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EDITORIAL

MIND-BODY RESPONSE AND NEUROPHYSIOLOGICAL CHANGES DURING STRESS AND MEDITATION: CENTRAL ROLE OF HOMEOSTASIS

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Stress profoundly impacts quality of life and may lead to various diseases and conditions. Understanding the underlying physiological and neurological processes that take place during stress and meditation techniques may be critical for effectively treating stress-related diseases. The article examines a hypothetical physiological homeostatic response that compares and contrasts changes in central and peripheral oscillations during stress and meditation, and relates these to changes in the autonomic system and neurological activity. The authors discuss how cardiorespiratory synchronization, which occurs during the parasympathetic response and meditation, influences and modulates activity and oscillations of the brain and autonomic nervous system. Evidence is presented on how synchronization of cardiac and respiratory rates during meditation may lead to a homeostatic increase in cellular membrane potentials in neurons and other cells throughout the body. These potential membrane changes may underlie the reduced activity in the amygdala, and other cortical areas during meditation, and research examining these changes may foster better understanding of the restorative properties and health benefits of meditation.

Modern life's demands lead to chronic stress and increased prevalence of stress-related conditions and stress has been found to be a contributing factor in human disease (1). Extensive research has been conducted on stress and the anxiety-reducing effects of meditation (2) but very little is known about the underlying processes. This article aims to provide insight into the physiological activity behind the stress response by comparing stress and meditation states in terms of oscillatory activity throughout the body and brain. This activity is then related to the proposed hypothesis of changes in cellular membrane potentials. These changes are suggested to underlie the restorative and health benefits of meditation. This proposed mechanism is similar to the widespread hyperpolarization that may underlie the restorative properties of sleep (3). Deeper knowledge of respiratory homeostasis may foster better understanding of physiological rhythms of the body in various states of consciousness. Additionally, it may further knowledge regarding the efficacy of interventions, such as meditation, for stress-related conditions.

Heart rate variability: influence of respiratory and cardiac oscillations

Respiratory and heart rate variations influence sympathovagal balance which in turn influences

Key words: oscillations, sympathovagal balance, stress, meditation

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cardio-respiratory activity and hemodynamics (4). Respiration profoundly influences sympathetic and parasympathetic responses. The shift of low frequency (LF, 0.1 Hz) to high frequency (0.3 Hz) heart rate variability (HRV) is indicative of a parasympathetic shift in sympathovagal balance. It has been established that HRV can be used as a proxy for vagal tone; however, the use of HRV to estimate sympathetic tone has been debated (5). Following *Vipassana* meditation, a mindfulness-based approach, there is a decrease in LF power (6). The increase in normalized high frequency (HF) which is the ratio of HF to LF and the decrease in Traube-Hering Mayer waves (neural oscillations coupled with respiration that are associated with LF power), indicate that the decrease in LF power following *Vipassana* influences overall HRV by increasing the ratio of HF to LF power.

Mind-body interventions such as yoga and mindfulness show significant improvements on stress, sleep quality, and HRV (7). During meditation, slow breathing inhibits sympathetic and limbic activity. Changes in functional connectivity differ between types of meditation and are detectable by fMRI (8).

Influence of oscillations on the autonomic nervous system during stress and meditation

The autonomic nervous system features a feedback loop with the cardiorespiratory system and brain. Under stress, the body shifts to a sympathetic state and cardiorespiratory synchronization decreases (9). However, slow, deep breathing, as in Dharma-Chan meditation, leads to cardiorespiratory synchronization and parasympathetic activation (10). Levels of cardiorespiratory synchronization increase as breathing rates decrease (11). During meditation, cardio-respiratory synchronization is predominantly at a ratio of 4:1 or 5:1, that is, 4 or 5 heartbeats for every 1 breath (12).

Laser Doppler cutaneous blood flow studies show respiration influences BP oscillations at 0.3 Hz (13). Studies have also found spontaneous correlation of slow rhythms of 1 Hz with cardiac and 0.1 Hz with intrinsic myogenic activity. The slowest 0.04 Hz rhythm was attributed to neurogenic factors (14). In another study assessing autonomic control of skin microvessels using a photoplethysmograph, different areas of the body revealed fluctuations of 0.1 Hz that increased in amplitude when subjects were standing. The synchronization between BP and 0.1 Hz oscillations was unrelated to respiration and suggested a common neural, non-local origin (15). During the sympathetic dominant state, BP and HRV are associated with low frequency Mayer waves ranging from 0.05 to 0.15 Hz (16) whereas during the parasympathetic state, HRV is at a higher frequency (0.3 Hz).

