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Biological mechanism study of meditation and its application in mental disorders

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ABSTRACT

In recent years, research on meditation as an important alternative therapy has developed rapidly and been widely applied in clinical medicine. Mechanism studies of meditation have also developed progressively, showing that meditation has great impact on brain structure and function, and epigenetic and telomere regulation. In line with this, the application of meditation has gradually been expanded to mental illness, most often applied for major depressive disorders and substance-related and addictive disorders. The focus of this paper is to illustrate the biological mechanisms of meditation and its application in mental disorders.

Over the centuries, meditation has been practised in different forms and in various cultures. Modern meditation techniques detached from religion are widely used in psychological and clinical medicine. At present, there is no unified definition of meditation, instead it can be classified into focused attention meditation (FA), open monitoring meditation (OM), transcendental meditation (TM), loving–kindness meditation (LKM), mindfulness meditation (MM) and body–mind meditation (B-M). FA and OM are traditional meditations derived from Zen, Vipassana and Tibetan Buddhism. The practice of FA entails the sustained and selective attention on a chosen object, of which respiration is common, so that the wandering mind is brought back to the selected object of attention, that is, 'just a thought prevailing over thoughts'.[1] OM only maintains the state of insight and awareness, paying attention to anything (thoughts, feelings, emotions and so on), without judging and evaluating these thoughts.[2] MM is the most extensively used in meditation techniques with an integrated FA–OM essence. The techniques which form the primary basis of mindfulness-based interventions (MBIs) are commonly implemented, including mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), dialectical behaviour therapy, acceptance and commitment therapy (ACT)[3] and mindfulness-based relapse prevention (MBRP). Tai chi, qi gong and yoga, which promote mental concentration, relief of pain and modulation of emotions, are currently popular meditation techniques belonging to the B-M method that combines exercise and FA as well as OM methods. Among these, tai chi represents the crystallisation of the collective wisdom in the Chinese cultural heritage and incorporates the basic theories of traditional Chinese medicine.[4] Nowadays, MBIs and B-M techniques are most commonly applied in mental disorders.

However, TM and LKM have not been widely applied for psychiatric disorders. TM practitioners from India or China[5] attempt to prevent distraction and reach deep physical and mental relaxation by repeating a mantra (uttered silently). This meditation technique has been applied in patients with post-traumatic stress disorder (PTSD). There is also a special type of Buddhist meditation designed to cultivate an unconditional kindness towards yourself and others, called LKM[6] which has been implemented in both depression and schizophrenia.

In this review, we will explore the biological mechanisms underlying meditation and introduce the application of various types of meditation in mental disorders.

BIOLOGICAL MECHANISMS OF MEDITATION

In recent years, biological mechanisms of meditation have been investigated step by step. Studies demonstrate that various kinds of meditation can change brain structure, adjust brain function, reconstruct brain networks and preserve the homeostasis of the autonomic nervous system (ANS). These fields about modulating epigenetics and improving telomere regulation are still in their infancy, with research focusing primarily on MM.

Insight on meditation and its brain mechanisms

Over the years, studies of the mechanism of meditation have received widespread attention. Meta-analysis[7] demonstrated that practising meditation can induce continuous changes of brain structure in eight regions: including frontal cortex related to metacognition, sensory cortex and insula connected with body consciousness, hippocampus linked to memory process, the anterior and medial cingulate cortex as well as orbitofrontal cortex relevant to self-awareness and emotion regulation and the upper longitudinal bundle and corpus callosum involved in cerebral intrahemisphere and interhemisphere communication. Recent studies have further confirmed that meditation increases the hippocampal volume[8] and enhances the cortical thickness of the prefrontal, insula and anterior cingulate cortex.[9 10] In short, meditation practice can change brain morphology with higher cortex thickness, grey matter volume and density.

Similarly, meditation training can improve function in many brain areas. Meta-analysis[11] elucidates that three regions of the brain in the caudate nucleus, the parahippocampus and the medial prefrontal cortex are activated when meditation practice was carried out. The caudate nucleus and putamen participate in attention and shield irrelevant information, which enable a meditative state to be realised and maintained; the parahippocampus prevents distraction; the medial prefrontal cortex enhances self-awareness during meditation. These activated areas may represent the core cortical network of meditation states. Moreover, there exists a dynamic process for brain activation by meditation. At the beginning of meditation, the bilateral subfrontal and temporal regions are obviously activated. As the meditation process goes deeper, the activation becomes weak by degrees, with activation concentrating just on the right subfrontal cortex/right insula and the meso/epithelial layer of right temporal lobe in the end.[12] It can be seen that the meditator experiences an initially intense self-control neural process to calm the brain and the reduction of neuron activity as the depth of meditation in silence increases.

