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Addressing the biological embedding of early life adversities (ELA) among adults through mindfulness: Proposed mechanisms and review of converging evidence

Shufang Sun [a,b,*], Margaret A. Sheridan [c], Audrey R. Tyrka [d], Shannon D. Donofry [e], Kirk I. Erickson [e,f,g], Eric B. Loucks [a,b]

[a] Department of Behavioral and Social Sciences, Brown University School of Public Health, United States
[b] Mindfulness Center at Brown University, United States
[c] Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States
[d] Initiative on Stress, Trauma, and Resilience, Department of Psychiatry and Human Behavior, Brown University Alpert Medical School, United States
[e] Department of Psychology, University of Pittsburgh, Pittsburgh, PA, United States
[f] Center for Neuroscience, University of Pittsburgh, Pittsburgh, PA, United States
[g] Center for the Neural Basis of Cognition, Pittsburgh, PA, United States

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ABSTRACT

Early life adversities (ELA) are prevalent and have a profound and adverse impact across the lifespan, including on age-related health outcomes, yet interventions to remediate its adverse impact are scarce. This paper presents evidence for mindfulness training to reduce the elevated mental and physical health risks linked to ELA among adults by targeting biological mechanisms of ELA leading to these adverse health outcomes. We first provide a brief overview of ELA, its adverse health impacts, and mechanisms that might be responsible. Next, we review converging evidence that demonstrates that mindfulness training influences key biological pathways involved in ELA-linked negative health consequences, including (a) brain networks involved in self-regulation, (b) immunity and inflammation, (c) telomere biology, and (d) epigenetic modifications. Further, we review preliminary evidence from mindfulness-based trials that focused on populations impacted by ELA. We discuss limitations of this review and provide recommendations for future research. If effective, a mindfulness-based approach could be an important public health strategy for remediating the adverse mental and physical health consequences of ELA.

Early life adversities (ELA) — encompassing various forms of maltreatment (e.g., abuse, neglect, interpersonal violence), chronic poverty, loss of a caregiver, malnutrition — is consistently linked to deleterious health outcomes and increased risk of chronic diseases in the course of human development (Felitti et al., 1998; Hoppen and Chalder, 2018; Hughes et al., 2017; Mandelli et al., 2015; Reiss et al., 2019). Evidence from population-based studies also suggests that ELA exposure is associated with greater vulnerability for premature mortality (E. Chen et al., 2016; Kelly-Irving et al., 2013). Meanwhile, recent research advances provide insight into the process through which ELA asserts health impact, by embedding into the biological systems of the child during sensitive periods of development (Berens et al., 2017; Hertzman, 2012). However, despite the past decades of accumulating scientific knowledge about the impacts and mechanisms of ELA, interventions addressing the adverse effects of ELA across the lifespan are scarce. Importantly, there is a lack of intervention research concerning ELA-exposed mid-to-late life adults (Reiss et al., 2019), despite that ELA-linked adverse health outcomes are prevalent and disabling during mid-to-late adulthood (e.g., E. Chen et al., 2016; Hughes et al., 2017; Takizawa et al., 2015). In response to this need, the National Institute on Aging (NIA) funded the Reversibility Network to foster interdisciplinary research and translate scientific knowledge to interventions aiming at reversing and remediating the detrimental health effects in mid-and-late life for people exposed to ELA via targeting risk mechanisms linking ELA to adult health. Guided by this overarching goal, this paper is a result of ongoing collaborations of members of the Reversibility Network.

Mindfulness is an intervention approach (described in detail below) that can address adversity-related health concerns in mid-to-late life

* Corresponding author at: Department of Behavioral and Social Sciences, Brown University School of Public Health, 121 S. Main St., Providence, RI 02906, United States.
E-mail address: shufang_sun@brown.edu (S. Sun).

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adults. In the past two decades, research on mindfulness has grown rapidly. Evidence-based, mindfulness interventions have demonstrated efficacy in improving mental health and well-being among various populations (de Vibe et al., 2017; Goldberg et al., 2018; Grant et al., 2017; Hopwood and Schutte, 2017; Khoury et al., 2015; Kuyken et al., 2016). This theoretical review paper examines mindfulness as an intervention approach that could potentially remediate the aging-related health impact of ELA via shared mechanistic pathways. As we describe below, emerging evidence appears to support that alternations in brain, immune, telomere, and epigenetic functions could be induced by mindfulness training (Black and Slavich, 2016; Gotink et al., 2016; Young et al., 2018). We further outline evidence that many of the specific effects of ELA on biological mechanisms of aging appear to be complimented by the salutary effects of mindfulness on similar mechanisms. Thus, it is plausible that mindfulness training could improve the health outcomes of ELA-affected adults by addressing the biological embedding through which ELA detrimentally affects health. As we will see, however, few studies have directly assessed whether mindfulness training can address the biological mechanisms or poor health outcomes in adults with ELA. Of those that have, results offer preliminary, supportive evidence. Thus, the main aims of this paper are to (a) provide a brief overview regarding the role of ELA in aging-related health outcomes, (b) synthesize evidence on the shared potential mechanisms of the health effects of ELA and mindfulness training among adults, (c) review effects of extant mindfulness intervention trials for adults with ELA exposure, and (d) provide recommendations for future research in this area.

1. Key concepts and definitions

1.1. Early life adversity

The term early life adversity describes a broad range of adverse experiences in early life, such as various forms of maltreatment (e.g., abuse, neglect), extreme poverty, parental loss, exposure to domestic/community/school violence, malnutrition, exposure to environmental hazards, etc. In this review we focus on postnatal exposures of ELA, particularly psychosocial forms of ELA, which often involve relationships (e.g., with family, peer, community) and adverse experiences relating to the developing child's psychosocial environment. This may include neglect, abuse, exposure to violence and crime, loss and incarceration of parents, and other causes of psychological trauma. Although the role of societal inequalities is beyond the scope of this review, it is important to recognize them (e.g., race, gender, sexual orientation, class, immigration status) as larger structural factors shaping the disproportionately high prevalence and severity of ELA among disadvantaged communities (McLaughlin et al., 2012; Slopen et al., 2016; Umberson et al., 2017).

1.2. Mindfulness

Mindfulness can be defined as "paying attention in a particular way, on purpose, in the present moment, and non-judgmentally" (Kabat-Zinn, 1994). Scholars have conceptualized an operational definition of mindfulness as involving (a) self-regulation of attention on one's present moment experience, and (b) adopting an orientation of curiosity, openness, and acceptance to one's experience (Bishop et al., 2004). In the past two decades, clinical trials using a mindfulness-based approach have increased exponentially (Fig. 1). Examples of mindfulness-based interventions (MBIs) include Mindfulness-based Stress Reduction (MBSR) (Kabat-Zinn, 2003) and Mindfulness-based Cognitive Therapy (MBCT) (Teasdale et al., 2000), which are evidence-based intervention programs that use a variety of experiential learning and meditation techniques (e.g., focused attention, open monitoring, walking meditation) to facilitate individuals' development of mindfulness skills.

1.3. Biological embedding

Biological embedding is the process "by which experience gets 'under the skin' to produce stable alternations in human biology that in turn influence health and development." (Nelson, 2017). ELA may become embedded through several pathways, such as via influence during a sensitive developmental period of the child with amplified plasticity (Nelson and Gabard-Durnam, 2020), altering the subsequent life trajectories and therefore elevating later risks exposure, a "dose-response" effect via cumulative, multiple ELA, as explained by the "allostatic load" concept (McEwen and Stellar, 1993), and epigenetic processes that drive gene expression alternations (Vaiserman and Koliada, 2017). We further detail conceptual models on key mechanisms of ELA following a brief overview of the health consequences of ELA.

2. Review strategy

As this paper focuses on a theoretical perspective and covers broad domains of scientific literature, we adopted a scoping review approach that focuses on overlapping biological processes of: (a) aging-related health consequences related to ELA and (b) those in which mindfulness training has shown to be potentially effective in addressing among

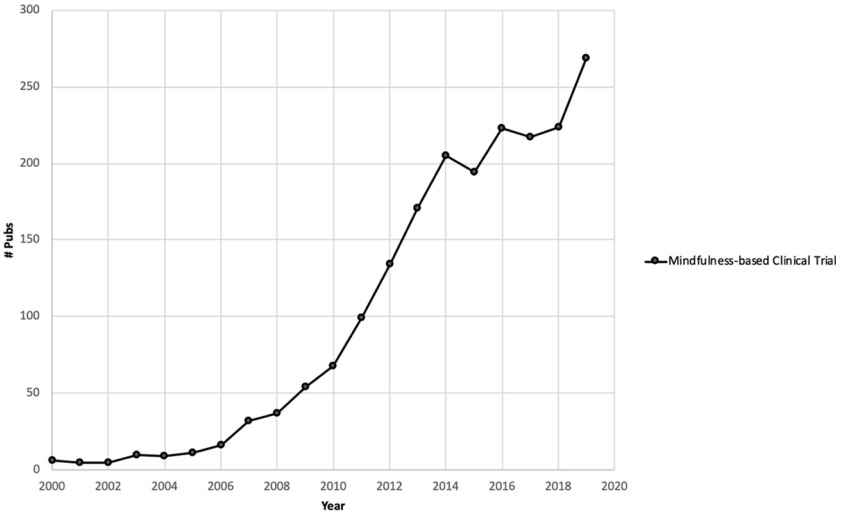

Fig. 1. Clinical trial publications appearing in PubMed including the term "mindfulness".

