ASSOCIATIONS BETWEEN RETROSPECTIVE REPORTS OF ADVERSE CHILDHOOD EXPERIENCES, SYSTEMIC INFLAMMATION, AND RESTING BRAIN CONNECTIVITY IN MIDLIFE ADULTS

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Adverse childhood experiences (ACEs) confer risk for negative mental and physical health outcomes across the life course. ACEs may confer this risk by affecting the functional connectivity of corticolimbic brain circuits implicated in threat processing, emotion regulation, contextual memory, and peripheral physiological regulation. Critically, the biological pathways that link ACEs to the brain are not well understood. The present study addresses this knowledge gap by considering mediators of systemic inflammation, in particular the proinflammatory cytokine interleukin(IL)-6, which may be increased following ACEs and may also influence corticolimbic brain circuits. In accordance with prior theoretical accounts, it was hypothesized that circulating IL-6 would statistically link retrospective reports of ACEs to corticolimbic connectivity in adulthood. Participants were 303 healthy midlife adults who retrospectively reported ACEs, underwent a blood draw to assess circulating IL-6, and underwent resting-state fMRI. Hierarchical linear regression analyses controlling for age, sex, race, BMI, and participant motion tested whether retrospectively reported ACEs predicts circulating IL-6 and resting corticolimbic connectivity, as well as whether circulating IL-6 predicts resting corticolimbic connectivity. Ancillary analyses tested whether corticolimbic connectivity associated with subclinical depressive symptoms, as well as whether ACEs moderated any brain-inflammation associations. Retrospective reports of physical abuse associated with IL-6 (β(SE) = 0.14(0.05), p

= 0.009), but not with corticolimbic connectivity (p = 0.165). IL-6 associated negatively with connectivity in a corticolimbic circuit comprising the amygdala, hippocampus, ventromedial prefrontal cortex, and subgenual anterior cingulate cortex (β(SE) = -0.17(0.06) p = 0.006). Subclinical depressive symptoms were unrelated to corticolimbic connectivity (p > 0.75) and ACEs did not moderate any brain-inflammation associations (p > 0.29). These findings agree with studies linking ACEs to systemic inflammation and systemic inflammation to adult functional connectivity, yet they diverge from those linking ACEs and adult functional connectivity. Collectively, these results do not fully support theoretical accounts linking ACEs to adult corticolimbic connectivity via systemic inflammation.

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INTRODUCTION

1.1 ADVERSE CHILDHOOD EXPERIENCES: EPIDEMIOLOGY, MEASUREMENT, AND UNDERLYING DIMENSIONS

Adverse childhood experiences (ACE) span a range of circumstances occurring during childhood and adolescence, including socioeconomic disadvantage, familial violence, parental loss, dysfunction, abuse, or neglect, environmental or national disasters, and acute traumas. These experiences are not uncommon. For example, in a nationally representative sample of midlife adults, over half endorsed experiencing one or more of these forms of adversity (Green et al., 2010). Moreover, at least 10% reported growing up during economic adversity, and 8% reported being physically abused by caregivers. While these experiences may have different psychological effects during childhood, a body of epidemiological research indicates that they further relate to negative mental health outcomes across the entire life course.

The most extensively documented mental health consequences of ACEs are increased risks for developing mood disorders, including depression, anxiety, and posttraumatic stress disorder (PTSD). As examples, the number of adverse experiences in childhood associates with a greater lifetime risk of developing depression in adulthood (Kessler & Magee, 1993), and retrospective reports of childhood abuse predict the onset of PTSD in individuals who are re-exposed to trauma in adulthood (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993).

Importantly, many associations that are reported between ACEs and adult health outcomes are statistically independent of more recently experienced stress in adulthood. Collectively, this suggests that ACEs might influence mental health outcomes many decades later.

In studies that examine associations between ACEs and adult health outcomes, childhood experiences are often measured with one of two methodologies. Each of these methodologies provides distinct advantages and disadvantages, all of which may affect the interpretations of any observed associations with health outcomes. The first of these methodologies uses prospective observations and reports of experiences and circumstances that are collected during longitudinal studies. These are typically derived from caregiver reports or custodial agencies, and are considered to be a gold standard in the field. The primary advantage of prospectively collected measures is that, of the two methodologies, they are thought to be less sensitive to reporting biases, because reports are usually provided by third-party (independent) observers. However, because of the significant social stigma that surrounds these experiences (e.g., parental abuse), there is a risk for potential underreporting by caregivers or under-detection by reporting agencies (Hardt & Rutter, 2004; Teicher, Samson, Anderson, & Ohashi, 2016). Moreover, Teicher et al. (2016) argue that by implementing regular screenings for childhood maltreatment and establishing procedures for responding to documented circumstances, these longitudinal studies ostensibly provide an intervention to what should otherwise be an observational study. Put differently, caregivers who participate in these studies may change their behavior in response to being monitored for activities such as parental abuse, in turn limiting the generalizability of findings.

The second methodology uses retrospective reports of childhood experiences, which are collected later in life, most commonly coinciding with collection of relevant health outcome

measures. These recollections are recorded via either self-report questionnaires [e.g., the Childhood Trauma Questionnaire (Bernstein et al., 1994)] or structured interviews [e.g., the Family History Screen (Milne et al., 2009)]. This methodology has the advantage of being significantly less costly and time consuming than methodologies of longitudinal designs. However, there are several disadvantages with this methodology, many of which involve reporting biases. Specifically, adults may be unable to remember past events at all or with certainty, particularly if they are traumatizing or stressful in nature (Pope & Hudson, 1995). Similarly, adults might suppress or minimize the severity of traumatizing experiences; indeed, studies that directly compare retrospective and prospective reports show that when using retrospective methodologies, participants tend to report lower incidence and reduced severity of ACEs (Shaffer, Huston, & Egeland, 2008). Therefore, these biases might increase false negatives in retrospective reports of ACEs (Usher & Neisser, 1993) and lower statistical power in studies that use them. Conversely, there is a possibility that personality or affective factors such as negative affectivity or neuroticism may negatively "color" a participant's subjective assessment of past childhood experiences, in turn increasing false positive rates in these reports. Furthermore, if these psychological factors are related to a health outcome under study (e.g., negative affectivity and depression diagnosis), there is a risk that recall biases related to personality factors could actually confound the relationship between ACEs and the health outcome (Watson & Pennebaker, 1989). However, the significance of these potential biases and confounds have been questioned (Brewin, Andrews, & Gotlib, 1993). A recent empirical comparison of prospective and retrospective reports (Reuben et al., 2016) found that the two methodologies provided moderately correlated responses ($r = 0.47$), yet differed in how they predicted physical and mental health outcomes. Retrospective reports more strongly associated

with mental illness diagnoses, subjective physical, and cognitive health; conversely, prospective reports more strongly associated with objective markers of physical health. Taken together, while it is not entirely clear which methodology is superior, both retrospective and prospective forms of measurement appear to capture the incidence of ACEs, albeit with varying levels of accuracy and with possible differential associations with health outcomes.

Broadly, different adversities are similar insofar as they occur over acute or chronic periods of perceived or real stress during development. However, it is not clear how different forms of ACEs may uniquely or commonly relate to later health outcomes. As an example, although growing up in poverty and experiencing chronic physical abuse both fall under the domain of ACEs, it is not clear whether the risk conferred by these different adversities would be similar or different for different later life health outcomes. And, it is often difficult to dissociate their associations or examine their synergistic or additive associations with later life health outcomes when they occur together. To address some of these issues, researchers have used various approaches to characterize the severity and dimensions of these experiences, three of which will be briefly reviewed.

First, a conventional approach used to summarize the gradation of childhood adversity, while maintaining the individual contributions of different forms of adversity, is to count the number of types of adversities that exceed a cutoff criterion of 'significance.' This approach is based on a 'cumulative risk model', and relationships tested between this additive metric and health risks hence test for a 'dose-response' relationship between adversity – broadly conceptualized – and health. Numerous population-based studies have shown that this additive metric of adversity significantly predicts mental health outcomes above-and-beyond individual types of adversity (Edwards, Holden, Felitti, & Anda, 2003; Green et al., 2010). However, an

assumption behind this metric is that different types of adversity affect health to an equivalent degree; moreover, the choices made in identifying different types of adversity and their threshold criteria for 'significance' are not standardized. The latter poses problematic issues for replication efforts.

Two other approaches each recognize that certain types of ACEs are more likely to be co-reported than others, in turn forming clusters of features that may reflect meaningful dimensions of adversity. One example of this approach groups together adversities that reflect aspects of the family environment; examples here include parental psychopathology, discord, and neglect (Repetti, Taylor, & Seeman, 2002). A more recent perspective separates types of adversity into dimensions of *deprivation* and *threat*. Experiences of *deprivation* would include institutionalization, neglect, socioeconomic disadvantage, and other conditions of environmental impoverishment. Experiences of *threat* would include events that involve actual or threatened death, serious injury, sexual violation, or other harm to one's physical integrity (McLaughlin, Sheridan, & Lambert, 2014). Critically, this latter approach is principally derived from neurobiological models of early life adversity and later health, providing a basis for testable hypotheses regarding the potential mechanistic pathways linking diverse forms of adversity and later life neural processes linked to mental and physical health. More specifically, McLaughlin, Sheridan, & Lambert argue that deprivation may affect sensory cortex development, as well as result in poorer performance on complex cognitive tasks and poorer social cognition. Separately, pathways that are hypothesized to relate to threat include changes in brain circuits that are implicated in emotion and threat processing (Sheridan & McLaughlin, 2014). Regarding the latter pathways, because many of the neurobiological pathways that align with the *threat* dimension also overlap considerably with brain circuits that are implicated in the

pathophysiology of affective disorders, the present study focused on the *threat* dimension as described by McLaughlin, Sheridan, & Lambert. The rationale for this focus is described next.

