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Stress and aging: A neurovisceral integration perspective

Julian F. Thayer¹ | Mara Mather^{2,3} | Julian Koenig^{4,5}

¹Department of Psychological Science,
University of California, Irvine, CA, USA

²Department of Psychology, Leonard Davis
School of Gerontology, University of
Southern California, Los Angeles, CA, USA

³Department of Biomedical Engineering,
University of Southern California, Los
Angeles, CA, USA

⁴Section for Experimental Child and
Adolescent Psychiatry, Department of
Child and Adolescent Psychiatry, Centre
for Psychosocial Medicine, University of
Heidelberg, Heidelberg, Germany

⁵University Hospital of Child and
Adolescent Psychiatry and Psychotherapy,
University of Bern, Bern, Switzerland

Correspondence

Julian Koenig, Section for Experimental
Child and Adolescent Psychiatry, Department
of Child and Adolescent Psychiatry, Centre
for Psychosocial Medicine, University of
Heidelberg, Heidelberg, Germany.
Email: Julian.Koenig@med.uni-heidelberg.de

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Abstract

Darwin emphasized the intimate relationship between the brain and the heart over 150 years ago. Healthy aging is associated with significant changes in both the brain and the heart. The changes between these, the two most important organs of the body, are linked via the vagus nerve. In this review, we examine the normative changes with aging and the effect that stress may have on how the brain–heart connection changes with age. We provide a framework based on the concept of neurovisceral integration and propose that stress regulation is emotion regulation. As such, studies that have investigated emotion regulation may yield insights into successful stress regulation that helps protect people from age-related decline. In addition, interventions that improve brain health also improve heart health and vice versa. We conclude by noting that significant sex and ethnic differences exist but that future studies are needed to more fully explicate how they may moderate the associations between stress and aging.

KEYWORDS

aging, amygdala, cortical thickness, heart rate variability, neurovisceral integration, stress

1 | INTRODUCTION

The intimate connection between the heart and the brain was clearly enunciated by Charles Darwin nearly 150 years ago (Darwin, 1872/1999). Commenting on the work of the French physiologist Claude Bernard, Darwin stated early in his landmark book on the expression of emotion in man and animals, that the actions of the heart and the brain were linked via the vagus nerve. Given what was known at the time about the heart, the brain, and the nervous system, this statement was nothing

short of astonishing. Subsequent research has borne out this connection between the brain and the heart but new findings continue to accumulate that help to further clarify this connection. Importantly, Darwin's work helped to bring into focus the idea that stress and emotions have physiological concomitants.

Healthy aging is associated with a wide range of changes and adaptations. However, one constant is that with increasing age the risk of morbidity and mortality increases ultimately leading to death. Despite this inevitable outcome, it is possible to have a long, healthy, and productive life. However, one

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factor that can adversely affect this trajectory is stress. The present review aims to provide a framework for understanding the effects of stress on aging from a neurovisceral integration perspective. Keeping with the theme put forward by Darwin, we will review the literature on the effects of stress on the structure and function of the brain and the heart with a special emphasis on the vagal connection.

By way of a roadmap, we first provide an overview of what is known about healthy aging of the brain and the heart separately. We should note that the separation of the organism into separate systems is more for pedagogical purposes than a statement of the underlying physiological processes. That is, the organism mounts a whole-body response to environmental challenges that draws upon many interrelated and redundant systems. This has evolved to allow for flexibility in functioning so as to better be able to produce context appropriate responses. We next review studies that have examined the healthy aging of both the brain and the heart. An emerging perspective on aging is that aging should be considered a disease (Lakatta, 2015). From this perspective, the physiological changes that accompany aging represent progressive changes in physiological functioning that when prolonged will lead to clinical signs of disease and ultimately death. We then introduce the concept of stress and detail the effects of stress on the brain and the heart. In the context of aging as a disease, stress can be viewed as a factor that can accelerate these age-related progressive changes. Next, we review some of the studies that have examined coping and resilience factors and overview studies that have measured the brain and the heart with special attention to emotion and stress regulation. Here, we propose that any factors that can modify or retard the progression of these physiological changes may be viewed as targets for intervention that can help to stave off the deleterious effects of stress and of aging itself. Before concluding,

we briefly review interventions that have been shown to have positive effects on the brain and the heart. It is hoped that this review will bring together some of the vast literature on aging and stress. As this literature is extensive, this review will, by necessity, be illustrative and not comprehensive.

2 | BRAIN CHANGES WITH AGING

Over the course of healthy development there are significant changes in the structure and function of the brain. Due to the long time scale associated with such changes, most of what we know is based on cross-sectional studies. One area that has received extensive study concerns changes in cortical thickness and brain volume. Until about the age of 2, there is an increase in global cortical thickness associated with healthy brain development (Koenig, 2020). However, there is a monotonic decrease in global cortical thickness with age starting at approximately 4 years of age and continuing throughout the life span (Fjell et al., 2015), as illustrated in Figure 1. A recent longitudinal study of nearly 1,000 participants aged 4–88 at baseline found that cortical thickness declined sharply from approximately age 4 to the early 20's with a more gradual decline thereafter (Fjell et al., 2015). Importantly, this decrease in cortical thickness throughout the life span is not uniform across the brain. The prefrontal cortex (PFC) is a critical region for emotion regulation and is one of the last regions to fully develop and one of the first to show age-related declines (Raz et al., 2005). In one of the early longitudinal studies (Raz et al., 2005), it was shown that the approximately 5-year change in cortical volume in a sample of over 100 men and women between the ages of 20 and 77 at baseline was greatest in the PFC including the lateral prefrontal cortex (LPFC) and