However, the influence of meditation is limited to certain brain regions and to extensive brain networks connections. LKM can not only increase cortical thickness, but also improve the brain function which is seen in multiple areas of the bilateral prefrontal and insula, which are involved in the social emotion networks in meditation practice.[9] The functional connectivity between the medial prefrontal cortex and bilateral insula/putamen is evidently strengthened during Sahaja yoga meditation, which is crucial for sensory, mood and attention regulation in the brain. In addition, the depth of meditation is closely associated with the medial frontal–insula–striatum network.[10] FA[13] can promote positive changes in the key neural signals (frontal theta inter-trial coherence and parietal P3b latency) of attention networks. Furthermore, meditation also attenuates activity of the default mode network (DMN),[14] with dysfunction of the DMN subsystem in the anterior (medial prefrontal cortex) and posterior (cingulate cortex) following a larger number of long-term meditations.[15 16] Our study[17] observed reduced DMN activity in monks following persistent meditation practice and reconstruction of the large-scale network of EEG gamma waves as well as theta waves by meditation.

In summary, the mechanisms underlying the effects of meditation on the brain may be far more complicated than what we found, which is more relevant to alterations in large-scale brain networks. Future research on brain mechanisms should emphasise complex network analysis.

Insight on meditation and its ANS

Prolonged meditation can enhance autonomic nerve function, increase parasympathetic nerve activity and decline sympathetic innervation. Heart rate (HR) and heart rate variability (HRV) are frequently used as biomarkers of ANS activity, especially high-frequency HRV. As is known, high-frequency HRV is an index of parasympathetic nervous system (PNS) activity, and it is correlated with attention, working memory and emotion regulation.[18] In contrast, HR, as an index of sympathetic nervous system (SNS) activity, is related to cognition arousal and subjective efforts.[19] As meditation time goes on, the subjective effort perceived by meditators will decrease, and then HR will decrease, while the high frequency HRV will increase. However, different meditation methods seem to have distinct influences on the ANS.[20] Meditations concerning positive psychological intentions, such as LKM and monitoring meditation can activate SNS and enhance alertness; FA can activate PNS to help practitioners reach relaxation. Our previous study explored the effects of traditional Tibetan Buddhist meditation on brain–heart interaction. The results demonstrated that meditation was linked to cardiac function through the coupling of neural viscera and the spontaneous massive spatiotemporal brain network activity and mediated the stability of ANS function. The immediate effect of meditation on heart regulation is connected with the reconstruction of the γ-wave brain network, and prolonged regulation of meditation for cardiac rhythm is related to the reconstruction of the θ-wave brain network.[17] In conclusion, our ability to preserve the homeostasis of the ANS will increasingly improve as we practice meditation more.

Insight on meditation and its inflammatory cytokines

Cytokines are regulators and controllers of the body's immune defence system. Meditation has been found to modulate the expression of inflammatory cytokines in various diseases. For example, MBSR could prevent interleukin (IL)-10 downregulation in patients with fibromyalgia.[21] Mindfulness practice is also linked to lower levels of IL-6 and tumor necrosis factor-α(TNF-α) in primary open-angle glaucoma patients.[22] The regulation of MBSR on inflammatory cytokines in patients with breast cancer may be affected by disease stage and treatment strategies (surgery, radiation or chemotherapy). It has been noted that expression levels of TNF-α and IL-6 reduced, while expression levels of interferon γ(IFN-γ) increased

in patients diagnosed with early breast cancer after meditation.[23] TNF-α and IL-6 levels appear to elevate during follow-up after meditation among survivors of breast cancer.[24] There was no alteration in IL-6 levels after meditation in breast cancer patients with adjuvant chemotherapy and/or radiation therapy.[25] Meditation can also monitor the immune system in normal individuals. Mindfulness intervention can diminish the level of C reactive protein in people with high inflammation (overweight or overstressed adults aged 45 years and over).[26] Yoga combined with meditation allowed the immunity of people to be boosted,[27] thereby enhancing both inflammatory cytokines and anti-inflammatory cytokines. In general, meditation helps inflammatory cytokines in vivo to maintain a fine-tuning balance, sometimes promoting inflammatory responses and sometimes suppressing excessive inflammatory responses.

