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Promoting brain health through physical activity among adults exposed to early life adversity: Potential mechanisms and theoretical framework

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Abstract

Adverse childhood experiences such as abuse, neglect, and poverty, profoundly alter neurobehavioral development in a manner that negatively impacts health across the lifespan. Adults who have been exposed to such adversities exhibit premature and more severe age-related declines in brain health. Unfortunately, it remains unclear whether the negative effects of early

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life adversity (ELA) on brain health can be remediated through intervention in adulthood. Physical activity may represent a low-cost behavioral approach to address the long-term consequences of ELA on brain health. However, there has been limited research examining the impact of physical activity on brain health among adults with a history of ELA. Accordingly, the purpose of this review is to (1) review the influence of ELA on brain health in adulthood and (2) highlight evidence for the role of neurotrophic factors, hypothalamic-adrenal-pituitary axis regulation, inflammatory processes, and epigenetic modifications in mediating the effects of both ELA and physical activity on brain health outcomes in adulthood. We then propose a theoretical framework to guide future research in this area.

Keywords

early life adversity; adverse childhood experiences; physical activity; brain health; midlife; aging; reversibility network

Introduction

Early life adversity (ELA) encompasses a range of negative experiences during childhood and adolescence, including poverty, abuse, and parental maladjustment which interfere with neurocognitive and socioemotional development. Unfortunately, ELA is common throughout the world, prevalent in both economically distressed and wealthy countries. It is estimated that 40–60% of individuals are exposed to at least one form of ELA, and a quarter of individuals experience multiple adversities (Felitti et al., 1998; Kessler et al., 2010; Merrick, Ford, Ports, & Guinn, 2018). Notably, marginalized and underserved populations such as racial and ethnic minorities, sexual and gender minorities, and low-income communities are overburdened with early life adversity (Merrick et al., 2018), contributing to health inequities in adulthood.

Exposure to ELA exerts profound and long-lasting effects on health and well-being that persist into late adulthood. Globally, ELA accounts for up to 30% of incident psychiatric disorders in adults (Kessler et al., 2010), and increases risk for the development of numerous chronic health conditions, such as Type II diabetes, obesity, and cardiovascular disease (Friedman, Karlamangla, Gruenewald, Koretz, & Seeman, 2015; Merrick et al., 2019; Su, Jimenez, Roberts, & Loucks, 2015). More recent evidence suggests that ELA also negatively impacts brain health in mid- and late life, accelerating the rate of age-related cognitive decline and heightening susceptibility to neurological illnesses such as Alzheimer's Disease (AD; Short & Baram, 2019). Further, retrospective studies have observed a link between ELA and brain structure and function in adulthood (Botros, Hodgins, & Nemeroff, 2019; Pechtel & Pizzagalli, 2011). These data suggest that the effects of ELA on brain health can be long-lasting and may underlie ELA-related susceptibility to psychological, cardiometabolic, and neurocognitive illness. These issues raise questions regarding whether and to what degree the negative effects of ELA on brain health in adulthood can be mitigated or reversed. In an effort to address such questions, the National Institute on Aging formed the Reversibility Network, an interdisciplinary research network focused on advancing understanding of the mechanisms of ELA-related declines in health in later life to

facilitate the development of behavioral interventions to remediate or reverse these effects. The present review was guided by and written in the service of the goals of the Reversibility Network.

Physical activity may be an effective low-cost and widely accessible behavioral approach to remediate the long-term negative health consequences of exposure to ELA. In addition to the well-documented benefits of physical activity for reducing chronic disease risk (Durstine, Gordon, Wang, & Luo, 2013), there is growing evidence that physical activity promotes improvements in brain health across the lifespan (Erickson et al., 2019; Hillman, Erickson, & Kramer, 2008), including enhanced psychological functioning and cognitive performance as well as alterations in brain structure and function (Erickson et al., 2019). Such benefits have been observed even among adults who have already experienced a decline in brain health due to illness or aging (Chirles et al., 2017; Fong et al., 2012; Lautenschlager et al., 2008; Oberlin et al., 2017; Smith et al., 2014). Further, evidence drawn from an observational study in adolescents has shown that physical activity can buffer against the negative effects of childhood abuse on later internalizing symptoms (Healy et al., 2021). There is also evidence that many of the mechanistic pathways through which ELA negatively impacts brain health are also modulated by engagement in physical activity, which we outline in detail below. Thus, physical activity may enhance and promote brain health in similar areas and potentially through similar but opposing mechanisms to those through which ELA precipitates adverse brain health in adulthood. Accordingly, the purpose of this review is to (1) summarize what is known about the influence of ELA on brain health in adulthood and (2) identify the overlapping pathways whereby physical activity may stimulate improvements in brain health among adults who have been affected by ELA. We will then propose a theoretical framework to guide future research efforts integrating across traditionally separate disciplines such as exercise physiology, developmental psychology, neurology, and health neuroscience. Given that both ELA and physical activity exert widespread and complex effects on most systems of the body, this review is intentionally broad in scope, intended to identify if there is scientific justification for future research examining the efficacy of physical activity interventions for mitigating or reversing the deleterious effects of ELA on adult brain health.

Key definitions

Early life adversity.

Adverse childhood experiences encompass a range of disadvantageous events to which a child must adapt, including psychosocial and material adversities such as parental maladjustment, abuse, neglect, discrimination, and poverty, as well as physical exposures to environmental toxins and malnutrition (for a detailed review of how to define ELA, please see (McLaughlin, 2016). For the purposes of the present review, we focus on psychosocial adversities and have adopted an inclusive definition of ELA that comprises any psychosocial adverse event or experience occurring during childhood that may negatively impact brain health across the lifespan. This includes experiences widely viewed as adverse such as physical or emotional abuse and neglect, as well as other psychosocial adversities such as socioeconomic disadvantage, exposure to domestic or community violence, caregiver

loss, caregiver criminality and/or incarceration, caregiver psychopathology, and bullying. Although exposures occurring during the prenatal period (e.g., maternal stress) have been linked to elevated lifetime risk for chronic health conditions and poor psychosocial functioning (Graignic-Philippe, Dayan, Chokron, Jacquet, & Tordjman, 2014; Tobi et al., 2018), we have limited the current review to postnatal adversities from birth to age 18. We broadly refer to these experiences as “early life adversities” (ELA), though occasionally examine the impact of specific forms of ELA when warranted (e.g., multiple lines of converging evidence to support an impact on brain health).

Brain health.

Similar to our approach to operationalizing ELA, we have also conceptualized brain health broadly to include brain structure and function as well as the cognitive and psychological processes that arise from brain function (e.g., executive functions, mood). This approach is consistent with the definition adopted by the 2018 Physical Activity Guidelines Scientific Advisory Committee. This committee was appointed by the U.S. Department of Health and Human Services to compile scientific evidence supporting beneficial effects of physical activity on the brain in the service of developing public health recommendations for preserving brain health across the lifespan (Erickson et al., 2019; Piercy et al., 2018). Thus, brain health as we have defined it includes normative variation in mood and cognition, as well as clinical syndromes characterized by deficits in these domains (i.e., psychiatric and neurological conditions). We also include in our definition of brain health normative and pathological variation in brain structure and function, as measured predominantly using structural and functional magnetic resonance imaging.

Physical activity.

In keeping with the 2018 Physical Activity Guidelines (Erickson et al., 2019), we have defined physical activity broadly to include any bodily movement that results in energy expenditure, regardless of the form (e.g., aerobic vs. anaerobic vs. strengthening), intensity (i.e., light, moderate, or vigorous intensity), and duration (e.g., acute bursts of activity vs. habitual activity sustained over days, weeks, or months). Where indicated, we have specified the effects of these different parameters of physical activity on brain health, but otherwise refer to physical activity in general terms. Further, although there are numerous studies linking cardiorespiratory fitness with indicators of brain health (Boots et al., 2015; Kramer & Colcombe, 2018; Weinstein et al., 2012) and cardiorespiratory fitness is a proximal outcome of regular physical activity (Lang et al., 2018), we have generally excluded these studies unless there was concomitant measurement of physical activity.