ELA-exposed mid-to-late life adults. As noted above, psychosocial forms of ELA are emphasized. We searched peer-reviewed evidence from several databases, including PubMed, PsycINFO, Medline, and Google Scholar. More recent research and evidence from systematic reviews and meta-analyses are emphasized. For the health impact of ELA and its potentially shared mechanisms with mindfulness training, it should be noted that evidence predominately comes from observational longitudinal and cross-sectional research, since it would be unethnical to experimentally induce ELA in children. Presented evidence regarding the role of mindfulness training emphasizes recent reviews, randomized controlled trials, and single arm trials (when RCTs are limited). Cross-sectional research on mindfulness is reviewed for complimentary evidence when clinical trials are limited. Research with adult samples is reviewed, with evidence from mid-to-late life adults highlighted given the greater morbidity with ELA- and aging-related illness in these groups.

3. A brief overview of ELA and aging-related health consequences

ELA is highly prevalent. Large national samples in the United States found 52 %–62 % of adults report an experience of ELA, measured by the adverse childhood experiences (ACEs) Questionnaire (Felitti et al., 1998), which captures exposure to ELA through experience with caregivers, such as abuse and neglect, witnessing domestic violence, caregivers' mental health issues, and separation and incarceration of caregivers (Bhan et al., 2014; Felitti et al., 1998; Merrick et al., 2018). Additionally, approximately one in six adults (15.81 %) report experiencing four or more ACEs (Merrick et al., 2018), a level of exposure likely to significantly impact health, well-being, and mortality (Bellis et al., 2019; Brown et al., 2009; Felitti et al., 1998; Hughes et al., 2017). ELA puts individuals at risk for adverse health across the lifespan. Below we review the most salient evidence from research in adults with a focus on mid-to-later life samples.

3.1. Psychological and neurocognitive disorders

Strong and consistent evidence suggests that ELA is linked to internalizing symptoms such as anxiety, depression, somatic complaints, as well as externalizing symptoms such as elevated aggression, impulsive behaviors, sexual risk behaviors, and delinquency (Chapman et al., 2004; Fergusson et al., 1996; Hoppen and Chalder, 2018; Lindert et al., 2014; Turner et al., 2006; Wilson & Widom, 2011). Adults reporting ELA also have elevated rates of PTSD, suicide risk, binge drinking, substance abuse and dependence, and other forms of psychopathology (Liu et al., 2017; Matheson et al., 2013; Wolitzky-Taylor et al., 2017). The World Health Organization (WHO) World Mental Health Survey Initiative surveyed 51,945 adults across 21 countries and estimated that 29.8 % of mental health disorders could be avoided by eradicating ELA (Kessler et al., 2010).

In addition, ELA appears to influence cognitive function in mid-to-late life (Short and Baram, 2019), though compared to psychological health outcomes, evidence on the association between ELA and impaired cognitive function is less consistent. Several population-based and large cohort studies found that ELA increases the risk for cognitive decline during middle age (Kaplan et al., 2001; Marden et al., 2017; Melrose et al., 2015; Pesonen et al., 2013) and for dementia and Alzheimer's disease in later life (Kaplan et al., 2001; Radford et al., 2017), yet the association between ELA and cognitive decline has not always been confirmed in studies and across populations (Barnes et al., 2012; Tian et al., 2020). This discrepancy in findings might be the result of how these studies describe ELA. For example, poverty may be a particularly salient environmental risk factor contributing to the influence of ELA on cognitive decline (Kaplan et al., 2001; Marden et al., 2017; Melrose et al., 2015). Emerging evidence suggests that physical neglect might also exacerbate or precipitate age-related cognitive decline more so than other forms of psychosocial-based ELA (e.g., abuse) (Grainger et al., 2019; Wang et al., 2016). In addition, presence of depressive symptoms, which occurs disproportionately in individuals with a history of ELA, also contributes to risk of age-related cognitive decline (Korten et al., 2014).

3.2. Physical health outcomes

A large and growing literature has documented links between ELA and diseases of aging. Psychosocial ELA appears to have a pervasive impact on physical health; systematic reviews reveal that exposure to ELA is associated with elevated risk of cardiovascular disease, respiratory disease, gastrointestinal disorders, chronic pain, and obesity over the life-course (Danese and Tan, 2014; Davis et al., 2005; Hemmingsson et al., 2014; Wegman and Stetler, 2009). Additionally, various types of ELA impact physical health, for example, a meta-analysis found that several types of childhood abuse (physical, sexual, emotional, and general) were predictive of adult obesity (Hemmingsson et al., 2014). Multiple ELA exposures can have a cumulative effect on physical health: a recent systematic review in adult samples found four ACEs to be moderately predictive of cancer, heart disease, and respiratory disease (Hughes et al., 2017). Finally, exposure to ELA increases the complexity of health conditions (e.g., comorbidity of physical and mental) (Gekker et al., 2018; Koball et al., 2019; Mandelli et al., 2015).

4. Theories on mechanisms linking ELA and adverse adult health

There are several theories about the nature of early adverse exposures that attempt to explain the mechanisms of risk for poor mental and physical health outcomes following ELA. Herein, we review three prominent theories, including (a) a cumulative risk perspective, (b) the dimensional model of adversity and psychopathology (DMAP), and (c) an accelerated life history perspective. These theories provide organizing structures in understanding the mechanisms of biological embedding of ELA.

The cumulative risk perspective proposes that the number of stressors to which a child is exposed broadly increases subsequent health risks via excessive activation of the biological stress response and resulting alterations of neurobiological function, neural development, peripheral physiology, and immune function. The cumulative risk perspective is informed by the allostatic load model which posits that the cumulative impact of adaptive physiological responses to maintain homeostasis can become dysregulated and damaging to health (McEwen and Stellar, 1993). Negative outcomes associated with ELA in this model focus on deficits in immune function, disrupted stress physiology, and the impact of stress physiology on neural structure and function with a focus on the function of the limbic system (e.g., the amygdala and hippocampus) and medial prefrontal cortex (Booth et al., 2015; McEwen, 2000, 2013, 2017; McEwen and Gianaros, 2011; McEwen and Rasgon, 2018). In addition, there has been an increasing interest in the role of telomeres in aging and disease susceptibility in response to psychosocial stress (e.g., Telomere Research Network, sponsored by the National Institute of Health). A cumulative risk perspective also proposes that that the consequences of ELA can be found at a cellular level through telomere shortening (Epel and Prather, 2018; Ridout et al., 2018a; Zalli et al., 2014).

The dimensional model of adversity and psychopathology (DMAP) (McLaughlin et al., 2014), emphasizes distinct dimensions of ELA: (a) deprivation, or an absence of social and cognitive stimulation that are critical for normal brain development, and (b) threat, or presence of learning experiences which constitute threat to one's safety and well-being (McLaughlin, 2016; McLaughlin et al., 2014; Sheridan and Mclaughlin, 2014; Sheridan and McLaughlin, 2016). These dimensions are proposed to affect health outcomes via distinct mechanisms (Miller et al., 2018, 2021). Threat is conceptualized as selectively disrupting

neural systems which support emotional reactivity and regulation including limbic structures and the ventromedial prefrontal cortex, and associated function. In contrast, deprivation is proposed to selectively disrupt regions supporting higher order cognition such as lateral prefrontal and parietal cortex and associated cognitive and linguistic abilities (McLaughlin et al., 2016; Sheridan et al., 2017).

An accelerated life history perspective offers an explanation to the biological acceleration among ELA-exposed individuals. Such acceleration has been observed in neural, immune, and other physiological systems following ELA exposure, such as in limbic system development (Callaghan and Tottenham, 2016), cellular aging (Colich et al., 2020), and early menarche (Boynton-Jarrett et al., 2013) particularly due to an accelerated life history strategy (Ellis et al., 2009). This evolutionary-developmental informed perspective proposes that exposure to ELA that constitute harsh and unpredictable environments induce adaptations to promote survival and/or reproduction, resulting in accelerated development (Belsky, 2019). For instance, children exposed to harsh and unpredictable environments would be expected to demonstrate accelerated biological development and reach reproductive capacity more rapidly than peers without ELA (Belsky, 2019; Shalev and Belsky, 2016). Specific patterns of advanced vs. delayed maturation may depend on ELA type, timing, and population (Colich et al., 2020; Keding et al., 2021; Marini et al., 2020). The cumulative effect of this accelerated developmental trajectory could be accelerated in aging processes in mid-to-late life (Colich et al., 2020).

