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Respiratory Epigenetic Modulation (REM): A Dynamic Oscillatory Framework Linking Breathing, Epigenetics, and Disease Reversibility

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Abstract

Studies of epigenetics have focused historically on spatial and static environmental exposures as well as chemical addendums that increase or decrease gene expression without DNA sequencing alteration. This article presents a new dynamic theory—the Respiratory Epigenetic Modulation (REM) Theory—which identifies breathing as a stable physiological oscillator supporting facilitation and retraction of epigenetic marks via bioelectrical, biochemical, and autonomic nervous system pathways. In addition, REM integrates Default Space Theory (DST)—the subsequent brain oscillations from respiratory dysrhythmia that change intermediate metabolic byproducts—and conscious learning and relearning, creating a basis for reversible disease states in psychiatric conditions, metabolic disease, and chronic inflammatory states. Finally, REM defines a relevant pathological component—Respiratory Epigenetic Syndrome (RES)— associated with chronic respiratory dysrhythmia and sympathetic predilection as well as maladaptive epigenetic markers. These findings present an innovative theoretical approach to respiratory-based precision modalities, from concepts of old and new as well as implications for aging populations, mental health, metabolic disease, and adaptogenic. Ultimately, viewing respiration as an arbitrary agitating factor instead of an active means by which gene regulation can occur creates a new sense of purpose surrounding specific breathwork that can reverse maladaptive gene expression in chronic disease states.

Keywords

Respiratory Epigenetic Modulation; Dynamic Oscillatory; Framework Linking Breathing; Epigenetics; Disease Reversibility.

Introduction

The field of epigenetics has been largely developed through work studying environmental exposures, nutrition, toxins and developmentally programmed changes. For example, classic work showing that nutrition and stress exposures can lead to epigenetic "marks" (i.e. DNA methylation, histone dynamics) over the life course and across generations have defined how and when scientists believe such changes can occur [1,2]. Yet respiration, which is a naturally occurring rhythm with great regulation potential fails to connect as a direct physiological process that modulates epigenetics from the outset. Among all physiological processes, respiration is the only rhythmic process with intermittent conscious and non-conscious control and integration with many systems (nervous, cardiovascular, metabolic, etc.), making it a central operator with real-time adjustment potential for feedback into the biohomeostasis world. Since breathing connects with autonomic function, bioelectric oscillations, pH regulation and redox status and emotional-cognitive endpoints, respiration can exert much more epigenetic influence relative to other systems and operates as a dynamic.

Respiratory fluctuations impact vagus nerve activity and heart rate variability (HRV), impact inflammatory dynamics and correlate with not only stress levels but also epigenetic states of stress- and immune-related genes. For example, diaphragmatic breathing increases (vagal) parasympathetic activity and correlates with lower stress hormones and decreased inflammatory signals from IL6 – changes with DNA methylation levels evidenced in NR3C1 (glucocorticoid receptor) and IL6. Inversely, a hyperactive, sympathetic breathing pattern (fight-or-flight mediated) promotes an oxidative stressed environment; psychoneuroimmunological changes prove elevated DNA methylation of stress-reactive genes involved in post-traumatic stress disorder (PTSD) (NR3C1, FKBP5). The REM model is derived from this information to add a twist—that respiration is more than just a simple metabolic facilitator but rather a therapeutic oscillator capable of real-time entrainment to epigenetic regulators.

Based on Default Space Theory (DST) – that investigative work defining the breath oscillation as a global regulator of neural oscillations [3]– REM proposes that breathing can actively entrain bioelectrical and biochemical mediators of epigenetic determinants. Thus, we can access DNA methyltransferases (in charge of genomic placement of methyl moieties) and demethylating events from TET enzymes (elimination of methyl moieties) as well as histone-modifying enzymes that modulate chromatin dynamics through the intentional act of breath. Therefore, respiration is positioned as not merely a metabolic function but a master regulator of genomic expression patterns. In addition, we hypothesize that through this connection of breathing patterns and subsequent epigenetic changes that chronic stresses across psychiatric, metabolic, inflammatory disease domains may be a result of a respiratory component that drives negative epigenetic programming. However, this programing is modifiable because unlike genetic mutations that set in stone fixed change, epigenetic marks are reversible; when accessing the breath properly, beneficial changes can begin within minutes to hours in an effective non-invasive manner.

In the sections to follow we detail the components of REM central to this hypothesis as well as the supportive literature proving those dynamic respirations impact epigenetics over time. This includes proposing the pathophysiological construct of Respiratory Epigenetic Syndrome (RES) – linked to chronic respiratory dysregulation – accessible through integrative work with DST to bring consciousness and cognition into play. Finally, we'll discuss therapeutic applications and translational ideas – through person-specific respiration approaches – while outlining future studies required in this exciting field of inquiry. Ultimately, by changing

how we consider breathing relative to the epigenome we expand precision medicine avenues for treatment for otherwise irreversible diseases.

Core Components of the REM Framework

Breathing as the central oscillator

Breathing patterns—frequency and volume, in addition to the degree of coupling between the cardiac and respiratory process—emit oscillatory bioelectric fields and biochemical oscillations across the body. The act of inhalation and exhalation corresponds to minuscule shifts in bioelectric potential (i.e. expansion/contraction of lungs, movement of diaphragm, increment/decrescendo of heartbeat concomitantly with breath) and statistically significant adjustments of blood gases (O_2 and CO_2) which change pH and redox characteristics among tissues. Moreover, these oscillatory phenomena are not merely differential; they serve as an oscillating signal that can meaningfully connect with cellular responses. For example, pH variations induced by differential components of respiration impact enzyme function: hypoventilation "traps" CO_2 at a higher level relative to O_2, inducing changes toward a more basic pH (respiratory alkalosis). Conversely, smaller volumes and faster breaths retain less CO_2, inducing a lower pH (mild acidosis). Enzymes that insert and delete epigenetic marks are often responsive to such conditions. DNA methyltransferases (DNMTs) insert methyl groups onto genomic loci while TET dioxygenases remove them; these rely upon cofactors and pH/redox conditions to be optimal (for example, TETs require Fe (II) and alpha-ketoglutarate at a certain reduced state). Therefore, by acutely inducing changes in CO_2 and oxygenation, theoretically breathing can shift the balance of DNMT and TET activity among cells in minutes. In addition, breathing at specific frequencies can provide resonance effects throughout the circulatory system, thereby providing amplifying signals. For example, breathing at ~6 breaths per minute (0.1 Hz) utilizes baroreflex resonance for maximal heart rate variability (HRV); thus, a state of respiratory-cardiac coherence occurs where large oscillations of heartbeats aligned with respiration (known as respiratory sinus arrhythmia) occur. Such coherent oscillations facilitate optimal gas exchange and efficiency of vagal nerve signaling to distal organs. Within the REM hypothesis, such coherence is believed to entrain epigenetic regulators: a calm rhythm of breath disseminates information from vagal afferents to blood-borne metabolites to bioelectric coefficients that can ultimately result in histone modifications and DNA demethylation in stress- related gene bodies—an intrinsic "safety signal" sent to the genome.

Physically, controlled breathing is the most accessed major oscillator in humans (we cannot control heart rhythm or brain waves externally but we can control breathing). Thus, it's an important mechanism for biofeedback. If one can become the "central oscillator," all other oscillatory phenomena—brain wave oscillations, cardiac rhythms, mitochondrial waves—can become entrained relative to respiratory rhythms. In fact, DST proposes that respiratory oscillations serve a global pacemaker. REM expands this idea for the epigenome, suggesting that the cyclic variation in O_2/CO_2 levels, blood flow, and vagal tone from breath provides a consistent oscillating signal where epigenetic enzymes and chromatin structures can lock on.

This is illustrated in figure 1 (conceptual): The Respiratory Epigenetic Oscillator demonstrates how slower/deeper breaths promote signals provided by increased CO_2 (i.e., slight acidosis) which inhibits DNMTs via requiring extreme alkalosis for maximal function while improved oxygenation and vagal engagement can facilitate TET-mediated demethylation resulting in overall chromatin opening and upregulation of stress resilience and metabolic-related genes.

Therefore, breathing becomes an interfacing channel between the environment and epigenome that instantaneously transforms breathing patterns into gene expression through downstream molecular signaling changes.

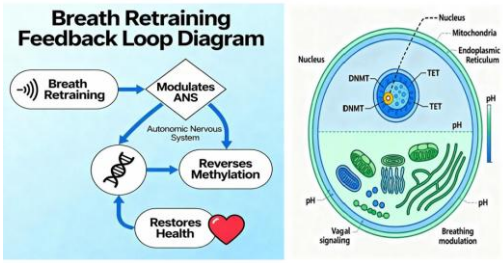

Figure 1: Breath Retraining Feedback loop.

