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Demystifying The Mind-Body Connection: The Neuroscience Behind How Thoughts Impact Physical Health

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Abstract

The beliefs, emotions, and experiences that constitute a mindset shape numerous aspects of one's reality, but in particular, health. Health is defined by not only the physical state of one's body, but also the content of one's mind. The integration of the mind and body is often associated with naturopathic medicines or pseudoscience, and thus is usually left out of Western medicinal practices. This review aims to demystify the mind-body connection in health and wellness by introducing it within an empirical, neuroscientific landscape. This research supports the hypothesis that *mind over matter* rings true even at the biochemical level. Activation of the immune system and the autonomic nervous system as well as changes in gene expression and connections between neurons, among many other things, modulate the body's physical responses to mindsets. Concepts like stress, somatization, mind-body therapies, and the placebo effect are discussed in relation to their neuroscientific mechanisms and resulting effects on bodily health. This review finds that many of these concepts share overlapping biochemical mechanisms that turn positive thoughts into healthier bodies, and vice versa; this research elevates the status of mindsets as powerful determinants of health that should be more heavily prioritized in Western medicine.

Demystifying The Mind-Body Connection: The Neuroscience Behind How Thoughts Impact Physical Health

Human beings are multidimensional organisms; with conscious minds and physiological systems boasting complexity beyond those of other living creatures, it should not come as a surprise that human minds and bodies construct each individual's reality in an intrinsically intertwined manner. With mind and body combined, humans achieve the highs of finishing a marathon and falling in love, yet also suffer the blows of illness and failure. The mind-body debate found its roots in Ancient Greek thinking and is still hotly debated today in both science and philosophy. The history of this debate would not be complete without mention of René Descartes and his defense of dualism, which emphasizes the completely distinct nature of both mind and body, although recent research and writings have shifted toward an embodied view that cognition and physical agency fundamentally depend on one another (Dijkerman & Lenggenhager, 2018). Numerous papers posit that one's sense of self and the plasticity therein depend on both top-down cognitive processes as well as bottom-up sensory signaling (Porciello et al., 2018; Riva, 2018); however, this union of mind and body supported in modern philosophy of mind, neuropsychology, and cognitive psychology seems to be largely neglected in the realm of healthcare.

Modern Western medicinal practices tend to divorce the mind and body during the healing process, administering treatments for one or the other without considering their inherent connection. Discussions about the mind-body connection are often thought to solely exist within Eastern/traditional medicine or wishy-washy pseudoscience landscapes, but this paper endeavors to demystify this concept by introducing it within empirical, neuroscientific conversation. This review contends that healing doesn't merely occur as a result of treatments with physiological

targets. Rather, thoughts and emotions have the potential to alter the biochemistry of the brain and body, which in turn changes our physiology – *mind over matter* applies on even a microscopic scale. What's going on in one's mind can contribute to either improved or poorer overall health, depending on the content of one's mental states. By understanding the power the mind holds over the body, healthcare practitioners and their patients can harness an arsenal of potential treatment options thus far left largely unattended by Western medicine. While more research is needed to strengthen the claims presented in this paper, the studies reviewed here provide a starting point for a greater understanding of the mind-body connection.

Evidence of the Mind-Body Connection

Defining Mindsets & Placebos

Mindsets drive the mind-body connection. The head of the Stanford Mind-Body Lab, Dr. Crum, defines a mindset as one's core beliefs about something that point one toward a certain set of expectations, goals, and explanations (Huberman, 2022). Mindsets can also be defined as a "mental frame or lens that selectively organizes and encodes information, thereby orienting an individual toward a unique way of understanding an experience and guiding one toward corresponding actions and responses" (Crum et al., 2013, p. 717). The placebo effect is a product of one's mindset about something. It is a form of a belief effect, meaning that it influences one's experience based on their *expectations* of something rather than any genuine properties of that thing. Many people think of a placebo as some inert substance or procedure without pharmacological or medicinal behavior; however, as explained by Benedetti, a placebo is not merely the inert substance but also the social and sensory stimuli associated with its administration (Benedetti, 2022). In fact, the effect of just about any kind of treatment relies on not only the chemical attributes of the treatment but also the context and mindset surrounding the

treatment. In other words, the total effect of something includes both what you're doing and your mindset surrounding what you're doing (Huberman, 2022).

Empirical Examples of the Mind-Body Connection

Recent evidence turns the colloquial words of wisdom *mind over matter* into empirical findings. The thoughts, beliefs, and emotions constituting one's mindset and attitude alter one's life on a biochemical and neurological level, especially when considering physical health parameters related to drugs, exercise, hunger and satiation, and stress, as well as sleep, aging, healing, and life expectancy (Hamilton, 2018; Huberman, 2022).

Drugs

Drugs and medical procedures vary in effectiveness depending on numerous factors that influence one's mindset or expectations about them: one's awareness of the treatment being administered; the packaging, color, and price of the treatment; the form of the therapy, either pill or injection; how the clinician presents themselves; and more. Thus, the placebo effect results from not just the physical, inert placebo substance administered to a patient, but also from the societal and perceptual stimuli associated with that substance and its administration (Benedetti et al., 2022a; Hamilton, 2018). The stimuli related to the context of a treatment have produced such a significant effect over time that individuals like Daniel Moerman call the placebo effect a *meaning response*, or a response to our perception of a treatment (Hamilton, 2018). The outcome of a therapy can vary by 12-18% due to a patient's expectations surrounding the therapy (Benedetti et al., 2022a). For example, a 2008 meta-analysis of multiple antidepressant medications found that 81% of the effect of the drugs could be accounted for by the placebo effect. The effectiveness of placebos compared to drugs used to treat conditions like high cholesterol, chronic fatigue syndrome, and heart diseases, are often within a few percentage

points of each other in clinical trials (Hamilton, 2018), alluding not to the ineffectiveness of the drug but the potency of the placebo effect. Interestingly, significant placebo effects are even observed under open-label conditions in which the participants are made aware that their treatment is inert. Kam-Hansen et al. (2015) ran a prospective, within-subjects study of episodic migraine patients. Subjects were randomly given either placebo pills or Maxalt (10-mg rizatriptan), and they were also randomly told that that pill was placebo, Maxalt or placebo, or Maxalt. This study showed that the efficacy of the placebo pill increased when patients believed it was Maxalt. They also found that the efficacy of Maxalt mislabeled as a placebo had nearly identical efficacy as the placebo mislabeled as the real drug. Further, open label placebo treatment produced significantly more effective results than no treatment; placebo accounted for over 50% of the drug effect relative to no treatment. Similarly, Kaptchuk et al. (2010) conducted a randomized, controlled three-week trial in patients with irritable bowel syndrome (IBS). One group received open label placebo pills with the description of "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes," while the other group received no treatment (Kaptchuk et al., 2010, p. 1). Both groups had identical amounts of time and quality of interaction with their healthcare providers. Their findings revealed that open-label placebo produced significantly greater global improvement, relief, symptom reduction, and quality of life than the no-treatment control for IBS patients.