Although these models emphasize different overarching hypothesized mechanisms for how ELA affects health outcomes, predictions arising from these models converge on alterations of neurobiological systems, including cortico-limbic structure and function, physiological stress responding, immunity and inflammation, and telomere shortening suggestive of cellular aging. In addition, epigenetic modifications involving DNA methylation and histone modifications can act as a key mediating factor that bridges between ELA as an environmental stress and the disruption of neurobiological systems noted above (Brown et al., 2019; Burns et al., 2018; Parade et al., 2021).

5. Shared mechanisms of ELA and mindfulness training on adult health outcomes

ELA generates a cascade of physiological and neurobiological adaptations that alter developmental trajectories and confer vulnerability to psychopathology and other health conditions. Mindfulness training has been shown to improve psychiatric health (Goldberg et al., 2018), cognitive outcomes (Gill et al., 2020), and some aspects of physical health (Grossman et al., 2004; Lee et al., 2020; Loucks et al., 2015; Pascoe et al., 2017). Since ELA increases risk for these same outcomes, mindfulness training may offer a pathway to mitigate the adverse effects of ELA and reduce risks for developing these conditions.

Below, we present a review of the evidence for overlapping mechanisms through which mindfulness and ELA affect aging-related health outcomes. By highlighting potential mechanisms through which mindfulness training may be able to address the biological embedding of ELA (Fig. 2), this review could guide future interventions and hypothesis testing in this field. Of note, a large body of literature in both the mechanisms of ELA and mindfulness has attended to neuroendocrine- and autonomic reactivity-related stress physiology processes. This mechanism is the most consistent with the view of the cumulative risk perspective (i.e., allostatic load). Specifically, ELA may adversely affect health outcomes via neuroendocrine alternations such as dysregulated HPA response (ACTH and cortisol) (Bunea et al., 2017; Fogelman and Canli, 2018), and mindfulness may improve these stress biomarkers, although its effects were inconsistent across biomarkers and study methods (de Vibe et al., 2017; Heckenberg et al., 2018; O'Leary et al., 2016). This domain of mechanism research has been the oldest and led to other lines of inquiry. Thus, in this paper, informed by theories on how ELA affects health outcomes, we review four mechanistic pathways (Fig. 2), including: (a) brain networks involved in self-regulation, (b) immunity and inflammation; (c) telomere shortening, and (d) epigenetic modifications. Within each mechanism, evidence on the impact of ELA is presented first, followed by research on how mindfulness training influences these pathways. Table 1 provides a summary of key evidence on these four proposed mechanisms and evidence from relevant systematic reviews.

5.1. *Brain networks involved in self-regulation*

Various theories of the impact and mechanisms of risk following ELA (i.e., cumulative risk model, DMAP, and accelerated life history model) posit that ELA affects health outcomes through its influence on cortico-limbic function, brain circuitry engaged to support self-regulation processes. Indeed, systematic reviews and meta-analyses of neuroimaging research consistently support the link between ELA and alterations in brain structure, function, and connectivity (Kraaijenvanger et al., 2020; Lim et al., 2020; Paquola et al., 2016; Teicher et al., 2016). In particular, alteration of brain networks necessary for self-regulation may be a key pathway by which ELA increases risk for psychopathology and addictive

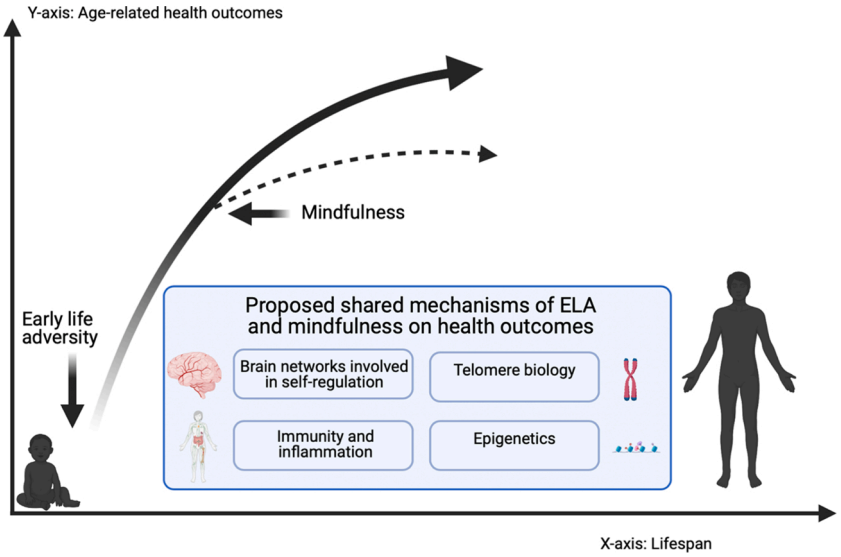

Fig. 2. Proposed theoretical framework.

Table 1
Summary of evidence on proposed mechanisms through which ELA and mindfulness affect age-related health outcomes.

	Changes Associated with ELA	Changes Associated with Mindfulness Training	Key Reviews/meta analyses
1. Brain networks involved in self-regulation			
The limbic system			Regarding ELA: Frodl and O'Keane, 2013; Hart and Rubia, 2012; Lim et al., 2020; Nemeroff, 2016; Teicher et al., 2012; Wang et al., 2019
Hippocampus, implicated in memory, learning, and emotion processing	Reduced grey matter volume in the hippocampus	Larger gray matter volume in hippocampus in long-term practitioners	
Amygdala, implicated in emotions and memory, particularly in emotions related to fear, stress, as well as rewarding stimuli	Alterations in amygdala circuity and function (e.g., hyperresponsiveness or blunted response)	Decrease in amygdala reactivity to emotional stimuli	
Insula, implicated in self-awareness	Reduced insula volume	Increased neural activation in the insula following mindfulness training	
Anterior cingulate cortex (ACC; connected to both the limbic system and prefrontal cortex), implicated in emotion regulation and impulse control	Reduced ACC volume; Reduced connectivity between ACC and the amygdala	Greater activation in ACC following mindfulness training; Reduced activation in sgACC following mindfulness training when presented with craving cues	
PCC related networks			
Dorsolateral prefrontal cortex (DLPFC), implicated in higher order cognition, executive function, and emotion regulation	Reduced gray matter volume in DLPFC; Decreased activation in the DLPFC in response to emotional stimuli	Greater activation in DLPFC following mindfulness training; Greater connectivity between DLPFC and other brain regions	Regarding Mindfulness: Fox et al., 2014; Fox et al., 2016; Gotink et al., 2016; Young et al., 2018; Chiesa et al., 2013
Default mode network (DMN), involved in self-referential functions	Reduced connectivity of DMN	Increased connectivity between DMN and PFC, and between DMN and left hippocampus following mindfulness training	
Brain connectivity and communication			
Corticolimbic connectivity, involved in processing and top-down regulation of emotions	Altered connectivity between the amygdala and regions of the PFC, such as ACC and vmPFC	Improved functional connectivity between the amygdala and PFC to emotional stimuli following mindfulness training	
Corpus callosum (CC), involved in interhemispheric communication and cognitive processing	Reduced corpus callosum volume	Greater volume of corpus callosum among long-term practitioners, particularly located in anterior CC, implicated in connection with prefrontal regions	
2. **Immunity and inflammation**			
	Chronic inflammation, as indicated by elevated inflammatory biomarkers (e.g., CRP, IL-6, TNF-*a*)	Reduce proinflammatory responses among mid-to-late life adults and adults with psychopathology	Regarding ELA: Coelho et al., 2014; Elwenspoek et al., 2017; Fagundes and Way, 2014; Kuhlman et al., 2020 Regarding Mindfulness: Black and Slavich, 2016; Fountain-Zaragoza and Prakash, 2017; Sanada et al., 2020
3. **Telomere biology**			
	More rapid telomere shortening	Increase telomerase activity, which is involved in telomere length maintenance	Regarding ELA: Epel and Prather, 2018; Hanssen et al., 2017; Li et al., 2017a,b; Ridout et al., 2018a,b Regarding Mindfulness: Conklin et al., 2019; Schutte et al., 2020; Schutte and Malouff, 2014
4. **Epigenetics**			
	DNA methylation in response to various forms of ELA in regions linked to adverse health outcomes (e.g., psychiatric symptoms, cardiovascular disease, etc.)	Downregulate epigenetic pathways by altering DNAm in regions included genes associated with immunity, inflammation, and psychiatric health	Regarding ELA: Cecil et al., 2020; Holmes et al., 2019; Parade et al., 2021; Wolf et al., 2018 Regarding Mindfulness: Kaliman, 2019