ANS Sympathetic vs. Parasympathetic Dominance

The autonomic nervous system is made up of two constituent parts—sympathetic ("fight or flight") and parasympathetic ("rest and digest")—and subsequently breaching patterns intimately reflect this relationship. For example, rapid, shallow breathing (panting, anxious hyperventilation) operates as a cause and consequence of sympathetic overload as it often occurs alongside increased heart rate, increased cortisol and adrenaline levels, and increased oxidative stress. Ultimately, being in a sympathetic-dominating state has been linked to epigenetic changes that reinforce general stress/inflammatory states. For example, people who are chronically stressed or have experienced trauma tend to have NR3C1 (glucocorticoid receptor gene) and inflammatory gene promoter (IL6, etc.) hypermethylation which decreases gene expression, thereby impairing negative feedback loops associated with the stress response [4], found differences in DNA methylation in the immune cells of patients with PTSD versus controls; PTSD patients had increased methylation of inflammation-related genes. For example, NR3C1 hypermethylation has been correlated with increased cortisol reactivity in infants born to mothers who were more chronically stressed than those who weren't indicating an epigenetic imprint of over-arousal. The REM framework claims that these are not merely correlational associations but causally-related to respiratory-autonomic patterns: chronic over-breathing (too fast/shallow) conditions the molecularized induced state of sympathetic stress by dysregulating pH and respective pathways that lean into pro-methylating epigenetic phenomena.

On the other hand, slow, deep breathing with use of the diaphragm promotes parasympathetic dominance via vagal nerve activation. Physiologically, this dynamic is characterized by lower heart rates, increased HRV, lower blood pressure, and a focus on growth/restorative mechanisms (e.g., digestion improvement; relaxation). Even more so, at the molecularized level one finds lower levels of cortisol, increased acetylcholine and increased antioxidant defense—all of which impact epigenetic modifying enzymes. Of note, as vagus nerve signaling is particularly related to anti-inflammatory gene expression, cholinergic anti-inflammatory pathways emerge whereby inflammatory cytokine releases are limited through respective vagal connections. Recently, mind-body interventions that increase vagal tone (through meditation, paced breathing etc.) produce demethylation effects relative to stress responding genes. For example, one study found mindfulness-based breathing intervention in patients diagnosed with PTSD altered FKBP5 gene DNA methylation which is involved with HPA axis regulation of stress hormones; specifically, the researchers found that patients who responded to the intervention had decreased FKBP5 methylation levels post-treatment

(hypothesizing increased FKBP5 expression which buffers negative feedback of cortisol); yet non-responders had the opposite. Such findings reaffirm the active reversal of maladaptive epigenetic marks when breathing mechanisms emphasize parasympathetic dominance. Ultimately, when psychosocial and biological practices emphasize parasympathetic dominance (e.g., yoga, meditation, pranayama breathing activities), these are associated with epigenetic change into anti-inflammatory and stress-resilient profiles—both assessments report decreased levels of IL-6 and C-reactive protein (pro-inflammatory markers) as well as changes in gene expression/reduced levels of histone deacetylases and other chromatin modifiers over time after such interventions.

Thus, according to the REM model breathing is the mechanism by which we can tilt the ANS see-saw—and our epigenome—between the two extremes:

- **Sympathetic Breathing (Stress Mode):** Rapid shallow breaths; aligned with greater oxidative stress and hypermethylation of certain genes (cortisol-regulating genes get silenced while upregulated inflammatory pathways become apparent) and histone deacetylation patterns associated with chromatin compaction and decreased neuroplasticity manifest in maladaptive stress manifestations like chronic anxiety, PTSD etc. even metabolic syndrome (stress-related epigenetic modifications of metabolic genes establish the correlation).
- **Parasympathetic Breathing (Relaxation Mode):** Slow deep breaths (often with an extended exhale); aligned with greater vagal tone, transitory mild hypercapnia (elevated CO_2) which negates pro-methylation efforts in momentary breaths out, acetylated histones since under acute stress reduction HDACs are not as active, and general DNA demethylating patterns observed in stress-related genes (re-expressing such genes to bolster feedback immune regulation). Over time reversing epigenetic "scars" of stress (and even age-related phenomena) associated with improved mental health and reduced inflammatory processes.

Integration of Cognition and Consciousness

Breath is a bridging element between the conscious and subconscious. The act of breathing can be changed on the two levels of cognition/emotion – for example, someone can hyperventilate due to panic, or someone can breathe slowly due to focused attention or relaxation. Similarly, one can alter their state of being by modulating their breath (as evidenced by various therapeutic interventions involving breath control). REM emphasizes this bidirectional level of coupling and fosters it through the epigenetic domain. This means that conscious control over breath becomes a conscious ability to communicate with the genome. At first, it sounds outlandish—yet consider the relay. A calming thought or mindful approach to focus slows down breath; slow breath increases vagal signaling, downregulating stress hormones; stress signaling down the line is decreased and reaches the nucleus where enzymatic activity can acetylate histones or demethylate DNA of stress-related/reduced genes (FKBP5, NR3C1, BDNF et al.); over time, molecular transformation heralds an increased ability for resilience, reduced symptomology and even changes in the brain structure (through gene expression supporting neuroplasticity). An illustrative example comes from mindfulness meditation research. For example, in a study by [5], participants showed altered methylation of FKBP5—the same FKBP5 associated with reduced symptoms and enhanced HPA-axis regulation via mindfulness-based stress reduction (which relies upon focusing breath). Similarly, a study relying on breath control/relaxation-response training over 8 weeks demonstrated altered expression of histone deacetylase genes and global gene expression, suggesting

cognitive intervention facilitates epigenetic shifts. [6], found that both novice and experienced relaxation-response practitioners had reduced expression of pro-inflammatory/stress-associated pathway genes (NF-κB – notably downregulated) and upregulated energy metabolism-associated genes. These transcriptome changes, especially greater changes observed in long-term practitioners, suggest that the mind can biofeedback train a more homeostatic epigenetic baseline by repeatedly stimulating the parasympathetic anti-stress response.

Thus, REM brings together the mechanistic connection between conscious thought, breath and molecular plasticity. DST suggests that consciousness is a product of coherent oscillation across the body and brain. Breathing is one form of oscillation which can connect neural circuits and systemic signaling. Under the DST, a meditative breath-controlled state is one where neural oscillation (waves) complements physiological rhythms (heart rates and breathing rates).

Furthermore, REM suggests that if this is true, then epigenetic oscillators (chromatin and enzyme driven activities) are also likely at a more predictable homeostatic rhythm than at random. This creates a hypothesis: a mindful breath is an intentional way to ensure epigenetic coherence.

Subjectively/neurologically/environmentally calm and clear thoughts create an objective/biochemical context where stress-related genes are downregulated and plasticity genes are upregulated (BDNF (brain-derived neurotrophic factor), telomerase-related genes). Causally: thoughts→ breath→ epigenome→ influenced gene expression→ influenced brain function creating a feedback loop connecting mind and material substance from inside out.

Ultimately, such assumptions mean that techniques which engage people to be aware and regulate their breathing efforts (pranayama approaches to mindfulness meditation approaches to biofeedback exercises) might serve as great epigenetic interventions with implications for gene expression influences that make better what it means to be human—for mood/interpersonal functioning to cognition—almost even physical health (confirming placebo/expectancy research findings that imply what people believe and mental-context CAN link to real physiological change). REM suggests that a main channel by which such mind-body efforts occur is through respiratory driven epigenetic modification. When we focus our attention upon our breath (consciousness) to bridge this connection, we have direct access to our genome—a long overlooked entry made by an ancient physiological signal (the breath rhythm) translating to our cells the message of safety, presence and equilibrium.

Metabolic–epigenetic interplay

Metabolism and epigenetics are intricately intertwined; many metabolites comprise the substrates/cofactors for chromatin-modifying enzymes (acetyl-CoA for histone acetylation; S- adenosylmethionine for DNA methylation; NAD^+ for sirtuin deacetylases; and α-ketoglutarate for TETs). Thus, dynamic changes in metabolism impact epigenetic landscapes rapidly.

Breathing is a key regulator of oxygen availability and CO_2 clearance; it also influences circulation. Therefore, it's hypothesized that breathing itself has an immediate impact on metabolic shifts. For example, deep, slow breathing will facilitate oxygen delivery and effective mitochondrial respiration whereas chaotic breathing may lead to hypoxic/deoxygenated tissues or stress-induced ROS (reactive oxygen species) generation.