Exercise

Consider the 2007 study by Crum & Langer, which found that the relationship between health and exercise is mediated by mindset. They researched a population of female hotel room attendants, who often get lots of exercise throughout their work days but may not be aware of it.

The researchers educated half of these women on the amount of exercise they were getting each day as well as the positive benefits of that exercise, while the other half continued their jobs as normal. After four weeks, the women in the treatment group reported improved health (decreased blood pressure, weight, waist-to-hip ratio, and body fat) even though they didn't report any changes in movement or diet compared to the control group (Crum & Langer, 2007). An additional study from Dr. Crum's lab demonstrated that when individuals believed they weren't getting enough exercise, or as much exercise as other people, their death rate increased (Huberman, 2022). Further, a longitudinal study which studied soldiers of the Swedish Army during both their induction into the army (1952-56) and decades later (1987-2010) found that the link between physical fitness and reduced risk of heart disease was significantly moderated by one's resilience to stress. In other words, the mental, social, and lifestyle-based components of one's life that determine one's resilience to stress had the capacity to turn the same amount of exercise into lesser or greater physiological health benefit (Fricchione et al., 2016). These studies, in combination with other studies on the topic (Hamilton, 2018), support the hypothesis that exercise is mediated by mindsets.

Hunger and Satiation

Hunger and satiation is also hypothesized to have a mental component. In one study, all participants drank two milkshakes, each with a week between each other. Although each milkshake was identical, one was labeled as high calorie and indulgent, while the other was labeled as light, healthy, and low calorie. Participants consistently felt more full after drinking the "high calorie" milkshake than the "low calorie" one. Their fullness was measured by monitoring levels of ghrelin, the so-called hunger hormone that rises in response to hunger. The more energy and nutrients that one intakes, the more one's ghrelin levels drop, and one feels

more satiated as a result. The ghrelin levels of the participants decreased more steeply when believing they were drinking a high calorie milkshake compared to the low calorie milkshake even though the calorie content of both shakes was identical. Thus, the ghrelin pathway is susceptible to thoughts – there seems to be some crossover between conscious thought and subconscious, autonomic pathways (Crum et al., 2011; Huberman, 2022).

Stress

Belief effects extend to stress and stress's physiological effects on the body as well. Stress is a fascinating phenomenon with a largely demonized public image. Typing "stress" into Google Images will result in a plethora of stock photos and cartoons depicting hopeless individuals with their heads in their hands (Figure 1). The popular media, including health-focused sources, often spout oversimplified messages portraying stress as a largely negative state resulting in adverse effects on one's health, happiness, and social life. For instance, Dr. Fricchione has labeled stress and its effects on each person and their communities as the largest health issue facing the contemporary world due to its impacts on cardiovascular, pulmonary, joint, and neurological health (Fricchione et al., 2016).

Figure 1

Common Depiction of Stress

Note: A common depiction of stress in the mass media. Here, stress is portrayed negatively through words, colors, and the individual's physical position (Brooks, 2021).

However, as Dr. Crum points out while discussing her research on the Huberman Lab podcast, the true nature of stress is a manifold paradox of both good and bad; contrary to popular belief, acute stress can serve to optimize human performance by enhancing focus, speeding up information processing, and more (Huberman, 2022). Stress evolved due to its selective advantage throughout time. Such arousal is useful to avoid threats and take advantage of opportunities; increased physiological factors like heart rate, glucose synthesis, depth of breathing, and sweating, as well as faster reaction times and other cognitive benefits, may have been the difference between life or death throughout human evolution (Nesse & Young, 2000). Thus, there is no single, unified way to view stress. Some individuals may employ a stress-is-debilitating (SID) mindset by focusing on the former view, while others may employ a stress-is-enhancing (SIE) mindset by focusing on the latter.

Dr. Crum's research has begun to elucidate that a stressor itself is not a standalone cause of one's stress response; rather, one's mindset about stress is a distinct variable which can significantly impact one's cognitive and physiological stress response. One study experimentally

manipulated participants' stress mindsets by showing educational videos featuring evidence skewed to either a SID or SIE view. After experiencing a stress-inducing event, the SIE group experienced more positive changes in self-reported work performance and psychological measures, including greater increase in growth hormones, attention paid to positive stimuli, cognitive flexibility, and positive affect, than the SID group (Crum et al., 2013; Crum et al., 2017). Navy SEALS with SIE mindsets similarly experienced more positive outcomes during training than their peers with SID mindsets — quicker obstacle course times, greater persistence, and less negative feedback from instructors and peers (Smith et al., 2020). Additionally, a 2022 study by Zion, et al. demonstrated that Americans' mindsets during the COVID-19 pandemic (either that the pandemic was a *catastrophe, manageable*, or an *opportunity*) led to self-fulfilling effects on each individual's wellbeing and emotions over several months. The negative tone of the *catastrophe* mindset oriented individuals toward poorer health behaviors and negative affect, while the more positive mindsets lended itself to further growth and wellbeing (Zion et al., 2022).

Hence, the mind-body connection plays a large role in numerous aspects of physical health through mindsets and placebos. The neurological and biochemical mechanisms of these examples will be explored in the next section.

Neuroscientific Mechanisms Of The Mind-Body Connection

Negative Mind → Negative Body

Maintaining negative mindsets promotes negative physiological outcomes. Poorer thoughts, expectations, and emotions generate poorer whole-body health. Stress is the main perpetrator of the negative mind – negative body connection.

Stress

Stress is a whole body experience consisting of specific neurological and biochemical changes that generate effects at the macro level, both physiologically and psychologically. How does the body transition from thinking a stressful thought to experiencing stress responses throughout the body, and how can those responses be mediated by controlling one's mindset about stress?

ANS and HPA Axis. Stress exerts its effects on individuals through three main neurological systems: the autonomic nervous system (ANS), the hypothalamus-pituitary-adrenal (HPA) axis, and the immune system. The ANS reacts rapidly, while the HPA axis and immune system feature delayed yet longer lasting responses. The two divisions of the ANS cover opposite domains, not unlike adrenaline and cortisol: the sympathetic nervous system (SNS) sparks a fight-or-flight response by releasing adrenaline (also known as epinephrine in the central nervous system) from the adrenal glands, while the parasympathetic nervous system (PNS) relaxes the body back into a normal state through signaling of the vagus nerve. Adrenaline is a catecholamine neurotransmitter that sparks many of the typical characteristics of the fight-or-flight response: dilated pupils and tensioned muscles, allowing sharper sensory detection and movements, respectively; faster heart rate and constricted blood vessels (alongside the release of fibrinogen, an anti-clotting agent), allowing for greater flow of glucose and oxygen to the lungs, muscles, and brain; faster breathing rate, allowing for the lungs to absorb more of the oxygen transported by blood; and slowed digestion coupled with a release of glucose and fats from stores within the body (glycogen and fatty acid stores, respectively), allowing the body a boost of extra energy. As a result, the brain and body are primed for optimal functioning and enhanced reactions to potentially dangerous stimuli.