According to our model, sympathetic activation during stress and the resulting decrease in membrane potential results in peripheral responses such as increases in skin conductance, heart rate, and BP (Fig. 1). Peripheral microcirculation observed with Doppler flow studies and BP correlates with sympathetic activity (17). Because skin conductance is measured in relation to sweat gland activity innervated by the sympathetic nervous system, it is used as an indicator of sympathetic response (18). During stressed states, peripheral responses are widespread. Skin conductivity (19) and BP (17) increase, and HRV decreases (20). For example during surgery, BP, epinephrine, and norepinephrine levels positively correlate with changes in skin conductance and can be used as an indicator of patient stress (19). Changes in HRV are indicative of autonomic balance and are strongly related to the central nervous system (21). For the purpose of this paper, oscillations in the brain less than 1.5 Hz are referred to as very slow waves and waves from 1.5 – 10 Hz (theta and slow alpha waves) are termed slow waves, while fast oscillations refer to oscillations greater than 10 Hz (beta, gamma, and theta waves.) Slow cardiac, respiratory, and other non-neural waves refer to oscillations less than 1 Hz and fast oscillations refer to oscillations greater than 1 Hz. fMRI brain scans show increased 0.1 Hz oscillations during stress associated with mind wandering and decreased functional connectivity in other brain areas (22) and is also supported by fMRI scans revealing decreased cortical activation during stress (23).

HRV recordings distinguish HF markers of parasympathetic activity (0.15-0.40 Hz), and LF components of sympathetic control (0.04-0.15 Hz). Spectral analysis of microcirculatory blood flow suggests the presence of similar rhythms

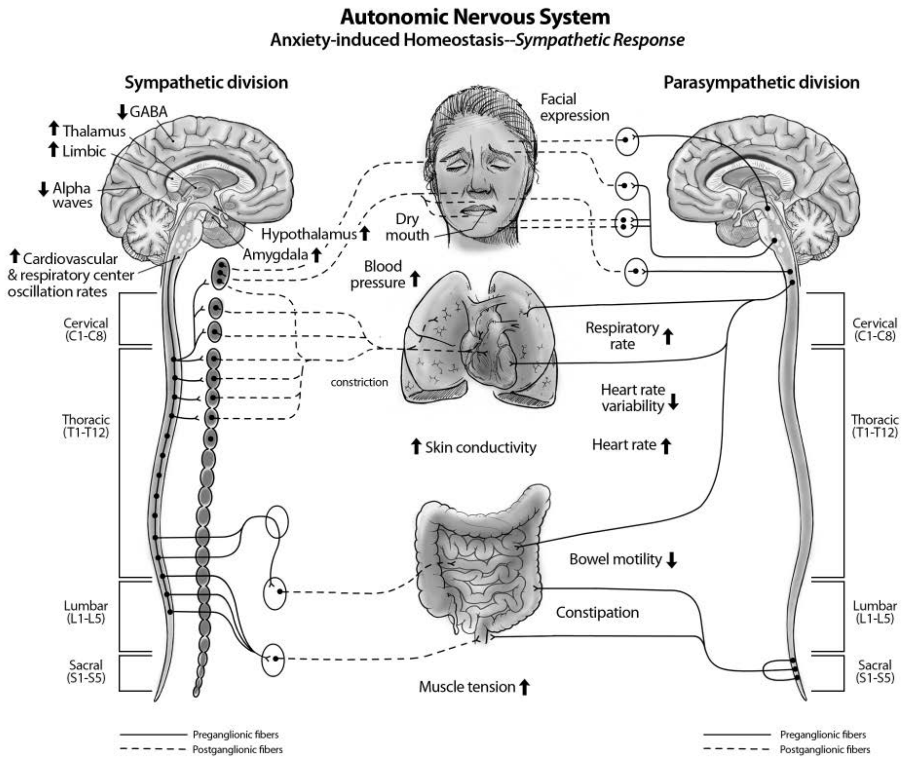

Fig. 1. *Responses associated with sympathetic dominance. The dual-sided autonomic nervous system is shown in which sympathetic activation outweighs the parasympathetic branch. Sympathetic dominance, as seen during the stressed state, leads to a variety of peripheral responses associated with depolarization of target organs. Functional connectivity and alpha waves decrease, while limbic and amygdala activity increase. Brainstem activity also increases, reflected by the increased respiratory center and cardiovascular center rates. Respiration and heart rate increase. Heart rate variability measures are dominated by low frequency components. Blood pressure, skin conductivity, and muscle tension increase. Bowel motility and salivary gland secretion are also hindered. The body is in a relatively depolarized state, including the various target organs and spinal cord. Facial expression depicts a stressed or unpleasant state.*

