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Self-regulation of breathing as a primary treatment for anxiety

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Abstract

Understanding the autonomic nervous system and homeostatic changes associated with emotions remains a major challenge for neuroscientists and a fundamental prerequisite to treat anxiety, stress, and emotional disorders. Based on recent publications, the inter-relationship between respiration and emotions and the influence of respiration on autonomic changes, and subsequent widespread membrane potential changes resulting from changes in homeostasis are discussed. We hypothesize that reversing homeostatic alterations with meditation and breathing techniques rather than targeting neurotransmitters with medication may be a superior method to address the whole body changes that occur in stress, anxiety, and depression. Detrimental effects of stress, negative emotions and sympathetic dominance of the autonomic nervous system have been shown to be counteracted by different forms of meditation, relaxation, and breathing techniques. We propose that these breathing techniques could be used as first-line and supplemental treatments for stress, anxiety, depression, and some emotional disorders.

Introduction

Though the source of human emotions is the brain and specific structures within the brain such as the amygdala, the experience of emotions causes widespread responses throughout the entire body (Cacioppo, 2000). An abundance of research has uncovered physiological changes that accompany emotions. For example, the autonomic nervous system (ANS) and respiratory activity have been shown to be closely associated with the experience of emotions (Kreibig, 2010). The validity of the use of specific patterns of autonomic activity as an indicator for specific emotions is disputed. There are certainly characteristics of sympathetic/parasympathetic activity and respiration that are correlated with certain emotional states such as anxiety or

happiness (Kop et al., 2011). We propose that negative mood states such as stress, anxiety, and depression cause sympathetic activation that is due to widespread depolarization throughout the brain and body, and that slow, deep breathing and meditation lead to parasympathetic activation due to widespread inhibition and hyperpolarization. Changes in neuronal cell membrane potentials may underlie neurophysiologic mechanisms of emotion (Murik, 2005) and we propose that these membrane potential changes occur throughout the body as well. Extending the investigation of physiological attributes of emotion to include homeostatic changes in membrane potential due to changes in respiration and autonomic activation may further our understanding of the physiological states of various emotions (Sequeira, Hot, Silvert, & Delplanque, 2009).

A considerable body of clinical research has been conducted on the physiological and psychological changes observed during different emotional states using functional MRI (Patin & Hurlemann, 2011), ANS monitoring (Kim, Bang, & Kim, 2004), and studying neurotransmitter receptor physiology (Wahlestedt, Pich, Koob, Yee, & Heilig, 1993). Research findings linking emotions and anxiety with autonomic, respiratory, and cardiac activity have helped clarify the relationship between emotions and the physiology, suggesting an underlying mechanism based on cellular membrane potential changes in response to physiological changes induced by different emotional states.

Relaxation treatments, such as meditation, target the mind and body as a whole (Jacobs, 2001) in comparison to pharmaceutical therapies which focus solely on neurotransmitter systems in the brain (Meyer, 2005) and do not address homeostatic alterations arising from prolonged changes associated with emotions. Instead they bypass the brain's processing systems and act directly on mechanisms that control emotion (Nesse & Berridge, 1997). Too often pharmacological treatments, such as anxiolytic drugs, have limited long term efficacy

(Youngstedt & Kripke, 2007), are symptom based, and are associated with severe side effects including adverse reactions, dependency (Buffett-Jerrott & Stewart, 2002), addiction (Buffett-Jerrott & Stewart, 2002; Lader, 1994), relapse, and resistance to treatment (Starcevic, 2012). A better understanding of the processes underlying human emotions may provide support for the administration of relaxation techniques such as meditation as a treatment for stress-related and anxiety disorders, as well as other psychiatric illnesses involving mood (Manzoni, Pagnini, Castelnuovo, & Molinari, 2008).