1.2 NEUROBIOLOGICAL PATHWAYS LINKING ACES TO MENTAL HEALTH RISK: FOCUS ON THE CORTICOLIMBIC CIRCUIT

As discussed previously, studies have extensively characterized the presence and strength of associations between ACEs and adult mental health outcomes. However, the *biological pathways* that link these experiences to later outcomes are less clear. Understanding the nature of these pathways is a critical step to developing interventions that can reduce poor health outcomes in affected individuals. Emerging animal and human models study how various forms of adverse experiences affect brain structure and function. This is because brain characteristics that associate with adverse experiences might serve as markers of risk for later mental health outcomes. Indeed, there is a diversity of alterations in brain structure and function that occur following ACEs (for review, see Teicher et al., 2016). Of these neurobiological effects, perhaps the most frequently observed alterations encompass those within a so-called *corticolimbic circuit*, which is the focus of the present investigation.

The corticolimbic circuit is thought to comprise a set of limbic structures, specifically the amygdala and hippocampus, along with prefrontal cortical regions, specifically the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC). Interactions between these networked brain systems are implicated in numerous psychological and physiological processes, including emotion (M. L. Phillips, Drevets, Rauch, & Lane, 2003), decision-making (Bechara, Damasio, Damasio, & Lee, 1999), and peripheral physiological

regulation (Beissner, Meissner, Bär, & Napadow, 2013). Relevant to ACEs and affective disorders, however, are functions that involve detecting and maintaining vigilance to environmental threats, regulating emotions, and encoding contextual memories. The amygdala supports detecting and assigning salience to cues in the environment (Davis & Whalen, 2001). These environmental cues engage the amygdala via input from lower level sensory systems (e.g., visual cortex) where they are rapidly evaluated in terms of their relevance and importance to the individual. In particular, threatening and fearful stimuli are quickly registered by the amygdala, which results in elevated attention to the stimulus as well as neuroendocrine and somatic signals associated with fear (LeDoux, 2003). In the context of adversity, adaptive amygdala responsivity may be critical for identifying potential sources of threat in the child's environment. Following exposure to the threatening stimulus, amygdala reactivity is quickly downregulated by PFC subregions via dense inhibitory connections (Amaral & Price, 1984). By downregulating amygdala reactivity in response to threat and negative affect, the PFC is thought to mediate aspects of emotion regulation (Ochsner & Gross, 2005). While both the amygdala and hippocampus are implicated in fear conditioning, the amygdala is more strongly involved in automatic information processing, while the hippocampus supports adaptive and contextual encoding of the stimulus (R. G. Phillips & LeDoux, 1992). More specifically, with respect to ACEs, the hippocampus supports the pairing of a stimulus with the broader context of its perception, and registers this pairing with previously remembered contexts. This is particularly relevant to ACEs because it supports learning systematic patterns about the external environment (Shohamy & Turk-Browne, 2013). In addition to downregulating amygdala responsivity, the PFC components of this circuit presumably support the psychological appraisal of threatening stimuli and their contexts (M. Roy, Shohamy, & Wager, 2012). Collectively, by identifying and

evaluating environmental cues that may signal threat or harm to the individual, the amygdala, hippocampus, and PFC form a network of brain regions that appear to be crucial to ensuring survival in the face of adversity.

Rodent studies using experimental models of early life stress, an animal model homologue of ACEs, demonstrate effects on morphology and synaptic plasticity in the hippocampus and amygdala (Derks, Krugers, Hoogenraad, Joëls, & Sarabdjitsingh, 2016). These models also demonstrate reductions in dendritic spine expression and long term potentiation in parvalbumin-containing inhibitory neurons in the mPFC (Chocyk et al., 2013; Holland, Ganguly, Potter, Chartoff, & Brenhouse, 2014; Radley et al., 2008). Human neuroimaging studies also show that ACEs associate with alterations in the corticolimbic circuit, and these associations span multiple developmental periods across the life course. Specifically, reports of childhood adversity relate to the volume of limbic structures (i.e., amygdala and hippocampus) in children, (Tottenham et al., 2010), adolescents (Edmiston et al., 2011), and adults (Evans et al., 2016; Gorka, Hanson, Radtke, & Hariri, 2014; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). Moreover, these associations are documented across a diversity of samples: childhood maltreatment associates with limbic alterations in healthy adults (Dannlowski et al., 2012; Teicher, Anderson, & Polcari, 2012), as well as adults with depression (Opel et al., 2014; Vythilingam et al., 2002), and borderline personality disorder (Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003). Similar associations have been observed for cortical structures, including the mPFC (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Hanson et al., 2012) and the ACC (R. A. Cohen et al., 2006; Jensen et al., 2015). In many of these studies, childhood adversity associated with *reductions* in limbic and cortical morphology, however it should be noted that some studies observed opposite effects [e.g., (Tottenham et al., 2010)]. Despite this

heterogeneity, the overall consistency of most findings across age groups and samples raises the possibility that alterations in the corticolimbic circuit may be a potential correlate of ACEs that may bias individuals towards vulnerability for mood disorders, due to its role in emotion processing and regulation .

Parallel to structural neural findings are those that identify ACE-related alterations in corticolimbic *function*. Studies in this area often use functional magnetic resonance imaging (fMRI) to examine changes in the blood-oxygen-level-dependent (BOLD) signal in response to threatening or emotional stimuli. Several studies report associations of childhood maltreatment with increased amygdala reactivity to fearful or angry faces in samples of children (McCrory et al., 2011, 2013) and adults (Dannlowski et al., 2012). These effects are similarly observed in samples of adults with mood disorders (Grant, Cannistraci, Hollon, Gore, & Shelton, 2011). In contrast to findings of increased limbic activity, ACEs also associate with *decreased* mPFC activity. For instance, early life adversity associated with a loss of sustained vmPFC activity over the course of an emotional word encoding task (Wang, Paul, Stanton, Greeson, & Smoski, 2013).

As mentioned previously, a key putative function of the corticolimbic circuit is the regulation of amygdala activity by the prefrontal cortex. Characterizing interactions across multiple brain regions, such as regulation of one brain region by another, requires conceptualizing them as a network. In this conceptual framework, the presence and strength of relationships between brain regions in a network are characterized using functional connectivity (Friston, 1994). Broadly, functional connectivity is indexed by the temporal covariation of activity across two brain regions. For instance, changes in connectivity between the mPFC and amygdala are thought to reflect changes in mPFC activity that 'downregulate' changes in amygdala activity (S. J. Banks, Eddy, Angstadt, Nathan, & Phan, 2007). Alternatively, changes

in connectivity may index relationships that are more complicated than unidirectional 'downregulation'; because of the bidirectional connections between the mPFC and amygdala, functional connectivity could relate to bidirectional regulation between the mPFC and amygdala, as well as dynamic interactions that involve unmeasured brain regions (Pessoa, 2017). Hence, methods to determine the exact causal nature of inter-regional relationships from fMRI data are not fully developed and remain an open area of work. Nonetheless, patterns of connectivity in the corticolimbic circuit are widely documented both while performing a task [e.g., responding to threat, (Gold, Morey, & McCarthy, 2015)] and in the absence of a task [i.e., resting state, (A. K. Roy et al., 2009)]. Alterations in corticolimbic functional connectivity, in particular reduced connectivity between the amygdala and PFC subregions, have been observed in depression (Anand et al., 2005; Tang et al., 2013), anxiety (Kim, Gee, Loucks, Davis, & Whalen, 2011), and PTSD (Stevens et al., 2013), and are thought to reflect deficits in emotion processing and regulation that are commonly reported in these disorders (H. Lee, Heller, van Reekum, Nelson, & Davidson, 2012). Taken together, interactions across distinct brain regions in the corticolimbic circuit as indexed by functional connectivity are increasingly considered as a phenotype for affective dysfunction.

Some emerging evidence suggests that connectivity in the corticolimbic circuit may be sensitive to the effects of ACEs. In healthy adult males, reports of childhood emotional abuse associated with reduced connectivity between the amygdala and ACC following a psychological stress task (Fan et al., 2014). Similarly, in a large sample of adults with and without depression, early life trauma, but not depression, associated with reduced connectivity between the mPFC and amygdala in response to emotional faces (Grant et al., 2014). Similar findings have been reported from experiments that did not utilize an overt task: in a sample of military veterans with

a range of PTSD severity, retrospective reports of childhood maltreatment associated with reduced mPFC connectivity with both the amygdala and hippocampus at rest (Birn, Patriat, Phillips, Germain, & Herringa, 2014). However, these connectivity findings have not been entirely consistent; trend-level *increases* in adversity-related amygdala-mPFC connectivity have been observed (Philip et al., 2013), in addition to null effects of adversity (van der Werff et al., 2013).