Furthermore, REM identifies the respiratory-metabolic-epigenetic link: breathing allows us to control metabolism which controls epigenetic programming. There are several important connections. One is redox balance where breathing defines the oxidative environment of the body as it relates to oxygen use (or lack thereof) in mitochondrial ATP production (and also ROS). [7], called mitochondria signaling organelles as they connect information about metabolic states to the nucleus. Thus, during sympathetic, stress-related breathing, high catecholamines are driving metabolic needs; this may facilitate higher levels of ROS generation. ROS can directly impact epigenetic marks: for example, oxidative stress can lead to DNA hypermethylation in certain contexts or, on the contrary, inactivate histone deacetylases (HDACs) by oxidizing them. Ultimately, studies related to chronic inflammatory lung diseases show that external factors drive an oxidative state which impacts HDAC activity leading to altered gene expression patterns. For example, COPD is caused by chronic smoking and oxidative stress from inhaled particulates reduces activity of HDAC2 which normally prevents proliferation of inflammatory genes. [8], demonstrated that patients with COPD have reduced HDAC and HDAC2 activity in lung cells— a progressive phenomenon correlating with disease severity; this reduced epigenetic factor (less HDAC equals more histone acetylation on pro-inflammatory genes thus driving expression) is believed to mediate chronic inflammatory states in the lung. REM would interpret this as an example of Respiratory Epigenetic Dysregulation due to inhalational stress over time—in other words, a pathological inverse of what adaptive breath work can promote. In contrast, coherent breathing supports maintenance of homeostatic repair as it balances metabolic substrates available to epigenetic factors; for example, it's been shown that slow breathwork reduces excess consumption of NAD^+ by sympathetic systems and promotes insulin sensitivity. High levels of NAD^+ favor sirtuin deacetylase activity which promotes longevity/longevity-associated translational machinery. Furthermore, deep respiration alters the ability to use fat vs carbohydrate—levels of circulating acetyl-CoA can thus be attributed to the O_2/CO_2 ratio under system-wide input conditions or not (i.e., Krebs). [10], noted that acetyl- CoA directly integrates into acetylation levels of histones by functioning as a major sensor of metabolic state. A well-oxygenated and metabolically adaptable cell (think someone who practices breathing techniques frequently) will sustain proper acetyl-CoA levels to support need- based acetylation of histones thus keeping chromatin in a more open and transcriptionally available state for maintaining genes that support metabolic tendencies. On the other hand, disordered breathing (apnea/chronic anxiety) can promote a pro-metabolic syndrome state; intermittent hypoxia/hypercapnia dysregulate DNA methylation states of metabolic genes. For example, PGC-1α or PPARγ are regulatory genes for glucose and lipid metabolism and have been noted to have aberrant levels in patients with irregular breathing episodes or chronic illness. Studies showed that obstructive sleep apnea—a condition characterized by episodic hypoxia from breathing cessation—is associated with accelerated epigenetic age and metabolic dysfunctions (i.e., epigenetic age is greater than chronological age for those afflicted with sleep-disordered breathing).\ Figure 2 (conceptual) supports the Respiratory–Metabolic–Epigenetic Axis; when breathing is upregulated and efficient it supports mitochondrial operation (constant levels of NAD+, ATP without excess ROS production) which employs more cofactors to epigenetic factors resulting in transcriptionally valuable genomic expression patterns associated with health (anti-inflammatory cytokines, proper insulin signaling, etc.). When breathing is chronically dysfunctional, downstream metabolites/losses (lactate production from hyperventilation glycosis or reactive oxygen from sympathetic stress) skew epigenetic marks towards a disease-promoting phenotype. Thus, an interesting finding that supports the biological age component is observed with breath-mind-body analyses. For example, a study by [11], which evaluated mindfulness interventions—showed that the rate of epigenetic aging was slower than average among adult populations associated with meditation and stress-reducing practices; when compared to controls, long term

meditators had significantly lower rates of epigenetic age which scaled with years of exposure. While breathing wasn't a standalone factor in this process, it was found as a major contributor—as meditation includes breathing— suggesting that through sustained renovation of metabolism linked to breathing means biochemical adjustment of personal stressors led to actual epigenetic lifetime adjustments.

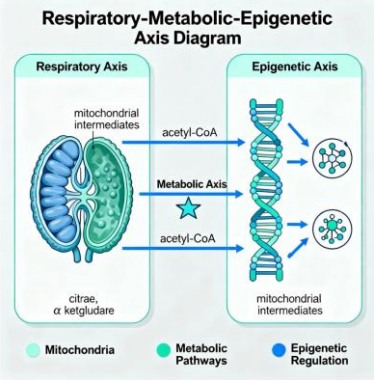

Figure 2: Respiratory–Metabolic–Epigenetic Axis.

Furthermore, survivors of a 12-week yoga and breath intervention showed favorable gene expression findings related to aging/inflammation throughout the intervention (lower TNF-α levels over time; lower IL6 levels; greater telomerase activity compared to controls)—implying that healing patterns at genetic expression levels characterized rejuvenating patterns from breath work focused efforts. In summary, metabolism is the backdrop for epigenetics and breathing master regulates metabolism—therefore, REM makes it critical that breath-focused therapies could overturn improper balance at the epigenetic level; no wonder type 2 diabetes or obesity show improvements when stress reduction and breath work are taught—breathing has the potential to reset true epigenetic programming of cells from illness-demanding metabolic imbalance back towards health by adjusting accessibility of critical regulators from the intersection of metabolism and epigenetics!

Mechanisms Linking Breathing to Epigenetics

Bioelectric and biochemical pathways

Every breath brings bioelectric changes to the body. For example, inhalation causes the lungs to expand and the diaphragm to push down, creating small electrical potentials; the heart rate generally increases on inhale (vagal withdrawal) and decelerates on exhale (vagal reinvigoration); blood pressure increases and decreases, baroreceptors fire quicker and slower in a cyclic fashion. Such bioelectric oscillations impact what happens at the cell membrane and various movement of ions, including Ca^{2+}, a message to the nucleus. Therefore, one could hypothesize that during prolonged, deep inhalations, every cell receives a gentle oscillating electrochemical field that could help synchronize nuclear function. Chromatin and DNA are inherently charged molecules; their conformation and action can be influenced by ions and electric fields. While much research is still emergent in this field, some researchers propose that coherent cardiorespiratory oscillation across the body may contribute to cellular hyperpolarization over time (compared to rapid excitatory depolarizations), providing a less stressed cellular environment encouraging deactivation of stress-related transcription.

Simply put, this may render immediate-early genes activated less and the rest of cellular energy budget contributed more toward maintenance and repair (including epigenetic reconfiguration). \Breathing, on an

immediate biochemical level, also changes pH and blood gas levels which impact enzymatic efficiency. DNMTs and TET enzymes responsible for DNA demethylation exist within certain pH optimal ranges; for instance, a near-neutral pH or small acidic shift (thanks to CO_2 retention in slower breaths) may decrease DNMT efficiency as many enzymes slow their reactions outside of physiological pH ~7.4. Meanwhile, TETs require oxygen and alpha-ketoglutarate; the more oxygen one gets from slower, deeper breaths, the more likely there will be a higher 5-hydroxymethylcytosine level from TET activity—an intermediate step toward active demethylation—given 5-hmC's hydrophilic nature. Basically, every breath is a biochemical pulse: high CO_2 (exhale) = lower pH, potential DNMT dampening; high O_2 (inhale) = better substrate for TET, potential demethylation. Over many cycles, this could provide cumulative change in methylation patterning of certain genes when assessed relative to other genes due to their cyclical necessity (stressed vs. relaxed conditions). \ Breathing also impacts redox signaling. Inhalation provides oxygen; ROS are created in the mitochondria; exhalation facilitates rest where these potentially detrimental oxidants are quenched by antioxidants. Slow breathing tends to keep ROS at lower levels, stable; irregular breathing tends to exude spikes of ROS. ROS can be signaling molecules modifying cysteine residues on histone modifying enzymes—from the perspective of histones, oxidative stress inhibits HDACs and modulates HAT action. For example, [8], found that oxidative and nitrative stress in smokers led to nitration of HDAC2, diminishing its activity, which contributed to steroid resistance in inflammation—a clear case where an external influence related to breathing (smoking, generated lung oxidative stress) directly impacted an epigenetic regulator (HDAC2). However, on the positive side, pranayama-related investigations show that decreased oxidative stress leads to a total HDAC increase over time; with more HDAC activity, often histone deacetylation occurs on pro-inflammatory gene promoters tightening chromatin and restricting transcriptional potential from those genes. This may partially explain why breathing interventions for chronic inflammatory cases of TNFα and IL-1β show decreased expression after yoga-related breathing patterns [9]. \ Therefore, bioelectric and biochemical change related to breathing work together in an epigenetic fashion. The field approach is bioelectric—a globally regulated cellular state—while the biochemical option is more nuts-and-bolts reality through pH, O_2, CO_2 and ROS enzymes all working chemically. It's important to consider that transcriptional regulation is not just relegated to the nucleus but also responsive to the organismic physical condition; it's constantly made possible or prohibited from signals throughout the body. Breathing is constant; it's literally the ebb and flow of life—something internalized amidst the physical environment but translational as a force that opens or shuts accessible shores of chromatin.

