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Underlying Mechanisms of Mindfulness Meditation: Genomics, Circuits, and Networks

Gu Y *et al.* Neuropsychological Mechanisms of Mindfulness Meditation

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Abstract

Understanding neuropsychological mechanisms of mindfulness meditation has been a hot topic in recent years. This review was conducted with the goal of synthesizing empirical relationships *via* the genomics, circuits and networks between mindfulness meditation and mental disorders. We describe progress made in assessing the effects of mindfulness meditation on gene expression in immune cells, with particular focus on stress-related inflammatory markers and associated biological pathways. We then focus on key brain circuits associated with mindfulness practices and effects on symptoms of mental disorders, and expand our discussion to identify three key brain networks associated with mindfulness practices including default mode network, central executive network, and salience network. More research efforts need to be devoted into identifying underlying neuropsychological mechanisms of mindfulness meditation on how it alleviates mental disorders symptoms.

Key Words: Mindfulness meditation; Gene expression; Neural circuits; Neural networks

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Core Tip: More recently, understanding neuropsychological mechanisms of mindfulness meditation (MM) has been a hot topic. We describe progress made in assessing ³ the effects of MM on gene expression in inflammatory processes, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss primary brain circuits related to MM and effects on symptoms of mental disorders, and three brain networks associated with MM including default mode network, central executive network, and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level would be necessary.

INTRODUCTION

Mindfulness meditation (MM) refers to a conscious, non-judgmental way of concentrating on the present^[1-3], which has originated from a systematically Buddhist notion 2,550 years ago^[4]. It is an instant and tranquil mental state with observing all mental contents (including virtually sensations, perceptions, cognitions and feelings) at any given moment^[5, 6]. MM was first introduced into the mainstream medical practices by Dr. Kabat-Zinn of the Massachusetts Medical School in 1982^[7]. MM developing strategies include sustained attention training, somatic and non-judgmental awareness, emotion control, detaching from a self-centered view and acceptance of the “here-and-now”^[8-10]. The great majority of these MM research is about clinical practices^[11], especially in mental disorders such as anxiety disorder, major depressive disorder, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, eating disorder and substance abuse^[12-16].

In recent years, there has been a burgeoning interest in underlying mechanisms of MM, mainly due to increasing evidence of its positive effects on mental disorders and physical well-being. In parallel to research evaluating the effectiveness of these MM approaches, a second line of investigation focuses on unraveling the neurophysiological and psychological processes involved^[17]. Recent functional and structural neuroimaging studies are beginning to provide evidence that diverse brain areas have been congruously found in both beginners undergoing temporary practice and experienced meditators^[18, 19]. These areas have been determined to specialize in some of these critical functions^[20]. However, many of these neural areas or correlates are much more complicated and the so-called “networks or neural circuits” are likely to perform higher-level processes and multiple mental functions^[21].

Understanding neuropsychological mechanisms of MM has been a hot topic in recent years. This review was conducted with the goal of synthesizing empirical relationships via the genomics, circuits and networks between MM and mental disorders. We describe progress made in assessing the effects of MM on gene expression in immune

cells, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss key brain circuits related to MM and effects on symptoms of mental disorders, and three brain networks associated with MM including default mode network (DMN), central executive network (CEN), and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level would be necessary.

GENETIC STUDIES OF MINDFULNESS MEDITATION

Genetic studies of MM showed that differential transcription occurs in genes involved in DNA damage response, oxidative stress, and inflammatory metabolism processes, in both short and long-term practitioners^[22-24]. In most studies, these results were correlated with reduced stress and fatigue, improved immune response, and clinical symptoms. A few cases study neurotrophins^[25, 26]. Transcriptomic analyses were performed in both healthy and clinical populations combining diverse MM activities in several longitudinal and mixed design studies and obtained similar results^[24, 27-29].

Creswell and colleagues reported NF- κ B-related gene expression in older adults responding to the Mindfulness-Based Stress Reduction (MBSR) intervention compared to a wait-list control group, in contrast, showed to be up-regulated^[30]. Bakker and collaborators showed that genetic variation for muscarinic acetylcholine receptor M2 (CHRM2) and the μ 1 opioid receptor (OPRM1) moderate the positive impact on the level of positive affect following Mindfulness-based Cognitive Therapy (MBCT) with depressive symptoms, and proposed that variation on genetic factors in response to MBCT may be contingent associated with the regulation of positive affect^[32].

In the study by Dada *et al*^[33], intraocular pressure in primary open angle glaucoma appeared significantly decreased after MM. Significant upregulation of the anti-inflammatory genes and downregulation of the proinflammatory genes were found in glaucoma patients who underwent a 3-week MM course. These results indicate that MM has direct impact on trabecular meshwork gene expression on ocular tissues. Similarly, the practice of MM was shown to improve immune function by normalizing

stress-related serum biomarkers, and positively modifying gene expression^[25]. Moreover, increased blood levels of brain derived neurotrophic factor (BDNF) indicated a positive impact on retinal ganglion cells rescue from death in patients with primary open angle glaucoma^[26].

