

**Exploring the Impact of Behaviour Modification:
Observing Human Brain Chemical Neurotransmitter
Changes and their Influence on Behaviour Abstract**
This research explores the effects of meditation on stress management and mental health. Meditation is a widely practiced technique known for its positive impact on various physiological systems, particularly those involved in depression. While its therapeutic benefits are recognized, the precise mechanisms through which meditation operates remain unclear. This study delves into the physiological abnormalities associated with stress-mediated depression and how different meditation techniques can reverse these anomalies. The focus is on the endocrine system's role, including axes like hypothalamic-pituitary-adrenal (HPA) axis.

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Abstract

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Abstract

Background: Organic chemistry and biological applications of the newly synthesized organic molecules

Objective: To identify the effects of neurotransmitter and the effects of chemical imbalance in human brain

Methods: Literature study, Experimental and analysis

Results: The effects of the chemical imbalance are highly responsible for many neurotransmitter disease.

Conclusions: In conclusion, meditation emerges as a valuable tool for mitigating the adverse effects of stress and promoting mental resilience. Despite the complexity of its mechanisms, research suggests that meditation exerts profound effects on physiological systems, particularly through modulation of the endocrine system. By reducing cortisol levels, increasing cerebral blood flow, and promoting neural plasticity, meditation offers tangible benefits for stress management and mental well-being. However, further research is needed to elucidate the specific mechanisms underlying its therapeutic effects and to optimize its application in diverse populations. Understanding the molecular-level impacts of meditation can pave the way for more targeted interventions and personalized approaches to mental health care.

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Original Manuscript

Exploring the Impact of Behaviour Modification: Observing Human Brain Chemical Neurotransmitter Changes and their Influence on Behaviour

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Abstract

This research explores the effects of meditation on stress management and mental health. Meditation is a widely practiced technique known for its positive impact on various physiological systems, particularly those involved in depression. While its therapeutic benefits are recognized, the precise mechanisms through which meditation operates remain unclear. This study delves into the physiological abnormalities associated with stress-mediated depression and how different meditation techniques can reverse these anomalies. The focus is on the endocrine system's role, including axes like hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid, and their influence on mental health outcomes. Despite the growing interest in meditation, further robust studies are needed to delineate its target populations, forms, dosages, and delivery modes. By understanding meditation's molecular-level effects, we gain insight into its physiological impacts, particularly its links to stress responses and mood regulation. Meditation, encompassing practices like, mindfulness, and transcendental meditation, yields profound health benefits. Beyond alleviating psychological burdens such as stress and anxiety, it fosters physical well-being by reducing blood pressure and heart rate. This systematic review delves into the impact of various meditation techniques on biochemical markers linked to mental health, including cortisol, serotonin, dopamine, oxytocin, and endorphins. These practices elevate oxytocin and endorphin levels, modulate dopamine and serotonin behaviour in the central nervous system, and curtail cortisol production. Such biological shifts correlate with enhanced stress, anxiety, and depression indicators, along with perceived well-being improvements.

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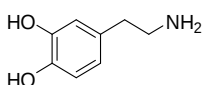
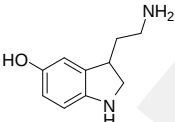
1. Introduction

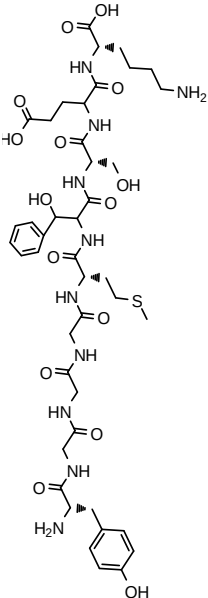
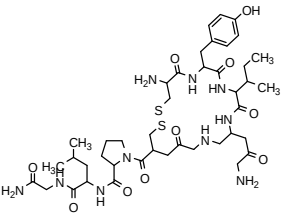
This present study evaluates briefly about meditation and its effects on stress mediated depression and the mechanisms underlying depression physiology.

Meditation is known for its ability to help relax and de-stress the mind and body with many different

approach type of meditation techniques includes into that. Meditation is a complex mental practice involving changes in sensory perception, cognition, hormonal and autonomic activity. It is widely used in psychological and medical practices for stress management as well as stress mediated mental disorders like depression. A growing body of literature has shown that meditation has profound effects on numerous physiological systems that are involved in the pathophysiology of major depressive disorder (MDD). Although meditation-based interventions have been associated with improvement in depressive symptoms and prevention of relapse, the physiological mechanisms underlying the therapeutic effects of meditation are not clearly defined and even paradoxical. This paper reviews many of the physiological abnormalities found in cytokine & stress mediated depression and the reversal of these anomalies by different meditation techniques. (Eshvendar Reddy et. al 2013).

Table 1. Effects of the different chemicals and different way of treatment

Chemical Name	Basic Chemical Composition	Effect	Symptoms	Possible way to treat
	L-Phenylalanine L- Tyrosine	Good feelings, Satisfaction, comfort, alertness	Lack of pleasure and rewards, fatigue, depression, lack of motivation	Good sleep, music, dancing, sports, exercise, good food
	L-Tryptophan Or 5-HTP	Emotional stability, self-confidence, pain tolerance, sleep quality, Happiness	Depression, obsessiveness, low self-esteem, violence, sexual promiscuity	Exercise, Sunlight, meditation, running, good food

	α -neoendorphin β -neoendorphin	Reduce pain and discomfort, anxiety, self-esteem support a healthy immune system support memory and cognitive function	Increases risk of depression and anxiety moodiness trouble sleeping	Exercise, Sunlight, meditation, running, good food, dark chocolates, laugh, travelling, self-love
	-	Trust, Gazing, Empathy, positivity, relationship moments	Depression, anxiety, fear, sexual differences, loss of bonding pattern and trust	Yoga, meditation, good food, exercise, atmosphere

Meditation continues to be used as a self-help and self-mastery technique, and as an adjunct to psychotherapy. (Jutkiewicz, E.M. and Bergman, J., 2004) Meditation is one of the well-known mind and body training methods which help in the management of stress, enhancing mental and physical development. Increasing evidence suggests that meditation practices may impact different physiological pathways such as neurotransmission, immune and neuroendocrine systems, which are affected by stress and are relevant to disease development and progression. (Karson, C.N., 1988). Some frequent concepts include cleansing one's mind of distractions, being aware of oneself and one's surroundings, concentrating on the present, and deliberately managing one's breath and bodily movements (Bishop, S. et al., 2004). As per reports, a typical transcendental meditator would spend 15–20 minutes in the morning and again in the evening, seated with eyes closed and mentally focusing on silently repeating a word or phrase to calm the mind and reduce mental distractions. Practicing meditation can promote physiological responses in the body such as decreased blood pressure and reduced breathing rate. Pioneering work by Herbert Benson described these effects as the “relaxation response,” which is produced by activation of the parasympathetic nervous system. (Benson, H.; Klipper, M. Z. Te 2009).

The relaxation response is opposite to the more commonly known fight to flight response which is produced by the activation of the sympathetic nervous system (Cannon, W. B. 1963). Analytical

experimental technique for concentration of biological chemical involve two general stages, first acquiring a biological sample from the subject and then measuring the concentration of molecule of interest. Some compounds can be measured from saliva or urine samples, which are relatively simple to acquire. The other compounds are best measured from blood serum or plasma samples, which must be obtained by trained experts. Some metabolites can be quantified by simple gas chromatography or high pressure liquid chromatography, but in many cases more complex assays are required (Lawrence, M.S. and Redmond, D.E., 1991). One common assay for measuring the usually very small concentration of metabolites in serum is a radioimmunoassay.

A second useful technique is an enzyme-linked immunosorbent assay (ELISA), which also uses immobilized antibodies to bind the isolated metabolite, but then uses enzyme-catalysed generation of colour or fluorescence as a readout instead of radioactivity. Many metabolites undergo natural changes in concentration throughout the day, and others are affected by eating particular foods, smoking, or other daily activities. Age and gender can also significantly affect some metabolites. For experiments assessing the long term effects of regular meditation, it can be difficult to isolate the effects of meditation versus effects that result from other lifestyle choices that may be more common in meditators versus non-meditators.