After stress initially activates the SNS, it then stimulates the HPA axis. The hypothalamus responds to stress by releasing corticotropin-releasing hormone (CRH), which then travels to the pituitary gland. This gland then releases adrenocorticotropic hormone (ACTH), which serves as a signal for the release of cortisol from the adrenal glands. Cortisol helps the body stabilize the stress response, operating in concert with the ANS to maintain a mental and physiological state of readiness so one can effectively conquer the source of their stress. Increased production of CRH in the hypothalamus, as well as reduced expression of the gene encoding the receptor for cortisol (the GR receptor), result from chronic stress.

The limbic, paralimbic, and cortical areas of the brain, including the amygdala, hippocampus, and medial prefrontal cortex, influence the stress response. There is a complex interplay between emotional, amygdala-driven responses to stress and hippocampal and cortical processes that can counter those responses in a top-down manner. Negative feelings such as fear activate the amygdala, which stimulates the hypothalamus. Different areas of the hippocampus regulate HPA axis activity in response to different types of stressors, varying by spatial and temporal contexts. Stimulation of the hippocampus also promotes the PNS, resulting in a decrease in blood pressure, heart rate, and respiratory rate. The prefrontal cortex, especially the medial prefrontal cortex, has the capacity to mediate these hippocampal effects through HPA axis inhibition. This is largely caused by glucocorticoid stress hormones. Glucocorticoids reduce the physiological stress response when they activate the glucocorticoid receptors that are present in both the hippocampus and the medial prefrontal cortex (Fricchione et al., 2016). Acute stress also increases the release of dopamine and norepinephrine in the prefrontal cortex, which impairs cognitive functioning in that area (Crum et al., 2018).

While these physiological alterations could be the difference between life and death in a high stress situation, maintaining a chronic stressful state (also known as *distress*) erodes the body. Chronic stressors rooted in early-life trauma, violence, poor socioeconomic status, and isolation have also demonstrated associations with increased immune system activation (Pariante, 2016). Through a process called allostasis, the brain constantly moderates physiological stability in response to various stimuli to balance energy expenditure. Maintaining a constant stress response throws off this balance, also known as *allostatic loading*. Excessive allostatic loading reduces the health of cells. Thus, the stress response within the HPA axis and ANS ties closely with the immune system.

Immune Function. First, adrenaline (epinephrine) and cortisol normally follow natural and healthy periods of rising and falling throughout one's daily circadian rhythm, and abnormal secretion of these hormones due to stress is often implicated in disorders like depression and PTSD (Fricchione et al., 2016). Stress also increases the amount of white blood cells in the body while simultaneously reducing the function of B and T cells (types of white blood cells). Thus, chronic stress diminishes antibody-mediated immunity, even though these effects boost innate immunity in the short term (Fricchione et al., 2016).

Numerous studies suggest that excessive psychological stress also negatively impacts the body through inflammation. The mechanism of this effect involves genome-wide changes in gene transcription; in other words, genes responsible for inducing inflammation become over-expressed while genes responsible for reducing inflammation become under-expressed. The release of adrenaline associated with stress, combined with substances like cytokines and free fatty acids, leads to activation of the transcription factor called the nuclear factor kappa light chain enhancer of activated B cells (NF-κB), which in turn upregulates genes involved in

inflammation (Fricchione et al., 2016; Koo et al., 2010; Muehsam et al., 2017). These genes include ones encoding pro-inflammatory cytokines like IL-1 and tumor necrosis factor (TNF-α), adhesion molecules, chemokines, acute phase proteins, inducible effector enzymes, and regulators of cell proliferation and apoptosis (Ghosh & Karin, 2002). The NF-κB pathway is additionally related to upstream regulators like TNF-α and RIPK1 (Niles et al., 2014). NF-κB serves as an important link between stress and disease due to its effects both within cells such as macrophages, endothelial, and fat (which promotes conditions such as obesity, diabetes, and heart disease) as well as neurons, especially those of the prefrontal cortex (Fricchione et al., 2016). Chronic stress has also been linked to reduced expression of genes encoding glucocorticoids, which are hormones that dampen the stress response (Fricchione et al., 2016; Muehsam et al., 2017). Beyond just NF-κB and glucocorticoid pathways, studies examining chronic stress in the forms of social isolation, interpersonal stress, and familial caregiving responsibility found that stress also impacts the JAK-STAT signaling pathway (which plays a role in the transcription and expression of immunity-, apoptosis-, differentiation-, proliferation-, and oncogenesis-related genes), transcription factors in the GATA and Oct families (which regulate inflammation), and CREB-binding protein interferon response factor (which activates transcription for genes like brain-derived neurotrophic factor, or BDNF). Additionally, chronic stress increases systemic C-reactive protein (or CRP, an inflammatory marker) and leukocyte inflammatory response while decreasing glucocorticoid sensitivity and the amount of mRNA related to anti-inflammatory markers (Muehsam et al., 2017). Neuroinflammation is also represented by elevated microglial activity. Microglia, the immune cells of the brain, are hypothesized to play a role in the stress response and its association with comorbid mental

illnesses since stressors in prenatal development, early life, and adulthood have demonstrated a correlation with increased microglial activity (Calcia et al., 2016).

Oxidative Stress. Stress diminishes overall health through oxidative stress as well as inflammation. Fricchione et al. (2016) defines cellular oxidative stress as the strain that results from an excess of reactive oxygen species, or free radicals. Stress contributes to undue cellular strain because of the heightened amount of metabolic energy required to maintain the physiological stress phenotype. In an individual suffering from stress, certain stress hormones and transmitters alert bodily tissues to alter their metabolisms (i.e., mitochondria within cells need to work harder to metabolize more oxygen), which can provide much-needed energy in the case of acute stress, but damages long-term health due to the production of unwanted by-products in the case of chronic stress. NF-κB is key in increasing oxidative stress during stress due to its role in producing pro-inflammatory cytokines (Fricchione et al., 2016).