behaviors linked to poor behavioral health (Carvalho Fernando et al., 2014; Lanius et al., 2010; Marusak et al., 2015). Improving self-regulation is considered a key mechanism of how mindfulness training improve well-being (Hölzel et al., 2011; Tang et al., 2015) and mindfulness practice is associated with altered cortico-limbic function (Fox et al., 2014; Tang et al., 2015). Below, we review the shared role of brain networks involved in self-regulation in response to ELA and mindfulness training, including (a) the limbic system (e.g., the hippocampus, amygdala, insula), (b) the prefrontal cortex and associated networks (e.g., the dorsolateral prefrontal cortex and default mode network), (c) connectivity between regions of the limbic system and the prefrontal cortex, and (d) the corpus callosum. We present evidence regarding how ELA affects these networks organized by two key aspects of self-regulation, namely emotion regulation (i.e., modulation of emotional experiences) and attentional control. Attentional control is a complex process that involves recruiting and sustaining attention on targeted object as well as inhibitory control to suppress task-irrelevant processing (Miyake and Friedman, 2012; Petersen and Michael, 2012).

Strong research evidence supports the link between childhood maltreatment and brain changes that are hypothesized to be responses and adaptations to a threatening environment. The limbic system of the brain, which include the hippocampus and amygdala as two major structures, is pivotal in emotional and social learning and may be especially responsive to ELA (Dannlowski et al., 2012). Systematic reviews and cross-sectional evidence suggest that hippocampal volume reductions are associated with duration and severity of childhood maltreatment (Andersen et al., 2009; Baker et al., 2013; Bremner et al., 1997; Frodl and O'Keane, 2013; Nemeroff, 2016; Teicher et al., 2012). Reductions in hippocampal volumes are observed with various stress-related psychiatric conditions such as depression and PTSD, as well as memory deficits (Gilbertson et al., 2002; Van Der Flier et al., 2004; Van Rooij et al., 2015). Evidence also suggests early and persistent

alterations in amygdala function as a result of ELA, and specific alterations may differ based on ELA type and timing. Amygdala and insula hyper-responsiveness to threatening facial expressions and stimuli has been observed in adults with a history of childhood maltreatment (e.g., abuse, violence) in several studies (Dannlowski et al., 2012; Fonzo et al., 2016; McCrory et al., 2011; Zhu et al., 2019). The specific neural correlates of ELA may vary depending on the timing of the adverse exposures. For example, one study observed heightened amygdala response among adults with early teen exposure to maltreatment, yet adults exposed to early childhood maltreatment had blunted amygdala response (Zhu et al., 2019). In addition, the anterior cingulate cortex (ACC) and the insula cortex, particularly its most anterior portion, are considered limbic-related and are implicated in processing and regulation of emotions, and for the insula processing of bodily sensations as well (Craig, 2009; Wiech et al., 2010; Zaki et al., 2012). Volumetric reductions have been observed in the ACC (Cohen et al., 2006) as well as insula (Baker et al., 2013) among adults with ELA exposure (Baker et al., 2013). In sum, multiple studies have observed alterations in limbic system structure and function in adulthood related to ELA exposure.

The prefrontal cortex is central for a wide array of executive functions and "top-down" regulation of input from the limbic system. In particular, the dorsolateral prefrontal cortex (DLPFC) is a region of the prefrontal cortex considered one of the most recently evolved parts of the human brain (Carlén, 2017) and implicated in higher order cognition, particularly executive function and emotion regulation (Braunstein et al., 2017; Curtis and D'Esposito, 2003; Ochsner et al., 2012). ELA exposure has been linked to structural and functional alterations of the prefrontal cortex, particularly DLPFC. A meta-analysis of 19 neuroimaging studies that investigated whole brain voxel based morphometry among ELA-exposed adults found a significant and strong association of ELA exposure with volumetric reductions in right DLPFC (Paquola et al., 2016). An fMRI study with 182 adults also found ELA exposure to be associated with reduced activation in the right DLPFC when viewing emotionally evocative stimuli (Fonzo et al., 2016). Given DLPFC's role, such altertions may be linked to cognitive and emotional dysregulation among ELA-exposed adults (Paquola et al., 2016).

Recent research has also linked circuit level dysfunction to ELA exposure. Cross-sectional neuroimaging studies with adult samples found functional changes within the amygdala-prefrontal circuitry associated with ELA exposure, most notably reduced resting state functional connectivity between the amygdala and regions of the prefrontal cortex, such as the anterior cingulate cortex (ACC) (Fan et al., 2014) and the ventromedial prefrontal cortex (vmPFC) (Birn et al., 2014). Both the ACC and the vmPFC are implicated in the processing of fear and critical in the regulation of amygdala activity and emotional control, and these changes may present disrupted emotion regulation processes (Teicher et al., 2016). Emerging evidence from neuroimaging research also found reduced functional connectivity in the default mode network (DMN) among adults exposed to childhood maltreatment (Daniels et al., 2011; Philip et al., 2013; Wang et al., 2019) and a history of childhood poverty (Sripada et al., 2014). The DMN is a network of brain regions that are active during resting state. Interestingly, alterations in the DMN have been implicated in age-related cognitive decline and disorders (Bluhm et al., 2009; Sripada et al., 2014; Tozzi et al., 2020).

The corpus callosum facilitates interhemispheric communication and is involved in cognitive processing. Narrative reviews and neuroimaging evidence suggest thining of the corpus callosum among adults with ELA (Andersen et al., 2009; Hart and Rubia, 2012; Lim et al., 2020; Spies et al., 2016; Teicher et al., 2010, 2016), which may represent diminished hemispheric integration and reduced integration of cognitive and emotional processes (Teicher et al., 2016).

In summary, the consequences of ELA on psychopathology and adverse neurocognitive outcomes in adulthood are likely at least partially due to its impact on limbic system and prefrontal structure and function as well as the role of these systems within larger networks. These regions and networks are vital to regulation of emotion, attention, and other cognitive processes.

5.1.1. *The role of mindfulness training in changes of brain networks*

Mindfulness practice has been associated with changes in many of the same brain networks that appear to be negatively affected by ELA as reviewed above. Several meta-analyses and systematic reviews reveal patterns of brain structure and function associated with meditation practice (Fox et al., 2014, 2016; Gotink et al., 2016; Young et al., 2018). Two meta-analyses focused on understanding brain structure and function in long-term meditation practitioners compared to meditation naïve counterparts (Fox et al., 2014, 2016). In a meta-analysis of 21 neuroimaging studies of meditation practitioners, Fox et al. (2014) found a medium effect size (Cohen's $d = 0.46$) in brain structural differences compared to meditation naïve controls. Notably, many of the findings associated with mindfulness training, including increased gray matter concentration and volume in hippocampus and increased cortical thickness in dorsal anterior cingulate cortex (dACC) and corpus callosum (Fox et al., 2014), overlap with regions of brain structural changes consistently associated with ELA exposure. Fox et al. (2016) conducted another meta-analysis of 78 task-based (i.e., meditation practice) functional neuroimaging studies to identify brain regions consistently activated by four types of meditation including focused attention, mantra recitation, open monitoring, and loving-kindness. Focused attention and open monitoring, practices commonly used in MBIs, activated anterior insula cortex, which supports self-awareness and bodily experience, as well as DLPFC and the dACC (Fox et al., 2016). Given the role of DLPFC and dACC in executive function and emotion regulation as well as the impact of ELA on these brain regions, it is possible that mindfulness could offer a path for altering the trajectory of brain changes as consequences of ELA. Two other systematic reviews aimed to understand the effect of MBIs on the structure and function of the brain for participants of MBI programs. Gotink et al. (2016) reviewed 11 neuroimaging studies that included both within- and between- participant changes in MBSR programs. Notably, these changes involved brain regions responsible for cognitive and emotion regulation, including increased activity in the prefrontal cortex, hippocampus, and cingulate cortex, decreased functional activity in the amygdala and improved functional connectivity between the prefrontal cortex and the amygdala following tasks involving emotional stimuli exposure (Gotink et al., 2016). A more recent review focused on within-participant, longitudinal changes in functional brain activity following MBIs in eight studies (Young et al., 2018), which identified moderate support for increased response of the ACC during emotional processing while changes of specific processes to subregions of the PFC (e.g., dmPFC) were less consistent. The most consistent evidence was found for increased insula activity following MBIs (Young et al., 2018), indicating enhanced present moment awareness.