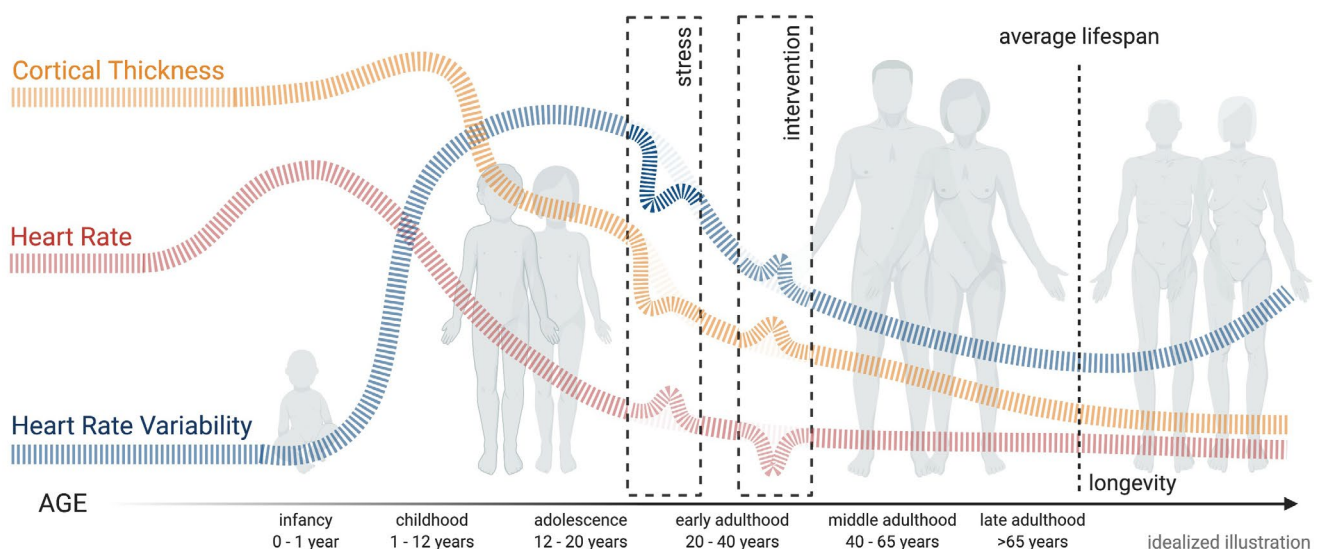


FIGURE 1 Changes in Brain Structure and Heart Function across the life span; idealized illustration of potential effects of stress and interventions; adapted from Koenig et al. (2020); Created with BioRender.com

the orbitofrontal cortex (OFC). More recent longitudinal studies also reveal that the PFC is especially vulnerable in aging (e.g., Fjell et al., 2013; Fjell, Westlye, et al., 2009).

A recent study examined gray matter volume changes across the life span using both cross-sectional and longitudinal methods (Narvacan et al., 2017). This study examined both cortical and subcortical brain volume changes. This is important as a prefrontal–amygdala circuit has been implicated in stress responses. Whereas the amygdala showed an initial increase in volume in the preteen years, subsequent changes were primarily decreases in volume which accelerated with increasing age. In contrast, the cortical gray matter showed a sharp decrease in volume until young adulthood at which time the decrease in volume changed more gradually with age. These changes resulted in a relative balance of cortical (relative lesser) to amygdala (relative greater) volumes that might favor greater stress-related responses through most of adulthood (see also Fjell, Walhovd, et al., 2009). Importantly, global brain volume has been associated with all-cause mortality. In a large study of middle-aged men and women with manifest arterial disease, it was found that smaller relative brain volumes were associated with greater risk for all-cause mortality during the more than 8-year follow-up period (van der Veen et al., 2014). Therefore, preservation of cortical thickness and brain volume plays an important role in healthy aging.

The nature of the early decline in cortical thickness is thought to reflect a different process than the later decline in cortical thickness. Whereas the exact nature of these processes is not completely known, the early decline has been suggested to reflect brain maturation-related cortical pruning associated with increased function and performance, for example, on cognitive tasks (Fjell et al., 2015; Koenig, 2020). The later cortical thinning is thought to be associated with dendritic shrinkage and age-related declines in function and performance (Fjell et al., 2015). In general, the changes in cortical thickness are not thought to reflect changes in the numbers of neurons as much as the dendritic arborization and structure of the neurons (Fjell et al., 2015). As such, it is important to understand the factors that can lead to such changes in dendritic arborization and structure, and the extent to which these changes, and their associated functional consequences with aging, can be mitigated.

3 | AUTONOMIC CHANGES WITH AGING

Similar to the age-related changes in the brain, age-related changes in autonomic function as indexed by changes in heart rate (HR) and heart rate variability (HRV) have been well documented (Antelmi et al., 2004; Zulfiqar et al., 2010). HRV refers to the beat-to-beat variability in the cardiac time series. HRV can be measured in both the time (e.g., using differences

in the timing between differences in interbeat intervals) and the frequency domain (e.g., using spectral analysis). Whereas the vagal influences cover the whole range of HRV, sympathetic nervous system and non-vagal influences are more reflected in the lower range. Thus, higher frequency HRV reflects primarily vagal influences (Laborde et al., 2017). As with the brain studies, most of these studies have been cross-sectional in nature. In one such cross-sectional study of 653 men and women aged 14–82, it was found that the root mean squared successive difference (RMSSD), a time-domain index of vagally mediated HRV, was approximately 3.6 milliseconds lower per decade of age (Antelmi et al., 2004). In another study of 344 men and women aged 10–99, it was found that RMSSD decreased sharply from child to early adulthood cohorts and then declined more gradually (Zulfiqar et al., 2010). However, the study only included $n = 22$ subjects between 10 and 19 years of age. Reviewing the sparse developmental literature (Koenig, 2020), it is more likely, that RMSSD increases postnatally up to late adolescence and only thereafter declines during postpubertal development. While the exact mechanisms are under debate, sex hormones likely contribute to this trajectory (Koenig, 2020). The steady decline from early adulthood to late-life, is similar to what is reported with respect to changes in cortical thickness (see Figure 1). Interestingly, it was found that RMSSD was greater in cohorts age 80 or older. It was speculated that this increase of vagally mediated HRV with older age was an index of longevity (Zulfiqar et al., 2010). This idea that HRV could serve as an index of biological age and longevity is not new. In an important paper, in *Science* in 1984, it was proposed that HRV could be used as an index of biological age (Hrushesky et al., 1984). More recently, researchers have used a version of the Framingham risk score to calculate biological age (Zmora et al., 2019). Importantly, we have shown that vagally mediated HRV and various cardiovascular risk scores including the Framingham risk score are inversely correlated such that the higher the RMSSD, the lower the cardiovascular risk score and thus biological age (Schuster et al., 2016).

