Biological Pathways Linking Mindfulness with Health

J. David Creswell
Carnegie Mellon University

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This handbook is testament to the impressive growth in research and scholarship in mindfulness science. Over the past decade, there has been a proliferation of methods developed for measuring and inducing mindfulness, and mindfulness training has been linked with a broad range of outcomes in healthy and patient populations. Some of the most well-publicized findings in this emerging literature have focused on how mindfulness interventions improve mental and physical health outcomes (for reviews, see Brown, Ryan, & Creswell, 2007; Ludwig & Kabat-Zinn, 2008). For example, randomized controlled trials (RCTs) show that mindfulness interventions reduce risk for major depression relapse in at-risk participants (Ma & Teasdale, 2004; Teasdale et al., 2000), improve immune system function (Barrett et al., 2012; Davidson et al., 2003; Rosenkranz et al., 2013), reduce pain (Zeidan et al., 2011), improve skin clearing rates in psoriasis (Kabat-Zinn et al., 1998), and delay clinical markers of disease pathogenesis in HIV-infection (Creswell, Myers, Cole, & Irwin, 2009; SeyedAlinaghi et al., 2012), to name just a few examples. There has been a lot of recent theorizing about the psychological mechanisms of mindfulness training (e.g., emotion regulation, acceptance, de-centering, self-awareness), predominantly for explaining improvements in clinical symptoms, such as psychological distress (e.g., Baer, 2003; Brown et al., 2007; E. N. Carlson, 2013; Hölzel et al., 2011). In this chapter I consider a complementary question, namely, what are the biological pathways linking mindfulness with these health outcomes?

In order to consider how this capacity of the mind ('mindfulness') impacts our biology, this chapter is divided into three parts. First, I formalize an account for how

mindfulness might affect health: the *mindfulness stress-buffering hypothesis*—and then consider the available evidence for this account. Second, I will ground this stress buffering account in an evidence-based biological model (Miller, Chen, & Cole, 2009) depicting how mindfulness influences stress-related neural and peripheral biological pathways, which in turn might explain a broad range of stress-related mental and physical health outcomes. Third, I conclude with thoughts about how this account stimulates new questions that could be fruitfully explored in subsequent research.

How Does Mindfulness Affect Health? The Mindfulness Stress Buffering Hypothesis

The stress buffering hypothesis was first formally described in the social support literature as a potential explanation for how social support improves health outcomes (Cohen & Wills, 1985; Dean & Lin, 1977). In an influential review, Cohen & Wills (1985) argued that the effects of social support on health could be explained by two possible pathways—either social support has direct effects on the physiological processes that cause disease (a direct effect model), or alternatively, social support protects individuals from the adverse effects of stressful events, which in turn impact health (a stress buffering model) (Cohen & Wills, 1985). Consistent with the stress buffering model, Cohen and Wills (1985) described how the perceived availability of interpersonal resources (i.e., the perception of social support) can act as a stress buffer by muting stress appraisals and reducing stress reactivity responses.

In parallel fashion*, the mindfulness stress buffering hypothesis posits that mindfulness mitigates stress appraisals and reduces stress reactivity responses, and that these stress reduction effects partly or completely explain how mindfulness affects mental and physical health outcomes.* At first blush, it may not seem all that novel to suggest