Specific to emotion regulation, mindfulness training enhances awareness of one's experience including emotions, which could provide cues for regulation (Chambers et al., 2009). A systematic review of clinical trials and neuroimaging studies suggest that mindfulness training supports emotion regulation through both "top-down" and "bottom-up" processes (Chiesa et al., 2013). Specifically, "top-down" processes in emotion regulation via mindfulness includes regulation of prefrontal brain regions associated with emotional reappraisal that could modulate limbic activity (e.g., greater DLPFC responses), as well as changes in brain regions associated with self-referential processing of the DMN, whereas "bottom-up" process may involve reduced activation of the limbic system (Chiesa et al., 2013). Findings suggest that the level of expertise matters, with novice meditators showing more top-down processes (i.e., strengthening prefrontal cognitive control mechanisms involved in emotion regulation) whereas meditation experts displayed more bottom-up processes and less cognitive control, which may indicate greater affect acceptance (Chiesa et al., 2013). For instance, among novice meditators diagnosed with Generalized Anxiety Disorder who

underwent Mindfulness-based Stress Reduction (MBSR) training, when engaging in affect labeling (using emotion provoking images), participants showed enhanced activation in the ventrolateral PFC (Hölzel et al., 2013). Mindfulness training also enhances amygdala-prefrontal cortex functional connectivity (Doll et al., 2016; Hölzel et al., 2013; Leung et al., 2015). Thus, for adults with ELA, mindfulness may facilitate emotion regulation through enhanced input from the prefrontal cortex and downregulated activity in regions involved in affect processing.

Mindfulness training also appears to facilitate other self regulation processes through altered brain function. As noted above, the ACC supports various self-regulatory processes such as attention allocation and modulation of emotions and impulses (Bush et al., 2000, 2002; Carter and Van Veen, 2007). The ACC is a brain region consistently associated with meditation, including increased ACC activity among meditation beginners (Cahn and Polich, 2006; Haase et al., 2015; Hölzel et al., 2007; Tang et al., 2012, 2009; Tang et al., 2010). Thus, greater ACC activation through mindfulness training may indicate more effortful performance of self-regulation such as attention and emotion regulation. DLPFC, a brain region associated with attention control and executive function, also shows altered activity with meditation training. Specifically, mindfulness training is associated with greater DLPFC activation during cognitive tasks as well as increased connectivity between DLPFC and other brain regions implicated in executive control such as the dorsal network, ventral network, and the DMN (Allen et al., 2012; Goldin and Gross, 2010; Kral et al., 2019; Taren et al., 2017). Thus, through mindfulness training, increased activation and greater connectivity of the DLPFC may partially account for improvement in attentional control, executive function, down-regulation of emotions, and working memory (Y. Tang et al., 2015). The role of mindfulness on DMN appear to be dependent on population and nature of testing (during mindfulness practice or longitudinal effect): among meditators, deactivation in DMN was found during practice, potentially indicating decreased mind-wandering during meditation (Brewer et al., 2011). Increased DMN (PCC seed) resting-state functional connectivity was found following mindfulness training among adult combat veterans with PTSD compared to baseline and control conditions, and such increase was associated with PTSD symptoms reduction (King et al., 2016). In another longitudinal study in older adults with mild cognitive impairment, increased DMN (PCC) connectivity with bilateral medial PFC and left hippocampus was found following MBSR training (Wells et al., 2013). Notably, research the role of the DMN in meditation and alterations through mindfulness training are still emerging, and extant findings may reflect increased capacity for executive function, attentional control, and meta-cognitive regulation of affect (King et al., 2016).

Overall, emerging and converging research evidence suggests that mindfulness training may affect brain networks involved in self-regulation that are vulnerable to the early adverse influence of ELA, including the cortico-limbic circuits and brain connectivity implicated in emotional and cognitive regulation. The longitudinal effect of mindfulness training specifically for adults with ELA on these structural and functional brain changes still needs to be ascertained by future research.

5.2. Immunity and inflammation

Both the cumulative risk model and the accelerated life history model emphasize the burden of ELA on immune function mediated by inflammatory responses. Local and acute inflammatory responses can be adaptive, yet when inflammation becomes chronic and systemic, it can lead to physical health decline. Chronic inflammation is considered to be a risk factor for age-related diseases such as hypertension, diabetes, atherosclerosis, osteoarthritis, and cancer (Frasca et al., 2017; Freund et al., 2010). Several systematic reviews suggest that ELA shows biological embedding into immune system function (Elwenspoek et al., 2017; Kuhlman et al., 2020), which can precipitate numerous health risks. Inflammatory responses such as elevated proinflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin 1β, and tumor necrosis factor (TNF or TNF-*a*), are also associated with the development of a variety of stress-related psychopathologies such as depression and PTSD (Dowlati et al., 2010; Osimo et al., 2019; Passos et al., 2015; Valkanova et al., 2013), and age-related neurocognitive disorders such as Alzheimer's disease (Swardfager et al., 2010).

Evidence from systematic reviews of a mix of cross-sectional and longitudinal studies indicates that ELA is linked to an elevated inflammatory responses across the life span (Coelho et al., 2014; Fagundes and Way, 2014; Kuhlman et al., 2020). Notably, several prospective longitudinal studies from birth found that ELA (measured prospectively in childhood, often a mix of ELA indicators including abuse, neglect, and socioeconomic disadvantage) predicted elevated inflammation (indicated by increased proinflammatory markers such as CRP, IL-6, etc.) in mid-life (Danese et al., 2007, 2009; Pereira et al., 2019; Takizawa et al., 2015). For instance, a 50-year prospective longitudinal birth cohort study found that pre-adolescent experience of bullying victimization was associated with increased CRP after adjusting for social class and other childhood and adult risk factors (e.g., psychopathology, health behaviors) (Takizawa et al., 2015). As shown in other longitudinal and large cross-sectional studies (Iob et al., 2020; Loucks et al., 2010; Nakamura et al., 2021), this effect appears to persist into late life. For instance, in the Framingham Heart Study, prospectively-assessed childhood socioeconomic position was associated with elevated inflammatory markers CRP, TNF-a, intercellular adhesion molecule-1 (ICAM-1), and lipoprotein phospholipase A2 (Lp-PLA2) measured in late life (sample mean age = 61.2) (Loucks et al., 2010). In older adults, elevated inflammation is also associated with poor physical and cognitive function as well as changes in brain regions implicated in cognition (e.g., greater regional cerebral blood flow decline in ACC and hippocampus) (Brinkley et al., 2009; Warren et al., 2018). Recently, in the English Longitudinal Study of Ageing, retrospectively assessed ELA (measured by ACE) was associated with higher CRP and depressive symptoms at baseline with adults aged 50 or older, and that baseline CRP mediated the relationship between ACE and increase in depression over a period of four years (Iob et al., 2020). In sum, ELA may accelerate age-related adverse health outcomes through potentiated inflammation in adulthood.

5.2.1. The role of mindfulness in inflammation

Evidence from several recent systematic reviews suggest that mindfulness training could support healthy inflammatory responses (Black and Slavich, 2016; Fountain-Zaragoza and Prakash, 2017; Sanada et al., 2020). In particular, several randomized controlled trials (RCTs) of MBIs demonstrated improvement of proinflammatory biomarkers (i.e., reduced levels of elevation) through mindfulness training, though findings have been mixed. Among them, several RCTs focused on mid-to-late life adults with various health conditions (Black et al., 2015; Creswell et al., 2012; Gallegos et al., 2013; Ng et al., 2020; Villalba et al., 2019). Overall, the effect of MBIs on inflammatory markers seemed to be contingent on the subpopulation, control condition, and parameter of inflammatory markers. For instance, a significant reduction in high-sensitivity C-reactive protein (CRP) following mindfulness training has been observed in RCTs of older adults with mild cognitive impairment compared to a health education control (Ng et al., 2020), healthy older adults compared to a waitlist control (Creswell et al., 2012), and subsamples of mid-to late-life adults ($\geq$ 45 years old) as well as those with a BMI $\geq$ 25 in an adult-focused RCT compared to pure monitoring and stress coping training (Villalba et al., 2019). Two RCTs found MBIs to down-regulate pro-inflammatory gene NF-κB expression from baseline to post-intervention, though between-group effects were only significant when compared to a waitlist control in healthy older adults (Creswell et al., 2012) and no between-group differences were found when compared to a sleep hygiene education among older adults with sleep disturbances (Black et al., 2015). Two RCTs in healthy older adults

did not find MBIs to impact IL-6 levels (Creswell et al., 2012; Gallegos et al., 2013). Overall, these findings indicate the potential of mindfulness in supporting immune function among mid-to-late life adults affected by ELA, and findings appear to be more promising in CRP and the transcription factor NF-κB than in interleukin levels.