Possible role of membrane potential in cardiorespiratory modulation of ANS and emotions

Cardiac vagal motoneurons are hyperpolarized and strongly inhibited during inspiration, depolarized during the first half of expiration, and again demonstrate variable inhibition during the second half of expiration. We propose that slower respiration rates, which correspond to increased levels of cardiorespiratory synchronization (Porta et al., 2000), lead to a shift towards parasympathetic dominance via widespread hyperpolarization and inhibition of amygdala and thalamic cells (Jerath, Barnes, Dillard-Wright, Jerath, & Hamilton, 2012). Cardiorespiratory synchronization is an interaction between the cardiovascular and respiratory systems in which cardiac and respiratory signals synchronize (Schafer, Rosenblum, Kurths, & Abel, 1998). Decreased levels of cardiorespiratory synchronization occur during stress and are negatively correlated to sympathetic activity (Zhang, Yu, & Xie, 2010), exhibiting increased heart rate and irregular breathing (Malliani, 1999). However, during meditation, the mind and body shift to a parasympathetic dominant state and correlate with increased levels of cardiorespiratory synchronization (Cysarz & Bussing, 2005; Lo & Chang, 2013; Wu & Lo, 2010). Cardiorespiratory synchronization occurs primarily in a ratio of 4:1 and 5:1 during meditation, with four or five heartbeats for every one breath (Wu & Lo, 2010).

It has been established that during respiration, inspiration inhibits sympathetic nervous system activity (Czyzyk-Krzeska & Trzebski, 1990; Dempsey, Sheel, St Croix, & Morgan, 2002; Seals, Suwarno, & Dempsey, 1990; St Croix, Satoh, Morgan, Skatrud, & Dempsey, 1999). In fact, slow-deep breathing has been shown to cause near-complete sympathoinhibition (Seals et al., 1990). This sympathoinhibition varies inversely with lung volume, with high lung volumes leading to the most inhibition (St. Croix, Satoh, Morgan, Skatrud, & Dempsey, 1999). Most of this sympathoinhibition also occurs in the second half of inspiration. For example, during slow-deep breathing, inhibition occurs from mid-inspiration to early-mid expiration (Seals et al., 1990). However, subjects who perform deep breathing from an elevated starting lung volume experience this sympathoinhibition earlier during inspiration. Findings suggest that depth of breathing, breathing pattern, and starting lung volume all influence degree of sympathoinhibition, with slower, deeper breathing causing the most sympathoinhibition (Seals et al., 1990). In addition, a study found that the extrathoracic trachea exhibited slow oscillating membrane potentials predominantly during the post-inspiratory phase (Kondo et al., 1993). In contrast, irregular breathing such as Cheynes-Stokes respiration which can involve shallow and/or deep, rapid breathing and periods of apnea, modulates the ANS leading to excitation of the sympathetic nervous system (Leung, Floras, & Bradley, 2006). These results are a prime example of respiration directly modulating the ANS by inhibiting the sympathetic nervous system as well as respiration affecting membrane potential.

During mindfulness meditation, neurons in the cerebral cortex are inhibited by gamma-aminobutyric acid receptor neurons, also known as GABAergic neurons (Guglietti, Daskalakis, Radhu, Fitzgerald, & Ritvo, 2013). GABAergic neurons are inhibitory neurons that increase firing in the cardiorespiratory network during inspiration (Frank & Mendelowitz, 2012). They

are highly involved in the creation of respiratory rhythms and they communicate between respiratory and cardiac centers in the medulla (Frank & Mendelowitz, 2012). GABAergic neurons also modulate excitatory transmissions in the amygdala (Wu et al., 2009). In fact, genetic deletion or blockade of GABA receptors in the amygdala increases anxiety behaviors while increased GABAergic transmission reduces excitatory transmissions in the amygdala (Wu et al., 2007). Another study found that GABA-mediated inhibitory post-synaptic potentials, i.e., hyperpolarizations, were reduced in the basolateral amygdala of stressed rats and that negative emotional responses are the result of reduced feedback inhibition of the amygdala (Isoardi, Bertotto, Martijena, Molina, & Carrer, 2007). Patients with panic disorders have been found to have a 22% reduction in GABA levels in the occipital cortex, suggesting that decreased levels of GABA may be involved in panic disorder pathophysiology (Goddard et al., 2001). In contrast, oral administration of GABA increases alpha waves and decreases beta waves, suggesting that GABA induces relaxation and reduces anxiety (Abdou et al., 2006). After a single yoga asana session, which consists of postures, *pranayama* (a yogic breathing exercise), meditation, and chanting, subjects experienced a 27% increase in GABA levels (Streeter et al., 2007). However, GABAergic neuronal activity throughout the brain is complex and may also be involved in vagal inhibition. For example, injection of a GABA receptor antagonist into the nucleus ambiguus of the brainstem shows a dose-dependent decrease in heart rate and blood pressure. This effect does not occur in any other areas of the brainstem, suggesting that GABA inhibits vagal outflow from the nucleus ambiguus (DiMicco, Gale, Hamilton, & Gillis, 1979). Inspiratory-modulated GABAergic neurons may be responsible for the inhibition of parasympathetic cardioinhibitory neurons that result in respiratory sinus arrhythmia (Frank & Mendelowitz, 2012). These findings