2. Theoretical Background

Behaviour modification involves the systematic application of psychological principles, such as operant and classical conditioning, as well as cognitive-behavioral techniques, to alter maladaptive behaviors and reinforce adaptive ones. A critical aspect of this process is its influence on brain neurochemistry, particularly neurotransmitter systems that regulate emotion, motivation, and cognition. Key neurotransmitters involved include dopamine, which is associated with reward and reinforcement learning; serotonin, which modulates mood and impulse control; GABA and glutamate, which regulate neural plasticity; and norepinephrine, which affects attention and stress responses. (Emma V. Parkins and Christina Gross 2024) Research from the Journal of Neuroscience demonstrates that behaviour modification techniques, such as positive reinforcement and cognitive-behavioral therapy (CBT), lead to measurable changes in these neurotransmitter systems. For instance, operant conditioning strengthens cortico-striatal pathways via dopaminergic modulation, while CBT enhances prefrontal-amygdala connectivity through serotonin and glutamate activity. Recent studies also highlight how neurofeedback and deep brain stimulation (DBS) can further modulate neurotransmitter release, improving self-regulation and treating conditions like obsessive-compulsive disorder (OCD) (Wei Lu et. al., 2025). Social reward learning has been shown to involve

interactions between oxytocin and dopamine, promoting prosocial behavior. These findings underscore the neuroplasticity underlying behaviour modification, offering insights into personalized therapeutic approaches, such as combining pharmacological treatments with behavioral interventions. Advances in neuroimaging and molecular neuroscience continue to refine our understanding of these mechanisms, paving the way for innovative clinical applications. Aberg, K.C., Toren, I. and Paz, R. (2023)

Among the metabolites affected by meditation, the hormone cortisol (William C. Daube 2015) is perhaps the best studied. Physical and psychological stress cause the body to increase its cortisol levels. Cortisol molecules travel throughout the body to activate various biological responses intended to improve the body's short-term performance in stressful situations, which is often called "the fight or flight response" (Fukuda, S.; Morimoto, K. Environ 2001). Biological effects of increased cortisol include increased blood pressure, blood sugar levels, and metabolism, which provides an extra boost of energy and suppression of the immune system, to divert energy towards the more immediate need. Chronic stress and long term elevation of cortisol cause the body to remain in this activated state and are associated with numerous diseases. (Esch, T.; Fricchione, G. L.; Stefano, G. B. 2003) Thus, cortisol is generally considered a biochemical indicator of stress and a risk factor for associated medical conditions.

The average plasma concentration of cortisol in a group of fifteen experienced transcendental meditators decreased by a statistically significant ($p < 0.01$) 27% after a 30-minute meditation session. In contrast, a group of fifteen control subjects untrained in meditation, who were simply allowed to rest instead of meditating, did not show a statistically significant change. The control subjects were trained in transcendental meditation and retested after three to four months of practice. After thirty minutes of meditation, this group did show a decrease in average cortisol but it was not as large of a decrease as the experienced meditators had produced ($p < 0.3$). All three groups (experienced meditators, controls, and controls after training) showed similar levels of cortisol in the time period before meditating or resting.

In one study after a six-week training period in Buddhist meditation, and meditating immediately prior to testing, a group of fifteen Tai boys age twenty to twenty-five showed an average 24% reduction ($p < 0.01$) in serum cortisol levels compared to their levels before the training began. (Sudsuang, R.; Chentanez, V.; Veluvan, K. 1991) A control group of thirty boys who stayed home on vacation instead of being trained showed no significant change in cortisol. Interestingly, a group of twenty-seven boys who were trained, but described themselves as not being able to find tranquillity during the meditation, also did not show any significant change in cortisol levels. Together these

results suggest that meditation can help reduce stress by lowering cortisol levels and that successful meditation is more than simply resting the body and is a mental skill that can be learned and improved through practice.

Dehydroepiandrosterone (DHEA) and its sulphate ester (DHEAS) are hormones that are abundant in the human body and serve as the biological precursor for other steroid-type hormones including testosterone and estrogen. Although DHEA and cortisol are similar in chemical structure and both made from cholesterol via several steps, their biological effects are completely different. Much interest in DHEA relates to its observed decrease with age and potential applications as “anti-aging” treatments for memory-loss, low-REM sleep, or skin issues. (Friess, E. et. al., 1995). DHEAS levels have been reported to correlate with meditation activity. In a large scale study, Glazer and co-workers measured DHEAS’s serum concentration in 423 people who regularly practiced transcendental meditation and 1252 people who did not. (Glaser, J. et. al., 1992) Higher average levels of DHEAS were observed in the meditators groups for both men ($p = 0.001$) and women ($p < 0.001$). Women showed increases, mostly in the 17–54% range, for every age group studied (20–74 years old) and men showed increases in older age groups (45 to over 70 years old). The authors note that while it is possible that other lifestyle differences between the meditator and non-meditator groups may be responsible for the differences in DHEAS, their results suggest that neither diet, smoking, nor alcohol consumption directly caused the observed differences in DHEAS. Currently, not enough is known to specifically define how or if higher levels of DHEAS may directly, or indirectly through modifying testosterone, estrogen, or cortisol levels, relate to improved health or youthful vigour.

Serotonin acts as a neurotransmitter in the central nervous system and is also involved in the digestive tract. It helps regulate physiological mechanisms such as maintaining body temperature, motor control, circadian rhythms, and also affects mood by producing a general sense of satisfaction and relaxation. 10 (Gershon, M.; Tack, J. *Gastroenterology* 2007.) Feelings of depression and anxiety are often associated with low serotonin levels, and several antidepressant drugs including Prozac function by increasing serotonin-based biological pathways.10 Serotonin is naturally metabolized into 5-hydroxyindole-3-acetic acid (5-HIAA) before being excreted, so 5-HIAA concentrations can serve as indicators of serotonin levels.

In one experiment, Bujatti & Riederer analysed urine concentrations of 5-HIAA in eleven subjects who regularly practiced transcendental meditation compared to fifteen healthy control subjects. (Bujatti, M.; Biederer 1976.) At the beginning of the test, the meditators already showed more than twice the average concentration of 5-HIAA compared to the control group ($p = 0.01$) and after thirty minutes of meditation, the meditator’s 5HIAA levels rose to more than triple that of the control

subjects ($p = 0.005$) who had spent the thirty minutes engaged in light activity and conversation, and whose 5-HIAA levels had not significantly changed.

In one study Walton and co-workers compared urine samples from twenty-two college students who regularly practice transcendental meditation to thirty-three control students. (Walton, K. et. al., 1995) Analysis of urine excreted during the night and early morning showed approximately 70% higher average concentrations of 5-HIAA in the meditators compared to the control subjects ($p < 0.015$). Together these results not only suggest that meditation can increase serotonin levels, but that these levels can remain elevated throughout the day and night. Serotonin has been called the “rest and fulfilment hormone,” and it seems possible that its effects could contribute to a general sense of happiness in those who meditate regularly. This hypothesis is supported by a study by Yu and co-workers that used a qualitative assessment of mood-states to identify mood changes in a group of fifteen individuals following a twenty-minute session of focused-attention breathing meditation.¹⁴ (Yu, X.; Fumoto, M. et. al., 2011.). After meditation, the subjects showed reduced average scores for tension and anxiety ($p < 0.01$), depression ($p < 0.001$), anger and hostility ($p < 0.05$).

The hormone melatonin plays an important role in regulating the sleeping–waking cycle. (Vanecek, J. *Physiological Rev.* 1998.) Melatonin levels increase in the evening and night as it is synthesized from serotonin. Interestingly, the biosynthesis of melatonin is inhibited by strong light, presumably to help match the sleeping–waking cycle with the natural day–night cycle. In addition to promoting sleep, melatonin’s biological effects include depression of the central nervous system, reduction of pain sensitivity, up regulation of the immune system, and promotion of general feelings of happiness. (Solberg, E. E. et. al., 2004) Some anti-insomnia drugs function by increasing melatonin pathways. Melatonin has also been shown to suppress the growth of some types of cancer. (Carlson, L. et. al., 2004)

In one study, Tooley and coworkers have reported that after performing transcendental meditation–Sidhi for sixty minutes in the late evening, a group of ten meditators showed an average plasma concentration of melatonin that was 22% higher ($p < 0.01$) than was observed in the same subjects on a different night after they sat quietly without meditating. (Massion, A. et. al., 1995) The groups did not show any difference in melatonin concentration before meditating and half the group acted as the control group on each night. The authors note that ambient lighting levels were maintained substantially below the intensities that are known to influence melatonin production. The results of this experiment suggest that, meditating before going to sleep may help the body transition into sleep and enhance the many known benefits of sleeping well. Brand and co-workers have reported that a group of nine experienced meditators scored substantially better on a qualitative sleep-quality index

($p = 0.02$) than did a control group of eleven novices. 19 (Brand, S. et. al., 2012.) After eight weeks of training in mindfulness-based stress reduction meditation, the novices' sleep-quality scores improved ($p = 0.008$), but not to the levels scored by the long-term meditators.

Epinephrine (also called adrenaline) and norepinephrine are two related hormones that are associated with biological responses to fear and physical exertion. 20 (Carrasco, G. A.; van de Kar, L. D. Eur. J. Pharmacol. 2003). These molecules temporarily produce high levels of alertness, which could help a person survive a dangerous situation. Epinephrine increases heart rate, respiratory rate, blood pressure, and metabolism. Norepinephrine increases heart rate, serves as a neurotransmitter in areas of the brain associated with alertness, and is the biological precursor for the synthesis of epinephrine.