stress buffering pathways for mindfulness-health effects. After all, Jon Kabat-Zinn described his well-known mindfulness training program as Mindfulness-Based *Stress Reduction* (MBSR) (Kabat-Zinn, 1990), and many people report using meditation practices to promote relaxation and stress reduction (cf. P. M. Barnes, Bloom, & Nahin, 2008). Thus, I don't present this basic mindfulness stress buffering hypothesis as new here, but I believe a deeper look at this hypothesis hints at some more provocative predictions and implications. First, the stress buffering account suggests that the most pronounced effects of mindfulness on health will be observed in contexts where participants carry high stress burdens (e.g., unemployed adults, participants high in psychological distress), and by contrast, that mindfulness training interventions are unlikely to have much impact on health outcomes in low stress participants. Second, the stress buffering hypothesis suggests that mindfulness effects on health will be present in populations where stress is known to trigger the onset or exacerbation of disease pathogenic processes, or where stress is known to alter health behaviors (e.g., smoking) which in turn impact disease. Again, by contrast, mindfulness interventions are unlikely to affect disease pathogenic processes that are less affected by stress. Notably, some health conditions and diseases have been shown to be quite sensitive to stress. For example, stress is thought to be an important trigger for the onset of Post-Traumatic Stress Disorder (PTSD) and major depression, and stress is known to exacerbate disease pathogenic processes in HIV infection, inflammatory and cardiovascular diseases, diabetes, obesity, and cancer tumor growth and metastasis. For a recent review of the human literature linking stress to disease, see Cohen, Janicki-Diverts, & Miller (2007). As I will discuss below, these stress sensitive health conditions and diseases are the same

types of health outcomes that have been shown to be altered by mindfulness interventions (Brown et al., 2007; Ludwig & Kabat-Zinn, 2008).

Does the current research base support the mindfulness stress buffering hypothesis? Two lines of evidence offer preliminary support. First, initial studies indicate that mindfulness reduces psychological and biological stress reactivity to stressor exposures. For example, studies show that participants higher in basic forms of dispositional mindfulness have reduced self-reported psychological stress reactivity to laboratory stressors (Arch & Craske, 2010; Weinstein, Brown, & Ryan, 2009), and lower daily life stress perceptions (e.g., Brown & Ryan, 2003; Ciesla, Reilly, Dickson, Emanuel, & Updegraff, 2012; Tamagawa et al., 2013). Mindfulness training studies show similar stress reduction benefits (cf. Baer, 2003; Speca, Carlson, Goodey, & Angen, 2000). Notably, several initial mindfulness training studies suggest that the training reduces biological stress reactivity, particularly using a standardized social stress laboratory paradigm (called the Trier Social Stress Test; TSST) where participants complete a 5-minute speech and then perform 5-minutes of difficult mental arithmetic calculations in front of evaluative panelists (Kirschbaum, Pirke, & Hellhammer, 1993). Specifically, these studies show that 8-week MBSR training reduces blood pressure reactivity to the TSST in high stress community adults (Nyklíček, Van Beugen, & Van Boxtel, 2013) and MBSR reduces anxiety and distress responses to the TSST in a sample of generalized anxiety disorder patients (Hoge et al., 2013). Moreover, as the stress buffering hypothesis might predict, these studies are consistent with the notion that mindfulness stress buffering effects are present or most pronounced in high stress populations (e.g., Arch & Craske, 2010).

In the most direct test of the mindfulness stress buffering hypothesis to-date, we recently measured undergraduate participants' basic dispositional mindfulness (using the Mindful Attention Awareness Scale; MAAS) and then manipulated whether participants completed a high or low stress challenge task (Brown, Weinstein, & Creswell, 2012). Specifically, participants were asked to perform the standard TSST speech and math performance tasks in front of evaluators (high stress condition) or the same tasks alone into an audio-recorder (low stress condition). Consistent with the stress buffering hypothesis, we found that higher levels of dispositional mindfulness were associated with lower stressor-evoked cortisol reactivity in the high stress condition, whereas there was no association between mindfulness and cortisol reactivity in the low stress condition (Brown et al., 2012).

Although studies provide initial support for the first part of the stress buffering hypothesis (i.e., mindfulness buffers stress reactivity), no studies have yet tested the more provocative stress-health predictions falling from this hypothesis, namely that stress buffering effects partially or completely account for mindfulness effects on improving clinically-relevant biological markers of mental and physical health. But the current mindfulness training literature suggests that this hypothesis might be worth pursuing, for three reasons. First, an initial study shows that mindful individuals have reduced stress appraisals and better coping under stress, which in turn mediated improvements in self-reported well-being at follow-up (Weinstein et al., 2009). Second, the most provocative demonstrations of mindfulness interventions on health outcomes have been observed almost exclusively in stress-sensitive mental and physical health outcomes, such as in HIV infection, depression, and inflammation (Creswell et al., 2009; Ma & Teasdale,

2004; Malarkey, Jarjoura, & Klatt, 2013; Rosenkranz et al., 2013; Teasdale et al., 2000).