suggest that inspiration may promote inhibitory activity in respiratory and cardiac centers in the brainstem and other areas of the brain, such as the amygdala and cortex.

During stress and anxiety states there is widespread excitatory activity throughout the body and brain increasing activity in the amygdala (Davis, 1992) and hypothalamic-pituitary-adrenal axis (Herman & Cullinan, 1997), causing release of excitatory neurotransmitters and hormones (Ranabir & Reetu, 2011), increased heart rate (Vrijkotte, van Doornen, & de Geus, 2000), respiration rate (Gomez, Stahel, & Danuser, 2004; Masaoka & Homma, 2001), blood pressure (Kulkarni, O'Farrell, Erasi, & Kochar, 1998; Vrijkotte et al., 2000), skin conductance (Storm et al., 2002), and muscle tension (Wijsman, Grundlehner, Penders, & Hermens, 2010). During the sympathetic fight or flight response, heart rate increases due to an increase in the cell membrane depolarization rate of the sinoatrial node (Wu et al., 2009). Also, membrane depolarization is essential for contraction of skeletal muscle (Liu et al., 2009), suggesting that increased muscle tension during stress is the result of widespread depolarization. In addition, during stress, the release of the excitatory neurotransmitter glutamate in the amygdala (Reznikov et al., 2007), and prefrontal cortex is mediated by depolarization (Musazzi et al., 2010). Stress and depression are also associated with increased amygdala activity and chronic stress leads to neuronal hyperactivity in the amygdala, suggesting that a reduction in this excitatory drive may be a potential treatment (Padival, Quinette, & Rosenkranz, 2013). We propose that this excitatory activity is the result of widespread depolarization which is inhibited by slow, deep breathing and some types of meditation. Studies have found decreased activity in the amygdala during mindfulness meditation (Desbordes et al., 2012) and during non-meditative states after mindfulness training (Desbordes et al., 2012). This decrease in amygdala response, after

meditation training, has been found in patients with social anxiety disorder (Goldin & Gross, 2010) as well as healthy patients (Desbordes et al., 2012; Taylor et al., 2011).

Studies on Transcendental Meditation[®] have shown reduced activity in the thalamus and hippocampus (Newberg et al., 2006). We propose that inhibition of these emotional processing areas of the brain, during meditation, is caused by a shift from sympathetic to parasympathetic dominance facilitated by slow, deeper breathing and cardiorespiratory synchronization (Jerath & Barnes, 2009). A study by Zagon and Kemeny found that low-intensity stimulation of the vagus nerve caused long-lasting slow hyperpolarization of neurons in the cerebral cortex. The study proposed that if stimulation of the vagus nerve is repeated, before the last inhibition response ends, then sustained inhibition may be maintained (Zagon & Kemeny, 2000). Animal studies have shown cardiorespiratory coupling ceases after bilateral vagotomy, suggesting that cardiorespiratory synchronization is mediated by the vagus nerve, which imparts parasympathetic control (Campbell & Egginton, 2007; Dick, Baekey, Paton, Lindsey, & Morris, 2009; Topchiy, Radulovacki, Waxman, & Carley, 2011). In addition, schizophrenic patients exhibit decreased levels of cardiorespiratory synchronization, which indicates decreased vagal modulation and inhibition in the brainstem (Peupelmann et al., 2009). A study by Masaoka and Homma found a positive correlation between increases in respiration frequency and anxiety scores during anticipatory anxiety (Masaoka & Homma, 2001). In another study, electroencephalogram (EEG) dipole tracing revealed that 350 to 400 ms after the onset of inspiration there was a wave of positive potentials in limbic areas of the brain. These positive waves are referred to as respiration-related anxiety potentials (RAPs). RAPs originate in the right temporal pole in low anxiety subjects and originated in the amygdala in more anxious subjects (Masaoka & Homma, 2000). These RAPs, produced during inspiration, illustrate how emotional