3. Neurotransmitter Function and Behaviour

Neurotransmitters play a pivotal role in modulating behaviour by facilitating communication between neurons and influencing neural circuits associated with cognition, emotion, and motivation. Dopamine, a key neurotransmitter in the mesolimbic pathway, regulates reward processing and reinforcement learning, making it essential for behaviour modification techniques such as operant conditioning (Ahmari, S.E. 2025). Serotonin, predominantly active in the prefrontal cortex and limbic system, modulates mood and impulse control, with dysregulation linked to anxiety and depression-conditions often targeted by cognitive-behavioural therapy (Bocchio, M., Nabavi, S. and Capogna, M. 2017). The balance between excitatory glutamate and inhibitory GABA critically influences synaptic plasticity, affecting fear extinction and adaptive learning (Rivera Quiles, C et. al., 2025). Norepinephrine, released from the locus coeruleus, enhances alertness and stress responses, with excessive activity contributing to maladaptive behaviours such as chronic avoidance. Recent advances in neuroimaging and optogenetics have further elucidated how behaviour modification strategies-ranging from neurofeedback to pharmacological interventions-induce lasting changes in neurotransmitter dynamics, thereby reshaping neural networks to promote adaptive behaviours. Understanding these neurochemical mechanisms not only enhances the efficacy of behavioural therapies but also paves the way for personalised interventions targeting specific neurotransmitter dysfunctions.

In one study, Infante and coworkers compared the plasma concentrations of epinephrine and norepinephrine of nineteen regular practitioners of transcendental meditation versus sixteen healthy control subjects. (Infante, J. R 2001). Average morning concentrations of epinephrine and norepinephrine in the meditators were approximately 30% lower ($p < 0.01$) and 40% lower ($p < 0.01$) respectively than those in the control subjects. Epinephrine and norepinephrine levels can also

be measured by measuring urine concentrations of vanillylmandelic acid (VMA), which is a metabolic product of each. Bujatti & Riederer's experiment showed that both before and after a thirty-minute session of meditation, or light activity for the control group, a group of regular meditators had VMA concentrations approximately 50% lower than those measured for control subjects ($p = 0.025$). Conversely, Walton and coworkers' experiment 12 suggests that elevated VMA levels can be more substantially influenced by high sodium intake (62% increase, $p = 0.002$) than by regular meditation (21% decrease, $p = 0.1$). While these studies highlight the importance of comparing meditators to well-matched control groups, the overall results do suggest that people who regularly meditate can maintain lower levels of adrenaline and thereby maintain a more relaxed mind-set.

Elias and co-workers have hypothesized that during meditation the body switches from glucose metabolism to fatty acid metabolism and that the altered concentration of product molecules being produced may lead to increased production of gamma-amino butyric acid (GABA) in the brain. (Elias, A. N.; Wilson, A. F. 2000). GABA is an inhibitory neurotransmitter and its increase can relax the mind. In one study, Guglietti and co-workers used trans cranial magnetic stimulation to analyse brain activity before and after a sixty-minute meditation session.²⁴ (Guglietti, C. L. et. al., 2019). A group of thirty-five people who meditated showed a 10% increase ($p = 0.02$) in average cortical-silent period, which is a measurement used to evaluate overall neural inhibition caused by GABA activated pathways. A control group of thirty-five people who watched television instead of meditating showed no change in their average cortical silent period. In a study that measured GABA directly, Streeter and co-workers reported that practicing yoga can elevate GABA levels (Streeter, et. al., 2007). Which is relevant to meditation because the similarities between the mental relaxation achieved through yoga and through meditation are well known. Some physiological responses produced by fasting are also similar to those produced by meditation. Fasting also produces a shift away from glucose and towards fatty acids as the primary energy source.²⁶ (Jevning, R. 1988.). It is possible that during meditation it is the combination of reduced muscle activity and reduced mental activity that causes a reduced energy demand that enables the biological shift away from glucose-based metabolism and towards a more restorative body state.

Major depression is the most common disabling psychiatric disorder that has been estimated to affect 21% of the world's population. According to reports published by World Health Organization (WHO), it is estimated that by 2030 depression will be the leading cause for disability worldwide (Cavanagh, J.F et. al., 2014). MDD is defined in DSM IV (Diagnostic and statistical manual of mental disorders-IV), as a condition characterized by loss of interest in usual activities and/or

diminished ability to experience pleasurable activities (anhedonia), together with a range of other features including anergia, changes in sleep and appetite, sadness, and suicidal tendency. (Elsworth, J.D. et al., 1991) Although meta-analyses from epidemiological studies indicate that depression is largely heritable, intense stress for long period has been attributed as one of the crucial components in the emergence of major depression. (Kaminer, J. et. al., 2011) Chronic stress activates peripheral and central immune systems accompanied with the release of inflammatory mediators. (Taylor, J.R. et al., 1999) Meditation is essentially a physiological state of reduced metabolic activity different from sleep e that elicits physical and mental relaxation and is reported to enhance psychological balance and emotional stability. (Groman, S.M. et al., 2014)

Sympathetic nervous system activated by stressors, result in release of epinephrine (E) and norepinephrine (NE) into the general circulation by activating adrenal medulla, so released NE and E acting through alpha and beta adrenergic receptors, can increase NF-kB DNA binding in relevant immune cell types, including macrophages, resulting in the release of proinflammatory cytokines (Armony, J.L. and LeDoux, J.E., 2000). (Andrews, T.J., Halpern, S.D. and Purves, D., 1997) In contrast parasympathetic nervous system (PNS) pathways serve to inhibit NF-kB activation and decrease the inflammatory response. These effects are mediated by the release of acetylcholine (Ach), which by binding to the nicotinic Ach receptor is able to inhibit activation of NF-kB (Bucci, D.J., Conley, M. and Gallagher, M., 1999)

3.1 Brain abnormalities in depression

Neuroimaging studies have shown that MDD is accompanied by structural and functional abnormalities in several brain areas (Byrne, K.A., Patrick, C.J. and Worthy, D.A., 2016) many of which are parallel to those found in chronic stress. These areas include; prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, basal ganglia and amygdala. (Kruis, A. et. al., 2016)

Amygdala: The amygdala is a part of the limbic system. The previous studies reported a reduction in glial cell density in the amygdala when a person is sad or clinically depressed. Numerous neuroimaging studies (fMRI; functional magnetic resonance imaging, PET; positron emission tomography, SPECT; (Kabat-Zinn, J., 1990) single positron emission computer tomography) on amygdala have found that blood flow and metabolism is abnormally higher in depressed patients compared to healthy controls. (Frane, J.W., 1998) (Lutz, A. et. al., 2008)

PFC: PFC exerts an inhibitory influence on the amygdala and therefore disruption of the PFC disinhibits the amygdala, which is generally observed in depression (MacCoon, D.G. et al., 2012). Several subregions of the frontal lobe have been shown to be functioning abnormally during depression, including dorsolateral prefrontal cortex (DLPFC), and ventromedial prefrontal cortex

(VMPFC) and orbitofrontal cortex (OFC). Neuroimaging studies revealed that reduction in gray matter volume, blood flow and metabolism, whereas increase in white matter lesions in PFC of depressed patients (Patton, J. and Stanford, M., 1995).

Hippocampus: Hippocampus found to be hypoactive during depression. Neuroimaging studies have consistently shown that depression is associated with reduction in gray matter volume (Destexhe, A., Contreras, D. and Steriade, M., 1998), neuronal cells, serotonergic binding, blood flow and metabolism of hippocampus. (Elias, A.N., Guich, S. and Wilson, A.F., 2000)

ACC: The ACC is another prefrontal area in which blood flow and metabolism are decreased in unipolar and bipolar depressives. Volumetric reduction and reduced serotonergic binding in the ACC has been found in depressed compared with controls (Patton, J.H., Stanford, M.S. and Barratt, E.S., 1995). Hypoactivation of the dorsal region of the ACC is associated with depression, and increased activity in this area has been found to coincide with successful antidepressant treatment (Stanford, M.S. et al., 2009). In addition to the prefrontal and limbic circuitry, there is considerable data supporting the involvement of the basal ganglia and specifically, the striatum, which is found to be hypoactive in the MDD. Available literature supports the reduction in volume, neuronal density, blood flow and metabolism of basal ganglia in persons with depression.