Cellular Aging. All these factors that damage cellular health contribute to more rapid cellular aging. First, cells cannot manage excitatory neurotransmitters as well upon aging. In a phenomenon called excitotoxicity, excessive cortisol output from stress results in an increased number of receptors for and sensitivity to glutamate. Mitochondria within the cell must overexert themselves to perform their jobs amidst the unmanageable cellular excitement, which causes oxidative stress through the production of free radicals (which further age the cell in a positive feedback loop) (Fricchione et al., 2016). Second, increased levels of psychological stress correlate with a small reduction in telomere length (Mathur et al., 2016). As one ages, telomeres at the end of DNA strands shorten, which makes the DNA more susceptible to damage. Telomere shortening becomes significantly more severe given both long- and short-term stress (Esch et al., 2018).

Neural Plasticity and Neurogenesis. Neurologically, chronic stress has been shown to impair the brain's capacity for plasticity and neurogenesis. Chronic stress can alter cells of the hippocampus, prefrontal cortex, and hypothalamus, which makes these areas less able to carry out their stress-reducing actions (Fricchione et al., 2016). Stress can change the structure of the dendritic spines of pyramidal cells in the hippocampus as well as cells in the prefrontal cortex, which play key roles in learning and memory. Acute stress leads to CRH-mediated loss of dendritic spines, while chronic stress reduces not only spines but also dendrites themselves. This means that stress, especially chronic stress, diminishes the capacity for neural plasticity (Fricchione et al., 2016; Laine & Shansky, 2022; Li et al., 2019). More specifically, stress impairs long term potentiation and enhances long term depression (Kim et al., 1996). Beyond dendritic remodeling, stress also alters neural plasticity by suppressing the generation of new neurons that create new functional synaptic connections in the hippocampus, also known as adult hippocampal neurogenesis (Li et al., 2019). The mechanism behind impaired neurogenesis has been shown to involve NF-κB and IL-1β (Koo et al., 2010; Koo & Duman, 2008). Koo & Duman (2008) found that when either acute stress or IL-1β was administered to male rats, hippocampal cell proliferation was suppressed. This suppression was removed upon blocking the IL-1β receptor, IL-1RI. Koo et al. (2010) builds on this work by demonstrating that NF-κB mediates the antineurogenic effects of stress because normal hippocampal neurogenesis ensued as a result of experimentally inhibiting NF-κB. Additionally, the levels of neurotrophins like BDNF in regions like the hippocampus, amygdala, and cortex are also modulated by stress. BDNF has been implicated in disorders such as depression. The specific variations in BDNF levels as a result of stress are determined by a number of factors, including age of onset, form, and duration of stress (Bath et al., 2013).

For all these reasons, stress and anxiety are often comorbid with many other physical conditions. A great example is interstitial cystitis / bladder pain syndrome (IC/BPS). There is a significant association between clinically significant anxiety and IC/BPS (Mahjani et al., 2021). Beyond the central nervous system stress mechanisms previously discussed, there is a theory that stress also exerts local effects on the bladder. Bladder afferent hyperexcitability, hypersensitivity, and hyperalgesia may be caused by the activation of TRPV1-sensitive and C-fiber afferents in the bladder. Other possible pathways include inflammatory pathways (as discussed earlier) as well as the TRPV4 and guanylate cyclase-C pathways. The bladder inflammation caused by chronic stress includes inflammatory cell infiltration, edema (swelling), and angiogenesis (formation of new blood vessels) (Gao & Rodríguez, 2022). IC patients normally exhibit clinically measurable physiological changes upon medical examination. However, there are other pathologies in which no discernible physical changes can be linked to the patient's symptoms, only mental phenomena. These cases are known as somatic symptom disorders.

Somatization

Somatization encompasses the presence of physical symptoms as a result of mental phenomena. Somatic symptom disorder (SSD) is a condition in which a patient experiences continuous somatic disturbance that disrupts normal functioning alongside related excessive, maladaptive thoughts and emotions concerning those symptoms (Dimsdale, 2022; Turiaco et al., 2022). The medically unexplained physical symptoms (MUPS), also known as somatization symptoms or functional somatic symptoms, aren't fabricated or intentional and usually cannot be medically explained upon examination of the affected bodily area (Dimsdale, 2022; Sharpe & Bass, 1992). MUPS can range from pain to functional disturbances to fatigue (Turiaco et al.,

2022). Thus, somatization represents another avenue through which thoughts and emotions of the mind impact bodily health (Figure 2).

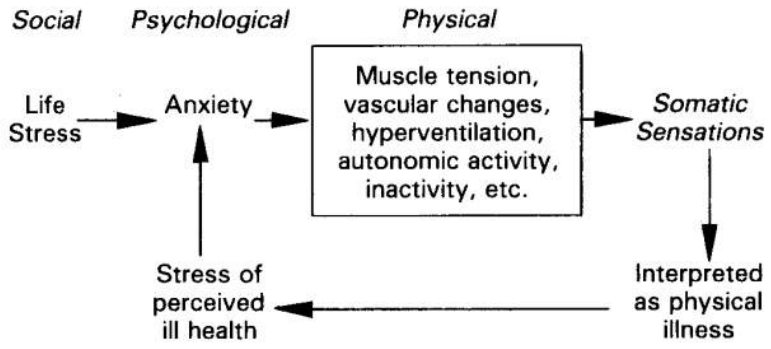
There are multiple theories of how and why SSD functions. Psychologically, somatization is influenced by one's degree and direction of attention, preexisting beliefs, mood, and personality traits (Sharpe & Bass, 1992). These factors may influence one's cognitive anticipation about their symptoms by setting expectations for probable bodily perceptions through the brain's prevision system. These predictive models then interact with the periphery to create MUPS, not unlike belief effects such as placebos. When one's illness representation, meaning one's perceptions about their symptoms – identity of the illness, timeline, causes, consequences, options for management, and emotions – are negative, the resulting frustration and helplessness often leads to stress and depressive symptoms, which in turn create poor health. A closely related psychological concept, interoception, encompasses the perception of one's internal physiological self. Interoception influences mood, and hence, aspects such as stress responses. Even simply imagining certain bodily symptoms could serve as a stepping stone to somatization. Further, issues concerning emotional control, recognition, and suppression are associated with somatization (Turiaco et al., 2022). Some evidence also suggests that the constant focus on bodily sensations may be a result of improper attentional focus, or a reduced ability to ignore unimportant sensory stimuli (Sharpe & Bass, 1992). Unsurprisingly, SSD is highly comorbid with depression and anxiety (Turiaco et al., 2022).