Similar to the age-related brain changes, the changes in autonomic function and HRV with age are associated with various underlying processes. The autonomic control of the heart is complex, involving intrinsic cardiac factors, structural cardiovascular factors such as cardiac and vascular stiffness, and genetic factors. However, autonomic neural control via the sympathetic (SNS) and parasympathetic (PNS) nervous systems have been identified as prominent factors (Nolte et al., 2017; Smith et al., 2017). Using HRV indices of sympathetic and parasympathetic activities, it has been noted that the change in vagal control with age is greater than the change in sympathetic control leading to an autonomic imbalance characterized by relative sympathetic activity with increasing age up to around age 80 (Zulfiqar et al., 2010). Interestingly, above age 80 relative parasympathetic dominance is found

(Zulfiqar et al., 2010). Thus, measures of vagally mediated HRV show a pattern of decreasing activity until around the age of the U.S. average life span, after which indices of vagally mediated HRV start to increase reaching levels similar to those found in much younger individuals (Zulfiqar et al., 2010; see also Almeida-Santos et al., 2016 for similar findings in Brazil). Indices of sympathetic activity, on the contrary, show a steady monotonic decrease with age with no sign of directional change late in life. Taken together, this leads to a greater vagally mediated HRV in very old age suggesting that HRV may serve as an index of longevity and health. Relatedly, we have shown HRV to be more strongly associated with self-rated health than other biomarkers such as cortisol, cholesterol, blood glucose, blood pressure, and C-reactive protein (CRP—a marker of systemic inflammation) (Jarczok et al., 2015). These associations are consistent with our framework that suggests the idea of aging as a disease (Lakatta, 2015).

The ventromedial PFC (encompassing medial OFC) is a key region involved in autonomic control of HRV (Thayer et al., 2012). One interesting observation is that whereas cross-sectional comparisons show relative sparing of the medial OFC across age cohorts (Fjell, Westlye, et al., 2009) in longitudinal analyses examining 1 or 2-year changes in cortical thickness, medial OFC is among the regions showing pronounced age-related declines in thickness (Fjell, Walhovd, et al., 2009). This disconnect between cross-sectional and longitudinal comparisons suggests that those with greater medial OFC cortical thickness may have a better chance of survival, and therefore, being represented among older samples than those with less cortical thickness in this particular region. This is likely to be related to the findings suggesting greater survival for those with higher HRV; as reviewed in the next section, OFC structural thickness relates to individual differences in HRV.

4 | STUDIES RELATING CORTICAL STRUCTURE/FUNCTION AND AUTONOMIC ACTIVITY

Given the similar time courses of the brain and autonomic changes with age, it is natural to ask if these changes might be related to each other within individuals. Of course, this was proposed by Darwin in the mid-eighteen hundreds with a special emphasis on the vagus nerve. As such, we and others have investigated the association between age-related brain changes and age-related autonomic changes as assessed by HR and HRV.

In one study, associations between cortical thickness and HRV were investigated in two independent samples of younger (age range 18–37) and older (age range 55–78) men and women (Yoo et al., 2018). RMSSD was found to be

significantly positively correlated with lateral OFC cortical thickness in both samples and in both age groups. However, associations between RMSSD and cortical thickness in the anterior cingulate cortex (ACC) were attenuated when controlling for age suggesting that this association was age related. Unlike the ACC, cortical thickness of the left lateral OFC survived adjustment for age. Thus, the age-related decline in cortical thickness in the more superior regions may contribute to the age-related decline in vagally mediated HRV (Yoo et al., 2018) as recently replicated in a mega-analysis (Koenig et al., 2020). In a recent mega-analysis of data from over 1,200 men and women drawn from 20 research groups from across the globe it was found that whereas both RMSSD and cortical thickness decreased with age, RMSSD was positively correlated with OFC cortical thickness independent of gender and age. These results were specific to HRV as no such associations were found with HR and these results remained in analyses of HRV “adjusted” for HR (Koenig et al., 2020). It was further suggested that the age-related decrease in HRV was related to the age-related decrease in OFC cortical thickness (see also Tsvetanov et al., 2020). However, these authors noted that longitudinal studies are needed to assess the direction, if any, of the causality.

Additional studies have examined associations between cortical function and autonomic activity. In one study of approximately 80 men and women, pharmacological blockade of the anterior portion of the brain via injections of sodium amobarbital into the left and right middle carotid arteries was used to assess associations with HR and HRV as a function of age (Thayer et al., 2009). Because the PFC tonically inhibits sympathoexcitatory circuits including the amygdala, blockade of the PFC should be associated with greater HR and lower vagally mediated HRV. Consistent with this idea, this inhibitory control, as reflected in the difference in HR between the baseline and the peak of the blockade, was greatly attenuated in the oldest age group (mean age = 47; mean HR difference = 3 beats per minute) compared with the younger (mean age = 20; mean HR difference = 9 beats per minute) and middle-aged (mean age = 34; mean HR difference = 11 beats per minute) groups. These results suggest that prefrontal inhibitory control, that is necessary for successful emotion and stress regulation, may show age-related associations.

The connectivity between the PFC and the amygdala has been associated with emotion regulation such that greater connectivity is associated with greater capacity to produce context appropriate emotional responses (Thayer & Lane, 2009). For example, it has been shown that prefrontal–amygdala connectivity and its association with vagally mediated HRV are both reduced in patients with posttraumatic stress disorder (PTSD) compared to non-PTSD control participants (Thome et al., 2017). In another study, using an explicit emotion regulation paradigm, it was shown that individuals with greater resting state HRV modulated both their

PFC and amygdala activity during the regulation of negative emotional responses using reappraisal compared to individuals with lower resting state HRV (Steinfurth et al., 2018). With respect to age-related associations, it was found that medial PFC (mPFC)–amygdala connectivity was positively correlated with vagally mediated HRV in both 20 younger (age range = 19–37) and 21 older (age range = 61–78) men and women (Sakaki et al., 2016). However, ventrolateral PFC (vlPFC)–amygdala connectivity was positively correlated with vagally mediated HRV in the younger sample but not the older sample. It was suggested that the age invariant mPFC–amygdala connectivity association with HRV may be associated with more implicit emotion regulation, whereas the vlPFC–amygdala connectivity association with HRV in the younger sample may reflect greater explicit emotion regulation utilized by younger individuals (Sakaki et al., 2016).