4. Neurochemical Correlates

Several neurotransmitter systems implicated in HPA axis regulation have been hypothesized to be dysfunctional in major depression. Serotonin (5-HT) 5-HT has been described as the major neurochemical system in the brain found to be dysregulated in patients with major depression (Steinberg, L. et. al., 2013). These findings include, reduced CSF and urinary concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT in drug-free depressed patients; reduced concentrations of 5-HT and its metabolites in postmortem brain tissue of depressed and (or) suicidal patients (Reise, S.P. et. al., 2013). Meditation's effects on 5-HT have mixed results. It has been observed in several studies that there is an increase in urinary excretion of 5-HT metabolites after meditation; this is thought to be mediated by stimulation of lateral hypothalamus and PFC during meditation (Shalgi, S., Barkan, I. and Deouell, L.Y., 2009). In contrary to the above finding, in some studies it was found that, in experienced meditators initial baseline levels of 5-HT were higher but decreased following meditation practice (Simmonds, D.J., Pekar, J.J. and Mostofsky, S.H., 2008).

Norepinephrine NE is the other monoamine which is believed to be dysfunctional in depression. NE is located mainly in the sympathetic postganglionic neurons and its concentration increases when the sympathetic tone is increased due to psychological stress (Ashburner, J., 2007). Many studies have

revealed that depressed patients have elevated levels of urinary and CSF concentrations of the NE metabolites such as 3- methoxy, 4-hydroxyphenylethylene glycol (MHPG) and its sulphated derivative (Ashburner, J. and Friston, K.J., 2000). The finding of lower concentrations of this hormone in meditation practitioners could reflect a lower sympathetic tone. Studies have also demonstrated low urinary and plasma levels of catecholamine metabolites after regular practice of TM in subjects with abnormally high levels (Ashburner, J. and Friston, K.J., 2000). Decrease in NE release from the locus ceruleus during meditation may decrease the production of CRH, which would ultimately decrease cortisol levels. These findings do not coincide with those found by Lang et al. (Cox, R.W., 1996), who found higher levels of urinary catecholamines and plasma NE in advanced meditators in comparison with beginners in the technique, though the same authors described a lack of increased NE after physical exercise in these practitioners.

4. Behaviour Modification Techniques

Behaviour modification techniques are grounded in psychological principles that aim to alter maladaptive behaviours and reinforce positive ones through systematic interventions. These techniques leverage learning theories, neurochemical adjustments, and cognitive restructuring to produce lasting behavioural changes (Crummy, E.A. 2025). Gamma amino butyric acid (GABA) GABA is the primary inhibitory neurotransmitter in the brain. There is a body of evidence which, although less voluminous than that for the monoamine hypothesis, strongly supports a GABA ergic dysfunction in depression. GABA synthesis, cortical GABA-A receptors and cortical GABA neurons were reported to be low in frontal cortex and striatum of depressed patients. Deficit in CSF and plasma GABA levels seen in depressed patients is reversed by chronic SSRI (Jenkinson, M. 2002). It has been found that GABA levels in the brain increase significantly after a yoga and TM. This potential increase in GABA has been proposed as a possible mechanism explaining the benefit that TM and yoga on depressive disorders associated with low GABA (Smith, S.M., 2002).

Dopamine (DA) Evidence from clinical investigations support the finding that depressed patients have reduced cerebrospinal levels of homovanillic acid (HVA), the major metabolite of DA in the central nervous system. Neuroimaging studies of depressed patients have found decreased ligand binding to the DA transporter and increased DA binding potential in the caudate and putamen, a finding consistent with the interpretation that depressed subjects have a functional deficiency of synaptic DA (Jenkinson, M. and Smith, S., 2001). A PET study using ¹¹C Raclopride to measure the dopaminergic tone during Yoga nidra meditation demonstrated a significant increase in DA levels during the meditation practice. In another study significant elevation of plasma DA levels through mindebody training was established (Andersson, J.L.R., Jenkinson, M. and Smith, S.M., 2007).

Glutamate Interest in studying the role of glutamate in depression has increased significantly, following the clinical findings of the antidepressant potential of N-methyl D-aspartate (NMDA) receptor antagonists. Increased activity of the glutamatergic system and NMDA receptor agonism is associated with depressed mood, and a reduction of the glutamatergic activity i.e NMDA receptor antagonism mediated increase of 5-HT levels in the brain exerts antidepressant effect. Proton magnetic resonance spectroscopy (PMRS) study in long-term Zen meditators was shown to decrease glutamate levels significantly in the left thalamus of brain (Di Martino, A. et al., 2008). In contrast to the above finding increased glutamate was observed in another such study, where they proposed that excess glutamate mediated excitotoxicity was kept in control by limiting the production of enzyme N-acetylated- α -linked-acidic dipeptidase that converts the endogenous NMDA receptor antagonist N-acetylaspartylglutamate (NAAG) to glutamate (Tomasi, D. and Volkow, N.D., 2012).

b-endorphin (b-END) b-END is an endogenous opioid neurotransmitter found in the neurons of both central and peripheral nervous system. Clinical study reports reveal that deficient levels of b-END are observed in MDD, and upon treatment with antidepressants there is an increase in b-END level in blood plasma indicating a positive response to therapy. Yogic meditation practice shown to increase the levels of b-END by glutamate mediated stimulation of arcuate nucleus of the hypothalamus, thereby exert antidepressant effect. This may be responsible for effects such as decreased pain, blissful and euphoric sensations during meditation (Richiardi, J. et al., 2015). Melatonin is an important neurotransmitter derived from 5-HT that influences mood and behavior. Comprehensive literature available supports melatonin as an anti-stress hormone as it activates the immune system and counteracts the immunosuppressive effects of stress (Barbato, G. et al., 2000). Low melatonin levels have been described as a 'trait marker' for depression and tend to rise with the remission. Although one study failed to find an effect of meditation on melatonin levels in cancer patients who have undergone mindfulness (Nazarpour, K. et al., 2008), various other studies have shown that meditation is coupled with a sharp increase of plasma melatonin (Goldberg, S.B. et al., 2016). Stimulation of the pineal gland by the lateral hypothalamus is considered to be responsible for this hike in melatonin. The increased melatonin level results in calmness and decreased awareness of pain, usually seen during meditation. (Herzog, H. et al., 1991).

4.1 Operant Conditioning

Operant conditioning, developed by B.F. Skinner, utilises reinforcement and punishment to shape behaviour. Positive reinforcement (e.g., rewards for desired actions) increases dopamine activity in the mesolimbic pathway, reinforcing adaptive behaviours. Conversely, negative reinforcement

involves removing aversive stimuli to strengthen behaviour, as seen in avoidance learning paradigms (Schultz, W. 2016).

4.2. Cognitive-Behavioural Therapy (CBT)

CBT targets dysfunctional thought patterns to modify behaviour. By restructuring cognitive distortions, CBT enhances serotonin and glutamate activity in the prefrontal cortex, improving emotional regulation. Techniques like exposure therapy further modulate GABAergic inhibition in the amygdala, reducing fear responses (Lüthi, A. and Lüscher, C. 2014).

4.3. Neurofeedback and Biofeedback

These techniques use real-time brain activity monitoring to teach self-regulation of neural functions. Neurofeedback has been shown to adjust dopamine and theta wave activity, improving attention and reducing impulsivity (Sitaram, R. 2017). Biofeedback, often paired with relaxation training, lowers norepinephrine levels, mitigating stress-related behaviours

4.4. Social and Environmental Modifications

Behaviour is also shaped by social reinforcement and environmental cues. Social reward learning, mediated by oxytocin-dopamine interactions, fosters prosocial behaviours while environmental enrichment promotes neuroplasticity, aiding habit change. Combining medication (e.g., SSRIs) (Hu, Y. 2023) with behavioural therapy optimises neurotransmitter function. For instance, fluoxetine enhances synaptic serotonin, while CBT reinforces adaptive coping mechanisms, proving effective in OCD treatment. (Pandey, S. 2025)

