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Oppressive Systems and Risk for PTSD in Minoritized Communities

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Oppressive Systems and Risk for PTSD in Minoritized Communities

By

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B.S.A Neuroscience, University of Texas, 2017

Advisor: Vasiliki Michopoulos, Ph.D.

An abstract of
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Abstract

Oppressive Systems and Risk for PTSD in Minoritized Communities

By Meghna Ravi

Black persons with few economic resources are disproportionately affected by PTSD, and pregnant Black persons may be particularly impacted. Environmental stressors like racism and biological factors like inflammation have been associated with greater PTSD symptoms, though little is known about how other environmental factors, like neighborhood poverty rates impact PTSD symptoms, or how these factors affect PTSD symptoms within pregnancy. In the current dissertation, I hypothesized that oppressive systems like racism and neighborhood poverty would be associated with greater PTSD symptoms in pregnant and non-pregnant persons, and that higher inflammation would relate to higher PTSD symptoms within pregnancy. I first determine the main and interactive effects of racial discrimination and neighborhood poverty on PTSD symptoms in a sample of non-pregnant Black women with few economic resources, and find that experiencing high amounts of racial discrimination or living in an area with a high rate of poverty are associated with high PTSD symptoms. I then follow up on this result and find that higher rates of neighborhood poverty predict greater PTSD symptoms six-months after experiencing a traumatic event in a non-pregnant sample of varied gender and socioeconomic status. Next, I focus on biological and environmental risk factors for PTSD within pregnant Black persons with few economic resources. I find that while neighborhood poverty is not associated with PTSD symptoms, higher amounts of racial stress (or stress caused by experiencing racism) are associated with more PTSD symptoms. I also find a trending positive association between systemic inflammation and PTSD symptoms. Lastly, I assess one mechanism by which racial stress can result in higher PTSD symptoms among pregnant Black persons, and find that racial stress is associated with more negative evaluations of therapy, which is in turn associated with greater PTSD symptoms. Overall, the results presented in this dissertation highlight that oppressive systems can exacerbate PTSD symptoms, and demonstrate the need for policies that promote racial and economic equity.

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CHAPTER 1: INTRODUCTION: STRESS, SYSTEMIC INFLAMMATION, AND PSYCHOPATHOLOGY WITHIN AND OUTSIDE OF PREGNANCY

1.1 Context, Authors' Contribution, And Acknowledgement Of Reproduction

The following Chapter reviews the relationships between stress, inflammation, and psychopathology within and outside of pregnancy. This work was conceptualized, researched, organized, and written by the dissertation author, with editorial feedback from Dr. Vasiliki Michopoulos. This Chapter is reproduced from Ravi, M., Miller, A., Michopoulos, V. The Immunology of Stress and the Impact of Inflammation on the Brain and Behavior. British Journal of Psychiatry Advances. (2021) and Ravi, M**.,** Bernabe, B., Michopoulos, V. Relationships Between Stress-Related Psychopathology and Inflammation in Pregnancy. Frontiers in Psychiatry. (2022).

1.2 Introduction.

Exposure to a vast array of stressors is pervasive throughout our modern-day society, and contributes significantly to the risk for adverse behavioral outcomes, including depression and anxiety (McEwen, 2008). One critical player in the response to stress and its impact on health is the immune system, which includes both innate and adaptive immune responses. Of special relevance is that the context (e.g., acute versus chronic) of stress exposure can significantly influence how the organism and the immune system responds to threat. While acute activation of the immune system in response to threat is homeostatically regulated by neuroendocrine mechanisms, chronic activation of the immune system arising from persistent stress exposure can contribute to an allostatic load with an inflammatory diathesis that has been implicated in the pathophysiology of mood and anxiety disorders (McEwen, 2008). Herein we will review the immunology of acute and chronic stress exposure, integrate this discussion with the emerging literature linking heightened immune activation and inflammation to mood and anxiety disorders,

and consider the translational implications of the immune system's role in these psychiatric conditions.

1.3 Homeostatic regulation of immune activation in response to acute stress exposure.

In the context of acute stressor exposure, rapid engagement of the sympathetic nervous system (SNS) results in the activation of cells mediating the innate and adaptive immune response via efferent projections from the SNS to the bone marrow and lymphoid tissues to prepare the body for injury and wound repair that may result from a threat (Segerstrom & Miller, 2004). The innate immune response functions quickly (within minutes to hours) to provide organismal defense against pathogens and/or tissue damage or destruction from wounding. This natural immunity is mediated by an array of leukocytes, including granulocytes (neutrophils, eosinophils, basophils, and mast cells), monocytes/macrophages, and natural killer (NK) cells, which produce inflammation (e.g., cytokines and reactive oxygen species) and engage in phagocytosis to destroy and dispose of the pathogens, respectively and initiate the wound healing process. While innate immunity is fast-acting upon threat exposure, acquired immunity requires days to generate response to specific pathogens. Cells mediating acquired immunity include different classes of lymphocytes that express antigen-specific receptor sites on their surfaces. The release of adrenaline and noradrenaline from the sympathetic-adrenal-medullary axis upon threat exposure activates monocytes/macrophages and lymphocytes via beta-adrenergic receptors to induce the innate (Scanzano & Cosentino, 2015) and specific (Kenney & Ganta, 2014) immune responses, respectively.

Upon exposure to an acute stressor, SNS signaling via adrenaline and noradrenaline induces rapid alterations in the absolute numbers and the proportion of leukocytes in circulation that function to traffic immune cells to sites of wounds across vertebrate species, including

humans (Herbert & Cohen, 1993). This occurs in tandem with a redistribution of leukocytes within compartments critical for immune system function, as there is an initial increase in lymphocytes and monocytes in the blood that is subsequently followed by a decrease as these cells enter organ compartments, such as the skin, lungs and lymph nodes, that may be a site of wounding and/or infiltration by pathogens (Dhabhar et al., 2012). For instance, acute stress exposure (e.g. physical restraint) in mice results in a more robust increase in the infiltration of leukocytes, including neutrophils, macrophages, and NK and T cells, at the site of surgery or wounding (Viswanathan & Dhabhar, 2005). A concomitant upregulation in gene expression of pro-inflammatory gene expression, including tumor necrosis factor (TNF), interferon gamma (IFNg), and interleukins 1beta (IL-1b) and 6 (IL-6), occurs upon at the site of this acute-stress induced redistribution of immune cells (Viswanathan et al., 2005).

The ability of acute stress exposure to induce changes in gene expression is mediated by the activity of nuclear factor-κB (NF-κB), a redox-sensitive transcription factor whose activity increases pro-inflammatory cytokine secretion from mononuclear cells. More specifically, translational studies show that increases in noradrenaline following acute psychosocial stress (e.g. Trier Social Stress Test; TSST) and immobilization (e.g. restraint) stress exposure, in humans and mice respectively activates NF-κB to induce IL-6 release (Bierhaus et al., 2003). *In vitro* and *in vivo* studies also show that pharmacological blockade of adrenergic signaling via a1-adrenergic antagonist blocks this stress-induced NF-κB activity (Bierhaus et al., 2003). It is important to note however that the ability for adrenaline to induce pro- or anti-inflammatory cascades within the innate immune system is dependent upon cell-specific expression of different beta-adrenergic receptors subtypes (for comprehensive reviews please see (Kenney & Ganta, 2014; Scanzano & Cosentino, 2015)).

Adrenaline and noradrenaline release upon threat-induced activation of the sympathetic-adrenomedullary axis occurs in tandem with aldosterone release that acts via mineralocorticoid receptors to decrease neutrophils, helper T cells and NK cells (Miller et al., 1994). Parallel threat-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis results in *de novo* cortisol synthesis and release from the adrenal cortex that acts via glucocorticoid receptors to impact immune cell distribution and activity (Miller et al., 1994). Low concentrations of corticosterone in rodents have been shown to enhance acute stress-induces redistribution of T cells and delayed-type hypersensitivity (DTH) of the skin, while also leading to trafficking of immune cells to the brain (meninges) in association with decreased anxiety-like behavior (Lewitus et al., 2008). In contrast, high doses and chronic doses of corticosterone or the synthetic glucocorticoid dexamethasone suppress dihydrotestosterone (DHT) (Dhabhar & McEwen, 1999) and increase anxiety- and depressive-like behaviors in laboratory animals. This bimodal, or biphasic, response of the immune system to acute stress-induced release of glucocorticoids is dependent upon negative feedback mechanisms at the level of the glucocorticoid receptor to inhibit NF-κB and the downstream release of pro-inflammatory cytokines (Rhen & Cidlowski, 2005), and restore homeostasis (McEwen & Wingfield, 2010). Taken together, existing data indicate that acute stress exposure enhances innate and acquired immunity to increase the chances of organismal survival in the face of potential wounding and pathogen entry, while chronic exposure to stress may have more detrimental effects.

1.4 Chronic stress-induced allostasis facilitates increased systemic inflammation.

Under conditions wherein organisms are exposed to chronic (e.g. unrelenting, constant) stressors, glucocorticoid negative feedback inhibition of immune activation is impaired in a manner that

drives allostasis (e.g. maintenance of organismal stability by altering physiological properties to counteract threats) (McEwen & Wingfield, 2010) and facilitates increased levels of systemic inflammation. Chronic stress exposure across rodents (Young et al., 1990), non-human primates (Michopoulos et al., 2012), and humans (Irwin, 2008) results in diminished glucocorticoid negative feedback of the HPA axis arising from glucocorticoid resistance (Cohen et al., 2012). Glucocorticoid resistance is believed to be due in part to inhibitory effects of cytokines on glucocorticoid receptor (GR) function, as well as stress-induced epigenetic modifications of molecules that regulate the GR, including FKBP5 (Zannas et al., 2019). Consequences of this glucocorticoid resistance includes hypercortisolemia and increased activation of the immune system that can result in heightened pro-inflammatory cytokine and increased risk for individuals to become sick upon pathogen exposure (Cohen et al., 2012).

Translational work in female rhesus macaques where the chronic psychosocial stress exposure associated with social subordination (e.g. constant harassment from higher-ranking animals) can be manipulated via social rank rearrangements shows that low social status causally alters immune gene expression profiles of NK, helper T cells, B cells and cytotoxic T cells towards expression profiles that denoted increased lymphocyte proliferation, heightened innate immune responses, and augmented cytokine responses (Snyder-Mackler et al., 2016). These social stress effects on pro-inflammatory gene expression at rest (e.g. in the absence of pathogen exposure) are most potently seen in NK and helper T cells, and are exacerbated upon *in vitro* stimulation with lipopolysaccharide (LPS) (Snyder-Mackler et al., 2016), a component of gram-negative bacteria that is used commonly to invoke a strong inflammatory response by binding toll like receptor 4 (TLR4) on monocytes. More specifically, LPS stimulation in subordinate, chronically stressed monkeys, results in the enrichment of genes associated with response to

bacterial infection, including the inflammatory response and cytokine production (Snyder-Mackler et al., 2016), and lower expression of genes involved in the antiviral response and type I interferon signaling (Sanz et al., 2019). Of note, this stress-related increase in expression of inflammatory genes and decreased antiviral genes (labeled the Conserved Transcriptional Response to Adversity) is believed to be related to chronic sympathetic nervous system activation and has been found in the context of a variety of chronic stressors in humans, including low socioeconomic status (Knight et al., 2016).

Genes upregulated by LPS and more highly expressed in subordinate female macaques include members of the NF-κB transcription factor complex, including *NFKBID*, *NFKNIZ*, and *NFKB1*, as well as the *STAT3* and *STAT5A* transcription factors that are involved in proinflammatory cytokine response (Snyder-Mackler et al., 2016). This LPS-induced increase in NF-κB activity in chronically stressed monkeys is due to the polarization of the TLR4 signaling cascade towards the inflammatory MyD88-dependent pathway and away from the antiviral Toll/IL-1R domain-containing adaptor-inducing IFN-β (TRIF)-dependent pathway that is favored in more dominant monkeys (Sanz et al., 2019; Snyder-Mackler et al., 2016). Interestingly, social subordination also drives an exaggerated expression of NF-κB and interferon-associated genes upon challenge with a viral mimic that can also be proinflammatory in nature (Sanz et al., 2019). Critically, the increase in proinflammatory response upon LPS-stimulation is mediated by diminished glucocorticoid sensitivity in low-ranking animals (Snyder-Mackler et al., 2016).

The alterations in immune cell gene expression described above due to chronic psychosocial stress exposure in female rhesus macaques are associated with changes in chromatin structure, and thus, DNA accessibility to glucocorticoids (Snyder-Mackler et al.,

2016). More specifically, low-ranking females present chromatin landscapes that are more accessible for NF-κB transcription factor binding sites, whereas high-ranking females show more accessible binding sites for AP-1, the glucocorticoid receptor cofactor that is involved in anti-inflammatory responses and inhibition of NF-κB (Snyder-Mackler et al., 2019). Importantly, *in vitro* dexamethasone administration also results in the enrichment of transcription factor binding sites for AP-1, suggesting that glucocorticoid resistance resulting from chronic subordination stress alters the dynamics of glucocorticoid-mediated gene expression in immune cells and chromatic accessibility to drive systemic inflammation (Snyder-Mackler et al., 2019). Taken together, these data underscore the mechanisms by which maladaptive allostatic consequences of chronic stress exposure can drive a pro-inflammatory state that increases risk for adverse health outcomes, including stress-related psychopathology (McEwen, 2008).

1.5 Increased inflammation in individuals with stress-related psychopathology.

Systemic inflammation is associated with stress-related psychopathology, including depression and anxiety (Haroon et al., 2012; McEwen, 2008; Michopoulos et al., 2017). Systematic reviews and meta-analyses of available data on the relationship between inflammation and depression and fear and anxiety disorders support the notion that these stress-related conditions are associated with increased systemic inflammation as assessed by circulating concentrations of C-reactive protein (CRP) and cytokines (Table 1.1). Meta-analytic results indicate that glucocorticoid resistance is an important component of this increased inflammation in patients with depression (Perrin et al., 2019).

It is important to note that while most work to date focuses on peripheral blood concentrations of inflammatory biomarkers in stress-related psychiatric conditions (Dargel et al.,

2015; Modabbernia et al., 2013; Osimo et al., 2020; Renna et al., 2018; Yang & Jiang, 2020)}(Cosco et al., 2019; Costello et al., 2019; Passos et al., 2015; Quagliato & Nardi, 2018), heightened inflammation is also seen in the brain. More specifically, a systemic review and meta-analysis shows that cerebral spinal fluid (CSF) concentrations of IL-6 and TNF are increased in individuals with depression (Enache et al., 2019). Increased microglia activation, the central mediators of the immune system, as assessed by PET neuroimaging, and greater expression of TNF and TLR4 in post-mortem brain tissue have also been described in individuals with depression (Enache et al., 2019). While these existing large-scale and reproducible data highlight the association between inflammation and stress-related psychiatric disorders, the cross-sectional nature of the majority of the studies limits our ability to determine the cause-and-effect relationship between stress-induced inflammation and behavior. Nevertheless, translational studies in human and pre-clinical models clearly show that peripheral and central inflammation can directly impact brain function to drive psychiatric symptoms and blocking inflammation can reduce symptoms of depression and anxiety in patients with increased inflammation.

1.6 Mechanisms by which inflammation contributes to stress-related symptoms.

The notion that stress-induced inflammation can induce affective symptomology was first highlighted by the finding that administration of the inflammatory cytokine, interferon-alpha, for the treatment of infectious diseases and cancer induced depressive symptoms (Raison et al., 2005). Since then, a significant body of literature has emerged that describes the causal effects of acute and chronic inflammatory stimuli on the emergence of affective symptoms. For example, administration of endotoxin or typhoid vaccination induces depressed mood, anhedonia, fatigue, and cognitive dysfunction (Capuron et al., 2012; Eisenberger et al., 2010;

Harrison, Brydon, Walker, Gray, Steptoe, & Critchley, 2009). Neuroimaging studies have further shown that these inflammatory stimuli as well as endogenous inflammation in patients with depression can alter the functional connectivity and activation of brain regions implicated in the pathophysiology of stress-related psychopathology, including the prefrontal cortex (PFC), striatum, dorsal anterior cingulate cortex (dACC) and amygdala (Harrison, Brydon, Walker, Gray, Steptoe, & Critchley, 2009; Harrison, Brydon, Walker, Gray, Steptoe, Dolan, et al., 2009; Muscatell et al., 2015). In addition, the impact of laboratory stress on reward prediction errors was found to be mediated by stress-induced levels of IL-6 in women (Treadway et al., 2017), and laboratory stress-induced levels of sTNFR2 were found to correlate with activation of dACC as a function of rejection sensitivity (Slavich et al., 2010). Overall, studies indicate that inflammation decreases functional connectivity between the PFC and striatum in a manner that predicts reward deficits, anhedonia and psychomotor slowing. Moreover, inflammation decreases functional connectivity between the PFC and the amygdala in a manner that predicts anxiety symptoms (Mehta et al., 2018) as well as increases in amygdala and dACC reactivity to threat (Eisenberger et al., 2010; Harrison, Brydon, Walker, Gray, Steptoe, & Critchley, 2009; Harrison, Brydon, Walker, Gray, Steptoe, Dolan, et al., 2009), which has been associated with increased IL-6 response to acute stress exposure in humans (Muscatell et al., 2015).

Cytokines released in the periphery in response to stress exposure can impact the brain by passing through leaky regions of the BBB, being actively transported across the BBB, activating endothelial and perivascular macrophages lining the brain to release their own cytokines into the brain parenchyma, and activating cytokine receptors on the vagus nerve and other peripheral afferent nerves to signal the brain (Haroon et al., 2012). Peripheral cytokines released in response to stress exposure can also recruit activated monocytes and macrophages from the

blood into the brain, wherein they produce their own cytokines and activate microglia, which themselves can release cytokines locally in the brain (D'Mello et al., 2009). Finally, recent data indicate that stress-induced activation of NF-kB and TNF signaling pathways in endothelial cells in the nucleus accumbens can lead to a local reduction in the integrity of the blood brain barrier (Menard et al., 2017), allowing direct access of inflammatory cytokines to this brain region and ultimately depressive-like behavior.

Once in the brain, cytokines can influence behavior via their ability to alter the metabolism of neurotransmitters, including monoamines and glutamate (for review, please see (Dunn et al., 1999)). These effects of central cytokines on neurotransmitters are mediated through effects on neurotransmitter synthesis, release and reuptake, leading to decreased monoamine availability and increased extrasynaptic glutamate, which can be excitotoxic (Haroon et al., 2012). In addition, increased activation of indoleamine 2,3 dioxygenase (IDO), the enzyme that acts to convert tryptophan into kynurenine, leads to greater levels of kynurenine. This increased kynurenine is then broken down into quinolinic acid, a N-methyl-D-aspartate (NMDA) receptor agonist, which can further contribute to glutamate excitotoxicity and oxidative stress (Qin et al., 2007). Increased kynurenine has been described in stress-related psychopathology, such as depression (Haroon et al., 2020) and in individuals with INF-alpha-induced depression (Raison et al., 2010). Cytokine-induced alterations in the IDO/kynurenine can decrease serotonin and dopamine levels, as well as increase glutamate levels (Haroon et al., 2012), which have been linked to increased stress-related symptoms, including depressed mood, anhedonia, and psychomotor slowing (Haroon et al., 2012).