These aspects exist alongside parallel, multifactorial physiological mechanisms that bridge both the central and peripheral nervous systems. Interestingly, much of somatization operates as a result of the same physical processes associated with stress: ANS arousal, altered HPA axis functioning, hyperventilation, muscle tension, cytokine-driven inflammation, altered

glucocorticoid activity, increased CRH release, and hyper- or hypotension (Sharpe & Bass, 1992; Turiaco et al., 2022). These changes are hypothesized to result from sensitization of certain CNS regions such as the limbic lobe. The implicated neural pathways become hyperexcited due to repeated noxious stimuli, thus amplifying the noxious response in the future. Hyperexcitation has been observed in many of the brain regions involved with pain perception: insula, thalamus, ACC, and somatosensory cortex. Hyperactivation in the amygdala, periaqueductal gray, posterior cingulate cortex, mid-cingulate cortex, ventrolateral prefrontal cortex, and precuneus implies that fear and hypervigilance play a large role in SSD. Additionally, increased pain sensitivity can result from the high pain sensitivity haplotype of the catechol-O-methyltransferase (COMT) gene (Turiaco et al., 2022). A lack of both sleep and physical activity can contribute to somatization disorder as well. Just as seen with the placebo effect, there is no single all-encompassing mechanism, but rather varied pathways engaged depending on the MUPS (Sharpe & Bass, 1992)

Figure 2

Somatization as a Positive Feedback Loop



Note: A model of somatization taking into account both psychological and physiological factors that contribute to a positive feedback mechanism. Reproduced with written permission (Sharpe & Bass, 1992).

Psychogenic fever is an example of a somatization disorder. Some individuals, mainly women, exhibit abnormally high core body temperatures as a result of acute and chronic stress. These stress-driven fevers do not originate from the same proinflammatory mediators as infectious fevers, but rather from non-shivering thermogenesis mediated by β3-adrenoceptors within brown adipose tissue. Additional evidence for the distinct mechanisms between psychogenic and infectious fevers comes from research demonstrating that only treatments targeting mental health, such as anxiolytic and sedative psychotropic medications, psychotherapy, or natural interventions, can effectively reduce psychogenic fevers; antipyretic drugs, by contrast, fail to work (Oka, 2015).

It is important to note that the etiology of SSD relies heavily on external developmental and environmental factors, which go on to influence one's mindsets, emotions, and thoughts. Sexual assault, insecure attachment patterns, and childhood trauma significantly increase one's risk of experiencing SSD (Turiaco et al., 2022). Even as a fetus, one's risk of developing SSD or general tendencies toward stress is influenced by their mother's perception of the safety or danger of her environment; in other words, a mother's stress response transfers to the fetus in the form of hormones crossing the placenta and epigenetic modulation (Buffington, 2009).

Positive Mind → Positive Body

Positive mindsets lead to positive physiological changes for a healthier body. Since stress is core to perpetuating negative physiological responses to negative mindsets, either changing one's mindset about stress or reducing one's stress level altogether can improve one's physical health.

Stress

Since both over- and under-circulation of cortisol in response to stress have negative effects on one's health, a moderate level of cortisol activity sets one up for the greatest wellness and performance benefits from stress (Crum et al., 2013). Operationalizing public speaking as a stressor, Crum et al. (2013) analyzed the cortisol levels of participants during both a normal day and a day in which an impromptu speech was required of them. This study concluded that, while there was no main effect of stress mindset on cortisol levels throughout this acute stressor, there was a marginally significant effect considering stress mindset and cortisol reactivity. Individuals with a stress-is-enhancing mindset displayed buffered cortisol levels; in other words, low cortisol responders experienced a boost in cortisol secretion and high cortisol responders experienced a reduction in cortisol secretion in a manner that brought them nearer to the healthy, moderate level. With a positive stress mindset, cortisol activity adapted to a moderate level at which peak performance and health could be achieved. This research demonstrates that something as immaterial as a mindset provokes bodily changes that impact health and performance.

Another study sought to build on these findings and uncover more evidence for the physiological underpinnings of the substantial effect of mindset on bodily stress response by examining potential genetic links to this phenomenon. Because of the previously demonstrated role of catecholamines in stress responses and placebo responses, Crum et al. (2018) separated individuals based on their specific variations of the COMT enzyme, which metabolizes catecholamines, and studied each group's affective and cognitive responses to a stressor. Participants in both groups were also experimentally manipulated to hold either an stress-is-enhancing (SIE) or stress-is-debilitating (SID) mindset. This experimental setup allowed the researchers to test whether the activity and metabolism of catecholamines modulate the effect

between stress mindsets and stress response. The study concluded that genetic variation in COMT did significantly alter individuals' responses to a stress mindset manipulation. Participants homozygous for the low activity allele responded to the stress mindset manipulation with improved cognitive performance, greater increases in positive affect, and happiness bias in the face of stress; participants either homozygous for the high activity allele or heterozygous, however, did not exhibit these responses. Individuals with the low activity allele have a higher number of catecholamine neurotransmitters circulating in the prefrontal cortex and other areas of the brain, which contributes to greater top-down control over one's otherwise automatic responses to stress; thus, these individuals displayed an enhanced ability to shift their responses to stress from negative to positive.

In conclusion, the physiological correlates of stress can be modulated by one's mindset about stress. The power to control stress mindsets stems from prefrontal cortex activity.