5. Immune and inflammatory correlates

Immune changes are a common physiological concomitant of stress and depression. HPA axis hyperactivity is a marker of GC resistance, i.e ineffective action of GC hormones on target tissues could lead to immune activation and equally, inflammation could stimulate HPA axis activity via both a direct action of cytokines on the brain and indirectly by inducing GC resistance (Karson, C.N et. al., 1982). As described earlier, many depressed individuals show suppression of specific immunity (natural killer cell activity, antibodies) and increased inflammatory cytokines (Interleukin (IL)-4, IL-6, IL-10 and TNF- α) compared to non-depressed individuals (Ingvar, D.H., 1994). Meditation has been found to decrease markers of inflammation such as high sensitivity C-reactive protein, IFN-g, TNF- α , IL-6, IL-10 (associated with cancer associated depression) and lymphocyte-1b (L-1b), whereas it increases the levels of anti-inflammatory cytokines like IL-4 (Frith, C.D. et. al., 1991). It also lowers oxidative stress by increasing the transcriptional expression of anti-oxidative

enzymes like glutathione S-transferase, CuZnSOD (CuZn-superoxide dismutase), Mn-SOD, glutathione peroxidase (GPX), and catalase (CAT). MBSR and Yogic practices downregulate the stress-mediated upregulation of pro-inflammatory NF- κ B-related gene expression in circulating leukocyte (Pardo, J.V., Fox, P.T. and Raichle, M.E., 1991). Other studies suggest that meditation reverses the negative impact of stress on the immune system by increasing cell-mediated immune response (e.g., varicella-zoster virus (VZV) specific cell-mediated immunity) (Lynch, J.C., 1980), greater rise in antibody titers in response to influenza vaccine. (Karnath, H.O., Ferber, S. and Himmelbach, M., 2001). Meditation practices have shown to improve telomerase activity thereby preventing telomere shortening associated with chronic psychological stress-mediated MDD (Vogt, B.A., Finch, D.M. and Olson, C.R., 1992). After stressful events, reduced lymphocyte proliferative responses and altered absolute and relative numbers of lymphocyte subsets have been reported. Meditation practices have found to increase the number of lymphocytes (both CD4 T cells and CD4/CD8 cell ratio) and their activity (Crosson, B. et al., 2001). In a study of cancer patients, SK and Pranayam meditation practices were shown to reduce stress and improve immune functions by increasing the natural killer (NK) cells and their activity significantly (Cornwall, J. and Phillipson, O.T., 1988).

Meditation is a popular practice for reducing stress and improving mental health and wellbeing. Its effects are mediated largely by the endocrine system, including the hypothalamic–pituitary–adrenal axis, the hypothalamic–pituitary–thyroid axis and the renin-angiotensin-aldosterone system, and energy homeostasis. The limited evidence available indicates that changes associated with endocrine function following meditation correspond with improvements in mental health. However, this field of study, the exact mechanisms by which meditation operates remain unclear and more robust studies are required to explore this by delineating the target populations, forms, dosages and modes of delivery of meditation, comparison groups, and health experiences and outcomes used. There is increasing interest in the practice of meditation and its effects on physiological markers of stress, mediated largely by the endocrine system, though the precise links and mechanisms by which these occur remain unclear. Most studies have investigated the effects of meditation practice on the hypothalamic–pituitary–adrenal axis, with comparatively little attention paid to other parts of the endocrine system. Growing but limited evidence indicates that changes associated with endocrine function after meditation may correspond with improvements in mental health outcomes. (Colzato, L.S. et al., 2009)

Daily challenges of life produce stress. Adaptation to stressful challenges requires maintenance of homeostasis by activation of neural, neuroendocrine and neuroendocrine-immune mechanisms. This

has been called “allostasis” or “stability through change”. Allostatic responses alter Hypothalamo-Pituitary-Adrenocortical axis function this causes altered levels of cortisol in the form of continuous high level of cortisol. Cortisol crosses blood brain barrier and change the architecture of brain by action on glucocorticoid and mineralocorticoid receptors present mainly on hippocampus, amygdala, prefrontal cortex, hypothalamus and thus alter the learning, thinking of stressed person. But recent researches showed that meditation reverse the effect of stress by decreasing the cortisol levels, increasing the blood flow with in brain near ventricles and other places, stimulating the brain and induce neurogenesis and synaptogenesis i.e. increases neural plasticity. Present review discusses Hypothalamo-PituitaryAdrenal axis (HPA) axis working during stress exposure, brain changes by raised cortisol due to HPA axis activation and also discuss the effect of meditation on HPA axis and brain to reverse the deleterious effects of stress. (Fish, D.R.et. al.,1993)

The word “stress” refers to facing “daily challenges in life”. According to Elliot and Eisdorfer’s taxonomy five categories of stressors - acute time-limited stressors, brief naturalistic stressors, stressful event sequences, chronic stressors and distant stressors (Saver, J.L. and Rabin, J., 1997).

Stress can be “positive stress”, “good stress” or “eustress” when person doing challenging work, assignment, studying hard during preparation for competitive examination or training. Stress can be “distress” or “toxic stress” when person face illness, hospitalization or death of loved ones, being abused or neglected, separation/death of spouse, legal stress, family stress, unemployment and hazardous work environment (Joseph, R., 1996).

Brain is the central organ of stress. The developing brain as well as adult brain changes its architecture after stress exposure by neuronal replacement, synapse turnover, dendritic remodelling. Eustress build brain circuitry stronger and produce resilient brain (Redding, F.K., 1967). A Young person if exposed to chronic stress during early days of life such as abuse and neglect have been prone to develop mental problems in the form of anxiety, depression, substance abuse and less able to cope with daily life stress (Newman, J. and Grace, A.A., 1999).

Most healthy individuals have the ability to control unwanted negative thoughts, worries and off task thinking easily but individuals with stress loss this ability and their mind wander from thought to thought. Stress significantly influences learning and memory (Chow, T.W. and Cummings, J.L., 1999). This is called “allostasis” or “stability through change”. Allostatic responses alter the functions of Hypothalamo-Pituitary Adrenocortical (HPA) axis = stress axis, nervous system, cardiovascular system, gastrointestinal system and immune system. Altered level of stress hormone glucocorticoid (cortisol in human) and suppressed neural plasticity also found in stressed patients.

Major depressive disorders (MDD) showed changes in the brain regions-hypothalamus,

hippocampus, prefrontal cortex (PFC), and amygdala. Stress activates release of neurotransmitters serotonin, norepinephrine and dopamine (Poletti, C.E. and Sujatanond, M., 1980).

Researchers showed that living in enriched environment-learning new skills, listening good music; adapting relaxation techniques – meditation & yoga in day to day life; doing stretching exercises, help to keep the brain healthy, mind sharp, prevent age related decline in memory, concentration, information processing and improve the ability to regulate thoughts. Studies showed that brain aging is reversible and stimulation of brain by learning new things activate neurogenesis and repeated practice make synaptogenesis strong, powerful and efficient (Adair, K.C. 1995). Meditation can reduce the effect of stress on brain by decreasing cortisol levels and thus also affect neural plasticity. Studies on long term meditators showed increase in the thickness of their cerebral cortex. The structural changes in the brain can occur in as little as 8 weeks duration by a mindfulness-based stress reduction (MBSR) program. Studies performed on undergraduate students undergone meditation training demonstrated increased ability to control stress and lower anxiety, depression, anger and fatigue (Fernandez-Duque, D. and Posner, M.I., 2001). This review paper discusses effect of stress on HPA axis functioning and changes in brain architecture by raised cortisol due to activation of HPA axis and the effect of meditation on HPA axis and brain architecture to reverse the deleterious effects of stress.

In view of HPA Axis during stress exposure when someone exposed to stress, the centromedian, basal and lateral amygdaloid (fear center) nuclei sends distress signal to the HPA axis, cerebral cortex, midbrain and other regions of brainstem which regulate adaptive responses to stress. Hypothalamus communicates directly to adrenal medulla through the autonomic nervous system (ANS) to release adrenaline (epinephrine). Adrenaline triggers the “fight-or-flight response”. Adrenaline work as alarm hormone and disappears immediately after completion of the stress situation. “Adrenalin surge” remain the “first response to stress exposure” (Steinmetz, M.A. et. al., 1987). After completion of initial adrenalin surge, the hypothalamus activates the “second component” of the stress response system “the hormonal system”.

Reaches to the anterior pituitary via portal vessels; binds to CRF receptors; stimulates Adrenocorticotrophic hormone (ACTH) synthesis and release into the systemic circulation to reach adrenal cortex. ACTH binds to adrenal cortex receptors and induces zona fasciculata for cortisol (Glucocorticoid) synthesis and release. ACTH release is facilitated by the plasma level of cortisol. Cortisol is also known as body’s “stress hormone”. Cortisol is a steroid hormone so easily cross blood brain barrier and produce its effect on brain through glucocorticoid receptor (GR) and mineralocorticoid receptors (MR) (Portas, C.M. et. al., 1988).

In brain MR is mainly present in limbic areas (more in the hippocampus, moderate in the amygdala and few in PFC). MR occupied first even in very low cortisol level. After stress exposure ACTH secretion is detectable within 5 minutes and cortisol secretion is detectable within less than 15 minutes (Cheramy, A., Romo, R. and Glowinski, J., 1987).

In normal conditions, Cortisol released rhythmically with both a circadian and an ultradian (pulsatile) pattern. At midnight (around 4 am or 3-5 hours after onset of sleep) very low or undetectable cortisol levels present in the blood. Cortisol level builds up overnight and reaching to peak in the early morning (around 8 am). Cortisol levels then decline slowly throughout the day. Ideally, once the stressor has been removed, a feedback loop within the hormonal system will restore normal levels of cortisol, and bring the body back into balance. However, chronic stress conditions prevent this rebalancing and cortisol levels remain elevated persistently due to continuous activation of HPA axis i.e. chronic stress can produce continuous high cortisol levels. This glucocorticoid circadian rhythm disruption leads to disease (Posner, M.I. and Petersen, S.E., 1990).