Taken together, these findings on the age-related concomitant brain–heart connections suggest that (1) consistent with Darwin's writings, the brain and the heart may be connected via the vagus nerve, (2) the magnitude of these connections vary as a function of age, and (3) these associations are linked with emotion regulation. Relatedly, it has been shown that persons with damage to their mPFC compared with persons with damage to another brain region or no brain damage, rated the standardized stress task (the Trier Social Stress Task) as more threatening and showed higher stress responses such that women showed greater cortisol responses and men showed greater HR and lower HRV (Buchanan et al., 2010).

The mechanisms of the brain changes with aging appear to be associated with the relative shift in the cortical thickness of the PFC and the amygdala such that with increasing age from adolescence through middle adulthood there is a relative decrease in the ability of the PFC to inhibit activity in stress response regions such as the amygdala. This may be due to changes in dendritic structure and integrity. Similarly, with aging there is a change in the autonomic balance toward a relatively greater sympathetic activity primarily driven by decreased parasympathetic activity. These concomitant changes in the brain and the autonomic nervous system lead to increased risk for poor health with increasing age and are consistent with the idea of aging as a disease.

5 | STRESS

Stress has been used as a general term to describe a wide range of phenomena (see Box 1). This “overly permissive” use of the term has been recently debated in the literature (Cohen et al., 2016; Kagan, 2016a, 2016b; McEwen & McEwen, 2016). Earlier, it was proposed that “stress” be subsumed under the larger topic of emotions (Lazarus, 1993). As such, stress regulation and coping is essentially emotion regulation (Lazarus, 1993). We have argued that despite decades

of stress research, most stress theories still cannot account for the large amount of prolonged stress-related physiological responses that are responsible for the deleterious effects of stress on health (Brosschot et al., 2016, 2017, 2018). We have argued that this is due to a wrong focus of stress theories on stressors and not what is the “active ingredient,” which we propose, is perceived safety. A detailed discussion of stress theories is beyond the scope of the present article but several reviews exist in the literature (Brosschot et al., 2016, 2017, 2018; Kivimäki & Steptoe, 2018; O'Connor et al., 2020). What is common to all stress theories is the notion that prolonged physiological dysregulation, such as exaggerated stress responses, blunted stress responses, or lack of perceived safety, is necessary for stress to have harmful effects on health. Thus, stress may be viewed as any factor that accelerates the changes in physiological functioning associated with aging. From this perspective, consistent with the aging as disease idea, stress serves to accelerate the physiological disease processes and can be viewed as premature aging. At the cortical level, various types of challenges or conditions considered to be stressors have been associated with effects on the structure and function of the hippocampus, amygdala, and the PFC. Moreover, autonomic imbalance in which sympathetic tone is high and parasympathetic tone is low has been associated with mortality and morbidity (Julius, 1995; Thayer & Lane, 2007; Thayer et al., 2010). Importantly, in a paper that has flown mostly under the radar, it was proposed that a major cause of this autonomic imbalance was an unrestrained defense response (Julius, 1995).

The autonomic imbalance idea of Julius (1995) and the generalized unsafety theory of stress (GUTS) model both take a neurobiological, evolutionary approach to understanding the effects of stress on health (Brosschot et al., 2016, 2017, 2018). As Julius noted “The sympathetic overactivity in hypertension reflects a chronic activation of the defense/vigilance reaction.” We have termed this “the default stress response” (Brosschot et al., 2018; Thayer et al., 2012). Julius documents the similarities between the physiological concomitants of the autonomic imbalance seen in hypertension and related disorders, and the defense/vigilance reaction. He further states, “The defense reaction may have been useful in evolution and may have offered survival advantage. In modern times with prolonged life expectancy the previously useful response (in evolutionary terms) contributes to a faster and deleterious wear and tear on the cardiovascular system.” This excess wear and tear has been termed “allostatic load” (McEwen, 1998). The short-term advantage conferred on organisms that had a prompt and efficient defense reaction may have led to evolutionary selection of those individuals such that their genes were passed on to future generations. Thus, individuals that erred on the side of caution as it were, and exhibited a stress/defense response to ambiguous or even potentially “safe” conditions survived during more threatening

BOX 1 A brief history of stress

The literature on stress is vast but not without controversy. Several scholars have written cogent histories of the stress concept and the issues associated with the term (e.g., Kagan, 2016; Lazarus, 1993; O'Connor et al., 2020). A U.S. National Institute on Aging funded Stress Measurement Network exists that provides a trove of information about stress including a range of psychological and physiological stress measures as well as consultations with stress researchers (<https://www.stressmeasurement.org/>). Controversy surrounds the fact that the term “stress” has been defined at different times by different researchers working from different perspectives in various ways leading to a lack of consensus about what exactly stress is. One major issue is whether stress is a unique construct that is distinct from emotions more generally or if stress is best viewed as a constellation within emotion theory (e.g., Lazarus, 1993). Stress concepts were largely viewed within emotion theories dating back at least to Darwin (1872/1999). What Darwin described as the “strong emotions” of rage, fear, and terror share much in common with more recent conceptions of stress. For example, the “fight or flight” responses commonly associated with stress are essentially the rage and fear described by Darwin with similar antecedents and consequences (Darwin, 1872/1999). Lazarus (1993) makes a strong case for viewing stress within emotion theory and we largely agree with this perspective especially in the sense that stress coping and emotion coping are essentially the same thing. Stevo Julius (1995) provides an evolutionary perspective on the source of the autonomic imbalance wherein sympathetic activity is elevated and parasympathetic or vagal activity is lower leading to a range of deleterious health effects as the result of an evolutionarily preserved adaptive defense/vigilance response. This view holds that only those organisms that were able to mount an efficient fight or flight response in an environment that was largely unsafe were able to pass their genes along. However, this previously adaptive response has become maladaptive in modern, relatively safe circumstances. We have termed this the default stress response. It represents erring on the side of caution in that this ability to mount a rapid fight or flight response is basically always “on” unless safety is clearly recognized either consciously or more likely nonconsciously (Thayer & Lane, 2009; Thayer et al., 2012; Brosschot et al., 2016, 2017, 2018). It is interesting to note that Darwin also thought that these emotions of rage and fear could also be elicited without conscious awareness (Darwin, 1872/1999). The generalized unsafety theory of stress (GUTS) further formalizes these ideas and proposes that safety is the active ingredient that inhibits the default stress response when safety is present (Brosschot et al., 2016, 2017, 2018). Importantly, unlike other stress theories, actual or perceived stressors are not necessary for the organism to exhibit stress-related physiology. This idea is consistent with Julius’ notion that the defense/vigilance reaction is the basis for the autonomic imbalance that characterizes diseases and disorders such as hypertension, coronary heart disease, diabetes, and heart failure (Julius, 1995).