A detailed review of the elegant stress-health physiology literature is beyond the scope of this chapter, but this basic stress literature suggests that these mindfulness health effects could be explained by stress (buffering) pathways. For example, stress has been shown to accelerate HIV viral replication (Cole, Kemeny, Fahey, Zack, & Naliboff, 2003; Cole, Korin, Fahey, & Zack, 1998) and accelerate HIV-related mortality (Capitanio, Mendoza, Lerche, & Mason, 1998); increase the likelihood major depressive episodes (Gold, Goodwin, & Chrousos, 1988); and increase inflammation (Steptoe, Hamer, & Chida, 2007).

Finally, some mindfulness training researchers appear to implicitly assume a stress buffering pathway to be driving mindfulness effects on biology and health, as mindfulness studies commonly recruit high stress populations (e.g., Creswell et al., 2009; Malarkey et al., 2013) or measure mindfulness training effects on biological markers of health after acute stress exposures (e.g., Nyklíček et al., 2013; Rosenkranz et al., 2013). Although these initial studies are consistent with a stress buffering account, future mindfulness training studies could more specifically measure stress reduction pathways and test whether they might account for mindfulness training effects on these stress-related mental and physical health outcomes using established methods for testing intervening or mediating variable effects (for methodological reviews, see Baron & Kenny, 1986; Jo, 2008; Lockhart, MacKinnon, & Ohlrich, 2011).

Using the Mindfulness Stress Buffering Hypothesis to Build a Biological Model of Mindfulness and Health

If mindfulness buffers stress, and this stress buffering helps explain how mindfulness gets under the skin to influence mental and physical health—what are the underlying biological stress reduction pathways? Here I draw from recent findings in my laboratory, and those of others, to sketch a testable biological account for mindfulness, stress buffering, and health. Specifically, this account offers some initial evidence on how mindfulness affects stress processing in the brain, which in turn is likely to change peripheral stress responses in the body, and subsequent risk for stress-related disorders and disease outcomes over time. Figure 1 depicts a model of these brain, peripheral physiology, and stress-related disease outcomes, which I describe below.

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The biology of mindfulness and stress buffering begins with the assumption that mindfulness will alter stress processing in the brain (for reviews of the neurobiology of stress, see Arnsten, 2009; Ulrich-Lai & Herman, 2009). It is important to note that emerging studies suggest that mindfulness can significantly change multiple brain networks (see Chapter 10, this volume), but here I focus on mindfulness and plausible alterations in neural stress processing. There is evidence for two promising neural stress buffering pathways in recent mindfulness studies: mindfulness may increase the recruitment of top-down regulatory regions of prefrontal cortex which may inhibit the reactivity of stress processing regions (a top down regulation pathway), and studies also suggest that mindfulness may have direct effects on modulating the reactivity of stress processing regions (a 'bottom up' reduced reactivity pathway). (We have recently written

about the top down vs bottom up accounts in a related paper on mindfulness and craving, see Westbrook et al., 2013)