1.7 Clinical considerations and implications regarding the immunology of stress.

Under conditions of chronic stressor exposure, the emergence of a proinflammatory allostatic state can contribute to psychiatric symptoms across depression and anxiety disorders via site-specific cytokine actions on neurotransmitters systems in brain regions underlying emotion regulation and affect (Figure 1.1). Accordingly, interventions targeting the immune system and its downstream effects on the brain for the treatment of depression and other psychiatric disorders has been of great interest. A number of strategies have been employed including blocking inflammation itself through pharmacologic or behavioral means or attempting to reverse the downstream effects of inflammation on neurotransmitter systems.

Probably the most convincing data that blocking inflammation can reduce depressive symptoms comes from studies using cytokine antagonists in patients with autoimmune and inflammatory disorders (Kappelmann et al., 2018), albeit the impact of these drugs on the underlying disease complicate interpretation of these findings. Meta-analyses of other medications that putatively target the impact of inflammation on the brain including COX-2 inhibitors, aspirin, and minocycline (a tetracycline antibiotic that decreases microglial activation) have revealed some evidence of effectiveness in otherwise healthy depressed individuals, however the off-target effects of these medications and the fact that increased inflammation occurs in only about 1/3 of depressed patients leaves some level of doubt regarding the specificity of findings relative to inflammation (Bavaresco et al., 2020; Osimo et al., 2019). Only a handful of studies have used anti-cytokine therapies in depression, and the results suggest that baseline inflammation (as reflected by CRP) is an important predictor of response, and symptoms that seem most responsive relate to anhedonia, psychomotor retardation and anxiety

(Bavaresco et al., 2020). The notion that baseline levels of inflammation may be an important consideration for pharmacological treatment extends past the use of anti-inflammatory agents, as greater inflammation in depression is also associated with resistance to conventional antidepressant treatments (Haroon et al., 2018). The variability in the inflammatory profiles of individuals diagnosed with major depression disorder (MDD) is highlighted by a recent systematic review and meta-analysis reports that approximately one quarter of individuals with MDD show low-grade inflammations (CRP of >3 mg/L) and approximately half show mildly elevated CRP levels (CRP of >1 mg/L) (Osimo et al., 2019).

Other pharmacological and behavioral interventions shown to be efficacious for the treatment of stress-related psychopathology may be immunomodulatory in nature, and thus could provide benefits through their abilities to attenuate systemic inflammation (Liu, Wei, et al., 2020). Therapy with serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, citalopram, escitalopram and fluvoxamine, decreases peripheral concentrations of IL-6, IL-1b, and TNF (Wang et al., 2019), although these effects appear to be largely related to treatment response and likely the associated reduction in stress. Moreover, treatment with SSRIs have been shown to be minimally effective in patients with increased inflammation (Haroon et al., 2018). Mindfulness-based interventions have been shown in meta-analyses to decrease biomarkers of inflammation, including IL-6 and TNF across depression and anxiety disorders (Sanada et al., 2020), and cognitive behavioral therapy for the treatment of depression normalizes cytokine levels (Dahl et al., 2016). However, the efficacy of cognitive behavioral therapy for decreasing inflammation across common stress-related mental conditions, including depression and anxiety, as studies assessing the relationship report equivocal findings (Memon et al., 2017). The adjunctive use of nutraceuticals (e.g. pharmaceutical-grade nutrients), such as S-

adenosylmethionine (SAMe), methylfolate, omega-3 polyunsaturated fatty acids (PUFAs), and vitamin D, in conjunction with other evidence-based treatments also provide benefit for stress-related psychopathology through their anti-inflammatory actions or support of neurotransmitter metabolism (Sarris et al., 2016). Finally, drugs such as ketamine (a NMDA antagonist) and levodopa (LDOPA; precursor of dopamine) that are efficacious for treating depression and PTSD (Park et al., 2019; Ross, Jain, et al., 2019) may be acting by blocking or circumventing the downstream effects of stress-induced cytokines on glutamate or dopamine, respectively.

Although existing data suggest targeting the immunology of chronic stress may be a valid intervention for stress-related psychopathology, the majority of research to date has taken place in the context of depression. Future translational and clinical research is necessary to better determine the mechanism by which the immune system and inflammation contributes to anxiety disorders and PTSD, and whether interventions targeting the immune system, or it effects on the brain are efficacious in these conditions. Other factors that contribute significantly to individual variability in the immunology of stress exposure and may be important for treatment considerations in stress-related psychopathology include genetics and epigenetics, biological sex, and the presence of other sources of inflammation that may interact with stress, such as smoking, diet, and comorbid medical conditions including obesity, metabolic syndrome, diabetes, cardiovascular disease or cancer. It is also important that more long-term studies leveraging these approaches are undertaken to assess whether the efficacy of the treatments are long-lasting, even in conditions where individuals continue to be exposed to chronic stressors. Finally, the importance of attenuating the maladaptive mental health consequences of the immunology of stress across the lifespan is highlighted by emerging data dysregulated immune system

functioning is related to psychopathology in children and adolescents (D'Acunto et al., 2019) and in pregnancy (Ravi et al., 2022).

1.8 Psychoneuroimmunology of Pregnancy

The literature reviewed above demonstrates a clear link between stress, the immune system, and stress-related psychopathology in non-pregnant persons, though considerably less work has focused on psychoneuroimmunology within pregnancy. Pregnancy is characterized by incremental changes in the immune system (Abu-Raya et al., 2020), and evidence indicates that pregnant persons are at increased risk for depression, anxiety, and PTSD (Borri et al., 2008; Goodman et al., 2014; Lee et al., 2007; Marchesi et al., 2009; Michopoulos, Rothbaum, et al., 2015; Records & Rice, 2007; Seng et al., 2009; Seng et al., 2010). In addition to directly impacting prenatal mental health, stress-related disorders during pregnancy can result in epigenetic alterations in offspring (Babenko et al., 2015) and are associated with greater parenting stress (Huizink et al., 2017), suggesting these disorders can have important implications for development of psychopathology and other adverse health outcomes in offspring. It is therefore vital to understand how biological mechanisms like inflammation affect risk for stress-related mood, anxiety, and fear-related disorders in pregnancy to inform targeted interventions to attenuate prenatal and intergenerational risk.

1.9 Pregnancy and the Immune System

Pregnancy is a period of complex and profound immunological change at the fetal-parental interface (Ander et al., 2019; PrabhuDas et al., 2015) and in the pregnant individual’s periphery (Abu-Raya et al., 2020). Overall, pregnancy is characterized by a shift in balance toward the non-specific innate (e.g., neutrophils, monocytes, and natural killer [NK] cells) immune system over the acquired and antigen specific adaptive (e.g., T cells and B cells) immune system (Sacks

et al., 1999; Schminkey & Groer, 2014). During the first trimester of pregnancy, a pro-inflammatory state is conferred by greater activity of the innate immune system to promote uterine binding and to establish fetal-parental vasculature (Mor & Cardenas, 2010). This pro-inflammatory state is thought to be at least partially responsible for the morning sickness symptoms experienced by many pregnant persons in the first trimester (Mor & Cardenas, 2010).

The second and third trimesters of pregnancy are characterized by shifts in the innate and adaptive immune systems (Schminkey & Groer, 2014) that results in an anti-inflammatory bias, which is characterized by the release of fewer pro-inflammatory cytokines and greater anti-inflammatory mediators (Mor & Cardenas, 2010). During these late trimesters, there is an increased ratio of M2 macrophages (that produce anti-inflammatory signals) over M1 macrophages (that produce Th1-type responses) at the parental-fetal interface (Brown et al., 2014; Faas, Spaans, et al., 2014a). More specifically, T helper (Th) cells in the adaptive immune system shift from pro-inflammatory Th1 cells to anti-inflammatory Th2 cells, while the balance of NK cells in the innate immune system shifts toward an NK2 cell bias over NK1 cells, which are characterized by the interleukin-18 (IL-18) receptor (Borzychowski et al., 2005). As a result of low levels of circulating IL-18, this shift in NK balance towards fewer NK1 cells typically results in reduced concentrations of the pro-inflammatory cytokine interferon-g (IFN-g) (Sargent et al., 2006) and tumor-necrosis factor alpha (TNFα) (Faas, Kunnen, et al., 2014). Furthermore, monocytes in pregnant individuals also produce lower concentrations of pro-inflammatory cytokines, such as IL-18, TNFα, and interleukin-6 (IL-6), under low levels of monocyte stimulation (i.e., by a pathogen such as E-coli or lipopolysaccharide (LPS)) than monocytes in non-pregnant persons after stimulation (Abu-Raya et al., 2020; Faas, Kunnen, et al., 2014; Faas, Spaans, et al., 2014b; Sargent et al., 2006). Overall, the balance of M2/M1 macrophages under

conditions of low monocyte stimulation is thought to be important in preventing rejection of the fetus and in maintaining a healthy pregnancy (Brown et al., 2014; Faas, Spaans, et al., 2014a). Concentrations of pro-inflammatory cytokines typically remain low until the end of the third trimester, when an increased pro-inflammatory state (induced by high concentrations of corticotropin-releasing hormone, CRH (You et al., 2014)) is thought to promote uterine contraction and expulsion of the fetus (Mor & Cardenas, 2010b; Schminkey & Groer, 2014).

Under conditions of high monocyte stimulation, monocytes produce greater concentrations of multiple cytokines than under conditions of low to no stimulation. One cytokine that is increased under conditions of high monocyte stimulation is IL-18, which activates the IL-18 receptor on NK1 cells (Borzychowski et al., 2005), resulting in increased concentrations of IFN-g by NK1 cells (Sargent et al., 2006). Importantly, when monocytes in pregnant persons are stimulated in the presence of IFN-g, they produce increased amounts of pro-inflammatory cytokines as compared to monocytes in non-pregnant persons stimulated under the same conditions (Abu-Raya et al., 2020; Faas, Spaans, et al., 2014). In addition, IFN-γ can induce monocytes to differentiate into M1 over M2 macrophages (Brown et al., 2014). Thus, initially higher stimulation of monocytes can result in an exaggerated pro-inflammatory response and altered decidual M2/M1 macrophage balance in pregnant persons (Sargent et al., 2006). This adaptation of the immune system during the second and third trimester of pregnancy provides pregnant persons with the ability to respond to sufficiently inflammatory threats, even while in a general state of reduced systemic inflammation.

The baseline anti-inflammatory bias for greater basal levels of anti-inflammatory mediators in circulation compared to pro-inflammatory signals but simultaneous exaggerated pro-inflammatory response to high levels of immune stimuli in late pregnancy likely contributes

to the equivocal nature of existing data describing alterations in systemic inflammation throughout pregnancy (Mor & Cardenas, 2010). For example, one study reported wide variability in the magnitude and direction of changes in concentrations of CRP between individuals; some individuals showed a decrease in IL-6 and CRP through pregnancy, while others showed an increase (Belo et al., 2005). Additionally, another study found that concentrations of the pro-inflammatory cytokine IL-6 generally decreased across pregnancy, but showed large variability in concentrations of IL-6 at each trimester of pregnancy (Denney et al., 2011). While several studies on the modulation of the immune system during pregnancy have focused on the effects of infection or fetal trophoblast particles (Liu, Wang, et al., 2020; Sargent et al., 2006), other factors that stimulate monocytes may also result in pro-inflammatory monocyte activation in pregnant persons, which may help account for the equivocal nature of data on the immune system in pregnancy to date.

1.10 Stress/Trauma Impact Sympathetic, Neuroendocrine and Immune Interactions in Pregnancy

One environmental factor capable of activating monocytes and facilitating a pro-inflammatory state is stress and/or trauma exposure (Michopoulos et al., 2016). More specifically, under conditions of acute and chronic stress exposure, the sympathetic nervous system induces pro-inflammatory cytokine release from monocytes, including the release of IFN-g, which can prime a pro-inflammatory immune response to other potential stimulations in pregnant women (Sargent et al., 2006). Thus, individual differences in stress and/or trauma exposure could partially explain the wide variation in immune signaling changes reported in pregnant women to date. For instance, pregnant individuals who experience few to no stressors might show a decrease in systemic inflammation throughout pregnancy (Figure 1.2A), while pregnant persons who

experience more stressors, such as those with mood and/or anxiety disorders, might show an increase in systemic inflammation over the course of pregnancy (Figure 1.2B).

Chronic exposure to stress and trauma in pregnancy may also impact HPA activity and glucocorticoid sensitivity, which are also changing due to pregnancy itself. Placental production of corticotropin-release hormone (CRH) increases over time during pregnancy, though much of this CRH is inactive due to its binding to the CRH-binding protein (CRH-bp) (Mastorakos & Ilias, 2000; Trainer, 2002). However, in late pregnancy concentrations of CRH-bp decrease, leading to greater levels of free and active CRH (Mastorakos & Ilias, 2000; Trainer, 2002). These higher concentrations of active CRH facilitate increased parental production of adrenocorticotropic hormone (ACTH) from the pituitary, followed by increased cortisol production (Mastorakos & Ilias, 2000; Trainer, 2002). While much of the cortisol in the third trimester of pregnancy is inactive (due to increased concentrations of cortisol binding globulin [CBG]), there is an increase in free cortisol and (Ho et al., 2007; Jung et al., 2011) a significant decrease in CBG in the late third trimester of pregnancy (Ho et al., 2007), which results in a state of hypercortisolemia (Mastorakos & Ilias, 2000). This increase in cortisol during late gestation may be due to diminished GC negative feedback as assessed by the dexamethasone suppression test (Nolten & Rueckert, 1981). Only one study to date has assessed GR sensitivity at the receptor level during pregnancy using *ex vivo* assays and found decreased GR sensitivity in late pregnancy (Katz et al., 2012).

Overall, dysregulation of the parental HPA axis and CRH concentrations during pregnancy (due to stress) can negatively impact fetal brain structure, neurogenesis, and neurocircuitry (Kassotaki et al., 2021), emphasizing the need to address stress/trauma exposure and stress-related psychopathology in pregnancy. Additionally, higher levels of systemic

inflammation and prenatal stress exposure can also contribute to risk for negative birth outcomes like preeclampsia (Caplan et al., 2021; Michalczyk et al., 2020; Yu et al., 2013) and preterm birth (Cappelletti et al., 2016; Shapiro et al., 2013), which can impact infant mortality and can have long-term health consequences for offspring (Platt, 2014; Ton et al., 2020). For example, depression during pregnancy is associated with shorter gestational length, poorer neurobehavioral outcomes in neonates, and increased cortisol concentrations after a stressor in one-year old offspring (Osborne et al., 2018). Prenatal concentrations of immune markers and evening cortisol in the third trimester of pregnancy are associated with infant cortisol reactivity at one years old, highlighting the role of antenatal immune and stress processes on infant outcomes (Osborne et al., 2018).

Stress and psychopathology during pregnancy can also alter epigenetic mechanisms in the fetus, which have been associated with greater vulnerability to psychopathology and other negative health outcomes in offspring (Cao-Lei et al., 2016). For instance, prenatal exposure to famine during pregnancy has been associated with less DNA methylation of the insulin-like growth factor II (IGF2) in offspring (Heijmans et al., 2008), and changes in offspring DNA methylation at many regions (including regions that regulate immune system functioning) that have been associated with adulthood triglyceride levels (Tobi et al., 2018). The effects of stress during pregnancy can also have transgenerational effects, as the grandchildren of persons who were exposed to violence while pregnant show altered DNA methylation in regions associated with regulating the circulatory system (Serpeloni et al., 2017). Psychopathology before pregnancy can also impact both pregnancy and offspring outcomes; one study found that women with a history of depression (but not depression during pregnancy) showed increased levels of the immune markers IL-8, VEGF, and MCP-1 during the third trimester of pregnancy, and their

children showed altered neurobehavioral responses compared to women without a history of depression (Osborne et al., 2022). Thus, the need for a better understanding of the relationships between inflammation, stress/trauma exposure, and mood and anxiety disorders in pregnancy is vital for the well-being of both the pregnant individual and offspring.

1.11 Inflammation and Stress/Trauma in Pregnancy

Relatively few studies have examined the associations between lifetime and/or current stress and/or trauma exposure and inflammation in pregnancy specifically (Table 1.2). One study by Coussons-Read and colleagues found that increased current life stress levels are associated with higher concentrations of IL-6 and the pro-inflammatory cytokine TNFα, and with lower concentrations of the anti-inflammatory cytokine Interleukin-10 (IL-10) in a racially diverse sample (Coussons-Read et al., 2005). This finding was replicated in a primarily White sample, where current life stress was associated with increased concentrations of IL-6 in early and late pregnancy, and with lower concentrations of IL-10 in early pregnancy (Coussons-Read et al., 2007). Stress levels in the second trimester of pregnancy and low levels of social support in the third trimester predicted elevated concentrations of CRP in the third trimester of pregnancy, and higher stress levels throughout pregnancy were associated with increased production of pro-inflammatory cytokines by stimulated lymphocytes in the third trimester of pregnancy (Coussons-Read et al., 2007).

In support of the association between stress exposure and increased inflammation in pregnancy, increased acculturation, which has been associated with acculturative stress (or the stressors that accompany being an ethnic minority), has been associated with increased IL-6 concentrations throughout pregnancy in a sample of Mexican-American women (Scholaske et al., 2018). Interestingly, Latina women tend to show better pregnancy outcomes in comparison to

other groups despite factors like lower socioeconomic status (the so-called Latina paradox) (McGlade et al., 2004); however, this advantage diminishes the longer an individual is in the United States (Argeseanu Cunningham et al., 2008), potentially due to acculturation stress (Scholaske et al., 2018). Additionally, Black pregnant women who experienced any amount of racial discrimination in their lifetime had higher concentrations of IL-6 and interleukin-4 (IL-4) in their second trimester compared to Black pregnant women who did not report any racial discrimination in their lifetime (Giurgescu et al., 2016). In contrast, a study with Black and white pregnant women found that pregnancy did not have an effect on IL-6 concentrations after an acute stressor (the Trier Social Stress Task; TSST); Black pregnant and non-pregnant women demonstrated stronger IL-6 responses in response to the TSST compared to white women, with pregnancy itself having no observed effect on IL-6 responses (Christian et al., 2013). However, this study focused on IL-6 responsivity to an acute stressor, while to the best of our knowledge, no studies have compared the effects of chronic stress on inflammation between pregnant and non-pregnant women.

In addition to general life stress exposure, trauma history may also impact inflammation in pregnancy. One study found that trauma exposure was associated with increased concentrations of TNFα, but not with concentrations of IL-6 in the second and third trimesters of pregnancy (Blackmore et al., 2011). Importantly, trauma exposure was defined categorically (any exposure to trauma or not) and not continuously, and less than 40% of the sample had experienced a criterion A trauma, meaning the study might not have had sufficient power to identify relationships between trauma history and concentrations of IL-6 (Blackmore et al., 2011). A similar study found that women who had experienced intimate partner violence (IPV) saw blunted increases in IL-6 between the second and third trimesters compared to women who

had not experienced IPV, though only the degree of change between trimesters and not absolute concentrations of IL-6 varied based on exposure to IPV (Robertson Blackmore et al., 2016). However, only 35 out of 171 total women in this study had experienced IPV, and the study did not account for severity, amount, or timing of IPV experienced, which are important factors that may impact inflammation in pregnancy (Robertson Blackmore et al., 2016).