1.3 BIOLOGICAL PATHWAYS LINKING ACES TO THE BRAIN: FOCUS ON INFLAMMATION

The evidence presented thus far suggests that ACEs may alter the structure, function, and connectivity in a brain circuit that is implicated in threat processing, emotion regulation, and contextual memory, and may moreover relate to risk for affective disorders. However, the biological pathways and mediators that could link early adverse experiences to these changes are not fully understood. One candidate biological pathway is *inflammation*, a complex innate immunologic response to infectious agents or tissue injury. The inflammatory response is primarily initiated by activation of macrophages and the production and release of cell-signaling proteins called pro-inflammatory cytokines that serve a broad array of functions throughout the body. In addition to mediating local inflammatory responses, cytokines enter the bloodstream and facilitate the production and release of acute phase proteins, such as C-reactive protein (CRP), by the liver. Inflammatory responses are critical to effectively mounting an immune defense to pathogens and infections. Upon clearing the pathogen, levels of inflammation typically decrease. However, sustained and chronically elevated levels of inflammation in the absence of disease can be maladaptive and confer risk for myriad chronic diseases (Nathan &

Ding, 2010).

A growing literature illustrates that ACEs consistently relate to alterations in inflammatory physiology, and such alterations have been interpreted within the context of a "biological embedding model" of early adversity (G. E. Miller, Chen, & Parker, 2011). This model posits that early adversity sensitizes peripheral immune cells to promote inflammation, eventually leading to a "pro-inflammatory phenotype". This phenotype is characterized by increased circulating markers of inflammation, such as interleukin-6 (IL-6) and CRP, and larger inflammatory responses to pathogens or injury. Supporting this model are animal studies showing, for example, that rats undergoing a postnatal maternal separation protocol during infancy had increased plasma levels of pro-inflammatory cytokines, in particular IL-6, later in adulthood (Wieck, Andersen, & Brenhouse, 2013). Separately, mice experiencing maternal separation during two weeks of life exhibit increased inflammatory responses when subjected to the influenza virus later in life (Avitsur, Hunzeker, & Sheridan, 2006). A separate line of human observational and longitudinal studies supports this model: in a large British cohort study, parental separation in childhood associated with adult CRP (Lacey, Kumari, & McMunn, 2013). Other studies have identified associations between childhood maltreatment and increased CRP (Andrea Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Matthews, Chang, Thurston, & Bromberger, 2014), as well as the co-occurrence of elevated CRP and depression (Andrea Danese et al., 2008) in adulthood. These associations also extend to acute *changes* in inflammatory physiology, reflecting propensities to respond to immune challenges. In two studies, recollections of child abuse associated with increased stressor-evoked inflammatory responses in both healthy adults as well as adults with depression (Carpenter et al., 2010; Pace et al., 2006). Another study found that socioeconomic status during childhood associated with

increased *in vitro* cellular inflammatory signaling (G. E. Miller et al., 2009). While the cellular mechanisms of such effects are not fully known, there thus appears to be accumulating evidence that increased systemic inflammation is a common biological outcome associated with ACEs.

Critically, systemic inflammation is implicated in negative mood states as well as affective disorders such as depression (Slavich & Irwin, 2014). In addition to their previously described immunological role of mounting responses to pathogens, pro-inflammatory cytokines also signal the brain to influence 'sickness behavior', which is a constellation of cognitive, affective, and behavioral changes that comprise subjective feelings of fatigue, nausea, loss of pleasure, sleep difficulty, and irritability (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). These changes are adaptive insofar as they motivate the individual to conserve energy, increase vigilance to threat, and send signals for aid from the social environment (Maier & Watkins, 1998). However, it is thought that chronic or dysregulated expression of these symptoms may overlap with symptoms that are reported by individuals with affective disorders, particularly depression (A. H. Miller, Maletic, & Raison, 2009). Moreover, associations between systemic inflammation and subclinical levels of these specific symptoms are documented in individuals without affective disorders (Jokela, Virtanen, Batty, & Kivimäki, 2016). Hence, sickness behavior represents a possible psychological pathway that may link systemic inflammation to risk for negative mental health outcomes.

Support for inflammation-related sickness behavior and its role in affective disorders derives from a large body of evidence identifying at least 3 potential pathways by which peripheral inflammation can access and modulate activity in the central nervous system (CNS) (Quan & Banks, 2007). First, peripheral inflammatory cytokines can cross the blood-brain barrier by way of an active transport mechanism (W. A. Banks & Kastin, 1991). Second,

cytokines such as IL-1 can passively cross the blood-brain barrier in membranes with increased diffusivity, such as the circumventricular organs (Blatteis et al., 1983). Finally, cytokines can activate the vagus nerve, which is a major ascending immunosensory nerve (Ek, Kurosawa, Lundeberg, & Ericsson, 1998). The vagus nerve subsequently propagates afferent immune information into the CNS via its projections through the nucleus tractus solitarius and ventrolateral medulla, stimulating a parallel central inflammatory response in the hypothalamus and amygdala (Bluthé et al., 1994; Rinaman, 2007). It should be noted that, in addition to these afferent pathways, there are efferent pathways through which the brain regulates peripheral inflammation, particularly via autonomic and neuroendocrine mechanisms (Sternberg, 2006). Together, these pathways establish a bidirectional feedback loop between the brain and peripheral inflammatory processes, and provide mechanisms by which peripheral inflammation can access and modulate brain function.

Peripheral inflammation can influence brain structure and function in the CNS, as supported by animal models and human neuroimaging studies. In both lines of work, the effects of peripheral inflammation on the CNS are interrogated by administering substances, such as endotoxin or typhoid vaccine, that provoke a peripheral inflammatory response. In animal models, peripherally stimulated inflammation results in the production of pro-inflammatory cytokines by microglial cells in the brain (van Dam, Bauer, Tilders, & Berkenbosch, 1995). Moreover, peripheral inflammation produces changes in activity (as measured by immunohistochemistry) in the amygdala, hippocampus, and hypothalamus (Frenois et al., 2007), and alters neurogenesis and long term potentiation in the hippocampus (Ekdahl, Claasen, Bonde, Kokaia, & Lindvall, 2003; Katsuki et al., 1990). Parallel to these animal models are human neuroimaging studies showing effects of peripheral inflammation on increased amygdala

reactivity to threatening faces (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012); in contrast, reducing peripheral inflammation via a tumor necrosis factor inhibitor has the opposite effect (Harrison, Cooper, Tibble, Voon, & Critchley, 2017). In addition, stimulating peripheral inflammation alters hippocampal activity and hippocampus-dependent memory function (Harrison, Doeller, Voon, Burgess, & Critchley, 2014). Finally, these studies show effects of systemic inflammation on activity in the ACC at rest (Harrison, Cooper, Voon, Miles, & Critchley, 2013) and in response to stressful social and cognitive tasks (Harrison, Brydon, Walker, Gray, Steptoe, Dolan, et al., 2009; Muscatell, Moieni, et al., 2016). In addition to the effects on regional activity, there is some evidence that peripheral inflammation relates to functional connectivity in the corticolimbic circuit. Specifically, typhoid vaccine-induced systemic inflammation reduced functional connectivity between the subgenual division of the ACC and amygdala during a face processing task (Harrison, Brydon, Walker, Gray, Steptoe, & Critchley, 2009). Notably, connectivity between the ACC and amygdala associated with individual differences in inflammation-related sickness behavior in this study. Separately, individual differences in inflammatory responses to a social stress associate with stressor-evoked changes in connectivity between the amygdala and mPFC (Muscatell et al., 2015). While human neuroimaging studies have not yet identified inflammation-related changes connectivity between the hippocampus and PFC, these studies collectively suggest that peripheral inflammatory processes can alter functionality in the previously described brain circuits that are also affected by ACEs.

It should be noted that not all the previously described mediators of systemic inflammation access the CNS in healthy individuals. Specifically, while it is accepted that pro-inflammatory cytokines, such as IL-6 and TNF, can influence CNS function (Sparkman et al.,

2006), acute phase proteins such as CRP cannot. Instead, these acute phase proteins are thought to be downstream indicators of ongoing inflammatory processes, and are therefore moderately correlated with levels of pro-inflammatory cytokines across individuals. For instance, in a sample of 645 midlife adults, IL-6 was moderately correlated (r = 0.33) with CRP (Marsland, McCaffery, Muldoon, & Manuck, 2010). The moderate correlation between these features of inflammation may explain why some studies show associations between CRP and brain function across individuals, even though the mechanistic basis supporting such an association is not as clear [e.g., (Swartz, Prather, & Hariri, 2017)]. Accordingly, the present study examined the pro-inflammatory cytokine, IL-6, given stronger mechanistic evidence for cytokine-based influences on the central nervous system.

1.4 AIMS AND HYPOTHESES

Taken together, ACEs may relate to changes in neurobiological and inflammatory mechanisms that in turn associate with risks for negative health outcomes. While this suggests that ACEs may induce parallel effects on multiple physiological systems, it is proposed here that, systemic inflammation instead may represent a mechanistic pathway by which ACEs could relate to neurobiological risk factors for affective disorders later in life. This inflammatory pathway has been recently proposed to be a component of a broader "neuroimmune network hypothesis," which states that, "early-life adversity amplifies crosstalk between peripheral inflammation and neural circuitries subserving threat-related, reward-related and executive control-related processes" (Nusslock & Miller, 2016). While individual components of the neuroimmune network hypothesis have been reviewed extensively (Andrea Danese & Baldwin, 2017; Hostinar, Nusslock, & Miller, 2017), a more comprehensive study of this hypothesis linking experiences,

physiology, neurobiology, and behavior has not yet been examined in a single human neuroimaging study.