GENOME-WIDE ASSOCIATION STUDIES

Genome-wide approaches to gene activity have started to elucidate the effects of MM on gene modulation^[34]. For example, utilizing microarray analysis of global mRNAs to study ⁵ the methylome of peripheral blood mononuclear cells of 17 experienced meditators of one-day intensive MM practice found 61 differentially methylated regions^[35]. Similarly, studying the transcriptomic effects in six individuals after twice-daily transcendental MM practice revealed 200 genes differentially expressed^[24]. ⁶ Studies focusing on the impact of MM for treating hypertension, irritable bowel syndrome and inflammatory bowel disease have observed that several genes related to fundamental pathways to be differentially expressed^[27, 28].

Nevertheless, most of the previous studies are cross-sectional studies with small sample sizes^[22, 26, 36, 37]. The Large-scale genomic study, by Chandran *et al*^[38], analyzed the meditation-specific core network of advanced MM practice, rather than changes in expression of a few individual genes. They observed that the up-regulated RNA coexpression networks are directly related to the immune response, including 68 genes differentially expressed after MM. Interestingly, these authors reported that the top 10 ⁶ hub genes in the up-regulated module included many previously identified genes known to regulate the immune system and related to type I interferon signaling pathway. They identified nine coexpression and protein-protein interaction networks associated with MM using a multistage approach. ⁵ This suggests that MM, as a behavioral intervention, may be an effective component in treating diseases characterized by increased inflammatory responsiveness with a weakened immune system.

NEURAL CIRCUITS RELATED TO MINDFULNESS MEDITATION

Feelings of Fear circuit related to MM

² The connections between the amygdala and key areas of the prefrontal cortex, specifically the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) can regulate the feelings of fear (Figure. 1). Specifically, the overactivation of these circuits may lead to feelings of fear. Anthony *et al*^[39] examined the neurobiological effects of 16-week mindfulness-based exposure therapy (MBET) compared with present-centered group therapy (PCGT) in task-evoked functional connectivity of combat veterans with PTSD. MBET group showed higher neural activation in the rostral ACC, dorsal medial prefrontal cortex (mPFC), and left amygdala that were significantly associated with improvement in PTSD symptoms. The interactive results of group and time show that MBET has the increased responses of the left medial PFC related to fearful faces, and the greater post-therapy effects on the fusiform/lingual gyrus and amygdala to angry faces, suggesting that MM practices may be related to greater involvement in threat cues of patients with PTSD. It also found that MBET was associated with the increased activation of the lingual/fusiform gyrus and amygdala to angry faces. It is proved that mindfulness-based art therapy (MBAT) is associated with significant changes in cerebral blood flow, including the insula, amygdala, hippocampus, and caudate nucleus, which is associated with a period of reduced anxiety within 8 weeks^[40]. These brain structures are involved in MM tasks and emotional processing related to anxiety^[41-43].

The physiology of fear circuit related to MM

Hoge and colleagues provide some support that MM would mitigate the elevated response to acute stress observed in generalized anxiety disorder on the HPA axis, by measuring blood levels of cortisol and adrenocorticotrophic hormone (ACTH) with treatment. Over the course of the treatment, participants in the MM group exhibit a reduction in their ACTH Area-Under-the-Curve concentrations^[44]. Similarly, Pace *et al* demonstrated that healthy participants who practiced more MM had a faster drop in

cortisol after the Trier Social Stress Test (TSST) than healthy participants who practiced MM less frequently^[45]. The physiological reaction to a fearful stimulus involves activation of multiple systems, including the autonomic nervous system, respiratory system, and endocrine system^[46, 47]. Part of the characteristic of the fear response may be endocrine influence^[48]. The hypothalamic pituitary adrenal (HPA) axis is responsible for endocrine output during the stress/fear response, and is regulated by the amygdala via reciprocal connections with the hypothalamus^[49-51].

Activation of autonomic system is regulated by connections between the amygdala, the locus coeruleus, and parabrachial nucleus and leads to an increase in heart rate, respiration rate and blood pressure that is necessary for a fight/flight reaction^[52, 53]. Several studies have consistently found an association between cardio-respiratory parameters and MM related to slow paced breathing^[54]. Park and Park^[55], and Stark *et al*^[56] found an increase of the high frequency power paralleled during paced breathing of MM at 10 b/min as compared to spontaneous breathing. Generally, slow breathing techniques (such as MM exercises) enhance interactions between autonomic nerves, cerebral, and mental flexibility, linking parasympathetic and central nervous system activities with emotional control and well-being. Slow breathing techniques seem to promote a predominance of the parasympathetic autonomic system with respect to the sympathetic one, mediated by the vagal activity^[57, 58].