This circadian rhythm is regulated by the main circadian oscillator (pacemaker) lie in the suprachiasmatic nucleus (SCN), located in hypothalamus. Continuous elevated cortisol circulates in the body and put effect on whole body because GR are present in every cell of body including neurons of the brain. In brain GR are located predominantly in the hippocampus, PFC, amygdala, and PVN of hypothalamus. High elevated cortisol down regulate hippocampal GR. In normal conditions these hippocampal GR send negative feedback to the HPA axis. Thus during stressed condition due to down regulation of hippocampal GR due to raised cortisol level in brain the HPA axis continuously remain activated and raised brain cortisol change the brain architecture. After 30 minutes of stress exposure glutaminergic system activates. Glutamate is an excitatory amino acid (EAA) and predominant excitatory neurotransmitter in the human body especially in human brain. Glutamate is also a potent neurotoxin responsible for toxic neuronal death of post synaptic neurons by creating free radicals. This is called 'glutamate neurotoxicity' (GNT). Cells in PVN of hypothalamus, hippocampus, PFC and the anterior pituitary gland express glutamate receptors. Glutamate also plays a major regulatory role in activation of HPA axis to stress. Glutamate is precursor for brain's main inhibitory neurotransmitter GABA. Glutamate play role in the physiologic process of learning and memory (d'Aquili, E.G. and Newberg, A.B., 1993).

Brain architecture change due to raised cortisol level and shows effect in MRI studies showed that that raised serum cortisol lowers total cerebral brain volume (shrinks the brain), low occipital and frontal lobe gray matter volumes (the ratio of the brain's white matter to gray matter is higher) especially hippocampus, PFC, amygdala. Hippocampus, amygdala and PFC play critical role in

complex behaviour, cognition and also regulate autonomic and HPA axis stress response (Lazar, S.W., Bush, G., Gollub, R.L. 2000).

In hippocampal dentate gyrus raised cortisol level causes disruption of synaptic plasticity by loss of dendritic spines, dendritic shrinkage, neuronal shrinkage, neuronal death and suppression of neurogenesis. These changes in hippocampus are associated with memory deficits. Hippocampus is responsible for learning, memory of daily events, spatial memory, mood regulation and helps shut off stress response. Normally, in healthy brain, in hippocampal dentate gyrus neurogenesis occur throughout life. In the hippocampus glucocorticoid and mineralocorticoid both receptors are present and GABA is the key neurotransmitter. GABA is important for the control of thoughts (Newberg, A.B., Alavi, A., Baime, M. 2001).

GABA is primary inhibitory neurotransmitter in the brain. Research studies showed negative correlation between GABA activity and anxiety i.e. lower GABA levels and GABA receptors are associated with higher levels of anxiety. In panic disorders decreased GABA activity was found in hippocampus, lingual gyrus, middle temporal gyrus, visual cortex, orbital cortex and insula (Lou, H.C. et. al., 1999).

Raised cortisol causes dendritic debranching and dendritic shrinkage in mPFC. Dendritic shrinkage is associated with cognitive rigidity. mPFC is most sensitive area of brain even to mild stressors. Dopaminergic system lies in mPFC. PFC is responsible for executive functions such as decision making, problem solving ability, working memory, self-regulatory behaviour such as mood, impulses and helps shut off the stress response. These changes in PFC may be responsible for age related loss of resilience, impaired memory, circadian disruption and extinction of fear memory. Orbitofrontal cortical neurons expand dendrites which denote increased vigilance during stress (Herzog, H., Lele, V.R., Kuwert, T. 1990).

Efferents from Hippocampal CA1 and subiculum go to the PFC. For better learning and memory good connection of hippocampus to the PFC is required. The PFC disrupt hippocampal retrieval processes or thought relay. Raised level of cortisol builds up (increases the size, activity level, and number of neural connections) fear center of brain k/as Amygdala (Greek word means almond). Acute traumatic stressors increased spine density on basolateral amygdala (BLA) neurons. Chronic stress produces expansion of BLA dendrites, while loss of spine in medial amygdala. Amygdala influences our likes and dislikes, thinking, memories and social interactions with others. Our amygdala reads other person emotions within milliseconds and activates, prepare us for flight and fight behaviour. The amygdala facilitates emotional responses such as pleasure, fear, anxiety and aggression and turns on stress hormones. An enlarged and hyperactive amygdala, along with

abnormal activity in other parts of the brain, leads to disturbances in sleep and activity patterns (Kleven, M.S. and Koek, W., 1996).

Effect of meditation which makes changes in brain architecture studies showed that meditation techniques alleviate stress and anxiety by producing varying neuro physiological effects. Yi-Yuan Tang et al did their study to see the effect of 4- weeks integrative body-mind training (IBMT)-a form of mindfulness meditation on white matter of brain by the help of non-invasive magnetic resonance imaging (MRI)-based technique known as diffuse tensor imaging (DTI) to delineate white matter fibers in vivo. They found improved fractional anisotropy (FA) in areas surrounding the anterior cingulate cortex, reduction in radial diffusivity (RD) and axial diffusivity (AD). Reduction in RD and AD interprets improved myelin and axonal density respectively. Their study results demonstrate improved white matter neuroplasticity in the form of increase myelin as well as axonal density (Karson, C.N. et. al., 1984).

Gotink RA and Vernooij MW did a cross sectional MRI study on 3742 participants to determine the effect of meditation practices on amygdala and hippocampal volume. They found that regular meditation practices lower right amygdala volume and lower left hippocampus volume (de Wit. et. al., 2002).

Normal proportion of gray matter (densely packed nerve cell bodies and glia cells) to white matter (myelinated axons = tracts) is 1:1. Gray matter is necessary for thinking, computing and decision making [40]. White matter affects brain functions such as learning, modulating the distribution of action potentials, acting as a relay and coordinating communication between different brain regions. People with high cortisol levels had lower memory, thinking skills and slightly lower total brain volume than those with normal levels. Stressful life events in previously normal subject are associated with decrease gray matter volume in the anterior cingulated cortex, the hippocampus and the parahippocampal gyrus within a 3 month period (Lee, B. et al., 2009).

Kislay kumar et al studied effect of yoga and meditation on serum cortisol level in first-year medical students and found 4.8% decrease in morning serum cortisol level (572.18 ± 168.03 to 544.98 ± 139.89) in yoga group and 3.4% increase in morning serum cortisol level (558.89 ± 162.69 to 577.26 ± 254.5) in control group. Serum cortisol level is considered as the marker of stress and inflammation (Ghahremani, D.G. et al., 2012). High cortisol level indicates high stress level. Hennekens MR assessed effect of yoga on the level of salivary cortisol in nursing students. He found significant decrease in post asana salivary cortisol level in comparison to pre asana (PREA) salivary cortisol level (Cole, D.M. et al., 2013).

A short term (30-minutes per day for 5-days) integrative body-mind training (IBMT) – a form of

meditation, significantly enhance cerebral blood flow (CBF) in left subgenual/adjacent ventral anterior cingulate cortex (ACC), mPFC and insula and thus improve positive mood and neuroplasticity in the form of improve attention and self-regulation. Left ACC and insula are critical brain areas in self-regulation. Yoga and meditation provide extra energy to neurons and glial cells by enhance capillary vasculature. The neuropil (neurons, glial cells, capillaries, combined together) expands, thickening the cortex (Kayser, A.S. et. al., 2012).

Meditation, which has its origins in India and dates as far back as 5000 BCE, has become increasingly popular and widely practiced as a secular and therapeutic activity. The word meditation stems from *meditatum*, a Latin term 'to ponder'. Meditation practices are techniques, such as mindfulness, transcendental meditation, and breath awareness that encourage and develop concentration, clarity, emotional positivity and a cultivation of non-judgmental awareness (Li, N. et al., 2013). Various forms –spiritual and secular - of meditation have been developed, with the latter emphasizing stress reduction and relaxation. The term meditation has been used to designate a variety of practices that differ enough from each other that they elude precise definition.

6. The Endocrine System and Stress

The endocrine system comprises a number of glands – the hypothalamus, pituitary gland and pineal gland in the brain, the thyroid and parathyroid glands in the neck, the thymus in between the lungs, the adrenal glands on top of the kidneys, the pancreas behind the stomach and the gonads in the pelvic region - that produce hormones which regulate many functions in the body and is important in managing and responding to stress. It is a chemical messenger system comprising of feedback loops regulated by hormones released by glands into the circulatory system to regulate distant organs, often mediated via the hypothalamus and pituitary (Angelides, N.H., Gupta, J. and Vickery, T.J., 2017)

Stress can be defined as disruption to homeostasis and activation of the stress response, or 'fight-or-flight' response. Humans, as with all living things, maintain a dynamic equilibrium – homeostasis – which is the stable state or balance of the organism and of optimal functioning. Humans are also constantly challenged by internal or external stressors, which can be real or perceived threats to homeostasis (or safety or wellbeing) and result in adaptive physiological and metabolic changes that maximise chances of surviving these threats (Cho, S.S. et al., 2013).