Accordingly, the present study had 4 primary aims, and 2 ancillary aims. Figure 1 describes how the primary aims relate to the presently hypothesized pathway.

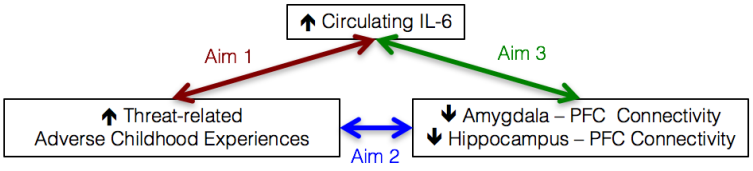

Figure 1. Specific Aims.

Specifically, Aim 1 (Figure 1, red) examined associations between threat-related ACEs and markers of pro-inflammatory cytokines in adulthood. As discussed previously, adverse experiences associated with *threat* (i.e., caregiver abuse and parental death) are thought to involve the corticolimbic circuit; accordingly, this dimension of adversity was the focus of the present study. Separately, the pro-inflammatory cytokine of interest was circulating IL-6, because it reflects ongoing inflammation in the periphery and can also influence CNS function. It was therefore hypothesized that increased adversity will associate with increased circulating IL-6, in line with existing evidence.

Aim 2 (blue) examined associations between threat-related ACEs and corticolimbic connectivity at rest. It was hypothesized that increased adversity will associate with decreased amygdala-PFC and hippocampus-PFC connectivity in these adults, in line with previous reports.

Aim 3 (green) examined associations between circulating IL-6 and corticolimbic connectivity at rest. It was hypothesized that increased circulating IL-6 will associate with decreased connectivity across the same brain regions.

The goal of Aim 4 was to use mediation modeling to test whether inter-individual variation in systemic inflammation statistically mediates the association between ACEs and brain connectivity. This aim would accordingly provide a comprehensive test for the neuroimmune network hypothesis in a sample of healthy midlife adults.

Finally, the present study had 2 ancillary aims. First, prior studies of ACEs and risk for affective disorders proposed that altered corticolimbic connectivity may represent a neural correlate of risk for and symptoms of affective disorders [e.g., (Herringa et al., 2013)], yet it is unclear whether these relationships are apparent in psychiatrically healthy midlife adults. To this end, the first ancillary aim will examine associations between corticolimbic connectivity metrics and subclinical symptoms of depression. Significant associations between corticolimbic connectivity and depressive symptoms would strengthen the clinical significance of the primary aims. Second, emerging evidence suggesting that ACEs might alter the *nature* of the relationship between peripheral inflammation and the brain. As mentioned previously, the neuroimmune network hypothesis posits that adversity "amplifies the crosstalk" between peripheral inflammation and the brain (Nusslock & Miller, 2016). By this premis, individuals reporting ACEs would be expected to exhibit greater cross-system communication than individuals without a history of ACEs. There is some emerging evidence in support of this notion. One study examined associations between ACEs, inflammation, and frontal brain asymmetry, an electroencephalography index that associates with negative emotionality (Wheeler, Davidson, & Tomarken, 1993) and amygdala reactivity (Zotev et al., 2016). It was observed that ACEs *moderated* the association between inflammation and frontal brain asymmetry, such that the two measures were only associated in individuals reporting ACEs (Hostinar, Davidson, et al., 2017). Similarly, a study of breast cancer survivors and healthy controls found that amygdala reactivity

associated with peripheral CRP only in the breast cancer survivors; here, the authors raised the possibility of a "stronger neural-immune pipeline among breast cancer survivors," possibly due to chronic stress (Muscatell, Eisenberger, Dutcher, Cole, & Bower, 2016). Given this somewhat limited evidence, the secondary ancillary aim tested for moderating effects of ACEs on the relationship between peripheral inflammation and corticolimbic connectivity, with the hypothesis that the brain-inflammation relationship would be stronger in individuals reporting ACEs.

2.0 METHODS

2.1 PARTICIPANTS

Participants were from a community sample of healthy midlife adults (age 30 – 51) recruited using mass mailings to residents of Allegheny County, Pennsylvania. Participants were free of a history of physical disease (e.g., inflammatory conditions, cardiovascular disease, prior cardiovascular surgery, kidney or liver conditions, Type I or II diabetes) and psychiatric diagnoses (e.g., mood disorder, substance abuse). In addition, participants were not taking any psychotropic, lipid lowering, or cardiovascular medications. Finally, participants were free of MRI contraindications (i.e., claustrophobia, head trauma, metallic implants, pregnancy).

2.2 PROCEDURES

Data relevant to the present study were collected during the first 2 Visits of the Pittsburgh Imaging Project (PIP) baseline study. Data collection for Visits 1 and 2 were separated by a period of 4 to 6 weeks. Measures encompass retrospectively recalled ACEs, circulating levels of IL-6, resting-state fMRI connectivity and motion metrics, subclinical symptoms of depression, and anthropometric attributes.

2.3 MEASURES

2.3.1 Adverse childhood experiences

Data on multiple types of ACEs were collected. The Childhood Trauma Questionnaire [CTQ, (Bernstein et al., 1994, 2003)] is a self-report questionnaire that assesses retrospective reports of childhood abuse and neglect. The CTQ assesses five subscales of ACEs: physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Each subscale comprises five questions regarding experiences in childhood (e.g., "People in my family hit me so hard that it left bruises or marks") and responses are recorded using five-point Likert scales. Each subscale is summed to form continuous scores, and these scores can be converted to binary scores using clinical cutoffs; studies using these cutoffs have observed specificity and sensitivity above 0.85 when comparing to clinical interviews (Walker et al., 1999). The CTQ has also demonstrated strong criterion-related reliability (Bernstein et al., 2003), test-retest reliability, and convergent validity (Bernstein et al., 1994; Walker et al., 1999). In accordance with the hypothesis that threat-related ACEs might relate to systemic inflammation and corticolimbic connectivity, analyses focused on measures of physical and sexual abuse (both continuous and categorical scores).

2.3.2 IL-6

Participants provided a fasting blood draw during the morning of Visit 2. Samples were stored at -70°C and IL-6 levels were determined in duplicate by high sensitivity quantitative sandwich enzyme immunoassay kit (R&D Systems, Minneapolis, MN) according to manufacturer's

directions. One participant with circulating IL-6 levels greater than 10 pg/mL was excluded from analyses, as these levels may reflect ongoing infection. The distribution of IL-6 values was positively skewed; accordingly, these values were log-transformed prior to statistical analyses.

2.3.3 Depression

Depressive symptoms were measured using the Beck Depression Inventory-II [BDI, (Beck, Steer, & Brown, 1996)]. Because of previously described role of inflammatory cytokines in sickness behavior and anhedonia (Swardfager, Rosenblat, Benlamri, & McIntyre, 2016), analyses focused on the somatic-affective dimension of the BDI, computed using factor coefficients described previously (Steer, Ball, Ranieri, & Beck, 1999). This dimension (henceforth referred to as 'somatic symptoms') principally includes measures of fatigue, loss of appetite, and loss of pleasure. Although the distribution of this variable was positively skewed in the sample, transformations were not applied, as this would plausibly obfuscate the clinical significance of this measure. Instead, ancillary analyses using this measure were conducted using nonparametric methods.

2.3.4 Covariates

All analyses controlled for age, sex, and race, as these demographic variables may confound study associations. Race was coded as white and nonwhite. In addition, due to the role of adiposity in producing pro-inflammatory cytokines such as IL-6, body mass index (BMI) was included in all analyses. Participant height and weight measurements were obtained to determine BMI (kg/m^2). Finally, participant head motion during fMRI acquisition was examined as a

possible confounding factor. This is because increased head motion during fMRI acquisition spuriously biases functional connectivity estimates, due to motion-induced increases in the BOLD signal across the brain (Van Dijk, Sabuncu, & Buckner, 2012). Importantly, it was recently observed that circulating IL-6 significantly correlates with individual differences in mean framewise displacement (FD), an index of frame-to-frame head motion (Marsland et al., 2017). Although data preprocessing steps are thought to mitigate the confounding effects of motion (see "Preprocessing" section), there nonetheless is a concern that increased ACEs or IL-6 may systematically associate with increased motion-related "spurious" connectivity, which may confound results. This concern is in part due to the currently incomplete understanding of the behavioral and physiological origins of individual differences in head motion (Hodgson et al., 2016; Siegel et al., 2016). Hence, associations were examined between ACEs, IL-6, and FD. In the presence of significant bivariate associations between these study variables, mean FD was used as an additional covariate in all analyses in order to conservatively adjust for these potential confounds (Power, Schlaggar, & Petersen, 2015).

2.3.5 Region of interest (ROI) definition

The following regions of interest (ROI) masks were used for connectivity analyses. The amygdala and hippocampus ROI masks were derived from the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) using the WFU PickAtlas Toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003). Because there are not strong hypotheses about the laterality of these structures regarding their relationships with inflammation and ACEs, left and right regions were combined into a bilateral mask for each structure. Masks pertaining to subdivisions of the ACC (dorsal, perigenual, subgenual) were created from the IBSM IBASPM 71 atlas

(Aleman-Gomez, Melie-García, & Valdés-Hernandez, 2006) according to (Gianaros et al., 2014). Finally, the vmPFC mask was created using the rectus and orbital gyrus regions labeled in the AAL atlas.