Insight into meditation and its epigenetics

Long-term meditation modulates epigenetics and promotes health-related gene expression. Advanced mindfulness meditators display changes in histone modification and chromatin-regulated gene expression after meditation.[28] The reduced expression of several histone deacetylase genes (HDAC 2, 3 and 9) and the altered overall modification of histones (H4ac and H3K4me3) is found in peripheral blood mononuclear cells. Meanwhile, the expression of the proinflammatory gene COX2, depending on the activity of deacetylated HDAC, is downregulated, which further explains the mechanisms of meditation in the treatment of major depressive disorder and inflammation-related diseases. Persistent MM also influences the epigenetic ageing rates (the level of deviation between the DNA methylation age and the chronological age).[29] The rate of epigenetic ageing significantly slows during meditation, thereby meditation has effects on anti-ageing. Additionally, long-term meditation exercises bring about consistent epigenetic responses in a broad range of genomic regions,[30] most of which are bound up with neurological and mental illnesses, cardiovascular diseases and cancer. Some reports have indicated that patients with PTSD in veterans have decreases in FKBP5 intron 7 methylation after a mindfulness intervention.[31] Although research on meditation methylation has been conducted, it is still in its infancy. Therefore, it is necessary that more investigations with more accurate tools and methods of data analysis are conducted to examine epigenetic regulation induced by meditation.

Insight into meditation and its telomere biology

Telomere length is an indicator of cell ageing and physiological stress, which gradually shortens during cell division and cell damages. Ornish *et al*,[32] who first studied the relationship between meditation training and telomerase activity, has found that patients with prostate cancer exhibit higher telomerase activity after meditation. A few reports demonstrated that meditation practice was associated with increased telomerase activity in peripheral blood mononuclear cells.[33] Several studies have also indicated that meditation intervention is related to an slight increase in telomere length[34] or no change without shortening.[35] In addition, meditation can also impact the expression of multiple telomere-related genes,[36] especially producing more positive effects on telomere regulation in meditation training.[37] Not only does telomere length increase, but also the expression of Gar1 and hnRNPA 1 (the gene encoding a protein that binds to telomerase RNA and DNA) elevate. To sum up, meditation training can improve telomere regulation, which ultimately contributes to health and ageing. However, the mechanisms of alterations in meditation remain to be further explored.

APPLICATION OF MEDITATION IN MENTAL DISORDERS

To date, meditation technology is gradually applied to the treatment and prevention of various mental illnesses. Particularly in major depressive disorders, it can be an alternative therapy of medication at the maintenance stage; meditation techniques may become an adjunctive treatment for patients with substance-related and addiction disorders as well as PTSD. However, the application of meditation techniques is still in its early stages in schizophrenia and attention deficit and hyperactivity disorders (ADHD), and more research is required to further verify its efficacy.

Major depressive disorders

At present, meditation techniques have been extensively implemented for treating major depressive disorders, mainly MBIs and B-M techniques (embodying tai chi and yoga). Meditation is relatively efficacious in the acute and subacute phase of treatment of depressive disorders,[38] and our research also indicates that 8 weeks of MM effectively relieves depression and anxiety emotions and improves sleep quality.[39] Meanwhile, meditation displays some adjunctive therapeutic effects on patients with severe major depressive disorder who are less effectively treated with antidepressant medication therapy.[40] Furthermore, meditation also can be used in the prevention of depressive relapse. The report of patients with depressive disorder with three or more relapses conducted by the British Medical Research Council revealed that the recurrence rate can reduce from 78% to 36% by using MBCT.[41] It can be further supported that the relapse rate (44%) in the MBCT treatment group alone is equivalent to the relapse rate (47%) in the antidepressant treatment group during maintenance therapy with 2 weeks of follow-up.[42] Therefore, MBCT is expected to become an alternative therapy after discontinued maintenance of antidepressant drugs for treatment. Other studies demonstrated that the physical and mental techniques of meditation, encompassing tai chi, qi gong and yoga, can significantly alleviate depression and anxiety in patients with major depressive disorder, which is considered to become an effective complementary approach for the current

mainstream drug therapy and psychotherapy.[43] In brief, both the recent systematic review and meta-analysis[38 43 44] have further evaluated the remarkable feasibility and efficacy of meditation techniques in people with depressive disorders.