Mechanistic models of early life adversity

There are numerous approaches to conceptualizing the pathways through which ELA impacts health and well-being across the lifespan, each with unique assumptions and methodologies (McLaughlin & Sheridan, 2016). Examples of prevailing theoretical frameworks include cumulative risk, dimensional, and accelerated aging models. Cumulative risk approaches to classifying ELA tally the number of ELA exposures over the course of childhood and adolescence to create a cumulative risk score (Evans, Li, & Whipple,

2013). The cumulative risk framework has been widely used to quantify ELA and determine its neurodevelopmental consequences, emphasizing in particular the influence of ELA on the development of stress response systems. Of note, this approach does not distinguish among subtypes of adverse events, nor does it typically account for duration, severity, or developmental timing of exposure, potentially obscuring important variation in exposure and the impact of that variability on outcomes in adulthood. More recent approaches have developed and expanded upon the cumulative risk method by defining ELA along core dimensions, each of which encompasses numerous experiences that vary in severity (McLaughlin & Sheridan, 2016). An example of a dimensional model includes the dimensional model of adversity & psychopathology (DMAP; McLaughlin & Sheridan, 2016), which distinguishes between experiences that involve threat of harm to a child and those that involve the absence of expected inputs. A second example is the harshness-unpredictability model, which characterizes the degree to which a child's environment does not meet physical and socioemotional needs (e.g., physical abuse, poverty) and/or is frequently changing in a manner that a child cannot predict (e.g., frequent housing relocation, changes in family composition; Ellis, Figueredo, Brumbach, & Schlomer, 2009). Dimensional models highlight additional mechanisms linking ELA to physical and psychological health outcomes beyond stress reactivity and programming, such as learning in the context of developmental plasticity. Thus, dimensional models provide additional avenues through which to develop mechanism-informed treatments aimed at preventing the downstream consequences of adversity. Finally, accelerated aging models focus on the role of ELA in programming premature aging of multiple organ systems (e.g., pulmonary, cardiovascular, renal etc.; (Belsky et al., 2015)) and cellular processes (e.g., advanced deterioration of telomeres and premature increases in DNA methylation; (Ridout et al., 2018; Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2019). According to this framework, ELA prompts accelerated decline of these systems, leading to increased risk for and earlier onset of age-related disease and mortality (Shalev & Belsky, 2016). These accelerated aging models often focus on harshness-unpredictability domains of ELA, but they are not theoretically incompatible with cumulative risk or other dimensional models. Rather, accelerated aging models shift focus from childhood and adolescent outcomes to outcomes in adulthood, with an emphasis on identifying novel mechanisms of aging that may be targeted through behavioral and pharmacological interventions delivered earlier in the lifespan. Each of these frameworks has contributed to furthering scientific understanding of the short and long term sequalae of ELA. Given that research focused on adult outcomes has emerged more recently compared to research focused on the consequences of ELA in childhood and adolescence, these conceptual models have not been as thoroughly examined in the context of adulthood, and few studies in adults specify whether the hypotheses and approach were guided by a particular framework. Nevertheless, we include them here as a means of introducing the prevailing theories regarding the mechanisms through which ELA impacts brain development and brain health and to highlight the complexities inherent to this type of research.

Influence of early life adversities on brain health in adulthood

Early life experiences can influence brain health across the lifespan. Healthy brain development in both animals and humans is shaped by early life experiences (Fox, Levitt, & Iii, 2010; Knudsen, 2004; McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). For example, responsive and dependable caregivers and environmental predictability foster a trajectory of normal brain development. In contrast, adverse childhood experiences such as neglect, abuse, or extreme poverty can interrupt normal brain development and set an individual up for a trajectory of aberrant brain, behavioral, and emotional development across the lifespan. Given the ethical challenges with manipulating ELA in humans, nearly all experimental work focused on ELA and brain health has been conducted using animal models. These models provide convincing evidence that exposure to ELA during sensitive periods disrupt typical brain development (Danese & McEwen, 2012; Bruce S. McEwen, 2003; Short & Baram, 2019) and these findings are supported by the small number of experimental studies in humans (e.g., Bick et al., 2015; Nelson et al., 2007). Although the human literature is limited predominantly to correlational and prospective studies, mounting evidence from these studies corroborates many of the patterns observed in experimental animal models. Below we highlight the most salient patterns that have emerged in this area and summarize these effects in Figure 1.

Psychological outcomes.

ELA has been associated with impaired psychological functioning in adulthood. Adults who have been exposed to ELA are more likely to be diagnosed with a psychiatric illness (Heinonen, Knekt, Härkänen, Virtala, & Lindfors, 2018), including major depressive disorder (Merrick et al., 2019; Nanni, Uher, & Danese, 2012), anxiety disorders (Jonker, Rosmalen, & Schoevers, 2017), bipolar disorder (Bruni et al., 2018; Shapero et al., 2017), and substance use disorders (LeTendre & Reed, 2017), among others (Bruni et al., 2018; Fuller-Thomson & Lewis, 2015; Hock et al., 2018; McLaughlin et al., 2017). There is also evidence that women exposed to ELA are at elevated risk for peripartum depression, anxiety, and substance use (Currie, Sanders, Swanepoel, & Davies, 2020; Gonzalez, Jenkins, Steiner, & Fleming, 2009; Heldreth et al., 2016; Jonas et al., 2013; Racine, Zumwalt, McDonald, Tough, & Madigan, 2020; Young-Wolff et al., 2018). Of note, direct and indirect experience of racism during childhood has been shown to predict more severe depressive symptoms during the postpartum period among Black and African American mothers (Heldreth et al., 2016), highlighting the importance of examining this specific form of adversity when evaluating adult health outcomes. Further, ELA is related to earlier onset and more severe course of illness (Heinonen et al., 2018), particularly among adults who experienced abuse or neglect (Carbone et al., 2019; Fuller-Thomson & Lewis, 2015). ELA also prospectively predicts higher likelihood of attempting suicide in adulthood (Wanner, Vitaro, Tremblay, & Turecki, 2012), thus contributing to psychiatric mortality. Unfortunately, a history of ELA reduces the efficacy of behavioral and psychopharmacological treatments for psychiatric illness (Nanni et al., 2012), prolonging suffering and potentially increasing susceptibility for other psychiatric and medical comorbidities. Moreover, exposure to ELA may lower the threshold of severity at which a stressful life experience in adulthood precipitates onset or recurrence of clinically elevated psychiatric symptoms (Shapero et al., 2017).

ELA has also been associated with a reduced capacity to regulate negative emotions as evidenced by observations that individuals with a history of ELA tend to rely on ineffective emotion regulation strategies such as suppression and rumination (Cameron, Carroll, & Hamilton, 2018; Hong et al., 2018). Insufficient emotion regulation skills may therefore be a key pathway by which ELA heightens vulnerability to psychological distress and psychiatric illness in adulthood. Finally, ELA may have a lasting impact on interpersonal functioning in adulthood. Childhood physical and emotional abuse has been related to reduced emotional closeness with family members in mid- and late-adulthood, an effect that persisted when controlling for concurrent depressive symptomatology (Savla et al., 2013). Thus, the psychological consequences of ELA are pervasive, impacting numerous facets of socioemotional functioning in adulthood.

Cognitive outcomes.

