Neuroscience and Biobehavioral Reviews 73 (2017) 165–181

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

The embodied mind: A review on functional genomic and neurological correlates of mind-body therapies

David Muehsam[a,f,*], Susan Lutgendorf[b], Paul J. Mills[c], Badri Rickhi[d], Gaétan Chevalier[e], Namuun Bat[f], Deepak Chopra[c,g], Blake Gurfein[h]

[a] National Institute of Biostructures and Biosystems, Italy
[b] Departments of Psychological and Brain Sciences, Urology, and Obstetrics and Gynecology, University of Iowa, Iowa City, IA, USA
[c] Department of Family Medicine and Public Health, University of California, San Diego, CA, USA
[d] Department of Medicine, University of Calgary, Alberta, Canada
[e] Earthing Institute, Psy-Tek Laboratory, Encinitas, CA, USA
[f] Consciousness and Healing Initiative, La Jolla, CA, USA
[g] The Chopra Foundation, Carlsbad, CA, USA
[h] Osher Center for Integrative Medicine, University of California San Francisco, CA, USA

ARTICLE INFO

Article history:
Received 30 May 2016
Received in revised form 14 September 2016
Accepted 20 December 2016

Keywords:
Mind body therapy
Meditation
Mindfulness
Mbsr
Yoga
Mental practice
Functional genomics
Gene expression
Psychosocial genomics
Inflammation
Glucocorticoid
Neuroimaging
Structural neuroimaging
Morphometric neuroimaging
Voxel based morphometry
Diffusion tensor imaging
Gray matter concentration

ABSTRACT

A broad range of mind-body therapies (MBTs) are used by the public today, and a growing body of clinical and basic sciences research has resulted in evidence-based integration of many MBTs into clinical practice. Basic sciences research has identified some of the physiological correlates of MBT practices, leading to a better understanding of the processes by which emotional, cognitive and psychosocial factors can influence health outcomes and well-being. In particular, results from functional genomics and neuroimaging describe some of the processes involved in the mind-body connection and how these can influence health outcomes. Functional genomic and neurophysiological correlates of MBTs are reviewed, detailing studies showing changes in sympathetic nervous system activation of gene transcription factors involved in immune function and inflammation, electroencephalographic and neuroimaging studies on MBT practices, and persistent changes in neural function and morphology associated with these practices. While the broad diversity of study designs and MBTs studied presents a patchwork of results requiring further validation through replication and longitudinal studies, clear themes emerge for MBTs as immunomodulatory, with effects on leukocyte transcription and function related to inflammatory and innate immune responses, and neuromodulatory, with effects on brain function and morphology relevant for attention, learning, and emotion regulation. By detailing the potential mechanisms of action by which MBTs may influence health outcomes, the data generated by these studies have contributed significantly towards a better understanding of the biological mechanisms underlying MBTs.

Contents

* Correspondence to: 2 East 75 St Apt 5A, New York, NY 10021, USA.
E-mail address: davmumu@yahoo.com (D. Muehsam).

http://dx.doi.org/10.1016/j.neubiorev.2016.12.027
0149-7634/

1. Introduction—physiological correlates of mind-Body therapies

The scope of mind-body therapies (MBTs) used by the public today is broad, and generally includes meditation, yoga, guided imagery, breathing exercises, progressive relaxation, Tai Chi Chuan, etc. (National Institutes of Health, 2007). Over the past several decades, substantial evidence has emerged that MBTs can enhance health outcomes, act as effective adjuncts to conventional medical treatment (Astin et al., 2003) and be effectively integrated into an evolving mainstream medical paradigm, referred to as "Integrative Medicine" (Giordano et al., 2002). In the most recent decade, a marked increase in clinical data has permitted literature reviews and meta-analyses of clinical trials, resulting in evidence-based integration of MBTs into clinical practice for the treatment of specific pathologies and recommendation of MBTs as preventative strategies for maintaining wellness (Ernst et al., 2007; Jonas et al., 2013).

Emotional, cognitive and psychosocial factors have been shown to significantly affect health outcomes (Cacioppo and Cacioppo, 2014; Cohen et al., 2007; Umberson and Montez, 2010), and the physiological correlates are becoming more clearly elucidated (Swaab et al., 2005). A cross-sectional study showed that high vs. low mindfulness was associated with improvements in markers of cardiovascular health, including smoking, body mass index, fasting glucose and physical activity (Loucks et al., 2015). Other studies using data from large-scale US health surveys have reported that psychosocial factors are correlated with multiple inflammatory markers in the blood (Loucks et al., 2006; Yang et al., 2013), including C-reactive protein, interleukin-6, fibrinogen, E-selectin, and intercellular adhesion molecule-1 (Yang et al., 2014). Notably, these studies used data from large databases of n = 3267 individuals (Loucks et al., 2015), n = 6729 (Yang et al., 2013), n = 647 (Yang et al., 2014) and n = 382 (Loucks et al., 2015), suggesting that psychosocial factors are linked with these inflammatory markers in the population at large.

While a broad range of data from diverse scientific disciplines has led to substantial progress in elucidating some of the general themes for biological substrates of MBT practices (Kuntsevich et al., 2010), here we provide a summary of studies reporting functional genomic and neurophysiological correlates of MBTs. Functional genomics and neurophysiology have provided key data on changes in gene expression and central nervous system function associated with MBT practices. These data provide clear indications for several biological substrates that may underlie MBTs, and contribute important foundations for a developing theory of MBTs and its applications to clinical pathology and preventative health. One challenge for interpreting these results is the large variety of MBT practices employed in different studies, which may be unfamiliar to some readers. For reference, the reader is referred to reviews on the scope of MBTs (National Institutes of Health, 2007) and the varieties of meditation practices (Travis and Shear, 2010).

Of central importance to interpreting results from functional genomics, developments in *psychosocial genomics* have demonstrated the relevance of psychosocial factors in gene expression (Cole 2014; Slavich and Irwin 2014), and identified some underlying processes, such as sympathetic nervous system activation of gene transcription factors (Cole, 2010; Cole et al., 2015; Slavich and Irwin, 2014). This growing body of data showing functional genomic correlates of stress and subjective emotional states has contributed to elucidating the mechanisms underlying many MBTs. Below, these functional genomic links with MBT practices are reviewed, and some of the mechanisms by which these techniques function (illustrated in Fig. 1), with particular emphasis on their role in alleviating the effects of psychological stress.

The data demonstrating neurophysiological correlates of MBTs is also surveyed, including the brain's response to different styles of practice and observations of persistent changes in neural function and morphology associated with these practices. In recent years, advances in neuroimaging and methods of neurophysiology have led to a clearer understanding of neuroanatomy and functions associated with higher-level brain functions such as emotional affect, attention, and diverse forms of cognition. Of particular relevance to MBTs, neuroimaging data has shed light on the influence of emotion on cognition, and vice versa, leading to a conception of mind wherein this interrelationship is of primary functional importance (Dolcos et al., 2011). Relatedly, because brain networks involved in attention, learning, cognition and emotional regulation are susceptible to neuromodulation, these may be important mechanisms by which cognitive and stress-reducing interventions influence behavioral development over the lifespan (Li 2013). These findings from the neurosciences, coupled with results from psychosocial genomics, have produced a much clearer conception of some of the specific means by which emotional, cognitive and psychosocial factors can influence central nervous system structure and function (Garland and Howard 2009).

2. Stress and gene expression

2.1. Social stress and inflammation

A large and growing body of research has elucidated some of the mechanisms involved in cellular responses to psychosocial stress and emotional factors. Human and animal studies have shown that noradrenaline-dependent adrenergic stimulation due to psychosocial stress results in activation of the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) protein complex, which controls genes expressed during inflammation (Bierhaus et al., 2003; Slavich and Irwin, 2014; Wolf et al., 2009). Similar results have been observed for social stressors also: DNA microarray analysis of circulating leukocytes (white blood cells involved in immune response) from high-loneliness vs. low-loneliness individuals showed genome-wide differences in gene expression activity, including over-expression of genes responsive to NF-κB transcription factors and reduced expression of transcripts bearing anti-inflammatory response elements for glucocorticoids (steroid hormones involved in innate immunity) (Cole et al., 2007). Several other gene expression control pathways were also affected in this study, including the inflammation-related glucocorticoid receptor, JAK-STAT signaling pathway (transmits extracellular chemical

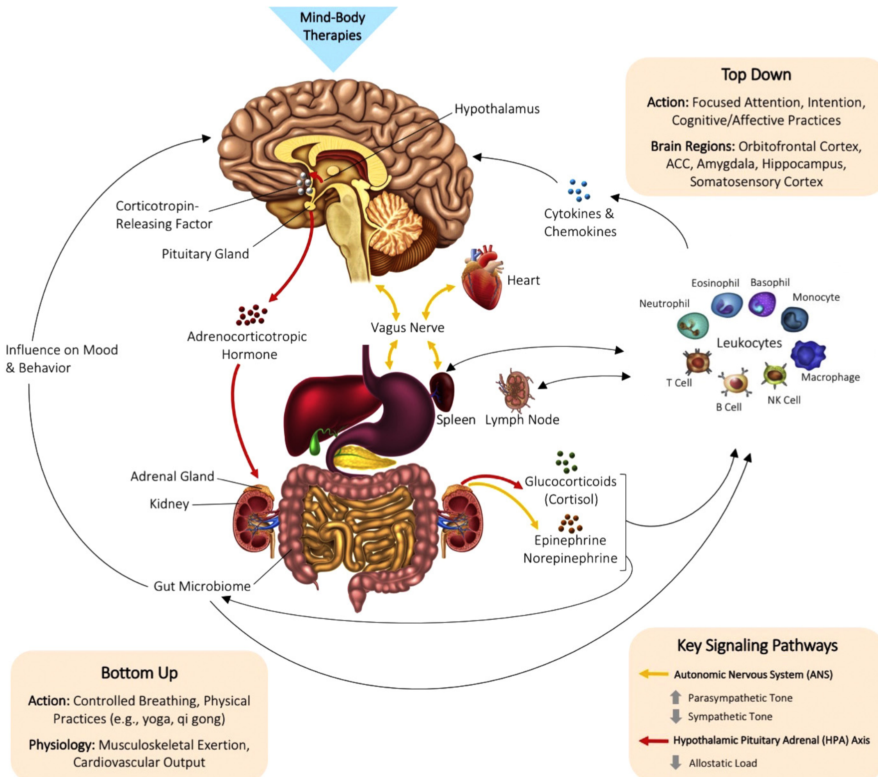

Fig. 1. Biological Mechanisms of Mind-Body Therapies. MBTs are believed to exert effects on biological function through Top Down or Bottom Up routes. MBTs that intervene with an individual's cognitive/affective state (e.g., contemplative practice) have been shown to influence activity in brain regions including orbitofrontal cortex, anterior cingulate cortex, amygdala, hippocampus, and somatosensory cortex. Concurrent with changes in brain activity, MBT practitioners often experience reductions in psychological stress and arousal, changes linked to increased parasympathetic and decreased sympathetic autonomic nervous system (ANS) tone, reduced production of inflammatory cytokines in circulating leukocytes, and enhanced sensitivity to glucocorticoid hormones such cortisol, produced via hypothalamic pituitary adrenal (HPA) axis signalling. Reductions in HPA and ANS sympathetic output have downstream effects including enhanced heart rate variability, modulation of immune function and inflammation in secondary lymphoid organs, and alterations in gut motility and microbiome activity. Importantly, the immune system and the gut microbiome both feed back to the brain and can potently influence mood and behavior. MBTs may also evoke meaningful biological changes via Bottom Up mechanisms related to controlled breathwork and physical practices such as yoga, qi gong, and tai chi. These practices can directly influence physiology via musculoskeletal exertion and increased cardiovascular output, which similarly have downstream effects on HPA activity, sympathetic/parasympathetic balance, immune function, and mood. These pathways together provide a framework for understanding how MBT interventions can positively impact long-term health outcomes.

signals to the cell nucleus resulting in DNA transcription and expression of genes involved in immunity, proliferation, differentiation, apoptosis and oncogenesis), CREB-binding protein interferon response factor (a protein that activates DNA transcription), and the GATA, and Oct families of transcription factors, (which also mediate inflammatory effects) (Cole et al., 2007), confirming that social isolation is correlated with genome-wide changes in transcription. Similarly, studies on a population living with stress, familial caregivers of cancer patients, found increased expression of transcripts with response elements for NF-κB (a gene transcription factor with key roles in innate immunity) in peripheral blood monocytes, decreased expression of transcripts bearing response elements for glucocorticoids (Miller et al., 2008, 2014), an increase in the systemic inflammatory marker, C-reactive protein (CRP), a decline in mRNA for anti-inflammatory signaling molecules and reduced glucocorticoid sensitivity (Rohleder et al., 2009).

Other studies have reported that exposure to a threatening stressful experience was associated with decreased sensitivity of immune cells to glucocorticoid hormones after exposure to a rhinovirus (L. Cohen et al., 2012; S. Cohen et al., 2012), familial caregivers of children with autism or attention deficit hyperactivity disorder displayed increased systemic CRP concentrations (Rohleder et al., 2009), chronic interpersonal stress was associated with increased NF-κB inflammatory signaling and leukocyte inflammatory response (Miller et al., 2009), and social rejection in adolescents was also associated with increased NF-κB activity (Murphy et al., 2013). Relatedly, increases in pro-inflammatory cytokines associated with social threat and adversity have been linked to depressive symptoms (Slavich and Irwin, 2014). For example, depressive symptoms in renal cell cancer patients were found to be predictive of survival, and positively correlated with increased expression of pro-inflammatory and pro-metastatic genes in circulating leukocytes (L. Cohen et al., 2012; S. Cohen et al., 2012).