Substance-related and addiction disorders

Increasingly, meditation techniques are being applied to substance-related and addiction disorders, including alcohol use disorders, substance use disorders, tobacco use disorders, cannabis and stimulant use disorders, with the most commonly used techniques being MBRP and ACT. Mindfulness practice reduces the emotion distress, craving and withdrawal symptoms for nicotine-deprived smokers,[45] in combination with lower relapse in smoking cessation.[46] ACT intervention decreases the craving behaviour of drug abusers[47] as well as reuse of substance,[48] relieves pain in patients with chronic pain comorbid with opioid addiction and suppresses craving for opioids.[49] Furthermore, MBRP eases the craving for alcohol in alcohol-dependent patients, alleviates anxiety and depression and improves quality of life.[50] In addition, it displays improvements in emotional problems in adults with depression and anxiety along with remarkable decreases in the use of stimulants.[51] Similarly, B-M technology can help young adults to regulate the management of emotion and decrease alcohol and drug abuse.[52] In summary, meditation-based interventions show significant reductions in dependence, craving and other addiction-related symptoms by mitigating emotional states and mood imbalances.

Post-traumatic stress disorder

PTSD is a complicated and refractory mental illness that easily occurs after severe trauma. Neither medication nor trauma psychotherapy (cognitive processing therapy) can completely eliminate its symptoms. Meditation interventions may be an alternative therapy in the management of PTSD, including TM, sudarshan kriya yoga and MM as common techniques. It is apparent that meditation interventions yield positive effects on PTSD among veterans,[53–55] which can alleviate intrusion and avoidance, modulate emotions and calm breathing. Moreover, MM can help reduce alcohol and drug abuse among veterans with PTSD.[56] Next, MM may be an adjunctive treatment for adults with PTSD who experienced sexual abuse in childhood, with interventions yielding effects on PTSD symptom reduction and anxiety as well as depression relief.[57] Other studies showed that TM also ameliorates the symptoms of PTSD and improves depressive emotions for college students in South Africa.[58] Subsequently, it can be seen that meditation technology can help more patients with PTSD to get rid of pain and return to a normal life.

Attention deficit and hyperactivity disorders

Up to now, the efficacy of meditation intervention in adult patients diagnosed with ADHD is relatively manifest, prevailingly using MBIs.[59] Mindfulness intervention can considerably improve attention in adults with ADHD,[60–63] with additional improvements in executive functioning,[63] working memory[60] and anxiety and depressive emotions.[61] Improved attention may be associated with increased activation of the left putamen, globus pallidus and thalamus.[63] However, meditation interventions provide insufficient evidence in children and adolescents with ADHD and it is hard to identify its efficacy.[64] Preliminary evidence shows that yoga and mindfulness interventions can decrease core symptoms of ADHD in children and adolescents[65 66] and that joint participation in mindfulness-based interventions between parents and children with ADHD can help to relieve parental stress and over-reactivity.[65 67] In conclusion, more high-quality randomised controlled trials are needed to substantiate the effectiveness of meditation interventions for children and adolescents with ADHD.

Schizophrenia

Meditation techniques have been tried for patients with schizophrenia over the years, with main techniques used being MBIs and ACT. Preliminary studies have suggested that MM can improve anger and aggression in acute patients with schizophrenia, schizoaffective disorder or bipolar disorder.[68] It can also diminish symptoms of depression and anxiety in stabilised patients with chronic schizophrenia.[69] In particular, it decreases pain and depressive emotions associated with auditory hallucinations[70] and reduces the occurrence of various crisis situations. Furthermore, MM can relieve partial positive symptoms[71 72] and negative symptoms[69 72] of schizophrenia, enhance patients' awareness of their disease, shorten lengths of inpatient stay and reduce rehospitalisation rates.[71 72] Our study exhibits that 8 months of meditation contributes to significant reductions in persistent hallucination and delusion symptoms of severe schizophrenic patients with more than a 20-year course.[73] Although meditation interventions make initial progress in patients with schizophrenia, the evidence from these findings appears to not be sufficient, and randomised controlled trials in larger cohorts are warranted to further validate.

CONCLUSIONS

Over the past two decades, meditation has been used in a great variety of fields to relieve stress, regulate emotions and promote physical and mental health. In recent years, the application of meditation in the psychiatric field has gradually received attention. It has become an adjunctive and alternative therapy for depression, PTSD and ADHD and has been carried out for the acute and remission stages of treatment for severe schizophrenia. Additionally, it can ameliorate emotional distress, craving and withdrawal symptoms in substance addiction. However, the current researchers adopt different meditation methods and

diverse training durations, which leads to the inability to systematically evaluate which type of meditation is more beneficial to which populations or diseases, and to completely elucidate the biological mechanism of meditation. In the future, further targets for selective meditation subtypes along with prescribed training time, and randomised controlled studies with sufficient samples are required to determine the efficacy of meditation on the one hand, and simultaneously study the mechanisms behind meditation on the mind–body interaction, which can better display the positive function of meditation as an ancient physical and mental healing method in promoting human health.

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