A growing body of evidence suggests that ELA disrupts cognitive processes that are critical for the maintenance of health and well-being across the lifespan (Short & Baram, 2019). Research has demonstrated that ELA confers substantial risk for the development of cognitive impairment and neurological illnesses such as AD in late life, many decades after exposure (for review, see (Danese & McEwen, 2012). Socioeconomic disadvantage in childhood has been one of the most widely studied forms of ELA with regard to the potential impact on cognitive outcomes in adulthood, perhaps due in part to the well-established relationship between educational attainment and cognitive decline in late life (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014; Stern et al., 1994). Low socioeconomic status in childhood, as typically indexed by parental education and income, has been associated with worse memory performance among older adults, even among those characterized as having high income at the time of assessment (Marden, Tchetgen Tchetgen, Kawachi, & Glymour, 2017). Further, childhood socioeconomic disadvantage may impact the trajectory of cognitive aging by accelerating the rate of age-related cognitive decline (Melrose et al., 2015). Similar patterns have been observed among adults who have experienced more severe forms of ELA such as neglect and maltreatment (Geoffroy, Pinto Pereira, Li, & Power, 2016).

Executive functions such as cognitive flexibility, inhibitory control, working memory, and planning are particularly affected by ELA, and have been consistently shown to be disrupted among adults with a history of ELA (Almanza- Sepulveda et al., 2018; Butler, Klaus, Edwards, & Pennington, 2017; Lovallo et al., 2013). ELA may also increase the likelihood and severity of executive dysfunction that may arise as a consequence of some medical conditions (Hawkins et al., 2020; Shanmugan et al., 2017, 2020), which may lead to poorer prognosis and lowered quality of life. Research on the effect of ELA on other cognitive domains is more limited, though some studies have documented lower performance on tests of visuospatial ability, episodic memory, language, and processing speed among adults who have been exposed to ELA (Beck et al., 2018; Duval et al., 2017; Greenfield & Moorman, 2019).

Of note, psychiatric illnesses that may emerge as a result of ELA such as major depressive disorder (MDD) have been shown to increase vulnerability to cognitive decline and

dementias (Byers & Yaffe, 2011), indicating that the effect of ELA on cognitive health in adulthood is complex. Importantly, animal models examining the impact of ELA on cognitive functioning across the lifespan have yielded similar patterns (for a review, see (Lesuis et al., 2018), lending support for a causal link between ELA exposure and subsequent cognitive impairment.

Brain structure and function.

The majority of studies focusing on ELA-related disruption of brain circuitry have focused on neurodevelopment in childhood and adolescence, with there being comparatively fewer studies in adults. Nevertheless, just as exposure to ELA has enduring effects on cognitive and psychological functioning, emerging research has documented brain abnormalities among adults with a history of ELA. The hippocampus appears to be particularly susceptible to the effects of ELA. For instance, exposure to adversity in childhood has been associated with reduced hippocampal volume in adulthood (Dannlowski et al., 2012; Frodl et al., 2012; Gorka, Hanson, Radtke, & Hariri, 2014; Teicher, Anderson, & Polcari, 2012; though see Khoury, Pechtel, Andersen, Teicher, & Lyons-Ruth, 2019 & Mikolas et al., 2019 for reports of opposing patterns), with this effect being most pronounced in the glucocorticoid-sensitive CA3 and dentate gyrus subfields (e.g., (Frodl et al., 2012; Teicher et al., 2012). Further, smaller hippocampal volumes prospectively predicted heightened symptoms of anxiety following the experience of a stressful life event among adults with a history of childhood maltreatment (Gorka et al., 2014), suggesting that differences in hippocampal structure may be one pathway through which ELA exposure increases psychological vulnerability in adulthood.

ELA exposure has also been linked to volume reductions in other prefrontal and subcortical regions that support cognitive and psychological processes known to be disrupted by ELA, including the orbitofrontal cortex (OFC), medial prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, amygdala, and caudate nucleus (Brooks et al., 2016; Dannlowski et al., 2012; Gorka et al., 2014; Holz et al., 2015; Underwood et al., 2019), with these effects being detectable many decades after the experience of ELA (Gheorghe, Li, Gallacher, & Bauermeister, 2020). White matter integrity has also been shown to be disrupted among adults exposed to ELA. For example, young adults with a parent diagnosed with a substance use disorder during their childhood were shown to exhibit reduced white matter integrity in frontocortical, frontostriatal, and frontoparietal tracts (Acheson et al., 2014). Another study demonstrated that white matter integrity of the uncinated fasciculus, a major tract connecting the amygdala to the ventromedial PFC, was lower in young adults exposed to maltreatment in childhood compared to those without maltreatment histories (Hanson, Knodt, Brigidi, & Hariri, 2015). Further, lower white matter integrity at baseline predicted elevated internalizing symptoms following subsequent exposure to a stressful life event. Unfortunately, changes in brain structure that arise in response to more severe forms of ELA such as deprivation and institutionalization may persist even when life circumstances in adulthood are otherwise salubrious (Mackes et al., 2020). This indicates that some ELA-related decrements in brain health may be more difficult to remediate and the efficacy of interventions applied in adulthood may be moderated by the severity of ELA, a hypothesis that warrants further testing.

In addition, early life adversity is associated with alterations in the function of brain regions embedded in functional networks that orchestrate cognitive and psychological processes impacted by ELA (for a detailed review please see (Herzberg & Gunnar, 2020). Several studies have demonstrated that ELA is associated with reduced resting state connectivity within the default mode network (DMN) (Elton et al., 2014; Sripada, Swain, Evans, Welsh, & Liberzon, 2014; L. Wang et al., 2014; Zeev-Wolf, Levy, Goldstein, Zagoory-Sharon, & Feldman, 2019). The DMN is a robust functional network comprised of regions in medial PFC (mPFC), temporal (e.g., hippocampus), and posterior cingulate cortices that supports internally-guided and self-referential cognitive processes (Buckner & DiNicola, 2019; Greicius, Krasnow, Reiss, & Menon, 2003), and has been shown to be disrupted in many conditions linked to ELA, including MDD (Greicius et al., 2007), substance use disorder (R. Zhang & Volkow, 2019), obesity (Donofry, Jakicic, et al., 2020; Tregellas et al., 2011), and AD (Greicius, Srivastava, Reiss, & Menon, 2004; Koch et al., 2012). Exposure to childhood trauma predicts reduced connectivity between the hippocampus, dorsomedial and dorsolateral PFC in veterans with symptoms of combat-related post-traumatic stress (Birn, Roeber, & Pollak, 2017). Further, among adults with a documented history of childhood poverty, lower resting connectivity between the hippocampus and posterior cingulate cortex was related to higher basal cortisol levels (Sripada et al., 2014). Several DMN hubs, including the mPFC and hippocampus, densely express glucocorticoid receptors (McEwen, De Kloet, & Rostene, 1986), and may therefore be more robustly dysregulated by exposure to ELA, particularly threat-related adversities. These findings suggest that alterations within the DMN may be one pathway through which ELA influences health and well-being in mid- and late life.

Altered patterns of task-evoked activation have also been noted among adults with a history of ELA. For instance, among adults diagnosed with MDD or an anxiety disorder, those with a history of ELA demonstrated exaggerated activation in corticolimbic regions such as the ACC, superior frontal gyrus, and parahippocampal gyrus in response to facial expressions of fear and anger (Herringa, Phillips, Fournier, Kronhaus, & Germain, 2013; Peters, Burkhouse, Kinney, & Phan, 2019). Interestingly, these patterns of activation mediated the relationship between childhood adversity and tendency to engage in rumination (Peters et al., 2019), a perseverative self-focused cognitive style that impedes the use of effective problem-solving skills (Bernstein, Heeren, & McNally, 2017). Further, one study found that the relationship between childhood socioeconomic disadvantage and amygdala reactivity to threatening facial expressions persisted even when controlling for other contemporaneous factors known to influence amygdala functioning, including adult socioeconomic status, symptoms of depression and anxiety, as well as dispositional emotionality (Gianaros et al., 2008). Similarly, ELA exposure has been linked to increased reward-related activation in the ventral striatum, putamen and ACC (Boecker et al., 2014; Boecker-Schlier et al., 2016; DelDonno et al., 2019), as well as heightened functional connectivity between reward-sensitive regions (e.g., ventral striatum, mPFC) during a monetary reward task (Hanson, Knodt, Brigidi, & Hariri, 2018). Further, ventral striatal – dorsal medial PFC connectivity evoked by reward feedback was strongest among those reporting both ELA and recent life stress, and partially accounted for the relationship between ELA and symptoms of depression and anxiety (Hanson et al., 2018), indicating that cumulative life stress may

potentiate psychopathology in adulthood by modulating reward neurocircuitry. However, other studies have observed ELA-related blunting of activation in reward-sensitive regions in both childhood (Birn et al., 2017; Mullins, Campbell, & Hogeveen, 2020) and adulthood (Gianaros et al., 2011; Hanson et al., 2016), highlighting the complexity and heterogeneity of the neurobiological effects of ELA.