This stress response is mainly regulated by the central nervous system through activation of the sympathetic and parasympathetic divisions of the autonomic nervous system and actions of neuro-humoral mediators such as the hypothalamic pituitary-adrenal axis and the catecholaminergic system. This includes increases in heart rate and blood pressure to send oxygen to muscles, pupil dilation to let in as much light as possible, and the downstream release of the glucocorticoid

hormone, cortisol, from the adrenal cortex, as well as suppression of nonessential systems, like the digestive and immune systems, to allow more energy for emergency functions (Bjork, J.M. et. al., 2009). Once the threat has receded the parasympathetic nervous system returns the body to homeostasis.

Stress induced physiological and metabolic changes are crucial for survival in the presence of an actual present-moment threat but can have a range of negative effects when activated unnecessarily and chronically. This is because stressors can be both real and perceived, and psychological stressors such as worry about the future, anticipation, reliving the past, rumination and arousal can lead to chronic activation of the stress response, which is detrimental to health and wellbeing as it increases the risk of health problems and contributes to a wide variety of diseases, disorders and difficulties (Korponay, C. et al., 2017).

worry and anticipation about the future and reliving the past are associated with activation of the default mode network (DMN), a large-scale network of interacting brain regions, most commonly shown to be active when the brain is at wakeful rest, when an individual is thinking about others, themselves, remembering the past, and planning for the future. Alterations in the DMN activity have been associated with a number of mental health problems, including depression and anxiety (Schilling, C. et al., 2012), which are characterised by high DMN activity such as worry and rumination.

Mindfulness practices, specifically various forms of meditation, which bring the person back to the present moment have been associated with reduced activity in the DMN. Activation of the stress response is associated with the onset and maintenance of mental health issues such as anxiety and depression (Holmes, A.J. et. al., 2017).

Stress-related increases in glucocorticoid levels and the further synthesis of pro-inflammatory cytokines (small cell signalling protein molecules involved in the innate immune response and inflammation) are normally regulated by a glucocorticoid negative feedback mechanism. However, persistent activation of the stress response disrupts this negative feedback mechanism and results in a cumulative physiological burden which can eventually contribute to the onset of disease, mental illness and poor wellbeing. As the neuroendocrine systems regulating the stress response are involved in the regulation of mood and emotion, mental illnesses such as clinical anxiety and depression are associated with increased expression of stress-induced pro-inflammatory cytokines, that stimulate the autonomic nervous system and hyper-secretion of corticotropin-releasing hormone (CRH), and increase circulatory cortisol and the production of pro-inflammatory cytokines. While the endocrine system is important in the management of stress, the effects of meditation on the

functioning of the endocrine system and wellbeing have been scarcely investigated (Matsuo, K. et al., 2009).

Meditation Influences the Hypothalamic–Pituitary–Adrenal (HPA) Axis The HPA axis is a neuroendocrine system that is involved in stress regulation and various other bodily processes and plays a key role in mental health and wellbeing. The HPA axis controls the synthesis and release of stress hormones including CRH, adrenocorticotropin hormone (ACTH), and cortisol, in response to stressors. The release of CRH from the hypothalamus results in release of ACTH, which then acts on the adrenal cortex to release cortisol into the blood. Cortisol subsequently acts in a negative feedback fashion to terminate the continued release of CRH. Disruptions in cortisol production can result in dysregulation of the HPA axis, which has been associated with a range of mental health problems, such as depression and anxiety (Heeren, A., Van Broeck, N. and Philippot, P., 2009).

The HPA axis has been the mostly widely studied of the endocrine systems in regards to the effects of meditation. A systematic review of 45 randomized controlled trials investigating the effects of focused attention, open monitoring and automatic self-transcending subtypes of meditation. On markers of stress, and compared to an active control group, found that focused attention, but not automatic self-transcending meditation, reduced cortisol levels. In this study, meta-analysis to investigate the effects of open monitoring meditations, such as mindfulness meditation, was unable to be performed due to an insufficient number of trials. Previous research, however, indicates that mindfulness-based meditation may also influence HPA axis stress hormone levels, and that this is associated with improved mental health and wellbeing (Sahdra, B.K. et al., 2011). For example, in a pre-post study of 16 individuals with clinical depression and anxiety, two months of mindfulness meditation improved psychological wellbeing and increased ACTH, indicating that mindfulness meditation can enhance psychological well-being and regulate hormonal parameters. In a randomized controlled trial of 150 healthy individuals, practising amrita meditation four times a week resulted in a decline in adrenaline and cortisol levels from as early as 48 hours after beginning the meditation program. The decline in adrenaline and cortisol levels was similarly present after eight months of engaging in amrita meditation four times a week, compared to progressive muscle relaxation and a no intervention control, In cross-sectional studies of regular transcendental meditation (a form of automatic self-transcending mediation) practitioners (three to five years of practice) and new transcendental meditation practitioners (three to four months of practice), the former group were associated with more marked and sustained declines in cortisol levels than the latter group (Jha, A.P. et. al., 2007).

In a study of 34 Chinese undergraduate students, two and four weeks of integrative body-mind

training, which included mindfulness training, reduced salivary cortisol levels both at rest and following a laboratory-based stress-inducing task, compared to relaxation. In a pre-post study of 59 patients with early stage breast or prostate cancer, a mindfulness-based stress reduction program, which included meditation, was associated with decreased cortisol levels as well as levels of pro-inflammatory cytokines, systolic blood and stress symptoms, indicating less stress and mood disturbance.

In a pilot study of 30 postmenopausal women, salivary and urinary excretion of cortisol following a metabolic stressor (oral glucose consumption) was higher in 16 long-term practitioners of transcendental meditation when compared with 14 non-meditators, which may reflect improved endocrine regulation in response to metabolic challenge. In a randomized controlled trial of 57 patients with colorectal cancer, a single mindfulness meditation practice delivered during active chemotherapy administration resulted in increased cortisol reactivity, suggesting that mindfulness practice can reduce the blunting of neuroendocrine profiles typically observed in cancer patients and supporting the use of mindfulness in oncology (Valentine, E. and Sweet, P., 1999). These studies collectively indicate that meditation influences the regulation of the HPA axis, which may reflect decreased stress levels among meditators.

Meditation Influences the Hypothalamic–Pituitary–Thyroid (HPT) Axis shows The HPT axis determines and regulates thyroid hormone production, which is vital to metabolism, nervous system development and thermogenesis, among other functions and appears to be involved in the pathophysiology of anxiety and depression. Thyroid-stimulating hormone (TSH) controls the synthesis and release of triiodothyronine (T3) and thyroxine (T4). Plasma levels of T3 and T4 are maintained within a narrow range and too much or too little can lead to hyperthyroidism or hypothyroidism, respectively (Kreek, M.J. et. al., 2005). Meditation and Insulin Resistance Insulin is a peptide hormone considered to be the main anabolic hormone and is necessary for the control of blood glucose levels as it signals the liver, muscle and fat cells to uptake glucose from the blood to be used for energy. A recent statement from the American Heart Association highlights that there is limited research regarding the effects of meditation on metabolism and insulin resistance.

