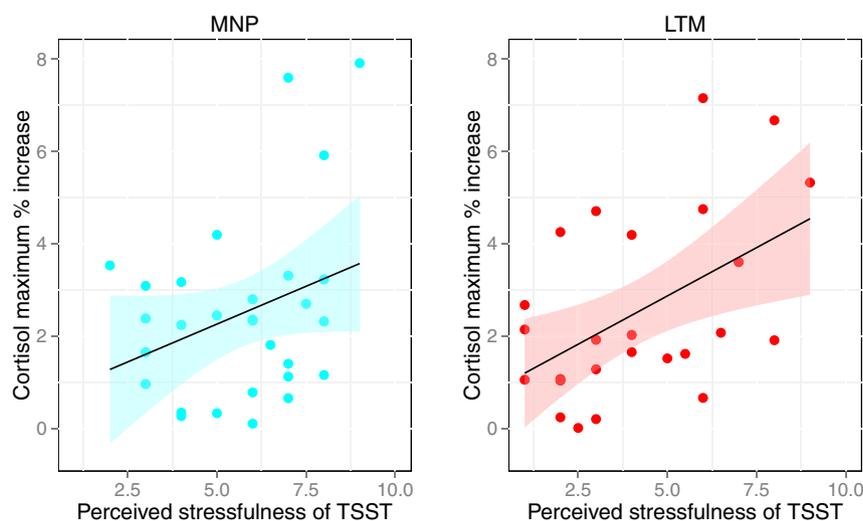
The outcome of regression analyses that tested relationships between cortisol variables and self-report measures, after accounting for variance attributed to age and sex, showed that cortisol response to the TSST was associated with positive and negative affect, personality factors, and aspects of mindfulness. Specifically, maximum increase in cortisol in response to the TSST showed a positive relationship with PANAS negative affect ( $t = 2.72, p = .009, sr = .36$ ), whereas cortisol AUC showed negative relationships with PANAS positive affect ( $t = -2.13, p = .038, sr = -.26$ ), the extraversion scale of the BFI ( $t = -2.06, p = .044, sr = -.26$ ), and the describe ( $t = -2.03, p = .047, sr = -.26$ ) and observe ( $t = -2.08, p = .042, sr = -.26$ ) scales of the FFMQ. However, after correcting for multiple comparisons, none of these relationships remain significant. These analyses were not performed for the alpha amylase response to the TSST, since group differences in alpha amylase variables were not observed.

Pearson's correlation revealed a positive relationship across groups between perceived stressfulness of the TSST and maximum cortisol response to the TSST ( $r = .36, p = .007$ ), though this relationship was driven more by the LTM group (LTM:  $r = .50, p = .009$ ; MNP:  $r = .24, p = .21$ ; Fig. 3). The difference in this correlation between groups was not significant. An analogous relationship was not observed with cortisol AUC ( $r = -.3, p > .1$ ) or with either alpha amylase variable (log AUC:  $r = -.04, p > .1$ ; maximum increase:  $r = -.04, p > .1$ ).

**Table 3**

Regression coefficients, semi-partial correlation coefficients, *p*-values, and 95% confidence interval for regression coefficients for each regression model. Age, sex, group, and perceived stressfulness of the TSST were additional IVs included in each model.

DV	IV	Coefficient	sr <sup>2</sup>	<i>p</i> -Value	95% CI for B
Cortisol percentage of maximum increase	Flare peak	2.42	.18	.14	−.82 to 5.65
Cortisol log AUC	Flare peak	.27	.13	.26	−.20 to .73
Cortisol percentage of maximum increase	Flare AUC	136.42	.26	.039*	7.48 to 265.35
Cortisol log AUC	Flare AUC	12.40	.15	.21	−7.15 to 31.95
Amylase percentage of maximum increase	Flare peak	.73	.03	.78	−4.55 to 6.01
Amylase log AUC	Flare peak	.16	.1	.40	−.22 to .54
Amylase percentage of maximum increase	Flare AUC	16.36	.02	.88	−204.19 to 236.90
Amylase log AUC	Flare AUC	5.18	.08	.52	−10.97 to 21.33



**Fig. 3.** Correlation between maximum percent increase in cortisol and perceived stressfulness of TSST in LTM (right) and MNPs (left). This relationship is significant across groups ( $r = .36$ ,  $p = .007$ ) and for the LTM group alone ( $r = .50$ ,  $p = .009$ ), but not for the MNP group alone ( $r = .24$ ,  $p = .21$ ). The difference in the correlation between groups is not significant.