Crucially, none of the above studies examined the role of childhood trauma on inflammation in pregnancy specifically, which is thought to have a particularly strong effect on both inflammation and psychopathology in adulthood, in part due to epigenetic alterations of genes involved in stress responsive systems like the HPA axis (Baumeister et al., 2016). One study that focused explicitly on childhood trauma exposure found that childhood sexual abuse or physical neglect was not associated with concentrations of CRP in pregnancy, but CRP was associated with childhood physical abuse, emotional abuse, and emotional neglect. (Mitchell et al., 2018). Although there were no direct relationships between childhood trauma types and IL-6 or TNF-α concentrations, pre-pregnancy body mass index (BMI) did mediate a relationship between physical abuse and IL-6 concentrations (Mitchell et al., 2018). BMI also mediated the relationship between physical abuse and CRP concentrations, suggesting that experiencing physical abuse as a child may increase the likelihood of having a higher BMI in adulthood, which could result in higher inflammation in pregnancy (Mitchell et al., 2018). Conversely, a study with pregnant Latina adolescents found that childhood physical, sexual, or emotional abuse was not associated with IL-6 or CRP concentrations in the second or third trimesters of pregnancy (Walsh et al., 2016).

Taken together, studies to date suggest that stress/trauma exposure confers increased risk for higher inflammation in pregnant women and even altered expression of immune genes two to

six years after pregnancy (Aschbacher et al., 2021). This relationship may be due to glucocorticoid resistance. One study examining chronic stress, cortisol levels, and inflammation found that pregnant women at high risk for chronic stress exposure (women of either minority or low income status) have higher cortisol concentrations than low risk women, and the higher cortisol concentrations associated with the high risk group are not accompanied by decreased inflammation (Corwin et al., 2013). Specifically, women in the low risk group demonstrate a negative relationship between average cortisol concentration and a pro-to-anti-inflammatory cytokine measure, but this negative relationship is absent in women in the high-risk group (Corwin et al., 2013). Future studies are needed to assess the role of glucocorticoid resistance as a mechanism underlying increased inflammation in pregnant women experiencing high levels of stress and/or trauma exposure.

1.12 Inflammation and Stress-Related Psychopathology in Pregnancy

While the studies reviewed thus far suggest that stress and/or trauma exposure influence inflammation in pregnancy, the relationships between stress-related psychopathology and inflammation in pregnancy are even less clear. Most studies to date have assessed the cross-sectional relationship between psychopathology and inflammation in pregnancy, assessing whether inflammation is associated with symptoms of psychopathology and vice versa. One study found that concentrations of IL-6 at approximately 15 weeks gestation were positively correlated with depressive symptoms (as measured by the Center for Epidemiologic Studies Depression Scale or CES-D) after controlling for BMI (Christian et al., 2009) (Table 1.3). This study included primarily low-income women, where a little over half the women had a probable diagnosis of depression (Christian et al., 2009). Pregnant women with depression also show increased concentrations of IL-6, IL-10, TNF-α, vascular endothelial growth factor (VEGF),

increased diurnal cortisol secretion, increased evening cortisol secretion, and a blunted cortisol awakening response in the third trimester as compared to pregnant women without depression (Osborne et al., 2018). In addition, in a sample of Hispanic women, higher depressive symptoms were associated with higher concentrations of the interleukin 1-receptor antagonist (IL-1RA) (Ruiz et al., 2007), which is elevated under conditions of increased inflammation (Dayer & Burger, 1994).

In contrast, other studies have found no association between certain pro-inflammatory cytokines and depressive and anxiety symptoms. For example, in a sample of Finnish women, IL-6 and TNF-α were not associated with either depressive, overall anxiety, or pregnancy-related anxiety symptoms in the second trimester, though symptoms were associated with other cytokines including IL-9, IL-12, and IL-13 (Karlsson et al., 2017). Another study with a Black sample of varying socioeconomic status also found that depression scores were not associated with CRP, but were associated with concentrations of IL-6, though only in women of lower BMI (Cassidy-Bushrow et al., 2012). The lack of association between depressive symptoms and IL-6 concentration in women with higher BMI might be due to a ceiling effect due to higher BMI resulting in greater inflammation (Cassidy-Bushrow et al., 2012). Furthermore, childhood sexual, emotional, and physical abuse interact with depression to predict higher concentrations of IL-6 in the second trimester in Latina adolescents (Walsh et al., 2016). Pregnant women with more depressive symptoms may also show sensitization to immune challenges, as in a study of 22 pregnant women, those in the highest tertile of depression scores had higher concentrations of the pro-inflammatory molecule macrophage migratory inhibitory factor (MIF) than women with in the lowest tertile of depression scores one week after receiving the influenza vaccine (Christian et al., 2010).

Psychopathology in pregnancy may also impact the expression of cytokine trajectories throughout pregnancy. In a study of primarily minority women, depressed women (defined by having a score on the Beck Depression Inventory >9) had higher concentrations of IL-6 in the third trimester of pregnancy and showed an increase in IL-6 concentrations across pregnancy (Osborne et al., 2019). Women who were not depressed showed the opposite pattern and experienced a decrease in IL-6 across pregnancy (Osborne et al., 2019). The same relationship between symptoms and IL-6 concentrations was also found for anxious women (defined by endorsing a score on the State Trait Anxiety Inventory <34) (Osborne et al., 2019). Anxious women had higher concentrations of IL-6 in the third trimester of pregnancy and showed an increase in IL-6 concentration across pregnancy, while less anxious women exhibited a decrease in IL-6 across pregnancy (Osborne et al., 2019). Importantly, relatively few participants in this study endorsed clinically significant symptoms of anxiety or depression (14% of the sample was in the depressed group and 29% in the anxiety group) (Osborne et al., 2019). These effects might be stronger in samples with higher rates of psychopathology.

1.13 Implications and Future Directions

Overall, the limited existing literature indicates that stress and/or trauma exposure and the presence of depression can impact inflammation in pregnancy. However, the equivocal natures of some studies and disparities in immune markers assessed highlight the need for future well-powered and longitudinal studies to tackle the critical gaps in knowledge that remain. Further work is necessary to better understand the relationship between psychiatric symptoms and inflammation in pregnancy, especially given the existing evidence showing increased risk for psychopathology during pregnancy (Borri et al., 2008; Goodman et al., 2014; Lee et al., 2007; Marchesi et al., 2009; Michopoulos, Rothbaum, et al., 2015; Records & Rice, 2007; Seng et al.,

2009; Seng et al., 2010). Furthermore, most studies examining associations between psychiatric symptoms and inflammation in pregnancy focus on depressive symptoms, with only a couple also including anxiety symptoms. No known studies have investigated associations between inflammation and fear-related disorders like PTSD in pregnant individuals, despite evidence of a relationship between inflammation and PTSD symptoms in non-pregnant persons (Michopoulos, Norrholm, et al., 2015; Michopoulos et al., 2016). This is an important gap that should be addressed, as previous studies show that pregnant persons are also at increased risk for PTSD and increased psychophysiological hyperarousal (Michopoulos, Rothbaum, et al., 2015; Seng et al., 2009). Finally, it is important to better understand how experiencing stress and adversity during pregnancy and the presence of stress-related psychopathology impacts inflammation through alterations in behavior, such as eating (Kiecolt-Glaser, 2010) and sleep (Dolsen et al., 2019).

Another limitation of existing studies characterizing the impacts of stress/trauma and psychopathology and inflammation in pregnancy, especially those on trauma exposure, consist of samples that have experienced relatively few traumatic events over their lifespan, including childhood trauma which confers disproportionate risk for adverse health outcomes in adulthood (Copeland et al., 2018). It is especially important to understand the relationships between stress/trauma exposure and inflammation in pregnancy in order to address health inequities in pregnancy-related adverse health outcomes that may be driven by increased systemic inflammation. For example, Black individuals are disproportionately affected by preterm birth and preeclampsia, even after accounting for education and socioeconomic status (Purisch & Gyamfi-Bannerman, 2017; Ross, Dunkel Schetter, et al., 2019). Importantly, studies suggest Black women have higher concentrations of IL-6 in the second and third trimesters of pregnancy

compared to non-Black women (Blackmore et al., 2014). Furthermore, Black women show greater IL-6 release in response to LPS stimulation of leukocytes across pregnancy, as well as greater glucocorticoid resistance, compared to white women (Gyllenhammer et al., 2021).

The health inequities that Black pregnant persons face are not due to Black race itself, but to high rates of stress and trauma exposure (Gluck et al., 2021) and experiences of racism (Williams et al., 2003). Racism is a multi-dimensional system designed to uphold white supremacy at the expense of other racial groups (Braham et al., 1992; Corneau & Stergiopoulos, 2012), and Black persons experience racism at the systemic level and individual level (i.e. racial discrimination) (Corneau & Stergiopoulos, 2012; Salm Ward et al., 2013). Racial discrimination can be thought of as a chronic and unpredictable stressor (Lewis et al., 2015; Utsey et al., 2000), and could therefore increase likelihood of chronic and systemic inflammation in Black persons. Crucially, experiencing racism has been linked to poor pregnancy outcomes like preterm birth (Bower et al., 2018; Collins et al., 2000; Slaughter-Acey et al., 2016).

In addition to racial discrimination, the context in which a person lives may serve as an additional stressor during pregnancy. Specifically, living in an area with a high rate of poverty is associated with several chronic stressors including increased exposure to violence and police brutality and lack of access to nutritious food and/or safe and stable housing (Diez Roux & Mair, 2010; Ellen et al., 2001; Saegert & Evans, 2003). Because living in an area with high rates of poverty can be stressful, neighborhood poverty may also impact systemic inflammation and mental health outcomes, both within and outside of pregnancy. Importantly, systemic policies have made Black persons more likely to live in neighborhoods with high rates of poverty as compared to other groups, making neighborhood poverty a manifestation of racism at the systemic level (Lynch et al., 2021). If, as predicted, pregnant persons are more sensitive to

immune threats, it is possible that Black pregnant individuals show stronger inflammatory responses to chronic racial discrimination and high neighborhood poverty rates than when they are not pregnant. Taken together, it is possible that experiencing racism at either the individual or systemic level might be responsible for health inequities in preterm birth by increasing inflammation. Thus, a better understanding of the effects of stress and trauma on inflammation in pregnancy is critical to address pregnancy health inequities experienced by Black individuals and inform intervention strategies to mitigate prenatal and intergenerational risk.

1.14 Overview of the Dissertation

In the current dissertation, we aimed to address the gaps in current knowledge on stress/trauma, PTSD, and inflammation in both pregnant and non-pregnant individuals. In Chapter 2, we describe the main and interactive effects of two environmental stressors, racial discrimination and neighborhood poverty, on PTSD symptoms in non-pregnant Black women with few economic resources. In Chapter 3, we expand on findings from Chapter 2 and determine the role of neighborhood poverty in the prospective development of PTSD symptoms in the acute aftermath of trauma exposure in a non-pregnant individuals of varied gender and socioeconomic status. In Chapter 4, we focus on the relationships between racism, neighborhood, and systemic inflammation with PTSD and fear psychophysiology within pregnant Black persons. Finally, in Chapter 5, we determine one mechanism by which racism exacerbates PTSD symptoms in pregnancy by assessing the role of negative evaluation of therapy in pregnant Black persons.

Results from this dissertation will provide more clarity the wide variability in immune system functioning seen in pregnant persons and identify those most at-risk for adverse behavioral health outcomes over the course of pregnancy. This research could allow for early identification of pregnant individuals at increased risk for abnormally high levels of

inflammation, allowing for preventative, targeted care to increase likelihood of a healthy pregnancy and healthy offspring.

Figure 1.1 Exposure to chronic stressors and threats drives adrenocorticotropic hormone (ACTH) and cortisol release, as well as increased activity of the sympathetic nervous system (SNS). SNS activation of Nf-kB activity in immune cells increases expression of pro-inflammatory cytokines (e.g. IL-1,IL-6, TNF, IFNg) and CRP. Glucocorticoid resistance develops wherein cortisol does not as effectivity inhibit Nf-kB activity, thus creating a proinflammatory allostatic state that can contribute to psychiatric symptoms via cytokine actions on glutamate, kynurenine, dopamine, and serotonin systems in brain regions underlying emotion regulation and affect, including the striatum, dorsal anterior cingulate (dACC), medial prefrontal cortex (mPFC), and amygdala.

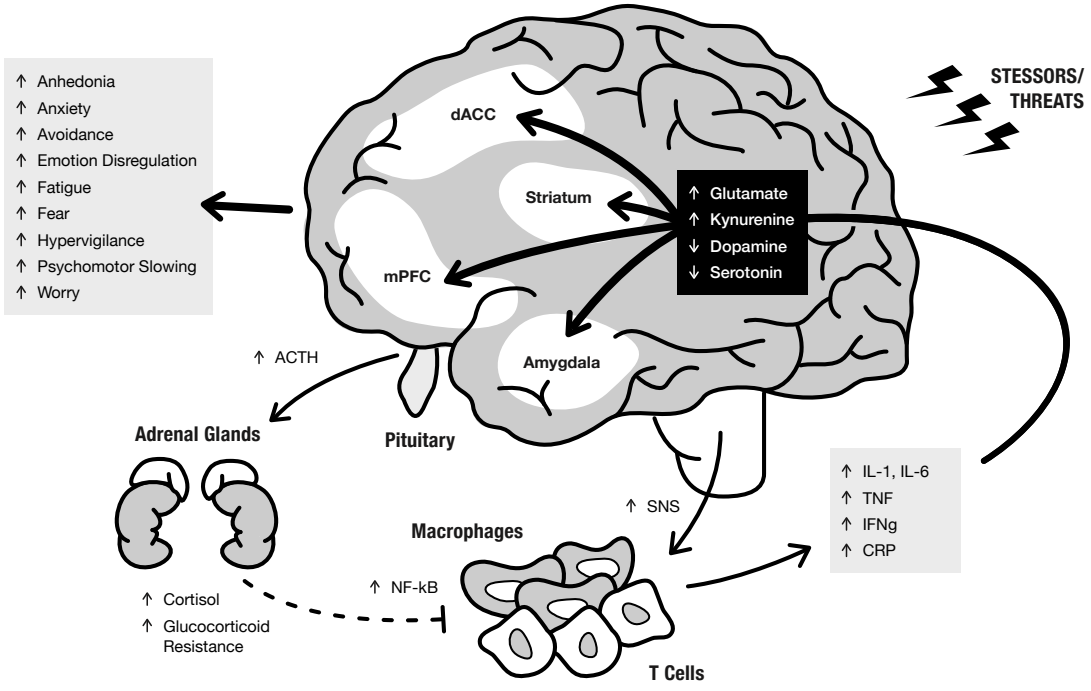


Figure 1.2: A) Under normal conditions, monocytes produce low concentrations of pro-inflammatory cytokines including TNFα, IL-12, and IL-18. Simultaneously, pregnancy is characterized by shift that reduces the proportion of NK1 (IL-18R1) cells in circulation. Existing NK1 cells are weakly stimulated by low concentrations of IL-18, resulting in low production of IFN-γ, ultimately resulting in more M2 decidual macrophages and a less pro-inflammatory environment that characterizes the second and third trimesters of healthy pregnancies. B) Under conditions of chronic stress, monocytes are stimulated at higher rates, resulting in greater production of pro-inflammatory cytokines, including IL-18. Higher concentrations of IL-18 activate NK1 cells at higher rates than under healthy conditions, leading to increased production of IFN-γ, which can promote an M1 over M2 bias in the decidua. When monocytes in pregnant individuals are stimulated in the presence of IFN-γ, the pro-inflammatory response is exaggerated, leading to even higher concentrations of pro-inflammatory cytokines, which could result in a pro-inflammatory bias in individuals experiencing chronic stress.

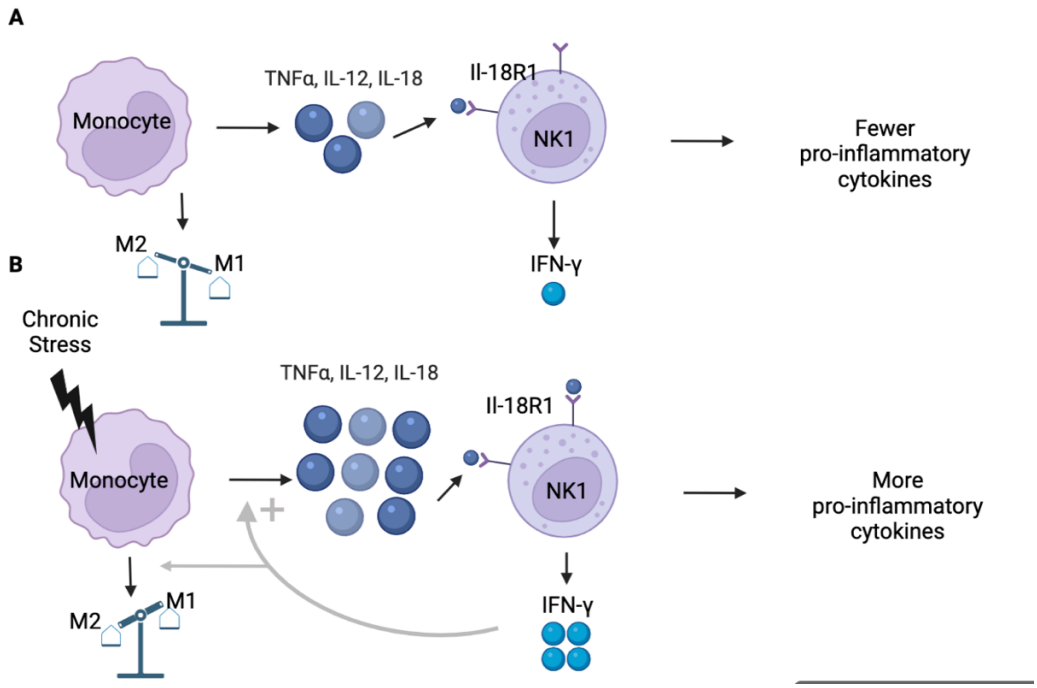


Table 1.1 Summary of systematic reviews and meta-analyses a on the relationship between inflammation and stress-related psychopathology.