In contrast to reports of increased activation and connectivity evoked by psychological stressors and reward stimuli among adults with a history of ELA, cognitive tasks (e.g., Stroop task, Go/No-Go task) evoke less activation in cognitive, emotion, and visceral control regions such as the dorsolateral PFC (dlPFC), ACC, amygdala, and hypothalamus in ELA-exposed individuals (Banihashemi, Sheu, Midei, & Gianaros, 2015; Harms et al., 2017). Notably, reduced activation of these regions was associated with slowed task response times (Harms et al., 2017) and more substantial task-induced increases in heart rate (Banihashemi et al., 2015). These findings suggest that ELA may contribute to less successful recruitment of prefrontal and subcortical regions in the face of increased cognitive demands, which may contribute to ELA-related susceptibility to poor psychological, cognitive and cardiovascular outcomes.

It is important to note that many of the psychiatric and physical health conditions that have been linked with exposure to ELA have also been shown to exert deleterious effects on the structure and function of the brain, making it difficult to disentangle the extent to which the relationship between ELA and brain outcomes are mediated by, independent of, or amplified by the effects of these conditions on the brain. Additional research is needed to clarify how ELA interacts with psychiatric and physical health conditions in adulthood to affect brain aging trajectories.

Influence of physical activity on brain health in adulthood

Physical activity improves many of the aforementioned negative outcomes known to be precipitated by ELA. This suggests that physical activity interventions may represent a promising approach for mitigating or reversing the negative consequences of ELA on brain health. In the following sections, we summarize the effects of physical activity on brain health with a particular focus on how physical activity may influence outcomes associated with ELA.

Psychological outcomes.

Evidence from prospective longitudinal studies suggest that engaging in regular physical activity reduces the likelihood of developing a psychiatric illness (Schuch et al., 2018; Suetani et al., 2017), and improves quality of life and psychiatric symptoms in adults with a diagnosable psychiatric illness (Cooney et al., 2013; Rosenbaum, Tiedemann, Sherrington, Curtis, & Ward, 2014). There is also encouraging preliminary evidence that physical activity interventions are effective in the treatment of MDD, with some studies suggesting that physical activity yields symptom improvement comparable to that of treatment as usual (e.g., pharmacotherapy or psychotherapy; (Bailey, Hetrick, Rosenbaum, Purcell, & Parker, 2018; Davis, Goodman, Leiferman, Taylor, & Dimidjian, 2015; Nyström, Neely, Hassmén, & Carlbring, 2015). Therapeutic effects of physical activity have also been found

in non-clinical populations (Conn, 2010; Rebar et al., 2015). For instance, a meta-meta-analysis aggregating data from randomized controlled trials (RCTs) of physical activity in community adults observed significant reductions in symptoms of depression and anxiety, with the benefits being most robust for depressive symptoms (Rebar et al., 2015). Physical activity also acutely induces transient elevations in mood (Bernstein & McNally, 2017; Tartar, Salzmann, Pierreulus, & Antonio, 2018; Zschucke, Renneberg, Dimeo, Wüstenberg, & Ströhle, 2015), an effect that emerges even with brief bouts of exercise (e.g., 10 minutes; (Crush, Frith, & Loprinzi, 2018). Higher levels of self-reported habitual physical activity have also been associated with lower perceived stress and less aberrant eating in a cross-sectional community sample of pregnant women with overweight and obesity (Donofry, Germeroth, Kolko Conlon, Venditti, & Levine, 2020), a population at elevated risk for adverse obstetric and maternal health outcomes. Further, among older adults reporting high levels of perceived stress, physical activity engagement has been prospectively associated with reduced ratings of perceived stress and to protect against the development of stress-related physical health symptoms such as chest pain, joint pain, or shortness of breath (Rueggeberg, Wrosch, & Miller, 2012). Together, these studies demonstrate the potential for physical activity interventions to facilitate improvements in psychological health and well-being in both clinical and community samples.

Cognitive outcomes.

Physical activity also has well-documented benefits for cognitive health across the lifespan, demonstrating efficacy for maintenance of cognitive functions as well as for partial remediation of declines in cognitive functioning with illness or aging (Erickson et al., 2019; Groot et al., 2016; Najar et al., 2019; Oberlin et al., 2017); though see (Brasure et al., 2017; Sabia et al., 2017; Sink et al., 2015) for contradictory patterns. For instance, findings from a meta-analysis of nine prospective studies examining the association between physical activity and risk for AD demonstrated that older adults who engaged in regular physical activity were significantly less likely to develop AD compared to their less active counterparts (Beckett, Ardern, & Rotondi, 2015). Physical activity also exerts beneficial effects on cognition among individuals who have already begun to experience cognitive decline. A meta-analysis of 18 RCTs of physical activity conducted in adults with dementia found that physical activity improved cognitive functioning regardless of the type (aerobic vs. non-aerobic) and frequency of exercise, and the effects did not differ based on dementia type (AD vs. other dementias; (Groot et al., 2016)). In addition to these broad effects on cognition and cognitive decline, there are several sub-domains of cognition that appear to be particularly sensitive to the effects of physical activity. Among older adults, physical activity is most strongly associated with improvements in attention, memory and executive control processes such as working memory, planning, and multi-tasking (Erickson et al., 2019). Findings from several large epidemiological cohort studies of older adults indicate that more frequent engagement in physical activity, particularly of moderate-to-vigorous intensity (MVPA; e.g., brisk walking, jogging), is associated with better performance on tests of delayed memory and verbal fluency (Daly, McMinn, & Allan, 2015; Zhu et al., 2015). Similar effects have been observed in RCTs of physical activity (Erickson et al., 2011; Groot et al., 2016; Nagamatsu, 2012; Nagamatsu et al., 2013), further strengthening support for implementing physical activity interventions to improve trajectories of cognitive

aging. Of note, light intensity activities such as slow paced walking and other such leisure time activities (e.g., light cleaning, gardening) may not promote significant improvements in cognitive performance (Zhu et al., 2015), suggesting that quantity as well as intensity of physical activity behaviors may moderate their impact on cognitive functioning (Lambourne & Tomporowski, 2010; McMorris & Hale, 2012). However, research examining how the dose of physical activity (as measured via quantity and/or intensity) influences cognitive outcomes is relatively limited (Erickson et al., 2019). In addition, comparatively fewer studies have examined the impact of physical activity on cognitive functioning in young and midlife adults, highlighting an important area for future research. Despite these limitations, there is moderate to strong evidence that physical activity enhances cognitive performance and prevents or slows age-related cognitive decline among older adults (Erickson et al., 2019).

Brain structure and function.

