



## A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation

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### ABSTRACT

Psychological stress is a major provocative factor of symptoms in chronic inflammatory conditions. In recent years, interest in addressing stress reactivity through meditation training in health-related domains has increased astoundingly, despite a paucity of evidence that reported benefits are specific to meditation practice. We designed the present study to rigorously compare an 8-week Mindfulness-Based Stress Reduction (MBSR) intervention to a well-matched active control intervention, the Health Enhancement Program (HEP) in ability to reduce psychological stress and experimentally-induced inflammation. The Trier Social Stress Test (TSST) was used to induce psychological stress and inflammation was produced using topical application of capsaicin cream to forearm skin. Immune and endocrine measures of inflammation and stress were collected both before and after MBSR training. Results show those randomized to MBSR and HEP training had comparable post-training stress-evoked cortisol responses, as well as equivalent reductions in self-reported psychological distress and physical symptoms. However, MBSR training resulted in a significantly smaller post-stress inflammatory response compared to HEP, despite equivalent levels of stress hormones. These results suggest behavioral interventions designed to reduce emotional reactivity may be of therapeutic benefit in chronic inflammatory conditions. Moreover, mindfulness practice, in particular, may be more efficacious in symptom relief than the well-being promoting activities cultivated in the HEP program.

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### 1. Introduction

Psychological stress is a potent trigger of inflammation (Welk et al., 2008; Steptoe et al., 2007; Pace et al., 2009) and as such, individuals suffering from chronic inflammatory conditions frequently turn to stress reduction methods in search of relief. Recent statistics from the National Center for Complementary and Alternative Medicine (Barnes et al., 2007) show that conditions associated with inflammatory processes motivate nearly 40% of the use of complementary and alternative medicine (CAM) services. Among those using CAM services, most are pursuing approaches such as meditation, biofeedback, and relaxation, which influence the body via the brain.

The ability of the brain to modulate the immune system is essential in anticipating and coordinating an effective immune response. Neural regulation of immune function, particularly inflammation, in

barrier tissues is especially important. Barrier tissues are tissues that interface between the external and internal environments, such as the skin and the gastrointestinal, respiratory, and urogenital tracts. These tissues are the first line of defense against invading pathogens and the inflammatory response is one of the primary means of resisting infection once a pathogen has circumvented the physical barrier (Kupper and Fuhlbrigge, 2004; Cua and Tato, 2010). Therefore, it is not surprising that barrier tissues are highly susceptible to stress- and emotion-related inflammation, since through the lens of evolution, it would seem that stress is an indicator of threat and the increased likelihood for bodily injury and pathogenic exposure (Kupper and Fuhlbrigge, 2004; Cua and Tato, 2010; Hart and Kamm, 2002; Arck et al., 2006; Liu et al., 2002).

The skin offers an appealing laboratory in which to examine stress modulation of barrier tissue inflammation. It has a surface area of approximately 1.5–2 m<sup>2</sup> in the average adult, rivaled only by the intestines and lungs in exposed surface area (Bender and Bender, 1995). Exposed surface area is vulnerable to pathogenic damage, and therefore requires close monitoring by the brain.

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Indeed, the skin has, on average, more than 500 nerve endings per square inch (McArthur et al., 1998), allowing for its rapid communication with the central nervous system (CNS) and intimate neural regulation.

Though advantageous in some regards, a high degree of neural input may also increase the vulnerability of the skin to inflammatory dysregulation. During psychological stress, inflammatory neuropeptides (e.g. substance P (SP) and calcitonin gene-related peptide (CGRP)) are released from the terminals of sensory nerves (Pavlovic et al., 2008; Peters et al., 2004). These neuropeptides act on the local immune cells and vasculature, in concert with norepinephrine released from local sympathetic nerves (Saint-Mezard et al., 2003; Banik et al., 2001; Drummond, 1995; Lin et al., 2003), to evoke an inflammatory response that is referred to as *neurogenic*. Indeed, stress-evoked immune changes that contribute to symptom onset and exacerbation have been documented in several inflammatory skin diseases (reviewed in Buske-Kirschbaum and Hellhammer, 2003; Wright et al., 2005) including psoriasis (Buske-Kirschbaum et al., 2007), atopic dermatitis (Buske-Kirschbaum et al., 2002), eczema (Bockelbrink et al., 2006), alopecia (Kim et al., 2006) and urticaria (Barrino et al., 2006). As such, the role of cutaneous nerves in stress-related inflammation has become a bigger research focus (Arck et al., 2006; Arck and Paus, 2006; Kleyn et al., 2008; Pavlovic et al., 2008; Peters et al., 2006; Scholzen et al., 1998). From this growing body of work, capsaicin-sensitive sensory nerves and the neuropeptides they contain, together with local sympathetic nerves and mast cells, have been identified as important contributors to the relationship between psychological stress and symptom expression in inflammatory skin diseases. Indeed, in a recent study, Pavlovic et al., (2008) show that stress-evoked symptom exacerbation in dermatitis was dependent upon the activation of sensory neuropeptide receptors. Therefore, in the present study, a capsaicin-induced inflammatory response and an acute laboratory stressor were used as a model in which to investigate psychological stress and neurogenic inflammation in the skin.