Additional studies have reported that social isolation was associated with reduced immune cell sensitivity to regulation via the hypothalamic pituitary adrenal (HPA) axis (regulator of a variety of functions, including reactions to stress and immune response) (Cole, 2008), and macaques subjected to unstable socialization have shown impaired physiologic regulation of leukocyte sensitivity to glucocorticoid regulation (Cole et al., 2009). Also, depression and rumination have been shown to affect leukocyte functional sensitivity to HPA over-activation and increased cortisol production (Compare et al., 2014; Swaab et al., 2005). In addition to the HPA axis, beta-adrenergic signaling (mediates sympathetic nervous system-induced fight-or-flight stress responses) associated with psychosocial stress also appears to be linked to differential gene expression. For example, a DNA microarray study of human ovarian carcinomas compared tumors from patients with high psychological risk (high depressive symptoms and low social support) and those from low-risk patients, and identified 266 transcripts that were differentially expressed, including several β-adrenergic-linked control pathways (Lutgendorf et al., 2009). The results of this study suggest increased activity of the sympathetic nervous system as a primary mechanism by which factors such as psychological stress impact gene expression in solid epithelial tumors, consistent with earlier observations that beta-adrenergic signaling can regulate tumor cell gene expression (Lutgendorf et al., 2003). Similarly, results of computational modeling of molecular interactions, in vitro biochemical analyses, in vivo animal modeling, and human molecular epidemiologic analyses, identified increased β-adrenergic activation of GATA1 target genes as one pathway by which psychosocial stressors may alter human health risk (Cole, 2010). A review of these and related results suggests directions for future research based on high throughput genomics methods for identification of multiple-gene signaling "themes" (Cole, 2014; Cole et al., 2010). Collectively, these data form a foundation for a genomics-based understanding of some of the ways in which mind, emotions and the cellular responses in the body are fundamentally intertwined.

Vagal regulation of inflammation (Thayer and Sternberg, 2006) may be one of the neurophysiological mechanisms underlying these results. This neural pathway forms a bi-directional connection between the immune and nervous systems (Tracey, 2002, 2007) that regulates inflammation and innate immune responses during tissue injury and pathogen invasion (Borovikova et al., 2000; Pavlov and Tracey, 2012). Vagal function is associated with glucose regulation, HPA axis function, and expression of inflammatory markers such as tumor necrosis factor, interleuken- 1 and -6, and CRP (Thayer and Sternberg, 2006). Depressed vagus nerve activity is associated with increased morbidity and mortality in sepsis, rheumatoid arthritis, lupus, sarcoidosis, inflammatory bowel diseases, trauma (Tracey, 2007) and stress (Porges, 1995). Low vagally-mediated heart rate variability, a risk factor for a variety of physiological and psychological pathologies, is linked to depression, generalized anxiety disorder, and post-traumatic stress disorder (Park and Thayer, 2014; Thayer and Sternberg, 2006), panic disorder, bipolar disorder, schizophrenia, and impaired emotion regulation (Park and Thayer, 2014). Vagal regulation of inflammation has been suggested as a pathway linking psychosocial factors to disease (Marsland et al., 2007; Thayer and Sternberg, 2006; Tonhajzerova et al., 2013), and increased vagal tone has been linked to increased social and psychological well-being (Kok and Fredrickson 2010).

2.2. Stress, positive psychological states and gene expression

A variety of stressors, including low socioeconomic status, chronic stress, bereavement, post-traumatic stress disorder and being informed of a cancer diagnosis have been documented to produce similar leukocyte transcriptome shifts (Cole, 2014). This conserved transcriptional response to adversity (CTRA) gene profile (Slavich and Cole, 2013), activated in response to extended periods of stress, threat, or uncertainty, including diverse forms of social adversity, consists of increased expression of pro-inflammatory genes and decreased expression of genes involved in Type I interferon innate antiviral responses and IgG antibody synthesis (Cole, 2014). While the CTRA profile is likely to have evolved to enhance short-term immune responses to changes in microbial threat due to changing socio-environmental conditions, chronic CTRA activation may promote inflammation-mediated cardiovascular, autoimmune, neurodegenerative and neoplastic diseases (Irwin and Cole, 2011). Relatedly, a recent cross-sectional analysis found differences at the transcriptional level in subjects grouped ($n = 84$) according to the tendency towards one of two forms of well-being associated with similar subjective feelings of happiness: *eudaimonic* well-being (derived from meaning and a noble purpose beyond simple self-gratification), and *hedonic* well-being (derived from simple pleasure-seeking) (Fredrickson et al., 2013). In this study, subjects evincing eudaimonic well-being showed significantly lower levels of CTRA-related gene expression, while those who showed higher levels of hedonic well-being showed significantly elevated CTRA gene expression. Thus, subjects showing greater eudaimonic well-being demonstrated a less threatened molecular profile corresponding to a more favorable long-term health outlook (Fredrickson et al., 2013).

While the authors noted that replication and longitudinal studies are needed to judge the generalizability of these effects (Fredrickson et al., 2013), the results suggest that different forms of subjective experience can be associated with different patterns of gene expression with functional implications for immune response and inflammation. Building upon this foundation in psychosocial genomics towards the possible clinical relevance of these results, changes in mental state and emotional affect have also been shown to produce specific changes in gene expression. For example, a review noted that several types of therapeutically beneficial biological changes resulting from successful psychotherapy have been shown to be dependent on shifts in gene expression (Feinstein, 2010). These included changes in gene expression resulting in amelioration of impaired immune function and reduction in elevated levels of cortisol and other stress hormones associated with some psychiatric conditions (Feinstein, 2010).

3. Functional genomic correlates of mind-body therapies

Interest in transcriptional changes driven by MBTs has grown in recent years, and is summarized in Table 1. Several studies have reported physiological responses to MBT practices suggestive of reductions in stress. A recent review surveyed reports of changes in gene expression with several yoga and meditative practices (Saatcioglu, 2013), concluding that these practices can positively affect gene expression profiles in circulating immune cells, an effect consistent with reductions in stress (Cole et al., 2010). This review also concluded that more detailed studies are required to evaluate the validity of these findings and identify the precise molecular networks involved. Another review concluded that, while further studies are needed to corroborate the findings, the Relaxation Response (RR), a counterpart to the stress response which is evoked by various forms of meditation, prayer, yoga, tai chi, deep breathing, etc. (Benson et al., 1975), altered the expression of genes associated with cellular metabolism and oxidative stress, suggesting the inhibition of cell injury due to chronic stress (Takimoto-Ohnishi et al., 2012). Several controlled studies have shed light on gene expression profiles resulting from MBT interventions. For example, a controlled study ($n = 19$) profiling polymorphonuclear leukocyte transcription in short-term and long-term practitioners of deep relaxation showed significant changes, compared with non-practitioners, in expression of genes involved in cellular metabolism, and key cellular processes such as oxidative phosphorylation, generation of reactive oxygen species, and response to oxidative stress (Dusek et al., 2008). While changes in gene expression occurred globally across the leukocyte genome, this study found that RR evoked gene-specific changes in the opposite direction from those associated with the stress response. Similar results were observed in a controlled trial ($n = 14$) examining gene expression in peripheral blood lymphocytes for healthy people practicing Sudarshan Kriya (SK), a yogic technique combining postures, breathing and meditation, compared with a control regimen of nature of walking and listening to relaxing music (Qu et al., 2013). In this study SK practice was also associated with a genome-wide increase number of genes expressed in peripheral blood lymphocytes within 2 h of start of practice, however, the functional roles of the full gamut of genes expressed were unclear (Qu et al., 2013). Another controlled trial ($n = 42$) on SK found an

Table 1
Functional Genomic Correlates of Mind-Body Practices.

Study	MBT	Comments	Findings	Study Design	Subjects in Active Group
Li et al. (2005)	Qigong (Falun Gong)	Whole blood neutrophil transcripts	Changes characteristic of enhanced immune response and resolution of inflammation, downregulation of cellular metabolism	Controlled Trial	6
Dusek et al. (2008)	Relaxation Response Training	Polymorphonuclear whole blood leukocytes	Gene-specific changes in direction opposite from those associated with the stress response	Controlled Trial	19
Sharma et al. (2008)	Sudarshan Kriya	Whole blood leukocytes	Upregulation of anti-apoptotic genes and genes related to survival from oxidative stress	Controlled Trial	42
Qu et al. (2013)	Sudarshan Kriya	Peripheral blood mononuclear cells; changes observed within 2 h of MBT practice	Rapid global changes in gene expression	Controlled Trial	10
Antoni et al. (2012)	Cognitive behavioral stress management	Whole blood leukocytes; early stage breast cancer patients; randomized controlled trial	Reversal of anxiety-related transcriptional dynamics: decreased GATA transcription factors and NF-κB/Rel activity; increased interferon response glucocorticoid receptor activity	Randomized Controlled Trial	34
Black et al. (2013)	Kirtan Kriya yogic meditation	Whole blood leukocytes of family dementia caregivers; randomized controlled trial	Reversal of stress-related NF-κB and interferon response factor transcriptome dynamics	Randomized Controlled Trial	23
Creswell et al. (2012)	Mindfulness-Based Stress Reduction	Whole blood leukocytes; randomized controlled trial	Decrease in pro-inflammatory NF-κB-related gene expression	Randomized Controlled Trial	40
Kaliman et al. (2014)	Mindfulness Meditation	Peripheral blood mononuclear cells	Reduced expression of histone deacetylase genes, alterations in global modification of histones, and decreased expression of pro-inflammatory genes	Controlled Trial	19
Bower et al. (2014)	Yoga (Iyengar)	Whole blood and plasma; breast cancer survivors	Reduced NF-κB activity, and increased activity of the anti-inflammatory glucocorticoid receptor	Randomized Controlled Trial	16
Carlson et al. (2014)	Mindfulness Meditation	Whole blood leukocytes; breast cancer survivors	Improved maintenance of telomere length	Longitudinal Randomized Controlled Trial	34
Lavretsky et al. (2013)	Kirtan Kriya Meditation	Peripheral blood mononuclear cells; dementia caregivers	Increased telomerase activity	Longitudinal Randomized Controlled Trial	23
Jacobs et al. (2011)	Buddhist meditation	Peripheral blood mononuclear cells; 3 month residential retreat	Increased telomerase activity	Controlled Trial	30
Ornish et al., 2008	Comprehensive Lifestyle Intervention	Peripheral blood mononuclear cells; low-risk prostate Cancer; aerobic exercise, yoga-based stretching, breathing, meditation, imagery, relaxation techniques, lowfat, whole foods, plant-based diet	Increased telomerase activity; decreased low-density lipoprotein cholesterol and psychological distress	Longitudinal Study 3 mos.	24
Ornish et al., 2013	Comprehensive Lifestyle Intervention; Prostate Cancer Patients	Peripheral blood mononuclear cells; low-risk prostate Cancer; aerobic exercise, yoga-based stretching, breathing, meditation, imagery, relaxation techniques, lowfat, whole foods, plant-based diet	Increased telomerase length	Controlled 5 year Follow-on	10

enhanced expression of anti-apoptotic genes and genes related to survival from oxidative stress in leukocytes isolated from whole blood in SK practitioners with at least 1 year of practice, compared with non-practitioners (Sharma et al., 2008). Similarly, a controlled study (n = 6) examining genomic profiles of whole blood neutrophil transcripts in Falun Gong Qigong practitioners, compared with non-practitioners, showed changes characteristic of enhanced immune response, downregulation of cellular metabolism, and changes in apoptotic gene expression favoring resolution of inflammation (Li et al., 2005). Relatedly, a controlled study (n = 19) of the effects of a single day of mindfulness meditation in experts vs. subjects with no meditation experience who engaged in leisure activities in the same environment found reduced expression of histone deacetylase genes, alterations in global modification of histones, and decreased expression of pro-inflammatory genes in peripheral blood mononuclear cells (Kaliman et al., 2014). The authors concluded that the results support the notion that NF-κB inhibition is a reproducible molecular outcome in blood cells in response to meditation-based practices, and that mindfulness meditation influences mechanisms similar to those targeted by anti-inflammatory drugs such as HDACi or cyclooxygenase inhibitors (Kaliman et al., 2014). While these controlled studies outline a common theme of reduction in stress markers with these MBT practices, the different protocols and MBT modalities employed, and small sample sizes in some of the studies, beg caution in reaching firm conclusions from these results.