Disorder/ Condition	Reference (Year)	# of Studies/ Cases	CRP	TNF	IL-1b	IL-6	IFNg	Others
Depression	Osimo et. al. 2020	107/5166	↑	↑	-	↑	-	↑ IL-3, IL-18, sIL-2R
Bipolar Disorder	Dargel et. al. 2015	11	↑	NA	NA	NA	NA	NA
	Modabbernia et. al. 2013	30/1351	NA	↑	-	↑	-	↑ sIL-2R, sIL-6R, IL-4, IL-10, sTNFR1
Anxiety, Traumatic Stress	Renna et al. 2018	41/1077	-	↑	↑	↑	-	NA
PTSD	Passos et. al. 2015	20/1109	-	-	↑	↑	↑	NA
	Yang et. al. 2020	42/1887	↑	↑	↑	↑	↑	↑ IL-2; ↑ leukocytes
Generalized Anxiety Disorder	Costello et al. 2019	14/1188	↑	NA	NA	NA	NA	NA
Panic Disorder	Quagliato et. al. 2018	11/887	NA	-	↑	↑	-	↑ IL-5
Obsessive Compulsive Disorder	Cosco et al. 2019	16/538	NA	-	-	-	-	NA

NA – Not assessed; - denotes null finding; ↑ denotes significantly higher in cases compared to healthy controls

Table 1.2: Stress/Trauma Exposure and Systemic Inflammation in Pregnancy

Year	Authors	Trimester	Phenotype Assessed	Inflammatory Markers	Main Findings
2005	Coussons-Read et al.	1, 2, & 3	Psychosocial Stress	IL-10, IL-6, TNFα	• Higher stress is associated with greater IL-6 and TNF-α • Higher stress is associated with lower IL-10 across all trimesters
2007	Coussons-Read et al.	1, 2, & 3	Psychosocial stress	Stimulated lymphocyte production of IL-1β, IL-6, IL-10, TNF-α; serum concentrations of TNF-α, IL-6, IL-10, CRP	• Higher stress is associated with lower IL-10 in the first trimester • Higher stress is associated with higher IL-6 in the first and third trimesters • No association between stress and IL-10 or IL-6 in the second trimester • Higher stress is associated with CRP in the second trimester but not the first or third trimesters • Higher average stress across all trimesters is associated with higher average CRP across all trimesters • Higher average stress across all trimesters is associated with greater

					lymphocyte production of IL-1β and IL-6
2009	Christian et al.	Any	Perceived Stress	Il-6, TNF-α	• Perceived stress is not associated with IL-6 or TNF-α
2011	Blackmore et al.	2 & 3	Trauma exposure	IL-6, TNF-α	• Trauma exposure is associated with TNF-α at both trimesters
2018	Scholaske et al.	1, 2, & 3	Acculturation	IL-6	• Higher acculturation is associated with higher IL-6 across all trimesters
2016	Giurgescu et al.	2	Racial Discrimination	IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10	• Experiences of racial discrimination is associated with higher IL-4 and IL-6, but not with any other cytokines measured
2016	Blackmore et al.	2 & 3	Intimate Partner Violence (yes/no)	IL-6, TNF-α	• History of IPV is associated with higher concentrations of TNF-α in the second trimester • History of IPV is associated with a smaller increase in IL-6 between the second and third trimesters
2016	Walsh et al.	2 & 3	Childhood Abuse	CRP, IL-6	• Childhood abuse is not associated with CRP or IL-6 at either the second or third trimester in adolescents

					• Adolescents with high depressive symptoms and who have experienced more abuse show higher IL-6 concentrations in the second trimester
2018	Mitchell et al.	1, 2, & 3	Childhood Abuse	CRP, IL-6, TNF-α	• Childhood physical abuse, emotional abuse, and emotional neglect are associated with CRP concentrations throughout pregnancy, but not with IL-6 or TNF-α. • BMI mediates a relationship between physical abuse and CRP and IL-6 concentrations across pregnancy. • The relationship between emotional abuse and CRP is not significant after controlling for BMI.

Table 1.3: Stress-Related Psychopathology and Systemic Inflammation in Pregnancy

Year	Authors	Trimester	Phenotype Assessed	Inflammatory Markers	Main Findings
2007	Ruiz et al.	2	Depressive symptoms	IL-1RA	• Higher depressive symptoms are associated with higher IL-1RA
2009	Christian et al.	Any	Depressive symptoms	Il-6, TNF-α	• Depressive symptoms are associated with higher IL-6 • Depressive symptoms have a trending association with TNF-α
2010	Christian et al.	Any	Depressive symptoms	MIF (baseline and 1 week post-influenza vaccine)	• Higher MIF one-week post-vaccine is associated with greater depressive symptoms
2011	Blackmore et al.	2 & 3	Depressive symptoms, anxiety symptoms, PTSD diagnosis	IL-6, TNF-α	• Depressive symptoms are not associated with IL-6 or TNF-α at either trimester • Anxiety symptoms are not associated with IL-6 or TNF-α at either trimester • PTSD diagnosis is not associated with IL-6 or TNF-α at either trimester
2012	Cassidy-Bushrow et al.	2	Depressive symptoms	CRP, IL-1β, IL-6, TNF-α, IL-10	• Depressive symptoms are associated with IL-6 and IL1-β, but not with CRP, TNF-α, or IL-10.

					• Depressive symptoms are associated with IL-6 concentrations in women with lower BMIs but not in women with higher BMIs. • Depressive symptoms are associated with higher IL-10 in women with lower BMIs but with lower IL-10 in women with higher BMIs.
2016	Walsh et al.	2 & 3	Depressive symptoms	CRP, IL-6	• Depressive symptoms in adolescents are not associated with CRP or IL-6 at either the second or third trimester. • Adolescents with high depressive symptoms and who have experienced more abuse show higher IL-6 concentrations in the second trimester.
2017	Karlsson et al.	2	Depressive symptoms, overall anxiety symptoms, pregnancy anxiety	IL-5, IL-9, IL-13, IL-12, IFN-ϒ, IL-4, IL-6, IL-10, TNF-α	• Higher depressive symptoms are associated with higher IL-9, IL-13, Il-12, IL-5, and a higher IFN-ϒ/IL-4 ratio. • Higher overall anxiety symptoms are associated with

					higher IL-9, IL-13, and IL-12 • Higher pregnancy related anxiety is associated with higher IL-12, IL-13, and Il-10. • IL-6 and TNF-α are not associated with any symptoms
2018	Osburne et al.	3	Depression diagnosis	IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, VEGF, EGF, MCP-1, CRP	• Depression is associated with higher concentrations of IL-6, IL-10, TNF-α, and VEGF.
2019	Osburne et al.	1, 2, & 3	Depressive symptoms, anxiety symptoms	Many including IL-6, Il-15, CCL3, C-X-C motif ligand 8 (CXCL8), and Granulocyte macrophage colony-stimulating factor (GM-CSF)	• Higher IL-15 is associated with depressive symptoms at the first and third trimesters. • Higher IL-6 and CCL3 are associated with depressive symptoms at the third trimester. • IL-6 and CCL3 decrease through pregnancy for less depressed women, but increase for more depressed women. • Higher CXCL8 is associated with anxiety symptoms in the first and third trimesters • Higher IL-6 and CCL3 is associated with anxiety symptoms

		at the third trimester • IL-6 increases through pregnancy for more anxious women, but not for less anxious women • GM-CSF decreased across pregnancy for less anxious women, but not for more anxious women.

CHAPTER 2: INTERSECTIONS OF OPPRESSION: EXAMINING THE INTERACTIVE EFFECT OF RACIAL DISCRIMINATION AND NEIGHBORHOOD POVERTY ON PTSD SYMPTOMS IN BLACK WOMEN

2.1 Context, Authors' Contribution, And Acknowledgement Of Reproduction

The following Chapter focuses on the main and interactive effects of racial discrimination and neighborhood poverty on PTSD symptoms. The dissertation author contributed to conceptualization, data analysis, and writing the manuscript under the guidance of Drs. Vasiliki Michopoulos, Abigail Lott, and Sierra Carter. Drs. Yara Mekawi, Jennifer Stevens, and Ms. Emily J Blevins assisted with methodology, data collection, and editing the manuscript. This Chapter is reproduced from Ravi M**.,** Mekawi Y., Blevins, EJ., Michopoulos, V., Stevens JS., Carter, S., Powers, A. Intersections of Oppression: Examining the Interactive Effect of Racial Discrimination and Neighborhood Poverty on PTSD Symptoms in Black Women. Journal of Psychopathology and Clinical Science (In Press).

2.2 Abstract

Black Americans living in urban environments are disproportionately impacted by posttraumatic stress disorder (PTSD). Both racial discrimination and neighborhood poverty are factors that contribute to this health disparity. However, studies focused on the intersection of these two oppressive systems on PTSD symptoms are lacking. To address this gap in the literature, we assessed the interactive effects of racial discrimination and neighborhood poverty on PTSD symptoms in an urban sample of trauma-exposed Black women (N=300). Simple moderation analysis was used to assess the main and interactive effects of racial discrimination and neighborhood poverty on PTSD symptoms. The overall model significantly predicted PTSD symptoms, with a main effect of racial discrimination (B=1.87, p=.009) and neighborhood poverty rate (B=0.27, p=.008), independent of prior trauma exposure and percentage of Black residents in the zip code. More frequent experiences of racial discrimination and higher rates of neighborhood poverty both predicted higher PTSD symptoms. There was also a trending

interaction of racial discrimination and neighborhood poverty (*B*=-0.05, *p*=.054), where the effect of neighborhood poverty on PTSD symptoms was only present for those who reported fewer experiences of racial discrimination. Our results suggest that people who have experienced more instances of racial discrimination show high levels of PTSD symptoms regardless of neighborhood poverty rates and highlight the importance of considering multiple levels of oppression that Black individuals face while diagnosing and treating stress-related psychopathology.

2.3 Introduction

Posttraumatic stress disorder (PTSD) is a debilitating disorder that can occur after a traumatic event and is characterized by a number of symptoms including hyperarousal, re-experiencing, and avoidance symptoms (APA, 2013). Black Americans are disproportionately affected by PTSD compared to other racial groups, and these disparities persist even after controlling for trauma exposure (Himle et al., 2009; Roberts et al., 2011; Sibrava et al., 2019). While lifetime rates of PTSD in the general population are about 7% (Keane et al., 2009), rates of PTSD in the overall Black population are 8.7% (Roberts et al., 2011), and much higher (53.8%) among Black women living in urban environments (Gluck et al., 2021). Consequently, examining factors that contribute to PTSD is necessary to better understand the development and etiology of symptoms for this disenfranchised population. Recent work examining factors that contribute to the high prevalence of PTSD symptoms among Black populations has highlighted the importance of social context (Bryant-Davis, 2019). Black individuals living in urban environments are situated at the intersection of numerous oppressive systems rooted in systemic racism, including racial discrimination and poverty, which could contribute to the severity of stress-related

symptomology in this population (Cole, 2009; Watson et al., 2016). However, little is known about the independent and interactive effects of racial discrimination and poverty in this population.

Racism refers to a complex and multidimensional form of oppression comprising the economic, social, cultural, and political spheres that ensures the dominance of the privileged racial group at the expense of other groups (Braham et al., 1992; Corneau & Stergiopoulos, 2012). Racism can range from explicit oppression to more subtle microaggressions (Corneau & Stergiopoulos, 2012; Sue et al., 2007). The chronic and pervasive nature of racism across various domains is inherently traumatizing (referred to as racial trauma) (Comas-Díaz et al., 2019) and negatively impacts Black individuals (Williams et al., 2003).

Racial discrimination is a behavioral manifestation of racism and comprises behaviors and attitudes (both intentional and unintentional) where Black individuals are treated unfairly due to their race (Jones, 2000; Lewis et al., 2012; Mays et al., 2007). Racial discrimination is pervasive, affecting Black Americans across socioeconomic status, age, and gender (Lewis et al., 2012; Mays et al., 2007). Experiencing racial discrimination is also linked to a variety of negative outcomes, including reduced life satisfaction (Broman, 1997) and higher levels of stress-related disorders (Williams et al., 2003), including symptoms of depression, anxiety, and substance misuse (Pascoe & Smart Richman, 2009; Williams & Mohammed, 2009). Given the stressful nature of racial discrimination, it is also known to negatively impact PTSD symptoms (Kirkinis et al., 2021). For example, experiences of racial discrimination are prospectively linked to PTSD diagnosis five years later among a clinical sample of Black and Latinx adults (Sibrava et al., 2019). Racial discrimination also predicts PTSD symptoms in Black Americans with lower socioeconomic resources, even after controlling for crime rates, perceived safety, and current

distress (Brooks Holliday et al., 2020). Thus, existing literature indicates that racial discrimination negatively impacts PTSD outcomes for Black individuals. Less is known about the degree to which experiencing racial discrimination in the context of other systemic stressors may exacerbate PTSD symptom severity for Black Americans.

Income inequality, or wide gaps in income between the highest and lowest wage earners in a society (Moss, 2002), is another oppressive system rooted in racism (Massey, 1990) that may contribute to high rates of PTSD in urban Black communities. One consequence of greater income inequality is higher rates of poverty (Moss, 2002), defined as having an income below the minimum income necessary for access to basic survival needs (Murali & Oyebode, 2004). Poverty is a well-established risk factor for poorer health outcomes (Antonovsky, 1967), including mental health outcomes (Murali & Oyebode, 2004). Neighborhood poverty, or a high rate of poverty in a given spatial area (Council et al., 1990), has been shown to negatively impact health outcomes in particular (Diez Roux & Mair, 2010; Ellen et al., 2001; Yen & Syme, 1999). While measures of individual poverty (e.g., income level) assess the more micro-level effects of poverty, neighborhood poverty puts more emphasis on the context and environment in which an individual lives, thereby focusing on the macro-level impacts of poverty (Massey et al., 1991). Neighborhood poverty is associated with less access to supermarkets and nutritious food, exposure to pollution and toxic waste, and lack of access to safe and stable housing (Diez Roux & Mair, 2010; Ellen et al., 2001; Saegert & Evans, 2003). Furthermore, neighborhoods with higher rates of poverty are less likely to have an adequate number and variety of health care practitioners and access to up-to-date medical technologies (Ellen et al., 2001). Even if such services exist, these neighborhoods often receive subpar infrastructure for adequate public transportation systems, making it difficult for residents to access existing healthcare options

(Ellen et al., 2001). All of these factors can negatively impact the health of residents of disadvantaged neighborhoods (Diez Roux & Mair, 2010; Ellen et al., 2001; Saegert & Evans, 2003). Given that neighborhood poverty can increase the likelihood of exposure to environmental and social stressors, as well as access to resources impacting health (Ellen et al., 2001), it is not surprising that areas in public health crises have been characterized with extreme poverty (Kolak et al., 2020). Furthermore, living in more socioeconomically disadvantaged areas is associated with greater mortality risk (Singh & Siahpush, 2002).

Despite the links between neighborhood poverty, exposure to stressors, and health outcomes, few studies have explicitly examined the role of neighborhood poverty on PTSD symptoms in adults. One such study found that greater neighborhood disorder (operationalized through a self-report measure on an individual's perceptions of their physical environment) predicted higher PTSD symptoms in adults (Gapen et al., 2011). Another study found that growing up in economically disadvantaged neighborhoods predicted PTSD in adulthood for individuals who were not maltreated in childhood (Schuck & Widom, 2019). However, to the best of our knowledge, no previous studies have used objective measures of neighborhood poverty in understanding the associations between neighborhood poverty in adulthood and PTSD symptoms among Black people. It is possible that higher rates of poverty among Black individuals living in urban environments contribute to the high rates of PTSD seen in these communities.

Importantly, due to a legacy of structural racism, or policies enacted to uphold white supremacy, Black Americans are more likely to be impacted by poverty (Feagin & Ducey, 2018). Policies like redlining, where neighborhoods with any number of Black residents were deemed undesirable, causing disinvestment in Black neighborhoods, resulted in lower house

values many years after these policies were officially outlawed, including to this day (Appel & Nickerson, 2016; Lynch et al., 2021; Massey, 1990). Furthermore, residential segregation, another important facet of structural racism and a result of redlining (Appel & Nickerson, 2016), resulted in primarily Black neighborhoods to be under-resourced and unsafe (Massey, 1990; Saegert & Evans, 2003). In addition to historical policies like redlining and residential segregation, discrimination in the labor market has affected current income for some Black people and has resulted in disparate rates of upward social mobility (Feagin & Ducey, 2018; Gaskin et al., 2004). Overall, the continued legacy of racism hinders Black Americans' ability to accumulate and transfer wealth (Hernandez, 2009), allowing for the effects of racial discrimination to persist across generations, and making Black Americans more likely to live in neighborhoods with high rates of poverty (Darity & Nembhard, 2000; Gaskin et al., 2004). Given that Black Americans are disproportionately affected by poverty and the known associations between high rates of neighborhood poverty and mental health, it is particularly important to focus on the relation between neighborhood poverty and PTSD symptoms in Black Americans.

Although racial discrimination and neighborhood poverty independently impact risk for psychopathology, these oppressive systems do not work in isolation. Evidence suggests that the intersection between multiple levels of oppression can increase severity of psychopathology, highlighting the need to consider their intersection when assessing risk for disorders like PTSD (Cole, 2009). For example, previous work has shown that experiencing higher levels of racial discrimination exacerbates the effect of intimate partner violence on PTSD symptom severity (Mekawi, Carter, et al., 2021). Due to the historical oppression of Black women in the U.S., this population has experienced unique and distinct forms of racial discrimination across time that impacts their higher risk of living in poverty, with reduced opportunities for social mobility

(Branch, 2011). Importantly, because both racial discrimination and the increased likelihood of Black neighborhoods to be under-resourced are due to racism, both are considered aspects of racial trauma, a concept that transcends individually-based experiences (Williams, Printz, et al., 2018). Since Black women are at highest risk for living in areas with high rates of poverty and for experiencing racial discrimination, it is necessary to consider the multiple aspects of racial trauma in the intersection of neighborhood poverty and racism in predicting risk for and severity of PTSD in Black women specifically. Taking an intersectional approach advances the literature on PTSD in Black women by elucidating the specific and interactive effects of systems of oppression that marginalize and disenfranchise Black women.

In the current study, we addressed these gaps in research by examining the interactive effects of racial discrimination and neighborhood poverty on PTSD in Black women seeking care in a publicly funded hospital primarily serving minoritized and low-income individuals in Atlanta, GA. We hypothesized that individuals experiencing both high amounts of racial discrimination and living in neighborhoods with high rates of poverty would show the highest PTSD symptoms. We also expected that racial discrimination would independently be associated with higher PTSD symptoms, and that higher rates of neighborhood poverty would be associated with higher PTSD symptoms. Finally, we conducted exploratory analyses to assess the effects of racial discrimination, neighborhood poverty, and their interaction in predicting the different PTSD symptom clusters (intrusive, avoidance/numbing, and hyperarousal).

2.4 Methods

2.4.1 Participants

The present study included 300 women aged 18 to 65 years old (M = 41.78, SD = 13.31). Sample characteristics can be found in Table 2.1. The majority of participants reported being

unemployed (58.7%) and having a monthly household income of less than $2,000 (77.6%). In terms of education, 16.7% of the sample did not complete high school, 29.7% were high school graduates, 5.7% obtained a GED, 26.7% had some college or technical school, 7% were technical school graduates, 10.7% were college graduates, and 3.7% had graduate education. Participants experienced an average of 5 different types of Criterion A traumatic events (*SD* = 3.28) in their lifetime (e.g., sexual assault, intimate partner violence, accident).

2.4.2 Procedure

Participants were enrolled in this study between 2014 and 2018 as part of a larger, on-going study on factors affecting risk and resilience to PTSD in a primarily Black and low-income sample (Gillespie et al., 2009; Gluck et al., 2021). Participants were approached at random (i.e., not based on any phenotypic criteria) from the waiting rooms of a publicly-funded hospital primarily serving racially and socioeconomically marginalized individuals. Participants were eligible for the study if they were 18 years or older, not actively psychotic, and able to give informed consent to participate. Willing participants gave informed consent and then completed self-report measures which were read aloud by a trained research assistant assessing demographics, trauma history, racial discrimination, and self-reported symptoms for psychopathology including PTSD. Only participants who self-identified as a Black or African American women and completed basic demographics and measures of racial discrimination and PTSD symptoms were included in this study. Participants were compensated $40 for their participation in the study, and all procedures were approved by the Emory University Institutional Review Board. This study was not preregistered.