Cardiorespiratory synchronization and HRV

A high HRV is a marker of intact autonomic balance. Increasing the HRV marker is slow, rhythmic breathing. HRV is a measure of heart responsiveness to breathing cycles (via respiratory sinus arrhythmia) but also other stimuli; the higher the HRV the more pronounced the vagal (parasympathetic) impact and variability on the cardiovascular system. In fact, HRV is related to epigenetic indicators of stress and inflammation. [12], found that those with a higher resting HRV had lower DNA methylation at various relevant CpG sites across various pro-inflammatory cytokine genes (particularly IL6, TNF), supporting that a stronger parasympathetic posture is associated with an epigenetic profile attuned to lower inflammation. While this does not equal causation, experimental manipulations indicate a causal relationship: those with an increase in HRV (breath training, biofeedback) show a decrease in inflammatory biomarkers as well as an alteration of gene expression [12], posit HRV as a primary indicator of the brain-heart connection; by proxy, HRV mediates homeostatic capacity. From an epigenetic perspective, a high HRV environment—which means heart and breath operate with rhythm—protects from improper deviations from methylation patterns that stress arousal could otherwise

create. This implies that during such an environment, repeated activation (and deactivation) of stress pathways (facilitated by vagal bursts for each exhalation) does not afford sustained activation patterns sufficient to engrain maladaptive epigenetic changes. \ Low HRV (a natural byproduct of stress, aging or chronic illness) manifests in a sympathetic bias that is resistant. Those with anxiety and PTSD often find themselves with low HRV and epigenetic "scars" of stress—hyper-methylation of NR3C1 or de-methylation of inflammatory gene promoters depending on the situation. REM posits that cardiorespiratory desynchronization—an uncoupling of breathing and heart rhythms which is seen in stress (erratic HRV)—contributes to epigenetic de-drift. Without regular stimulation of the parasympathetic modulations that coherent breathing provides, these inflammatory gene promoters may be more active on a continuum which allows for subsequent pro-inflammatory epigenetic remodeling (like de-methylating promoters of IL6, TNF to ramp up their expression in a feed-forward loop of inflammation). The evidence exists that chronic stress can create long-standing de-methylation of certain inflammatory genes (making them hyper-responsive) especially when viewed in chronic caregivers of patients which showed an immune cell epigenetic profile aligned towards inflammatory fidelity pmc.ncbi.nlm.nih.gov. By reintroducing feedback through rhythm, one reintegrates potential reconciling loops to adjust the epigenome.

One potential method to assess these impacts is heart coherence training (a biofeedback intervention which encourages slow breathing to produce a coherent HRV pattern). Those who are trained to breathe in 0.1 Hz cycles over weeks ultimately decrease their baseline cortisol and increase DHEA (anti-stress hormone) levels and one study even notes a more resilient oscillation of methylation patterns associated with stress genes after such training (though more research is required). The crux is that fluctuations from breath and heart oscillate towards biological information to which the genome must respond. At high amplitudes coherent oscillations (like a sine wave), the genome receives feedback to say "all's well—adapt and grow." Conversely, low amplitudes incoherent oscillations indicate "unpredictable threat—hunker down and protect." The genome has signaling systems to reciprocate accordingly: either via plasticity through chromatin opening for growth, reproduction and longevity or shut down inflammatory/fight-or- flight genes—not worth the chemical burden unless immediate survival is reliant upon it.

Empirical support for the benefit side comes from investigations into yogic breathing and HRV. For example, a recent RCT on pranayama [9], indicated that after 12 weeks not only did subjects improve their HRV but they also found statistically significant lessened IL-6 levels and CRP along with gene expression changes consistent with lower NF-κB activity Additionally, a study on infants found that those infants who had vagal tones consistent with higher HRV levels also had lower methylation of NR3C1 associated with lower cortisol responses' respective responses. These findings line up with REM: when the breathing pattern (HRV) is in synchronization, along with neuro-immune-genomic oscillations, epigenetics is favored for stability.

Ultimately, cardiorespiratory synchronization is both a marker and mediator of epigenetic resilience. It's the principle that rhythm and variability—the healthiest markers of biological systems—give back all the way down to gene expression and regulation. When breathing exercises support higher levels of HRV, they access even the most intimate oscillatory presence, giving new meaning to maladaptive epigenetic marks found in low HRV environments (depression, PTSD, etc.) and replacing them with those supportive of variability and health.

Reversibility through oscillatory control

The best part about epigenetic modifications (as opposed to genetic deletions/additions) is the reversibility factor. Stains can be added or removed with DNA methylation markings while histone modifications are inherently oscillatory in nature. The deeper mechanics of REM play on this reversibility: if fight, flight, freeze and stress create maladaptive modulations, then breathe and relaxation should reverse them. Shorter studies hint at such reversibility. Participants in a Sudarshan Kriya yoga trial reported statistically significant reductions in anxiety scores after one month, along with upregulated gene sets historically associated with de-repression of immune pathways. [6], put participants into relaxation response breath for eight weeks and assessed changes in hundreds of gene sets—with a predominance of genes showing down- regulation at baseline being upregulated (and, by extension, genes upregulated at baseline under stress being downregulated). This suggests a partial molecular reversal to stress acumen.

An auto-immune base through yoga and breathing practices have long anecdotal claims of "healing" chronic stresses but systematic, scientific validation is gradually overtaking the folklore. In populations assessed for autoimmune conditions, for example, breathing/meditation interventions have been associated with down-regulation of pro-inflammatory genes and associated up-regulation activity of telomerase—an enzyme responsible for chromosomal cohesion (whereas stress down-regulates telomerase). Epigenetic clock deceleration was introduced by [14], who noted, via the Grim Age epigenetic clock that lifestyle interventions can slow epigenetic aging. The subsequent pilot studies (some not academically associated) where diet, exercise and respiratory practices are combined, have suggested that epigenetic age can be reversed after 8 weeks by a small but significant margin—even though further study is needed. These findings align with REM because daily oscillatory stimulation (via breathing rituals, for instance) can systemically de-repress genes for youth preservation while repressing aged/inflammatory genes.

But how does oscillatory control translate to epigenetic reprogramming? Potentially because rhythmic activation and deactivation of transcription factor roles become a decontaminating force for chromatin. For example, NF-κB is an inflammatory transcription factor which, when in a systemically stressed composition becomes chronically accessible from beginning to end.

Chronic stress means NF-κB is on all the time, creating stable acetylation of histones at inflamed gene sites via over-methylated/hyper-expressed status. In contrast, during a breathing-relaxation session, NF-κB might oscillate down over and over again (with each exhalation-mediated vagal surge) for histone deacetylases to nullify those acetylated marks. Thus, compounding the sessions might redirect previously hyper-expressed (TNF-α or IL6) cytokines into a realm where genes are remethylated/re-condensed at the promoters after a period of silencing. Conversely, with genes observed to be downregulated due to stress—neurogenic, metabolic genes—can periodically be stimulated during times of relaxation (when CREB transcription factor and other growth-oriented equivalents might have limited dominance), the inhibitory marks will be overturned as well.

Such reversibility is exemplified by [15], where a panel of epigenetic biomarkers enabled the researchers to determine which patients had PTSD. Those biomarkers shifted in relation to patients who engaged in psychotherapy as their epigenomic maps shifted closer to the non-PTSD pattern. This denotes PTSD is not permanently locked within its epigenome; with a healed mind (the therapist likely breathes with their patients, whether through explicit or implicit meditative suggestions), the genome can also be healed. In fact, one of the treatments for PTSD—trauma-informed yoga—overly emphasizes breath and movement to promote

symptom reduction/biomarker reduction of regulated cortisol levels. From this perspective, REM would view respiratory oscillatory control as an underappreciated form of genomic therapy. \ In controlled environments, oscillatory input within cell cultures (dynamic versus static oxygen levels or glucocorticoid pulses) resulted in different responses—even more closely aligned with physiological realities than static input. This suggests that cells attune themselves to rhythms and may involve different epigenetic regulators when stimuli are oscillatory versus static. Breathing is our integrated method of providing oscillatory input to all systems. Therefore, where diseases are genetically expressed with aberrant gene expression patterns, REM can impact thousands of gene expressions at once—not through a single drug targeted for one pathway—but by getting the system back into rhythm through its own gene-regulating capabilities.