Re-experiencing circuit related to MM

Sevinc *et al*^[59] investigated potential neural correlates of MM intervention and in extinction learning (the context-dependent recall of extinction) using MBSR training. Group-by-time interactions found MBET was associated with greater increases in the hippocampus and the supramarginal gyrus during extinction recall. And during the early phase the MBSR training group showed increased hippocampal connectivity to the supramarginal gyrus. It also found increased connectivity between the hippocampus and primary somatosensory cortex during retrieval of extinguished stimuli following MBSR training^[60]. Further, Sevinc *et al*^[61] demonstrated an association

between functional changes in the hippocampal connectivity and changes in anxiety following MM training. These evidences provide a better understanding of the mechanisms through which MM training relieves anxiety. Anxiety can be triggered not only by an external stimulus but also internally through traumatic memories stored in the hippocampus (Figure. 2), which can activate the amygdala, causing the amygdala, in turn, to activate other brain regions and generate a fear response^[46, 62]. This is known as re-experiencing and is a central feature of posttraumatic stress disorder (PTSD)^[63].

Worry/obsessions circuit related to MM

Anthony *et al*^[64] studied the potential neural relevance of MBET among combat veterans who suffer from PTSD deployed to Afghanistan and/or Iraq. MBET showed increased connectivity with the dorsolateral prefrontal cortex (DLPFC) and dorsal ACC following therapy by a group \times time interaction; and posterior cingulate cortex (PCC)-DLPFC connectivity was related to improvement of avoidant and hyperarousal symptoms in PTSD. Worry refers to anxious misery, apprehensive expectation, catastrophic thinking, and obsessions (Figure. 3). It is hypothetically related to a cortico-striatal-thalamic-cortical (CSTC) loop originating in the DLPFC and projecting the striatal complex, than the thalamus, and ending in the DLPFC^[65, 66]. Overactivation of the DLPFC can result in symptoms such as worry or obsessions^[67-69].

MINDFULNESS MEDITATION AND BRAIN NETWORKS

In identifying the neural mechanism of MM, most inferences have focused on the role of isolated brain areas in supporting the observed cognitive processes and concurrently enhancing behavioral outcomes, however, consisting of key areas that are temporally correlated with one another (a large-scale brain network) must be considered^[70]. There are three key functional networks related to attention, cognitive control and interoceptive awareness: default mode network (DMN), central executive network (CEN), and salience network according to the former neuroimaging literature on MM^[71].

The DMN is associated with task-irrelevant and mind-wandering thoughts^[72, 73]. Greater activations in core nodes of PCC, mPFC, and bilateral parietal cortices, lead to introspective thought, including activities like daydreaming or retrieving memories^[74-77]. The CEN, with core nodes located in the bilateral parietal cortices and DLPFCs, is typically associated with increased activation during distractibility and goal-directed behavior ^[78-80]. The CEN is linked to decision making by converging external information with internal representations^[75, 81-83]. The salience network is responsible for changing and monitoring the states of the CEN and the DMN, and presumably accepts the distribution of attentional resources to support cognitive control^[84].

Based on structural and functional neuroimaging studies, MM is related to the activities and connections in three networks, each of which is responsible for different stages of MM for experienced practitioners^[85-87]. The activity and connectivity of DMN have been suggested as potential biomarkers for monitoring the effect of MM^[88]. It describes that MM may improve DMN, CEN and salience network functions to target symptoms of anxiety disorders^[9]. Anthony *et al*^[64] investigated potential neural correlates of MBET in patients with PTSD compared with an active control therapy. After MM training, the connection between the DMN and CEN increase, which may improve the ability to shifting of voluntary attention. There is increased connection between DMN and the DLPFC areas in CEN before and after MBET.

FUTURE DIRECTIONS

Currently, few scientific researches have investigated the neural connections of MM at the level of critical genes and brain networks^[90-94]. Notably, ⁴ there has been a shift from isolated areas to large-scale networks, circuits or large-scale genetic changes^[38, 89, 95]. Further research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level would be necessary^[96, 97]. As the knowledge of brain function increases, we can better understand what the neural connections that affect clinical symptoms are. In turn, this will better characterize the specific deficiencies of any particular patient. We can predict that the development of

neuroscience research on MM will help strengthen neuronal circuits that are damaged by mental disorders, and help develop personalized interventions for individuals' unique defects and strengths.

CONCLUSION

More recently, understanding neuropsychological mechanisms of MM has been a hot topic^[98-100]. We describe progress made in assessing ³the effects of MM on gene expression in inflammatory processes, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss primary brain circuits related to MM and effects on symptoms of mental disorders, and expand our discussion to identify three brain networks associated with MM including DMN, CEN, and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level would be necessary.

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