2.4.3 Measures

Demographic variables including self-reported race, sex, household income, employment status, and zip code were collected.

Experiences of Discrimination (EOD) Questionnaire *(Krieger et al., 2005)*

Racial discrimination was assessed using the EOD. Participants were asked, "Have you ever experienced discrimination, been prevented from doing something, or been hassled or made to feel inferior in any of the following situations because of your race, ethnicity, or color?" and then told to indicate if they experienced discrimination in nine different situations (e.g., school, work). Each item was scored with a 0 (*never happened*) or 1 (*happened at least once*), and scores for each item were summed to produce a total score.

Traumatic Events Inventory (TEI)(Gillespie et al., 2009)

Trauma history was assessed via the TEI, which assesses for types of exposure to traumatic events.

Modified PTSD Symptom Scale (PSS)*(Foa & Tolin, 2000)*

PTSD symptoms were assessed via the PSS, a validated self-report scale assessing PTSD symptoms based on DSM-IV criteria. The PSS consists of 17 questions, each pertaining to a symptom of PTSD as defined by the DSM-IV, and gives a score for total PTSD symptoms as well as sub-scores for intrusive, avoidance/numbing, and hyperarousal symptoms (Foa & Tolin, 2000). For each question, participants give a response ranging from 0 (*not at all)* to 3 (*5 or more times per week/very much*) (Foa & Tolin, 2000). Scores for each individual item are summed to yield total score (Foa & Tolin, 2000).

American Community Survey

The American Community Survey (ACS) is an annual survey conducted by the US Census Bureau which assesses the sociodemographic factors of different geographical areas

within the US. We used the 2014-2018 ACS 5-Year Summary File to calculate neighborhood poverty rates and racial makeup within participants' self-reported zip codes (U.S. Census Bureau, 2020). Neighborhood poverty rates were defined by the percentage of people living below the poverty line in an individual's zip code. Using the same 2014-2018 ACS Summary File, we also calculated the percentage of residents who identified as Black/African-American within the zip code, as the percentage of Black people living in an individual's zip code might affect the type and frequency of racial discrimination they face (Hunt et al., 2007).

2.4.4 Data Analytic Plan

First, we conducted preliminary analyses on basic descriptive information. A summary of reliability scores (Cronbach's alpha), means, and standard deviations are included in Table 2.2. Next, we examined correlations between the main variables in our model: racial discrimination, neighborhood poverty, and PTSD symptoms. We followed up on bivariate analyses with a simple regression model with our two main predictors on PTSD symptoms, racial discrimination and neighborhood poverty, to determine a main effect of each variable with the other predictor included in the model. We then ran a simple moderation analysis using the PROCESS Macro in R (Hayes et al., 2017) to assess for the interactive effect of racial discrimination on neighborhood poverty rate in predicting PTSD symptoms. We ran a total of four moderation models predicting the following outcomes: overall PTSD symptoms, intrusive symptoms, avoidance and numbing symptoms, and hyperarousal symptoms. In each model, trauma exposure and percentage of Black residents in each zip code were included as covariates since trauma exposure is associated with PTSD symptoms (Gluck et al., 2021) and the percentage of Black people living in a person's zip code might impact experiences of racial discrimination (Hunt et al., 2007). We also included individual SES (using a composite variable of individual income,

employment status, and education) as a covariate to assess the macro-level effects of poverty on PTSD symptoms. To probe statistically significant interaction effects, we first examined the ΔR^2 value and then calculated the conditional effects at different levels of the moderator (16th, 50th, and 84th percentiles). All analyses were conducted in SPSS version 28 and figures were created in R 3.5.2. There was no missing data. Data are not publicly available, as the inclusion of participant zip codes in the analyses is an identifier.

2.5 Results

2.5.1 Correlational and Regression Analyses

As shown in Table 2.2, a higher level of racial discrimination was significantly associated with overall PTSD symptoms (r=.282, p<.001) and with symptom clusters (r's=.223 to .277, all p's<.001). Neighborhood poverty was significantly associated with racial discrimination (r=-.123, p=.033), but did not correlate with overall PTSD symptoms (r=.078, p=.180) or with symptom clusters (r's=.02 to .092, p's=.112 to .725). In a follow-up regression analysis, when controlling for racial discrimination, $F(2, 297)= 15.063$, MSE=137.13, $p < .001$, neighborhood poverty was significantly associated with PTSD symptoms (B=.158, SE=.08, p=.042), supporting the next step of moderation analysis (Supplementary Table 2.1).

2.5.2 Overall PTSD Symptoms

Next, to address our main hypothesis, we tested the interactive effects of racial discrimination and neighborhood poverty rate on overall PTSD symptoms (Figure 2.1). The model accounted for 28.14% of the variance in overall PTSD symptoms, $F(6, 293) = 19.12$, $MSE = 110.12$, $p < .001$. Neighborhood poverty ($B = 0.27$, SE =0.11, p=.01) and racial discrimination ($B = 2.06$, $SE = 0.71$, $p = .004$) significantly predicted PTSD symptoms. The interaction between neighborhood poverty and racial discrimination was significant ($B = -0.06$, $SE = 0.03$, $\Delta R^2 = .01$, $p = .03$), so

we conducted follow-up analyses on the conditional effects at different levels of the moderator (racial discrimination). Follow up analyses revealed that the association between neighborhood poverty rate and overall PTSD symptoms was strongest at the 16th percentile of racial discrimination (B = 0.27, SE = 0.11, p = .01). The interactive effect was also significant at the 50th percentile (B = 0.15, SE = 0.08, p = .05), but not at the 84th percentile (B = -.02, SE = .09, p = .87). These results indicate that the association between neighborhood poverty and overall PTSD symptoms is strongest for participants who reported relatively fewer experiences of racial discrimination.

2.5.3 Intrusive PTSD Symptoms

The next model examined the interactive effects of racial discrimination and neighborhood poverty rate on intrusive PTSD symptoms. The model accounted for 19.67% of the variance in intrusive symptoms of PTSD, $F(6, 293) = 11.96$, MSE = 12.63, $p < .001$. As with overall PTSD symptoms, neighborhood poverty (B = 0.07, SE = 0.04, p = .05) and racial discrimination (B = 0.72, SE = 0.24, p = .003) significantly predicted intrusive symptoms. Additionally, their interaction (B = -0.02, SE = 0.009, ΔR^2 = .02, p = .01) significantly predicted intrusive symptoms. Follow up analyses on the conditional effects of the moderator revealed the association between neighborhood poverty and intrusive symptoms was strongest at the 16th percentile of racial discrimination (B = 0.07, SE = 0.04, p = .05). The association between neighborhood poverty and intrusive symptoms was not significant at the 50th percentile of racial discrimination (B = 0.03, SE = 0.03, p = .32) or at the 84th percentile (B = -0.04, SE = 0.03, p = .18).

2.5.4 Avoidance and Numbing PTSD Symptoms

The third model assessed the main and interactive effects of neighborhood poverty and racial discrimination on avoidance and numbing PTSD symptoms. The model accounted for 27.30% of the variance in avoidance and numbing symptoms, $F(6, 293) = 18.34$, $MSE = 21.93$, $p < .001$. As with the previous models, neighborhood poverty ($B = 0.12$, $SE = 0.05$, $p = .01$) and racial discrimination ($B = 0.73$, $SE = 0.32$, $p = .02$) significantly predicted avoidance and numbing symptoms. The interaction between neighborhood poverty and racial discrimination was trending but not significant ($\Delta R^2 = .008$, $p = .08$). Follow up analyses on the conditional effects of the moderator revealed the association between neighborhood poverty and avoidance/numbing symptoms was strongest at the 16th percentile of racial discrimination ($B = 0.12$, $SE = 0.05$, $p = .01$). The interactive effect was also significant at the 50th percentile ($B = 0.08$, $SE = 0.04$, $p = .02$), but not at the 84th percentile ($B = .02$, $SE = .04$, $p = .64$).

2.5.5 Hyperarousal PTSD Symptoms

The final model tested the main effects of neighborhood poverty and racial discrimination and their interaction in predicting hyperarousal PTSD symptoms. The model accounted for 20.78% of the variance in hyperarousal symptoms $F(6,293) = 12.81$, $MSE = 15.56$, $p < .001$. While racial discrimination ($B = 0.60$, $SE = 0.26$, $p = .02$) significantly predicted hyperarousal symptoms, neighborhood poverty was not significant but trending ($B = 0.07$, $SE = 0.04$, $p = .07$) and their interaction was not significant ($\Delta R^2 = .004$, $p = .20$).

2.6 Discussion

To date, very little research has focused on the effects of neighborhood poverty on PTSD symptoms, and no previous studies have examined the interactive effects of neighborhood poverty and racial discrimination in predicting PTSD symptoms among Black women. Our findings address this gap by a) identifying an association between neighborhood poverty and

PTSD symptoms when accounting for racial discrimination and b) identifying an interactive effect between racial discrimination and neighborhood poverty in predicting PTSD symptoms. Specifically, we found that racial discrimination predicted more severe PTSD symptoms overall and across each of the symptom clusters, as we predicted. In contrast to our hypothesis, we did not find a direct association between neighborhood poverty and PTSD symptoms, however after controlling for racial discrimination, we saw that living in areas with higher rates of poverty was associated with more PTSD symptoms. In addition, the results showed an interaction between experiences of racial discrimination and neighborhood poverty, such that higher levels of neighborhood poverty predicted greater overall PTSD symptoms and intrusive symptoms, but only for Black women reporting fewer experiences of racial discrimination. Black women reporting more experiences of racial discrimination had higher overall PTSD symptoms and intrusive symptoms regardless of neighborhood poverty rate. Overall, our results support the hypothesis that experiencing oppression, either through neighborhood poverty or racial discrimination, can negatively impact PTSD outcomes.

Our findings regarding the independent effect of racial discrimination replicate previous studies (Brooks Holliday et al., 2020; Kirkinis et al., 2021; Sibrava et al., 2019) and further demonstrate that racial discrimination is related to higher levels of PTSD symptoms. One explanation is that the nature of racial discrimination is particularly conducive to stress-related symptomology. Racial discrimination manifests in chronic and unpredictable ways, and Black individuals may feel unsafe in many everyday situations (Lewis et al., 2015; Utsey et al., 2000). As a result, racial discrimination acts as a significant and chronic stressor that can exacerbate responses to traumatic events (Utsey et al., 2013; Utsey et al., 2000) and also function as a traumatic stressor in and of itself (Carter, 2007; Kirkinis et al., 2021; Williams, Metzger, et al.,

2018). Experiences of racial discrimination can result in traumatic stress responses, including hypervigilance, re-experiencing symptoms, negative cognitions, and avoidance, all of which are cardinal symptoms of PTSD (Carter & Forsyth, 2010). Some of these symptoms may manifest in an attempt to prepare for the threat of racist encounters; given that racial discrimination is unpredictable and can occur in any setting, symptoms like hypervigilance or avoidance may help Black individuals stay safe across a variety of potentially racism-laden threatening situations (Mekawi, Hyatt, et al., 2021). Taken together, these results are in line with a body of work that supports the association between racial discrimination and more severe PTSD symptoms, and further highlights the need to pay attention to experiences of racial stress and discrimination in the broader context of trauma and PTSD.

We also found that neighborhood poverty predicts PTSD symptoms when accounting for the effect of racial discrimination. It is possible that we did not see a direct effect of neighborhood poverty on PTSD symptoms because the majority of the sample experienced racial discrimination, leading to generally high PTSD symptoms overall. When racial discrimination is not accounted for, neighborhood poverty alone may not explain the high levels of PTSD symptoms, but when racial discrimination is included in the model, much of the remaining variance in PTSD symptoms is accounted for by neighborhood poverty. Additionally, because we recruited from a community with few economic resources, it is possible that there was not enough variability in neighborhood poverty rates to see a direct association between neighborhood poverty and PTSD symptoms.

There are several direct and indirect reasons why neighborhood poverty may produce more severe PTSD symptoms. Environmental factors associated with high rates of neighborhood poverty (Diez Roux & Mair, 2010; Ellen et al., 2001; Saegert & Evans, 2003) might serve as

chronic stressors that can increase the likelihood of developing stress-related disorders or exacerbate existing symptoms of PTSD (Davidson & Baum, 1986). Importantly, reduced access to quality healthcare also results in fewer treatment options for stress-related disorders like PTSD, resulting in the persistence and chronicity of symptoms. Additionally, PTSD symptoms may manifest to cope with the stressors related to living in neighborhoods with high poverty. Hyperarousal, in particular, may be an adaptive mechanism for individuals living in areas of high poverty, in order to promote survival in an environment that is chronically unsafe, as could be the case for individuals experiencing high amounts of racial discrimination. Nevertheless, our results indicate the importance of considering the rates of neighborhood poverty in an individual's environment over and above an individual's own poverty status.

Notably, structural racism has ensured that Black Americans are more likely to live in disadvantaged neighborhoods compared to individuals of other races, especially white Americans (Feagin & Ducey, 2018). This history of structural racism underscores the importance of considering the effects of neighborhood poverty and its intersection with other oppressive systems that comprise racial trauma among Black Americans specifically. It is especially important to understand the effects of neighborhood poverty in Black women, who often experience two oppressive systems (racism and sexism), making them disproportionately affected by neighborhood poverty (Branch, 2007). Due to sexism, racism, and gendered racism, Black women have historically been excluded from more desirable jobs (more so than Black men and white women), and are disproportionately represented in low-wage jobs, which continues the cycle of poverty (Branch, 2011; Branch, 2007). Black women living in poverty also experience a unique type of racism; for example, a pervasive stereotypical image of Black women affected by poverty is that they are "lazy; welfare queens" (Monnat, 2008). It is therefore necessary to focus

on the effects of neighborhood poverty and its interaction with racial discrimination in Black women specifically, due the legacy of gendered racism (i.e. the idea that individuals have social experiences based on both gender and race together) that makes Black women disproportionately affected by poverty (Branch, 2011; Branch, 2007; Monnat, 2008).

Inconsistent with our hypothesis, the effects of neighborhood poverty and racial discrimination on PTSD were not additive (i.e., highest severity of PTSD was not found at relatively high racial discrimination and neighborhood poverty). Instead, our results showed that more frequent racial discrimination was associated with greater PTSD symptom severity regardless of neighborhood poverty rates. In addition, individuals who experienced both high amounts of racial discrimination and who lived in areas with high rates of poverty did not differ in PTSD symptoms from those who only experienced high amounts of racial discrimination or those who lived in high neighborhood poverty areas without experiencing frequent racial discrimination. It is possible that experiencing more frequent racial discrimination triggers a similar PTSD response as does living in high poverty areas while experiencing relatively less racial discrimination. Both types of oppressive systems might recalibrate an individual's baseline functioning to increase PTSD symptoms, especially hyperarousal and avoidance and numbing symptoms, in order to promote survival in an unsafe environment, but there could be a ceiling effect from each type of oppression, preventing an additive effect. This is supported by the main effects of racial discrimination and neighborhood poverty (after accounting for racial discrimination) on PTSD symptoms in this sample, as individuals who experienced either type of oppression had higher PTSD symptoms. Alternatively, the change in baseline functioning after experiencing one type of oppression may be sufficient to cope with the effects of the other type

of oppression as well. Thus, individuals who experience both may have developed skills that protect them from experiencing more severe PTSD symptoms.

Taken together, our finding that PTSD symptom severity was not highest at the intersection of both racial discrimination and poverty highlights the importance of using an intersectional framework that simultaneously considers both systems of oppression. This importance is especially emphasized by the lack of effect of neighborhood poverty on PTSD symptoms without controlling for racial discrimination. Without also examining the effect of racial discrimination on PTSD symptoms, the intersectional context of neighborhood poverty on PTSD symptoms is lost. It is possible that experiences of oppression that happen at the intersection of racism and poverty are unique for Black women (e.g., exposure to structural inequities such as being denied a housing loan that are embedded in multi-level racism) and thus cannot be assessed using an additive approach. The idea that experiences of gendered racism are a unique type of stressor – and not just experiences of both racism and sexism combined (Lewis & Neville, 2015) – highlights the need to understand the nature of stressors that simultaneously occur at intersection of different systems of oppression.

In a clinical context, the effects of racial discrimination and neighborhood poverty on PTSD symptoms highlight the importance of addressing both systems of oppression in terms of assessment, case conceptualization, and treatment. When treating PTSD symptoms, it may be important to go beyond merely assessing Criterion A events and examining other identity-based stressors and traumas associated with living in neighborhoods with low socioeconomic resources (e.g., neighborhood disorder, lack of access to care etc., (Williams, Metzger, et al., 2018)). More comprehensive, culturally informed assessment can allow for more accurate case conceptualizations. When developing case conceptualizations with Black clients it may be

particularly important to use caution before pathologizing certain symptoms and instead, interpret them in context. For example, rather than immediately pathologizing hypervigilance, it may be important to identify the function of the hypervigilance to determine whether it is adaptive for a particular individual given their context. Furthermore, and in line with our moderation analyses examining the role of other systems of oppression that individuals are exposed to may allow the clinician to identify strengths and protective factors. Doing so may then be conducive to developing a treatment plan that validates Black Americans' lived experiences, maximizes opportunities for benefit, and minimizes opportunities for harm. Finally, while racial discrimination and neighborhood poverty can be considered distinct oppressive systems, it is important to note that both of these systems are rooted in racism, and are each types of racial trauma. It is therefore important for clinicians to understand how oppressive systems are connected for marginalized communities, and to conceptualize racial discrimination and neighborhood poverty as both individual systems as well as well as consequences of racism on a larger scale.

The effect of neighborhood poverty on PTSD symptoms (after controlling for racial discrimination) in this study emphasizes the importance of policy changes that will invest in neighborhoods with high rates of poverty. Previous work demonstrates that high rates of neighborhood poverty are often the result of structural racism through historical policies of racial segregation (Massey et al., 1991) and redlining (Appel & Nickerson, 2016), and that racial segregation helps explain racial health inequities (White et al., 2012; Williams & Collins, 2001). Yet, there remains a dearth of research specifically examining structural racism and mental health outcomes. The current study points to the need for future research that provides crucial insights on potentially modifiable factors for addressing mental health disparities that could be

targeted via population and policy-focused interventions. In order to address health inequities, future policy agendas need to be created in consultation with community members and should actively invest in historically redlined and segregated neighborhoods.