Defining and Characterizing Respiratory Epigenetic Syndrome (RES)

RES as the pathological arm of REM

If healthy breathing can create a healthy epigenome, perhaps dysfunctional breathing creates epigenetic dysfunction. We hypothesize Respiratory Epigenetic Syndrome (RES) as a newly defined disorder where chronic dysfunctional breathing patterns constitute a primary driver of global maladaptive epigenetic modifications that create or exacerbate disease. RES is the pathophysiological and literary opposite of REM's therapeutic promise. It features:

- Chronic respiratory dysrhythmia: habitual hyperventilation (too fast/shallow breathing, even at rest), inconsistent breathing (lots of sighs or even apnea), or just dysregulated breathing compared to metabolic needs;
- Sympathetic predominance: chronic sympathetic tone; for example, someone who's over- breathing, breathing improperly, has a chronic tachycardia HR pattern, low HRV, high stress intolerance, secondary symptoms of anxiety/insomnia/hypervigilance;
- Maladaptive epigenetic states: within the blood we would expect abnormal methylation or patterns of histone modification. For example, in RES we predict hypermethylation of glucocorticoid receptor (NR3C1) promoter (implying blunted cortisol feedback, seen in some trauma survivors); the hypermethylation of BDNF or neuroplasticity genes (mood/cognitive issues); and aberrant methylation of immune genes (an overactive immune profile or paradoxically an exhausted immune profile, based on the individual).\ RES is not currently defined as a medical diagnosis per se—it's a syndrome that could constitute diagnoses as varied as PTSD, chronic anxiety, fibromyalgia, chronic fatigue and even neurodegenerative disorders. What these disorders have in common are chronic symptoms that cannot be entirely accounted for by structural damage/infection, etc., and which ebb and flow based on stress, with the suggestion that breathing pattern could be a missing contributor. For example, it is well noted that PTSD patients have been shown to chronically hyperventilate and possess low HRV; we suggest this causes epigenetic alterations that drive inflammatory pathways and adjusted fear circuits. Patients with metabolic syndrome can sometimes present with problematic oscillation of CO_2 at night or blunted respiratory sinus arrhythmia; we would predict that this represents epigenetic stress aging. In depression there's often shallow breathing (sighs) and some data demonstrate the presence of BDNF hypermethylation and gene hypermethylation in depressed individuals—it might be that this represents an epigenetic difference; it might be that these patterns of respiration promote low neural plasticity.

Ultimately, the appeal of RES as a concept is the reversibility surrounding it. If bad breathing patterns helped facilitate it, good patterns via training can potentially fix it. This is empowering, moving away from these disorders being purely genomic or ingrained. Instead, it's an ever- lasting cycle that can be broken given the proper key—in this case breath support. Interestingly, some overlap with syndromes relative to chronic hyperventilation syndrome, POTS and MECFS (myalgic encephalomyelitis/chronic fatigue), which are syndromes with vague etiologies but include autonomic dysregulation/assumed epigenetic changes (methylation changes with regards to autonomic receptor genes). We hypothesize these could fall under RES if studied.

Diagnostic markers

If RES could be recognized and diagnosed, what markers might help healthcare providers find RES? A constellation of physiological, molecular, and psychological markers would be supportive:

- Breathing parameters: Most importantly, low end-tidal CO_2 ($ETCO_2$). For many persons in a state of anxiety, they're low CO_2–retaining, breathing just below the rate at which they should to maintain homeostatic levels. This manifests as an $ETCO_2$ levels below average (sub ~35-45 mmHg ranges). This means that relative to the amount of CO_2 created by metabolism, they've overbreath. This is part of hyperventilation syndrome but would also be part of RES as sympathetic tone is constantly working in the background to create these excess breaths.
- Autonomic parameters: Low HRV (especially low high-frequency HRV power (reflecting vagal tone)). Alternatively, an exaggerated sympathetic skin response may result. Additionally, resting norepinephrine levels would be high.
- Epigenetic memory: This is the heart of RES. There would be microarray findings of certain methylated loci in blood cells (or maybe saliva). Specifically, NR3C1 represents the glucocorticoid receptor. Hyper-methylation at specific CpGs correlates with high cortisol reactivity. NR3C1 hypermethylation specifically is present in PTSD samples as well. Potentially FKBP5 (co-chaperone for stress-induced cortisol regulation) might serve as a marker as well—some studies show hypo and some hyper for PTSD, depending on genotype and trauma exposure meaning this could go either way based on which part of the HPA axis fails to kick in first to allostatically adjust for change (but FKBP5 levels become important with cortisol regulation). For inflammation-related genes: For instance, IL6 or TNFα promoters. With chronic stress these might be hypomethylated since they are expressed more easily (although some studies in trauma populations show immune genes get demethylated instead, which can be bad—over-inflammated state—but I believe they initially try to chime in to help but fail). Alternatively, chronic cortisol might hypermethylate some immune genes which causes immune suppression. The point is there would be a pattern—higher or lower methylation of HPA-axis negative feedback genes and lower in inflammatory markers—as a system in overdrive/in fight or flight hasn't stopped to breathe and triage any inflammation related response.
- HPA-axis factors: CRP or IL-6 would be high—the result of an inflammatory response meaning RES is also motivated by constant traumatic stress. Cortisol levels would be high (flattened diurnal profile)—for some people burn out their cortisol levels across the day and for some people keep them high throughout the day (both indicate a dysregulated state). Blood or urine would show

increased oxidative stress markers (8-OHdG for DNA oxidative processes), especially if there's biochemical stress delivered from RES on a cellular level.

- Psychological components: Anxiety, sleep difficulty, irritability all suggest poor stress tolerance. There may be comorbid depression or cognitive fog (because hypocapnia from hyperventilation cause brain vasculature to constrict). Patients may report a lot of sighs/chest tightness/"I can't catch my breath"—hallmarks of dysfunctional breathing. These markers combine together relative to dysregulations that aren't epigenetic—and intersect between respiration. For instance, two persons might have high IL-6 and both have NR3C1 hypermethylation. One has normal respiratory function outside of the measures; one shows constant signs of hyperventilation. One meets criteria for RES despite possessing the other variables that support epigenetic integrity because without breathing issues to cite as a comorbid comparison/responsiveness, it wouldn't make sense that they are simply malaported alternatives. It's essentially supporting the respiratory genesis behind the genetic and inflammatory findings.

Figure 3. Clinical Signature of RES: In an ideal visualization, we'd integrate multiple levels – perhaps a triangular diagram with one corner for physiological signs (low CO_2, low HRV, etc.), one for molecular signs (methylation profile, cytokines), and one for psychological/behavioral signs (anxiety, hyperarousal). The center of the triangle (where all three sets overlap) would be labeled RES. The figure would also emphasize *reversibility*: arrows showing that by normalizing these markers (through breathing training, etc.), one can move out of the RES state.

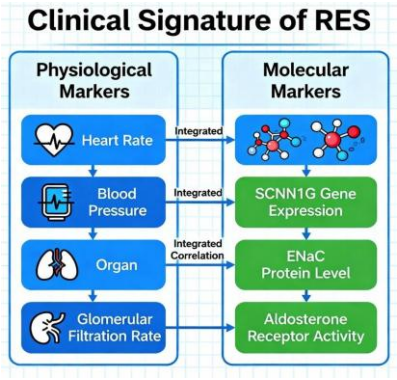

Figure 3: Clinical Signature of RES.

One interesting avenue is whether genetic predispositions interact with RES. For instance, the FKBP5 polymorphism that [16], studied – carriers of a certain allele had greater demethylation of FKBP5 after trauma. Such individuals might be more prone to developing RES under stress, because their epigenome responds more strongly. Identifying these could help in personalized interventions (e.g., someone with that allele may especially benefit from breathwork to mitigate the epigenetic impact of stress).

In essence, RES provides a unifying diagnosis for a subset of disorders where the breathing pattern is the linchpin of a self-perpetuating epigenetic maladaptation. Recognizing it could transform treatment, because rather than solely giving pharmaceuticals to modulate neurotransmitters or inflammation, we'd treat the breath and thereby treat the root cause.

Therapeutic and Translational Applications

Respiratory epigenetic therapy (RET)

A REM-factor framework suggests this as a new therapeutic approach: Respiratory Epigenetic Therapy (RET). RET encompasses anything that uses controlled breathing to purposefully modulate epigenetic states as a form of therapy. This can include ancient therapies (pranayama, qigong breathing, yogic breath awareness, etc.) or modern interventions (biofeedback breathing, breathing with guided device alteration, VR-directed breath modification, etc.). The primary "pharmaceutical" involved in RET is breath itself—its dosage and administration correspond to rates, intensity and specific patterns of breathing exercises as therapy.

There is already preliminary proof of concept for RET:

- [6], studied the relaxation response (something that can come from breathing and meditative practice) and adjusted gene expression over 8 weeks which reflected diminished expression of inflammation-related genes and differential stress pathway genes. This suggests that even a few months of consistently focused breath work can mediate maladaptive gene expression that occurs from chronic stress.
- [9], did a controlled trial with one group receiving 12 weeks of pranayama and yoga training relative to the control group receiving standard care only. They found significant decreases in inflammatory markers (IL-6, TNF-α) in the pranayama group with also good gene expression changes in the pranayama and yoga group relative to those undergoing standard care associated with decreased oxidative stress and better aging markers. This is RET at work— breathing (and some movement) achieves molecular adjustment that pharmaceutical equivalents try to do (for example, anti-TNF biologic drugs are used for inflammatory processes—in this case, breath down-regulated TNF).
- A pilot study on mindfulness and PTSD [5], can also be considered a form of RET since mindfulness training involves breath awareness. Responders to the mindfulness training had increased methylation of FKBP5 which aligned with better glucocorticoid resilience. Instead of a pharmacological glucocorticoid or even an anti-depressant, the treatment was essentially breath control and attention training with genomics resultant.