In addition to the benefits of physical activity for mood and cognitive functioning, emerging research suggests that physical activity modifies the structure and function of the brain. In particular, physical activity appears to have the most robust effects on prefrontal, parietal and temporal regions that support the same cognitive and psychological processes known to be impaired by ELA. Just as the hippocampus is particularly sensitive to the effects of ELA, the hippocampus appears to be one of the most consistently reported regions affected by physical activity. Numerous studies have demonstrated that aerobic exercise promotes increases in hippocampal volume in children (Migueles et al., 2020) and adults (Erickson, Leckie, & Weinstein, 2014; Erickson et al., 2011; Firth et al., 2018) and may slow the trajectory of hippocampal volume loss that typically occurs with aging (Erickson et al., 2011; Firth et al., 2018). Furthermore, these effects may emerge relatively rapidly, with one study documenting increases in hippocampal volume and axonal myelination within six weeks of adopting a routine exercise program among midlife adults (Thomas et al., 2016). Importantly, exercise-induced increases in hippocampal volumes have been linked to improvements in cognition. Older adults randomized to 12 months of brisk walking exhibited a two percent increase in hippocampal volume, with increased volume predicting intervention-related improvement in spatial working memory (Erickson et al., 2011). This suggests that the effects of physical activity on brain volume translate to meaningful benefits to other indices of brain health that have a direct impact on quality of life. Physical activity is also associated with the volume of prefrontal cortical regions that support executive processes and typically shrink with advancing age. For instance, MVPA has been positively correlated with dlPFC volume in older adults (Northey et al., 2020). Further, a longitudinal investigation of the effects of regular physical activity found that individuals who were more active in midlife exhibited higher total prefrontal grey matter volume in late life relative to their sedentary counterparts (Rovio et al., 2010). In addition to these effects on regional grey matter volume, physical activity has also been prospectively associated with reduced deposition of beta-amyloid (Aβ), a hallmark of AD pathophysiology that develops prior to the onset of cognitive symptoms, among cognitively healthy older adults (Rabin et al., 2019; Stillman et al., 2017). Moreover, physical activity moderated the association between Aβ accumulation, cognition and brain volume, with more active individuals exhibiting less pronounced declines in both cognitive function and grey matter volume (Rabin et al., 2019).

These studies provide evidence that physical activity is protective against age-related volume loss and development of neuropathology characteristic of AD.

Physical activity has also been associated with variation in the function of regions embedded in networks known to be disrupted by ELA (Stillman, Donofry, & Erickson, 2019). Higher levels of physical activity have been positively correlated with DMN connectivity in observational (Boraxbekk, Salami, Wåhlin, & Nyberg, 2016; Santaella et al., 2019) and intervention studies (Voss et al., 2010), a pattern which opposes that documented among ELA-exposed adults (e.g., (Sripada et al., 2014). Further, findings from a recent meta-analysis of 20 exercise RCTs conducted in adults provide converging evidence that exercise is associated with increased activation of regions in the DMN, such as the precuneus and medial temporal lobe (including hippocampus), as well as regions in the executive control network (ECN), including the inferior and superior parietal cortex during cognitively demanding tasks (Yu et al., 2020). Moreover, physical activity was related to increased functional connectivity between sub-regions of the ECN (Yu et al., 2020). Of note, this meta-analysis was limited to studies documenting an association between intervention-related changes in brain activation patterns and changes in cognitive functioning. Thus, these findings provide further evidence that physical activity-induced changes in brain structure and function translate into meaningful improvements in cognitive functioning. Interestingly, a single session of MVPA has been shown to preserve inhibitory control (as measured via performance on the Stroop task) following experimental disruption of dlPFC activity via continuous theta burst stimulation (Lowe, Staines, & Hall, 2017). This neuroprotective effect of exercise on inhibitory control was not observed after engagement in light intensity activities (Lowe et al., 2017), consistent with other data suggesting that higher intensity physical activity may be necessary for cognitive benefits to emerge (Lambourne & Tomporowski, 2010; McMorris & Hale, 2012). Together, these studies demonstrate that physical activity promotes neuroplasticity into late adulthood and potentially in the presence of neurodegenerative disease. In light of this evidence, physical activity represents a promising behavioral approach for remediating the deleterious effects of ELA on brain health in adulthood.

Overlapping mechanistic pathways through which physical activity might buffer the negative consequences of early life adversity on adult brain health

Given that ELA and physical activity both prompt widespread changes in numerous and overlapping biological systems of the body, physical activity may exert opposing effects on many of the mechanistic pathways through which ELA influences adult brain health. Here, we provide an overview of the literature examining four mechanistic pathways with some of the strongest evidence linked to both ELA and physical activity. These include: (1) neurotrophic factors, (2) HPA axis regulation, (3) inflammatory processes, and (4) epigenetic modifications. Figure 2 illustrates these pathways and provides a framework for understanding how physical activity may mitigate the negative consequences of ELA on brain health in adulthood. This model is intended to serve as a guide for future research efforts examining the efficacy of physical activity among adults exposed to ELA.

Neurotrophic factors.

Neurotrophic factors are endogenous peptides that support the survival and growth of developing and mature neurons. They are critically involved in the regulation of experience-dependent brain plasticity. The neurotrophin class of neurotrophic factors have been the most thoroughly investigated for their role in neuronal and synaptic remodeling, particularly brain-derived neurotrophic factor (BDNF), which is abundantly expressed throughout the brain (Thoenen, 1995). Animal models of ELA have shown that exposure to adversities modulates BDNF expression in regions that support learning, memory, cognitive control and emotion regulation, including PFC, hippocampus, and amygdala, and ELA-related disruption of BDNF signaling pathways has been linked to abnormal brain development (Bondar & Merkulova, 2016; Miskolczi, Halász, & Mikics, 2019). Although human studies have not yet supported a causal link between ELA, BDNF signaling, and brain health, evidence suggests that individuals who are genetically predisposed to reductions in the expression of BDNF are also more vulnerable to the harmful effects of ELA on brain health (Carballedo et al., 2013; Casey et al., 2009; Elzinga et al., 2011).

In contrast, physical activity has been shown to enhance BDNF expression and signaling in both animal and human studies. For instance, experimental studies conducted in rodents have shown that aerobic exercise increases BDNF levels in the striatum (Marais, Stein, & Daniels, 2009), hippocampus (Vaynman, Ying, & Gomez- Pinilla, 2004; Wrann et al., 2013), and PFC (D.-C. Wang et al., 2020). Moreover, the neuroprotective effects of aerobic exercise in animal models of Parkinson's Disease and AD are dependent in part on increased production of BDNF (Real et al., 2013; Xiong et al., 2015), with blockade of BDNF receptors attenuating exercise-induced improvements in brain health (Real et al., 2013; Vaynman et al., 2004). Observational studies in humans have demonstrated that both acute and habitual aerobic exercise are associated with increases in peripheral BDNF levels (Dinoff et al., 2016; Szuhany, Bugatti, & Otto, 2015). Further, higher concentrations of peripheral BDNF following participation in an exercise intervention mediated intervention-related improvements in executive functioning (Leckie et al., 2014) and memory (Whiteman et al., 2014). Exercise-induced increases in serum BDNF levels have also been correlated with increased hippocampal volume (Erickson et al., 2011) and functional connectivity (Voss et al., 2013) following an exercise intervention, providing additional support for the hypothesis that exercise promotes brain health through modulation of BDNF signaling pathways. As such, it is possible that engaging in physical activity may mitigate the effects of ELA on brain health by promoting BDNF expression.

HPA axis regulation.