The current study had several strengths, including the use of measures cutting across ecological levels (i.e., neighborhood context and individual-level racial discrimination). Despite the strengths of the study, there are limitations that should be addressed in future studies. First, racism and neighborhood poverty are not entirely separate constructs; racial segregation often prevents Black individuals from accessing healthier residential environments (Massey, 1990; Saegert & Evans, 2003), and the majority of participants in this study endorsed experiencing some amount of racial discrimination. However, this relation further highlights the necessity of considering multiple levels of oppression when assessing risk for and treating PTSD, because deeply rooted racist systems might make a Black individual particularly at risk to be affected by many systems of oppression. Second, although we examined two important systems of oppression, we did not consider the role of sexism. Specifically, we did not examine how sexism interacts with racial discrimination and neighborhood poverty in predicting PTSD symptoms in our sample of women. It is possible that sexist systems impact the associations between poverty, racism, and PTSD symptoms. Sexist systems and associated societal expectations could also make Black women more likely to live and stay in under-resourced areas, and/or experience more frequent racial discrimination. Future well-powered studies should consider interactions between more systems of oppression in predicting mental health outcomes. Furthermore, our use of an additive approach to assess the intersection of racism and poverty is an important first step, but does not entirely capture the intersectionality of racial discrimination and neighborhood poverty (del Río-González et al., 2021; Else-Quest & Hyde, 2016). Rather than assuming

separate examination of each system captures the unique experience of living at their intersection, future studies should utilize more nuanced methods to test components of intersectionality theory (del Río-González et al., 2021). Third, because race is a social construct (Bryant et al., 2022; Carter et al., 2022) and dependent on how a participant identifies, our definition of race is not strictly precise. Regardless, because we are focused on the racial discrimination participants may face due to the way they are perceived in society, we believe self-reported race is the best measure for the purposes of this study. Fourth, because study recruitment was in a community with few economic resources, we likely do not see as wide a range in neighborhood poverty rates as we would see in the general population, which could help explain the lack of direct association between neighborhood poverty and PTSD symptoms in this sample. Furthermore, the relatively limited range in neighborhood poverty limits generalizability to communities with broader ranges in neighborhood poverty. Future studies should recruit participants from a variety of communities to better discern the role of neighborhood poverty on PTSD symptoms. Lastly, PTSD symptoms were assessed using the PSS (a self-report measure) instead of the gold-standard Clinician Administered PTSD Scale (CAPS), though the PSS has been used in multiple studies and correlates strongly with the CAPS (Foa & Tolin, 2000). Using a diagnostic assessment may better capture issues related to functional impairments, which may be particularly relevant for treatment implications.

Our results indicate that both racial discrimination and neighborhood poverty contribute to PTSD symptoms, though the effects of neighborhood poverty are dependent on the amount of racial discrimination an individual has faced. Given the heterogeneous nature of PTSD, it is important to consider multiple factors and systems of oppression when determining presentation of symptoms, and failing to consider. Future work on the intersection of oppressive symptoms is

needed to better understand the onset, etiology, and maintenance of psychopathology in marginalized groups.

Figure 2.1: Interaction Between Neighborhood Poverty and Racial Discrimination in Predicting PTSD Symptoms

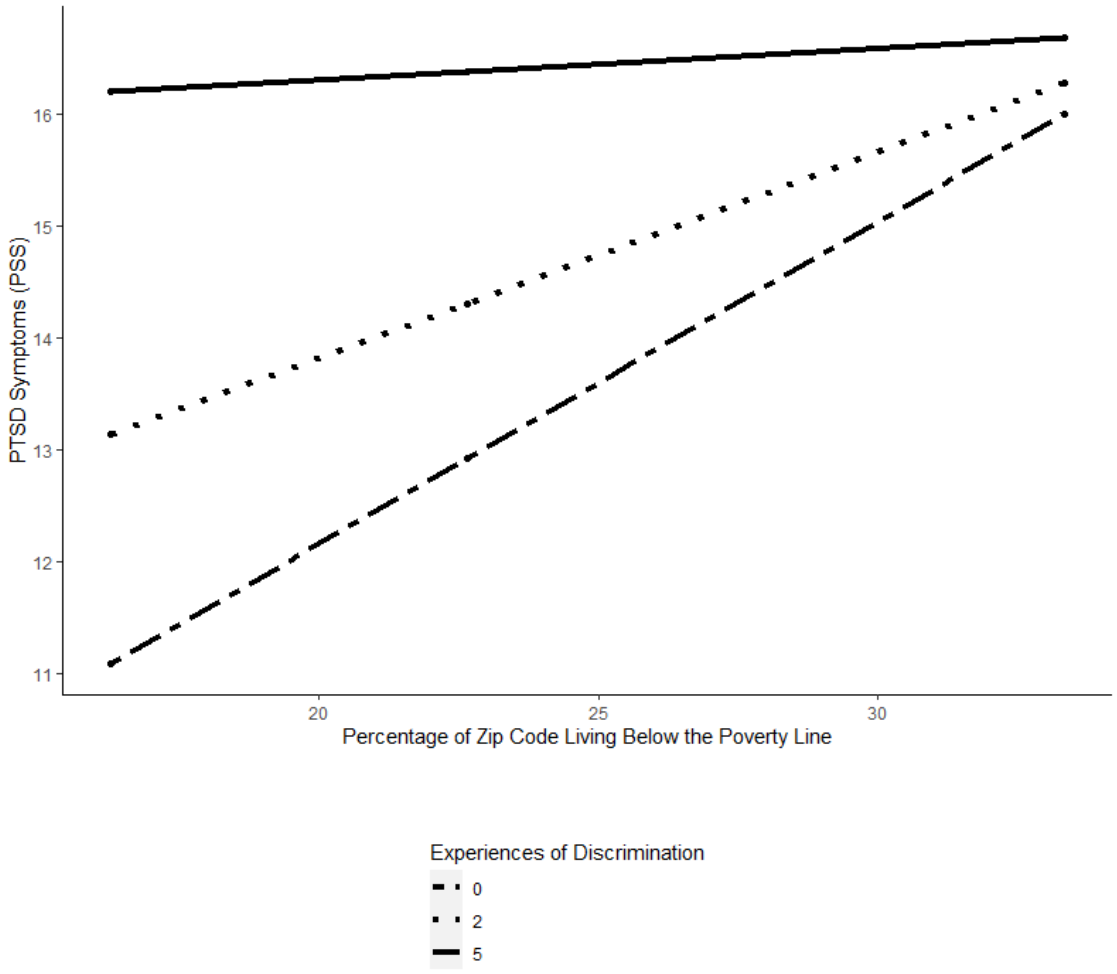


Table 2.1: Sample Demographics

Demographic	M	SD	%
Age (years)	41.78	13.31	
Total types of trauma (witnessed or experienced)	5.00	3.28	
Percentage of Black people in zip code	75.60	22.34	
Monthly household income			
$0-$249			11.9
$250-$499			6.8
$500-$999			24.5
$1000-$1999			34.4
$2000 or more			22.4
Education			
Less than 12th grade			16.7
12th grade/high school graduate			29.7
GED			5.7
Some college or technical school			26.7
Technical school graduate			7.0
College graduate			10.7
Graduate school			3.7
Employment			
Currently unemployed			58.7

Table 2.2: Means, Standard Deviations, and Correlations Among Variables of Interest

Variable	Cronbach's α	M	SD	1	2	3	4	5	6
1. Racial discrimination	.821	2.47	2.51	-	-.123*	.282**	.223**	.252**	.277**
2. Neighborhood poverty		23.27	9.20		-	.078	.02	.092	.086
3. Overall PTSD symptoms	.907	15.04	12.25			-	.878**	.920**	.875**
4. Intrusive symptoms	.841	3.65	3.92				-	.723**	.667*
5. Avoidance and numbing symptoms	.807	5.82	5.44					-	.691*
6. Hyperarousal symptoms	.741	5.56	4.34						-

Supplementary Table 2.1: Step-wise Regression Analyses

	R^2	*F*	Beta Coefficient	*t*	*p*
Model 1	.092	15.063			<.001
Constant			7.634	3.504	<.001
Neighborhood Poverty			.158	2.044	.042
Racial Discrimination			1.441	5.307	<.001
Model 2	.102	11.211			<.001
Constant			10.793	3.875	<.001
Neighborhood Poverty			.211	2.557	.011
Racial Discrimination			1.435	5.304	<.001
Percentage of Black Individuals in Zip Code			-.058	-1.810	.071
Model 3	.249	24.425			<.001
Constant			6.644	2.546	.011
Neighborhood Poverty			.138	1.816	.070
Racial Discrimination			.594	2.187	.030
Percentage of Black Individuals in Zip Code			-.057	-1.920	.056
Trauma Exposure			1.572	7.592	<.001
Model 4	.27	21.79			
Constant			7.22	2.79	.006
Neighborhood Poverty			.11	1.40	.164

Racial Discrimination			.67	2.48	.01
Percentage of Black Individuals in Zip Code			-.06	-1.97	.05
Trauma Exposure			1.59	7.76	<.001
Individual SES			-2.60	-2.95	.003
Model 5	.28	19.12			
Constant			2.99	.92	.36
Neighborhood Poverty			.27	2.50	.01
Racial Discrimination			2.06	2.91	.004
Percentage of Black Individuals in Zip Code			-.06	-1.95	.05
Trauma Exposure			1.60	7.84	<.001
Individual SES			-2.70	-3.08	.002

Neighborhood Poverty by Racial Discrimination	-.06	-2.13	.03

CHAPTER 3: NEIGHBORHOOD POVERTY PROSPECTIVELY PREDICTS PTSD SYMPTOMS SIX-MONTHS FOLLOWING TRAUMA EXPOSURE

3.1 Context, Authors' Contribution, and Acknowledgement of Reproduction

The following Chapter focuses on the prospective role of neighborhood poverty on PTSD symptoms six-months post-trauma exposure. The dissertation author contributed to conceptualization, data analysis, and writing the manuscript under the guidance of Drs. Vasiliki Michopoulos. Drs. Abigail Lott, Barbara Rothbaum, and Jennifer Stevens assisted with data collection and editing the manuscript. This Chapter is reproduced from Ravi M., Powers, A., Rothbaum, BO., Stevens, JS., Michopoulos, V. Neighborhood Poverty Prospectively Predicts PTSD Symptoms Six-Months Following Trauma Exposure. Mental Health Science (Under Revision).

3.2 Abstract

Individuals living in areas with high rates of poverty are disproportionately affected by posttraumatic stress disorder (PTSD). Despite this association, little is known about how neighborhood poverty rates impact risk for PTSD development. In the current prospective study, we determined the relationship between neighborhood poverty rate and PTSD symptoms six-months after experiencing a traumatic event in a sample of varied race, gender, and socioeconomic status. Participants (N=252) were enrolled in a hospital emergency department after experiencing a traumatic event. Demographic information (including zip code of residence), baseline PTSD symptoms, and baseline trauma history was assessed in the emergency department. PTSD symptoms were again assessed six-months post-trauma. Neighborhood poverty rate was determined using the American Community Survey. Correlation analyses revealed that neighborhood poverty was significantly associated with baseline PTSD symptoms (r=.181, p=.004) and PTSD symptoms six-months post-trauma (r=.163, p=.009). A regression analysis controlling for baseline trauma exposure and clinician-rated trauma severity

demonstrated that neighborhood poverty predicted PTSD symptoms six-months post-trauma (R^2= 0.094, *b*= 0.132, *p*=0.031), but this relationship was no longer significant when baseline PTSD symptoms was added as an additional covariate (R^2=.303, *b*= 0.062, *p*>0.05). Overall, results suggest that neighborhood poverty generally increases risk for PTSD, and the context in which an individual lives should be considered when conceptualizing risk for PTSD.

3.3 Introduction

Posttraumatic stress disorder (PTSD) is a heterogenous disorder that can develop after a traumatic event and is characterized by recurring memories of the traumatic event, avoidance of trauma reminders, and hyperarousal symptoms. While approximately 90% of the population will experience at least one traumatic event in their lifetime, only about 7% will go on to develop PTSD. Crucially, Black individuals with few economic resources, living in urban environments, and seeking care at a publicly funded hospital are at risk for experiencing multiple traumatic events in their lifetimes, with an average of 2.5 types of non-childhood abuse traumatic events (Gillespie et al., 2009; Gluck et al., 2021; Smith & Patton, 2016). This high rate of trauma exposure is associated with disproportionately high rates of PTSD in Black individuals with few economic resources living in urban areas, with lifetime rates as high as 46% (Gillespie et al., 2009). It is therefore essential to understand factors that contribute to the development of PTSD symptoms in order to reduce PTSD symptom burden for individuals at highest risk.

One factor that may increase risk for PTSD is neighborhood poverty or living in an area with high rates of poverty (Council et al., 1990). While individual poverty has been associated with worse mental health outcomes, including depression, substance use disorder, higher risk for suicide (Murali & Oyebode, 2004), and higher rates of PTSD (Nayback, 2008), studies on the effects of neighborhood poverty on the development of adverse mental health conditions are

lacking. Unlike measures of individual poverty, which assess the micro-level effects of poverty, neighborhood poverty emphasizes the context and environment in which an individual resides and focuses more on the macro-level effects of poverty. Neighborhood poverty is associated with several chronic stressors, including reduced access to supermarkets and nutritious food, lack of access to safe and stable housing, and exposure to pollution and toxic waste (Diez Roux & Mair, 2010; Ellen et al., 2001; Saegert & Evans, 2003). Neighborhoods with higher rates of poverty are less likely to have adequate health care options and practitioners, and so treatment for mental and physical illness is more difficult than areas with more resources. Neighborhood poverty is associated with exposure to crime and violence (Graif et al., 2014; Sampson et al., 1997). All of these chronic stressors negatively impact the health of those living in areas with high rates of poverty; specifically, living in disadvantaged neighborhoods is associated with shorter telomere length (a marker of biological age) (Massey et al., 2018; Needham et al., 2014), dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Janusek et al., 2017; Karb et al., 2012), and differences in immune system functioning (Finegood et al., 2020; Janusek et al., 2017), which all can impact mental and physical health (Li et al., 2017; Michopoulos et al., 2016; Pearson et al., 2003; Rasmusson et al., 2017; Ravi et al., 2021). Unsurprisingly, mortality risk is higher in areas with high rates of poverty compared to wealthier neighborhoods (Singh & Siahpush, 2002).

Despite the known associations between neighborhood poverty, chronic stressors/violence, and negative behavioral and physical health outcomes, very few studies have focused on the role of neighborhood poverty on risk for and severity of PTSD symptoms. One study found that greater neighborhood disorder (defined using a self-report measure on an individual's perception of their environment) predicted higher PTSD symptoms in adults (Gapen et al., 2011). Growing up in areas with high rates of poverty has implications for PTSD

development in adulthood; for example, one study found that living in disadvantaged areas as a child predicted more PTSD symptoms in adults who had not been maltreated as children (Schuck & Widom, 2019). We have recently shown that living in areas with high rates of poverty, defined as the percentage of an individual's zip code living below the federally defined poverty line, is associated with more PTSD symptoms in chronically trauma-exposed Black women (Chapter 2). Importantly, most of these previous studies have been cross-sectional in nature. Prospective studies immediately following trauma exposure are critical to understand better the development of PTSD and can help determine individuals who might benefit from early intervention, such as prolonged exposure (Rothbaum et al., 2014). In the current prospective study, we determined the effect of neighborhood poverty on PTSD symptom development six-months post-trauma exposure. We hypothesized that living in areas with higher rates of poverty at the time of trauma exposure would predict worse PTSD symptoms six-months after experiencing a traumatic event.

3.4 Methods

3.4.1 Procedure

Participants (N=252; 115 females) were enrolled between 2012 and 2016 in the emergency department of a large level 1 trauma center serving the broader area of Atlanta, Georgia. Study procedures have been described previously in detail (Michopoulos, Maples-Keller, et al., 2019). Inclusion criteria included experiencing a DSM-IV traumatic event in the last 24 hours, English language fluency, and ability to provide informed consent. Exclusion criteria included current or past history of mania, schizophrenia or other psychoses, or significant suicidal ideation within the last month. Participants were also excluded for severe intoxication, respiratory distress, active labor, severe pain, anticipation of immediate surgery or intensive care unit admission, medical instability, and hemodynamic compromise. All study procedures were approved by the

Emory Institutional Review Board and the Grady Research Oversight Committee in accordance with the Declaration of Helsinki.

3.4.2 Measures

At enrollment, demographic information including race, age, sex, and address was collected. Clinicians in the emergency department were also asked to rate the traumatic event as "mildly severe", "somewhat severe", "clearly severe", or "very severe" (Sterina et al., 2022). Baseline trauma history and PTSD symptoms related to these pre-occurring traumatic events were determined using the Posttraumatic Diagnostic Scale (PDS), a 49 item self-report measure assessing severity of PTSD symptoms related to a single traumatic event. (Foa et al., 1997). The PDS gives a total severity score ranging from 0 to 51 (Cronbach's α=.81), reflecting the frequency of the 17 symptoms of PTSD as defined by the DSM-IV (Foa et al., 1997). Follow-up visits were conducted six-months post-trauma exposure, where PTSD symptoms related to the traumatic event that brought the person to the emergency department were assessed with the modified PTSD Symptom Scale (mPSS) (Foa & Tolin, 2000). The mPSS is a 17-item self-report measure, where each item pertains to a symptom of PTSD as defined by the DSM-IV. For each question, participants give a response ranging from 0 (*not at all)* to 3 (*5 or more times per week/very much*). Scores for each individual item are summed to yield total score (Cronbach's α=.90) (Foa & Tolin, 2000). Finally, neighborhood poverty rates were defined by the percentage of people living below the poverty line in an individual's zip code, as determined by the American Community Survey (ACS). The ACS is an annual survey conducted by the US Census Bureau which assesses the sociodemographic factors of different geographical areas within the US. We used the 2012-2016 ACS 5-Year Summary File to calculate neighborhood poverty rates within participants' self-reported zip codes (U.S. Census Bureau, 2020).

3.4.3 Data Analytic Plan

First, we assessed basic demographic information for the sample. Next, we ran basic correlations of variables of interest. We then ran step-wise linear regressions with PTSD symptoms six-months post-trauma as the dependent variable and neighborhood poverty as the independent variable. In block one, we included baseline trauma exposure, clinician rated trauma severity, and individual socioeconomic status (SES) (using a composite variable of individual income, employment status, and education) as covariates, and in block two, we added baseline PTSD symptoms as an additional covariate. All analyses were done in SPSS version 27 and alpha level set to $p<.05$.

3.5 Results

3.5.1 Sample Demographics

Sample demographics are summarized in Table 3.1. The mean age of the sample was 36.21 years (SD=12.69). 75% of the sample was Black, 15.9% was white, 4.4% was Mixed, 1.6% was Asian, and 3.2% identified as other. 6.5% of the sample had a monthly household income less than $250, 6.5% had a monthly income between $250 and $499, 14.3% had an income between $500 and $999, 21.8% had an income between $1000 and $1999, and 48.8% had an income greater than $2000 per month. In terms of education, 13.5% did not complete high school, 24.6% were high school graduates, 40.1% had some college or technical school, 21.8% were college graduates, 7.9% had some graduate school, and 7.5% had a graduate degree. 52.8% of the sample was employed full-time. 11.5% of the sample experienced a traumatic event that the emergency department clinicians rated as “mildly severe”, 34.1% experienced a traumatic event that was “somewhat severe”, 35.3% experienced an event that was “clearly severe”, and 17.1%

experienced an event that was “very severe”. Participants had experienced on average 2.78 types of traumatic events before they were enrolled, and mean PTSD symptoms at baseline was 8.60. The mean neighborhood poverty rate was 22.9% (SD=9.76).