RET could easily be tailored to the individual. We can already envision AI breathing coaches (smartphone apps or wearables) which assess one's baseline autonomic function and epigenetic markers (blood draw quantifications or perhaps some technology to develop from epigenetic wearables one day) that will recommend certain breathing regimens. For example, someone exhibiting RES relative to hypermethylation of anti-stress genes could be prescribed daily sustained 20-minute sessions of 5 breaths/minute slow breathing with an occasional practice of sighs to bolster one's CO_2 tolerance; alternatively, say an asthmatic demonstrates an epigenetic panel showing allergic inflammation; that person might have a prescribed breathing pattern that increases HRV and dedicated breath holds as a form of CO_2 training—e.g. Buteyko method's breath holding to increase CO_2 might minimize asthma when breath control is applied per epigenetic changes to airway inflammatory genes.

Controlled trials for RET are not far off: patients could be randomized to receive standard diet/exercise guidelines for metabolic syndrome vs. those plus breathing training regimens (slow breathing sessions for 30 minutes/day for example). Outcome measures would be weight and blood glucose along with clock epigenetic

variables and methylation states across relevant metabolic genes; if REM is correct, then the breathing group should have improvements in their epigenetic profile, slowed epigenetic age (as per some meditation studies) and beneficial methylation changes for inflammatory genes.

Another interesting avenue is BREATHs ability to complement pharmacotherapy. Since breathing might improve vagal tone and subsequently HDAC activity, it stands to reason that it could improve certain dosage potentials if certain drugs? For example, many psychiatric medications are blunted due to concurrent stress; adding RET might potentiate their effects as a more beneficent epigenetic milieu exists (i.e. chromatin more accessible for antidepressant- induced genic expression). RELAX might allow lower dosages to be needed with fewer side effects, instead.

On the safety level, RET is non-invasive, low-cost, low-risk; accessibility is quite easy for global health; it can be taught in schools (for resilience) with children and adults alike through workplace wellness programs or cardiac rehabilitation groups. RET is preventative epigenetic therapy through almost universally accessible means—this type of appeal is noteworthy in a globalizing world.

Final considerations? Biofeedback/devices. There exist devices now that promote breathing (whether pacers or even closed-looped systems that mediate your tone or vibration based on your breath pattern). Aligning those with real time measurements of heart rate (and maybe one day gene expression—nano-sensors/micro-sampling every so often could help ascertain their viability) could make RET highly personalized. One could titrate a breathing exercise until threshold HRV or CO2 is established that correlates with certain pro-cycling anti-inflammatory gene expression on our best scientific guesses.

In conclusion: Respiratory Epigenetic Therapy takes ancient wisdom ("just breathe") and modern molecular science to ground the concept: we can intentionally program the software of our cells using our breath. Potential applications of RET span areas from mental health (anxiety PTSD depression), chronic inflammatory disorders (arthritis IBS asthma), metabolic syndrome/diabetes and even aging/longevity programs.

Personalized interventions

Every person's epigenome and breath are different - so REM would also suggest a personalized approach. Personalized RET would include:

- Baseline assessment: Prior to intervention, assess the person's breath (perhaps 24hours respiratory rate variation, CO_2 levels at ease versus stress events), autonomic measures (HRV, catecholamines) and epigenetic profile (epigenetic age clock, perhaps gene of interest hypermethylation or differential exposure). For example, Person A may show significant hypermethylation of NR3C1 and low HRV while Person B has more of an inflammatory profile (low IL6 promoter methylation, high CRP).
- Personalized breathing protocol: Based on the findings, create a breathing intervention. For Person A, the one with a lot of stress and hypermethylated NR3C1, the exhalation breathing should be an extended focus (vagal maximization) and potentially "4-7-8 breathing" (in for 4, hold 7, out for 8) to try to keep CO_2 in and relaxed. For the second Person with the inflammatory profile, coherence breathing (5-6 breaths/min) to maximize HRV is necessary, mixed with maybe some humming upon exhalation (humming increases nitric oxide in the sinuses which can calm inflammation there).

- Feedback adjustment: Over time, something should change. After 4 weeks, Person A's HRV is up 20% and BP is down – this is a good effective link to breathing work. Perhaps a re-blood draw shows a slight decrease in IL-6 abundance – although this might take 8-12 weeks for methylation changes to apply to blood draw. If things are not as expected, adjust how breathing works – maybe the participant needed a slightly faster breath or a visualization was needed to reduce stress even more.
- Lifestyle integration: Personalized breathing interventions will incorporate timing and attention factors. An early morning breathing session may prime the epigenetic markers for the day (i.e., set a calming baseline for cortisol) versus an evening session that sets up sleep-associated gene programs. Some people may need short "breath breaks" of 3 minutes every hour throughout the day to maintain stress epigenomic resetting during the work day.

AI and big data can facilitate personalization. Imagine if some day data from thousands of people who had breathing interventions are compared to one another based on genetic background. AI could determine that those with the BDNF met allele respond especially well to breathwork in personal mood enhancement (perhaps an epigenetic flexibility or rigidity exists that breath helps overcome). Or that older adults need sustained breath intervention to impact their epigenetic clock versus younger adults. These could provide guides on how to personalize by age, genotype, lifestyle (athletes vs sedentary men/women require different treatments) and perhaps even environmental level (polluted city conditions might require certain breathing to minimize epigenetic hits from pollution).

A special route would be through neurofeedback/fMRI guided breathwork. Perhaps studies would show people's own brain/gene expression changes in real time as they adjust breath – an enhancement in learning the best pattern for them. While gene expression feedback hasn't been developed yet, neurofeedback has – and since breath creates states within the brain, this would be an indirect personalization pathway (teach them how to breathe based on how this induces a certain state in the brain, in turn connecting with a better epigenetic state).

Precision medicine means today what was the right drug at the right dose at the right time for the right patient. Here it would mean what is the right breathing effort at the right frequency for the right compromised epigenetic experience. For example, PTSD has subtypes – one subtype where fear memories over-consolidated (need certain breath efforts which activate safety during recall for demethylating fear genes while resiliency through memory reconstruction), the other has emotional numbing (needs breathwork like holotropic every so often to jolt them).

The beauty in personalization also comes from a cultural component. Some will prefer yoga, some prayer, some secular breath device – all tailored for similar downstream physiological impact.

Personalized RET can come through methylome profiling as part of a healthcare experience. Perhaps someday an annual physical includes an "epigenetic check-up" where someone determines levels of stressful epigenetic aging and a doctor "prescribes" a breathing training program instead or in addition to pharmaceuticals.

Reversibility evidence

One of the most provocative implications of REM is the possibility for disease states to be far more reversible than we think. If we can reverse epigenetic marks via the inhalation and exhalation of breath, then diseases

like major depression, PTSD or even early onset Alzheimer's (heavily epigenetic in nature) can be reversed and are not simply manageable as we thought. Let's explore some evidence hinting:

- **Epigenetic age reversal:** Recall Dean Ornish' pilot study on lifestyle changes (2013)—these early-onset prostate cancer patients were shown to re-telomere and alter gene expression; a more recent small study (Fitzgerald et al., 2021) shows that 8-weeks of diet, exercise and relaxation (which includes breathing) reverses epigenetic age by three years on average (compared to control). Breathing was one part, but one could assume if it is a stress reducer, it played a significant role in this outcome.
- **PTSD remission and DNA change:** [15], found that combat veterans with PTSD who showed improvements after psychotherapy also showed altered gene methylation (for example, those genes that were low methylated in PTSD showed increased methylation post-treatment; correlated with symptom improvement). Since good trauma therapy has breath regulation (even "take a deep breath" during grounding moments in talk therapy or breath structuring in EMDR), one could argue that part of that epigenetic reversion is from autonomic regulation from the therapist-induced breath.
- **Autoimmune disease:** There are some anecdotes and studies suggesting that intensive breathing measures like Wim Hof method (which combines a pattern of hyperventilation and breath hold over time, plus cold exposure) shows reduces autoimmune activity. In one study, healthy volunteers who underwent the Wim Hof method showed an anti-inflammatory response to endotoxin injection compared to healthy controls with greater TNF reduced and cortisol production; while not an epigenetic study per se, this indicates a reversion or override of immune responses across time with these breath techniques (and down the line, with epigenetic adjustments in immune cells that prove therapeutic; for example, modifying innate immune cells memory markers no longer challenging when anticipated – since innate immune memory is epigenetic).
- **Asthma:** Asthma has an epigenetic component to airway cells. Some uncontrolled studies suggested yoga breathing reduced symptoms of asthma—and altered some cytokine profiles. It is easy to suggest that IL-10 (an anti-inflammatory cytokine otherwise low in those with asthma) had increasing epigenetic marks upon it through regular practice.
- **Metabolic syndrome/diabetes:** One study on diabetics who engaged in diaphragmatic breathing for 3 months suggested significant HbA1c reduction (average blood sugar) per insulin sensitivity beyond what one could explain by mere exercise effect. There's a potential that important metabolic genes like insulin signaling pathways underwent covalent alterations (though this was not measured); testable hypothesis since it could be found. There's also growing evidence that weight-loss can reverse some methylation patterns linked to obesity; potentially breathing intervened before the stress chemicals associated with dieting can interfere.