In discussing the nature of “stress” responses, Lazarus argues that the nonspecific stress response proposed by Selye (1956/1976) is basically the concept of “activation” from early motivation theory (Lazarus, 1993). This simplified view of stress, it is argued, does not do justice to the diverse patterns of physiology that characterize stress responses when viewed from an emotion theoretic perspective. Similarly, the allostatic load model of McEwen (1998) builds upon the dynamic general adaptation syndrome (GAS) of Selye to highlight the process of the stress response and its unfoldment over time. The stress response can manifest as an exaggerated response to a specific stressor, the repeated activation of such a response, or a prolongation of the response past the time that the stressor has ended (McEwen, 1998). Krantz and Manuck (1984) described this repeated activation or recurrent activation as they termed it in the so-called reactivity hypothesis. The reactivity hypothesis proposed, like McEwen, that repeated activation of the stress response could lead to long-term health problems (Krantz & Manuck, 1984). More similar to the defense/vigilance reaction of Julius or the default stress response of GUTS, Manuck and Krantz (1984) proposed the prevailing state model. In this model, the stress response was not an exaggerated response to a stressor but a more trait-like elevation of physiological responding that led to prolonged wear and tear on the system (Manuck & Krantz, 1984). The GUTS model goes one step further, however, and specifies that this prevailing state is basically “on” (the default response) unless safety is perceived either consciously or unconsciously, by the organism. This idea has its basis in evolutionary theory as well as neurobiology in the form of the Hughlings Jackson principle of hierarchical integration through inhibition whereby evolutionarily preserved older brainstem sympathoexcitatory circuits are inhibited by newer cortical brain regions (Jackson, 1884).

times and represent the ancestors of modern humans. Julius concludes “What could have provided a relatively short term advantage for the passage of genes across generations may have under the contemporary conditions of a prolonged life become deleterious to the organism. If we wish to further extend the life under modern circumstances, it may be necessary to dampen the defense response.” What we and others have shown is that this dampening of the stress response involves prefrontal inhibition of tonically active sympathoexcitatory circuits in the context of the relative perceived safety of modern life (Era et al., 2021; Thayer et al., 2012; Thayer & Lane, 2009).

6 | EFFECTS OF STRESS ON THE BRAIN

However, one defines stress, it is clear that stress affects the brain. One of the pioneers of the effects of stress on the brain was the late Bruce McEwen. It is not possible to do justice to the breadth and depth of the work of the McEwen lab in this review. However, there are many fine reviews of this work that interested readers can find (e.g., McEwen & Gianaros, 2011; McEwen & Morrison, 2013; McEwen et al., 2016). Much of the initial work of the effects of stress on the brain involved the hippocampus in rodents. This work showed that various types of stress (both acute and chronic) led to changes in hippocampal structure and function. For example, stress-related dendritic shrinkage in the hippocampus was associated with increased peripheral stress responses as well as behavioral changes such as mood disorders and age-related memory loss (McEwen et al., 2016). Both acute and chronic glucocorticoid levels have been associated with hippocampal remodeling. Thus, the increased cortisol levels associated with stress may have deleterious effects on hippocampal structure and function. While, the effects of acute versus chronic stress may differ, one of the important findings of this work was that the brain showed remarkable plasticity. Whereas stress such as chronic life stress and work stress was associated with reduced hippocampal volume and dendritic shrinkage, salubrious activities such as physical exercise could reverse these effects (McEwen et al., 2016).

Particularly relevant to the present review, the work on the hippocampus was subsequently expanded to examine the effects of stress on the amygdala and the PFC. Whereas the effects of stress on the hippocampus involved reduced hippocampus volume and dendritic shrinkage, the effects on the amygdala involved increased amygdala volumes and increased dendritic sprouting in the basolateral amygdala (McEwen et al., 2016). Thus, stress increased volume and dendritic expansion in a brain region associated with increased stress responses. As noted above, functional connectivity between the PFC and the amygdala is associated

with HRV (Sakaki et al., 2016). One pathway involves tonic inhibition of the amygdala via intercalated neurons from the PFC (Thayer, 2006).

The effects of stress on the mPFC were similar to the effects of stress on the hippocampus (McEwen & Morrison, 2013; McEwen et al., 2016). That is, stress was associated with decreased PFC volumes and dendritic shrinkage in rodent models. Interestingly, in these models stress was associated with increased dendritic sprouting in the OFC. It was hypothesized that these differential effects of stress on the mPFC and the OFC are associated with the differing roles that they serve in emotion and stress regulation. Specifically, whereas the mPFC serves to regulate amygdala activity, the OFC may be associated with vigilance to threats and thus may increase in size with stress exposure (McEwen et al., 2016). An interesting study in rabbits further highlights the role of the mPFC and the amygdala in coping with threats (Brusini et al., 2018). These researchers showed that domestication in rabbits was associated with increased PFC volume and reduced amygdala volume. Domesticated rabbits are known to have a decreased fear response compared to wild rabbits and the authors suggest that the decreased fear responses are associated with these brain morphological changes. In humans, decreased mPFC connectivity, decreased mPFC volume, and increased amygdala volume are associated with chronic stress (McEwen & Morrison, 2013; McEwen et al., 2016).

Taken together these studies show that the effects of aging and the effects of stress on the brain show striking similarities. Specifically, both aging and stress are associated with decreased cortical volume and thickness in areas associated with emotion regulation and dampening of stress responses. This may be due to the common mechanism of dendritic shrinkage. Stress and aging are also associated with increased volume and dendritic branching in the amygdala which is a site for regulation of stress responses. Thus, both aging and stress are associated with a shift in the relative balance in emotion regulation circuits toward a more active stress response and less active stress dampening.

7 | EFFECTS OF STRESS ON THE AUTONOMIC NERVOUS SYSTEM

Of particular relevance to this review, we and others have repeatedly shown that low vagally mediated HRV is associated with various measures of both acute and chronic stress (for reviews see Brosschot et al., 2018; Jarczok et al., 2020; O'Connor et al., 2020; Thayer et al., 2012).