3.5.2 Correlations

Zero-order correlations can be seen in Table 3.2. Neighborhood poverty rate was significantly associated with lower income (r=-.236, p<.001), less education (r=-.254, p<.001), greater baseline PTSD symptoms (r=.181, p=.004), and more PTSD symptoms six-months post-trauma (r=.163, p=.009) (Figure 3.1). Neighborhood poverty rate was not associated with clinician-rated trauma severity (r=.085, p=.178) or with baseline trauma exposure (r=.088, p=.164). PTSD symptoms six-months post-trauma was associated with lower income (r=-.155, p=.015), less education (r=-.175, p=.005), higher clinician-rated trauma severity (r=.234, p<.001), more baseline trauma exposure (r=.156, p=.013), and more baseline PTSD symptoms (r=.507, p<.001).

3.5.3 Regression Analyses

In block one of our regression analyses, we tested the effect of neighborhood poverty on PTSD symptoms six-months post-trauma and included baseline trauma history, clinician-rated trauma history, and individual SES as covariates. The overall model accounted for 9.9% of the variance in total PTSD symptoms six-months post-trauma exposure, F(4,251)=6.80, p<.001. Neighborhood poverty (B=.15, SE=.07, p=.04) significantly predicted greater PTSD symptoms six-months post-trauma exposure. In block two, we added baseline PTSD symptoms as an additional covariate. The overall model accounted for 30.4% of the variance in PTSD symptoms six-months post-trauma exposure, F(5,251)=21.45, p<.001. Neighborhood poverty (B=.07 SE=.06, p=.26) no longer significantly predicted PTSD symptoms six-months post-trauma exposure after the addition of baseline PTSD symptoms as an additional covariate (Table 3.3).

3.6 Discussion

In the current study, we examined the prospective role of neighborhood poverty on PTSD symptoms six-months after experiencing a traumatic event. We found that neighborhood poverty predicted higher PTSD symptoms six-months post-trauma exposure when including clinician rated trauma severity and baseline trauma history as covariates, but this association was no longer present after adding baseline PTSD symptoms (related to prior traumas) as an additional covariate. Importantly, neighborhood poverty was significantly associated with baseline PTSD symptoms (Table 3.2), suggesting that neighborhood poverty is generally associated with risk for PTSD symptoms.

Our results support previous work demonstrating that neighborhood poverty is associated with worse PTSD outcomes, though existing studies primarily only include Black community samples with few economic resources (Gapen et al., 2011)(Ravi et al., in press). In the current study, we extend these findings to a sample of varied race and socioeconomic status. Neighborhood poverty is associated with several chronic stressors, including unstable housing, or generally unsafe environments (Ellen et al., 2001), and with altered neurocircuitry among brain regions involved in affective processing (Webb et al., 2021), all of which can contribute to greater PTSD symptoms (Davidson & Baum, 1986b; Kühn & Gallinat, 2013; Webb et al., 2021). Crucially, neighborhood poverty is also associated with reduced access to adequate health care, including mental health care (Ellen et al., 2001), which can prevent recovery after experiencing a traumatic event. The relationship between neighborhood poverty and preexisting PTSD symptoms may be particularly important in determining risk for PTSD after experiencing a new traumatic event, as baseline PTSD symptoms were strongly associated with PTSD symptoms six-months post-trauma. In support of this, previous findings show that prior PTSD symptoms were the strongest predictor of subsequent PTSD symptoms, with a stronger effect than other

predictors of baseline PTSD (Gould et al., 2021). Thus, there are many direct and indirect ways in which neighborhood poverty may contribute to the prospective development of PTSD.

The current prospective study highlights the importance of understanding the neighborhood context in which individuals live in determining risk for PTSD after experiencing a traumatic event. The acute aftermath of a traumatic event can be critical in mitigating risk for the development of PTSD, and so it is important to identify those who may be at higher risk so that risk-reducing steps can be taken. For example, previous work has shown that an exposure-therapy session in the acute aftermath of a traumatic event reduced later PTSD symptoms in individuals determined to be genetically at risk for developing PTSD (Rothbaum et al., 2014). Our results suggest that when assessing risk for PTSD, the environment in which a person lives should also be considered, and those living in areas with higher rates of poverty should be provided with accessible resources to foster recovery from trauma exposure. Use of patient zip code may be a particularly easy, low-cost method to determine risk for PTSD and identify those who would benefit most from early intervention, especially in conjunction with other methods to assess risk, such as autonomic responsivity (Hinrichs et al., 2019) or immune markers (Michopoulos, Beurel, et al., 2019).

Beyond determining individual risk, the current results emphasize the need for policy reforms and population-level interventions that will reduce trauma exposure and other chronic stressors associated with areas with high rates of poverty and thus reduce PTSD symptom burden in communities with high rates of poverty. For example, interventions aimed at providing permanent housing to individuals experiencing homelessness, without additional stipulations like sobriety, significantly improve quality of life and decrease mental illness (Castillo et al., 2018; Castillo et al., 2019). Similarly, expanding health insurance (thereby making healthcare more

accessible) is associated with lower rates of depression (Castillo et al., 2018). Neighborhoods with high rates of poverty are often the result of policies like red-lining, where neighborhoods with any number of Black or non-white residents were rated undesirably by the federal government (Appel & Nickerson, 2016; Lynch et al., 2021). As a result of policies like red-lining, non-white neighborhoods were under-invested in, and although red-lining was officially outlawed decades ago, its effects are still being felt today (Appel & Nickerson, 2016; Lynch et al., 2021). In order to address health inequities that are the result of historical policies like red-lining, policy-makers should work with affected communities to actively invest in historically under-invested neighborhoods.

Although the current study had several strengths, including the prospective design, there are several limitations that should be addressed. First, our measure of neighborhood poverty was at the zip code level, and thus captures a larger area than an individuals' immediate environment. While the current study is a good initial step in understanding how neighborhood poverty impacts prospective PTSD symptom development, future studies should utilize more granular measurements of neighborhood poverty, such as measurements based on census tract, to better understand the effects of the most immediate environment on PTSD risk. Second, we utilized self-report measures of PTSD symptoms, as opposed to the gold-standard Clinician Administered PTSD Scale (CAPS). However, both the PDS and PSS show strong reliability with the CAPS (Foa et al., 1997; Foa & Tolin, 2000), and so we are confident in our measurement of PTSD. Finally, we did not assess the effects of other chronic stressors such as racial stress or sexism, which may affect the ways in which neighborhood poverty impacts PTSD symptoms (Cole, 2009; Else-Quest & Hyde, 2016). Future well-powered studies should assess the impact of multiple oppressive systems to better understand contextual factors that impact the prospective

risk for PTSD. Overall, our results indicate that neighborhood poverty predicts worse PTSD outcomes in a diverse sample. Future work should better understand how the context in which people live impacts risk for PTSD, so that at-risk persons can be provided with adequate, accessible resources, and so that population-level reforms can be developed.

Figure 3.1: Neighborhood Poverty is Associated with PTSD Symptoms Six-Months Post-Trauma

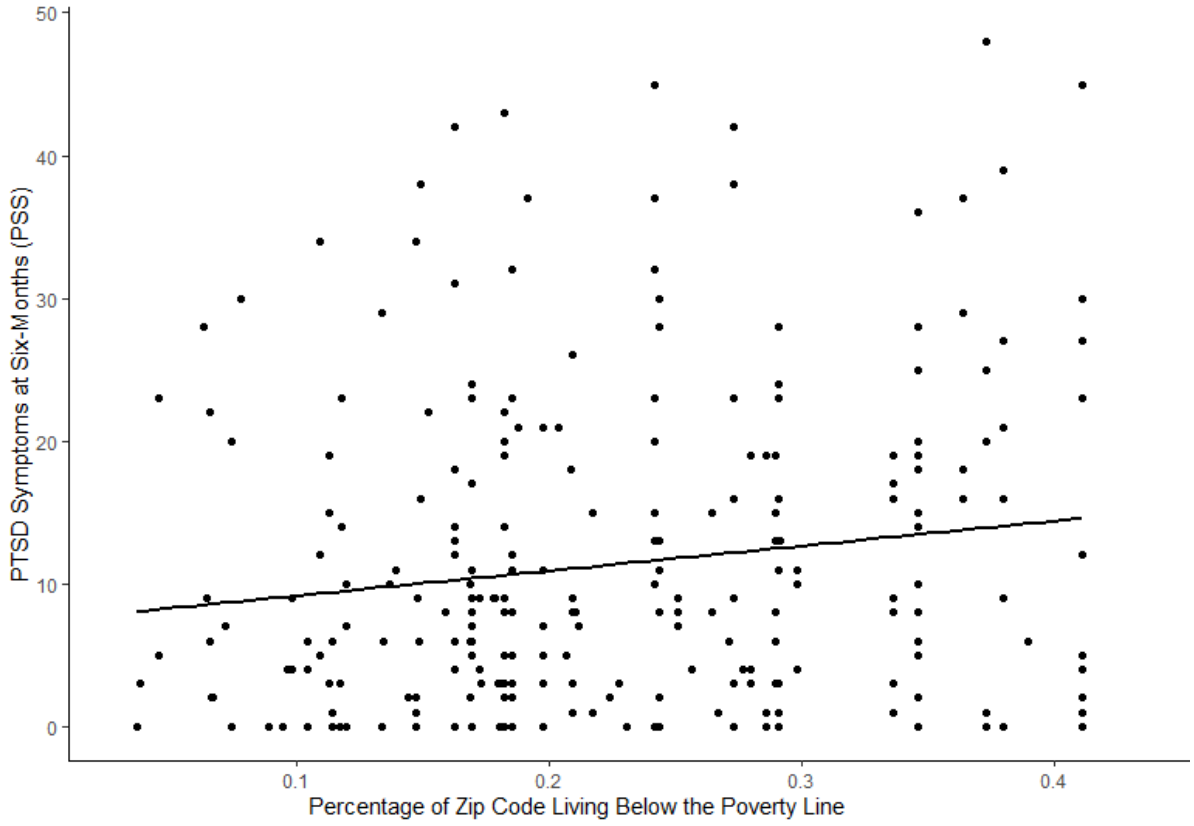


Table 3.1 Sample Demographics

Demographic	M	SD	%
Age (years)	36.21	12.69	
Sex			
Male			54.4
Female			45.6
Race			
Black			75
White			15.9
Asian			1.6
Mixed			4.4
Other			3.2
Monthly Household Income			
$0-$249			6.5
$250-$499			6.5
$500-$999			14.3
$1000-$1999			21.8
$2000 or more			48.8
Education			
Less than 12th grade			13.5
12th Grade/High School Graduate			24.6
Some College or Technical School			40.1
College Graduate			21.8
Some Graduate School			7.9
Graduate School Degree			7.5
Employment			
Currently Unemployed			19.4
Part-Time			12.7
Full-Time			52.8
Receiving Disability			5.6
Student			9.5
Clinician Rated Trauma Severity			
Mildly Severe			11.5
Somewhat Severe			34.1
Clearly Severe			35.3
Very Severe			17.1
NA			2
Baseline Trauma Exposure	2.78	1.84	
Baseline PTSD Symptoms (PDS)	8.60	9.40	
PTSD Symptoms Six-Months Post-Trauma (PSS)	11.37	11.15	

Table 3.2 Zero-Order Correlations

Measure	1	2	3	4	5	6	7
1. Neighborhood Poverty Rate	-	r=.163, p=.009	r=-.236, p<.001	r=.254, p<.001	r=.085, p=.178	r=.088, p=.164	r=.181, p=.004
2. PTSD Symptoms Six-Months Post-Trauma (PSS)		-	r=-.155, p=.015	r=.175, p=.005	r=.234, p<.001	r=.156, p=.013	r=.507, p<.001
3. Income			-	r=-.336, p<.001	r=-.095, p=.138	r=.015, p=.812	r=-.145 p=.023
4. Education				-	r=.137, p=.03	r=.016, p=.806	r=.129, p=.041
5. ED Clinician Rated Trauma Severity					-	r=.026, p=.676	r=.108, p=.086
6. Baseline Trauma Exposure						-	r=.484, p<.001
7. Baseline PTSD Symptoms (PDS)							-

Table 3.3: Step-wise Linear Regression Results

	R^2	*F*	*B*	*t*	*p*
Step 1	.099	6.80			<.001
Constant			-1.12	-.44	.66
Neighborhood Poverty			.15	2.10	.04
Clinician Rated Trauma Severity			2.59	3.68	<.001
Baseline Trauma History			.83	2.25	.03
Individual SES			-1.54	-1.15	.25
Step 2	.304	21.45			<.001
Constant			.86	.38	.71
Neighborhood Poverty			.07	1.13	.26
Clinician Rated Trauma Severity			2.04	3.27	<.001
Baseline Trauma History			-.67	-1.82	.07
Individual SES			-.53	-.45	.65
Baseline PTSD Symptoms			.63	8.50	<.001

CHAPTER 4: ENVIRONMENTAL AND BIOLOGICAL RISK FACTORS FOR PTSD IN PREGNANT BLACK PERSONS

4.1 Context and Authors' Contribution

The following Chapter focuses on the relationships between racial stress, neighborhood poverty, and PTSD symptoms during pregnancy, and on associations between PTSD symptoms, fear potentiated startle and CRP concentrations during the second trimester of pregnancy. The dissertation author contributed to data collection, conceptualization, data analysis, and writing the manuscript under the guidance of Drs. Vasiliki Michopoulos.

4.2 Abstract:

Black pregnant persons are disproportionately impacted by PTSD, and a better understanding of the factors underlying this risk is required to identify potential interventions and reduce symptom burden. Both environmental factors like racism and neighborhood poverty and biological factors like systemic inflammation have been linked to PTSD in non-pregnant persons, though their relationship to PTSD symptoms in pregnancy have not yet been determined. To address this gap, we examined the relationships between racial stress, neighborhood poverty, and PTSD symptoms in pregnancy. We also assess the relationships between PTSD, CRP concentrations, and fear potentiated startle, a biomarker of PTSD, within the second trimester of pregnancy. Neighborhood poverty was not associated with PTSD symptoms at either the census tract ($r=.031$, $p=.744$) or zip code ($r=.123$, $p=.14$) level. On the other hand, more racial stress was associated with higher PTSD symptoms ($r=.244$, $p<.001$). There was also a main effect of PTSD symptoms on startle magnitude, where more PTSD symptoms were associated with greater startle magnitude ($F(1,31)=8.835$, $p=.006$). There was not a significant effect of CRP concentration on startle magnitude $F(1,11)=.193$, $p=.669$, but there was a significant interaction between CRP concentration and block in predicting PTSD symptoms $F(3,121)=3.258$, $p=.024$.

Follow-up analyses on this interaction did not reveal a significant relationship between CRP concentration and startle magnitude at any block. Finally, there was a trending association between CRP concentrations and PTSD symptoms (ß=.411, p=.064), and a significant positive association between CRP concentration and avoidance/numbing PTSD symptoms (ß=.454, p=.039), and negative alterations in mood and cognitions (ß=.453, p=.039). Overall study results provide initial insight on environmental and biological factors underlying PTSD in pregnant Black persons with few economic resources.

4.3 Introduction

Posttraumatic stress disorder (PTSD) is a heterogenous psychiatric disorder that can occur after a traumatic event. PTSD is characterized by intrusions/re-experiencing the traumatic event, avoidance of trauma reminders, negative changes in cognition and mood, and hypervigilance and increased startle (APA, 2013). PTSD is associated with altered psychophysiology, including increased startle magnitude and fear potentiated startle during fear acquisition and extinction paradigms. Black individuals experience disproportionately high rates of PTSD; while rates of lifetime PTSD are approximately 7% in the general population (Keane et al., 2009), rates in Black communities with few economic resources are much higher at 46% (Gillespie et al., 2009). Pregnant Black persons are at even higher risk for PTSD (Seng et al., 2011), with lifetime PTSD rates as high as 56% (Powers et al., 2020). It is therefore crucial to understand environmental and biological factors that may contribute to risk for PTSD and alterations in fear psychophysiology among pregnant Black individuals with few economic resources to reduce symptom burden.

One environmental factor that is associated with worse PTSD symptoms among Black individuals and could explain high rates of PTSD among pregnant Black persons is racism.

Racism is a complex system occurring at the individual, cultural, and institutional levels that is designed to uphold white supremacy at the expense of other racial groups. Previous work from our group and others demonstrates that racism is associated with worse PTSD outcomes (Chapter 2) (Mekawi, Carter, et al., 2021; Sibrava et al., 2019). Despite this association, little is known about how racism impacts PTSD symptoms in pregnant Black persons. Racism impacts Black individuals across the lifespan, including pregnancy (Jackson et al., 2001), highlighting the importance of understanding the effects of racism on PTSD symptoms within pregnancy specifically.

Another environmental factor that may contribute to high rates of PTSD in pregnant Black persons is neighborhood poverty. Neighborhood poverty is defined as the rate of poverty for a given spatial area (i.e. zip code, census tract). High rates of neighborhood poverty are associated with a number of chronic stressors, including reduced access to adequate health care, lack of infrastructure, increased exposure to violence and policing, and decreased accessibility to supermarkets and nutritious food. Despite the associations between neighborhood poverty and these chronic stressors, studies on the relationship between neighborhood poverty and PTSD symptoms in adulthood are generally lacking, though work from our group suggests that high rates of neighborhood poverty are associated with higher PTSD symptoms and increased risk for the development of PTSD symptoms after experiencing a traumatic event (Chapters 2 and 3). However, to the best of our knowledge, no previous studies have focused on the role of neighborhood poverty on PTSD symptoms within pregnancy. Because pregnant individuals need frequent engagement with the health care system, they may need to overcome barriers associated with living in higher poverty areas, such as poor healthcare and transportation infrastructures, more often than when not pregnant. Thus, living in an area with a high rate of neighborhood

poverty may be particularly stressful during pregnancy, emphasizing the importance of understanding how neighborhood poverty contributes to PTSD symptoms during pregnancy.

Pregnancy is also associated with significant biological changes that may impact PTSD symptoms, such as changes in the immune system. Higher concentrations of the immune marker C-Reactive Protein (CRP) are associated with worse PTSD symptoms in non-pregnant persons. Inflammatory profiles change significantly during pregnancy, though data on the magnitude and direction are equivocal, making it difficult to discern the relationship between inflammatory markers and PTSD symptoms during pregnancy. Importantly, most previous studies on inflammatory markers in pregnancy do not account for childhood and adulthood trauma exposure, which contribute to inflammation in non-pregnant individuals and could therefore contribute to disparate results between studies. Inflammation during pregnancy is particularly important to understand, as too much or too little of a pro-inflammatory profile has been associated with negative pregnancy outcomes such as preterm birth or preeclampsia. It is crucial to understand the relationships between trauma, inflammation and PTSD symptoms in pregnancy in order to identify pregnant persons at risk for PTSD or other negative pregnancy outcomes related to dysregulated inflammatory processes and provide targeted interventions.

