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Precision Medicine for Breath-Focused Mind-Body Therapies for Stress and Anxiety: Are We Ready Yet?

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Abstract

In this viewpoint, we present an argument for transdisciplinary "precision medicine" approaches that combine studies of basic neurobiology of breathing in animal and human models of stress that can help characterize physiological and neural biomarkers and mechanisms of breathing control and emotion regulation in humans. Such mechanistic research is fundamental for the development of more effective and mechanism-based mind-body therapies. The potential for this research to positively impact public health is high, as breathing techniques are inexpensive, accessible, and cross-culturally accepted, with fewer complications then observed with other standard therapies for stress-related disorders.

Keywords

precision medicine, controlled paced breathing, mind-body therapies, stress, anxiety

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While stress is a normal part of life, when it becomes severe or prolonged, it can negatively impact mental and physical health. In 2020, with global stress heightened by COVID-19 pandemic, financial insecurities, racial and political tensions, and natural disasters, our individual and community resilience was challenged. Better, simpler, and cheaper tools for stress reduction, especially those that do not require pharmacological intervention, would be of great benefit. One such set of tools involve mind-body practices rooted in ancient meditative traditions that incorporate controlled paced breathing, such as yoga, Tai Chi, Qi Gong, which are therapeutic in alleviating symptoms of stress, anxiety, and chronic pain disorders.[1–4] Yet, without clear understanding of the underlying neural and physiological mechanisms, development of better treatments is problematic, especially with a goal of optimal personalized options per the NIH precision medicine initiative.[5]

In many fields of human health, advances in understanding of our physiology and behavior require the development and use of non-human mammalian models. To date, there are no current non-human translational models of mind-body practices, particularly for unraveling the mechanisms underlying the effects of controlled paced breathing. The development of translational models of the neurobiology of breathing in rodents can advance our understanding of basic mechanisms important for mind-body practices.[6] Although human neuroimaging studies can identify neural sites and pathways involved in regulation of stress responses, studies of breathing control are severely limited by methodological issues, such as difficulty in controlling for the effects of changes in blood O_2/CO_2 concentration that affect BOLD signals, and the inability to effectively image brainstem structures critical for breathing (e.g., preBötzinger Complex)[6,7] and for regulation of the Autonomic Nervous System (ANS).[8–10] Another challenge is measuring the subjective interoceptive

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experience of breathing in: 1) humans focusing on internal cues, and how it might underlie the effects of slow breathing on stress and emotions,[11] and; 2) rodents, in whom only indirect measures of internal experience are possible (e.g., heart rate variability (HRV)). Recognizing advantages and limitations of human and of animal experiments, combining them offers essential synergy for deepening our understanding of the power of controlled paced breathing to affect stress-related physiology and pathophysiology.

Cross-Species Breathing Mechanisms

Breathing regulates O_2 intake essential for aerobic metabolism and its byproduct CO_2, in turn also regulating pH.[6] Breathing rhythms are generated in the brainstem that result in periodic movement of inspiratory and expiratory muscles driven by cranial and spinal motoneurons. The principal engine for generating breathing rhythm is the preBötzinger Complex,[6] a compact bilateral medullary nucleus. In addition to driving movements underlying ventilation, breathing activity affects suprapontine brain structures (e.g., hippocampus, prefrontal cortex, amygdala)[12] to significantly influence cognitive and emotional function.[13] Understanding how these breathing-related signals affect these higher structures and functions is key to delineating mechanisms underlying the effectiveness of controlled paced breathing on stress.

Advantage of Using Animal Models

Experiments on rodents allow investigation of the bottom-up influence of breathing-related neural activity originating in the brainstem that may include breathing-modulated olfactory and pulmonary signals. Brainstem activity with the necessary spatiotemporal resolution is impossible to ethically assess in human subjects using current technologies. Rodents are an excellent model to probe these mechanisms at the molecular, cellular and network level: 1) breathing in rodents and humans is similar, involving lungs, diaphragm and other equivalent respiratory muscles, and equivalent brainstem structures for generation and control of breathing movements (e.g., preBötzinger Complex),[6] 2) various presentations of stress, including anxiety, fear and panic that are serious emotional disturbances, have been studied in well-vetted models in rodents providing considerable insight into the underlying mechanisms in humans,[14] 3) advanced technologies that cannot be considered or easily implemented in studies of humans (e.g., transgenic manipulation, optogenetic stimulation and recording, trans-synaptic neuroanatomical mapping) are routine procedures in rodents, allowing incisive studies of mechanisms with exceptional spatiotemporal, single cell and network resolution; 4) rodent experiments do not need to consider placebo effects that is a confound in studies of human subjects, so that hypothesis testing of mechanistic processes of breath control is independent of appraisal and cognition; 5) higher cortical structures affected by paced breathing in humans, as identified, can be targeted for more detailed mechanistic studies in rodents.

Advantages and Limitations of Using Human Models of Breathing Control

Experiments on human subjects can address top-down processes of cortical regulation of breathing, such as related to emotional responses in stressful situations, interoceptive awareness of dyspnea, or acute or chronic changes in blood gases. The processes underlying regulatory breathing normally operate unconsciously; however, breathing can enter conscious awareness, such as during exercise, airway restriction (asthma) or obstruction, or through interoceptive awareness training such as in yoga or mindfulness meditation. Breathing is integral to the mind-body connection where increases in breathing rate are induced by stressful emotional states, such as fear, anxiety, and panic.[14] Just as breathing processes can influence mental states, conscious processes can change breathing frequency, depth or pattern, as well as one's interoceptive awareness of breathing.[15,16] Breathing is unique relative to other physiological systems, e.g., gastrointestinal, insofar as volitional or emotional control can immediately impact breathing, with both rapid and chronic effects on emotion and cognition. Moreover, subjective awareness of distress and abnormal breathing may contribute to mechanisms by which cortical control of breathing patterns can in turn affect emotion regulation to alleviate stress response.