The results above are paralleled by randomized controlled trials reporting that MBT practices reduced inflammatory NF-κB activity and/or increased activity of interferon response factors and the glucocorticoid receptor. A 10-week randomized controlled clinical trial (n = 45) of women with early stage breast cancer reported that a cognitive behavioral stress management (CBSM) intervention produced a reversal of anxiety-related transcriptional dynamics in peripheral blood leukocytes (Antoni et al., 2012). This study reported decreased expression of pro-inflammatory and metastasis-related genes, up-regulation of type I interferon response genes in peripheral blood leukocytes, with bioinformatics analyses suggesting that these transcriptional changes were mediated by decreased GATA transcription factors, decreased NF-κB/Rel activity, and increased activity of interferon response factors and glucocorticoid receptors. Notably, this study also reported that at a 12-month follow-up, CBSM subjects showed reduced expression of genes for pro-inflammatory cytokines and increased expression of genes for type I and II interferons, and is the first study to report an MBT-induced *reversal* of stress-induced gene expression (Antoni et al., 2012). Similarly, another recent randomized clinical trial (n = 23) reported that 8 weeks of structured daily yogic meditation produced a reversal of stress-related NF-κB and interferon response factor transcriptome dynamics in peripheral blood leukocytes of dementia caregivers (Black et al., 2013). Also, a randomized controlled trial (n = 40) found a reduced sense of loneliness and a decrease in pro-inflammatory NF-κB-related gene expression in older adults practicing mindfulness-based stress reduction for insomnia (Creswell et al., 2012). These latter three randomized clinical trials, from well-established research groups, provide perhaps the clearest evidence of the efficacy of CBSM interventions for stress, and make notable steps towards delineating the underlying mechanisms of action (Antoni et al., 2012; Creswell et al., 2012; Black et al., 2013). Further, a randomized controlled trial (n = 16) of a 12-week Iyengar yoga intervention for breast cancer survivors also reported reduced NF-κB activity, and increased activity of the anti-inflammatory glucocorticoid receptor in whole blood. However, the control group used was a health education program, rather than comparing Iyengar yoga, which emphasizes physical postures, to more physically-oriented control conditions (Bower et al., 2014). Again, while the diversity of protocols and MBTs employed in these studies calls for replication and further longitudinal studies, a common theme emerges for MBT-induced reductions in stress and concomitant reductions in inflammatory activity and enhanced innate immune response.

3.1. Stress, mind-body therapies and cellular aging

A recent review summarized evidence that traumatic stress, depression, and post-traumatic stress disorder are associated with reduced telomere length, a measure of cellular aging at the chromosomal level (Zhang et al., 2014), suggesting a link between cellular aging and various forms of stress. In a similar vein, a study on stress in maternal caregivers reported that the magnitude and duration of subjective stress are significantly associated with higher oxidative stress, lower telomerase activity, and shorter peripheral blood mononuclear cell (PBMC) telomere length (Epel et al., 2009). Relatedly, several studies reported associations between stress, MBT practices, and cellular aging. This review also reported that mindfulness meditation was associated with decreased stress arousal, which has been shown to produce reduced age-related telomeric shortening, and upregulation of hormonal factors that may promote telomere maintenance (Epel et al., 2009). Supporting this result, a longitudinal randomized controlled study (n = 34) with distressed breast cancer survivors recently reported that mindfulness meditation combined with gentle Hatha yoga and group therapy (promoting emotional expression and group support) resulted in improved maintenance of PBMC telomere length (Carlson et al., 2014). This longitudinal study consisted of 8 weekly group counseling sessions of 90 min, a six-hour retreat, and blood sample collection before and after the intervention. Another longitudinal randomized controlled trial (n = 23), conducted over eight weeks, reported enhanced PBMC telomerase activity in dementia caregivers practicing yogic Kirtan Kriya meditation, and also found lower levels of depressive symptoms and greater improvement in mental health and cognitive functioning, as compared to a control group listening to relaxing music (Lavretsky et al., 2013). Also, a controlled trial using participants in a 3-month residential Buddhist meditation retreat reported that increased PBMC telomerase activity in meditators (n = 30) was significantly correlated with psychological scales measuring perceived control, neuroticism, and purpose in life (Jacobs et al., 2011). This study suggests a correlation between psychological affect and physiological changes relevant to cellular aging, and may also shed light on the therapeutic possibilities presented by intensive meditation practice in a structured retreat setting. An uncontrolled longitudinal study with biopsy-diagnosed low-risk prostate cancer patients (n = 24) investigated the impact of a comprehensive lifestyle program (comprised of moderate aerobic exercise, stress management through gentle yoga-based stretching, breathing, meditation, imagery, progressive relaxation techniques, and a lowfat, whole foods, plant-based diet) and found increased PBMC telomerase activity, decreased low-density lipoprotein cholesterol, and decreased psychological distress (Barrows and Jacobs, 2002). A follow-up study reported that patients enrolled in this comprehensive lifestyle change program had increased relative PBMC telomere length after 5 years, and suggested that larger randomized controlled trials are warranted to confirm this finding (Ornish et al., 2013). While these last two studies support the use of a comprehensive lifestyle intervention, because several interventions were used, it is difficult to determine the degree to which specific intervention factors or the combination of these were responsible for the results.

Again, further studies, including replications and longitudinal studies, are needed to confirm these findings, and to more fully understand the underlying biological mechanisms. Also, most of the studies described here investigated the gene expression and cell biology of leukocytes, which are critical for health and homeostasis, but may not capture the impact of MBTs on other cell types or organelles such as mitochondria, which are important determinants of long term health. To address this challenge, researchers may consider sampling other accessible tissues (e.g., biopsy of skin or muscle) for the purposes of comparing gene expression profiles to what is observed in leukocytes. Also, due the diversity of bulk PBMC cell types, further work aimed at parsing transcriptional and functional changes in immune cells subsets may yield important information regarding the underlying mechanisms of MBTs. This may start to compose a more holistic understanding of the variety of ways that MBTs influence cellular biology, systems biology, and ultimately health outcomes.

4. Neurological correlates of mind-Body therapies

4.1. Electroencephalography

While studies on the effects of MBTs on gene expression have focused largely on inflammation and immune function, a diverse picture has emerged from research on the neurological results of these practices. In recent years, advances in EEG and neuroimaging techniques have produced detailed maps of the interrelationships between neural activity and cognitive/emotional content. This has enabled reviews of the growing literature on EEG profiles associated with MBT practice, summarized here in Table 2, with various forms of meditation being the most commonly studied practices. A review of studies dating back to the 1960s on EEG measurements taken during or after many types of meditation reported a wide variety of effects across the entire range of frequencies captured by EEG (Fell et al., 2010). Another review concluded that different meditative techniques have been reported to produce different EEG effects, negating the usefulness of averaging results from different practices (Travis and Shear, 2010). Of relevance to stress reduction, a review on EEG and imaging studies of meditation reported an overall slowing in EEG rhythm, with increases in low-frequency theta (4–7 Hz) and alpha (8–15 Hz) activation correlating with proficiency of practice, suggesting an overall relaxation response (Cahn and Polich 2006). Relatedly, controlled studies (Travis et al., 2002), (n = 50) (Travis et al., 2004, 2002), (n = 17), with long-term practitioners of Transcendental Meditation (TM) showed broadband EEG coherence during contingent negative variation (CNV) tasks, and increased alpha power and decreased gamma (>32 Hz) power, as compared to non-meditators and less experienced TM practitioners. While the authors pointed out the need for further work, including longitudinal studies to assess the veracity of the results, these studies are suggestive of a learning effect with higher levels of practice. Also, a review by the lead author reported that meditators' descriptions of subjective inner state as "inner self-awareness" or "Cosmic Consciousness," persisting continuously during waking, sleeping, and dreaming, corresponded with coexistence of increased alpha frontal coherence with delta EEG during deep sleep (Travis, 2014). A controlled trial (n = 10) with proficient Tantric Yoga (Ananda Marga) meditators comparing experienced meditators with novices and naïve controls reported that experienced meditators showed increased autonomic activation during meditation, whereas, inexperienced meditators exhibited decreased autonomic tone (Corby et al., 1978). While the age and small sample size of this early study reflect the need for further more comprehensive trials, these results suggest that EEG correlates in experienced meditators can be substantially different from those of novices, and do not necessarily occur via a relaxation response (Cahn and Polich, 2006).

Studies with advanced meditators have reported enhanced activity normally associated with attention and wakefulness, rather than relaxation or resting. For example, synchronized high-amplitude, high-frequency gamma band activity (gamma activity is normally considered to representative of cognition, learning and memory) has been reported in an advanced Tibetan Buddhist meditator (n = 1) (Lehmann et al., 2001; Lutz et al., 2004), and a controlled trial (n = 8) with advanced Tibetan practitioners of loving-kindness meditation reported increased gamma amplitude and inter-hemispheric gamma synchrony. These results suggested that the compassion-based practice involved cultivation of attention and affective processes (Lutz et al., 2004), a result that contrast with studies that found an increase in slow alpha or theta rhythms during meditation (Cahn and Polich, 2006). Notably, in this study, high-amplitude gamma synchrony was observed to persist outside of the formal meditative practice, and the authors note that such amplitudes were, to their knowledge, "the highest reported in the literature in a nonpathological context" (Lutz et al., 2004). While the generalizability of these studies is limited by the small numbers of subjects, they were selected for their high degree of experience and expertise in traditional practice. Other studies with advanced practitioners reported that long-term Vipassana meditators (n = 16) showed increased frontal theta and parieto-occipital gamma activity during meditation, (Cahn et al., 2010), and decreased early-evoked delta activity coupled with increased event-related alpha desynchronization, as compared to resting and mind-wandering, interpreted as a decrease in reactivity to distraction and enhanced perceptual clarity (Cahn et al., 2013). A recent comparison of two forms of Buddhist meditation in long-term practitioners reported that a practice typical of the Theravada school (Kasina Meditation) was associated with enhanced parasympathetic activation indicative of a relaxation response (n = 10), whereas a different practice typical of the Vajrayana school (Kyerim Deity Meditation) was associated with sympathetic activation (n = 14), indicative of arousal (Amihai and Kozhevnikov, 2014). While these studies are suggestive of the diversity of correlates in highly experienced meditators, they lacked comparison to naïve controls. However, EEG studies enable a real-time view of brain activity during meditative practice, which allows comparison to resting baselines to assess meditation-specific changes in activity. The diversity of the above results runs contrary to the notion that meditative states are characterized by a single type of response. While one might attempt to rationalize the different results reported for various types of meditation through a classification scheme based upon focused attention vs. open monitoring (Lutz et al., 2008; Travis and Shear, 2010), the small sample sizes and diverse experimental designs render this classification secondary to further replication with larger numbers of subjects and direct comparisons between meditation techniques. However, these data do indicate that while individual response may vary widely, particular forms of meditation in experts vs. novices have been associated with distinct patterns of EEG activity, including increases in activity in specific brain regions, supporting the suggestion that some forms of meditation involve active brain states that may stimulate cortical plasticity and involve changes in neural structures associated with cognitive restructuring and learning (Fell et al., 2010).

4.2. Neuroimaging

Neuroimaging technologies such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided insights into which brain regions are more/less active during particular cognitive states. Of relevance to MBTs, patterns of brain activity typically related to the sense of self and mind-wandering (Northoff et al., 2006), imagery, and sustained attention have been identified (Cabeza and Nyberg, 2000; Nebel et al., 2005). Also, neuroimaging has led to a clearer view of the inter-relatedness of emotion and cognition (Dolcos et al., 2011), demonstrating that

Table 2
EEG Correlates of Mind-Body Practices.

Study	MBT	Comments	Findings	Study Design	Subjects in Active Group
Fell et al. (2010), Travis et al. (2010), Cahn et al. (2006)	Several styles of meditation	Review articles	Wide variety of EEG changes across range of frequencies; correlations with meditative proficiency	Review	–
Travis (2014)	Transcendental Meditation	Long-term Vipassana meditators	Increased alpha frontal coherence; coexistence of alpha with delta EEG during deep sleep	Review	–
Corby et al. (1978)	Tantric Yoga (Ananda Marga)	Long-term meditators	Increased alpha and theta activity in experienced vs inexperienced meditators	Controlled Trial	10
Lehmann et al. (2001)	Traditional Tibetan	Senior Tibetan meditator	Increased gamma activity	Single Subject	1
Lutz et al. (2004)	Traditional Tibetan compassion meditation	Senior Tibetan meditators; controlled trial	Increased gamma activity; inter-hemispheric gamma synchrony	Controlled Trial	8
Cahn et al. (2010)	Vipassana meditation	Long-term Vipassana meditators	Increased frontal theta and parieto-occipital gamma activity	Single group control meditation vs. resting	16
Cahn et al. (2013)	Vipassana meditation	Long-term Vipassana meditators	Decreased early-evoked delta activity; increased event-related alpha desynchronization	Single group control meditation vs. resting	16
Travis et al. (2002)	Transcendental Meditation	Long-term Vipassana meditators	Broadband EEG coherence; increased alpha activity; decreased gamma activity	Controlled Trial	50
Travis et al. (2004)	Transcendental Meditation	Long-term Vipassana meditators	Broadband EEG coherence; increased alpha activity; decreased gamma activity	Controlled Trial	17
Ornish et al., 2013	Comprehensive Lifestyle Intervention	Low-risk prostate cancer patients	Increased telomerase activity	Retrospective follow-up	10
Amihai and Kozhevnikov (2014)	Theravada and Vajrayana Buddhist Meditations	Long-term meditators	Enhanced parasympathetic activation – Theravada; sympathetic activation – Vajrayana	Single group control meditation vs. resting	10; 14

emotional affect has both short and long-lasting effects on many forms of cognitive processing, for example, the experience of better memory for events having emotional significance (Dolcos et al., 2011). These results are of particular significance to MBT practices such as compassion (loving-kindness) meditation, wherein the practitioner consciously cultivates positive emotions.