Neural Stress Reduction Pathways: Top-Down Regulation by the Prefrontal Cortex

In support of the top down regulatory pathway, both basic dispositional mindfulness and mindfulness training interventions have been shown to increase the recruitment of regulatory regions of the prefrontal cortex (e.g., ventral and dorsal regions of lateral prefrontal cortex), particularly in contexts where participants are asked to engage in active emotion regulatory tasks (e.g., affect labeling, reappraisal) (Creswell, Way, Eisenberger, & Lieberman, 2007; Farb et al., 2007; Hölzel et al., 2013; Modinos, Ormel, & Aleman, 2010). Moreover, we have recently found that mindfulness meditation training (relative to a structurally matched relaxation training intervention) increases the coupling of individuals' resting state default mode network with regulatory regions of the prefrontal cortex (e.g., bilateral dorsolateral prefrontal cortex), and we find that this increased coupling statistically explains how mindfulness meditation training reduces inflammation at follow-up in a sample of stressed unemployed community adults (Creswell et al., in preparation). It is important to note that little research has evaluated whether activation (or increased connectivity) in these regions of prefrontal cortex describe actual stress regulation pathways per se, but some work suggests that activation of these top down regulatory pathways fosters the reduction of both pain and distress (e.g., Eisenberger, Lieberman, & Williams, 2003; Lieberman et al., 2004; Riva, Lauro, DeWall, & Bushman, 2012; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

Neural Stress Reduction Pathways: Reduced Central Reactivity (of the Amygdala)

Regardless of whether top down regulation pathways are recruited, mindfulness stress buffering effects would be expected to occur if there is reduced reactivity in central stress processing brain regions responsible for signaling peripheral stress response cascades (e.g., amygdala, anterior cingulate cortex, ventromedial prefrontal cortex, hypothalamus, parabrachial pons) (for a review, see Ulrich-Lai & Herman, 2009). There is initial evidence that mindfulness might directly affect neural stress processing dynamics. For example, research suggests that mindfulness alters amygdala function and structure, a region which is important for gating fight-or-flight stress responses (Arnsten, 2009; Gianaros et al., 2008; Hölzel et al., 2010). We have found that more mindful individuals have reduced resting state amygdala activity (Way, Creswell, Eisenberger, & Lieberman, 2010), and smaller right amygdala volumes (Taren, Creswell, & Gianaros, 2013). These mindfulness-related alterations in amygdala function and structure may be accompanied by changes in the resting state functional connectivity of the amygdala with other stress processing regions. We have recently found that both basic dispositional mindfulness and mindfulness training reduce stress-related right amygdala resting state functional connectivity with the subgenual anterior cingulate cortex, suggesting that mindfulness may reduce the strength of connectivity of brain networks driving stress reactivity (Taren et al., under review).

Peripheral Stress Pathways: the SAM and HPA Stress Response Systems

So far I have described several initial neuroimaging studies we and others have conducted which suggest that mindfulness may increase stress regulatory signals from the prefrontal cortex, and also reduce activity and functional connectivity in stress processing regions (e.g., amygdala) responsible for gating fight-or-flight stress response cascades

(Arnsten, 2009). How might these changes in central stress processing change peripheral (bodily) stress responses? There are two well-characterized peripheral biological stress response systems: the sympathetic-adreno-medullary (SAM) and hypothalamic-pituitary-adrenocortical (HPA) stress response axes. It is possible that mindfulness might alter SAM axis activation either (a) via reducing sympathetic nervous system activation and its principle stress effectors (secretion of the catecholamines-- norepinephrine and epinephrine) or (b) via counterregulatory systems known to alter SAM axis activation, such as through increasing activity in the parasympathetic nervous system, which can brake sympathetic nervous system fight-or-flight stress responses via the vagus nerve (Thayer & Lane, 2000). No studies to my knowledge have evaluated whether mindfulness alters the secretion of epinephrine and norepinephrine in stressed populations (an interesting direction for future research) although there is some research suggesting that mindfulness meditation may increase parasympathetic nervous system activation (Ditto, Eclache, & Goldman, 2006), which in turn might foster greater SAM axis stress regulation over time (Thayer & Lane, 2000).