#### 4. Discussion

Our results suggest that individuals with a long-term meditation practice experienced less stress in response to the TSST, as indicated by both self-report and salivary cortisol measures, compared to a control group with no meditation experience. Moreover, though the difference between the correlations was not statistically significant, the perception of stress in response to the TSST more closely reflected the HPA-axis response in long-term meditators, suggesting that this group may have better accuracy in perceiving their internal state or less emotional elaboration of physiological cues. The LTM group also had a smaller inflammatory response to capsaicin. Importantly, the magnitude of inflammatory response to capsaicin was positively associated with the magnitude of the cortisol response, which supports previous evidence that psychological stress potentiates the neurogenic inflammatory response (Arck et al., 2003; Joachim et al., 2007; Kimata, 2003; Liu et al., 2013; Pavlovic et al., 2008; Peters et al., 2014, 2004; Singh et al., 1999). These observations confirm and extend our previous findings, which showed that individuals randomized to an 8-week MBSR intervention had smaller capsaicin-induced flare responses post-training, relative to individuals randomized to a validated active control condition (MacCoon et al., 2012; Rosenkranz et al., 2012). Together with our previous findings, these data suggest that meditation practice may be an effective buffer for the effects of stress on local neurogenic inflammation.

In our previous work, we speculated that the mechanism underlying the reduced inflammatory response in those who participated in MBSR training was related to a reduction in sympathetic nervous system responsiveness to stress. This speculation is not supported

by our current data, since alpha amylase (a salivary marker for sympathetic activity) response to the TSST is unrelated to the size of the flare response. An alternative mechanism that could underlie this effect involves modulation of sensory neuropeptide expression (Rosenkranz, 2007). Though primarily associated with communicating sensory information to the CNS, non-adrenergic, non-cholinergic nerve fibers (NANC; Forsythe, 2015; Kraneveld et al., 2000), also release inflammation-promoting sensory neuropeptides into the tissues they innervate, via an axon reflex (Koivisto et al., 2014), and are an important mediator of local immune regulation. Plasticity at the level of the peripheral and central ganglia (Koivisto et al., 2014; Rivat et al., 2010), brainstem nuclei, and possibly higher subcortical (e.g. amygdala) and cortical (e.g. insula) regions all contribute to the strength of the descending axon reflex, as well as to systemic descending responses (reviewed in Rosenkranz, 2007).

While our data cannot clarify the precise mechanism through which the reduction in the capsaicin-induced flare response in the LTM group was achieved, existing data on the effects of stress on neural expression of substance P (SP) provide some clues. Capsaicin exposure evokes the release of SP from sensory nerve endings, through the mechanisms described above. In rodent models, psychological stress, via the actions of nerve growth factor, increases expression of SP and calcitonin-gene related peptide (CGRP) in both skin-innervating dorsal root ganglia (DRG) neurons, as well as nerve fibers in the skin (Arck et al., 2003; Joachim et al., 2007; Pavlovic et al., 2008; Peters et al., 2004). Moreover, psychological stress has been shown to cause CRH-dependent skin mast cell degranulation (Singh et al., 1999; Theoharides et al., 1998), which synergizes with the effects of SP and CGRP to potentiate the inflammatory

response (Marshall and Waserman, 1995). Given the diminished stress response shown by the LTMs, the smaller flare response in this group may be a combined result of decreased CRH release and down-regulation (or lack of up-regulation) of DRG and skin expression of SP and CGRP.

The mechanisms through which practice of meditation may reduce stress responsivity remains an outstanding question. Previous research suggests that meditation practice is associated with greater grey matter volume in the hippocampus/extended amygdala complex (Hölzel et al., 2011; Kurth et al., 2015; Luders, 2009; Luders et al., 2015, 2013)—a region known to play important roles in regulating the cortisol response to stress. Indeed, chronic exposure to psychological stressors is associated with the opposite effect, a reduction in grey matter volume in this area (Hanson et al., 2014, 2011; Luby et al., 2013; Lui et al., 2013). Further, evidence of increased engagement of neural circuits important in regulating emotion has been demonstrated in both experienced meditators (Taylor et al., 2011) and in novice meditators following training (Allen et al., 2012; Goldin and Gross, 2010; Taylor et al., 2011). In our data, we observed a higher concordance between perceived stress and cortisol response to the TSST in the LTM group, which may lead to more effective recruitment of emotion regulatory circuits. Therefore, we can speculate that the reduced cortisol response to the TSST observed in the experienced meditators may be due, at least in part, to better structural integrity of brain regions that regulate HPA-axis activity, and perhaps improved ability to regulate emotion in the context of the social stressor.

Though few of the results of analyses performed on self-report data remained significant after correcting for multiple comparisons, the pattern of results generally corroborates our physiological data, suggesting that a long-term meditation practice may be associated with psychological factors known to contribute to resilience and greater wellbeing, such as the belief that a person can change (Tamir et al., 2007; Yeager et al., 2014). Indeed, several of these factors, e.g. greater positive and less negative affect, were also associated with a smaller cortisol response to stress.