Meditation is the most commonly employed MBT in neuroimaging studies (data summarized here in Table 3), and the substantial data has permitted several reviews. Key findings from these studies include: a meta-analysis of 21 imaging studies (~300 meditation practitioners) found eight brain regions that were consistently structurally altered in meditators, including areas key to meta-awareness, such as body awareness, memory, and emotion regulation (Fox et al., 2014); a review of functional and structural neuroimaging studies reported that mindfulness meditation typically involves the medial cortex and its associated default mode network, and also the insula, amygdala, lateral frontal regions, basal ganglia, and hippocampus (Marchand, 2014); a review of EEG, evoked potential and imaging studies concluded that increased regional cerebral blood flow occurs during meditation, and that generalized changes in activity occurred in the anterior cingulate cortex and dorsolateral prefrontal areas (Cahn and Polich, 2006). Relatedly, a fMRI study on mantra meditation (n = 5) showed group-averaged changes in neural structures involved in attention and control of the autonomic nervous system, including the dorsolateral prefrontal and parietal cortices, hippocampus, temporal lobe, pregenual anterior cingulate cortex, striatum, and pre- and postcentral gyri (Lazar et al., 2000). As with EEG studies, although the diversity of meditation styles and experience levels make the development of clear conclusions difficult, several common themes emerge including the association of MBTs with changes in structure or activation of orbitofrontal and anterior cingulate cortex (emotion regulation), insula (body awareness and emotion), amygdala and hippocampus (learning and memory), and somatosensory cortex (sensory reception).

4.3. MRI neuroimaging in diverse styles of meditation; experts vs. novices

While the general themes described above have been noted by reviews, studies comparing different practices have produced a clearer view on how different forms of meditation produce a diversity of effects on brain activity. One review detailed differences in brain activity for studies comparing different meditative practices or experienced vs. novice meditators, and concluded that while some styles of meditation are associated with passive relaxation states, other styles involve active states of cognitive restructuring and learning (Fell et al., 2010). For example, a study using fMRI blood oxygen-level-dependent imaging showed task-specific differences in neural activity for focused-attention meditation (FAM) as compared to loving-kindness meditation (LKM) (n = 11) (Lee et al., 2012). While performing a cognitive number recognition task, FAM experts showed reduced activity in the right thalamus as compared to novices, whereas LKM experts showed no task-specific changes in any neural regions. Affective processing also differed, with FAM practitioners showing increased activity in the left anterior insula (related to the interaction between arousal and valence), with LKM showing increased left ventral anterior cingulate cortex activity (related to emotional identification and production of affective states). This result is consistent with the notion that FAM activated regions involve attention-related processing, whereas LKM involves regions associated with emotion regulation processes (Lee et al., 2012). Similarly, one of the first fMRI studies to report on individuals performing two different types of meditation practices found that focused-based (FB) and breath-based (BB) meditations (n = 10) were both associated with changes in cerebral blood flow (CBF) in brain frontal regions, anterior cingulate, limbic system and parietal lobes during meditation with different patterns of CBF for each of the two practices. (Wang et al., 2011). FB meditation practice produced significantly increased CBF in the medial prefrontal cortex (associated with the intense focus) while BB produced less prefrontal cortex activation and significant activation of limbic structures including hippocampus, amygdala and insula, which were attributed by the authors to the more strenuous nature of breathing exercises (Wang et al., 2011). Also, a study using fMRI with experienced Japanese monks (n = 8) reported that two different types of Buddhist recitation meditation showed different regions of brain activation: mantra recitation was associated with increased prefrontal cortex activity (suggesting increased attention regulation), whereas recitation of memorized scriptures was associated with left dorsolateral prefrontal cortex and right parietal cortex activation, interpreted by the authors as suggestive of increased visuospatial attention (Shimomura et al., 2008).

Neuroimaging studies comparing expert vs. novice meditators have shed light on long-term changes in brain activity reflective of attention, learning and affective processing. For example, a comparison of the response of expert meditators vs. novices (n = 16) to emotion-conveying sounds (during meditation) showed increased activation in the amygdala, right temporoparietal junction, and right posterior superior temporal sulcus and left middle insula in experts (n = 16) (Lutz et al., 2008), suggestive of increased activation of neuronal circuitries associated with empathy and responsiveness to emotional stimuli (Lutz et al., 2008, 2009). An fMRI study on loving-kindness meditation (n = 20) reported stronger coupling in experts vs. novices between brain regions involved in self-monitoring and cognitive control (posterior cingulate, dorsal anterior cingulate, and dorsolateral prefrontal cortices), both at baseline and during meditation (Garrison et al., 2014). Also, a study with Theravada Buddhist monks (n = 8) reported that expert meditators vs. novices were able to engage in self-regulation of frontoparietal (attention) and insula (body awareness and emotion) in the left hemisphere, and thus limit engagement in awareness of sensory-related thought and emotion contents (Manna et al., 2010). This study also concluded that meditation-related neuroplasticity enables a functional reorganization of patterns of activity in the left-hemispheric prefrontal cortex and in the insula, suggestive of modulation of executive function and internal state awareness (Manna et al., 2010).

Such studies comparing experts vs. novice meditators suggest that some practices involve directed skills acquisition through long-term practice. For example, a randomized, controlled longitudinal study using fMRI reported that practitioners of a cognitive-based compassion training (CBCT) had, after 8 weeks of practice, increased scores on an empathic accuracy test, which were correlated with increased activity in the inferior frontal gyrus and dorsomedial prefrontal cortex (n = 16). These data were interpreted as indicative of enhanced processing of affective cues and enhancement of neural activity related to increased mental state attribution and processing of visual stimuli (Mascaro et al., 2013). And a single-blind randomized controlled trial using fMRI in stressed unemployed adults (n = 35) reported that a 3-day intensive mindfulness meditation training intervention reduced right amygdala-subgenual anterior cingulate cortex resting state functional connectivity (associated with stress reactivity), as compared with a similar 3-day relaxation training intervention that did not include mindfulness meditation (Taren et al., 2015). The authors note that further studies with a non-intervention usual care group are needed to determine the effect in the control group of attending a 3-day relaxation retreat. Also, supporting the notion of skills acquisition through meditation, a study using subjects with less than 2 years of meditation practice in the Kundalini yoga or Acem traditions (n = 8) reported activations in the bilateral hippocam-

Table 3
Functional Neuroimaging (fMRI) Correlates of Mind-Body Practices.

Study	MBT	Comments	Findings	Study Design	Subjects in Active Group
Cahn et al. (2006)	Several styles of meditation	Broad review on EEG, event-related potential, and neuroimaging correlates	Changes in activity in anterior cingulate cortex and dorsolateral prefrontal areas	Review	–
Marchand (2014)	Mindfulness meditation	Review	Changes in function of medial cortex and its associated default mode network, and also the insula, amygdala, lateral frontal regions, basal ganglia, hippocampus	Review	–
Fox et al. (2014)	Several styles of meditation	Meta-analysis of 21 imaging studies	Changes in structure of frontopolar cortex, sensory cortices, insula, hippocampus, anterior and mid cingulate, orbitofrontal cortex, superior longitudinal fasciculus, corpus callosum	Review	–
Fell et al. (2010)	Several styles of meditation	Diversity of correlates for different meditation styles and novice vs. experienced meditators	Significant differences in brain activity for different practices and for novices vs. experienced meditators	Review	–
Lee et al., 2012	Focused-attention vs. loving kindness	novice vs. experienced meditators	Significant differences in brain activity for different practices and for novices vs. experienced meditators	Imaging during meditation vs. resting baseline	11
Lazar et al. (2000)	Mantra meditation (Kundalini school)	Long-term meditators	Increased activity in dorsolateral prefrontal and parietal cortices, hippocampus/ parahippocampus, temporal lobe, pregenual anterior cingulate cortex, striatum, and pre- and post-central gyri.	Imaging during meditation vs. resting baseline	5
Wang et al. (2011)	Focus-based and breath-based meditations	Cerebral blood flow (CBF); Long-term meditators	Different meditation practices resulted in different CBF patterns; results correlated with practitioners' subjective sense depth of meditation	Imaging during meditation vs. resting and control task	10
Shimomura et al. (2008)	Two forms of Buddhist recitation	Long-term meditators: Japanese monks	Activation of prefrontal cortex for repetitive mantra recitation; activation of left dorsolateral prefrontal cortex and right parietal cortex for recitation of memorized scriptures.	Imaging during meditation vs. resting baseline	8
Garrison et al. (2014)	Loving-kindness meditation	Comparison of novices to experienced meditators	Reduction in posterior cingulate cortex/precuneus activity; increased functional connectivity in experienced meditators	Imaging during meditation vs. resting baseline	20
Lutz et al. (2008)	Loving-kindness meditation (Tibetan)	Comparison of novices to experienced meditators' response to emotion-conveying sounds	Increased activation in amygdala, right temporoparietal junction, right posterior superior temporal sulcus, left middle insula	Imaging while subjects listened to emotional sounds	16
Manna et al. (2010)	Theravada Buddhist meditation	Comparison of focused attention and open monitoring meditation in expert monks vs. novices	Self-regulation of left frontoparietal and insular areas;reorganization of patterns of activity in the left-hemispheric prefrontal cortex and in the insula	Imaging during meditation vs. resting baseline	8
Brewer et al. (2011)	Mindfulness meditation	Comparison of novices to experienced meditators	Stronger coupling between brain regions involved in self-monitoring and cognitive control (posterior cingulate, dorsal anterior cingulate, and dorsolateral prefrontal cortices)	Imaging during meditation vs. resting baseline	12
Engström et al., 2010	Kundalini and Acem meditation	Meditators with 2 yrs experience vs. control group	Activation in bilateral hippocampus/parahippocampal regions	Imaging during meditation vs. resting baseline	8
	Cognitive-based compassion training	8 weeks practice vs. control group	Increased activity in inferior frontal gyrus and dorsomedial prefrontal cortex	Randomized controlled longitudinal study; Imaging during empathic accuracy test	16

pus/parahippocampal, regions involved in memory consolidation (Engstrom et al., 2010). While these results are suggestive that skills involving attention and learning may be acquired through meditation, further longitudinal studies are needed to more clearly assess the nature of possible long-term changes in brain activity through meditation and other MBTs. Again, the diversity of these practices and variability in study design and number of subjects begs caution in grouping them for analysis, however the reports consistently suggest a demonstrable difference in brain activity between experienced and novice practitioners. These imaging markers may be valuable in understanding the neurological impact of MBTs and also may be harnessed for optimizing intervention development and training.

4.4. MBT practices, default mode activity and brain morphology

The association between change in brain activity and level of practitioner experience suggests learning effects that could lead to alterations in brain function and structure. A number of studies have reported persistent changes in brain default mode network (DMN) activity and morphology. The DMN consists of a distributed network of brain regions characterized by a high degree of functional connectivity that is more active during rest than during attention-demanding tasks (Whitfield-Gabrieli and Ford, 2012). In addition to the above functional changes, MBT practices have been shown to be associated with several aspects of DMN activity and underlying anatomy, summarized here in Table 4. Supporting this, a review of mindfulness-based interventions reported increased DMN activity associated with the medial cortex, a broad region that in part underlies attention, awareness, and emotion (Marchand, 2014). Such differences in DMN resting state activity relative to that of control subjects are reminiscent of persistent changes in resting EEG reported for MBT practitioners. For example, higher baseline (non-meditating) ratios of gamma/slow activity have been observed for advanced, as compared to inexperienced meditators (n = 8) (Lutz et al., 2004). Similarly, experienced mindfulness meditators (n = 29) exhibited increased parietal-occipital EEG gamma power during non-rapid eye movement sleep relative to non-meditators, positively correlated with total lifetime daily meditation practice (Ferrarelli et al., 2013). Also, Qigong meditators (n = 10) have been reported to show increased delta EEG activity compared with non-practicing control subjects in brain areas involved in detection and integration of sensory information (portions of the prefrontal cortex and anterior cingulate cortex) and decreased delta activity in areas involved in appraisal including motor, somatosensory and visual association cortices (Tei et al., 2009). The authors interpreted higher delta activity as an indicator of cortical inhibition in this study, although no significant changes were found in other frequency bands.