Acute laboratory stressors that incorporate uncontrollability and social-evaluative threat have been reliably shown to evoke increases in measures of physiological stress and peripheral inflammation (Dickerson and Kemeny, 2004; Dickerson et al., 2009; Gruenewald et al., 2004; Kirschbaum et al., 1993; Pace et al., 2009; Rohleder et al., 2006). As these features characterize some of the most commonly experienced daily stressors (e.g. work-related, financial, travel-related, social/peer pressure), laboratory manipulations, such as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), that incorporate uncontrollability and social-evaluative threat are good choices to model the types of real-world stressors that contribute to symptom exacerbation in those with chronic inflammation. For this reason, we used the TSST to evoke acute psychological stress in this study.

Interest in meditation as a method to reduce psychological stress has grown substantially in the last several years (Barnes et al., 2007; Kabat-Zinn et al., 1998; Carlson et al., 2004; Pace et al., 2009; Kemeny et al., 2011). Despite the rapid increases in usage and spending on these therapeutic techniques, relatively little is known about the mechanisms or specificity of their efficacy. Mindfulness-based stress reduction (MBSR) is the dominant form of meditation training in healthcare settings in the United States (for a recent review see Chambers et al., 2009). Mindfulness was initially defined, in the context of MBSR, as “paying attention in a particular way: on purpose, in the present moment, and non-judgmentally” (Kabat-Zinn, 1990). More specific, operational definitions of mindfulness practice have since been proposed (e.g. Bishop et al., 2004; Chambers et al., 2009) and continue to be developed (Kabat-Zinn, 2011; Grossman and Van Dam, 2011). In brief, mindfulness practice cultivates an open, and accepting awareness of whatever is occurring in the present moment,

without reacting or being absorbed in the contents of the experience (Chambers et al., 2009; Kabat-Zinn, 2011). Thus, the aim of this training is not to explicitly change the content of experience, but rather to change one’s relationship to it.

Since its inception in 1979, MBSR has shown benefit in alleviating symptoms of a broad array of conditions from anxiety disorders to diabetes (Gregg et al., 2007; Ma and Teasdale, 2004; Grossman et al., 2007; Pradhan et al., 2007; Speca et al., 2000; Kabat-Zinn et al., 1998). However, across the rapidly growing number of published empirical reports describing the use of MBSR as an intervention, there is little evidence for its efficacy relative to other treatments or for mindfulness practice *per se* as a specific mechanism for change. The vast majority of studies have evaluated the effectiveness of MBSR based on pre to post-training changes and wait-list or no treatment comparison groups. While these studies certainly establish that MBSR is effective across a wide range of populations and conditions and, when added to standard treatment, can improve some health outcomes, they are not designed to test whether MBSR is superior to other treatments or whether mindfulness, itself, is the active ingredient leading to these positive outcomes (for further discussion see MacCoon et al., 2012).

Therefore, this experiment was designed to investigate the ability of mindfulness training to buffer the effects of psychological stress and dermal neurogenic inflammation in healthy individuals. It is important to note this experiment was not designed to test the impact of an acute laboratory stressor on the inflammatory response or vice versa. However, these effects have been well-documented elsewhere (e.g. Brydon et al., 2009; Pace et al., 2009; Rohleder et al., 2006; Pavlovic et al., 2008; Carroll et al., 2011). In order to address questions of specificity of the benefits of mindfulness training, we compared MBSR to an active comparison condition, designed to carefully match MBSR in non-specific factors that promote wellbeing. We predicted that, in measures of neurogenic inflammation and physiological stress, those randomized to MBSR training would show a less robust post-training stress and inflammatory response, relative to pre-training responses and relative to those randomized to the active comparison condition. Furthermore, we predicted that time spent practicing MBSR, but not HEP, should predict the relative reductions in these measures. Laboratory assessments included the induction of experimental inflammation and psychological stress, as well as the collection of biological measures for quantification of stress and inflammation and the collection of standard self-report measures (see MacCoon et al., 2012). Laboratory assessments were performed within 4 weeks before the start of training (T1) and within 4 weeks after completion of training (T2). All measures were collected again at 4 months after completion of training (T3).

## 2. Methods

### 2.1. Participants

Participants included 49 community volunteers (10 male) between the ages of 19 and 59 ( $M = 45.89$  years,  $SD = 10.92$ ), recruited through advertisements in local newspapers. The groups did not differ with respect to age ( $t(47) = 1.47$ ,  $p > .1$ ; HEP:  $M = 48.9$  years, MBSR:  $M = 44.4$  years). All participants were screened and criteria for exclusion included: significant previous experience with meditation or other mind-body techniques (e.g. tai-chi, Qigong), remarkable exercise habits (engagement in moderate sport or recreational activities  $>5\times$  per week; engagement in vigorous sport or recreational activities  $>4\times$  per week; inability to walk), use of psychotropic or steroid drugs, night-shift work, diabetes, peripheral vascular disease or other diseases affecting circulation (e.g. Raynaud’s disease), needle phobia, pregnancy,

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