As noted above, one of the major causes of autonomic imbalance is the chronic activation of the defense/vigilance response (Julius, 1995). From a psychological perspective, this defense/vigilance response is associated with perseverative cognition (e.g., worry, rumination, and angry

brooding). Both laboratory and ambulatory studies have shown perseverative cognition to be associated with lower vagally mediated HRV. An early study in patients with generalized anxiety disorder (GAD) and matched non-anxious participants showed that an acute bout of worry was associated with decreased HRV compared to a baseline condition in both groups (Thayer et al., 1996). In addition, patients with GAD, the cardinal feature of which is chronic worry, also showed lower HRV at baseline as well as during the worry condition. An ambulatory study of school teachers using ecological momentary assessments of worry found that HRV was reduced during worry episodes and remained reduced for up to 2 hr after a worry episode (Pieper et al., 2010). Finally, a recent meta-analysis linked perseverative cognition to endocrine, cardiovascular, and autonomic activities such as increased cortisol, blood pressure (BP), and heart rate (HR) and decreased vagally mediated HRV (Ottaviani et al., 2016).

One area of emerging research is on the effects of psychological stress on circadian variation of ANS activity. Nighttime or sleep should represent a period of restoration, relative safety, and associated relative decreases in SNS and increases in PNS activity. Both acute and chronic stress have been associated with a blunted HRV increase at night. In one study, healthy young adults were randomly assigned to either give a public speech in the morning or simply to relax the next morning (Hall et al., 2004). HRV was recorded throughout the night and both rapid eye movement (REM) and non-REM sleep-associated HRV calculated. Participants in the morning speech group showed a blunted nighttime increase in both REM and non-REM HRV the night before the speech. Work stress has also been associated with a blunted HRV increase at night particularly in older workers (Loerbroks et al., 2010).

The effect of work stress on HRV was examined in two recent systematic reviews. In one study, the association between work stress and HRV was systematically reviewed from 19 studies representing over 8,000 employees from 10 countries published between 1976 and 2008 (Jarczok et al., 2013). Adverse work conditions were generally associated with decreased HRV. This systematic review was recently updated. Eighteen studies published between 2013 and 2019 representing over 29,000 participants were reviewed. Adverse work conditions again were generally associated with decreased HRV (Jarczok et al., 2020). A recent large study in over 9,000 working men and women reported that low levels of vagally mediated HRV were associated with elevated risk in the clinical range (odds ratios ranging from 1.5 to 3.5) for a wide range of biomarkers (Jarczok et al., 2019). Thus, these studies and reviews showing stress to be associated with both acute and importantly, prolonged, decreases in vagally mediated HRV may have important implications for risk for a wide range of cardiometabolic and inflammatory diseases. Prolonged stress responses are needed to produce deleterious

health effects and studies with data collected during periods of rest or sleep may be particularly informative. Integrative models such as GUTS may be especially useful in providing a framework to further investigate the effects of stress on age-related central and peripheral physiological responses.

8 | COPING AND RESILIENCE TO STRESS

Successful adaptation to modern life involves the ability to produce context appropriate responses across various domains including cognitive, affective, behavioral, and physiological responses. This also involves dampening of the default stress response as suggested by Julius (1995) and by the GUTS model (Brosschot et al., 2016, 2017, 2018). Aging and stress may interact to influence these processes. For example, one study examined the effects of age on psychological and cardiovascular responding to unpleasant events in an ambulatory setting (Wrzus et al., 2013). In two studies (one using only self-reports and a second also using HRV), these researchers found that when the unpleasant events were circumscribed (relating to only one life domain as opposed to complex unpleasant events relating to multiple life domains) there were no age-related differences in the psychophysiological responses. In fact, older participants actually showed a small increase in HRV. This is consistent with studies that have shown successful emotion regulation to be associated with increased HRV (e.g., Butler et al., 2006). However, when the events were complex, older individuals showed greater psychophysiological stress responses as indexed by greater self-reports of negative emotions and decreased HRV. These researchers proposed that as long as the resources were not outstripped by the demands, age was not a factor in emotion regulation. But with increasing age and decreased resources, complex unpleasant events “overpowered” the older individuals leading to greater stress responses.

In another study, emotion regulation ability was found to mediate the relationship between chronic stress and cardiovascular disease risk (Roy et al., 2018). In a large cross-sectional study of young to middle-aged community dwelling adults a composite index of chronic stress was comprised of items from the Cumulative Adversity Interview and the Perceived Stress Scale. Emotion regulation ability was indexed by the Difficulties in Emotion Regulation Scale (DERS) which has several subscales that measure emotional awareness, emotional clarity, nonacceptance of emotional responses, access to emotion regulation strategies, impulse control, and goal-oriented behavior. A composite measure of cardiovascular disease risk was composed of blood pressure (BP), body mass index (BMI), and insulin resistance. In multivariate models adjusted for a number of covariates, they found that the DERS scores mediated the association

between the composite stress measures and cardiovascular risk. Specifically, they found that chronic stress was associated with cardiovascular disease risk only among those individuals with low emotion regulation ability as measured by the DERS. The effects of chronic stress were not associated with cardiovascular disease risk in those persons with good emotion regulation ability.

The vulnerability of the PFC to age-related decline is puzzling when considered in the context of research on aging and emotion. Older adults tend to favor attending to and remembering positive rather than negative stimuli (e.g., Charles et al., 2003; Mather & Carstensen, 2003; for meta-analysis see Reed et al., 2014), and these age-related positivity effects are eliminated when participants are given a concurrent cognitive load that demands PFC resources, suggesting that older adults employ PFC in order to help regulate their emotions (Kennedy et al., 2019; Mather & Knight, 2005). More generally, longitudinal studies indicate that the relative ratio of positive to negative affect experienced on a daily basis increases with age (Carstensen et al., 2011; Charles et al., 2001). Also suggesting effective emotion regulation outcomes among older adults, in a nationally representative sample surveyed during the COVID pandemic (in April 2020), when there was an omnipresent message that older adults were at high risk, these age differences in well-being were maintained, with age inversely associated with negative emotions despite being positively associated with perceived risk (Carstensen et al., 2020).

This disconnect between which brain regions are especially affected in aging and older adults' ability to maintain and even enhance their well-being has been called the "emotion paradox in the aging brain" (Mather, 2012). How can we explain this apparent paradox? One prior suggestion has been that not all of the PFC is equally vulnerable to aging (Mather, 2016), as cross-sectional studies suggest a relative sparing of the medial PFC (Fjell, Westlye, et al., 2009). However, longitudinal results do not always show the same pattern (Fjell, Walhovd, et al., 2009).