Further information about MBT-associated changes in DMN activity has been provided by other MRI neuroimaging studies (see Table 4). One such study of DMN connectivity during resting states reported that subjects experienced in mindfulness meditation (n = 13), compared with beginning meditators, had weaker functional connectivity between the ventro-medial prefrontal cortex and dorso-medial prefrontal cortex (involved in self-referential processing and emotional appraisal), and showed increased connectivity between the dorso-medial prefrontal cortex and right inferior parietal lobule (associated with attention, reorienting and motor preparation), with the authors concluding that long-term practice of meditation may be associated with long-lasting changes reflecting strengthened present-moment awareness (Taylor et al., 2013). Another study of experienced practitioners of mindfulness/insight meditation (n = 12), compared with compared with non-meditators, found reduced activity in the main nodes of the DMN, associated with the medial prefrontal and posterior cingulate cortices, with the authors suggesting that resting-state experience may be transformed into one resembling a meditative state, i.e. a new "default mode," observable during both the resting state and during meditation (Brewer et al., 2011). Also, fMRI imaging performed while resting, rather than during meditation practice, showed that subjects experienced in a contemporary form of moving meditation (n = 33) showed greater DMN functional connectivity within the medial prefrontal cortex area, but not posterior cingulate cortices, compared to inexperienced subjects, with the authors suggesting that long-term practice can produce persistent functional changes in DMN regions related to internalized attention (Jang et al., 2011). It should be noted that two of these studies (Taylor et al., 2013; Brewer et al., 2011) involved subjects seated in a meditation posture, and reported increased MPC connectivity, whereas decreased MPC connectivity was seen for a form of moving meditation (Jang et al., 2011), suggesting that further studies are needed to more clearly delineate effects due to internalized aspects of the meditative practices (i.e., focused attention, silent repetition of mantras, use of visualizations, etc) from those due to movement. A possible limitation intrinsic to DMN activity as a measure of the effects of MBT practices is that DMN activity itself has been shown to involve a variety of forms of spontaneous and directed mentation, including self reflection and mind wandering (Brewer et al., 2011; Andrews-Hanna, 2012) that are themselves likely to be involved in some MBTs (and certainly, there are many anecdotal reports from meditators of minds wandering). Also, while MRI imaging studies report intriguing associations between MBTs and DMN activity in the prefrontal cortex, these results are correlative rather than causative, and controlled longitudinal studies are needed to determine if DMN activity changes over long-term practice. However, these reports of alterations in DMN activity are not altogether surprising in meditators with years of practice, which in many cases involves training and focusing of attention on an object such as the breath or a mantra. Supporting this, the EEG studies summarized above show changes in activity occurring during meditation in brain regions associated with attention, learning, memory and emotion regulation, which could be expected to influence DMN activity over the course of many months or years of training. The proposition that regular MBT practice could over time change the distribution and activity of the DMN is provocative, and could be more clearly addressed by longitudinal studies of novice meditators as they advance their practice.

MRI imaging studies have also reported persistent differences in brain morphology of MBT practitioners when compared with controls. For example, a study using voxel-based morphometry (VBM), a neuroimaging technique for assessing morphology, of MRI data (n = 20) reported increased gray matter concentration in regions typically activated during Vipassana meditation: left inferior temporal gyrus and right hippocampus and right anterior insula (involved in interoceptive awareness) (Holzel et al., 2008). In this study the mean gray matter concentration in the left inferior temporal gyrus was positively correlated with the total amount of meditation training, suggesting a causal link with meditation (Holzel et al., 2008). MRI imaging of meditators vs. non-meditators showed that experienced Dzogchen Tibetan Buddhist meditators (n = 10) exhibited increased gray matter density in the prefrontal cortex (attention direction), anterior lobe of the cerebellum and brainstem, regions involved with cardiorespiratory control (Vestergaard-Poulsen et al., 2009). Also a study in pain sensitivity in experienced Zen meditators (n = 17), compared with non-meditators, reported that numbers of years of practice was correlated with increased thickness in the dorsal anterior cingulate cortex and bilaterally in secondary somatosensory cortex, regions linked to pain processing (Grant et al., 2010). Another recent study (Fayed et al., 2013), using MRI techniques to evaluate brain metabolite patterns in long-term Zen Buddhist

Table 4
Persistent Changes in Brain Function and Morphology Associated with MBTs.

Study	MBT	Comments	Findings	Study Design	Subjects in Active Group
Lutz et al. (2004)	Traditional Tibetan compassion meditation	EEG; Senior Tibetan meditators	Increased ratio of gamma/slow activity	Imaging during meditation vs. resting baseline	8
Tei et al. (2009)	Qigong meditation	Long-term meditators vs. novices	Increased delta activity in portions of the prefrontal cortex and anterior cingulate cortex; decreased delta activity in motor, somatosensory and visual association cortices, left superior temporal gyrus, left precuneus, left temporo-parietal junction, and bilateral fusiform gyrus)	EEG during resting	10
Ferrarelli et al. (2013)	Mindfulness meditation	EEG; meditators with >3y practice	Increased parietal-occipital EEG gamma power during non-rapid eye movement sleep, positively correlated with length of lifetime daily meditation	EEG gamma power during non-rapid eye movement sleep	29
Taylor et al. (2013)	Mindfulness meditation	fMRI default mode network connectivity	Weaker connectivity between ventro-medial prefrontal cortex and dorso-medial prefrontal cortex; increased connectivity between dorso-medial prefrontal cortex and right inferior parietal lobule.	Imaging during resting	13
Brewer et al. (2011)	Mindfulness meditation	Comparison of novices to experienced meditators. fMRI default mode network connectivity	Stronger coupling between brain regions involved in self-monitoring and cognitive control (posterior cingulate, dorsal anterior cingulate, and dorsolateral prefrontal cortices)	Imaging during meditation vs. resting baseline	12
Jang et al. (2011)	Brain-wave vibration meditation	fMRI – default mode network connectivity	Increased connectivity in medial prefrontal cortex	Imaging during resting	35
Hölzel et al. (2008)	Mindfulness meditation	MRI comparison of experts with non-meditators	Increased gray matter concentration in left inferior temporal gyrus positively correlated with total amount of meditation training	MRI –cerebral morphology	20
Vestergaard-Poulsen et al. (2009)	Tibetan meditation	MRI comparison of experts with non-meditators	Increased gray matter density in prefrontal cortex, anterior lobe of the cerebellum and brainstem regions involved with cardiorespiratory control (portions of the medulla oblongata, i.e. solitary tract nucleus)	MRI –cerebral morphology	10
Grant et al. (2010)	Zen meditation	MRI comparison of experts with non-meditators; correlated with number of years practice	Increased thickness in the dorsal anterior cingulate and bilaterally in secondary somatosensory cortex	MRI –cerebral morphology	17
Pagnoni and Cekic, 2007	Zen meditation	MRI comparison of experts with non-meditators	Meditators did not exhibit typical age-related decline in gray matter volume	MRI –cerebral morphology	13
Kang et al. (2013)	Moving meditation	MRI comparison of experts with non-meditators	greater cortical thickness in anterior brain areas; reduced cortical thickness in posterior regions; higher fractional anisotropy and greater cortical thickness adjacent to the medial prefrontal cortex	MRI –cerebral morphology	46
Fayed et al. (2013)	Zen meditation	MRI comparison of experts with non-meditators; Buddhist monks	alterations in glutamate, N-acetyl-aspartate, ratio of N-acetyl-aspartate/creatine in posterior cingulate gyrus and left thalamus; reduced apparent diffusion coefficient in left posterior parietal white matter	MRI metabolite assessment; diffusion coefficient	10
Luders et al. (2009)	Various styles of meditation	MRI comparison of experts with non-meditators	increased gray matter volume in right orbito-frontal cortex and right hippocampus	MRI –cerebral morphology	44
Luders et al. (2013a)	Various styles of meditation	MRI comparison of experts with non-meditators	increased gray matter volume in hippocampus	MRI –cerebral morphology	50
Luders et al. (2013b)	Various styles of meditation	MRI comparison of experts with non-meditators	increased gray matter volume in hippocampus and hippocampal subiculum	MRI –cerebral morphology	30
Luders et al., 2015	Various styles of meditation	MRI comparison of experts with non-meditators	Reduced age-related gray matter loss	MRI –cerebral morphology	50
Leung et al. (2013)	Theravada loving kindness meditation	MRI comparison of experts with non-meditators	increased gray matter volume in right angular and posterior parahippocampal gyri and left temporal lobe	MRI –cerebral morphology	10
Hölzel et al. (2008)	Vipassana meditation	MRI – morphology;	Increased gray matter volume in left temporal lobe	MRI –cerebral morphology	20

meditators recruited from a monastery (n = 10), compared with non-meditators, reported significant alterations in the metabolites glutamate, N-acetyl-aspartate, and the N-acetyl-aspartate/creatine ratio in the posterior cingulate gyrus (internally-directed cognition) and left thalamus (control for a variety of cognitive functions), indicative of altered metabolism in these regions. This study (Fayed et al., 2013) also found a reduced diffusion coefficient in the left posterior parietal white matter (suggestive of increased local neuronal structure and connectivity) (Le Bihan et al., 2001) for meditators, which was significantly negatively correlated with years of meditation. Again, the relatively small number of subjects and diversity of MBTs employed begs caution in generalizing from these results, and replications with larger numbers of subjects are likely to shed more light on the functional significance of the brain regions involved.

Some progress towards these ends has been made in larger studies comparing experienced meditators with non-practicing control groups. For example, a study using practitioners of a moving-meditation technique (n = 46) reported greater cortical thickness in anterior brain areas, and reduced cortical thickness in posterior regions, with higher fractional anisotropy and greater cortical thickness in the region adjacent to the medial prefrontal cortex (Kang et al., 2013). The authors suggested that changes occurring in the frontal cortex may be associated with repeated practice of attentional and emotional regulations, but concluded that further study is needed to understand why both increases and decreases in local cortical thickness were observed. Also, a study comparing experienced meditators (n = 44 combined from several meditative traditions) using VBM showed increased gray matter volumes in the right orbito-frontal cortex and right hippocampus, areas involved in emotional regulation and response control (Luders et al., 2009). These results were confirmed specifically in the hippocampus and hippocampal subiculum in a subsequent study and analysis of previous data with experienced meditators compared with non-meditators (n = 50; n = 30 combined, from several meditative traditions) (Luders et al., 2013a,b). Interestingly a principal activity of the subiculum is to inhibit the HPA axis, thus limiting the response of the HPA axis to stressors, and perhaps providing insight into findings that social stress can affect gene expression act via HPA activation (Cole, 2008; Cole et al., 2009). While the latter three morphological studies (Luders et al., 2009, 2013a,b) each employed several styles of meditation, limiting the ability to attribute the results to particular practices, the relatively large sample sizes in these studies strengthens the general association between MBT practitioners and brain morphology and supports the need for longitudinal studies to determine if meditation per se can cause the changes of the type reported, or if other factors are relevant.

Although no studies have yet systematically compared the effects of different MBT practices on cerebral morphology, one VBM analysis of MRI data reported increased GM volume in the right angular and posterior parahippocampal gyri and left temporal lobe in subjects with 5 years or more practice in the Theravada tradition of Loving Kindness Meditation (n = 10), as compared with novices (Leung et al., 2013). While increased GM volume in the left temporal lobe had previously been observed in Vipassana meditators (Holzel et al., 2008), the right angular gyrus, which had not been previously reported to be involved with meditation (Decety and Lamm, 2007), is an important region within the temporoparietal junction involved in social cognition and empathy (Decety and Lamm, 2007). Again, while longitudinal studies comparing practices with controls are needed, these results support the notion that different types of MBTs employing different cognitive/emotional techniques could be chosen to preferentially activate different brain areas, a finding which could significantly inform the clinical use of MBTs by providing a rationale for recommending particular interventions in a patient- and pathology-matched manner.

Lastly, akin to results found for telomere activity as a measure of stress and aging, age-related gray matter loss is one neurological correlate of aging (Good et al., 2001). A study using VBM found that, while control subjects showed decreases with age in gray matter volume and attentional performance, this did not occur for experienced practitioners of Zen meditation (n = 13) (Pagnoni and Cekic, 2007). Similarly, a recent study using VBM with practitioners of a variety of meditation techniques (n = 50) reported that age-related gray matter loss was less pronounced in long-term meditators than in controls (Luders et al., 2014). Also, a systematic review concluded that meditation can offset age-related cognitive decline (Gard et al., 2014), suggesting the possibility of neuroprotective effects. If supported by longitudinal studies, these results would underscore the potential clinical and preventative value of MBTs in mitigating the well-documented loss of cortical volume associated with aging and could represent a low-cost methodology for reducing or delaying the onset of neuronal loss associated with some neurodegenerative diseases.

5. Discussion and conclusions

The studies reviewed here report a variety of functional genomic and neurological correlates of MBT practices. These build upon a background of studies investigating the physiology of mental/emotional stress and the neurological substrates of cognition and emotion, which have therein provided tools for developing a deeper understanding of MBT practices. These studies have significantly advanced our understanding of transcriptional pathways and neurological mechanisms relevant to MBTs, as well as the potential mechanisms of action by which MBTs influence health outcomes. Fig. 1 illustrates the most prominent mechanisms of action arising from the literature reviewed here.

Our subjective experience of self is reflected in a variety cognitive-affective processes for which correlates have been identified at multiple levels in the physiology of the nervous system. As shown in Fig. 1, the impact of MBTs can be categorized as "top/down," i.e., stimulated by focused attention, intention, and cognitive practices, or "bottom/up," i.e., driven by practices such as meditation, breathing, and physical yoga, that produce direct effects on physiology and the nervous system (Taylor et al., 2010). These categories provide a foundation for an integrative psychophysiological framework that can be probed to further our understanding of the underlying substrates of MBTs (Taylor et al., 2010). In considering MBTs as a collection of approaches that unite the mind and the innate ability of the body to heal (Spencer and Jacobs, 2003), a broad theme emerges from the literature in which MBTs act as both neuromodulatory and immunomodulatory interventions, lending support to their implementation as potential wellness tools.