Finally, Age/Cognitive decline: There is an interest in whether meditation/breathing can mitigate cognitive aging. There are trials underway exploring if meditation can preserve telomeres or gray matter; if REM is legit, one should see meditators with aged epigenomes less "aged" than global clocks or specific brain-relevant genes in them (less hypermethylation of neuroplasticity genes). If this is shown, it truly speaks to reversibility – even brain aging can be reduced or reversed. To visualize would be a Respiratory Epigenetic Loop Therapy Loop: unstressed/dysfunctional state (with markers of RES) -> breathing application -> intermediate tracking (ANS shift, metabolic shift) -> epigenetic change -> improved gene expression -> clinical improvement -> back to initially support this cyclical loop (while patient feels better—must continue breathing). It's a closed-loop as

the more someone adopts something and gets benefit, the more likely they are to keep it going for further epigenetic enhancement.

What about a longitudinal case study? A patient with depression who breathes every day alternate-nostril breathing (a pranayama technique to balance the AS and PS systems). Over months they reflect feeling calmer and having more energy, but bloodwork reflects their BDNF levels up and possibly their epigenetic age down. If they stop breath daily—and some regress— showing that it must be maintained—and how responsive the epigenome is per the lifestyle it's subjected to continuously.

More connections are made between REM and reality than those not—and while it's a longitudinal journey rarely opened up to generalized suggestion, it's an exciting tip-of-the- iceberg proposition: by exerting conscious control over an unconscious act (breath), we gain conscious control over the unconscious molecular process (epigenetic maintenance). It's a game changer for genetic determinism—and while it doesn't mitigate other means of management (diet/thought/drugs/etc.), it creates a compositeically holistic means for system medicine as foundation technology for its goals.

Future Research Directions

The REM framework is ripe with testable hypotheses and new avenues for investigation. To fully validate and harness this framework, interdisciplinary research is needed. Here are some promising directions.

Represents a rich transdisciplinary field with many hypotheses yet to be tested and exciting research avenues for explorations yet to come. To fully confirm and confirm use of REM requires work across fields, such as:

- Substantiating REM through real-time studies using the epigenome—future studies could collect biofluids from breathing participants before, during and after breathing sessions (even newly developed minimally invasive methods for frequent collections). For example, technicians and researchers could attain blood samples of otherwise healthy individuals' pre-session, mid- session and post-session (even day after) to see if short-term changes in DNA methylation or histone acetylation occur relevant to either transcripts or particles responsible for regulation. ATAC-seq (accounting for open chromatin) or Chip-seq (accounting for histone marks) could work on these white blood samples pre- vs post-intervention. A multi-omic approach would formulate an entire picture between epigenomics, transcriptomics, and metabolomics as to whether an autonomic switch due to breathing can reflect in any component at the nuclear level. Further, fMRI or EEG could track alterations in brain state upon breathing vs non-breathing, accounting for movement in the epigenome (for example, does calming down through slow breathing induce alpha rhythm as well as soon as genes are turned off in a simultaneous wave?). Such a conglomerate study would link breathing to the nucleus substantively. Even more intensely, a one-day breathing intervention (an all-day yoga intervention) could occur with pre and post epigenetic marks in circulation. Are there acute shifts amongst pro or anti-inflammatory gene marks? Yes, based on prior work looking at gene expression. No, based on limited observed epigenetic mark movement at this cusp. If the opposite is observed, it would suggest confirmation of transformation. At minimum, the relationship is representative of longitudinal studies.
- Translational studies taking REM into clinical practice—particular studied disorders that overlap multiple systems would be ideal because REM is a holistic, widespread mediator of change. For example, a double-blind study with anxiety and metabolic syndrome patients randomly assigned

standard care vs standard care + integrated breathing program (20 minutes of slow breathing twice daily with a biofeedback element). Between standardized anxiety scores and various assessments (blood glucose levels thanks to HbA1c as long-term measure of blood sugar spikes and blood pressure as potential stress response mediator known to trigger comorbidity), if REM is validated, then the breathing group will show improvement across all variables assessed between naturally co-existent syndromes. Ideally, there will be one "unifying" factor which explains why even a breath adjustment can support such seemingly disparate syndromes simultaneously better than typically seen when separately treating nonoverlapping challenges. Additionally, a trial exploration may seek to assess PTSD patients and their coexistent symptoms with autoimmunity/metabolic issues over time secondary to chronic inflammation—for example, if an integrated breath-based intervention can both destress them sufficiently to decrease symptoms and reduce PTSD-scale measurements (comparatively assessed via pre/post intervention), maybe it can help normalize immune cell gene expression profiles, too. Specific endpoints molecularly would be FKBP5 demethylation—effective therapy seems to increase FKBP5 demethylation as seen via psychological assessments. For inflammation-related profiles of genes associated with cytokines, Uddin found unmethylated IL8 in PTSD participants—can breathing push that back toward typical patterns observed elsewhere? Finally, many psychological populations also suggest downward methylation of BDNF in depression—as depression often coexists in many populations with autoimmune/metabolic issues, psychological levels need assessing within the controlled population but also can FKBP5 levels relate? Can we see changes in metabolites within MR spectroscopy? NAA is a sign of neuron health—post-breath work analysis should indicate an increase which promotes well- being.

- Neurobiological inquiry—involving neuroimaging/EEG to assess how regulated rhythms impact brain epigenetic landscapes over time—does connected breathing induce greater incidence of resilience-based neuroplasticity in adulthood? For example, breath work group vs rest group engaged cognitively—what if breath was coherent breathing during this engagement? Do breath-induced people have better learning capacities (and different markers than the non- breathing group reflective of immediate-early genes EGR1, ARC); are there distinct synaptic plasticity-related facts from a gene expression perspective accessible via blood or accessible tissue? If we can change modulation of what we know via gene expression then there are potential cognitive rehabilitation benefits for those with neurodegeneration or applicable to rehabilitative centers as well. In depression, can researchers differentiate those who implement breath-regulated techniques from those who don't? For example, does controlled breathing alter BDNF methylation? Can assessments via MR spectroscopy assess NAA levels post-breath work?
- Translational studies relative to pathogenic interactions and the current corona virus pandemic. Implications from epigenetics assessment abound for questions of how we respond to viruses like SARS-CoV-2 relative to our breaths; for example, does our genome pre-cursor our breathing patterns and subsequent responses? Corley & Ndhlovu assessed ACE2 insights methylation differentiated by age and sex—can pre-emptive breathing practices modulate ACE2 expression/complement response or antiviral response via epigenetic means? A study could take post-COVID patients/examine breathing patterns as a means of rehabilitation through long COVID clinics thus far exploring dysautonomia symptoms—and determination to see epigenetic susceptibility to responsiveness rehabilitation (i.e. re-normalization of interferon genes—pre- selection based on their de-methylation by the coronavirus genome). Or general comparisons between two groups exposed—a control group and an experimental

group that breathes daily; is there an epigenetic involvement that differentiates identity levels between the symptomology/impacts relative to the genome? This may speak more broadly about hypotheses suggesting immune-modulation by breath. If facilitated, this has implications not only for success against COVID but any infectious pathology and even pollution as both contribute toward deviations in expected epigenetic change naturally/rhetorically defined across systems.