The HPA axis is the principle neuroendocrine system responsible for orchestrating physiological responses to physical or psychological challenges, with these responses being mediated by the systemic release of the glucocorticoid hormone cortisol from the adrenal cortex (Spencer & Deak, 2017). Prolonged exposure to events that stimulate HPA axis reactivity, such as is the case with ELA, disrupts homeostatic regulation of this system, thus reducing the capacity of the body to adequately respond to new or worsening challenges (Jankord & Herman, 2008). Indeed, ELA disrupts the development of the HPA axis by programming the system to respond sub-optimally to environmental demands (McLaughlin

et al., 2015; van Bodegom, Homberg, & Henckens, 2017). The impact of ELA on HPA axis regulation is complex and may vary across developmental periods or based on the type, timing, and severity of ELA exposure, as well as according to whether studies are examining basal or stressor-evoked HPA axis activation (Bunea, Szentágotai-Tătar, & Miu, 2017; van Bodegom et al., 2017). Accordingly, some studies have observed hyper-reactivity of the HPA axis among adults exposed to ELA (Butler et al., 2017; Friedman et al., 2015), while others have observed blunting of HPA axis activation (Bunea et al., 2017; Karlamangla et al., 2019; Kuras et al., 2017; Lovallo et al., 2013). Nevertheless, there is general scientific consensus that childhood adversity is associated with altered HPA functioning in adulthood. Of note, the pro-inflammatory state provoked by ELA has been implicated in abnormal development of the HPA axis (Nusslock & Miller, 2016), suggesting that dysregulation of one biological system following exposure to ELA may potentiate dysregulation in other systems involved in maintaining brain health. Further, disruption of the HPA axis has also been associated with increased risk for psychiatric and medical conditions that are prevalent among adults with a history of ELA, including MDD (Belvederi Murri et al., 2014), Type II diabetes (Joseph & Golden, 2017), cardiovascular disease (Jokinen & Nordström, 2009), and AD (Popp et al., 2015). Moreover, several brain regions involved in cognitive and emotional processing, most notably the hippocampus, densely express glucocorticoid receptors and are therefore sensitive to maladaptation in the HPA system (Gianaros et al., 2007; Meijer, Buurstede, & Schaaf, 2019; Seo, Rabinowitz, Douglas, & Sinha, 2019). Thus, dysregulation of the HPA axis following exposure to ELA is likely a mechanism underlying heightened vulnerability to stress-related psychopathology and chronic disease.

Physical activity behaviors are energetically demanding and therefore require robust neuroendocrine adaptations in order to mobilize resources and maintain physiological homeostasis. As such, it is perhaps unsurprising that physical activity evokes acute changes in HPA axis activation that mirror those observed in the context of psychosocial stress. However, according to the cross-stressor adaptation hypothesis (Sothmann et al., 1996), habitual engagement in physical activity may facilitate homeostatic regulation of the HPA system and mitigate disruption of HPA axis functioning prompted by chronic exposure to psychosocial stressors, including ELA (Zschucke et al., 2015). Individuals who engage in regular physical activity exhibit attenuated cortisol responses to laboratory-based mental stress tasks (Gerber et al., 2017; Rimmele et al., 2009; Strahler, Fuchs, Nater, & Klaperski, 2016; Wood, Clow, Hucklebridge, Law, & Smyth, 2017; Wunsch et al., 2019), including those reporting elevated negative affect (Pauly et al., 2019; Puterman et al., 2011). Although there have been relatively few RCTs of physical activity to examine change in HPA axis regulation as an outcome of intervention, there is some preliminary data to suggest that habitual physical activity alters HPA axis functioning (Drogos et al., 2019; Klaperski, von Dawans, Heinrichs, & Fuchs, 2014; Saxton et al., 2014), converging with evidence from the aforementioned cross-sectional studies. Interestingly, regular engagement in mind-body interventions that combine elements of mindfulness and physical movement practices such as tai-chi and yoga have also been shown to reduce basal cortisol output (Campo et al., 2015; Gothe, Keswani, & McAuley, 2016; Sarubin et al., 2014). For instance, older adults randomized to an eight-week hatha yoga program exhibited reduced cortisol levels following the intervention, an effect that was not observed in a stretching control group

(Gothe et al., 2016). Further, reductions in cortisol were associated with intervention-related improvements in executive functioning (Gothe et al., 2016). Together, these data suggest that physical activity may promote brain health by improving HPA axis regulation, which may help to remediate the enduring physiological impacts of childhood adversity.

Inflammatory processes.

Dysregulation of the immune system is one pathway through which ELA may become biologically embedded and influence brain health across the lifespan (Muscatell, Brosso, & Humphreys, 2020; Nusslock & Miller, 2016). Exposure to ELA has been associated with chronic elevation in circulating pro-inflammatory molecules such as C-reactive protein (CRP) and cytokines such as interleukin-6 (IL-6) and tumor necrosis factor – alpha (TNF-α), with this pro-inflammatory state persisting into adulthood (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016). For instance, a small (N = 69) study in which participants were exposed to an acute stressor found evidence that adults with a self-reported history of childhood maltreatment exhibited greater acute IL-6 release following stressor exposure, as well as higher sustained IL-6 concentrations, compared to individuals without a history of maltreatment (Carpenter et al., 2010). Interestingly, all participants were free of psychiatric diagnoses such as major depression or post-traumatic stress disorder, suggesting that group differences in IL-6 concentrations were not attributable to a higher prevalence of these conditions in adults with a history of maltreatment. Data drawn from the MIDUS and 1958 British cohorts (N = 8,916) similarly found that exposure to ELA, particularly physical abuse, was associated with elevations of basal CRP and fibrinogen, a glycoprotein that facilitates blood clotting (Pinto Pereira, Stein Merkin, Seeman, & Power, 2019). These associations were attenuated when accounting for adult adiposity, indicating that obesity may partially mediate the relationship between ELA and adult inflammation (Pinto Pereira et al., 2019). Of note, Black race has been shown to prospectively predict higher levels of circulating CRP and hypertension in adulthood independently of other factors such as family and neighborhood poverty measured in childhood (Nikulina & Widom, 2014). These startling findings suggest that race and racism are independently related to poor health in adulthood above and beyond childhood socioeconomic indicators known to robustly predict poor health outcomes. Importantly, prolonged dysregulation of the immune system such as that observed among individuals with a history of ELA may in turn increase vulnerability for numerous psychiatric and medical conditions in adulthood, including MDD (Stewart, Rand, Muldoon, & Kamarck, 2009; Zalli, Jovanova, Hoogendijk, Tiemeier, & Carvalho, 2016), cardiovascular disease (Packard et al., 2011; Ruparelia, Chai, Fisher, & Choudhury, 2017; Stewart et al., 2009), and mild cognitive impairment and dementia (Darweesh et al., 2018; Ozawa, Shipley, Kivimaki, Singh-Manoux, & Brunner, 2017). Further, elevations in circulating IL-6 have been shown to mediate the relationship between childhood adversity and functional connectivity between regions in the corticolimbic circuit that support affect regulation (Kraynak, Marsland, Hanson, & Gianaros, 2019). Thus, ELA may contribute to poor brain health in adulthood by provoking chronic pro-inflammatory processes, potentially initiating or exacerbating a cascade of negative physical and psychological health outcomes.

Habitual physical activity, conversely, has been associated with improved inflammatory profiles. Large observational studies have demonstrated that both self-reported (Mayat,

Giardina, Liao, & Aggarwal, 2020; Papenberg et al., 2016; Vella et al., 2017) and objectively measured physical activity (Draganidis et al., 2018; Nilsson, Bergens, & Kadi, 2018) are negatively correlated with circulating levels of pro-inflammatory markers such as IL-6 and CRP, even after adjusting for factors such as central adiposity known to promote inflammation (Hamer et al., 2012; Vella et al., 2017). Interestingly, data from a large epidemiological study found evidence that the frequency (i.e., number of days per week) of objectively measured MVPA was a stronger predictor of circulating CRP than was total volume (i.e., minutes per week) among adults (Loprinzi, 2015), suggesting that consistent engagement in MVPA may be necessary to elicit anti-inflammatory effects. However, because few studies have compared the impact of various parameters of physical activity on such outcomes, additional research is needed to strengthen this hypothesis. Prospective cohort studies have similarly found that higher habitual physical activity at baseline, particularly MVPA, predicts lower concentrations of IL-6 and CRP up to 10 years later (Braskie et al., 2014; Fuentes et al., 2020; Hamer et al., 2012; Martinez-Gomez et al., 2019; Menezes et al., 2019). Data from randomized controlled trials (RCT) of physical activity lasting between four and 78 weeks also indicate that structured physical activity programs reduce inflammation among healthy adults as well as in adults with chronic medical conditions (Freitas et al., 2017; Lin et al., 2015; Tartibian, FitzGerald, Azadpour, & Maleki, 2015; Tomeleri et al., 2016), providing more definitive evidence that physical activity improves immune system functioning. Interestingly, the pro-inflammatory effects of cancer treatments such as chemotherapy and radiation therapy may be mitigated by physical activity. Several intervention trials conducted among women with breast cancer found that women randomized to a physical activity program did not exhibit elevations in circulating inflammatory markers that typically occur following cancer treatment, while women in the control groups demonstrated the expected post-treatment spike in cytokine concentrations (Hagstrom et al., 2016; Mustian et al., 2015; Schmidt et al., 2016). Together, these studies suggest that physical activity reduces inflammation and may therefore be an effective approach to restoring immune system functioning following exposure to ELA.