In addition to studies in mid-to-late life adults, several intervention trials have examined the effect of mindfulness training on inflammatory biomarkers among adults with psychiatric conditions (e.g., depression, anxiety, PTSD) (Creswell et al., 2016; Dutcher et al., 2021; Gallegos et al., 2015; Hoge et al., 2018; Memon et al., 2017; Walsh et al., 2016), which adults with ELA are disproportionately affected by. Again, findings are overall promising, with some variations across trials that may be related to population and control type. One single-arm trial found that mindfulness training led to reductions in IL-6 levels among trauma-exposed, low-income women (Gallegos et al., 2015). Other RCTs found that, compared with passive or attention control, MBIs showed reductions in IL-6 and TNF-a among young adult women with depressive symptomology (Walsh et al., 2016), as well as adults with Generalized Anxiety Disorder (GAD) (Hoge et al., 2018). However, one RCT that compared a mindfulness-based group therapy to cognitive-behavioral therapy among patients with mild to moderate depression and anxiety symptoms did not find changes in inflammatory markers (IL-6, IL-8, CRP) in either condition, despite significant reductions in psychiatric symptoms (Memon et al., 2017). Recent MBI trials investigating mechnisms of change suggest that improvement in inflammatory response through mindfulness is also connected to alterations of brain circuitry involved in self-regulation: IL-6 reductions following MBIs was associated with improved functional connectivity between the DMN and DLPFC (Creswell et al., 2016), and decreases in IL-6 and CRP was associated with increases in left ventral stratum reactivity to rewarding images (Dutcher et al., 2021).

In summary, preliminary evidence suggests that mindfulness may reduce proinflammatory responses and affect cell-mediated immunity pathways (e.g., via NF-κB expression) through which ELA affects various age-related health outcomes, such as hypertension, diabetes, atherosclerosis, osteoarthritis, cancer onset and progression, as well as psychopathology.

5.3. Telomere shortening

Telomeres, the DNA protein structures that contains repetitive nucleotide sequences at both ends of each linear chromosome, have important functions in protecting the genome from nucleolytic degradation and interchromosomal fusion (Blackburn et al., 2015). Telomere shortening occurs with each DNA replication until a critically-short limit is reached, limiting the proliferation of cells (Blackburn et al., 2015). Telomeres shorten with age and telomere length can serve as a biomarker of cellular aging (Epel et al., 2004). Telomerase is a cellular enzyme that adds telomeric DNA onto the 3′ ends of the telomere; its activation prevents aging in some cells by lengthening telomeres (Verdun and Karlseder, 2007). Evidence from meta-analytic and systematic reviews consistently show an inverse association between telomere length and risks of various age-related health outcomes in humans including all-cause mortality (Q. Wang et al., 2018), cardiovascular disease (Haycock et al., 2014), type II diabetes mellitus (D'Mello et al., 2015), hypertension (Tellechea and Pirola, 2017), as well as psychopathology such as depression (Ridout et al., 2016), anxiety (Malouff and Schutte, 2017), and PTSD symptoms (Li et al., 2017a).

Both the cumulative risk model and the accelerated life history model are consistent with the hypothesis that exposure to ELA affects cellular aging process through telomeres, which shorten most rapidly during early life (Colich et al., 2020; Price et al., 2013). Telomere shortening as a result of ELA exposure appears to start early in life. For instance, a longitudinal twin study with a nationally representative cohort found that children exposed to two or more types of violence had significantly more telomere erosion between ages 5 and 10, after adjusting for demographic variables and body mass index (BMI) (I. Shalev et al., 2013). Meta-analytic evidence supports that such an effect persist into adulthood: A meta-analysis found that childhood trauma is associated with accelerated telomere erosion in adulthood (Li et al., 2017b). Two other meta-analyses including adult samples (age mean- = 42 years for Hanssen et al., 2017, focusing on psychosocial ELA and age mean = 31 years for Ridout et al., 2018a,b, focusing on ELA of various types) also found a significant inverse relationship between ELA and telomere length (Hanssen et al., 2017; Ridout et al., 2018b). The strength of this association varies by ELA assessment and timing: studies that had more comprehensive adversity measures (abuse, neglect and other sources of ELA) yielded a larger effect size (Cohen's d = -0.71) compared to those with more narrow range of ELA assessment, and the association between ELA and telomere length was stronger when ELA exposure occurred earlier in developmental periods (Ridout et al., 2018b).

5.3.1. The role of mindfulness in telomere maintenance

Three reviews and meta-analyses have examined the evidence base for a role of mindfulness meditation in telomere biology (Conklin et al., 2019; Schutte et al., 2020; Schutte and Malouff, 2014). Overall, evidence from these reviews suggest that compared to individuals in control conditions, mindfulness training is linked to significantly increased telomerase activity (Cohen's $d = 0.46$, $p = .001$) (Schutte and Malouff, 2014), yet the association with longer telomeres was small and insignificant (Hedge's $g = .16$, $p = .14$) (Schutte et al., 2020). As suggested by a recent review and theoretical model (Conklin et al., 2019), mindfulness training likely affects telomere biology by influencing both the psychological response to stress (e.g., appraisal) as well as physiological responses including telomerase activity (e.g., telomerase).

Herein, we provide a brief review of evidence from randomized controlled trials of mindfulness training have provided preliminary evidence for the protective role of mindfulness in telomerase activity, which promotes telomere maintenance. Overall, most trials found increases in telomerase activity following mindfulness training, while those that assessed telomere length did not find significant differences. Among them, three trials focused on mid-to late-life adults. Of these, two RCTs found a significant increase in telomerase activity in the MBI condition for family dementia caregivers (mean age = 60.3 years) with mild depression symptoms compared to a relaxation control (Lavretsky et al., 2013) as well as for mid-to-late age breast cancer survivors (mean age = 55.3 years) compared to treatment-as-usual (Lengacher et al., 2014). Regarding telomere length, Lengacher et al. (2014) did not find between-group difference, while another RCT, also with breast cancer survivors (mean age = 54.6 years), found those in MBI exhibited significantly higher telomere length maintenance compared to telomere length decline in a stress management control (Carlson et al., 2015). One three-arm trial dissected specific types of meditation practice compared mindfulness meditation (defined in the study as awareness of breath, body, and emotions), loving-kindness meditation, and a waitlist control (Le Nguyen et al., 2019). The study found that there was signficiantly less telomere length attrition in the loving-kindness meditation group compared to waitlist control following the 6-week intervention, while awareness-based meditation had intermediate effect between these two conditions (Le Nguyen et al., 2019), indicating potentially varied effects on telomere length based on meditation training type.

Other adult-focused trials (not specific to mid-to late-life adults) reported similar findings. Two RCTs found greater telomerase activity following mindfulness training compared to waitlist controls among overweight women (Daubenmier et al., 2012) and healthy adults (Jacobs et al., 2011). Two RCTs found no significant differences in telomere length following 8-week MBIs among individuals with mixed-level psychological distress for both within-group comparisons (pre-to-post comparison) and compared to a CBT control (Wang et al., 2017) as well as among healthy adults compared to music-based stress reduction (Keng et al., 2020), though the latter found a trend for increased

telomere length for those engaged in more at-home mindfulness practices (Keng et al., 2020). Additionally, a few cross-sectional comparisons have been conducted to compare telomere length of meditators to naïve controls, and found that meditation practitioners have signficiantly longer telomere length (Alda et al., 2016; Hoge et al., 2013).

In summary, mindfulness might support healthy aging through improving telomere maintainance and protecting against accelerated cellular aging commonly reported among ELA-exposed adults.

5.4. Epigenetics

In addition to telomere regulation, experience can drive other epigenetic changes, such as DNA methylation or histone modification, which alter DNA and can influence phenotype without changing genotype (Song & Johnson, 2018). Epigenetic modifications may be a molecular-level mechanism through which ELA impacts the neurochemical systems as reviewed above (e.g., brain, immune system) and subsequent susceptibility to age-related illnesses (Silberman et al., 2016; Vaiserman and Koliada, 2017). Broadly speaking, epigenetic changes may involve various mechanisms including DNA methylation (DNAm), histone modification, telomere regulation, and nucleosome positioning (Song & Johnson, 2018). Among them, DNA methylation (DNAm) is the most extensively researched and a focus of this review. DNAm refers to a biological process by which methyl groups are added to a specific nucleotide (cytosine guanine dinucleotides, or CpG sites) in the DNA, which leads to changes in gene expression. Methylation of regulatory regions are often associated with gene silencing, whereas loss of methylation could lead to gene expression and activity (Razin, 1998). Modification of the histone proteins that initiate or block gene transcription can occur in tandem with DNA methylation to repress transcription and result in gene silencing (Cedar and Bergman, 2009; Fuks, 2005). Of note, there are several methodological challenges in researching the impacts of ELA and mindfulness on epigenetics. These include evolving technologies on analysis, the rapid responsiveness of some epigenetic changes over a short period of time to environment and lifestyle perturbations, and different patterns of gene regulation in various cell types (Fiori and Turecki, 2016; Kaliman, 2019).