There is evidence that mindfulness may alter stress related HPA-axis activation, which results in the release of glucocorticoids, most notably the stress hormone cortisol (Matousek, Dobkin, & Pruessner, 2010). Several studies suggest that mindfulness may reduce (or potentially normalize) diurnal cortisol secretion (Brand, Holsboer-Trachsler, Naranjo, & Schmidt, 2012; L. E. Carlson et al., 2013; L. E. Carlson, Speca, Faris, & Patel, 2007; L. E. Carlson, Speca, Patel, & Goodey, 2003; Jacobs et al., 2013; Matousek et al., 2010). Although these studies provide an initial indication for an effect of mindfulness on changes in diurnal HPA-axis alterations, it is important to note that

several published and unpublished reports do not support a mindfulness-diurnal cortisol link (e.g., Gex-Fabry et al., 2012) and it is unclear whether mindfulness would be expected to alter morning or evening cortisol secretion (or both) from this body of research. As mentioned earlier, we have published some initial research indicating that more mindful individuals show reduced cortisol reactivity to a high stress challenge task (Brown et al., 2012), lending support to the idea that mindfulness can buffer stress-related cortisol secretion. In summary this brief review of the studies examining mindfulness and changes in SAM and HPA axis activation provides some initial support for peripheral stress buffering effects, and more work is needed to evaluate these stress signaling pathways and their role in stress related mental and physical health outcomes.

Stress Buffering and Disease Outcomes

If mindfulness buffers central (e.g., amygdala) and peripheral (SAM and HPA axis) stress response cascades, how might these stress buffering effects impact disease pathogenic processes? Here a biological model of mindfulness and health diverges into specific biologic disease-specific pathways for both mental (e.g., depression, generalized anxiety) and physical (e.g., HIV-pathogenesis, inflammatory disease risk) outcomes. Critically, the assessment of stress-disease pathways depend on identifying the proximal biological processes driving disease pathogenesis, and then evaluating how biological stress mediators (e.g., epinephrine, cortisol) interact with these specific disease pathogenic processes (e.g., Miller et al., 2009). In many diseases the stress-disease links are increasingly well characterized— which permits the building of biologic disease-specific models for mindfulness, stress buffering, and health. As just one example of this approach, one of our previous studies focused on recruiting a moderate to high stress

HIV-positive sample and testing how mindfulness meditation training (using 8-week

MBSR) might delay disease pathogenic processes in a small randomized controlled trial

(Creswell et al., 2009). This work was guided by a biologically-informed model—we

first identified the proximal biological processes driving disease pathogenesis: HIV viral

particles replicate and attack specific compartments of the immune system, reducing

CD4+ T lymphocyte counts and increasing risk for opportunistic infections and death

(Sloan, Collado-Hidalgo, & Cole, 2007). We then considered the role of stress in

accelerating HIV replication and CD4+ T lymphocyte declines, noting an established

literature showing that stress mediators (such as norepinephrine, cortisol, and perceived

stress) can accelerate HIV replication and CD4+ T lymphocyte declines (Capitanio et al.,

1998; Cole et al., 2003, 1998; Ironson et al., 2005). Our mindfulness training findings

were consistent with a stress buffering account, in that the 8-week MBSR program

reduced stress and buffered CD4+ T lymphocyte declines in our sample of high stress

HIV+ community adults, providing one of the first controlled demonstrations that

mindfulness training can directly impact a biologic (and clinically relevant) disease

process (Creswell et al., 2009).

The stress buffering account and a consideration of the underlying biological

stress buffering pathways can inform future research aimed at evaluating whether

mindfulness affects biological health and disease outcomes. What might be stress-related

disease outcomes one might test in mindfulness intervention studies? Recent studies have

shown that dysregulated glucocorticoid signaling increases inflammatory disease risk (P.

J. Barnes & Adcock, 2009; Cohen et al., 2012) and risk for depression relapse (Zobel et

al., 2001), and catecholamines have been implicated in fostering tumor growth and

metastasis in ovarian carcinoma (Thaker et al., 2006). To the degree that the stress buffering model is accurate, it suggests that mindfulness would alter neural stress processing dynamics in high stress volunteers, reduce SAM or HPA-axis reactivity (or normalize dysregulated stress signaling in these systems), and subsequently impact stress-related disease specific biological processes (e.g., reduce tumor growth and metastasis in some cancers).