Epigenetic modifications.

Gene expression is regulated not only by transcription and translation of DNA, but also through experience-dependent modification of the structure of chromatin, which determines the degree to which a transcription site is exposed and available to initiate gene transcription (Jaenisch & Bird, 2003). DNA Methylation, the process through which methyl groups are added to the cytosine nucleotide, is the most common epigenetic mechanism through which environmental exposures alter the expression potential of genes (Jaenisch & Bird, 2003). An emerging body of research suggests that ELA induces widespread epigenetic modifications that may underlie many of the observed physiological, behavioral, and neural abnormalities in adulthood that have been linked to ELA (Vaiserman & Koliada, 2017). A study of post-mortem brain tissue among individuals who completed suicide identified 362 promotor regions at which the degree of methylation differed between those with and without a history of ELA, with many of the affected genes being involved in neural development and plasticity (Labonté et al., 2012). Famine exposure in infancy has been associated with hypermethylation of genes that regulate energy and lipid metabolism in adulthood, and the degree of methylation in these genes mediated the relationship between

famine exposure and adult body composition and circulating triglyceride levels (Tobi et al., 2018), suggesting that the impact of ELA on gene expression patterns is enduring and may influence key indicators of health in adulthood. Longitudinal analyses in the New England Family Study showed evidence that several methylation sites in adipose tissue mediated the relation between childhood socioeconomic adversity and adulthood adiposity, including many sites that are biologically relevant for the development of obesity, such as fatty acid synthase, transmembrane protein 88, and neuritin 1 (Loucks et al., 2016). Of particular relevance to brain health, methylation of the BDNF gene has been shown to be elevated in adults reporting ELA (J. A. Smith et al., 2017; Unternaehrer et al., 2015), which may reduce neural plasticity in adulthood and contribute to premature declines in brain health.

Other studies have demonstrated that genes involved in HPA axis and immune system regulation are particularly sensitive to ELA. For instance, childhood adversity has been associated with hypermethylation of the gene encoding the glucocorticoid receptor, NR3C1 (Farrell et al., 2018; Tyrka, Price, Marsit, Walters, & Carpenter, 2012) and the FKBP5 gene, which encodes a protein that modulates the sensitivity of the glucocorticoid receptor (Harms et al., 2017; Klengel et al., 2013). Further, FKBP5 hypermethylation negatively correlated with dorsolateral PFC activation during the performance of a Go/No-go task among adults with a history of ELA (Harms et al., 2017), providing preliminary evidence that epigenetic modifications affecting HPA axis regulation may disrupt neurocognitive functioning. Methylation of immune-regulating genes has also been associated with ELA, with one study demonstrating that neighborhood disadvantage in childhood related to hypermethylation of seven genes involved in inflammatory processes (J. A. Smith et al., 2017). In addition, methylation of a IL-6 promotor region has been shown to be reduced among individuals exposed to neighborhood violence and other more severe forms of childhood trauma, and predicted elevated levels of circulating IL-6 evoked by a psychosocial stressor (Janusek, Tell, Gaylord-Harden, & Mathews, 2017). Thus, exposure to childhood adversity may become biologically embedded through epigenetic modifications to genes that regulate processes integral to neurodevelopment and the maintenance of brain health across the lifespan. Given that research examining the impact of ELA on DNA methylation in humans has only emerged relatively recently, there is a need for additional well-designed studies linking ELA-related epigenetic modifications to brain health outcomes in adulthood.

Physical activity is similarly associated with widespread epigenetic modifications that may underlie its observed benefits for health and well-being. Overall, DNA methylation across the genome is positively correlated with the extent of routine physical activity engagement, though the consequences of physical activity-related methylation patterns are varied and dependent upon the molecular pathways affected by changes in gene expression (Boyne et al., 2018; F. F. Zhang et al., 2011). For instance, habitually engaging in physical activity of any intensity has been associated with higher methylation of the apoptosis associated speck-like protein containing a caspase recruitment domain (ASC) gene, which encodes a protein involved in cellular apoptosis and stimulation of IL-1β cytokine release (Nakajima et al., 2010; Nishida et al., 2019). Further, observational evidence suggests that ASC methylation is positively correlated with aerobic fitness capacity and mediates the effect of cardiorespiratory fitness on reductions in IL-1β levels (Butts, Butler, Dunbar, Corwin, & Gary, 2017), indicating that increased ASC methylation due to routine physical activity

may promote a more favorable immune profile. Engaging in three months of physical activity has also been related to increased methylation of genes that encode proteins that regulate endothelial function and vasoconstriction, including Endothelin-1 and Nitrous Oxide Synthase-2, with increased methylation of these genes predicting improvements in blood pressure (Ferrari et al., 2019). In contrast, data from an RCT of aerobic exercise among women with breast cancer demonstrated that physical activity reduced methylation of a tumor suppressor gene, L3MBTL1, thus increasing expression of a protein that mitigated tumor progression (Zeng et al., 2012). Importantly, physical activity-induced reductions in L3MBTL1 methylation predicted lower rates of breast cancer recurrence and mortality (Zeng et al., 2012). These findings indicate that physical activity influences health through epigenetic modifications of many of the same molecular pathways impacted by ELA.

Summary and future directions

Early life adversity exerts broad, profound and enduring effects on brain health in adulthood. Evidence suggests that physical activity interventions also affect multiple indices of brain health and modify the molecular pathways through which ELA impacts brain health, including neurotrophic factors, HPA axis regulation, inflammatory processes, and epigenetic mechanisms. However, although physical activity interventions show promise as a low-cost behavioral approach to enhancing brain health, it remains unclear whether the benefits of physical activity extend to individuals who have been exposed to ELA. There are a number of important areas for future investigation that will serve to establish the efficacy of physical activity for remediating the deleterious effects of ELA on brain health. As an initial step toward this aim, it will be necessary to conduct observational studies exploring whether ELA moderates the relationship between physical activity and brain health outcomes in adulthood, both cross-sectionally and longitudinally. It will also be critical to conduct rigorous RCTs of physical activity to examine whether ELA impacts the efficacy of physical activity interventions, and if so, the mechanisms underlying ELA-related differences in outcomes. For instance, adverse childhood experiences increase vulnerability to adversities in adulthood, including lower socioeconomic status and higher risk of work disability (Halonen et al., 2017; Montez & Hayward, 2014). The socioeconomic and socioemotional consequences of ELA are significant barriers to participation in research, particularly time intensive clinical trials of physical activity that may require numerous in-person visits each week over the course of several months. Therefore, to better serve this population, the format in which physical activity is delivered may need to be adapted to accommodate the challenges associated with ELA. Modifications to the type (e.g., aerobic versus resistance), intensity, format (e.g., in-person versus virtual), and duration of physical activity interventions should be explored, followed by comparative investigation of the effectiveness of tailored versus standardized interventions. This should include exploration of the impact of physical activities not typically well-represented in RCTs, including dance, yoga, martial arts, and structured sports programs. Relatedly, it is likely that the type, timing, and severity of ELA will impact intervention outcomes. Thus, careful and thorough evaluation of ELA histories will be crucial for establishing whether individual differences in ELA exposure profiles moderate intervention effects. Given the aforementioned issues that remain regarding how to best operationalize ELA and its neurodevelopmental consequences,

it will be important for research in this area to be guided by a sound theoretical framework with explicit disclosure of the assumptions and limitations of the chosen framework.