Despite challenges, a growing research has investigated the role of ELA on epigenetics. A recent systematic review has aimed to identify candidate genes and genome-wide DNAm associated with ELA (Parade et al., 2021). Among adult-focused studies, altered levels of DNAm has been observed in response to various forms of ELA (largely retrospectively measured), such as in glucocorticoid receptor (NR3C1) (for the mechanistic role of NR3C1 in ELA and depression predisposition review, see Holmes et al., 2019 for a systematic review), 5HTT (SLC6A4, gene for serotonin transpoter), and FK506 binding protein (FKBP5), although there is considerable variability in findings across studies (Parade et al., 2021). In addition to identifying candidate genes, increasingly, ELA research has attempted to examine patterns of alternations in DNAm. This includes understanding DNAm as a measure of molecular aging as well as exploring epigenome-wide association to explore markers across the entire genome. DNAm patterns are strongly associated with chronological age, and evidence from meta-analysis and systematic reviews support a positive link between ELA (childhood trauma) and accelerated DNAm age ($p = .03$) (Cecil et al., 2020; Wolf et al., 2018). Overall, studies in adult samples suggest epigenetic effects across the genome following ELA, although the specific effects may depend on forms of ELA (Parade et al., 2021). For instance, in a study of prospectively assessed socioeconomic adversity during childhood, mediation analysis supported association between socioeconomic adversity in childhood and body mass index in adulthood for 91 methylation sites in men and 71 sites in women; many of these sites involved genes relevant for development of obesity, including fatty acid synthase, transmembrane protein 88, signal transducer and activator of transcription 3, and neuritin 1 (Loucks et al., 2016). Houtepen et al. (2018) assessed the association between various types of ELA and genome-wide DNAm in two large cohorts from the Avon Longitudinal Study of Parents and Children and the MRC National Survey of Health and Development. Specifically, the study found nine differentially methylated regions (DMRs) in midlife across cohorts associated with cumulative ELA (assessed via ACE score) as well as various parental health related ELA (e.g., parental mental illness, parental death) (Houtepen et al., 2018).

Systematic reviews and meta-analyses consistently find DNAm to be linked to various diseases and disorders among adults, including psychiatric symptoms (e.g., depression, suicidality) (Bakusic et al., 2017; D. Chen et al., 2017; Policicchio et al., 2020), cardiovascular disease (e.g., coronary heart disease, diabetes mellitus, hypertension) (Fernández-Sanlés et al., 2017; Kim et al., 2010; Muka et al., 2016), and neurodegenerative disorders (Lu et al., 2013; Wen et al., 2016). Thus, DNAm may be a key biological mechanism through which ELA is embedded to adversely affect adult health (Silberman et al., 2016; Szyf and Bick, 2013; Vaiserman and Koliada, 2017). In addition, DNAm has also been proposed as a potential epigenetic molecular mechanism underlying the formation of fear conditioning effects in the hippocampus and amygdala in response to ELA (Zovkic and Sweatt, 2013). It should be noted, however, very few studies have tested the potential mediating role of DNAm in ELA and health consequences and findings have been mixed (Bustamante et al., 2018; Misra et al., 2019; Parade et al., 2016; Tobi et al., 2018; Wiegand et al., 2021).

5.4.1. The role of mindfulness in epigenetic mechanisms

Research in the area of epigenetics and mindfulness training is still in its infancy (Kaliman, 2019). A recent review on mindfulness meditation and epigenetics suggest that MBIs could improve age-related health outcomes through downregulating epigenetic pathways (Kaliman, 2019). Regarding prominent DNAm in candidate genes linked to ELA, two recent trials have explored the role of mindfulness in altering the DNAm in these genes. Employing an RCT design, Stoffel et al., 2019 examined the effect of a 3-month MBI among healthy medical students who prepared for a stressful exam and found a significant group X time interaction effect in SCL6A4 DNAm change ($p = .02$), such that the average SCL6A4 DNAm decreased in MBI while change was only marginal in the comparison group. Another trial studied a small sample of veterans with PTSD symptoms ($N = 22$) who participated in an 8-week MBSR program (Bishop et al., 2018). Specifically, Bishop et al. (2018) conducted comparative analysis regarding the DNA methylation levels at CpG sites in regions of the serotonin transporter (SLC6A4), which is linked to depression, and HPA axis-associated FK506 binding protein 5 (FKBP5), between those who responded well to MBSR and those who did not, based on their PTSD symptom reduction. No difference was found in SLC6A4, yet there was a significant decrease in responders and a significant increase in non-responders of MBSR in methylation of FKBP5 Intron 7 (Bishop et al., 2018). As FKBP5 DNAm may play a key role in relation to ELA and the development of PTSD later in life, such that allele-specific demethylation is linked to dysregulation of the stress hormone system (Klengel et al., 2013), it might be a relevant mechanistic pathway through which mindfulness modifies ELA-affected stress regulatory processes. No know MBI research has investigated the role of mindfulness in DNAm in NR3C1. Another pilot trial investigated the impact of an intensive day-long mindfulness training on genome-wide DNAm patterns (Kaliman et al., 2014). Kaliman et al. (2014) found that following 8 h of intensive meditation, compared to naïve participants who engaged in leisure activities in the same environment, experienced meditators had lower levels of histone deacetylase gene expression (HDAC 2, 3, & 9), alterations in global histone modification in PBMCs, and decreased expression of proinflammatory genes (RIPK2 and COX2). Further, the downregulation of HDAC2 and RIPK2 genes predicted a better cortisol recovery after the Trier Social Stress Test (TSST) in the sample (Kaliman et al., 2014). As these genes are linked to depression and inflammatory illnesses (Shakespear et al., 2011; Sun et al., 2013), epigenetics may represent a mechanism through which mindfulness affects these outcomes. As a follow-up analysis, the

methylome of peripheral blood mononuclear cells (PBMCs) was examined in this sample (Chaix et al., 2020). No between-group differences at baseline were found, yet after a day-long mindfulness meditation exposure, meditators displayed 61 differentially methylated regions (DMRs) that are enriched with genes associated with immunity, inflammation, and aging (Chaix et al., 2020). This significantly different methylation profile following mindfulness exposure compared to controls suggests the relevance of methylation changes and a pathway by which mindfulness may assert an impact on immunity and inflammation.

In addition, a few cross-sectional studies have investigated patterns of DNAm among experienced meditators compared to naïve participants (García-Campayo et al., 2018; Mendioroz et al., 2020). Mendioroz et al. (2020) found DMRs in subtelomeric regions, which regulate telomere length, and also reported that telomere length was associated with DNAm levels in long-term meditators involving GPR31 and SERPINB9 genes (Mendioroz et al., 2020). Further, telomere length was not associated with age among meditators, in contrast to the significant inverse relationship between telomere length and age in control conditions (Mendioroz et al., 2020). This suggests that DNAm may be a mechanism linking mindfulness training and telomere maintenance. García--Campayo et al. (2018) found 64 DMRs in long-term meditators compared to controls that corresponded to 43 genes. About a quarter of the mindfulness related DMRs clustered in telomeric chromosomal regions and about half involved genes linked to neurological and psychiatric disorders, cardiovascular illness, and cancer (García-Campayo et al., 2018). These cross-sectional comparison studies provide insight into potential long-term impact of epigenome regulation linked to accelerated aging by mindfulness training.

In summary, limited longitudinal and cross-sectional research provide initial evidence that mindfulness training may be capable of modifying or reversing epigenetic variation in methylation. Given that DNAm is hypothesized as a mechanism of the embedding of ELA leading to various health consequences, mindfulness training might ameliorate these adverse outcomes through altering the DNAm process.

6. Preliminary evidence of mindfulness training for ELA-affected adults

Treatment approaches targeting ELA-affected adults, especially aging populations, are still early in development, including mindfulness-based interventions. Does any evidence exist regarding the effect of mindfulness training on health outcomes for adults affected by ELA? We identified five MBI trials that targeted adults with ELA. Herein, we provide a brief summary of these trials and their findings.