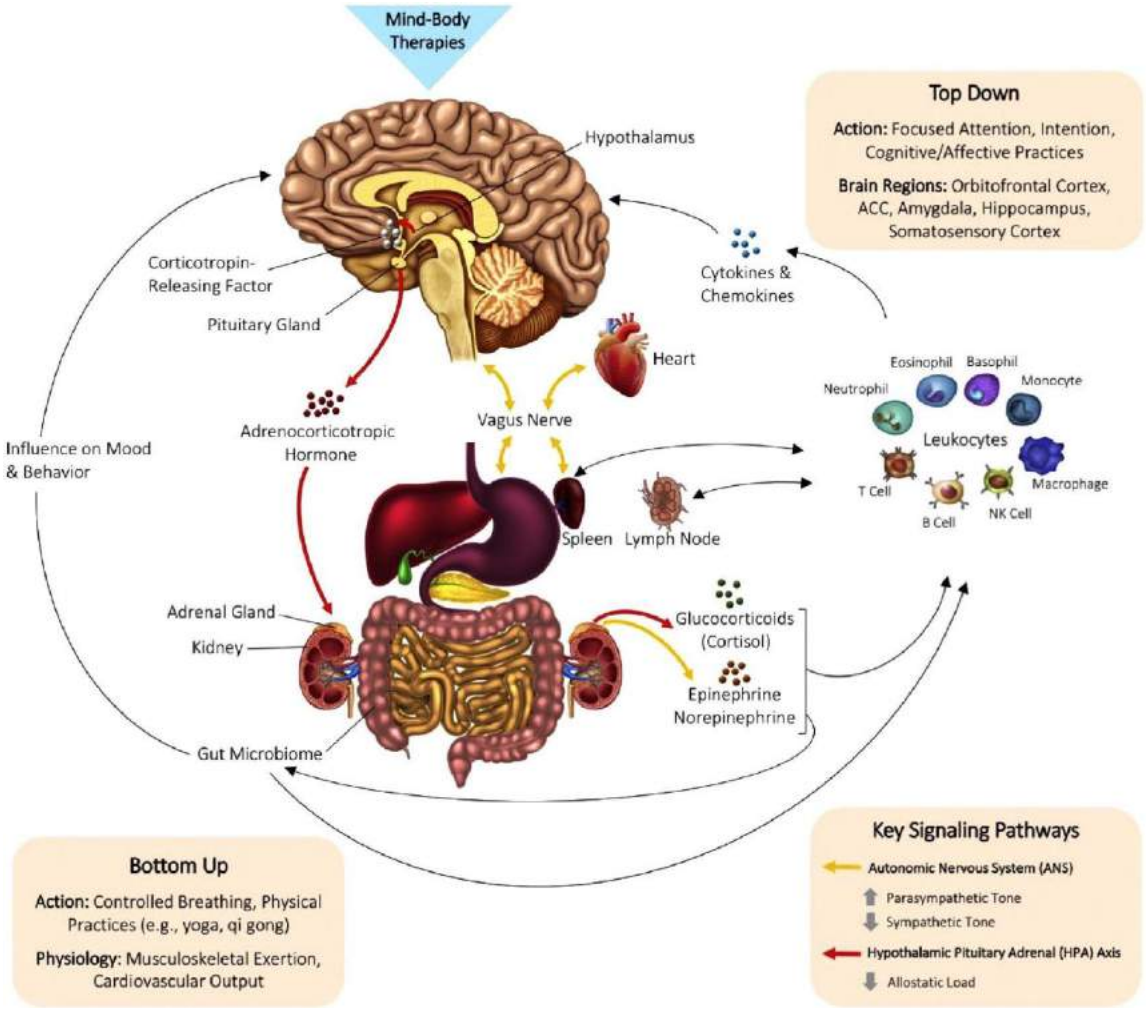
Mind-Body Therapies

Mind-body medicine (MBM), or mind-body therapies (MBTs), recognize the intrinsic links between mind – including emotions, spirituality, sociality, and experiences – and body. MBTs attempt to heal in a complimentary manner to traditional Western medicine by targeting the mind rather than just the physical body. Muehsam et al. (2017) describes MBTs as a collection of practices that unite the mind and body to spark the innate ability to heal oneself. These techniques emphasize salutogenesis, an approach that reframes medicine in terms of health promotion and maintenance rather than simply disease triggers and treatment (Esch & Stefano, 2022). MBTs include breathing exercises, meditation, yoga, guided imagery, tai chi, acupuncture, hypnosis, and progressive relaxation. These exercises focus the mind on promoting health and reducing stress through top-down methods like relaxation and present-centered focus.

MBTs also promote health through bottom-up methods that modulate physiological markers related to stress, such as breathing rate and muscle tension (Figure 3). MBTs combine both behavioral intervention and lifestyle intervention (Fricchione et al., 2016; Kripalani et al., 2021; Wolsko et al., 2004). Thus, MBTs have the potential to transform unhealthy mindsets, including the thoughts and emotions therein, to healthy ones that promote healthy physiology.

Figure 3

Overview of the Mind-Body Connection in MBTs



Note: The mind and body are intrinsically connected through hormones, nerves, and the immune system. MBTs exercise their effects on the body from both top-down and bottom-up approaches.

Mind-Body Integrative Medicine Equation. Fricchione et al. (2016) introduces the Mind-Body Integrative Medicine equation, in which one's propensity to illness is equivalent to a ratio of the amount of chronic stress (in the numerator) to one's resilience (denominator). Fricchione et al. (2016) defines resilience as the capacity to make dynamic adjustments to preserve one's stability, development, and viability in the face of stress-inducing challenges. MBTs decrease one's propensity to illness by either decreasing one's amount of chronic stress, increasing resilience, or both. Research shows that MBTs have the potential to do both. A phenomenon called the relaxation response (RR), the physiological opposite of the stress response, is mainly responsible for lowering the distress component in the numerator. The RR represents a self-induced state that counteracts stress by improving one's breathing efficiency (greater carbon dioxide elimination alongside reduced oxygen consumption) and decreasing metabolism (reduced respiratory rate, heart rate, and arterial blood pressure). Numerous types of MBTs, thought processes, and any practices that promote prosociality, spiritual connectedness, and cognitive skills (especially cognitive behavioral therapy) bolster the resilience denominator of the aforementioned ratio to promote the RR (Fricchione et al., 2016). For example, one review found that mind-body therapies improved resilience in older adults (Wu et al., 2023). Another study found that dance/movement therapy significantly enhanced resilience in individuals suffering from chronic pain (Shim et al., 2017). When practiced and brought forth regularly, the RR promotes healing mechanisms not just at the time of elicitation but throughout the day (Stefano et al., 2001). The alteration of mental states caused by MBTs results correlates with

changes in the activity of the HPA axis and ANS. The downstream effects of these systems involve gene expression, immune function, CNS function, and cellular aging.

Gene Expression and Immune Function. The physiological effects of MBTs reflect a reduction in stress by shifting gene expression in the opposite direction as the stress response does. The RR from various MBTs inhibits cellular damage from stress in manifold ways. Studies found altered expression of genes related to oxidative stress, such as the generation of reactive oxygen species, as well as a reduction in the levels of proinflammatory cytokines (Muehsam et al., 2017; Niles et al., 2014). Practitioners of MBTs also exhibit gene expression changes that enhance functioning of the immune system and downregulated pathways related to cellular metabolism and inflammation (Muehsam et al., 2017). A number of studies have spelled out a likely mechanism for these alterations: NF-κB inhibition and glucocorticoid activity enhancement, in addition to increased activity of response factors of interferons and decreased transcription factors of GATA (Muehsam et al., 2017; Niles et al. 2014). For example, meditation and yoga have demonstrated the ability to reduce the activation of one's NF-κB pathway, which in turn reduces much of the inflammation and oxidative stress associated with stress (Fricchione et al, 2016). Interestingly, these mechanisms mirror those of anti-inflammatory drugs like cyclooxygenase inhibitors and HDACis (Muehsam et al., 2017). NF-κB activity is also modulated by nitric oxide (NO). NO is an effector molecule that influences stressful and inflammatory responses as well as reward physiology and self-regulation by modifying transcription factors like NF-κB and other mitochondrial, chromosomal, and nuclear processes (Stefano et al., 2022). NO likely reduces the activity of proinflammatory NF-κB pathways. The RR associated with MBTs have been shown to increase NO levels, which decreases the expression of proinflammatory genes (Esch et al., 2018). A meta-analysis of the effects of MBTs

on immune function conducted in 2014 found that these interventions have a moderately significant effect on CRP reduction, a small yet insignificant effect on IL-6 reduction, and a negligible effect on TNF-α. Negligible effects were also found for anti-viral and enumerative measures, but some evidence points toward an increase in immune response to vaccination as a result of MBTs (Morgan et al., 2014).