states can lead to membrane potential changes of cells. As the frequency of respiration increases, due to anxiety, this leads to positive waves that increase membrane potentials and depolarize limbic areas of the brain. These RAPs, produced during inspiration, illustrate how interconnected respiration and stress, anxiety, and emotions provide evidence of respiration's influence on emotion areas of the brain. We hypothesize that anxiety and other stress-related emotions promote sympathetic dominance and subsequent widespread depolarization of emotion areas in the brain.

Parasympathetic stimulation leads to hyperpolarization of frog taste cells (Sato, Nishishita, Kato, Okada, & Toda, 2006), suggesting that hyperpolarization may occur during parasympathetic dominance, similar to that which occurs during slow deep breathing and may occur during positive emotions. Under sympathetic dominance, which occurs during emotional states such as fear and stress, we propose that there is a homeostatic response of widespread depolarization. In addition, slow deep breathing may lead to the widespread inhibition of neuronal firing that occurs throughout the brain during slow-wave sleep and may be responsible for the restorative function of sleep (Jerath, Harden, Crawford, Barnes, & Jensen, 2014).

In addition to the many inhibitory mechanisms discussed that occur via hyperpolarization, oxygen may also play an important role in these proposed widespread membrane potential changes. The basis for membrane potential changes lies in the transfer of ions across cell membranes, creating a gradient. We propose that oxygenation, may be an important factor in the widespread membrane potential changes that may occur during slow, deep breathing and meditation. Oxygen is vital for the electron transport chain during cellular respiration (Alberts et al., 2002). In fact, the mitochondrial electron transport chain has been found to be inhibited in hypoxic placentas (Colleoni et al., 2013) and oxygen and cytochrome C

are limiting factors of mitochondrial respiration (Gnaiger & Kuznetsov, 2002). Electron acceptors, such as oxygen, are responsible for the proton gradient and hyperpolarization that occur in the electron transport chain during mitochondrial cellular respiration (Alberts et al., 2002) suggesting that fluctuations in oxygen, even minor fluctuations that occur during inspiration and expiration, may affect the degree of mitochondrial hyperpolarization and subsequently affect the rate of cellular respiration. Slow deep breathing, which has been shown to increase oxygenation (Bernardi et al., 1998; Bilo et al., 2012), may therefore lead to a slight but widespread increase in hyperpolarization of cellular membranes (Jerath, Crawford, Barnes, & Harden, 2015). In addition, the existence of voltage dependent channels that transfer ions between the mitochondrial outer membrane and the cytosol (Fieni et al., 2010; Kmita & Stobienia, 2006) suggests that mitochondrial membrane potential changes may affect the entire cell.

Breathing and meditation techniques for reducing negative emotions

In view of the close association between respiration, ANS activity, and emotions presented, it is apparent that individuals possess the ability to alter emotional states using the voluntary control of breathing and mindset. One of the oldest and arguably, most efficient treatments of excessive stress is controlled breathing (Everly & Lating, 2013). Various types of techniques that involve slow, deep breathing such as yoga, *pranayama*, and some forms of meditation, have been practiced throughout history to increase well-being (Ospina et al., 2007). However, the clinical use of such practices, especially in current Western culture, has yet to gain widespread acceptance, though popularity is increasing. Breathing and meditation techniques are readily available, and do not pose risk of side effects. However, patients may respond faster or more effectively to medication than some types of meditation. Medications may have

advantages over meditation, such as convenience; whereas meditation and breathing techniques may require cost, time, and special training in addition to considerable time required for practice. In stress and anxiety states, motivation for meditation practice may be low and negative thought processes might reduce compliance with regular meditation practice. We propose that the mindfulness, compassion, and practice of positive mood states may also contribute to widespread hyperpolarization by inhibiting excitatory signaling. Research has shown positive outcomes when these exercises are used as treatment for anxiety or stress-related disorders. A study on patients with asthma found that breath retraining improved control of asthma symptoms, panic, and anxiety (Laurino et al., 2012). In addition, a study on major depression found that mindfulness meditation was as effective as medication. The double blind study, found relapse rates of 27% in the medication group, 28% in the meditation group, and 71% in the placebo group (Stubenrauch, 2011).