Two single-arm MBSR trials were conducted with adults who experienced childhood trauma and maltreatment (Gallegos et al., 2015; Kimbrough et al., 2010). Gallegos et al. (2015) found that following MBSR, ELA-exposed women in mid-life (75 % witnessed family violence, 56.2 % physical abuse, 43.7 % pre-adolescence sexual abuse, 37.5 % loss of a loved one) had significantly reduced psychological symptoms (depression, anxiety, & PTSD) and emotion dysregulation (Gallegos et al., 2015). In addition, greater session attendance was associated with greater decreases in IL-6 levels (Gallegos et al., 2015). Another single-arm trial with child abuse survivors found large effect sizes (Cohen's *ds* $>$ 1.0) of reduction for all psychological outcomes (depression & PTSD) and mindfulness following MBSR (Kimbrough et al., 2010). Further, a 2.5-year follow-up of participants from this trial was conducted, which found long-term improvements in all outcomes, with moderate to large effect sizes (*ds* ranged from .50 to 1.1) (Earley et al., 2014). In addition, three RCTs have investigated the effect of MBIs for adults with childhood maltreatment (a mix of abuse and neglect) (Caldwell and Shaver, 2015; Joss et al., 2019) and women with a history of early abuse (physical or sexual) (Andersen et al., 2021). In comparison to waitlist controls, participants in MBIs had significant improvements in psychological outcomes (depression, anxiety, stress, rumination), emotion regulation, as well as mindfulness and self-compassion (Andersen et al., 2021; Caldwell and Shaver, 2015; Joss et al., 2019). Further, in an RCT that randomly assigned women with and without early life abuse to MBSR or a social support condition, a three way interaction of Time X Condition X Abuse history was found such that MBSR was associated with reduced cortisol response for women with a history of ELA over time, while social support was associated with reduced cortisol response for those without ELA) (Andersen et al., 2021).

In addition to trials specifically focused on ELA-exposed adults, evidence from other non-ELA focused MBI trials suggest that adults with a history of ELA might be more responsive to mindfulness training than their peers without ELA exposure. Specifically, two RCTs of mindfulness-based cognitive therapy (MBCT) found that mindfulness training reduced the risk of relapse to major depressive disorder (MDD) for adults with a high severity of childhood trauma, in comparison to antidepressant treatment (Kuyken et al., 2015) as well as psychoeducation and treatment-as-usual (Williams et al., 2014). For instance, there was a significant interaction ($p = .03$) between severity of childhood abuse and treatment group, where MBCT reduced the risk for depression relapse compared to maintenance of antidepressant medication in those with high severity of childhood abuse, while there was a slightly higher risk of relapse in those with low severity of childhood abuse (Kuyken et al., 2015). Overall, these preliminary findings suggest that mindfulness training could be effective at improving the psychological outcomes among ELA exposed adults.

7. Limitations, future directions of research, and conclusion

Several limitations of this review should be noted. First, there is significant overlap between ELA and psychiatric disorders, making it difficult to determine whether biological mechanisms in ELA-affected samples are linked to ELA only or confounded by psychopathology. For instance, depression is also linked to reduced grey matter in hippocampus, inflammation, and telomere shortening (Arnone et al., 2013; Osimo et al., 2019; Ridout et al., 2016). Second, in studies that compared long-term practitioners to MBI naïve controls, long-term practitioners may have personality, cognitive, and lifestyle characteristics that led them to be interested in and dedicated to long-term meditation, thereby contributing to selection bias. Third, many mechanisms still need to be linked to outcomes on psychological and behavioral measures to further our understanding on their role in disease processes following ELA. For instance, few research exist to understand the mediating role of these mechanisms (e.g., altered brain network, epigentics) among ELA-exposed adults in age-related health outcomes longitudinally. Fourth, the strength of evidence varies based on the mechanism and relevant research in ELA/mindfulness. In particular, research regarding brain networks involved in self-regulation may be the most advanced (e.g., based on the number of studies and the number of mindfulness-based RCTs included in relevant reviews), whereas studies on epigenetics are relatively new and emerging, particularly concerning the impact of mindfulness training. Fifth, due to the limited scope of this review, we focus on brain and biological mechanisms with strong overlapping evidence and theoretical grounding that go beyond neuroendocrine-related stress physiology. We caution against the view that these four mechanisms reviewed in this paper (brain networks involved in self-regulation, immunity and inflammation, telomere biology, and epigenetic modifications) are the only potential pathways through which ELA and mindfulness both affect adult health. For example, emerging work on reward processing suggests that alterations may explain the link between ELA and addiction in adult health (Duffy et al., 2018) and also function as a potential mechanism through which mindfulness alters addictive behaviors (Garland et al., 2014; Ludwig et al., 2020). Metabolic health, mitochondrial functioning, and gut microbiome are also potential shared pathways that warrant more research in the future (Loucks et al., 2015; O'Mahony

et al., 2017; Pervanidou and Chrousos, 2012; Zitkovsky et al., 2021). Further, various, nuanced cognitive and psychological processes are implicated in the self-regulatory process in the brain networks we reviewed above, such as inhibition, motivation, self-monitoring, memory, and research is needed to understand in greater depth regarding how ELA and mindfulness may affect these processes to impact self-regulation.

At last, although MBI trials focused on ELA-exposed adults support the potential of mindfulness in improving psychological outcomes, only one of them measured a potential mechanism (i.e., inflammation) (Gallegos et al., 2015). For this line of research to fully achieve its potential, more rigorous, theory-driven research is needed. Below, we provide recommendations for directions of future research.

First, although preliminary findings of extant mindfulness trials support the potential of mindfulness for psychological health in ELA exposed adults, more evidence is needed to examine the efficacy and effectiveness of mindfulness for this population. In particular, future trials are encouraged to consider outcomes beyond psychological symptoms, the use of an active control, and longer follow-up assessments.

Second, we encourage future trials in this area to examine proposed mechanisms outlined in this paper. Assessment of mechanisms should consider their fitness to the specific research question and the clinical features of the sample affected by ELA. For instance, use of fMRI may help answer questions regarding brain networks among ELA exposed individuals with psychiatric symptoms, while inflammatory biomarkers could be useful in ELA exposed mid-to-late life adults with or at risk for cardiometabolic diseases.

In a related vein, so far research has primarily concerned one type of mechanisms in study design and there has been emerging evidence on the interdependent nature of mechanisms reviewed above. For instance, a theoretical review poses that chronic inflammation and telomere dysfunction may synergistically drive aging and related diseases (Zhang et al., 2016). We encourage future MBI trials to comprehensively examine the relationships among these mechanisms in driving changes in health outcomes among ELA-affected adults.

Third, to further understand the efficacy and mechanisms of mindfulness for ELA exposed adults on age-related health outcomes, researchers are encouraged to measure characteristics of ELA in their samples. For instance, it is likely that the strengths of mechanistic pathways differ based on ELA type (e.g., neglect and abuse). Given overlap of psychiatric symptoms, which are prevalent in ELA exposed adults, and the proposed mechanisms, researchers should also measure psychiatric symptoms in their sample to clarify the use of mindfulness among symptoms-free individuals and ELA exposed individuals also suffering from psychiatric symptoms.

Fourth, for mindfulness-based intervention trials that focus on adults disproportionately affected by ELA, such as those with psychiatric symptoms, diabetes and hypertension, or communities disproportionately exposed to ELA (e.g., racial minorities, low-income populations), we encourage researchers to adopt a baseline measurement of ELA. This can help us further understand the relevance and utility of mindfulness for subpopulations, as well as whether ELA may serve as an intervention moderator, such that those exposed to ELA may respond to MBI differently (Kuyken et al., 2015).

Fifth, we encourage future research to also identify potential psychological mechanisms through which ELA and mindfulness may impact adult health. This area of work is out of scope for the current paper yet carries utmost significance given the detrimental psychological effects of ELA and the salient psychological component of mindfulness training. Such mechanisms may include emotion dysregulation, cognitive reactivity, attachment, self-esteem, and others (Pechtel and Pizzagalli, 2011; Rincón-Cortés and Sullivan, 2014). Identifying these processes could be key to guide adaptation of MBIs in order to engage and address the needs of ELA-affected adults successfully.

Finally, given the scale and impact of ELA on age-related health outcomes among adults, particularly mid-to-late life adults, future research on adaptation, implementation, and dissemination of mindfulness interventions, if proven to be effective, will also be needed.

In sum, ELA is highly prevalent and its biological embedding has profound consequences on age-related health outcomes. Thus, interventions that are capable of addressing the mechanisms through which ELA generates health risk are crucial to the possibility of remediating ELA-associated adversities and promoting health outcomes for affected adult populations. We note initial promise of mindfulness training in affecting shared pathways impacted by ELA, including brain networks involved in self-regulation, immunity and inflammation, telomere biology, and epigenetic modifications. Preliminary evidence from MBI trials also support the potential utility of mindfulness in improving psychological health of ELA exposed adults. Future research is needed to validate the candidate mechanisms proposed here and the efficacy of mindfulness training for adults affected by ELA. Ultimately, if proven to be effective, a mindfulness-based approach might serve as an important, low-cost, and scalable public health strategy to address multiple health disparities and remediate the psychological and physical health consequences of ELA.

Declaration of Competing Interest

None of the authors have any conflicts of interest to disclose.

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