Another possibility is that brain regions more associated with generating stress responses might be especially affected in aging. One such brain region is the amygdala, a brain region involved in threat and salience detection. Ventromedial PFC inhibition of the amygdala seems to help avoid excess emotional reactivity and stress (Andrewes & Jenkins, 2019; Brosschot et al., 2017). Thus, changes in the relative dominance of these two brain regions may contribute to age-related changes in emotional well-being.

As noted above, research has suggested that the availability of coping resources such as cognitive and executive function abilities, and greater levels of HRV may interact with the difficulty or complexity of the emotions to be regulated. In addition to the complexity of the emotion to be regulated, concurrent tasks that tap resources may impact emotional

responses (Cotter et al., 2020; Mather & Knight, 2005; Reed et al., 2014). Specifically, older adults that had greater cognitive resources available were more likely to show a positivity bias (Mather & Knight, 2005). A meta-analysis of 100 studies in over 7,000 individuals that examined the age-related positivity effect found that this effect was greatest when participants were more "unconstrained" in their information processing, that is had fewer task-related restrictions and experimental manipulations, compared to more constrained situations (Reed et al., 2014). A recent longitudinal study of over 700 older adults (mean age 67.9) followed between 1 and 13 years (mean 2.5 years) reported that those with better executive functioning were more likely to maintain a positive mood over the follow-up period (Cotter et al., 2020). Thus, having cognitive or physiological resources available allows older individuals to better cope with difficult situations, complex emotions, and stress.

9 | CORTICAL ACTIVITY, HRV, AND STRESS/EMOTION REGULATION

Numerous studies have reported an association between HRV, and stress and emotion regulation (Appelhans & Luecken, 2006; Thayer et al., 2012; Thayer & Lane, 2009). Directly related to the above study on the DERS, we have reported that higher scores on the DERS, reflecting greater emotion regulation difficulties, were negatively correlated with resting vagally mediated HRV (Williams et al., 2015). Specifically, in a sample of approximately 180 students, we found that after controlling for a number of covariates including trait anxiety and trait rumination, DERS scores were negatively correlated with RMSSD. In a second study of over 350 college students, we again found that DERS scores were negatively correlated with RMSSD (Williams et al., 2019). Importantly, in this study, we found that after controlling for a number of covariates including age, ethnicity, BMI, and respiration rate, gender moderated this association such that the effect was stronger for women compared to men. This is consistent with the lower risk for morbidity among premenopausal women such as the college-aged students that were participants in these studies.

In a series of studies examining implicit or non-intentional emotion regulation, we have found that HRV was associated with activity in the ventromedial PFC (vmPFC). Specifically, in one study, we found that during an emotional counting Stroop task where emotional salience was in the background, activity in the vmPFC was positively correlated with coincident vagally mediated HRV (Lane et al., 2013). In a second study, we examined the association between HRV and emotion regulation-related brain regions in a sample of depressed patients and nondepressed control participants. In this study,

participants were scanned four times over the course of a 12 week treatment with sertraline in the depressed patients with the nondepressed individuals scanned at similar times over 12 weeks. Whereas associations between cortical and HRV measures were largely absent in the depressed patients at the first scanning, they increased and did not differ from the nondepressed controls by the end of the 12 week treatment (Smith et al., 2014). In the control participants, the associations between cerebral blood flow and HRV were remarkably consistent across the four scans over 12 weeks. In a third study, we found in a sample of depressed patients and non-depressed participants, that mPFC connectivity with a region in the pons thought to be associated with vagal motor control (i.e., the nucleus ambiguus) was positively correlated with coincident HRV and negatively correlated with depression symptoms in the depressed patients (Smith et al., 2015). Taken together these findings provided evidence that brain activity in emotion regulation-related brain regions was positively correlated with vagally mediated HRV. In addition, it suggests that individual differences exist in these associations such that persons with low resting HRV, like those with depression, have greater difficulty regulating their emotions.

As noted earlier, in a study involving explicit emotion regulation, we found that individuals with higher resting HRV compared to those with lower resting HRV, were better able to recruit prefrontal brain regions to modulate amygdala activity during reappraisal (Steinfurth et al., 2018). In a recent study, in a biracial community sample of over 550 middle-aged adults, we examined associations between cerebral blood flow, resting vagally mediated HRV, and self-report measures of emotion regulation including reappraisal and suppression (Thayer & Koenig, 2019). There were a number of interesting findings. First, in the total sample greater reports of emotion suppression as measured by the Emotion Regulation Questionnaire (Gross & John, 2003) were associated with greater resting vagally mediated HRV. Second, greater cerebral blood flow in the ACC in the propensity score matched European American sample was negatively correlated with suppression. Third, reappraisal was negatively correlated with HRV in the European Americans but positively correlated with HRV in the African Americans. Finally, in the African American sample, anger-in and anger-out assessed with the State-Trait Anger Expression Inventory (STAXI; Spielberger et al., 1988) were positively and negatively correlated respectively with HRV. These latter two findings highlight that fact that there are individual differences in stress and emotion regulation. Ethnic differences, as well as gender differences, may be related to the necessity to differentially regulate one's behavior due to evolutionary or social learning forces. For example, with respect to gender differences, females may use a tend and befriend as opposed to a fight or flight strategy to cope with stress as they may be of smaller stature and thus less adept at fighting or fleeing than their male counterparts (Taylor et al., 2000). With respect to

ethnic differences, individuals from groups exposed to unfair treatment may have to inhibit fight or flight responses when confronted with discrimination-related stress or aggression (Thayer et al., 2020). These differential behavioral responses will necessarily encumber differential concomitant physiological responses.

Finally, a recent study of young adult men and women investigated the effects of left dorsolateral PFC (dlPFC) inactivation on prolonged cardiovascular and cortisol responses to a stressful task (Era et al., 2021). Given that the PFC tonically inhibits subcortical sympathoexcitatory circuits (e.g., Thayer et al., 2009), it was hypothesized that inactivation of the dlPFC using transcranial magnetic stimulation (TMS) should be associated with greater HR, lower HRV, and larger cortisol responses to a perseverative cognition induction compared to inactivations of a motor brain region or sham stimulation. These researchers indeed found that dlPFC inactivation was associated with higher HR, lower vagally mediated HRV, and greater cortisol responses that extended into the recovery period compared to the other conditions (see also Angius et al., 2019; De Witte et al., 2020; Pulpulos et al., 2020). These findings provide compelling evidence for the relationships among the PFC, and autonomic and endocrine stress responses.