There are a few noteworthy limitations to these data. First, as this was not a prospective study, individuals were not randomly assigned to practice meditation. Therefore, it is possible that there is something fundamentally different about those who initiate and persist at meditation training. For example, it is possible that long-term meditators have an innate increased capacity for critical self-reflection and the discomfort or distress that can accompany such mental processes, which could underlie the reduced cortisol response to the TSST, independent from any direct effects of meditation practice. Relatedly, the reduced stress and inflammatory responsiveness may be attributable to the accouterments of meditation practice, such as being embedded in a community or sangha that provides social support and with which one shares common values, rather than to the practice itself. Indeed, we did observe a group difference in self-reported social connectedness with LTMs reporting higher connectedness than MNPs, though this result did not remain significant after correcting for multiple comparisons. Both perceived and objective measures of loneliness are potent risk factors for early mortality, comparable with that of obesity or substance abuse (Holt-Lunstad et al., 2015), and increased basal HPA-axis activity has been associated with chronic social isolation (Cacioppo et al., 2015). In this case, similar results would be expected from membership in any comparable social group. This is an intriguing possibility that warrants future inquiry. An alternative possibility is that the LTMs have greater resources, which allow them more time to spend in leisure activities (including meditation), and this is the underlying cause of their reduced stress and inflammatory responsiveness. Though this is a credible possibility, it does not appear to be the case in our data, as there were no group differences in socioeconomic status.

Despite these limitations, the data presented here support the claim that a long-standing practice of meditation can promote both physical and psychological wellbeing. The neurogenic inflammatory response employed in the paradigm presented here is relevant to the disease mechanisms that underlie chronic inflammatory diseases in the skin, including atopic dermatitis, alopecia, and psoriasis, but also to chronic inflammatory diseases in other tissues such as asthma, irritable bowel syndrome (IBS), and rheumatoid arthritis (RA). In the skin, inflammatory neuropeptide-containing nerve fiber density is increased in patches with psoriasis (Al'Abadie et al., 1995) or atopic dermatitis (Pincelli and Steinhoff, 2013) lesions, relative to healthy areas of skin. In addition, there is increased contact between mast cells and sensory nerve endings. Mast cells are activated by the neuropeptides released by these nerve endings in lesioned skin and this interaction is thought to be an important mechanism in perpetuating the neurogenic inflammatory response (Järvikallio et al., 2003). A similar relationship between NANC nerves and cells of the innate immune system seems to be involved in the aspects of the pathogenesis of asthma (Kraneveld et al., 2000). Importantly, psychological stress has been shown to upregulate the expression of sensory neuropeptides and to decrease the response threshold of neurons in peripheral ganglia to propagate the axon reflex (Hermann et al., 2005; Joachim et al., 2007; Rivat et al., 2010). Thus, during psychological stress, a less intense sensory stimulus can evoke a more intense axon reflex and elicit the release of greater quantities of sensory neuropeptides, leading to a larger neurogenic inflammatory response. This effect likely contributes substantively to the exacerbating effects of stress on symptoms of chronic inflammatory diseases (Black, 2002).

Our data may help to identify individuals whose symptoms are most likely to benefit from training in mindfulness. Indeed, training in meditation as a therapeutic intervention has been investigated in individuals with psoriasis (Kabat-Zinn et al., 1998), IBS (Berrill et al., 2014; Ljótsson et al., 2011; Zernicke et al., 2013) and RA (Pradhan et al., 2007; Zautra et al., 2008) with mixed results. All of these studies report some benefit of mindfulness training, primarily in mood, distress, and quality of life. Zautra and colleagues randomized individuals with RA to receive cognitive behavioral therapy (CBT), mindfulness and emotion regulation training, or education only (Zautra et al., 2008). While those randomized to CBT benefited more in terms of self-reported pain control and *in vitro* stimulated peripheral blood mononuclear cell production of IL-6, those randomized to mindfulness and emotion regulation training, who had a history of depression, benefited most in terms of physician-rated joint tenderness and swelling, and mood. On the other hand, Pradhan et al. reported improvement in distress and psychological wellbeing, in a sample of RA patients, but no effect of meditation training on RA disease activity (Pradhan et al., 2007). Unfortunately, these studies are in the distinct minority in measuring objective and clinically relevant measures of inflammation and disease activity. The majority of studies examining the benefit of mindfulness training in samples with chronic inflammatory disease rely on self-reported outcome measures. While subjective perception of pain and wellbeing are inarguably valuable outcomes not to be undermined, they tell us little about the direct impact of mindfulness training on the physiological mechanisms that underlie disease progress and these measures may be confounded by demand characteristics. Moreover, of the studies that do include physiological measures, almost none include local measures of inflammation from the affected tissue. Such measures, like the one presented here, point to possible underlying biological mechanisms of the benefits of meditation and may provide a more sensitive and clinically meaningful assessment of the efficacy of wellbeing-promoting practices like mindfulness training.

## Conflict of interest

Dr. Richard J. Davidson serves on the board of directors for the following non-profit organizations: The Mind and Life Institute and the Center for Investigating Healthy Minds, Inc.

## Contributors

MAR conceived of and designed the study, analyzed the data, and wrote the manuscript.

AL contributed to the conception and design of the study, interpretation of data, and revision of the manuscript.

DMP contributed to analysis of the data and revision of the manuscript.

DRWB contributed to data acquisition and revision of the manuscript.

BSS contributed to analysis of the data and preparation and revision of the manuscript.

DGM contributed to conception and design of the study.

RJD contributed to conception and design of the study, interpretation of data, and revision of the manuscript.

All authors have approved the final article.

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## 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.2016.02.013>.

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