Another two potential treatments of emotion-related disorders is the use of *pranayama* or Sudarshan Kriya yogic (SKY) breathing. Both techniques have shown reductions in stress, anxiety, and/or depression symptoms in several studies (Bhimani, Kulkarni, Kowale, & Salvi, 2011; Brown & Gerbarg, 2005a; Marshall, Basilakos, Williams, & Love-Myers, 2013). SKY breathing is a technique involving breathing cycles ranging from slow, calming breathing to fast, stimulating breathing (Zope & Zope, 2013). SKY breathing was shown to be helpful in the reduction of negative emotional states such as stress, depression, post-traumatic stress disorder (PTSD), anxiety, and insomnia following major disasters such as tsunamis (Descilo et al., 2010) and Hurricane Katrina (Gerbarg, 2005) These benefits were also reported in other clinical studies (Agte & Chiplonkar, 2008; Brown & Gerbarg, 2005a; Janakiramaiah et al., 2000). The slow breathing cycles are suggested to stimulate the vagus nerve (Brown & Gerbarg, 2005b) while the

fast breathing cycles provide mild sympathetic stimulation similar to regular exercise that may boost stress tolerance (Brown & Gerbarg, 2005a). The combined cycles of slow and fast breathing may aid in emotional processing by reducing excitation with slow breathing and emotional calming (Zope & Zope, 2013).

Pranayama breathing yields similar positive outcomes. For instance, *pranayama* practice over a two month period led to significant stress reductions in medical students (Bhimani et al., 2011). Three months of *pranayama* practice also decreased anxiety and depression levels in 60 to 70 year olds (Gupta, 2010). Significant reductions in stress and anxiety levels were achieved with short term practice of *pranayama* which also led to improvements in test performance (Nemati, 2013). A program incorporating *pranayama*, yoga, and relaxation training found that severity of depression was greatly reduced at one and three month follow-ups (Naveen et al., 2013). In a comparison of techniques having positive impacts on mood and energy (both physical and mental), *pranayama* produced a significantly greater positive impact on mood and energy than relaxation and visualization techniques (Wood, 1993). A study examining stress management, found that deep breathing, relaxation, meditation, and guided imagery techniques resulted in reduced levels of anxiety, anger, neuroticism, hopelessness, salivary cortisol, and respiration levels (Iglesias et al., 2012). Deep breathing exercises have been shown to reduce PTSD-like symptoms and normalized abnormal cortisol levels (Kim et al., 2013).

While the efficacy of various techniques, for positively adjusting emotions is gaining increasing support, the specific mechanism through which these exercises achieve their results is poorly understood. However, evidence has supported better understanding of characteristics of the underlying physiology of controlled breathing and meditation. Deep breathing and meditation practice leads to an overall reduction in sympathetic tone and an increase in parasympathetic

output which combats increased sympathetic activity during stress (Brown & Gerbarg, 2005b; Jerath, Edry, Barnes, & Jerath, 2006; Streeter, Gerbarg, Saper, Ciraulo, & Brown, 2012). Indeed, evidence shows reductions in sympathetic signatures of autonomic markers during controlled breathing (Pal, Velkumary, & Madanmohan, 2004). For example, skin conductivity increases during sympathetic activity (Cowings, Suter, Toscano, Kamiya, & Naifeh, 1986; Isu, Koo, & Takahashi, 1987) while skin resistance increases during meditation, which is indicative of decreased sympathetic activity (Delmonte, 1984; Telles, Nagarathna, & Nagendra, 1995; Wallace, 1970; Wallace, Benson, & Wilson, 1971). In addition, heart rate variability (HRV), an indicator of the state of the ANS (Sztajzel, 2004), increases as respiratory rate decreases (Song & Lehrer, 2003). The highest HRV occurs at four breaths per minute and decreases as respiratory rate increases. A similar inverse relationship is demonstrated between cardiorespiratory synchronization and respiratory rate, with the highest cardiorespiratory synchronization occurring at lower respiratory rates (Porta et al., 2000). The ANS can affect many tissue cells simultaneously via diffuse release of neurotransmitters. Gap junctions between cardiac and smooth muscle cells can affect an entire tissue by spreading electrical activity from a single discharge from an autonomic nerve, and by releasing neurotransmitters and hormones in the blood that are circulated throughout the body (McCorry, 2007). A study on the relaxation response during meditation found that during stress the subjects in the meditation group had the same levels of plasma norepinephrine as the non-meditators but the responsiveness of the sympathetic nervous system was reduced in the meditators (Hoffman et al., 1982). The study demonstrates how the ANS can modulate responsiveness to neurotransmitters, suggesting that the modulation of the ANS may be a more powerful treatment tool than the current trend of targeting individual neurotransmitters in the brain. Though norepinephrine levels were not