Additional research is also needed to determine whether the proposed mechanistic pathways through which physical activity may promote brain health are indeed related to intervention outcomes among adults exposed to ELA, and to compare the extent to which each pathway mediates intervention effects. It is also possible that certain brain health outcomes are more responsive to intervention than others, highlighting the need for studies that measure multiple indices of brain health to evaluate whether there is specificity of the effects of physical activity. It will also be important to compare the effects of physical activity among adults exposed to ELA to outcomes observed in existing psychotherapeutic approaches to treat trauma, such as trauma-focused Cognitive Behavioral Therapy, Prolonged Exposure Therapy, or Cognitive Processing Therapy. Finally, given evidence that early intervention typically produces more robust and durable improvements (Karoly, Kilburn, & Cannon, 2005), it will be important to examine whether the age at the time of the intervention delivery moderates the efficacy of physical activity for remediating the negative health consequences of ELA. It is clear that physical activity is effective for enhancing brain health in late adulthood, even among individuals who have begun to experience neurocognitive decline (Chirles et al., 2017; Hillman et al., 2008; Oberlin et al., 2017). However, it may be the case that older age in combination with a history of ELA limits the impact of physical activity on indicators of brain health. Alternatively, should physical activity prove to be effective in this population, it would suggest that there is not a “point of no return” beyond which the negative consequences of ELA become irreversible.

Finally, there is a critical need for research exploring the impact of racism and other forms of discrimination on brain health in adulthood, and to determine whether and how physical activity may mitigate these effects. It is clear that there are marked racial disparities in the prevalence of age-related cognitive impairment and neurocognitive illnesses such as AD, with Black and African American individuals being at two to three times higher risk for such outcomes compared to White individuals (Lee et al., 2012; Mehta & Yeo, 2017; Weuve et al., 2018). These disparities are driven in part by the fact that psychiatric and cardiometabolic risk factors for cognitive decline and dementia are more prevalent in minority communities (Eack & Newhill, 2012; McGuire & Miranda, 2008; Topel et al., 2018; Wassink, Perreira, & Harris, 2017). However, given that minority communities are also disproportionately burdened by ELA of all forms (Merrick et al., 2018), exposure to ELA is likely to account for some proportion of racial health disparities. Further, minority communities experience the additional burden of racism, a form of adversity known to uniquely impact adult health outcomes (Nikulina & Widom, 2014). This has prompted calls to expand theoretical models of ELA to include racism as an independent form of ELA to promote research aimed at better understanding the influence of racism-related experiences on health and well-being across the lifespan (Bernard et al., 2020). Yet, there is a relative paucity of research to specifically explore the contribution of racism experienced during childhood and adolescence to the emergence of racial disparities in brain health in mid- and late life. The impact of racism on physical activity engagement and on the efficacy of physical activity interventions for improving aspects of brain health is also understudied.

These represent critical scientific gaps that must be addressed in order to narrow racial disparities in brain health.

To conclude, physical activity represents a promising, low-cost and readily disseminated approach to mitigating or remediating the negative consequences of ELA on brain health in adulthood. However, given the lack of studies exploring the efficacy of physical activity for improving brain health outcomes specifically among adults affected by ELA, additional research is needed to evaluate the hypotheses put forth in this review. Pursuit of the research aims outlined above will establish whether physical activity modifies the processes that underlie the long-term consequences of ELA on brain health, which has the potential to benefit the millions of adults globally who have been exposed to ELA.

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Highlights

- Early life adversity (ELA) exerts profound effects on brain health across the lifespan
- Physical activity is a low-cost and effective approach to improving brain health
- ELA and physical activity influence overlapping mechanistic pathways
- Physical activity may remediate the effects of ELA by modulating these pathways

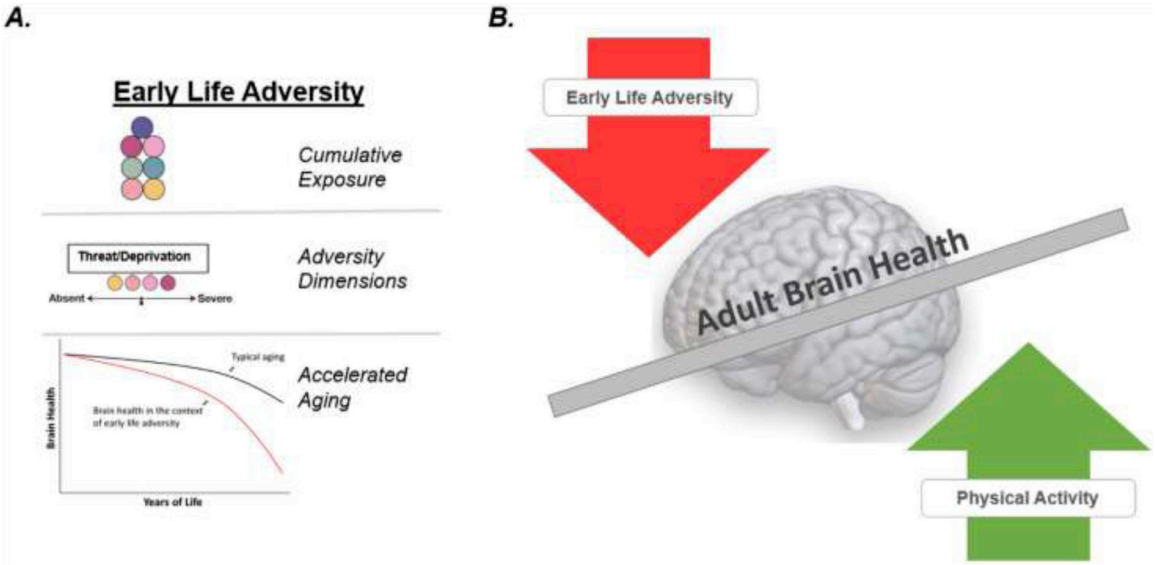

Figure 1.

(A) Theoretical models of the impact of early life adversity on brain health in adulthood. (B) Influence of early life adversity and physical activity on adult brain health.

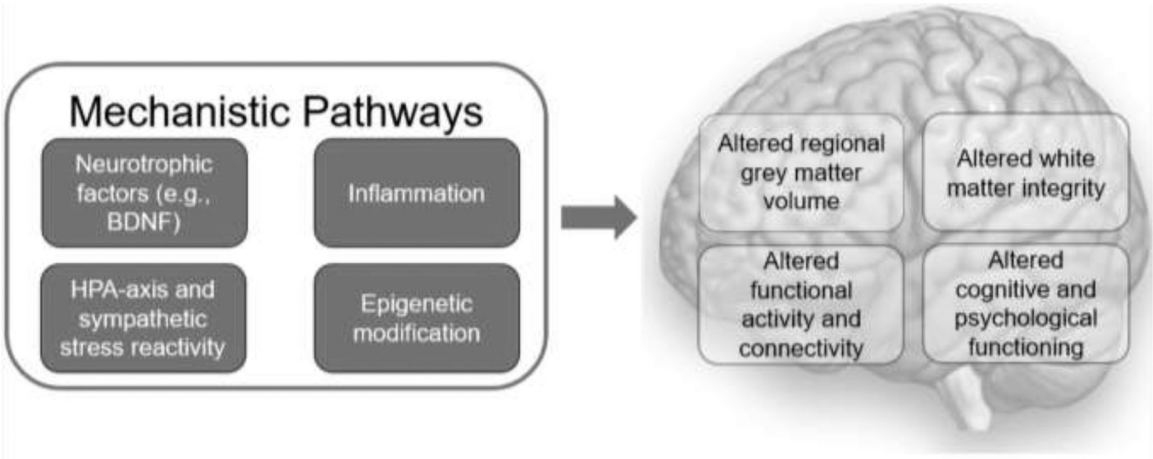

Figure 2.

Theoretical model representing the mechanistic pathways and brain health outcomes associated with early life adversity that are also modified by physical activity. *Note.* BDNF = brain-derived neurotrophic factor; HPA = hypothalamic-pituitary-adrenal.