(24). The pattern characterizing the spectral profile of heart rate and arterial pressure variability consists of LF and HF markers related to vasomotor and respiratory activity, respectively (25). For example, decreased HRV in response to a stressor is related to anxiety and depression (26). Wavelet analysis of HRV reveals the existence of frequencies between 0.145 and 0.6 Hz corresponding to respiration and shows modulation of heart rate by respiration (respiratory sinus arrhythmia) (27). Indeed, Tang et al. (2009) demonstrated sympathetic markers decreased in subjects after training in mind-body techniques compared to a control group (28). In Dharma-Chan meditation, advanced practitioners exhibit a high degree of cardiorespiratory synchronization even during rapid breathing (10). High levels of cardiorespiratory synchronization are also seen during Zen and Kinhin meditation (29). Decreased breathing rate during meditation mediates cardiorespiratory synchronization and a parasympathetic response (30) (Fig. 2) while decreased synchronization of hemodynamic and respiratory rhythms is seen during stress (31). Conversely, meditation has been shown to provide significant benefit for the cardiovascular system (32). Meditation has also been shown to improve anxiety, pain, stress, mental health, and quality of life (33). In addition, after stress, mindfulness meditation results in significantly less neurogenic inflammation than in controls, despite equivalent amounts of stress

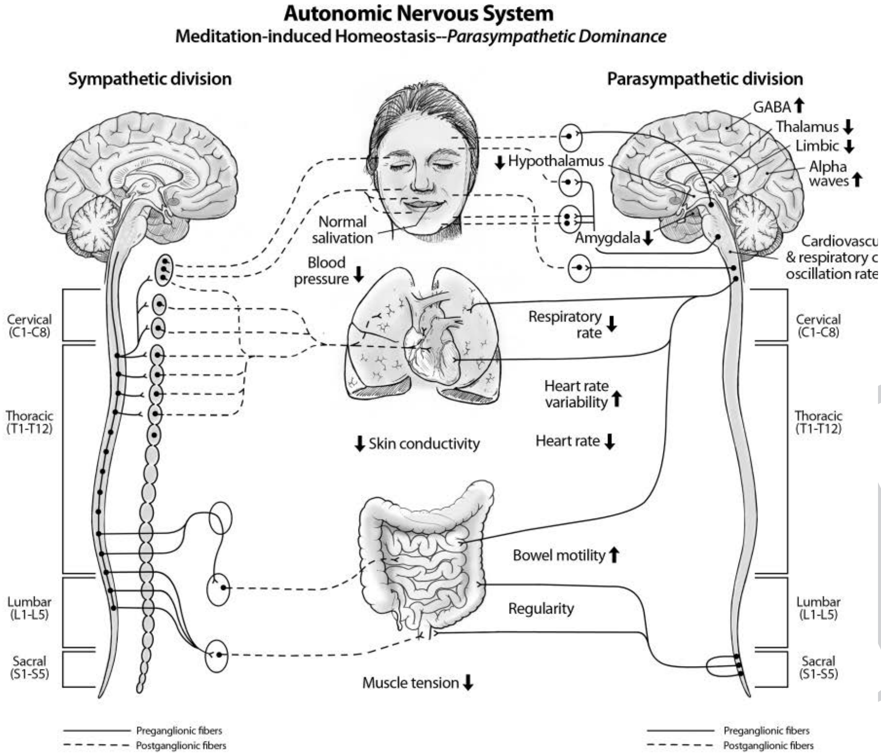

Fig. 2. *Responses associated with parasympathetic dominance. The dual-sided autonomic nervous system is shown, in which parasympathetic activation outweighs the sympathetic branch. In contrast to sympathetic dominance, a shift to prominent parasympathetic activation leads to peripheral responses associated with membrane potential hyperpolarization and the reversal of the effects seen in Fig. 1. In this state, there is an increase in functional connectivity and alpha waves and a decrease in limbic and amygdala activity. Brain stem activity decreases, which is reflected in decreased respiratory center and cardiovascular center rates. Heart rate, respiratory rate, blood pressure, and muscle tension all decrease. High frequency heart rate variability is increased. This parasympathetic shift can be readily achieved through meditation and deep breathing techniques. A pleasant facial expression and widespread hyperpolarization is associated with this state compared to the relatively depolarized state in Fig. 1.*

hormones (34).