The Role of Interoception in Breath-Based Mind-Body Therapies

Anxiety is a shared emotional experience of stress and a part of many mind-body disturbances in the context of psychosomatic disorders. It is accompanied by psychological distress and is associated with altered breathing, perception of breathing, and response to manipulations of breathing.[17,18] In patients with anxiety or respiratory diseases, interoceptive sensations from cardiorespiratory organs including chemosensors for blood gases, can trigger panic attacks via catastrophic misappraisal or conditional fear responses.[17–21] During panic attacks, common sensations include cardiovascular, respiratory and psychological symptoms of asphyxiation, palpitations, chest pain, dyspnea, choking, nausea, dizziness, flushing, supported by objectively measured elevated heart rate and blood pressure, changes in breathing pattern, and exaggerated startle response.[22] For some patients, dyspnea (i.e., breathlessness) is useful as a physiological marker of anxiety as well as a treatment target using interoceptive interventions. In addition, to acute effects, anxiety disorders often promote or reflect the development of chronic homeostatic and allostatic disturbances, requiring different methods of assessing subjective and behavioral responses to emotionally negative stimuli. A network of cortical brain regions including the insula and anterior cingulate cortex (ACC) is proposed as the critical substrate for interoceptive awareness.[15] These neural networks enable human awareness of the cardiovascular and respiratory state of the body.[23] In animal models, various experimental acute or chronic exteroceptive or interoceptive stressors can be used to model stress-response, such as in threat avoidance and pain paradigms.[23,24]

Numerous pathways are implicated in the processing of interoceptive signals, beginning with the widespread direct and indirect central projections of autonomic afferents, including in autonomic ganglia, spinal cord, brainstem and suprapontine structures. Several brainstem (nucleus of the solitary tract, parabrachial nucleus, and periaqueductal gray), subcortical (thalamus, hypothalamus, hippocampus, and amygdala), and cortical (insula and somatosensory cortices) sites are key for processing afferent signals.[15] A complementary set of regions involved in visceromotor actions generate efferent signals, including the anterior insula, anterior cingulate, subgenual cingulate, orbitofrontal, ventromedial prefrontal, supplementary motor, and premotor areas. These regions coincide closely with other sites critical for other functional systems, especially those involved in emotion regulation.

In *Vivo* fMRI Imaging of Breathing Control

Functional neuroimaging in humans could identify homologues of bCPG as delineated in rodents, with considerable potential to observe changes associated with breath-holding or active expiration. Importantly, human neuroimaging studies can illuminate the contribution of forebrain centers to reflexive, emotional, and volitional regulation of breathing and advance our understanding of interactions between interoception of breathing and cognitive and emotional experience of stress. Hypothesized interoceptive awareness pathways, such as one involving visceral afferents projecting to the insula, or skin afferents projecting to somatosensory cortex can be tested in fMRI experiments.[15,25]At the same time, fMRI paradigms of emotion regulation currently use protocols that allow *in vivo* experimentation that elucidates emotional reactivity to stress and emotion regulation to negative stimuli, and can be helpful in experiments in breath control to further understanding of the interaction between breathing and emotional responses to stress. However, in large part because of the influence of blood gas changes on BOLD signal detection, current neuroimaging in humans remain challenging in terms of allowing detailed examination of brainstem or determining the effects of changes in breathing effort while in the MRI scanner.[8,10]

In summary, transdisciplinary approaches that combine studies of basic neurobiology of breathing and stress and translational mind-body medicine present the opportunity to identify and characterize physiological and neural biomarkers and mechanisms of breathing control and emotion regulation across species. Conversion neuroscience that combines transdisciplinary efforts of basic, translational and clinical science can provide innovative methods of investigation that will propel the neuroscience of mind-body medicine forward by illuminating the role of voluntary breath control in the management of stress-related illness via its effects on emotion regulation.[25] Such mechanistic research is foundational for development of more effective and easily accessible breath-based therapies.

Future steps could consider collaborative projects that would address similar paradigms of breathing control and stress in animal and human models of stress that will provide a dissection of the neural pathways involved in emotion regulation. Such efforts should be able to map the pathways from various components of the bCPG to suprapontine structures important in emotion regulation (e.g., locus coereuleus and other suprapontine projections), thus explaining how breath manipulation can affect stress response and related emotional stats of fear, anxiety and panic, and ability to regulate emotions. Answering these questions in rodents and humans can lead to the development of the mechanism-based preventive and treatment interventions for stress-related disorders. The currently available tools that can facilitate this type of cross-species modeling includes measuring physiological parameters of cardiopulmonary coupling, i.e., HRV, and fMRI neuroimaging that can be analyzed by using machine leraning.[26] This approach will advance our understanding of the neural mechanisms responsible for the positive effect of controlled breathing-based mind-body therapies on stress response and emotion regulation, which will shift the science of mind-body medicine into the "precision medicine." Identification of specific sites that play a key role in the therapeutic effects of breathing therapies on providing relief from anxiety, fear or stress opens the possibility of their therapeutic manipulation. Rapidly advancing brain-stimulation techniques could then be targeted to affect one or more of these regions in a manner that alters their activity with resultant therapeutic improvement. The potential for this research to positively impact public health is high, as breath-based techniques are inexpensive, accessible, and cross-culturally accepted, with fewer complications then observed with more invasive therapies.

Declaration of Conflicting Interests

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