lowered by Transcendental Meditation[®] in subjects throughout the day, they were found to be lower for meditators in the morning when compared with controls (Infante et al., 2001). Another study, utilizing an Integrated Amrita Meditation Technique involving meditation, *pranayama*, and yoga, found that practicing these techniques was effective in reducing adrenaline levels (Vandana, Vaidyanathan, Saraswathy, Sundaram, & Kumar, 2011). The mechanism by which meditation blocks or inhibits response to norepinephrine is now understood in terms of decreased activation and/or reactivity of the sympathoadrenal system and the HPA axis (Innes & Selfe, 2014). Meditation has also been shown to increase dopamine tone (Kjaer et al., 2002) and increases levels of 5-hydroxyindole-3-acetic acid, a metabolite of serotonin (Bujatti & Riederer, 1976). Slow deep breathing and relaxation techniques can modulate the ANS, leading to homeostatic changes throughout the body and brain, as well as affecting levels of and responsiveness to neurotransmitters. These techniques are therefore excellent candidates for treating various stress disorders.

Development of better technology to measure membrane potential activity with regards to respiratory and autonomic modulation during the experience of negative emotions may help further our understanding of the physiological mechanism of breathing and meditation techniques. We believe the shift in sympathovagal balance induced by controlled respiration and/or meditation leads to inhibition of negative emotions and widespread hyperpolarization which contributes to the beneficial effects observed following practices such as *pranayama* or mindfulness. Current technology does not allow for accurate and ongoing membrane potential measurements to be taken during meditation. There are some methods that have had some success in examining membrane potential changes, such as intramuscular electrodes to study somatic cells and various dipole tracing methods using EEG to study neuronal cells. However,

these technologies have limited capabilities. They may not be able to detect subtle membrane potential changes, have varying levels of accuracy, and are unable to measure phenomenon over long periods of time.

Conclusion

Emotions and respiration are closely linked in a complex feedback loop. Understanding this interrelationship between respiration and emotions is essential to better understand how to treat anxiety, stress, depression, and emotional disorders. Many of the detrimental effects of negative emotional states and sympathetic dominance of the ANS have been shown to be counteracted by different forms of meditation, relaxation, and breathing techniques. Meditation and breathing techniques reduce stress, anxiety, depression, and other negative emotional states. The underlying mechanism by which these and other benefits occur is poorly understood. We propose that the ANS is modulated by breathing so that in sympathetic dominant states like stress and anxiety, slow-deep breathing techniques and meditation can shift sympathetic dominance to parasympathetic dominance. This slow, deep breathing and cardiorespiratory synchronization may lead to homeostatic increases in cellular membrane potentials and a generalized decrease in intrinsic excitability of pacemakers such as the heart and amygdala, causing physiologic inhibition of negative emotions. We propose that these breathing techniques could be used as first-line and supplemental treatments for stress, anxiety, depression, and some emotional disorders. These disorders are mainly treated with medications that affect neurotransmitters in the brain, rather than treatments that affect the entire body and brain. Widespread homeostatic changes occur during stress and anxiety so treatments that shift the ANS from sympathetic to parasympathetic can be very effective. Throughout this article we have demonstrated that emotions can affect respiration and respiration can also influence

emotions, yet this well-established relationship is not utilized in conventional treatments.

Breathing and meditation techniques are simple, easy, and cost-effective yet they are not widely used as treatments.

Conflict of interest

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