2.3.6 Functional connectivity estimation

Connectivity metrics were computed in the CONN toolbox using ROI-to-ROI procedures. For ROI-to-ROI estimation, the average BOLD timeseries was extracted from each ROI and mean-centered. For every pair of four cortical (e.g., perigenual ACC) and two limbic (e.g., amygdala) ROIs, functional connectivity between the two respective timeseries was estimated using Pearson's correlation, resulting in estimates for eight corticolimbic connections. These estimates were then each transformed using the Fisher *r-to-z* transform. Because examining these eight connectivity estimates would require conducting a large number of tests to address each study aim, the eight estimates were further reduced using Factor Analysis. The number of components was decided using visual inspection of the Scree plot (Cattell, 1966) and the eigenvalues-greater-than-one rule (Kaiser, 1960). Factors were derived using varimax rotation and scores were computed using regression. This resulted in two factors that explained 59% of the total variance in corticolimbic connectivity. The first factor comprised functional connectivity (correlations) between the ventral cortical subregions (i.e., vmPFC and sgACC), the amygdala, and the hippocampus (factor loadings > 0.72), whereas the second factor comprised connections between the dorsal cortical subregion (i.e., dACC), the amygdala, and the hippocampus (factor loadings > 0.71). In line with this ventral-dorsal distinction, connections between the pgACC, amygdala, and hippocampus moderately loaded on both factors (0.40 - 0.62). These factors are henceforth

referred to as ‘limbic - ventral PFC connectivity’ and ‘limbic - dorsal PFC connectivity’, respectively.

2.4 STATISTIAL ANALYSES

Distributions of all study variables were examined to identify potential outliers or violations of normality. Bivariate associations between continuous study variables were examined using Pearson’s correlations. Differences in study variables based on categorical ACEs were examined using independent sample t-tests. Associations between ACEs of interest, IL-6, and extracted corticolimbic connectivity estimates (Aims 1-3), adjusting for covariates, were conducted using separate linear regression models in R (R Development Core Team, 2016). Specifically, Aim 1 tested the prediction of IL-6 by each ACEs measure (categorical and continuous), controlling for age, sex, race, BMI, and participant motion. Aim 2 tested the prediction of each resting state connectivity factor by each ACEs measure, controlling for the above covariates. Finally, Aim 3 tested the prediction of each resting state connectivity factor by IL-6, controlling for the above covariates.

Aim 4 brings the prior 3 aims together, and hence tests the neuroimmune network hypothesis using a three-path mediational analysis (Baron & Kenny, 1986). To this end, the three primary paths of this model, termed *Path a*, *b*, and *c*, align closely with the first three study aims. According to this path model, associations of ACEs with IL-6 are tested as the effect of X on M, corresponding to Path *a*. Associations of IL-6 with corticolimbic connectivity controlling for ACEs are tested as the effect of M on Y, corresponding to Path *b*. Associations between ACEs and corticolimbic connectivity *without controlling for IL-6* would are tested as the total effects of

X on Y, or Path *c*. Standard approaches to mediation modeling require that point estimates for Paths *a*, *b*, and *c* be statistically significant prior to testing for mediation within the full model (Baron & Kenny, 1986). If these point estimates for these three paths were indeed significant, then associations between ACEs and corticolimbic connectivity *while controlling for IL-6* would be subsequently tested as the direct effects of X on Y, or Path *c'*. Finally, indirect path effects of the association of ACEs and corticolimbic connectivity – as mediated by IL-6, would be tested as the indirect effects of X on Y through M, and calculated as the product of Paths *a* and *b*. Statistical significance of the indirect effect will be assessed using nonparametric bootstrapping (5000 iterations) of the indirect (*a* x *b*) path effects (Preacher & Hayes, 2008).

Analyses of the ancillary aims used Spearman's rank-order correlation to test whether corticolimbic connectivity associates with subclinical symptoms of depression. To test whether ACEs moderate the association between IL-6 and corticolimbic connectivity, an interaction term reflecting the centered product of ACEs (e.g., physical abuse) and IL-6 was calculated and entered into a separate linear regression model, adjusting for main effects of the ACEs and IL-6 variables and covariates.

3.0 RESULTS

3.1 DESCRIPTIVE STATISTICS

Of the 331 participants enrolled in the study, 303 had complete data on all study variables, and hence comprised the analytic sample. Demographic characteristics for the analytic sample are in Table 1. Participants in the analytic sample did not significantly differ from excluded participants on any study variables (all $p > 0.15$).

Table 1. Descriptive statistics

	Mean or N	SD or %
Age (years)	40.3	6.24
Sex (female)	149	49.17
Race		
White	213	70.30
Nonwhite	90	29.70
BMI (kg/m2)	26.82	5.03
Smoking Status		
Never	191	63.04
Former	60	19.80
Current	52	17.16
BDI		
Total	3.53	3.50
Somatic Symptoms	1.07	1.22
CTQ: Physical Abuse		
Score	6.44	2.54
Meets cutoff	56	18.48
CTQ: Sexual Abuse		
Score	6.09	3.28
Meets cutoff	37	12.21
IL-6 (pg/mL)	0.2	0.6
Framewise displacement (mm)	0.24	0.18

3.2 BIVARIATE ASSOCIATIONS BETWEEN STUDY VARIABLES

Several bivariate associations between study variables were observed (Table 2). Of note, the continuous measure of physical abuse associated positively with IL-6 ($r = 0.18$, $p < 0.001$), and IL-6 associated negatively with the limbic – ventral PFC connectivity factor ($r = -0.17$, $p < 0.001$). Variables reflecting fMRI motion (framewise displacement, percent of scans flagged) associated with BMI ($r = 0.30$, $p < 0.001$), consistent with prior reports (Siegel et al., 2016). Because framewise displacement also associated with IL-6 ($r = 0.11$ $p = 0.05$), it was an additional covariate for subsequent multivariate analyses. It should be noted, moreover, that framewise displacement related to the limbic – dorsal PFC connectivity factor ($r = -0.34$, $p < 0.001$), but not the limbic – ventral PFC connectivity factor ($p = 0.14$).

Table 2. Bivariate correlations

	1	2	3	4	5	6	7	8
1. Age								
2. BMI	0.09							
3. BDI: Somatic	-0.00	0.05						
4. Physical Abuse (continuous)	-0.10	0.09	0.03					
5. Sexual Abuse (continuous)	0.00	0.06	-0.02	**0.28*****				
6. IL-6	**0.12***	**0.35*****	**0.14***	**0.18****	-0.01			
7. Mean Framewise Displacement	0.07	**0.30*****	**0.12***	0.08	0.07	**0.11***		
8. Limbic - Ventral PFC Connectivity	-0.01	**-0.14***	-0.01	-0.09	-0.07	**-0.13***	**-0.15****	
9. Limbic - Dorsal PFC Connectivity	-0.05	**-0.16****	-0.05	**-0.12***	-0.03	-0.06	**-0.29*****	-0.05

*Note: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$*

Bivariate associations were additionally observed with respect to the binary measures of ACEs. Individuals reporting physical abuse exhibited greater levels of IL-6 ($t = 2.65$, $p = 0.009$). Individuals reporting sexual abuse also exhibited more motion during resting-state fMRI, but this relationship did not reach conventional statistical significance ($t = 1.80$, $p = 0.07$). There were no other statistical differences in study variables on the basis of binary ACEs variables. Sex differences were observed in both continuous ($t = 3.76$ $p < 0.001$) and binary ($\chi^2 = 13.08$ $p < 0.001$) measures of sexual abuse, whereby women reported more abuse; however, statistical sex differences in physical abuse were not observed (both $p > 0.25$).

3.3 TEST OF AIM 1

As noted above and depicted in Figure 2, IL-6 associated with both binary ($t = 2.65$ $p = 0.009$) and continuous ($r = 0.18$, $p < 0.001$) measures and physical abuse. Sexual abuse was not associated with IL-6 (both $p > 0.59$).

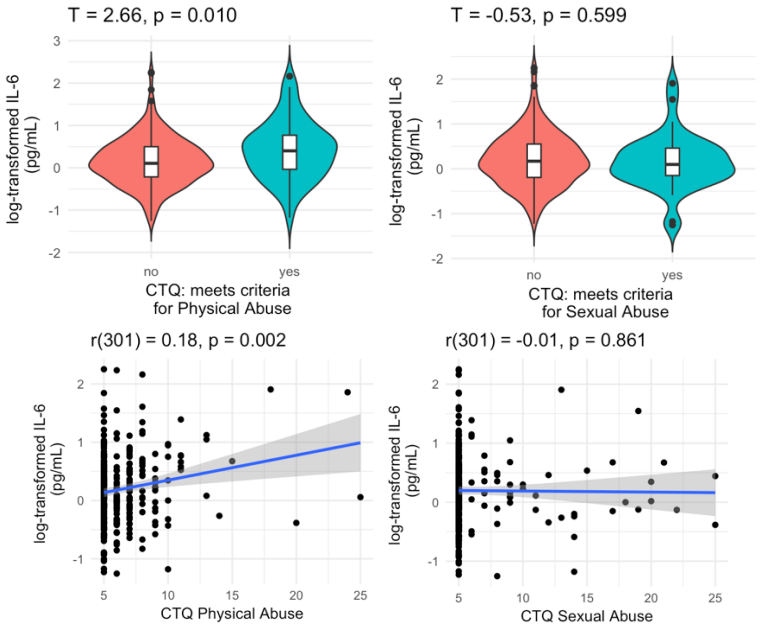

Figure 2. Association of threat-related ACEs and circulating IL-6 (Aim 1).