Influence of neural oscillations during stress and meditation

Meditation is generally associated with relaxation but many of the changes that occur during meditation do not occur during relaxation alone. For example, relaxation is not associated with the typical hemodynamic changes associated with meditation. Higher levels of cardiorespiratory synchronization that occur during meditation are hypothesized to lead to increases in membrane potential in the cardiovascular system, brainstem, limbic system and higher cortex. The subsequent homeostatic increases in membrane potential may lead to inhibition of emotion centers and increased functional connectivity of the medial prefrontal cortex, thereby increasing focus, memory, and feelings of well-being (35). Another way that mindfulness meditation differs from simple relaxation is that the meditator is aware of moment-to-moment thoughts, feelings, and sensations. We propose that by decreasing stressful or anxious thoughts, that involve greater depolarizations, the practice of mindfulness involves widespread inhibition and membrane hyperpolarization of neurons and in turn contributes to the shift towards parasympathetic activity. Overall, relaxation may be involved in meditation but simply trying to relax does not always relax the mind or stop stressful thoughts. Therefore, we propose that mindfulness meditation is associated with greater widespread hyperpolarization and inhibition than relaxation alone.

Alpha oscillations have frequencies ranging from 8-13 Hz (36). In a study, using magnetoencephalography, Yamamoto et al. found an increase of alpha wave activity in the medial prefrontal cortex and anterior cingulate cortex during Transcendental Meditation® or automatic self-transcending meditation (TM) (37). Examination of EEGs during automatic self-transcending meditation has shown that there is an increase in alpha-1 wave activity in the brain (38). Alpha waves have been associated with suppressing irrelevant brain activity and improving mental focus (39). Also, it has been suggested that alpha waves play an important role in selective attention and information processing (40). A study by Saggar et al. using EEG found a reduction in beta waves among subjects performing focused attention meditation when compared to the control groups (41). In addition, increases in left hemisphere activity are seen during meditation, which is associated with stronger immunity (42) and increased vaccination response (43).

Meditation practice has been linked to GABAergic cortical inhibition, which has been shown to be associated with improved cognition and regulation of emotions (44). A reduction in GABAergic cortical inhibition has been shown to be linked with memory impairment in schizophrenic patients (45). GABAergic neurons tonically inhibit supraoptic neurons in the hypothalamus and modulate the excitatory effects induced by interleukin-1 (46), suggesting that that the increased cortical GABA modulation associated with meditation (44) may underlie the decreases in interleukins-6 levels (47). GABAergic neurons are important in the process of generating respiratory rhythms and communication between the cardiovascular and respiratory centers in the brainstem. GABAergic neurons have been shown to work as inhibitory neurons that increase their spontaneous firing during inspiration. This suggests that inspiration promotes inhibitory activity in the brainstem and decreases cardiovascular and respiratory center oscillation rates during parasympathetic dominance (48). Injecting GABA into the amygdala increased HRV, consistent with a parasympathetic response, and the injection of glutamate induced a sympathetic response (49). This study suggests that increased levels of GABA in the brain are involved in the parasympathetic response. In addition, stress has been shown to attenuate GABAergic inhibition in the amygdala (50). During stress, there is increased activity in the hypothalamo-pituitary-adrenocortical axis (51) and an increase in activity and stimulation of the amygdala (52). Studies have found a decrease in amygdala activity during mindfulness meditation (53) and during non-meditative states, after participating in mindfulness or compassion meditation training (54). Also, reduced activity in the hippocampus, thalamus, and occipital lobe has been shown after practice of TM (55). During stress, the adrenal medulla increases secretion of the neurotransmitter epinephrine, which reaches the hypothalamus and acts on the central nervous system (56) and elevated cortisol levels from stress (57) may be responsible for decreased serotonin function in the brain during depression (58). During meditation, these neurotransmitters levels reverse. Studies have found decreased levels of stress hormones such as cortisol (59), epinephrine and norepinephrine (60) after meditation. In addition, a stress management study training subjects in deep breathing, relaxation response, and meditation, found reduced anxiety and salivary cortisol levels (61). Levels of the anti-depressant and feel good hormones serotonin (62) and dopamine (60) increase during meditation.

Concentration, Loving-Kindness, and Choiceless Awareness forms of meditation have all been shown to increase functional connectivity in areas involved with self-monitoring and cognition (63). The differences in EEG and neuroanatomical activation in fMRI studies reflect the different meditation approaches being used such as loving kindness, concentration, open monitoring, or focused attention, as well as cardio-respiratory events. For example, in Loving-Kindness meditation, the practitioner focuses on heartfelt compassionate feelings which lead to decreased amygdala activity (63) and activation in the insular and anterior cingulate fMRI signals with associated theta waves. Focused attention meditation leads to activation of more executive function areas and beta/gamma activity (38) supported by cardiorespiratory synchronization, while TM is associated with increased medial prefrontal cortex activity and alpha wave appearance (64). Autogenic meditation is a practice in which the person uses verbal cues to help induce a feeling of warmth and relaxation.