Open Questions and Future Research Directions

This chapter is designed to shed new light on the question of how the capacity to pay attention to one's experience moment-by-moment (mindfulness) affects underlying biological systems that drive mental and physical health outcomes. The emerging research described here suggests initial progress in addressing this big question, but many open questions remain. One central question is whether the stress buffering account best captures how mindfulness affects most health outcomes. I believe the extant evidence strongly supports the idea that mindfulness may serve as a protective factor against the catabolic effects that stress can have on disease pathogenic processes (the stress buffering account). It is also possible that mindfulness may have direct effects on disease processes independent of stress reduction pathways (a direct effects account). As just one example of a direct effects pathway, mindfulness may have salutary effects like those observed in the aerobic exercise literature, which suggest that aerobic exercise interventions directly increase central and peripheral growth factors (e.g., Brain-Derived Neurotrophic Factor, BDNF), which are known to foster neuroplasticity and positive health in older adults (Cotman, Berchtold, & Christie, 2007; Cotman & Berchtold, 2002).

There are also open questions about the psychological processes that might foster mindfulness stress buffering effects. It is reasonable to step back and ask why this attentional capacity would buffer stress responses in the first place. If mindfulness is about fostering greater attention towards one's present moment experience, it could be argued that mindfulness might *increase* stress appraisals and reactivity under stress. I suspect that mindfulness is not simply about enhanced attention, but about fostering a capacity to receptively observe stressors as they arise with equanimity (cf., Anālayo, 2003), which in turn would alter initial stress appraisals. Consistent with this idea, a recent study found that more dispositionally mindful individuals showed neural (electroencephalographic) patterns consistent with reduced threat appraisals to threatening and other emotionally evocative images, an effect that was observed within the first second of viewing the threatening images (Brown, Goodman, & Inzlicht, 2013). Not only is it important to consider the psychological processes linking mindfulness with initial stress appraisals, but also downstream effects on how mindfulness alters stress responses and coping efforts under stress. There are many anecdotal reports of how mindfulness training alters psychological and behavioral coping responses; for example, a participant reported changes in how they respond to stressors after 8-weeks of MBSR training "*I began living my life more consciously, for example, in regard to how I coped with stress. I started to ask myself: how do I want to deal with this? How am I reacting to my environment? In stressful situations I could sometimes take a step back and pause before I responded*" (Majumdar, Grossman, Dietz-Waschkowski, Kersig, & Walach, 2002). Although more research is needed to clarify how mindfulness affects one's response to stress, this participant's experience highlights how mindfulness fosters

greater awareness into how one is reacting to stress (e.g., perhaps via meta-awareness or de-centering), which may in turn reduce rumination (Ciesla et al., 2012; Jain et al., 2007) and buffer working memory declines (Jha, Stanley, Kiyonaga, Wong, & Gelfand, 2010), and enable more effective approach oriented coping (Weinstein et al., 2009).

In framing the mindfulness and the stress buffering hypothesis, mindfulness has at times been depicted as a static trait using measures of dispositional mindfulness or via consideration of extensive mindfulness training intervention effects (e.g., 8-week MBSR). But mindfulness is a capacity that can vary by situations and can be developed over time with appropriate training—hence mindfulness is probably best described as a dynamic process. This consideration of the dynamic nature of mindfulness also has implications for the mindfulness stress buffering hypothesis. For example, there are open questions about whether mindfulness training might initially make individuals more sensitive to stress exposures. For example, in contrast to stress buffering effects observed in 8-week mindfulness training studies or in dispositionally mindful individuals (e.g., Brown et al., 2012; Nyklíček et al., 2013), we recently found that a relatively brief 3-session mindfulness training intervention buffered psychological stress perceptions but also *increased* cortisol reactivity to the TSST (Creswell, Pacilio, Lindsay, & Brown, under review). One potential implication of these findings is that mindfulness training, in the early stages of skill development, may be more effortful to sustain, leading to greater biological stress reactivity. With greater amounts of practice, the capacity to be mindful under stress may become more automatic, reducing stress reactivity. We do not have good models of mindfulness training effects over time, but clearly these models (and

future studies in this area) would be helpful for understanding how the stress buffering effects of mindfulness might change over time.