Given the bivariate associations with physical abuse, hierarchical linear regressions were conducted to determine the independent prediction of IL-6 by physical abuse, controlling for age, sex, race, and BMI. In a base model comprising the predictors age, sex, race, and BMI, only BMI associated with IL-6 (Table 3, Model 1, β(SE) = 0.33(0.05), $p < 0.001$), whereas age had a weaker association (β(SE) = 0.09(0.05), p = 0.09). Adding the ACEs measures to this model in independent second steps revealed that reporting physical abuse independently associated with increased IL-6 (Model 2, β(SE) = 0.14(0.05), p = 0.009). Significant independent associations were similarly observed for the continuous measure of physical abuse (Model 3, β(SE) = 0.16(0.05), p = 0.005). Hence, the hypothesis that threat-related ACEs relates to midlife inflammation was supported by the present study.

Table 3. Linear regressions predicting IL-6 (Aim 1).

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	*SE*	*β*	*SE*	*β*	*SE*	*β*	*SE*	*β*	*SE*
Age	0.09	0.05	0.1	0.05	**0.11***	**0.05**	0.09	0.05	0.09	0.05
Sex	-0.04	0.05	-0.04	0.05	-0.05	0.05	-0.03	0.06	-0.04	0.06
Race	0.08	0.05	0.05	0.06	0.05	0.05	0.09	0.06	0.09	0.06
BMI	**0.33*** **	**0.05**	**0.33*** **	**0.05**	**0.32*** **	**0.05**	**0.34*** **	**0.05**	**0.33*** **	**0.05**
Physical Abuse (binary)			**0.14** **	**0.05**						
Physical Abuse (continuous)					**0.16** **	**0.05**				
Sexual Abuse (binary)							-0.08	0.06		
Sexual Abuse (continuous)									-0.03	0.06
R^2 / adj. R^2	.139 / .128		.159 / .145		.162 / .148		.145 / .131		.140 / .126	
F-statistics	12.076***		11.234***		11.509***		10.080***		9.709***	

*Note: *** p < 0.001, ** p < 0.01, * p < 0.05*

3.4 TEST OF AIM 2

As noted above and depicted in Figure 3, none of the binary or continuous ACEs measures significantly associated with either the limbic – ventral PFC or the limbic – dorsal PFC connectivity factors in bivariate analyses (all $p > 0.26$). Given these null findings, no further multivariate testing of these relationships was performed. Hence, the hypothesis that threat-

related ACEs relates to resting connectivity in the corticolimbic circuit was not supported by the present study.

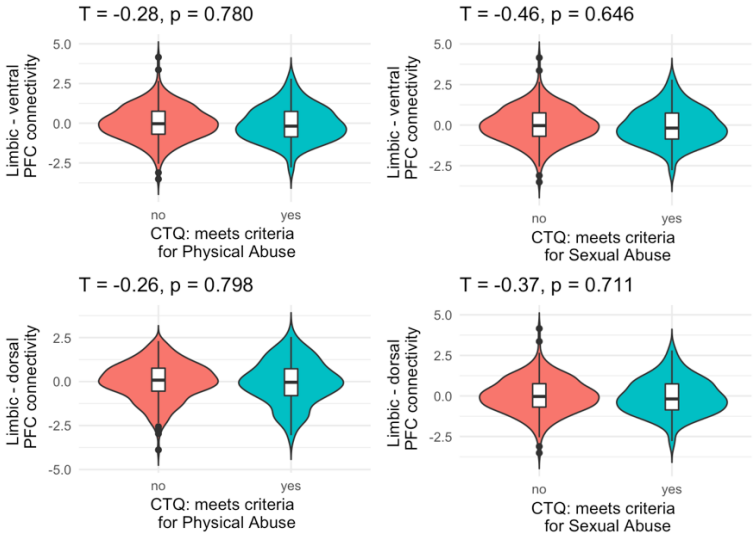

Figure 3. Association of threat-related ACEs and corticolimbic connectivity (Aim 2).

3.5 TEST OF AIM 3

In bivariate analyses, IL-6 was negatively associated with the factor reflecting limbic – ventral PFC connectivity (r = -0.16 p = 0.004), but not with the factor reflecting limbic – dorsal PFC connectivity (r = -0.03 p = 0.57) (Figure 4). Given the bivariate associations with the ventral connectivity factor, hierarchical linear regressions were conducted to determine the independent prediction of this factor by IL-6, controlling for age, sex, race, BMI, and participant motion. Model 1 of Table 4 shows that there were sex differences in this connectivity factor, with females exhibiting less connectivity than males (β(SE) = -0.15(0.06), p = 0.009). Moreover, individual differences in participant motion associated with this connectivity factor (β(SE) = -

0.14(0.06), p = 0.023), although it should be noted that this relationship was not significant in bivariate analyses (p = 0.14).

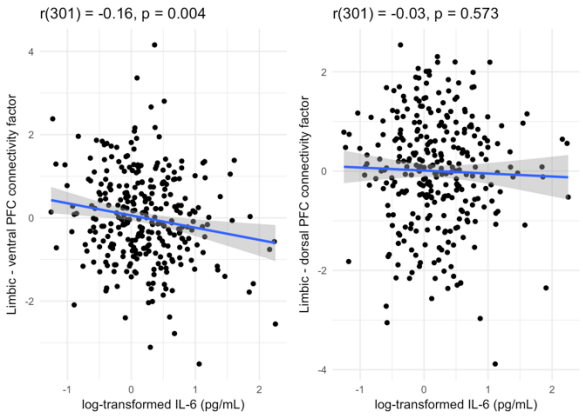

Figure 4. Association of circulating IL-6 and corticolimbic connectivity (Aim 3).

Table 4. Linear regressions predicting limbic – ventral PFC connectivity from IL-6 (Aim 3).

	Model 1		Model 2	
	β	*SE*	*β*	*SE*
Age	-0.02	0.06	-0.01	0.06
Sex	**-0.15****	**0.06**	**-0.16****	**0.06**
Race	-0.1	0.06	-0.09	0.06
BMI	-0.06	0.06	-0.01	0.06
Motion	**0.14***	**0.06**	0.14*	0.06
IL-6			**-0.17****	**0.06**
R^2 / adj. R^2	.047 / .031		.071 / .052	
F-statistics	2.927*		3.746**	

*Note: *** p < 0.001, ** p < 0.01, * p < 0.05*

3.6 TEST OF AIM 4

Prior to mediation modeling, the point estimates for the 3 primary paths were estimated, controlling for prior covariates. For illustration purposes, the full model and point estimates for each of the 3 primary paths, specifically using the continuous physical abuse measure and limbic – ventral PFC connectivity factor, are depicted in Table 5. Here, in line with the findings of Aims 1 and 3, evidence for both the *Path a* and *Path b* estimates was observed. Put differently, physical abuse predicted IL-6, and IL-6 predicted limbic – ventral PFC connectivity while controlling for physical abuse. However, as shown in Table 5 and in line with the findings of Aim 2, the *Path c* estimate (reflecting the Total Effect) did not reach statistical significance, as physical abuse did not predict limbic – ventral PFC connectivity. Similar findings were observed using the binary physical abuse variable (not shown). In line with the "causal steps approach" to mediation modeling (Baron & Kenny, 1986), mediation was not tested because there was insufficient evidence for *Path c*.

Table 5. Linear regressions depicting paths of mediational model (Aim 4).

	Path a, DV = IL-6		Path b, DV = limbic-ventral PFC connectivity		Path c, or Total Effect, DV = limbic-ventral PFC connectivity	
	β	*SE*	*β*	*SE*	*β*	*SE*
Age	**0.11***	**0.05**	-0.01	0.06	-0.03	0.06
Sex	-0.05	0.05	**-0.16****	**0.06**	**-0.15***	**0.06**
Race	0.06	0.06	-0.08	0.06	-0.09	0.06
BMI	**0.33*****	0.06	-0.01	0.06	-0.06	0.06
Motion	-0.03	0.06	**0.14***	**0.06**	**0.14***	**0.06**
Physical Abuse (continuous)	**0.16****	**0.05**	-0.02	0.06	-0.05	0.06
IL-6			**-0.16****	**0.06**		
R^2 / adj. R^2	.163 / .146		.071 / .049		.049 / .030	
F-statistics	9.604***		3.222**		2.545*	

*Note: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$*

3.7 TESTS OF ANCILLARY AIMS

Ancillary analyses first examined whether factors reflecting corticolimbic connectivity associated with subclinical symptoms of depression. Spearman's rank-order correlation analyses demonstrated that neither of the connectivity factors statistically associated with depressive symptoms (both $p > 0.52$).

A second set of ancillary analyses examined whether the presence of ACEs moderated the relationship between peripheral inflammation and corticolimbic connectivity. Linear regression models addressing this question are in Table 6. Centered product terms reflecting the interaction of ACEs and IL-6 were computed and entered into regression models, controlling for prior covariates, ACEs, and IL-6. These interaction terms did not statistically associate with

either connectivity factor (all $p > 0.29$). Hence, ACEs did not appear to moderate any brain-inflammation relationship in the present study.