Do homeostatic changes in neuronal membrane potentials modify the neurotransmitter release that underlies stress, anxiety, and meditation responses?

Membrane potential changes can create currents that synchronize various oscillations throughout the body. The process by which cardiovascular and respiratory rhythms synchronize is not well understood. However, hyperpolarization-activated currents have been shown to synchronize rhythmic cellular activity between the cardiovascular and respiratory centers in the brainstem (65) and within the central nervous system (66). This suggests that cardiorespiratory synchronization is associated with hyperpolarization.

According to our hypothesis, respiration and cardiorespiratory synchronization influence hemodynamic elements, as well as the autonomic nervous system, cerebral blood vessels, and neural elements, by increasing the membrane potential of excitable and non-excitable cells. In animal studies, repetitive parasympathetic stimulation of taste cells led to a hyperpolarization of -9 mV (67) while sympathetic stimulation depolarized toad sinus venosus cells (68). In addition, low-intensity stimulation of the vagus nerve causes long lasting, slow hyperpolarization of cortical neurons. This inhibits neuronal firing and may involve activation of potassium channels by acetylcholine and GABA receptor activity. In humans, inhibition of cortical neurons may be sustained if vagal stimulation is repeated before the last inhibition response has ended (69) suggesting that slow, deep breathing during meditation that stimulates the vagus may sustain this inhibition. These studies suggest that parasympathathetic drive leads to increased cellular membrane potentials and sympathetic drive may lead to decreased membrane potentials, as seen when sympathetic activation during stress leads to decreased membrane potentials of heart cells (70).

Studies monitoring membrane potential changes during sympathetic or parasympathetic states are needed to further understand the homeostatic modulation of cardiac, respiratory, blood pressure (BP) rhythms. An animal study examining the somatosensory cortex found that neurons at -55 mV were almost completely silent while pyramidal neurons at -85 mV had very reliable transmissions (71). This study suggests that cortical neurons with higher membrane potentials may have more reliable transmissions than those with lower membrane potentials. The typical resting state potential of pyramidal neurons is -85 mV to -60 mV (72) therefore if this study had examined transmissions at around -65 mV or -70 mV, we propose that the neurons would have fired more rapidly. We suggest that the increased membrane potentials during meditation in human subjects may increase transmission efficiency and functional connectivity via decreased firing rates while more depolarized neurons fire rapidly, resulting in less efficient and more chaotic transmissions.

We propose hemodynamic de-synchronization leads to a global decrease in membrane potential during stress and hemodynamic synchronization during meditation allows an increased potential to be conducted to all cells. This is reflected peripherally by decreased skin conductivity, BP, heart rate and increased HRV (28) which may be due to the hemodynamic synchronization brought on by the shift to parasympathetic dominance (35) and membrane hyperpolarization.

Our hypothesis focuses on mindfulness meditation but increased levels of cardiorespiratory synchronization are experienced during forms of meditation such as inward-attention (12), Chan (10), Zen, and Kinhin meditation (29), and further research is needed to measure synchronization in other forms of meditation involving slow, deep breathing. Increased levels of synchronization and hemodynamic changes lead to widespread hyperpolarization and inhibition which modulate the autonomic nervous system and brain activity. We propose that eyes closed, open-monitoring, inward-attention, and mindfulness practices may enhance this widespread inhibition.

CONCLUSION

Physiological and behavioral changes differ profoundly between states of meditation and anxiety. During anxiety, heart rate increases, breathing becomes irregular, and HRV decreases. These changes are accompanied by faster EEG rhythms and changes in neurotransmitters associated with negative emotions. In comparison, the mind-body relaxation response is associated with reverse changes and calm, focused thoughts. What causes these global changes in rhythms and thought processes? Is it a central process regulated by the hypothalamus and brain or by specific neurotransmitters? According to our hypothesis and review of literature, the mechanism is based on homeostatic modulation of intrinsic cellular excitability. Decreases in homeostatic membrane potentials during anxiety increase intrinsic cellular excitability, which in turn brings about changes in neuronal firing, neurotransmitters, and peripheral rhythms. Cardiorespiratory synchronization, during the mind-body response, leads to increases in homeostatic membrane potentials and decreased intrinsic cellular excitability that underlies the changes that modulate the autonomic nervous system and brain activity. Further studies are needed to confirm this hypothesis and elucidate the specific role of the hypothalamus in stabilizing the membrane potential set points of dynamic homeostasis during anxiety and the mind-body response.

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