Kripalani et al. (2021) reviewed the epigenetic effects of various MBTs. A study of women who practice yoga found a significant decrease in methylation of the TNF gene compared to controls. Long-term meditators demonstrate decreased expression of genes encoding histone deacetylase enzymes (such as HDAC2, 3, and 9) and pro-inflammatory genes (such as RIPK2), which correlates with more rapid cortisol recovery and increased overall histone modifications. Meditators have also displayed specific methylation sites in nearly every chromosome of peripheral blood mononuclear cells (PBMCs) on genes related to immunity and aging (Kripalani et al., 2021). Since research on this topic produces contradictory results sometimes, more replication of these studies should be completed.

Additional potential functional genomic mechanisms behind MBTs include changes in the expression of genes regulating apoptosis, though research has not yet uncovered the exact direction of these changes. The ubiquitin-dependent protein catabolic pathway involving the breakdown of unnecessary or injured proteins by proteasomes has also been shown to be downregulated in MBT practitioners (Niles et al., 2014). However, research in this area has limitations such as small sample size or conflicting data that warrant further research to confirm their findings (Muehsam et al., 2017; Niles et al. 2014).

Cellular Aging. Research has shown a negative correlation between the number of years one has practiced meditation regularly and their intrinsic epigenetic age acceleration. Similarly, a

study looking at female practitioners of tai-chi found a reduction in the natural decline in DNA methylation that occurs as one gets older, thus slowing cellular aging (Kripalani et al., 2021). Additionally, MBTs combat the cellular aging caused by stress by promoting maintenance of telomere activity and length. MBTs and other healthy lifestyle interventions display protective effects on the length of telomeres (Esch et al., 2018). PBMC telomere length correlates significantly with psychological states related to feeling purpose and control in one's life. It is also associated with telomerase activity, mortality rate, and risk for chronic disease (Muehsam et al., 2017; Niles et al., 2014). One longitudinal study found that individuals who participated in a comprehensive lifestyle change program, involving MBTs as well as healthy exercise and diet changes, had increased PBMC telomere length for over 5 years after enrolling in the program (Muehsam et al., 2017). Practicing MBTs over both short- and long-term time periods results in increases in telomerase activity and upregulation of genes associated with telomere maintenance. The existing research is not entirely conclusive. For instance, telomeres lengthened for female participants in a study on meditation, but not for male participants (Niles et al., 2014).

Neurological Correlates. Research has also been conducted on the neurological correlates of MBTs, primarily meditation. Neuroimaging techniques including EEG, PET, and fMRI suggest that MBTs are associated with either activation or changes in structure of the somatosensory cortex, anterior cingulate cortex, amygdala and hippocampus, and insula, which moderate the senses, emotions, learning and memory, and body awareness and emotion (respectively). These associations vary in degree depending on the level of one's experience practicing the MBT, suggesting that learning plays an important role in the mechanisms behind MBT's health benefits (Muehsam et al., 2017). Changes have been found in the default mode network as a result of practicing MBTs. The default mode network is a pathway made of specific

regions in the brain that are more active during rest than during wakeful, cognitively-demanding tasks (Muehsam et al., 2017; Niles et al., 2014). Some studies on meditation also report increased gray matter concentration in areas related to interoception, attention, and cardiorespiratory control (left inferior temporal gyrus, right hippocampus, right anterior insula, prefrontal cortex, cerebellum, and brainstem) as well as increased thickness in areas related to pain processing, emotional and attentional regulation, and HPA axis inhibition (dorsal anterior cingulate cortex, secondary somatosensory cortex, anterior brain regions, and hippocampal subiculum). Though much further research with larger sample sizes is needed to confirm these results, these studies demonstrate a possibility that different MBTs alter the brain in slightly varied ways that could allow more personalized treatment options for each individual (Muehsam et al., 2017; Niles et al., 2014).

BERN Framework. Esch and Stefano (2022) takes all the above evidence into consideration to create a framework that encompasses MBTs and lifestyle interventions: the BERN framework. The four pillars of the BERN framework include behavior (B), exercise (E), relaxation (R), and nutrition (N). Aspects such as spirituality, mindfulness, and social support are included within those categories. Everyday lifestyle choices about diet, exercise, and sleep play major roles in resilience; for example, aerobic exercise increases BDNF levels (which leads to increased hippocampal neurogenesis), enhances hippocampal inhibitory mechanisms to buffer the overstimulation of the amygdala under stress, and reduces the oxidative stress that results from stress (Fricchione et al., 2016). By focusing one's mind on stress-free relaxation and innate healing through MBTs and lifestyle changes, one can negate the harmful effects of lasting stress and rejuvenate the body's natural healing ability.

Placebo Effect

The placebo effect represents one of the most relevant products of the mind-body connection in medicine. The placebo effect occurs when one receives benefit from some treatment due to their belief in the efficacy of the treatment, not any medicinal properties of the treatment itself. Although the word *placebo* may be thrown about colloquially, the exact meaning and mechanism of action of placebos are thus-far unanswered topics that have sparked lots of research in recent years. It is clear that some force other than simply regression to the mean, bias, or spontaneous remission is responsible for the placebo effect observed throughout medical research and practice (although, these forces certainly also play a part). Thus, the placebo effect doesn't just rely on deception or concealment - how, then, do placebos enact their effects within our bodies?

The phrase *placebo effect* is somewhat misleading in itself, as there is no single placebo effect with a unique neurobiological signature, but rather various placebo effects with distinct mechanisms according to the condition they're associated with. From a broad perspective, placebo effects are rooted in expectation and learning. A conditioned stimulus (CS), such as the taste of a certain medication, can become associated with an unconditioned stimulus, such as the effect of that medication, after enough exposure has occurred. As a result of this conditioning, then, the CS alone can produce a similar effect as the pharmacologically-active medication itself. This behavioral conditioning has been demonstrated for immune and endocrine responses involving compounds such as IL-2, interferon-γ (IFN- γ), and cortisol. Positive expectations serve to reduce stress and activate reward pathways (with the therapeutic benefit acting as the reward), which stimulates self-healing processes (Benedetti et al., 2022a; Esch & Stefano, 2022). Beyond these anticipation and motivation systems, including limbic reward regions, placebo

effects implicate executive functioning of the frontal lobe, modulation of the reward system from the salience network, and self-reference and self-processing from the default mode network (Esch & Stefano, 2022).