Table 6. Linear regressions predicting corticolimbic connectivity from the interaction of ACEs and IL-6**.**

	limbic-vmPFC connectivity		limbic-vmPFC connectivity		limbic-dmPFC connectivity		limbic-dmPFC connectivity	
	β	*SE*	*β*	*SE*	*β*	*SE*	*β*	*SE*
Age	-0.01	0.06	-0.01	0.06	-0.03	0.06	-0.03	0.06
Sex	**-0.16****	**0.06**	**-0.16****	**0.06**	-0.03	0.05	-0.02	0.06
Race	-0.09	0.06	-0.08	0.06	-0.09	0.06	-0.09	0.06
BMI	-0.01	0.06	-0.00	0.06	0.03	0.06	0.03	0.06
IL-6	**-0.17****	**0.06**	**-0.17****	**0.06**	0.00	0.06	0.02	0.06
FD	**0.14***	**0.06**	**0.14***	**0.06**	**-0.32*****	**0.06**	**-0.32*****	**0.06**
Physical Abuse (binary)	0.02	0.06			0.01	0.06		
Interaction of IL-6 and Physical Abuse (binary)	0.01	0.06			-0.00	0.06		
Physical Abuse (continuous)			-0.03	0.06			0.02	0.06
Interaction of IL-6 and Physical Abuse (continuous)			0.02	0.06			-0.07	0.06
R^2 / adj. R^2	.071 / .046		.071 / .046		.127 / .103		.130 / .107	
F-statistics	2.818**		2.827**		5.349***		5.508***	

*Note: *** p < 0.001, ** p < 0.01, * p < 0.05*

4.0 DISCUSSION

The present study examined associations between retrospectively reported ACEs, circulating IL-6, resting brain corticolimbic connectivity, and somatic depressive symptoms. There were two main findings. First, retrospective reports of physical abuse, a threat-related form of adverse childhood experiences, was associated with circulating IL-6 in midlife, independent of age, sex, race, and BMI. Second, circulating IL-6 was associated with resting brain connectivity within a limbic – ventral PFC network. The latter comprised the amygdala, hippocampus, vmPFC, and sgACC. In contrast to these findings, several predicted associations were not observed. Foremost was that retrospectively reported ACEs were not related to corticolimbic connectivity, a finding that is discordant with some prior work (Birn et al., 2014). In addition, resting brain corticolimbic connectivity was not found to associate with subclinical symptoms of depression, calling into question its utility as a marker of risk for affective disorders (Fox & Greicius, 2010). To our knowledge, this is the first study to examine ACEs, peripheral inflammation, and fMRI metrics of brain connectivity in a single sample.

4.1 AIM 1: ACES AND SYSTEMIC INFLAMMATION

The present study found that retrospectively reported ACEs associated with midlife systemic inflammation, consistent with prior reports (Carroll et al., 2013). A recent meta-analysis

summarized twenty-five studies on childhood trauma and adulthood inflammation, examining heterogeneous samples and multiple markers of inflammation (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016). Interestingly, our study as well as this meta-analysis observed associations between IL-6 and physical abuse, but not sexual abuse. Moreover, this meta-analysis did not observe associations between IL-6 and emotional abuse, which was not an *a priori* focus of this study. Explanations for the heterogeneous associations between ACE types and IL-6 are currently unclear. In the context of physical and sexual abuse, differences in factors such as their timing, exposure, or other interpersonal characteristics could plausibly explain differences in effects on peripheral physiology (Tottenham & Sheridan, 2010). Future studies with more detailed phenotyping of ACEs and later health outcomes will be needed to explore this area of research.

Conceptually, these findings are in line with the "biological embedding model" of early adversity (G. E. Miller et al., 2011). The physiological basis for an effect of ACEs on midlife systemic inflammation is not fully understood; however, according to this model, it is thought that ACEs may promote inflammation later in life by sensitizing peripheral immune cells to stress and other environmental inputs. Examining our results in the context of this model, it is not entirely clear how the ACEs might be developmentally "embedded" in the body along the life course to promote increased inflammation at midlife. By one perspective, ACEs may sensitize immune cells and promote inflammation during childhood and adolescence, which subsequently follows a normal rate of inflammatory aging. This is perspective is supported by several studies linking ACEs to concurrent systemic inflammation in children and adolescents (A. Danese et al., 2011; Slopen, Kubzansky, McLaughlin, & Koenen, 2013). By another perspective, the physiological effects of ACEs may not be apparent until later in life. As an example, a recent

study observed that individuals with ACEs displayed an accelerated age-related trajectory in blood pressure that was not apparent until after the age of 30 (Su et al., 2015). Although to our knowledge no studies have examined trajectories of peripheral inflammation across the life course in the context of ACEs, these perspectives on ACEs, development, and inflammatory risk for disease will be important for future studies to consider.

Both the binary (determined via a standard clinical cutoff) as well as the continuous measures of physical abuse associated with IL-6, a pair of findings that might significantly inform these relationships above and beyond their individual parts. Moreover, each of these two findings may provide empirical support for different perspectives of the stress-health relationship (S. Cohen, Gianaros, & Manuck, 2016). These perspectives are historical academic traditions that have used differing approaches to describe how psychological stress can affect health. Specifically, the finding with the binary physical abuse variable suggests that increased inflammation at midlife may be a consequence of the mere *exposure* to clinically significant levels of physical abuse. In the context of stress-health perspectives, this finding is consistent with the *psychological tradition*, which posits that an individual's response to stressful events is influenced by their subjective appraisal of those events, as well as other factors such as the availability of resources to cope with them (Folkman, Lazarus, Gruen, & DeLongis, 1986). Along these lines, it may be interpreted that individuals experiencing physical abuse of sufficient duration or severity to meet standard clinical criteria are likely to have fully appraised these experiences as stressful, possibly exhausting their coping resources, and ultimately conferring physiological risk. In contrast to this perspective, the finding with the continuous physical abuse variable suggests that midlife inflammation may also associate with the *magnitude* of the recollected physical abuse. In the context of stress-health perspectives, this finding is consistent

with the *biological tradition*, which indicates that stress affects the body by influencing physiological systems involved in homeostasis. Specifically, this tradition draws heavily from the work of Selye, who emphasized that there should be a linear relationship between the severity of stressful experiences and the magnitude of the physiological response (Weiner, 1992). Our result is consistent with this perspective insofar as there appears to be a positive linear relationship between individual differences in physical abuse severity and midlife inflammation. It should be noted that these two perspectives are not mutually exclusive, yet likely explain complementary features of the stress-health relationship (S. Cohen et al., 2016).

Finally, as described previously, systemic inflammation also associates with risk for physical diseases of aging, including atherosclerosis (Libby, Ridker, & Maseri, 2002) and hypertension (Vaziri & Rodríguez-Iturbe, 2006). Moreover, adults who report ACEs also are more likely to have *co-occuring* risk for poor mental and physical health outcomes. Accordingly, it has been suggested that inflammatory processes may provide a "common root" for these co-occurring vulnerabilities (Nusslock & Miller, 2016). Taken together, these findings indicate that ACEs such as physical abuse may be an important psychosocial construct for later physical health outcomes, independent of its influence on the brain and other brain-related outcomes.

4.2 AIM 2: ACES AND CORTICOLIMBIC CONNECTIVITY

The present study found that ACEs did not associate with resting brain corticolimbic connectivity. These results diverge from prior studies that observed associations between ACEs and adulthood metrics of corticolimbic activity and functional connectivity (Birn et al., 2014; Dannlowski et al., 2012). It is not entirely clear why the expected associations were not

observed. On reason for the discrepant results may relate to the derivation of connectivity estimates (M. H. Lee, Smyser, & Shimony, 2013). There is not a clearly accepted approach to conducting resting-state connectivity studies on individual differences. Prior studies used different approaches to examining functional connectivity, termed "voxel wise" analyses. In voxel wise analyses, the connectivity between a "seed region" (e.g., the right amygdala) and every voxel in the brain is estimated. Subsequently, at each voxel, the association between connectivity and ACEs is accordingly estimated. This approach differs from the present study, which aimed to identify latent patterns of corticolimbic connectivity, distributed across groups of brain regions, that could be subsequently compared to ACEs. When examining hypotheses in large areas of cortex (e.g., mPFC), voxel wise approaches are advantaged in that they can localize the strongest effects in subregions or subdivisions of the brain that might not demonstrate a clear anatomical boundary. However, these voxel wise approaches are disadvantaged in that they require stringent statistical corrections for multiple comparisons, which can have the effect of reducing statistical power and increasing the false negative rate, or, in combination with insufficient approaches to statistical thresholding, can have the effect of increasing the false positive rate (Eklund, Nichols, & Knutsson, 2016). As stated previously, there is not a clearly accepted approach to this line of research, but in contrast to voxel wise analyses, it is plausible that the analytic steps taken to average across large swaths of cortex and decompose these averages into latent factors, while appropriate for reducing the number of statistical tests at the analysis stage, could have obfuscated fine-grained signal in the corticolimbic circuit that associates with ACEs.

Along with studies reporting associations between ACEs and resting corticolimbic connectivity, several other studies have reported associations with task-evoked reactivity and

functional connectivity within and across these regions (Fan et al., 2014; Grant et al., 2014). The correspondence between resting-state connectivity, task-evoked activity, and task-evoked connectivity is not currently well understood, and likely depends on contextual factors such as the nature of the task and the circuit under investigation (Cole, Ito, Bassett, & Schultz, 2016). Moreover, this correspondence is understood even less in the context of ACEs and inflammation. As such, there are too few studies to systematically examine the size and reliability of the effects of ACEs on these metrics of brain activity and connectivity. Accordingly, it is plausible that other metrics of brain activity or connectivity along the corticolimbic circuit may be better suited to test aspects of the neuroimmune network hypothesis, particularly if they are more stable, more reliable, or less subject to artifact or other confounds than resting state connectivity (Choe et al., 2015).