Conclusions

The mindfulness stress buffering account provides an initial theoretical and biologically-based approach for relating mindfulness to mental and physical health. I believe it has the potential to clarify *when* and *how* mindfulness affects not only psychological adjustment, but also health and disease outcomes. Specifically, the 'when' refers to high stress populations who have health conditions that are known to be triggered or exacerbated by stress (e.g., people who report recent significant life stressors or high levels of perceived stress). The 'how' refers to the underlying biological stress pathways by which mindfulness gets under the skin to influence health. Herein I have offered some initial ideas on some promising central (brain) and peripheral (HPA and SAM axes) stress buffering pathways in mindfulness studies. Finally, I conclude with the hope that formally describing the mindfulness stress buffering hypothesis is generative. Future studies can be developed to test the psychological and biological pathways and mechanisms underlying mindfulness stress buffering effects, helping to explain how the capacity to be mindful produces such a broad range of beneficial effects for health and well-being.

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Figure Caption

Figure 1. A Conceptual Model of the Biological Pathways Linking Mindfulness, Stress Buffering, and Stress-Related Disease Outcomes. Black shaded regions depict regulatory pathways that are activated in mindful individuals or after mindfulness training, whereas grey shaded regions depict stress reactivity pathways that are reduced in mindful individuals or after mindfulness training interventions. The brain regions depicted in the neural pathways highlight how mindfulness increases the regulatory activity of areas in prefrontal cortex (in black), while turning down reactivity in areas such as the perigenual and subgenual anterior cingulate cortex, the amygdala, and corresponding brain regions implicated in HPA (hypothalamus, pituitary gland) and SAM (sympathetic nerve fibers in brainstem and spinal cord) axis responses (in grey). Note that this diagram does not include parasympathetic nervous system projections or interactions, which may play an important regulatory role for SAM axis responding. Mindfulness is posited to decrease stress-related HPA-axis activation, which results in cortisol production and release from the adrenal cortex. Mindfulness may also decrease activation of the SAM-axis, reducing the release of norepinephrine from sympathetic nerve endings and epinephrine release from the adrenal medulla. Cortisol and epinephrine/norepinephrine are important chemical messengers for mobilizing energy and engaging bodily organ systems for fight-or-flight, but when these biological stress responses become recurrent, excessive, or dysregulated, they can increase stress-related disease risk.
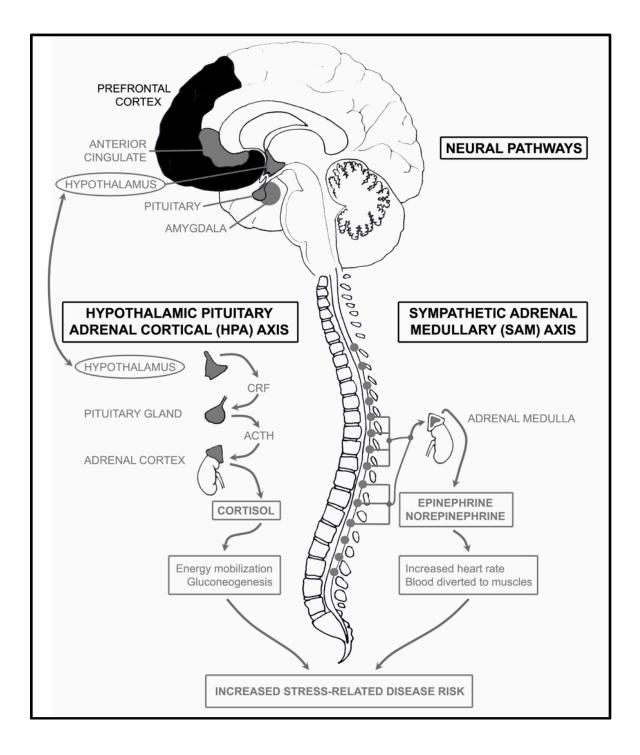
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