Enhanced salutogenesis via MBT practices is supported by the large proportion of studies surveyed here reporting reductions in stress. The biological foundations for using MBT practices for stress reduction and wellness are becoming more well-understood (Chiesa and Serretti, 2009; Praissman 2008; Sharma et al., 2008). Studies suggest that MBTs may impact health outcomes through a few interrelated pathways including HPA axis production of glucocorticoids and ANS balance of sympathetic and parasympathetic activity (see Fig. 1) which are key upstream mediators of gene expression, cellular aging, immune function, and healthy CNS function. The importance of HPA and ANS activity during periods of stress and rest is corroborated by the large literature on the effects of acute and chronic stress on immune function in states of both health and disease (Morey et al., 2015). A growing body of work has demonstrated the existence of stress-related gene expression markers (Cole, 2010), and identified HPA axis stress responses as an underlying substrate. A primary means of HPA axis stress modulation is via glucocorticoid receptor-meditated production of the stress-response protein corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), both of which are produced in response to biological stress and mediate the production of cortisol (Fig. 1). Stress-induced cortisol production is also associated with neuronal loss (Bao et al., 2008), changes in neural network activity (vanCampen et al., 2015), over-expression of genes responsive to pro-inflammatory NF-κB transcription factors and reduced expression of transcripts bearing anti-inflammatory response elements for glucocorticoids (Cole, 2010). Chronic cortisol elevations due to psychological and psychosocial stress can cause the immune system to become less sensitive to cortisol, resulting in compromised immune responses (Morey et al., 2015; Cole et al., 2009). Stress reduction through MBT practices may improve health outcomes by lessening allostatic load and the associated neuroendocrine signaling that results in downstream immunologic and nervous system consequences. More plainly put, MBTs can act by removing or ameliorating the harmful effects of chronic stressors, thus allowing the body's innate healing responses to be fully expressed. Given these insights, it may be useful for future studies of MBT interventions to prioritize sensitive and frequent measurement of HPA and ANS activity for greater mechanistic understanding and also potential optimization or refinement of interventions.

A related mechanism by which MBTs may modulate the immune system is via the cholinergic anti-inflammatory pathway (Tracey, 2007). The vagus nerve complex forms a bi-directional neural connection between the immune and nervous systems (Tracey, 2002, 2007) which acts to regulate inflammation and innate immune responses during tissue injury and pathogen invasion (Fig. 1). Efferent vagal signaling from prefrontal cortex and amygdala (Thayer and Sternberg, 2006) can inhibit cytokine production via acetylcholine receptor signaling in the spleen (Tracey, 2007). Conversely, afferent vagal signaling is reflected in instantaneous heart rate variability (Tracey, 2007). Depressed vagus nerve activity is associated with increased morbidity and mortality in sepsis, rheumatoid arthritis, lupus, sarcoidosis, inflammatory bowel diseases, trauma (Tracey, 2007), depression and stress (Porges, 1995). Enhanced vagal tone is associated with a variety of benefits, including increased social and psychological well-being (Kok and Fredrickson, 2010), and has been suggested as a neurological basis for the effects of acupuncture and meditation (Oke and Tracey, 2009) and yoga (Field, 2011). While these results are in accord with data indicating positive relationships between stress, adversity, and inflammation, further research is required to empirically establish vagus nerve activity as a focal substrate for improved health related to MBTs.

Another means by which MBTs impact the body is through influencing the activity of the nervous system, or neuromodulation. Neuromodulation via MBTs is supported by studies demonstrating that particular MBTs can elicit characteristic patterns of brain activity, including increased activity in specific brain regions and specific changes in connectivity (Fig. 1). Such a viewpoint is in accord with the notion that meditation can stimulate cortical plasticity and produce changes in neural structures associated with cognitive restructuring and learning (Fell et al., 2010), and is supported by the broader view that cognitive interventions can exert their effects on brain and behavioral development through neuromodulatory mechanisms involving plasticity (Li, 2013). Further studies aimed at elucidating the roles of MBTs in changing structure and/or function of brain areas associated with attention, learning, and emotional regulation may help to develop a set of guidelines for using MBTs for specific neurobehavioral goals.

A promising direction for future research is the study of the microbiome. The bi-directional gut-brain axis, composed of hormonal and neuronal signaling pathways, enables changes in the gut microbiota to influence brain activity, including mood (Conlon, 2015) (Fig. 1). From the "top/down," stress can alter colonic motor activity, in turn affecting gut microbiota profiles, for example by reducing the numbers of potentially beneficial Lactobacillus (Lutgendorff et al., 2008). Microbiota profiles are dependent upon stress and other lifestyle factors such as exercise (Conlon, 2015), suggesting that stress reduction via MBT practices could favorably impact the microbiome, in turn facilitating enhanced physical and mental well-being. Further research is needed to more clearly elucidate the degree to which microbiota are sensitive to MBTs, however the emerging research indicates that the microbiome is sensitive to stress and dramatically influences the immune system, brain, and behavior.

The diversity of practices and physiological correlates reviewed here also suggests that it is important for researchers to understand the fundamentals of therapies they are studying (Lutz et al., 2008). Such an integrative and immersive approach requires that researchers work closely with experts in MBTs to better understand the non-Western systems from which many therapies originate (Loizzo 2014), a process that is likely to benefit both scientists and practitioners (Rapgay et al., 2000). Also, it may be important to consider personal and cultural factors such as, "place," "person," and "practice," in order to more clearly delineate the effects of MBT techniques themselves (Thomas and Cohen, 2014).

While clear progress has been made in elucidating the physiological correlates of MBT practices, significant questions and limitations remain. A large proportion of the studies surveyed here report correlations rather than causal relationships with MBT practices, indicating the need for replications and longitudinal studies to assess veracity and causality with MBT practices. This is especially important in light of the broad range of MBTs studied, the diversity of experimental designs employed, and other factors such as significant lifestyle differences that may exist between control subjects and dedicated MBT practitioners. Controlled studies on gene expression and psychosocial stress emerge in large part from one research group (Cole, 2014; Slavich and Cole, 2013), and a broader research effort is now needed to answer many of the questions raised by these studies. And while much has been learned about the physiology of psychosocial stress, only a small number of studies have directly addressed the effects of MBT practices on gene expression. While the results surveyed suggest that different practices may yield different gene expression profiles, raising the possibility of choosing particular practices to treat inflammation, depression, hyperactivity, etc., further work on gene profiling and associated proteomics is needed to support this hypothesis. The results of EEG and neuroimaging studies present a broad patchwork of correlations and effects of MBT practices, yet clear, replicated data is lacking on clinically important questions regarding the interpretation and relevance of the results, variability across populations, targeting of specific brain functions, and the possible use of specific techniques for treating particular brain pathologies such as neurodegenerative diseases. Controlled longitudinal studies are needed to determine the efficacy and potential therapeutic specificity of particular practices. Finally, almost no studies have been done to address possible contraindications for using MBT techniques in patient populations with, for example, mental illness or other conditions.

The results of many of the studies reviewed here show that the physiological data cannot be meaningfully understood without equally considering the role of subjective experience. For example, a study on the functional genomic correlates of subjective social isolation found that the results were independent of the objective size of an individual's social network; the significant factor was the subjective sense of loneliness (Cole et al., 2007). For this study, an objective measure of social support would have failed to uncover the relationship between perceived loneliness and inflammatory gene response. Similarly, results from neuroimaging have relevance beyond merely knowing which brain regions are involved in particular tasks. Neuroimaging has led to a clearer view of the neural patterning involved in many high-level tasks, and the interrelatedness of emotion with various types of cognition, including perception, attention, memory, and decision making (Dolcos et al., 2011). Further, the data reviewed here supports the hypothesis that MBTs using particular emotive/cognitive processes are able to modulate brain function and alter morphology. This suggests a need for study designs that clearly account for subjects' subjective internal states; qualitative analyses derived from interviews with study participants may be helpful in further interpretation of the psychospiritual factors involved in MBTs (Moritz et al., 2011).

The body of research reviewed here illustrates the existence of a number of clinically relevant physiological correlates of MBTs. Results from functional genomics and neuroimaging have begun to elucidate some of the pathways by which emotional, cognitive and psychosocial factors can influence health outcomes and well-being, and this knowledge has significantly contributed to a developing psychophysiological theory of MBTs (Taylor et al., 2010). These results have already contributed to a clearer notion of the role of stress in health and well-being, a better understanding of the use of MBTs for stress reduction (Chiesa and Serretti, 2009; Praissman, 2008; Sharma et al., 2008) and to advances in understanding the means by which MBT practices may act as neuromodulators via activation of neural structures associated with cognitive restructuring and learning (Fell et al., 2010).

In recent years, basic sciences and clinical data have fostered the evidence-based integration of MBTs into clinical care (Ernst et al., 2007; Jonas et al., 2013). While further studies are needed to clarify the clinical efficacy of many MBTs (Jonas et al., 2013), to assess safety and possible contraindications, and to determine which aspects of specific MBTs are principally responsible for benefits (Creswell et al., 2012), integration into clinical practice of MBTs and other Integrative Medicine modalities holds significant promise for reducing the burden of chronic diseases and lowering the overall cost of healthcare (Herman et al., 2014).

References

Amihai, I., Kozhevnikov, M., 2014. Arousal vs. relaxation: a comparison of the neurophysiological and cognitive correlates of Vajrayana and Theravada meditative practices. PLoS One 9 (7), e102990.

Andrews-Hanna, J.R., 2012. The brain's default network and its adaptive role in internal mentation. Neuroscientist 18 (3), 251–270.

Antoni, M.H., Lutgendorf, S.K., Blomberg, B., Carver, C.S., Lechner, S., Diaz, A., Stagl, J., Arevalo, J.M., Cole, S.W., 2012. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol. Psychiatry 71 (4), 366–372.

Astin, J.A., Shapiro, S.L., Eisenberg, D.M., Forys, K.L., 2003. Mind-body medicine: state of the science, implications for practice. J. Am. Board Fam. Pract. 16 (2), 131–147.

Bao, A.M., Meynen, G., Swaab, D.F., 2008. The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain. Res. Rev. 57 (2), 531–553.

Barrows, K.A., Jacobs, B.P., 2002. Mind-body medicine. An introduction and review of the literature. Med. Clin. North Am. 86 (1), 11–31.

Benson, H., Greenwood, M.M., Klemchuk, H., 1975. The relaxation response: psychophysiologic aspects and clinical applications. Int. J. Psychiatry Med. 6 (1–2), 87–98.

Bierhaus, A., Wolf, J., Andrassy, M., Rohleder, N., Humpert, P.M., Petrov, D., Ferstl, R., von Eynatten, M., Wendt, T., Rudofsky, G., Joswig, M., Morcos, M., Schwaninger, M., McEwen, B., Kirschbaum, C., Nawroth, P.P., 2003. A mechanism converting psychosocial stress into mononuclear cell activation. Proc. Natl. Acad. Sci. U. S. A. 100 (4), 1920–1925.

Black, D.S., Cole, S.W., Irwin, M.R., Breen, E., St Cyr, N.M., Nazarian, N., Khalsa, D.S., Lavretsky, H., 2013. Yogic meditation reverses NF-kappaB and IRF-related transcriptome dynamics in leukocytes of family dementia caregivers in a randomized controlled trial. Psychoneuroendocrinology 38 (3), 348–355.

Borovikova, L.V., Ivanova, S., Zhang, M., Yang, H., Botchkina, G.I., Watkins, L.R., Wang, H., Abumrad, N., Eaton, J.W., Tracey, K.J., 2000. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 405 (6785), 458–462.

Bower, J.E., Greendale, G., Crosswell, A.D., Garet, D., Sternlieb, B., Ganz, P.A., Irwin, M.R., Olmstead, R., Arevalo, J., Cole, S.W., 2014. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial. Psychoneuroendocrinology 43, 20–29.

Brewer, J.A., Worhunsky, P.D., Gray, J.R., Tang, Y.Y., Weber, J., Kober, H., 2011. Meditation experience is associated with differences in default mode network activity and connectivity. Proc. Natl. Acad. Sci. U. S. A. 108 (50), 20254–20259.

Cabeza, R., Nyberg, L., 2000. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J. Cogn. Neurosci. 12 (1), 1–47.

Cacioppo, J.T., Cacioppo, S., 2014. Social relationships and health: the toxic effects of perceived social isolation. Soc. Pers. Psychol. Compass 8 (2), 58–72.

Cahn, B.R., Polich, J., 2006. Meditation states and traits: EEG, ERP, and neuroimaging studies. Psychol. Bull. 132 (2), 180–211.

Cahn, B.R., Delorme, A., Polich, J., 2010. Occipital gamma activation during Vipassana meditation. Cogn. Process. 11 (1), 39–56.

Cahn, B.R., Delorme, A., Polich, J., 2013. Event-related delta, theta, alpha and gamma correlates to auditory oddball processing during Vipassana meditation. Soc. Cogn. Affect. Neurosci. 8 (1), 100–111.

Carlson, L.E., Beattie, T.L., Giese-Davis, J., Faris, P., Tamagawa, R., Fick, L.J., Degelman, E.S., Speca, M., 2014. Mindfulness-based cancer recovery and supportive-expressive therapy maintain telomere length relative to controls in distressed breast cancer survivors. Cancer 121 (3), 476–484.

Chiesa, A., Serretti, A., 2009. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. J. Altern. Complement. Med. 15 (5), 593–600.

Cohen, S., Janicki-Deverts, D., Miller, G.E., 2007. Psychological stress and disease. JAMA 298 (14), 1685–1687.

Cole, S.W., Nagaraja, A.S., Lutgendorf, S.K., Green, P.A., Sood, A.K., 2015. Sympathetic nervous system regulation of the tumour microenvironment. Nat. Rev. Cancer. 15 (9), 563–572.

Cohen, L., Cole, S.W., Sood, A.K., Prinsloo, S., Kirschbaum, C., Arevalo, J.M., Jennings, N.B., Scott, S., Vence, L., Wei, Q., Kentor, D., Radvanyi, L., Tannir, N., Jonasch, E., Tamboli, P., Pisters, L., 2012. Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: role of inflammatory signaling. PLoS One 7 (8), e42324.

Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., Turner, R.B., 2012. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc. Natl. Acad. Sci. U. S. A. 109 (16), 5995–5999.

Cole, S.W., Hawkley, L.C., Arevalo, J.M., Sung, C.Y., Rose, R.M., Cacioppo, J.T., 2007. Social regulation of gene expression in human leukocytes. Genome Biol. 8 (9), R189.

Cole, S.W., Mendoza, S.P., Capitanio, J.P., 2009. Social stress desensitizes lymphocytes to regulation by endogenous glucocorticoids: insights from in vivo cell trafficking dynamics in rhesus macaques. Psychosom. Med. 71 (6), 591–597.

Cole, S.W., Arevalo, J.M., Takahashi, R., Sloan, E.K., Lutgendorf, S.K., Sood, A.K., Sheridan, J.F., Seeman, T.E., 2010. Computational identification of gene-social environment interaction at the human IL6 locus. Proc. Natl. Acad. Sci. U. S. A. 107 (12), 5681–5686.

Cole, S.W., 2008. Social regulation of leukocyte homeostasis: the role of glucocorticoid sensitivity. Brain Behav. Immun. 22 (7), 1049–1055.

Cole, S.W., 2010. Elevating the perspective on human stress genomics. Psychoneuroendocrinology 35 (7), 955–962.

Cole, S.W., 2014. Human social genomics. PLoS Genet. 10 (8), e1004601.

Compare, A., Zarbo, C., Shonin, E., Van Gordon, W., Marconi, C., 2014. Emotional regulation and depression: a potential mediator between heart and mind. Cardiovasc. Psychiatry Neurol. 2014, 324374.

Corby, J.C., Roth, W.T., Zarcone Jr., V.P., Kopell, B.S., 1978. Psychophysiological correlates of the practice of Tantric Yoga meditation. Arch. Gen. Psychiatry 35 (5), 571–577.

Creswell, J.D., Irwin, M.R., Burklund, L.J., Lieberman, M.D., Arevalo, J.M., Ma, J., Breen, E.C., Cole, S.W., 2012. Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized controlled trial. Brain Behav. Immun. 26 (7), 1095–1101.

Engström, M., Pihlsgård, J., Lundberg, P., Söderfeldt, B., 2010. Functional magnetic resonance imaging of hippocampal activation during silent mantra meditation. J. Altern. Complement. Med. 12, 1253–1258.

Decety, J., Lamm, C., 2007. The role of the right temporoparietal junction in social interaction: how low-level computational processes contribute to meta-cognition. Neuroscientist 13 (6), 580–593.

Dolcos, F., Iordan, A.D., Dolcos, S., 2011. Neural correlates of emotion-cognition interactions: a review of evidence from brain imaging investigations. J. Cogn. Psychol. (Hove) 23 (6), 669–694.

Dusek, J.A., Otu, H.H., Wohlhueter, A.L., Bhasin, M., Zerbini, L.F., Joseph, M.G., Benson, H., Libermann, T.A., 2008. Genomic counter-stress changes induced by the relaxation response. PLoS One 3 (7), e2576.

Engstrom, M., Pihlsgard, J., Lundberg, P., Soderfeldt, B., 2010. Functional magnetic resonance imaging of hippocampal activation during silent mantra meditation. J. Altern. Complement. Med. 16 (12), 1253–1258.

Epel, E., Daubenmier, J., Moskowitz, J.T., Folkman, S., Blackburn, E., 2009. Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and telomeres. Ann. N. Y. Acad. Sci. 1172, 34–53.

Ernst, E., Pittler, M.H., Wider, B., Boddy, K., 2007. Mind-body therapies: are the trial data getting stronger? Altern. Ther. Health Med. 13 (5), 62–64.

Fayed, N., Lopez Del Hoyo, Y., Andres, E., Serrano-Blanco, A., Bellon, J., Aguilar, K., Cebolla, A., Garcia-Campayo, J., 2013. Brain changes in long-term zen meditators using proton magnetic resonance spectroscopy and diffusion tensor imaging: a controlled study. PLoS One 8 (3), e58476.
Feinstein, D.C.D., 2010. Modulating gene expression through psychotherapy: the contribution of noninvasive somatic interventions. Rev. Gen. Psychol. 14 (4), 283–295.
Fell, J., Axmacher, N., Haupt, S., 2010. From alpha to gamma: electrophysiological correlates of meditation-related states of consciousness. Med. Hypotheses 75 (2), 218–224.
Ferrarelli, F., Smith, R., Dentico, D., Riedner, B.A., Zennig, C., Benca, R.M., Lutz, A., Davidson, R.J., Tononi, G., 2013. Experienced mindfulness meditators exhibit higher parietal-occipital EEG gamma activity during NREM sleep. PLoS One 8 (8), e73417.
Field, T., 2011. Yoga clinical research review. Complement. Ther. Clin. Pract. 17 (1), 1–8.
Fox, K.C., Nijeboer, S., Dixon, M.L., Floman, J.L., Ellamil, M., Rumak, S.P., Sedlmeier, P., Christoff, K., 2014. Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. Neurosci. Biobehav. Rev. 43, 48–73.
Fredrickson, B.L., Grewen, K.M., Coffey, K.A., Algoe, S.B., Firestine, A.M., Arevalo, J.M., Ma, J., Cole, S.W., 2013. A functional genomic perspective on human well-being. Proc. Natl. Acad. Sci. U. S. A. 110 (33), 13684–13689.
Gard, T., Holzel, B.K., Lazar, S.W., 2014. The potential effects of meditation on age-related cognitive decline: a systematic review. Ann. N. Y. Acad. Sci. 1307, 89–103.
Garland, E.L., Howard, M.O., 2009. Neuroplasticity, psychosocial genomics, and the biopsychosocial paradigm in the 21st century. Health Soc. Work 34 (3), 191–199.
Garrison, K.A., Scheinost, D., Constable, R.T., Brewer, J.A., 2014. BOLD signal and functional connectivity associated with loving kindness meditation. Brain Behav. 4 (3), 337–347.
Giordano, J., Boatwright, D., Stapleton, S., Huff, L., 2002. Blending the boundaries: steps toward an integration of complementary and alternative medicine into mainstream practice. J. Altern. Complement. Med. 8 (6), 897–906.
Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14 (1 Pt 1), 21–36.
Grant, J.A., Courtemanche, J., Duerden, E.G., Duncan, G.H., Rainville, P., 2010. Cortical thickness and pain sensitivity in zen meditators. Emotion 10 (1), 43–53.
Herman, P.M., Dodds, S.E., Logue, M.D., Abraham, I., Rehfeld, R.A., Grizzle, A.J., Urbine, T.F., Horwitz, R., Crocker, R.L., Maizes, V.H., 2014. IMPACT-Integrative Medicine PrimAry Care Trial: protocol for a comparative effectiveness study of the clinical and cost outcomes of an integrative primary care clinic model. BMC Complement. Altern. Med. 14, 132.
Holzel, B.K., Ott, U., Gard, T., Hempel, H., Weygandt, M., Morgen, K., Vaitl, D., 2008. Investigation of mindfulness meditation practitioners with voxel-based morphometry. Soc. Cogn. Affect. Neurosci. 3 (1), 55–61.
Irwin, M.R., Cole, S.W., 2011. Reciprocal regulation of the neural and innate immune systems. Nat. Rev. Immunol. 11 (9), 625–632.
Jacobs, T.L., Epel, E.S., Lin, J., Blackburn, E.H., Wolkowitz, O.M., Bridwell, D.A., Zanesco, A.P., Aichele, S.R., Sahdra, B.K., MacLean, K.A., King, B.G., Shaver, P.R., Rosenberg, E.L., Ferrer, E., Wallace, B.A., Saron, C.D., 2011. Intensive meditation training, immune cell telomerase activity, and psychological mediators. Psychoneuroendocrinology 36 (5), 664–681.
Jang, J.H., Jung, W.H., Kang, D.H., Byun, M.S., Kwon, S.J., Choi, C.H., Kwon, J.S., 2011. Increased default mode network connectivity associated with meditation. Neurosci. Lett. 487 (3), 358–362.
Jonas, W.B., Eisenberg, D., Hufford, D., Crawford, C., 2013. The evolution of complementary and alternative medicine (CAM) in the USA over the last 20 years. Forsch. Komplementmed. 20 (1), 65–72.
Kaliman, P., Alvarez-Lopez, M.J., Cosin-Tomas, M., Rosenkranz, M.A., Lutz, A., Davidson, R.J., 2014. Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators. Psychoneuroendocrinology 40, 96–107.
Kang, D.H., Jo, H.J., Jung, W.H., Kim, S.H., Jung, Y.H., Choi, C.H., Lee, U.S., An, S.C., Jang, J.H., Kwon, J.S., 2013. The effect of meditation on brain structure: cortical thickness mapping and diffusion tensor imaging. Soc. Cogn. Affect. Neurosci. 8 (1), 27–33.
Kok, B.E., Fredrickson, B.L., 2010. Upward spirals of the heart: autonomic flexibility, as indexed by vagal tone, reciprocally and prospectively predicts positive emotions and social connectedness. Biol. Psychol. 85 (3), 432–436.
Kuntsevich, V., Bushell, W.C., Theise, N.D., 2010. Mechanisms of yogic practices in health, aging, and disease. Mt. Sinai J. Med. 77 (5), 559–569.
Lavretsky, H., Epel, E.S., Siddarth, P., Nazarian, N., Cyr, N.S., Khalsa, D.S., Lin, J., Blackburn, E., Irwin, M.R., 2013. A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. Int. J. Geriatr. Psychiatry 28 (1), 57–65.
Lazar, S.W., Bush, G., Gollub, R.L., Fricchione, G.L., Khalsa, G., Benson, H., 2000. Functional brain mapping of the relaxation response and meditation. Neuroreport 11 (7), 1581–1585.
Le Bihan, D., Mangin, J.-F., Poupon, C., Clark, C.A., Pappata, S., Molko, N., Chabriat, H., 2001. Diffusion tensor imaging: concepts and applications. J. Magn. Reson. Imaging 13, 534–546.
Lehmann, D., Faber, P.L., Achermann, P., Jeanmonod, D., Gianotti, L.R., Pizzagalli, D., 2001. Brain sources of EEG gamma frequency during volitionally meditation-induced, altered states of consciousness, and experience of the self. Psychiatry Res. 108 (2), 111–121.
Leung, M.K., Chan, C.C., Yin, J., Lee, C.F., So, K.F., Lee, T.M., 2013. Increased gray matter volume in the right angular and posterior parahippocampal gyri in loving-kindness meditators. Soc. Cogn. Affect. Neurosci. 8 (1), 34–39.
Lee, T.M., Leung, M.K., Hou, W.K., Tang, J.C., Yin, J., So, K.F., Lee, C.F., Chan, C.C., 2012. Distinct neural activity associated with focused-attention meditation and loving-kindness meditation. PLoS One 7 (8), e40054.
Li, Q.Z., Li, P., Garcia, G.E., Johnson, R.J., Feng, L., 2005. Genomic profiling of neutrophil transcripts in Asian Qigong practitioners: a pilot study in gene regulation by mind-body interaction. J. Altern. Complement. Med. 11 (1), 29–39.
Li, S.C., 2013. Neuromodulation and developmental contextual influences on neural and cognitive plasticity across the lifespan. Neurosci. Biobehav. Rev. 37 (9 Pt. B), 2201–2208.
Loizzo, J., 2014. Meditation research, past, present, and future: perspectives from the Nalanda contemplative science tradition. Ann. N. Y. Acad. Sci. 1307, 43–54.
Loucks, E.B., Sullivan, L.M., D'Agostino Sr., R.B., Larson, M.G., Berkman, L.F., Benjamin, E.J., 2006. Social networks and inflammatory markers in the Framingham Heart Study. J. Biosoc. Sci. 38 (6), 835–842.
Loucks, E.B., Britton, W.B., Howe, C.J., Eaton, C.B., Buka, S.L., 2015. Positive associations of dispositional mindfulness with cardiovascular health: the new england family study. Int. J. Behav. Med. 22 (4), 540–550.
Luders, E., Toga, A.W., Lepore, N., Gaser, C., 2009. The underlying anatomical correlates of long-term meditation: larger hippocampal and frontal volumes of gray matter. Neuroimage 45 (3), 672–678.
Luders, E., Kurth, F., Toga, A.W., Narr, K.L., Gaser, C., 2013a. Meditation effects within the hippocampal complex revealed by voxel-based morphometry and cytoarchitectonic probabilistic mapping. Front. Psychol. 4 (398).
Luders, E., Thompson, P.M., Kurth, F., Hong, J.Y., Phillips, O.R., Wang, Y., Gutman, B.A., Chou, Y.Y., Narr, K.L., Toga, A.W., 2013b. Global and regional alterations of hippocampal anatomy in long-term meditation practitioners. Hum. Brain Mapp. 34 (12), 3369–3375.
Luders, E., Cherbuin, N., Kurth, F., 2014. Forever young(er): potential age-defying effects of long-term meditation on gray matter atrophy. Front. Psychol. 5 (1551).
Luders, E., Cherbuin, N., Kurth, F., 2015. Forever Young(er): potential age-defying effects of long-term meditation on gray matter atrophy. Front. Psychol. 5, 1551.
Lutgendorf, S.K., Cole, S., Costanzo, E., Bradley, S., Coffin, J., Jabbari, S., Rainwater, K., Ritchie, J.M., Yang, M., Sood, A.K., 2003. Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. Clin. Cancer Res. 9 (12), 4514–4521.
Lutgendorff, F., Akkermans, L.M., Söderholm, J.D., 2008. The role of microbiota and probiotics in stress-induced gastro-intestinal damage. Curr. Mol. Med. 8 (4), 282–298.
Lutgendorf, S.K., DeGeest, K., Sung, C.Y., Arevalo, J.M., Penedo, F., Lucci 3rd, J., Goodheart, M., Lubaroff, D., Farley, D.M., Sood, A.K., Cole, S.W., 2009. Depression, social support, and beta-adrenergic transcription control in human ovarian cancer. Brain Behav. Immun. 23 (2), 176–183.
Lutz, A., Greischar, L.L., Rawlings, N.B., Ricard, M., Davidson, R.J., 2004. Long-term meditators self-induce high-amplitude gamma synchrony during mental practice. Proc. Natl. Acad. Sci. U. S. A. 101 (46), 16369–16373.
Lutz, A., Brefczynski-Lewis, J., Johnstone, T., Davidson, R.J., 2008. Regulation of the neural circuitry of emotion by compassion meditation: effects of meditative expertise. PLoS One 3 (3), e1897.
Lutz, A., Greischar, L.L., Perlman, D.M., Davidson, R.J., 2009. BOLD signal in insula is differentially related to cardiac function during compassion meditation in experts vs. novices. Neuroimage 47 (3), 1038–1046.
Manna, A., Raffone, A., Perrucci, M.G., Nardo, D., Ferretti, A., Tartaro, A., Londei, A., Del Gratta, C., Belardinelli, M.O., Romani, G.L., 2010. Neural correlates of focused attention and cognitive monitoring in meditation. Brain Res. Bull. 82 (1-2), 46–56.
Marchand, W.R., 2014. Neural mechanisms of mindfulness and meditation: evidence from neuroimaging studies. World J. Radiol. 6 (7), 471–479.
Marsland, A.L., Gianaros, P.J., Prather, A.A., Jennings, J.R., Neumann, S.A., Manuck, S.B., 2007. Stimulated production of proinflammatory cytokines covaries inversely with heart rate variability. Psychosom. Med. 69 (8), 709–716.
Mascaro, J.S., Rilling, J.K., Tenzin Negi, L., Raison, C.L., 2013. Compassion meditation enhances empathic accuracy and related neural activity. Soc. Cogn. Affect. Neurosci. 8 (1), 48–55.
Miller, G.E., Chen, E., Sze, J., Marin, T., Arevalo, J.M., Doll, R., Ma, R., Cole, S.W., 2008. A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-kappaB signaling. Biol. Psychiatry 64 (4), 266–272.
Miller, G.E., Rohleder, N., Cole, S.W., 2009. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. Psychosom. Med. 71 (1), 57–62.
Miller, G.E., Murphy, M.L., Cashman, R., Ma, R., Ma, J., Arevalo, J.M., Kobor, M.S., Cole, S.W., 2014. Greater inflammatory activity and blunted glucocorticoid signaling in monocytes of chronically stressed caregivers. Brain Behav. Immun. 41, 191–199.
Morey, J.N., Boggero, I.A., Scott, A.B., Segerstrom, S.C., 2015. Current Directions in Stress and Human Immune. Function. Curr. Opin. Psychol. 1 (5), 13–17.
Moritz, S., Kelly, M.T., Xu, T.J., Toews, J., Rickhi, B., 2011. A spirituality teaching program for depression: qualitative findings on cognitive and emotional change. Complement. Ther. Med. 19 (4), 201–207.