Placebo Drugs. Digging deeper, research has illuminated some neurobiological mechanisms through which these expectation and learning effects operate. One of the largest shifts in placebo research was the realization that placebos often activate similar biochemical pathways and receptors as the pharmacological drugs which would normally be administered for a certain condition. For example, just as drugs targeting Parkinson's disease increase dopamine levels in the striatum, so do placebo treatments within that condition. Many pharmaceutical and recreational drugs enact neural pathways that mirror identical endogenous pathways (Benedetti et al., 2022a). Placebo analgesia, a highly studied area in placebo research, demonstrates this concept. Rather than relying on exogenous opioid drugs for pain reduction, placebo analgesia works through the endogenous opioid system, which is activated through naturally occurring peptides like endorphins and enkephalins. Under placebo analgesia, μ-opioid receptors within this neural pathway experience greater activation and produce greater neurotransmission in brain areas such as the insular cortex, rostral anterior cingulate, nucleus accumbens, and dorsolateral prefrontal cortex. This mechanism has been substantiated by research showing that the μ-opioid antagonist naloxone can prevent placebo analgesia, even in the case of open-label placebos. Further, in both animal and human models, naloxone negated the effects of placebo analgesia only in the treatment group that had been previously conditioned with morphine (an opioid), not the treatment group that has been conditioned with aspirin (a non-opioid); this supports the notion that placebo effects operate by activating similar biochemical pathways of drugs that were

used and conditioned previously (Benedetti et al., 2022b). The endocannabinoid system has also been implicated in producing placebo analgesia (Benedetti et al., 2022a).

Connection to MBTs. Physiological pathways associated with the placebo effect often parallel physiological responses to mind-body medicine. Esch & Stefano (2022) combines research within the scopes of both MBM and placebo studies to conclude that the mechanisms for mind-body interactions converge on similar self-healing, self-regulating processes of the central nervous system involving not just reward-motivation pathways but also reduction of stress and inflammation. A belief can lead to either stress or a placebo/relaxation response depending on its content (Stefano et al., 2001; Stefano et al., 2022). Placebos, as well as MBTs, rely on a previously embedded, or conditioned, positive experience that inspires positive expectations and trust for future results. An individual's conditioning, and therefore the potency of the MBM and placebo effects they respond to, is determined not only by specific experiences but also cultural frameworks and situational attributes (Esch & Stefano, 2022). The self-healing potential of both the RR and the placebo response stems from several overlapping mechanisms, such the actions of nitric oxide (NO). It seems, then, that self-healing could be considered *placebo medicine*, as MBTs are akin to *applied placebo effects* (Stefano et al., 2022).

Discussion

The studies reviewed in this paper explore examples of the mind-body connection and dive into their mechanisms on a biochemical and neurological basis. It has been shown that mindsets exert effects on the body in both negative and positive ways. The poor physical health that results from stress and SSD results from numerous overlapping mechanisms including activation of the HPA axis, ANS, and immune system, as well as modulation of hormone release, gene expression, and neural plasticity. However, just by changing your mindset about stress from

stress-is-debilitating to stress-is-enhancing, one can protect themselves from the damaging effects of stress and instead reap the physiological benefits of acute stress. In fact, MBTs and placebo effects operate largely through reducing the negative consequences of stress and inducing self-healing processes in the CNS. Placebo effects demonstrate that physical responses to stimuli are largely rooted in conditioning, so much so that just believing you're taking a certain drug will activate the same biochemical or neurological pathway as the drug itself. Thus, stress plays a central role in bodily health. Eliminating stress and other destructive mindsets can benefit physical health through documented, scientific means. In other words, as stated in Esch & Stefano (2022, p. 5), "... healing is possible and lies within the intentional window of perception and probability." Self-directed or externally-motivated shifts in mindset and expectation spark a biochemical, neurological cascade of changes throughout the body that affect health in ways that are sometimes even more powerful than typical modern medical practices.

Research like this could potentially alter the course of Western medicine for the better, offering greater hope and autonomy for patients as well as lower economic burden on the healthcare system. First, a greater understanding of placebo effects has driven more accurate clinical trials for drugs like analgesics. Also, since research has uncovered that a physician's attitude can push patients' expectations about a treatment in a more negative or positive direction, and that attitude can alter the outcome of the treatment, physicians can now make efforts to promote a positive outlook to their patients. Doctors can also make sure to administer pain medications in plain sight, since the placebo aspect of analgesia enhances their effectiveness (Benedetti et al., 2022a). Recognizing the important position of the mind in healthcare can steer medical treatments in an additional, complementary, and lower-cost direction. By incorporating MBTs or perhaps placebos in a treatment regimen, less money and time would be spent by

patients, physicians, researchers, biotechnology companies, and the government on doctor's appointments and the development of pharmaceutical drugs and medical devices.

Research on self-healing has the dangerous potential of being misinterpreted by the public and taken advantage of by pseudoscientists. First, physicians may be led to dismiss cases such as SSD on the basis of being in the *mind* rather than a *real, physical* disorder – this would be completely improper, as the mental origin of physical symptoms does not negate their very real effects for the patients. Rather, this research should provide physicians with more adequate options for diagnosis and treatment. Second, the number of non-medical organizations that cite research like this to support their quack non-scientific interventions has dramatically increased in recent years. People try to make money off *treatments* with no pharmacological benefits, justifying them on the basis of the placebo effect. This phenomenon is especially dangerous and unethical when marketed to desperate individuals with incurable illnesses. Mind-body interventions, especially placebo effects, have limits; there is a plentitude of conditions insensitive to placebos. Infectious diseases, cardiovascular diseases, and even pregnancy are just a few cases in which medical intervention is required (Benedetti et al., 2022a).

The main limitation to this review is a need for further research. Many of the studies cited in this paper need replication to substantiate their claims. Also, the predominance of correlational rather than causational evidence, especially when discussing MBTs, should be noted (Muesham et al., 2017). It is also worth mentioning that not everyone will respond to mind-body interventions to the same degree, just as not everyone responds to traditional medical interventions the same way (Benedetti et al., 2022a). The demystification of the mind-body connection and its integration into modern healthcare systems requires not just education through papers like this, but also a cultural and perceptual shift over time.

Future research should expand on this review by integrating information about the bidirectional gut-brain axis. The effects of mindsets on intestinal microbiota, and vice versa, present potential self-healing treatments that could operate along similar lines as the aforementioned concepts (Muesham et al., 2017). Visualization studies, such as Ramachandran's work with phantom limbs or Chopra's visualization-based meditation, would also provide further insight into the mind-body connection. Additional research should also explore the interaction between mind-body effects and different preexisting conditions such as mental illnesses. The use of placebos in clinical practice instead of their true pharmacological counterparts may also have ethical and legal implications that should be further explored.

Overall, the mind-body connection is not a pseudoscientific mystery, but a very real phenomenon that can dramatically improve people's health and quality of life if adequately understood.

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