Taken together, these findings provide evidence that greater HRV and greater activity in emotion regulation-related brain regions are correlated with both implicit and explicit emotion and stress regulation. Given that emotion regulation is associated with effective stress regulation and resilience, and emotion regulation ability mediates the association between chronic stress and cardiovascular disease risk, better understanding of the neurovisceral concomitants of emotion regulation may help to explicate the effects of stress and aging on health.

10 | INTERVENTIONS

As noted by Julius (1995), it is necessary to “dampen” the stress response if one is to avoid the deleterious effects of our previously evolutionarily adaptive response on our long-term health. The natural dampening is provided by a healthy PFC inhibiting prolonged peripheral stress responses. Given the intimate connection between the heart and the brain, it is not surprising that interventions that benefit the brain also benefit the heart and vice versa. Therefore, several studies have examined the effects of a range of interventions on both brain and heart health.

In a recent prospective, observational study of nearly 1,000 middle to older aged men and women it was reported that greater levels of physical activity were associated with greater brain volume in men only over the 4-year follow-up period (Kim et al., 2018). Interestingly, it was found that the highest levels of physical activity seem to attenuate the deleterious effects of smoking on brain volume in men.

Another study reported that regular physical activity was associated with increased PFC blood flow and better executive function (Erickson et al., 2011). Similarly, numerous studies have reported that higher levels of physical activity are associated with higher levels of vagally mediated HRV. In one study of college students, it was reported that men and women with higher levels of physical activity as measured by the University of Houston Non-Exercise Test had higher levels of vagally mediated HRV at baseline as well as during a range of stressor tasks compared to those with lower levels of physical activity (Rossey & Thayer, 1998). A randomized controlled trial examined the effects of aerobic training versus strength training on aerobic capacity, HR, and vagally mediated HRV (Sloan et al., 2009). In this study, approximately 150 healthy younger men and women (age = 30.4 years) were randomized to 12 weeks of aerobic training or 12 weeks of strength training. In addition, after the 12 weeks of conditioning participants engaged in a 4-week detraining period. The aerobic training condition was associated with increased aerobic capacity in both men and women. However, the results showed that in men only the aerobic training condition was associated with lower HR, and greater HRV compared to the strength training group. Furthermore, these salubrious effects returned to baseline levels after the detraining period.

Psychological interventions have also been shown to affect the brain and the heart. One study investigated the effects of cognitive behavior therapy in a group of patients with chronic fatigue syndrome (CFS) and healthy controls on cortical volume (de Lange et al., 2008). Patients with CFS had lower cortical volumes at baseline compared to healthy controls. However, after the 16 session intervention, cortical volume in the lateral PFC increased in the CFS patients and this change in cortical volume was accompanied by increases in cognitive performance. Other studies reported that a mindfulness-based stress reduction (MBSR) intervention was associated with changes in prefrontal and amygdala volume (Hölzel et al., 2010, 2011). In this study, a group of healthy but stressed men and women had their amygdala volume assessed before and after an 8-week MBSR intervention. Results showed that this intervention was associated with decreased self-reported stress that was accompanied by a reduction in amygdala volume. Finally, in a study that examined both cortical and autonomic activity, a group of young adult men and women had their autonomic and brain activity assessed at baseline, and during and after 5 days of integrative body-mind training (IBMT) (Tang et al., 2009). Compared to participants that received the same amount of muscle relaxation training, the IBMT group showed greater vagally mediated HRV during and after the training. In addition, in a subgroup of participants that underwent brain imaging, IBMT participants had greater cerebral blood flow in the right anterior cingulate, among other regions, compared to

the muscle relaxation group following the 5-day intervention. Taken together, these findings suggest that both physical and psychological interventions can improve cortical and cardiovascular function. Such interventions may prove effective in mitigating the effects of both aging and stress on these important organ systems (see Figure 1).

There is also a growing literature on bioelectrical interventions. As noted above, several studies have used TMS targeted to the brain to affect peripheral physiology (e.g., Era et al., 2021). In addition, a meta-analysis showed that brain stimulation via TMS or transcranial direct current stimulation (TDCS) was associated with increased HRV, and decreased HR and blood pressure especially when stimulating prefrontal brain regions (Makovac et al., 2017). Furthermore, we have recently reviewed the literature on transcutaneous vagus nerve stimulation and report a wide range of effects (Farmer et al., 2021). These interventions show promise but much more research is needed before they become common.

11 | CONCLUSIONS

Healthy aging is associated with significant changes in both the brain and the heart. With increasing age cortical thickness and related functions decrease. The physiological basis for these changes may be associated with changes in dendritic structure and function. Stress is also associated with changes in dendritic structure and function such that stress decreases dendritic arborization in the hippocampus and the PFC but increases dendritic branching in the amygdala. Over the course of aging there is a shift in the relative balance between prefrontal cortical thickness and amygdala volume such that stress responses may be disinhibited. This shift is exacerbated by stress. In a related manner, cardiovascular aging is associated with a relative shift toward SNS dominance until very old age. Similarly, this autonomic imbalance is exacerbated by stress. These two trajectories and their potentiation by stress may be related. Therefore, factors that affect one may affect the other. The view of aging as a disease suggests that these changes represent the accumulation of factors that when prolonged lead to clinical signs of disease and ultimately to death. Coping and resilience to stress involve the regulation of emotion and stress responses at both the level of the brain and the heart. Interventions that have salubrious effects on the heart have similar effects on the brain and vice versa. However, as alluded to in the reviewed studies, there are significant sex and ethnic differences. These differences will require additional studies that are powered to adequately interrogate these effects. This review sought to provide a framework based on the concept of neurovisceral integration to further examine the effects of stress on aging of the brain and the heart. It is hoped that this review will spur further research at the interface of the brain and the heart.

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AUTHOR CONTRIBUTIONS

Julian F Thayer: Conceptualization; Project administration; Supervision; Writing-original draft. **Mara Mather:** Conceptualization; Supervision; Writing-review & editing. **Julian Koenig:** Conceptualization; Software; Visualization; Writing-review & editing.

ORCID

Julian Koenig  <https://orcid.org/0000-0003-1009-9625>

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