Murphy, M.L., Slavich, G.M., Rohleder, N., Miller, G.E., 2013. Targeted rejection triggers differential pro- and anti-inflammatory gene expression in adolescents as a function of social status. Clin. Psychol. Sci. 1 (1), 30–40.
National Institutes of Health, 2007. What is complementary and alternative medicine?, Retrieved 1/20/2015, 2015, from http://www.health.state.mn.us/divs/fpc/cww/CamBasics.pdf.
Nebel, K., Wiese, H., Stude, P., de Greiff, A., Diener, H.C., Keidel, M., 2005. On the neural basis of focused and divided attention. Brain Res. Cogn. Brain Res. 25 (3), 760–776.
Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential processing in our brain-a meta-analysis of imaging studies on the self. Neuroimage 31 (1), 440–457.
Ornish, D., Lin, J., Daubenmier, J., Weidner, G., Epel, E., Kemp, C., Magbanua, M.J., Marlin, R., Yglecias, L., Carroll, P.R., Blackburn, E.H., 2008. Increased telomerase activity and comprehensive lifestyle changes: a pilot study. Lancet Oncol. 9 (11), 1048–1057.
Ornish, D., Lin, J., Chan, J.M., Epel, E., Kemp, C., Weidner, G., Marlin, R., Frenda, S.J., Magbanua, M.J., Daubenmier, J., Estay, I., Hills, N.K., Chainani-Wu, N., Carroll, P.R., Blackburn, E.H., 2013. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. Lancet Oncol. 14 (11), 1112–1120.
Oke, S.L., Tracey, K.J., 2009. The inflammatory reflex and the role of complementary and alternative medical therapies. Ann. N. Y. Acad. Sci. 1172, 172–180.
Pagnoni, G., Cekic, M., 2007. Age effects on gray matter volume and attentional performance in Zen meditation. Neurobiol. Aging 28 (10), 1623–1627.
Park, G., Thayer, J.F., 2014. From the heart to the mind: cardiac vagal tone modulates top-down and bottom-up visual perception and attention to emotional stimuli. Front. Psychol. 5 (278).
Pavlov, V.A., Tracey, K.J., 2012. The vagus nerve and the inflammatory reflex-linking immunity and metabolism. Nat. Rev. Endocrinol. 8 (12), 743–754.
Porges, S.W., 1995. Cardiac vagal tone: a physiological index of stress. Neurosci. Biobehav. Rev. 19 (2), 225–233.
Praissman, S., 2008. Mindfulness-based stress reduction: a literature review and clinician's guide. J. Am. Acad. Nurse Pract. 20 (4), 212–216.
Qu, S., Olafsrud, S.M., Meza-Zepeda, L.A., Saatcioglu, F., 2013. Rapid gene expression changes in peripheral blood lymphocytes upon practice of a comprehensive yoga program. PLoS One 8 (4), e61910.
Rapgay, L., Rinpoche, V.L., Jessum, R., 2000. Exploring the nature and functions of the mind: a Tibetan Buddhist meditative perspective. Prog. Brain Res. 122, 507–515.
Rohleder, N., Marin, T.J., Ma, R., Miller, G.E., 2009. Biologic cost of caring for a cancer patient: dysregulation of pro- and anti-inflammatory signaling pathways. J. Clin. Oncol. 27 (18), 2909–2915.
Saatcioglu, F., 2013. Regulation of gene expression by yoga, meditation and related practices: a review of recent studies. Asian J. Psychiatr. 6 (1), 74–77.
Sharma, H., Datta, P., Singh, A., Sen, S., Bhardwaj, N.K., Kochupillai, V., Singh, N., 2008. Gene expression profiling in practitioners of Sudarshan Kriya. J. Psychosom. Res. 64 (2), 213–218.
Shimomura, T., Fujiki, M., Akiyoshi, J., Yoshida, T., Tabata, M., Kabasawa, H., Kobayashi, H., 2008. Functional brain mapping during recitation of Buddhist scriptures and repetition of the Namu Amida Butsu: a study in experienced Japanese monks. Turk. Neurosurg. 18 (2), 134–141.
Slavich, G.M., Cole, S.W., 2013. The emerging field of human social genomics. Clin. Psychol. Sci. 1 (3), 331–348.
Slavich, G.M., Irwin, M.R., 2014. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol. Bull. 140 (3), 774–815.
Spencer, J.W., Jacobs, J.J., 2003. Complementary and Alternative Medicine: an EvidenceBased Approach. Mosby, St. Louis, MO.
Swaab, D.F., Bao, A.M., Lucassen, P.J., 2005. The stress system in the human brain in depression and neurodegeneration. Ageing Res. Rev. 4 (2), 141–194.
Takimoto-Ohnishi, E., Ohnishi, J., Murakami, K., 2012. Mind-body medicine: effect of the mind on gene expression. Pers. Med. Universe 1 (1), 2–6.
Taylor, A.G., Goehler, L.E., Galper, D.I., Innes, K.E., Bourguignon, C., 2010. Top-down and bottom-up mechanisms in mind-body medicine: development of an integrative framework for psychophysiological research. Explore (NY) 6 (1), 29–41.
Taylor, V.A., Daneault, V., Grant, J., Scavone, G., Breton, E., Roffe-Vidal, S., Courtemanche, J., Lavarenne, A.S., Marrelec, G., Benali, H., Beauregard, M., 2013. Impact of meditation training on the default mode network during a restful state. Soc. Cogn. Affect. Neurosci. 8 (1), 4–14.
Tei, S., Faber, P.L., Lehmann, D., Tsujiuchi, T., Kumano, H., Pascual-Marqui, R.D., Gianotti, L.R., Kochi, K., 2009. Meditators and non-meditators: EEG source imaging during resting. Brain Topogr. 22 (3), 158–165.
Thayer, J.F., Sternberg, E., 2006. Beyond heart rate variability: vagal regulation of allostatic systems. Ann. N. Y. Acad. Sci. 1088, 361–372.
Thomas, J.W., Cohen, M., 2014. A methodological review of meditation research. Front. Psychiatry 5, 74.
Tonhajzerova, I., Mokra, D., Visnovcova, Z., 2013. Vagal function indexed by respiratory sinus arrhythmia and cholinergic anti-inflammatory pathway. Respir. Physiol. Neurobiol. 187 (1), 78–81.
Taren, A.A., Gianaros, P.J., Greco, C.M., Lindsay, E.K., Fairgrieve, A., Brown, K.W., Rosen, R.K., Ferris, J.L., Julson, E., Marsland, A.L., Bursley, J.K., Ramsburg, J., Creswell, J.D., 2015. Mindfulness meditation training alters stress-related amygdala resting state functional connectivity: a randomized controlled trial. Soc. Cogn. Affect. Neurosci. 10 (12), 1758–1768.
Tracey, K.J., 2002. The inflammatory reflex. Nature 420 (6917), 853–859.
Tracey, K.J., 2007. Physiology and immunology of the cholinergic antiinflammatory pathway. J. Clin. Invest. 117 (2), 289–296.
Travis, F., Shear, J., 2010. Focused attention, open monitoring and automatic self-transcending: categories to organize meditations from Vedic, Buddhist and Chinese traditions. Conscious. Cogn. 19 (4), 1110–1118.
Travis, F., Tecce, J., Arenander, A., Wallace, R.K., 2002. Patterns of EEG coherence, power, and contingent negative variation characterize the integration of transcendental and waking states. Biol. Psychol. 61 (3), 293–319.
Travis, F., Arenander, A., DuBois, D., 2004. Psychological and physiological characteristics of a proposed object-referral/self-referral continuum of self-awareness. Conscious. Cogn. 13 (2), 401–420.
Travis, F., 2014. Transcendental experiences during meditation practice. Ann. N. Y. Acad. Sci. 1307, 1–8.
Umberson, D., Montez, J.K., 2010. Social relationships and health: a flashpoint for health policy. J. Health Soc. Behav. 51 (Suppl), S54–S66.
vanCampen, J.S., Jansen, F.E., Pet, M.A., Otte, W.M., Hillegers, M.H., Joels, M., Braun, K.P., 2015. Relation between stress-precipitated seizures and the stress response in childhood epilepsy. Brain 138 (8), 2234–2248.
Vestergaard-Poulsen, P., van Beek, M., Skewes, J., Bjarkam, C.R., Stubberup, M., Bertelsen, J., Roepstorff, A., 2009. Long-term meditation is associated with increased gray matter density in the brain stem. Neuroreport 20 (2), 170–174.
Wang, D.J., Rao, H., Korczykowski, M., Wintering, N., Pluta, J., Khalsa, D.S., Newberg, A.B., 2011. Cerebral blood flow changes associated with different meditation practices and perceived depth of meditation. Psychiatry Res. 191 (1), 60–67.
Whitfield-Gabrieli, S., Ford, J.M., 2012. Default mode network activity and connectivity in psychopathology. Annu. Rev. Clin. Psychol. 8, 49–76.
Wolf, J.M., Rohleder, N., Bierhaus, A., Nawroth, P.P., Kirschbaum, C., 2009. Determinants of the NF-kappaB response to acute psychosocial stress in humans. Brain Behav. Immun. 23 (6), 742–749.
Yang, Y.C., McClintock, M.K., Kozloski, M., Li, T., 2013. Social isolation and adult mortality: the role of chronic inflammation and sex differences. J. Health Soc. Behav. 54 (2), 183–203.
Yang, Y.C., Schorpp, K., Harris, K.M., 2014. Social support, social strain and inflammation: evidence from a national longitudinal study of U.S. adults. Soc. Sci. Med. 107, 124–135.
Zhang, L., Hu, X.Z., Li, X., Li, H., Smerin, S., Russell, D., Ursano, R.J., 2014. Telomere length—a cellular aging marker for depression and post-traumatic stress disorder. Med. Hypotheses 83 (2), 182–185.