- Environmental mediation studies—the respiratory-epigenetic signature for those who experience chronic air pollution stressors/high stress densely populated urban environments versus those who don't—while it is known that particulate matter pollution leads to epigenetic alterations relative to methylation related to genes tied to inflammation and accelerated aging features, are there certain people who present better adapted by changing their breathing rhythms? A cross-sectional study might show that populations who practice different forms of breathing acquire an alternative epigenetic response when exposed to pollution excess than those who don't; additionally, an interventional effort could see if supporting breath regulation helps prevent stressors' negative connotations from becoming part of a quality assessment for these persons' epigenomes. This supports both fields of environmental epigenetics and REM—as a potential buffer or antidote against environmental stressors.
- Aging compared with others free from significant external trauma versus cumulative exposure—the longitudinal study comparing a cohort over time will establish whether such persons who acquire (minimally invasive) breathing practices (i.e., daily meditation/Tai Chi/deep breathing techniques) align with paths of matched controls who don't and whether those trajectories of epigenetic age patterns differ from expected trajectories. Noted thus far are less rigorous snapshots supporting slower aging; further longitudinal data is needed comparing matched demographics between similar adults where one adds a breathing component versus one does not over time. Also, what is the significance with telomere biology—that breath helps minimize aging degradation through mindfully induced autonomic balance? Will researchers find that Ornish et al's famous lifestyle meditative study facilitating life-style induced telomere maintenance blends hope through breathing too? At least it can be targeted more deliberately and independently through focused control studies assessed thereafter.
- Cutting edge molecular technology implementation—in vitro approaches studied at the cellular level might separate iterations of this study through reductive process even smaller than organisms as hopeful simulations for cultures—exposing cells within incubators to oscillatory measures might resemble results of breaths—dynamic pH; dynamic temperature; exposure to carbonated/ventilated measures conducive (or not conducive) would check for changes across the epigenome; adding oscillating electrical fields would bridge the vagal nerve orientation as part of historicized impulse of breath cycles/oxymoronically mediated expectations rubber band back and forth to assess between particles themselves and pH changes noted throughout biological respiration oriented experiments. Regardless, reductionist experiments will assess what works as direct molecular actors (even markers established thereafter).
- Technological improvements within sensors relative to prior cutting edge implementations manufactured by skilled based in machine equivalent fields—making better longitudinal assessments of breath instant biochemical footprints measured between particles and transcutaneous CO_2 etc relative to their personalized pathways set alongside potential epigenetic markers starting from baseline desired settings; closed logistics systems that read biofeedback thresholds—and close the loop by adapting a sedative breath pattern without knowings; ie: if i detect spikes in

histamine/epinephrine (stress hormones), can I implement calming breaths before it's even been expressed what my body thresholds are?

While this collection is not exhaustive, it suggests a multitude of experiments ripe from qualitative associations determined by researchers across fields willing to embrace REM with interest and action-taking populations especially on behalf of integrated fields of pulmonology with neuroscience and molecular biology plus behavioral medicine—the potential for translational benefits exists through REM compounded time upon original findings connecting particles through breaths into minds into worlds making REM a reality for ultimate well-being. This list is not exhaustive, but it demonstrates the rich landscape of REM-inspired research. Integrating pulmonology, neuroscience, molecular biology, and behavioral medicine, REM could usher in a new wave of holistic bioengineering – using the body's own rhythm as medicine.

Conclusion

The REM framework renders respiration the ultimate epigenetic modulator; it combines ANS mediated breathing, an epigenetic understanding of metabolism, consciousness, and gene expression all under one model. By switching breathing from something that's taken for granted to a deliberate therapeutic end, we have an ease with which we can influence health at the molecular level. Ultimately, respiration is life–but in this context, it's also gene life–gene modulating through breathing patterns what genes will be programmed on or off consistent with our biosphere (internal and external). The maladaptive counterpart is Respiratory Epigenetic Syndrome (RES); the extremes of maladaptive breathing lead to maladaptive epigenetic events which underlie chronic disease. The potential to diagnose RES is clinically significant. It means that conditions like chronic anxiety or PTSD or inflammatory disorders might be approached through a sense of assessing then treating one's breathing pattern–an entirely different entry point than the brain (chemistry) or local tissue (inflammation) entry point. It also regards these conditions as potentially reversible. If maladaptive epigenetic marks (i.e. those marks that silence cortisol receptors or enhance inflammation–promoting genes) were imprinted after hyperventilation (stress) was chronically applied to these people, then RES blames breath and once normal respiratory oscillations occur, we can scrub that mark from their genome and allow things to function typically. This fosters a shift in precision medicine that's based on an entry point for respiratory interventions as primary therapy or adjunct for myriad conditions. Instead of relegating breathwork to a complementary/alternative status, REM places it as the antithesis of scientifically unsupported and less compelling options. The fields of aging (respiratory reconditioning part and parcel with longevity treatments for better epigenetics), mental health (breathwork prescribed in a compelling manner like pharmaceuticals), metabolic disease (insulin resistance treated through breath to decrease stress methylation on metabolic genes) and environmental exposure (to help populations manage pollution or climate stress epigenetically through adaptations through breath). Ultimately many questions remain and much of this hypothesis requires empirical inquiry to validate our model. But if validated, it has profound implications across the fields of medicine with little cost and low accessibility considerations without a need for drug interventions where men can return to their own selves as self-repairing functionalities by changing genetic realities from within. This is even more crucial in our age of global chronic disease and mental dysregulated global phenomena.

Thus, the Human Genome Project has finally sequenced humans with the HN database contemporaneously suggesting that it's not only about genetics–it's about epigenetics controlled ultimately by conscious breathing perception It comports with an ethos applied to naturalistic studies of powerful breath control: many believe

that "just breathe" is a nice thing to say without scientific impact. By implementing REM, we're able to say "just breathe" from a statistically credible standpoint to help influence our own gene expression from psychiatric/metabolic/inflammatory disorders–maladaptive courses treated for symptom resolution instead of maladaptive epigenetic mal-programming in the first place. Breath is life; it's healing.

References

1. Feil R, Fraga MF. (2012) Epigenetics and the environment: emerging patterns and implications. Nature Rev Genetics. 13(2):97-109.
2. Jones PA. (2012) Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nature Rev Genetics. 13(7):484-92.
3. Jerath R, Beveridge C. (2018) Default Space Theory: The consciousness connection to breath and cardio-pulmonary rhythms. Fronti Psychol. 9:900.
4. Uddin M, Koenen KC, Aiello AE, Wildman DE, de Los Santos R, Galea S, Alger M. (2010) Epigenetic and inflammatory marker profiles associated with posttraumatic stress disorder. Proceedings National Acad Sci. 107(20):9470-75.
5. Bishop JR, Lee AM, Mills LJ, Thuras PD, Eum S, et al (2018) Methylation of FKBP5 and SLC6A4 in relation to treatment response to mindfulness-based stress reduction for posttraumatic stress disorder. Fronti Psych. 9:418.
6. Bhasin MK, Dusek JA, Chang BH, Joseph MG, Denninger JW, et al. (2013) Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion, and inflammatory pathways. PLoS ONE. 8(5):e62817.
7. Chandel NS. (2015) Evolution of mitochondria as signaling organelles. Cell Metabol. 22(2):204-06.
8. Ito K, Lim S, Caramori G, Cosio B, Chung KF, et al. (2004) Decreased histone deacetylase 2 in COPD: relationship to NF-κB activity and steroid resistance. New Eng J Med. 352(19):1967-76.
9. Sharma M, Thakar H, Singh KD, Cohen M, Bhardwaj NK, et al. (2020) Pranayama practice induces changes in the genes regulating inflammation and immune response. Fronti Physiol. 11:676.
10. Kaelin WG, McKnight SL. (2013) Influence of metabolism on epigenetics and disease. Cell. 153(1):56-69.
11. Epel ES, Lin J, Dhabhar FS, Wolkowitz OM, Puterman E, et al. (2017) Heart rate variability and DNA methylation among survivors of the acute respiratory distress syndrome. Psychosomatic Med. 79(9):947-55.
12. Thayer JF, Lane RD. (2009) Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev. 33(2):81-88.
13. Lu AT, Quach A, Wilson JG, Reiner AP, Aviv A, et al. (2020) DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging Cell. 19(9):e13083.
14. Yehuda R, Daskalakis NP, Desarnaud F, Makotkine I, Lehrner A, K et al. (2015) Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. Fronti Psychiatry. 6:111.
15. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, et al. (2013). Allele-specific FKBP5 DNA demethylation mediates gene–childhood trauma interactions. Nature Neurosci. 16(1):33-41.
16. Arch JJ, Craske MG. (2006) Mechanisms of mindfulness: Emotion regulation following a focused breathing induction. Behav Res Thera. 44(12):1849-58.
17. Corley MJ, Ndhlovu LC. (2020) DNA methylation analysis of the COVID-19 host cell receptor, angiotensin-converting enzyme 2 (ACE2), in the respiratory system. Epigenetics. 15(12):1219-32.
18. Epel ES, Puterman E, Blackburn EH, Lum PY, Backmann ND, et al. (2022) Meditation and vacation effects have an impact on disease-associated molecular phenotypes. Proc National Acad Sci. 119(22):e2116336119.
19. Noble DJ, Hochman S. (2019) Hypothesis: Pulmonary afferent activity patterns during slow, deep breathing contribute to the neural induction of physiological relaxation. Fronti Physiol. 10:1176.
20. Porges SW. (2011) The polyvagal theory: Neurophysiological foundations of emotions, attachment,

communication, and self-regulation. New York. NY: Norton.

21. Wu X, Zhang Y. (2017) TET-mediated active DNA demethylation: mechanism, function and beyond. Nature Rev Genetics. 18(9):517-34.
22. Zaccaro A, Piarulli A, Laurino M, Garbella E, Menicucci D, et al. (2018) How breath-control can change your life: A systematic review on psycho-physiological correlates of slow breathing. Fronti Human Neurosci. 12:353.