With age, TSH levels gradually increase, possibly due to decreased biological activity of the peptide hormone, or increasing thyroid resistance to TSH. In long-term practitioners of transcendental meditation, TSH levels are seen to decrease. This is apparent in a prospective study of 11 men who had been practising transcendental meditation for at least three years, where an advanced transcendental meditation practice (termed TM-Sidhi) was associated with a decline in TSH levels, but not in cortisol, T4 or T3 levels, indicating that transcendental meditation may effect some, but

not all, markers of neuroendocrine function (Duckworth, A.L. and Seligman, M.E., 2005). In a randomized controlled trial of 49 healthy Caucasian males, four months of transcendental meditation practice, 15-20 minutes twice a day, was associated with a decrease in TSH and cortisol levels and an increase in growth hormone levels, compared with stress education transcendental meditation. It is possible that transcendental meditation was associated with a decrease in cortisol levels in this study as individuals were meditation naive at baseline whereas in the earlier study as individuals had already been practising transcendental meditation for at least three years, any changes in cortisol levels had already occurred (Zgierska, A. et al., 2009). A more recent non-randomized study of 45 healthy men and women found that a 12-week yoga program including an unspecified form of meditation increased TSH levels in men, and decreased T3 and T4 levels in both men and women, compared to a waitlist control group. It is possible that a yoga program including physical postures may differ from meditation alone in terms of effects on thyroid function, as physical yogic postures can influence HPT axis function. This is consistent with research showing that other forms of physical activity and exercise influence HPT axis function. For example, in a study involving six rowers, three weeks of high-intensity resistance training decreased TSH and T3 levels, while three weeks of endurance training increased TSH levels. In obese women, TSH levels have been shown to increase during and decrease immediately after 60 minutes of aerobic exercise, while TSH levels increase and T3 levels decrease after three months of aerobic exercise training. These studies collectively suggest that meditation as well as yoga including meditation may influence TSH levels, albeit in differing ways, and perhaps that these effects may be sex-specific. This hypothesis is supported by findings that in 20 middle-aged sedentary women, an eight-week yoga program that included an unspecified form of meditation did not influence TSH, T4 or T3 levels, compared to a no intervention control group indicates meditation intervention did not influence thyroid function. In sixteen individuals (nine female) with elevated depression and anxiety symptoms, two months of mindfulness meditation practised at least three times a week similarly did not influence TSH, T3 and T4 levels, though this study did not assess males and females separately 11. In a pilot study of 22 women with hypothyroidism, however, six months of yoga practice four times a week, including cyclic meditation, resulted in a non-significant reduction in TSH, cholesterol, triglycerides, low density lipoprotein and high-density lipoprotein levels (Zylowska, L. et al., 2008). These results indicate that meditation may improve thyroid function in women with thyroid dysfunction more effectively than in women with normal thyroid function, or that interventions of longer duration are required in order to detect benefits following meditation interventions. In addition, it should also be noted that only those studies delivering transcendental meditation were found to decrease TSH

levels, and therefore different forms of meditation may also account for the divergence in results. Overall, the limited evidence suggests that some forms of meditation may influence thyroid function, which may reflect more efficient functioning of the HPT axis, and that these effects may be sex- or population specific.

In one study of eight male college students who had been practising transcendental meditation for at least two years, plasma renin activity increased during transcendental meditation, compared to a quiet rest condition (Murphy, C. and MacKillop, J., 2012). Interestingly these meditators had a smaller increase in cortisol following venepuncture, compared to people who were not meditators, indicating that transcendental meditation may reduce stress reactivity. A cross-sectional study of 22 healthy students who had practised transcendental meditation for 8.5 years found that, compared to 33 non-meditators, they had lower levels of aldosterone, cortisol, and excretion of the norepinephrine metabolite vanillylmandelic acid, and higher levels of the serotonin metabolite, 5-hydroxyindoleacetic acid, which corresponded with lower levels of mood disturbance and anxiety. This indicates that meditation-associated changes in the RAA system correspond with improved well-being and changes in hormonal stress markers. Meditation Influences Energy Homeostasis Energy homeostasis depends on the balance between energy intake and expenditure. The physiological control of energy homeostasis involves multiple mechanisms and physiological systems and organs, such as the brain and white adipose tissues (Peters, J.R. et. al., 2011).

Meditation and Leptin – Leptin is hormone secreted by fat cells, Leptin (C87 H138 N22 O28 S2) effects on reproduction, adaptive immunity, blood pressure, Heart attack, body weight and bone mass. Leptin is a hormone secreted by and in proportion to adipose cells and regulates energy by inhibiting hunger. Leptin plays a role in inflammatory process; specifically, as increases in leptin are associated with an increase in C-reactive protein (190). The limited data indicate that meditation does not appear to influence leptin levels. For example, in a randomized controlled trial of 186 university faculty and staff with an elevated C-reactive protein level, and with or at risk of cardiovascular disease, a two-month workplace mindfulness program incorporating mindfulness meditation, compared to lifestyle education, was not associated with any changes in leptin (Lattimore, P., Fisher, N. and Malinowski, P., 2011). Similar results were found in a randomized controlled trial of 68 African American individuals who had high metabolic system risk factors, as 12 months of consciously resting meditation, which is a sound or mantra based meditation, when compared to health education, was not associated with any changes in leptin, or any of the other inflammatory biomarkers assessed. These findings are not surprising given that leptin is produced by adipocytes adipose cells and is correlated with body fat and as meditation practices are unlikely to

result in losses in body fat (190).

7. Discussion

Meditation is a practice that induces a physiological state characterized by reduced metabolic activity, distinct from sleep, leading to physical and mental relaxation, enhancing psychological balance, and promoting emotional stability. In Western psychology, three states of consciousness are commonly recognized: sleep, dream, and wakefulness. However, Eastern philosophy introduces a purportedly "higher" state of consciousness known as the "fourth state of consciousness" or "thoughtless awareness," characterized by the cessation of incessant thinking processes, resulting in deep mental silence. The practice of meditation aims to achieve thoughtless awareness, as described in ancient scriptures.

Meditation is a practice that involves making changes in how we perceive things, think, and regulate our body functions. It's often used in psychology and medicine to manage stress and conditions like depression. While it's known to have positive effects on the body, particularly in systems involved in depression, the exact ways it works aren't fully understood. Research suggests that meditation affects various physiological systems related to stress, mainly through hormones (Neurotransmitter – brain chemical) like cortisol, serotonin, dopamine, oxytocin and many hormones. Stress, a result of life's challenges, impacts our body and brain, potentially leading to mental health issues. However, meditation seems to counteract this by reducing cortisol levels, increasing blood flow in the brain, and promoting neural growth, ultimately improving mental resilience. This is crucial because stress affects our ability to concentrate, learn, and remember things. So, understanding how meditation works on a molecular level can shed light on its benefits for mental health and stress management.

Meditation, encompassing diverse practices like mindfulness, and transcendental meditation, emerges as a potent tool for holistic well-being. Beyond its renowned psychological benefits of reducing stress and anxiety, it intricately influences physical health by lowering blood pressure and heart rate. This systematic review delves into the intricate biochemical dance orchestrated by meditation, examining its effects on key markers such as cortisol, serotonin, dopamine, oxytocin, and endorphins-crucial players in mental health. Through various meditation modalities, oxytocin and endorphin levels surge, while dopamine and serotonin behaviours undergo beneficial modulation, concomitantly reducing cortisol production. Such shifts herald improved stress, anxiety, and depression indicators, bolstering overall well-being. In the face of life's daily stressors, meditation fosters adaptation through allostasis-maintaining equilibrium amidst change-via intricate neural, neuroendocrine, and neuroendocrine-immune mechanisms. Recent research underscores meditation's remarkable ability to counteract stress, ameliorating cortisol levels, enhancing cerebral blood flow,

and fostering neural regeneration, thereby enhancing cognitive resilience. This review elucidates the interplay between meditation, the Hypothalamo-Pituitary-Adrenal axis, and brain architecture, highlighting its pivotal role in mitigating stress-related neurophysiological alterations. Despite its complexity, meditation remains a cornerstone in stress management, wielded across psychological and medical realms to alleviate conditions like depression. Yet, while evidence mounts regarding its physiological efficacy, the precise mechanisms underlying meditation's therapeutic prowess remain elusive, necessitating robust exploration. Understanding its molecular intricacies promises deeper insights into its profound physiological impacts, bridging the gap between stress response and emotional equilibrium. As a pervasive tool for stress reduction and mental well-being enhancement, meditation's influence extends through the intricate pathways of the endocrine system, heralding a promising avenue for comprehensive health interventions. The lack of consensus on meditation definitions and methodologies underscores the need for rigorous, targeted studies to unlock its full therapeutic potential and elucidate its nuanced mechanisms.

Meditation offers promising avenues for stress reduction and enhancing mental well-being. Through its practice, individuals can experience changes in sensory perception, cognition, and hormonal activity. Notably, the endocrine system plays a significant role in mediating the effects of meditation, particularly in regulating stress hormones like cortisol. This study emphasizes the importance of investigating various meditation techniques and their impacts on physiological markers of stress. While much attention has been given to the hypothalamic-pituitary-adrenal axis, further exploration of other endocrine pathways is warranted. Understanding how meditation influences neurotransmitters and hormones like serotonin, dopamine, and oxytocin can provide valuable insights into its therapeutic potential for managing stress and mental disorders.

8. Conclusion

In conclusion, meditation emerges as a valuable tool for mitigating the adverse effects of stress and promoting mental resilience. Despite the complexity of its mechanisms, research suggests that meditation exerts profound effects on physiological systems, particularly through modulation of the endocrine system. By reducing cortisol levels, increasing cerebral blood flow, and promoting neural plasticity, meditation offers tangible benefits for stress management and mental well-being. However, further research is needed to elucidate the specific mechanisms underlying its therapeutic effects and to optimize its application in diverse populations. Understanding the molecular-level impacts of meditation can pave the way for more targeted interventions and personalized approaches to mental health care.

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