It should be noted that the neuroimmune network hypothesis encompasses predictions about other brain systems, namely the reward and executive control networks (Nusslock & Miller, 2016). These networks were not examined in the present study and could potentially provide a direction for future work. In the context of the present study, brain alterations linked to retrospectively reported ACEs are likely to be found in circuits that are affected at a later stage along the pathways described by the neuroimmune network hypothesis. In contrast, studies of children recently exposed to ACEs are more likely to observe alterations in circuits that are more proximally affected by their experiences. Indeed, this model proposes that ACEs may exert more proximal effects on threat-related circuitry, and more delayed effects on reward and executive control circuitry. In the context of the neuroimmune network hypothesis, the reward and executive control networks may be a promising avenue for future research on retrospectively reported ACEs.

In addition to the reward and executive control networks, one brain *region* not considered by the neuroimmune network hypothesis that may nonetheless be relevant to this study is the insula. The insula is involved in sensing physiological condition of the body, as well as the cortical regulation of peripheral physiological systems (e.g., inflammatory, autonomic) (Aleksandrov & Aleksandrova, 2015). Moreover, the insula is implicated in integrating peripheral physiological signals such as systemic inflammation into motivational biases and feeling states (Craig, 2009) that may play a large role in depressive pathophysiology (Avery et al., 2014). In line with this hypothesized role, activity and functional connectivity of the insula is uniquely sensitive to systemic inflammation, both at rest and during cognitive and affective processes (Hannestad et al., 2012; Lekander et al., 2015; Rosenkranz, Busse, Sheridan, Crisafi, & Davidson, 2012). Finally, resting connectivity of the insula may be affected by ACEs in adults (Teicher, Anderson, Ohashi, & Polcari, 2014). Given this set of findings, the insula may comprise another candidate brain region that is suited to the neuroimmune network hypothesis.

4.3 AIM 3: SYSTEMIC INFLAMMATION AND CORTICOLIMBIC CONNECTIVITY

The present study found that IL-6 associated with a factor reflecting resting brain limbic – ventral PFC connectivity. This factor primarily comprised the amygdala, hippocampus, vmPFC, and sgACC. To our knowledge, this is the first study to report inflammation-associated connectivity within this network. A prior study examined associations between IL-6 and connectivity of the default mode network, consisting of regions including the mPFC, but did not

report inflammation-associated connectivity with limbic areas such as the amygdala or hippocampus (Marsland et al., 2017).

The physiological basis for these findings can be described by both afferent and efferent pathways linking the brain and peripheral inflammation. First, afferent pathways could describe how IL-6 in the periphery influences corticolimbic connectivity. The hippocampus and mPFC have dense IL-6 receptors, and systemic inflammation can influence local physiological processes such as neurotransmitter metabolism, long term potentiation, and synaptic plasticity in these areas (Yirmiya & Goshen, 2011). Gray matter morphometry in these areas have accordingly been shown to associate with peripheral inflammation (Marsland et al., 2015; Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008), and it is thought that functional connectivity across distributed circuits may in part depend on the structural integrity of those circuits, including gray matter morphology (Honey et al., 2009). Given this, it is plausible that peripheral inflammation could influence resting corticolimbic connectivity via its effects on local morphological and functional properties of individual regions within the network. In contrast to afferent pathways, efferent pathways could describe how corticolimbic connectivity influences peripheral IL-6. Specifically, in addition to their role in threat processing and emotion regulation, components of the corticolimbic circuit are implicated the generation and regulation of autonomic, neuroendocrine, and inflammatory responses to stress (Beissner et al., 2013; Ginty, Kraynak, Fisher, & Gianaros, 2017). Dysregulated physiological responses to stress in turn are thought to associate with risk for stress-related physical disease. Hence, the association between peripheral IL-6 and corticolimbic connectivity could alternatively be explained by reduced functional integrity in a network involved in regulating peripheral physiology, in turn resulting in dysregulation along inflammatory and other physiological systems. Future studies examining the

temporal relationships between peripheral IL-6 and corticolimbic connectivity have the potential to clarify the nature of these bidirectional pathways.

It should be noted that, given the latter perspectives on efferent neural control over inflammation, ACEs may affect peripheral physiology (e.g., inflammation) via its effects on homeostatic and visceral control circuits in the brain. The present study, however, does not provide clear evidence in support of this notion, as ACEs related to peripheral inflammation *in the absence of any association with the brain.*

Interestingly, IL-6 did not associate with connectivity in the other connectivity factor, which primarily comprised the amygdala, hippocampus, and dACC. There is mixed evidence in for this network's role in peripheral inflammation. In one study, individual differences in stressor-evoked inflammatory reactivity associated with connectivity between the amygdala and dorsomedial PFC, an area anatomically located near the dACC. However, in a recent meta-analysis on the neural correlates of peripheral inflammation, meta-analytic connectivity analyses did not report connections between these dorsomedial cortical areas and limbic areas across studies. Given these null results in the context of contradictory findings, it is unclear how limbic - dorsal PFC connectivity may relate to ACEs or inflammation.

4.4 ANCILLARY AIMS

The findings that corticolimbic connectivity was unrelated to subclinical depressive symptoms raise questions about the validity of these neuroimaging measures in the context of affective disorder risk. More concretely, these findings cast doubt on prior studies that propose altered limbic – PFC connectivity to be a state or trait marker of negative affect or risk for

psychopathology. Altered connectivity within this circuit has been previously described reflecting the "regulatory capacity of the fear circuit", (Herringa et al., 2013) and "the trait-like ability to regulate negative emotion," (H. Lee et al., 2012) yet our results are inconsistent with these descriptions insofar as corticolimbic connectivity can relate to subclinical levels of depression. However, in line with the limitations of Aim 2, it is possible that the relatively low severity of depressive symptoms across this healthy sample may have reduced the power to detect significant associations.

Ancillary aims did not support the notion that ACEs could statistically *moderate* associations between corticolimbic connectivity and systemic inflammation, line with the concept that early adversity "amplifies the crosstalk" between these two systems (Nusslock & Miller, 2016). Despite the null findings, this hypothesis is in line with emerging theoretical perspectives on the neurobiology of stress-related cardiovascular disease (CVD) risk. Here, acute and chronic stress may confer CVD risk by altering viscerosensory and visceromotor networks in the brain. These networks regulate peripheral autonomic and vascular physiology, (Ginty et al., 2017) possibly by anticipating signals from the periphery and issuing commands via predictive control (Jennings & Gianaros, in press). Critically, it is thought that psychological stress may specifically impact the functionality of this predictive control mechanism and thereby influence CVD risk. Anatomically, the brain networks for autonomic and vascular predictive control appear to overlap substantially with those for peripheral inflammatory physiology (Beissner et al., 2013; Kraynak, Marsland, Wager, & Gianaros, in prep), raising the possibility that a similar perspective can be applied to ACEs-related physical and mental disease risk. Although these ancillary aims do not appear to support this hypothesis in the context of the corticolimbic system at rest, their motivating hypothesis may nonetheless be interesting for future research.

5.0 LIMITATIONS AND FUTURE DIRECTIONS

There are a number of limitations to the present study that warrant attention. As described previously, there is not a broadly accepted method of determining how ACEs should be measured or computed to examine their effects on mental or physical health outcomes; however, this study may have limitations with regard to its measurement of ACEs, for three reasons. First, the retrospective nature of the ACEs measurement has the potential to introduce recall and other forms of bias and therefore influence observed associations. However, to our knowledge, no prospective studies have examined the effects of ACEs on *both* inflammatory and neurobiological outcomes. Hence, the present study provides a reference point for future prospective studies in this area. Second, the ACEs measurements accepted a broad perspective of the developmental timing of adversity; put differently, measures of adversity in the present study differentiate between events occurring at age 5 versus age 12. Indeed, there is some evidence suggesting that the timing of adversity may have strong implications for mental and physical health outcomes (Slopen, McLaughlin, Dunn, & Koenen, 2013). Hence, this study may not have sufficiently addressed the role of developmental timing, which may be crucial to effectively characterizing later life outcomes. Third, measurement of ACEs in the present study prespecified certain qualitative features of ACEs to focus on *threat*, which may have ignored other important features of ACEs that associate with systemic inflammation (e.g., deprivation) (McLaughlin et al., 2014).

Some other limitations should be noted. First, the study design was cross-sectional, which limits causal inferences that can be drawn from observed associations. Second, the present study utilized a relatively healthy midlife adult sample that was free of physical health conditions and

diagnosed psychiatric disorders. As a result, the base-rate of endorsing ACEs was relatively lower than other samples with known trauma or diagnosed affective disorders. As a result, we may have been underpowered to detect significant inflammatory or brain outcomes on the basis of ACEs.

In conclusion, the present study provided empirical evidence in support of components of the neuroimmune network hypothesis, namely, demonstrating associations between ACEs and systemic inflammation, and between systemic inflammation and resting brain corticolimbic connectivity. However, some important components of this hypothesis were not supported (i.e., associations between ACEs and corticolimbic connectivity). Collectively, future research in this area may help to identify and increase our mechanistic understanding of potentially modifiable biological processes, such as systemic inflammation, that may link ACEs to later mental and physical health outcomes in adulthood.

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