In addition to understanding factors contributing to PTSD in pregnancy, it is important to understand the psychophysiology of PTSD to characterize the neurobiological underpinnings of PTSD during pregnancy. One psychophysiological process that is impacted by PTSD in non-pregnant persons is fear potentiated startle (FPS), a fear-conditioning paradigm that produces increased acoustic startle to a startle probe in the presence of a conditioned stimulus that is associated with an aversive unconditioned stimulus. The FPS paradigm consists of two conditioned stimuli: one paired with the aversive unconditioned stimulus (danger signal, or CS+)

and one stimulus not paired with the unconditioned stimulus (safety signal, or CS-). In military and non-pregnant civilian populations, people with PTSD show increased startle to all stimuli, and increased also increased startle to the safety signal (impaired fear inhibition). Previous work shows fear potentiated startle to a safety signal is associated with hyperarousal symptoms of PTSD in pregnancy, though this study included pregnant persons at different stages of pregnancy. Studies focused on relationships between PTSD, FPS, and inflammation at specific stages of pregnancy are necessary to reduce the variability in these relationships due to pregnancy stage, and allow for a better understanding on how PTSD, FPS, and inflammation are related in pregnancy.

In the current study, we determine associations between racism and neighborhood poverty and PTSD symptoms at any stage of pregnancy within Black persons with few economic resources. We also examine the relationships between trauma exposure, CRP, FPS, and PTSD symptoms in the second trimester of pregnancy. We hypothesize that experiencing more racism and living in an area with higher rates of poverty will be associated with more PTSD symptoms. We also expect that higher CRP will be associated with higher overall FPS during fear acquisition, more PTSD symptoms, and greater trauma exposure.

4.4 Methods

4.4.1 Procedure

Participants (N=270) seeking prenatal care at a publicly funded hospital were recruited and enrolled in a study assessing the relationship between maternal trauma exposure and perinatal mental health and obstetric outcomes. Participants were enrolled between 2018 and 2022 at any gestational age. Research staff approached patients in the prenatal clinic for recruitment to the study or called and invited individuals to participate via telephone during the COVID-19

pandemic. Eligibility criteria included pregnancy, self-identified Black race, age between 18 and 40 years old, no active psychosis, and ability to provide informed consent. If persons agreed to participate, they gave informed consent and underwent an interview administered by a trained research assistant that assessed demographic information including their address, PTSD symptomatology, childhood and adulthood trauma history, and racial stress. Participants in their second trimester were also invited to attend an in-office visit where they completed the FPS paradigm and were administered a blood draw. Participants were compensated $40 for visits where interview measures were administered, and $50 for completing FPS and the blood draw. All procedures were approved by the Emory University Institutional Review Board and Grady Research Oversight Committee.

4.4.2 Measures

Index for Race-Related Stress (Brief)(IRRS) (Utsey, 1999)

The IRRS is a 22-item scale that assesses for racial stress, or the stress from experiencing racism, across the individual, institutional, and cultural domains. For each question, participants are asked to answer on a Likert scale ranging from 0 (this event never happened to me) to 4 (this event happened to me, and I was extremely bothered by it). Total racial stress was assessed by taking the average of all the items on the scale to ensure each domain had equal weight for the total racial stress score. The Cronbach's α for the sample was .939.

PTSD Checklist for DSM-5 (PCL-5) (Blevins et al., 2015)

The PCL-5 is a well-validated, 20-item scale assessing PTSD symptoms across the four symptoms clusters as defined by the DSM-5: avoidance, negative changes in mood and cognition, intrusions/re-experiencing symptoms, and hyperarousal/increased reactivity. For each item, participants respond on a Likert scale from 0 (*not at all*) to 4 (*extremely*). Each item was

summed to yield symptom cluster scores and total PTSD symptoms. The Cronbach's α for the sample was .941.

Traumatic Events Inventory (TEI) (Gillespie et al., 2009)

Lifetime trauma history was assessed using the TEI, which determines exposure to different types of traumatic events through childhood and adulthood.

American Community Survey (ACS)

The ACS is administered annually by the US Census Bureau, and determines sociodemographic factors for a given spatial area within the US (U.S. Census Bureau, 2020). We used the 5-year ACS summary file (2017-2021) to assess rates of neighborhood poverty at both the census tract and zip code level. Neighborhood poverty was defined as the percentage of people living below the federally mandated poverty line in the participant's census tract or zip code. Participant census tracts were determined by their address, and extracted using the censusxy package in R (Prener & Fox, 2021). Only participants enrolled through 2021 were included in analyses with neighborhood poverty (N=147).

4.4.3 Fear Potentiated Startle (FPS)

A subgroup of participants in their second trimester completed the FPS paradigm (N=33). The FPS paradigm consisted of two phases: 1) an initial habituation phase in which the conditioned stimuli (CS) were presented without the unconditioned stimulus and 2) an acquisition phase that consisted of three blocks with four trials of each type of CS (reinforced conditioned stimulus, CS+; non-reinforced conditioned stimulus, CS−; noise probe alone, NA), with each CS appearing. The acquisition phase immediately followed the habituation phase without any break. Both CSs were colored shapes (i.e., blue square, purple triangle) shown to participants on a computer screen. The unconditioned stimulus (US; aversive stimulus) was a 250-msec air blast

of 140-psi intensity to the larynx that has previously been shown to produce an FPS response (Glover et al. 2011; Norrholm et al. 2011). The air blast was delivered from a compressed air tank via a polyethylene tub and controlled by a solenoid switch. The startle probe was a 108-dB, 40-msec burst of broadband noise delivered to participants binaurally through headphones. Each CS was presented for six seconds total, and was shown 5250 ms before the startle probe. The inter-trial intervals were randomized to be between nine and 22 seconds in duration. Startle response data were collected using the electromyography (EMG) module of the BIOPAC MP150 for Windows (Biopac Systems, Goleta, California). The data were filtered, rectified, and smoothed using the MindWare software suite (MindWare Technologies, Gahanna, Ohio) and exported for statistical analyses. The eye-blink component of the acoustic startle response was measured by EMG recordings of the right orbicularis oculi muscle with two 5-mm Ag/AgCl electrodes filled with electrolyte gel as previously described (Glover et al. 2011; Jovanovic et al. 2010). One electrode was positioned 1 cm below the pupil of the right eye, and the other was placed 1 cm below the lateral canthus. A ground electrode was placed on the mastoid bone. Impedance levels were less than six kilohms for each participant. The EMG signal was sampled at a frequency of 1 kHz and filtered with low- and high-frequency cutoffs at 28 and 500 Hz, respectively. The maximum amplitude of the eye-blink muscle contraction 20 to 200 msec after presentation of the startle probe was used as a measure of the acoustic startle response.

4.4.4 CRP

A subgroup of participants in their second trimester provided a blood sample for CRP analyses (N=32). Plasma samples were stored at -80°C until time of high sensitivity CRP assay (hsCRP). hsCRP was measured using the immunoturbidometric method with a Beckman AU480 chemistry analyzer and Ultra WR CRP kit (Sekisui Diagnostics). Any participants with a CRP concentration greater than 20 mg/L were excluded to rule out persons with acute infection (N=7).

4.4.5 Data Analytic Plan

We ran bivariate correlations to test associations between total PTSD symptoms and symptom clusters, neighborhood poverty (at both the census tract and zip code level), and racial stress. Analyses on PTSD symptoms, neighborhood poverty, and racial stress included individuals at all stages of pregnancy. We also ran bivariate correlations to determine any associations between CRP concentrations and PTSD symptoms and their subclusters or trauma exposure in the second trimester. For FPS and CRP analyses, we first checked the skew of the startle magnitude and CRP concentration data. All FPS and CRP analyses were conducted with the log transformed values for both startle magnitude and CRP concentration due to a positive skew of the raw data. To assess the role of PTSD symptoms, trial type, and block on startle magnitude in the second trimester, we ran a linear mixed effects model, and included PTSD symptoms, trial type, and block as independent variables, with trial type and block as repeated measures and participant as a random factor. To assess the role of CRP on startle magnitude in the second trimester, we ran a linear mixed effects model with CRP, trial type, and block as the independent variables and startle magnitude as the dependent variable, with trial type and block as repeated measures and participant as a random factor. Follow up correlational analyses were conducted on any significant interactions. To determine associations between CRP and PTSD symptoms in the second trimester, we ran five step-wise linear regressions, with total PTSD symptoms or one of the four PTSD symptom clusters as the dependent variable and CRP as the independent variable in each model. Before running the regression models, we checked for associations between CRP, body mass index (BMI), and age, as these variables might influence CRP concentrations (Delongui et al., 2013). Significant associations were added as covariates in subsequent steps of each model of CRP and PTSD symptoms. To assess the role of trauma history on CRP concentrations in the second trimester of pregnancy, we ran an additional step-wise linear

regression, with trauma history as the predictor and CRP as the dependent variable. We added BMI and/or age as covariates in subsequent steps if they were significantly associated with CRP. All analyses were conducted in SPSS 28 and R 4.1.2. Analyses with p values <0.05 were considered significant.

4.5 Results

4.5.1 Participants

The average age of the overall sample (N=270) was 27.26 (SD=5.50), and participants experienced on average 5.05 (SD=3.81) types of traumatic events. 15.9% of the sample had an education less than 12th grade, 40% had completed high school, 3.7% had a GED, 23.7% had some college or technical school, 3.7% were a technical school graduate, 11.5% were college graduates, and 1.5% had graduate education. 54.6% of the sample was unemployed. 15.5% of the sample had a monthly household income less than $250, 6.6% had a monthly income between $250 and $499, 15.5% had an income between $500 and $999 per month, 25.8% had an income between $1000 and $1999, and 36% had a monthly household income of $2000 or more. Sample demographics can be seen in Table 4.1.

4.5.2 Neighborhood Poverty and PTSD

Neighborhood poverty was not associated with total PTSD symptoms at either the census tract (r=.031, p=.744) or zip code (r=.123, p=.14) level. Neighborhood poverty at the zip code level was significantly associated with more re-experiencing/intrusive symptoms (r=.182, p=.027), but not with any of the other symptom clusters (r's=.022-.115, p's>.05). Neighborhood poverty at the census tract level was not associated with any PTSD symptom subclusters (r's=.006-.053, p's>.05). Zero-order correlations can be seen in Table 4.2.

4.5.3 Racial Stress and PTSD Symptoms

Total racial stress was significantly associated with total PTSD symptoms (N=217) (r=.244, p<.001), re-experiencing symptoms (r=.180, p=.008), avoidance (r=.141, p=.038), negative thoughts/cognitions (r=.221, p<.001), and hyperarousal symptoms (r=.271, p<.001). Total racial stress was also associated with total (childhood and adulthood) trauma exposure (r=.328, p<.001).

4.4.4 FPS and PTSD Symptoms

The linear mixed effects model revealed a significant effect of PTSD symptoms $F(1,31)=8.835$, p=.006, where more PTSD symptoms were associated with greater startle magnitude. There was also a significant effect of trial type $F(2,341)=26.636$, p<.001 and block $F(3,341)=7.210$, p<.001 on startle magnitude. The interaction between PTSD symptoms and trial type was not significant $F(2,341)=2.038$, p=.131, nor were the interactions between PTSD symptoms and block $F(3,341)=.258$, p=.855, trial type and block $F(6,341)=1.220$, p=.295, or PTSD symptoms by trial type by block $F(6,341)=.391$, p=.885. Results can be seen in Figure 4.1.

4.5.5 CRP, PTSD Symptoms, Trauma History, and FPS

We first assessed relationships between CRP, BMI, and age to determine appropriate covariates in our regression models. CRP was significantly associated with BMI (r=.411, p=.046), but not with age (r=.084, p=.690). Thus, we only included BMI as a covariate in the second step of each regression model. In our first step-wise regression model, we assessed the relationship between CRP concentrations and total PTSD symptoms in the second trimester of pregnancy (N=21). CRP had a trending positive association with total PTSD symptoms (ß=.411, p=.064), and this relationship was weakened BMI was included as a covariate (ß=.360, p=.128). CRP was not associated with intrusive symptoms (N=21, ß=.293, p=.197), including when BMI was included as a covariate (ß=.290, p=.242). CRP was significantly associated with avoidance and numbing

symptoms (N=21, ß=.454, *p*=.039), but this relationship was no longer present when BMI was included as a covariate (ß=.398, *p*=.087). CRP was also associated with negative changes in mood and cognition (N=21, ß=.453, *p*=.039), but this association was also not present when BMI was included in the model as a covariate (ß=.406, *p*=.083). Lastly, CRP was not associated with hyperarousal symptoms (N=21, ß=.312, *p*=.168), including when BMI was added as a covariate (ß=.229, *p*=.334). Regressions controlling for BMI assessing the relationship between CRP and PTSD were not significant (Table 4.3)

We then assessed the relationship between trauma exposure and CRP concentrations in the second trimester of pregnancy (N=23). Total trauma exposure (childhood and adulthood) was not associated with CRP concentrations (ß=.080, *p*=.717), even when BMI was included as a covariate (ß=.107, *p*=.604) (Table 4.4).

As far as startle magnitude (N=13), CRP concentrations were not associated with overall startle magnitude $F(1,11)=.193$, $p=.669$, but trial type ($F(2,121)=7.405$, $p<.001$) and block ($F(3,121)=8.435$, $p<.001$) were associated with startle magnitude. There was also a significant interaction between CRP concentration and block on startle magnitude $F(3,121)=3.258$, $p=.024$ (Figure 4.2). Follow-up correlational analyses did not reveal a significant correlation between CRP concentration and startle magnitude in block 1 ($r=-.05$, $p=.76$), block 2 ($r=-.03$, $p=.87$), block 3 ($r=.24$, $p=.14$), or block 4 ($r=.24$, $p=.14$). The interactions between CRP by trial type $F(2,121)=.325$, $p=.724$, trial type by block $F(6,121)=.943$, $p=.467$, and CRP by trial type by block $F(6,121)=.924$, $p=.480$ were not significant.

4.6 Discussion

In the current study, we aimed to understand environmental and biological factors contributing to PTSD symptoms and FPS in a pregnant Black sample. Neighborhood poverty at

the zip code level was associated with re-experiencing symptoms of PTSD, but not with total PTSD symptoms or with other PTSD symptom subclusters. At the census tract level, neighborhood poverty was not associated with total PTSD symptoms or with any PTSD symptom subclusters. On the other hand, racial stress was associated with total PTSD symptoms and with all symptom subclusters. From a biological perspective, CRP concentrations had a trending positive association with total PTSD symptoms, avoidance/numbing symptoms, and significantly interacted with block to predict startle magnitude, though follow-up post-hoc analyses did not reveal a relationship between CRP concentrations and startle magnitude at any block. Finally, PTSD symptoms were associated with greater startle magnitude across block and trial type during fear acquisition. Overall, study results provide a better understanding on how environmental factors impact PTSD symptoms and FPS in Black pregnant persons, who are both at disproportionately high risk for PTSD and largely excluded from biomedical research.

Our finding that neighborhood poverty was not associated with total PTSD symptoms in pregnant persons was unexpected, and not in line with previous findings on relationships between neighborhood poverty and PTSD symptoms in non-pregnant persons (Chapter 2, Chapter 3). The lack of association between PTSD symptoms and neighborhood poverty at the census tract may be due to census tract itself. More specifically, the census tract may be too small a spatial area to capture relationships between neighborhood poverty rate and PTSD symptoms, as individuals likely spend much of their time outside of their home and census tract, but still in nearby areas such as their zip code. This could explain the relationship between neighborhood poverty rate at the zip code level and re-experiencing symptoms, but the lack of relationship between re-experiencing symptoms and neighborhood poverty at the census tract level. Although we found a relationship neighborhood poverty at the zip code level and re-

experiencing symptoms in pregnant persons, we did not find a relationship with total PTSD symptoms, which does not corroborate our previous work reported in Chapters 2 and 3 that was also conducted at the zip code level. Importantly, the data in our previous studies (Chapter 2 and Chapter 3) were collected from 2012-2018, and the data in the current study were collected from 2019-2021. Atlanta and its metropolitan area, where these studies were conducted, has changed significantly in recent years, with high rates of gentrification of previously under-resourced neighborhoods (Foell & Foster, 2022), and skyrocketing rent prices (US Bureau of Labor Statistics, 2023). Gentrification may reduce the number of individuals living below the poverty line in a previously under-resourced area for a period of time before individuals who originally lived in these neighborhoods are displaced due to rising costs (Zuk et al., 2015). Future longitudinal work is needed to disentangle the effects of living in a neighborhood that becomes gentrified on PTSD symptoms in both pregnant and non-pregnant individuals.

Our finding that racial stress is associated with PTSD symptoms extends previous work on relationships between racism and PTSD symptoms to a sample of pregnant individuals. Racial stress is a chronic stressor that is also unpredictable in nature (Utsey et al., 2013; Williams, Metzger, et al., 2018), which could explain our finding that PTSD symptoms were associated with racial stress but not neighborhood poverty, which is a chronic stressor that is less unpredictable. Unpredictable stressors are associated with PTSD-like symptoms in animal models (Finsterwald et al., 2015), and have been associated with greater anxiety among individuals with PTSD (Grillon et al., 2009). Racial stress may be particularly poignant during pregnancy, as pregnant individuals have more frequent contact with the healthcare system, where they may be at increased risk for experiencing racism at every level (Hoberman, 2012; King, 1996), highlighting the need to understand the effects of racism on mental health during

pregnancy. Racial stress exacerbates PTSD symptoms, and in pregnancy, this increased stress may lead to negative pregnancy outcomes like pre-term birth and preeclampsia, which Black pregnant persons are disproportionately impacted by. Overall, our finding on the relationship between racial stress and PTSD symptoms within pregnancy demonstrate the need for anti-racist policies and practices, including among health care workers.

We also saw a trending association between CRP concentrations and PTSD symptoms, and a significant association with avoidance symptoms and negative thoughts (when we did not control for BMI). Because there was not a main effect of BMI on PTSD symptoms, the lack of effect of CRP on avoidance symptoms and negative thoughts while controlling for BMI is likely due to low sample size and power. While our study was under-powered, the direction of these associations supports prior literature on relationships between inflammation and PTSD symptoms (Michopoulos, Norrholm, et al., 2015; Michopoulos et al., 2016; Passos et al., 2015; Ravi et al., 2021). The relationship between CRP and avoidance symptoms partially supports prior work, where avoidance of trauma reminders was associated with fibrinogen, an acute phase reactant, but not CRP in non-pregnant persons (O'Donovan et al., 2017). Unlike the study by Donovan et al, in this study we found that CRP was associated with PTSD symptoms (before controlling for BMI), though our results do support the notion that inflammation is associated with avoidance symptoms. Additionally, non-pregnant Japanese women who experienced high amounts of childhood maltreatment with the C allele on the rs2794520 location of the CRP gene, which is associated with higher concentrations of CRP, show greater avoidance symptoms (Otsuka et al., 2021). Future well-powered studies could therefore look at interactions between trauma history and CRP concentrations and their association with avoidance symptoms in pregnancy.

The relationship between CRP and negative thoughts corroborates previous work on the relationships between inflammation and rumination, which consists of repeated reflection on negative thoughts, events, and feelings across psychiatric disorders (Szabo et al., 2022). Several studies have found an association between rumination and inflammatory markers, and rumination is known to activate the hypothalamic-pituitary-adrenal (HPA) axis, which when chronically activated can lead to increases in systemic inflammation (Ravi et al., 2021; Szabo et al., 2022). In addition to supporting previous work on relationships between inflammation and rumination, the relationship between CRP and negative thoughts supports prior literature on relationships between inflammation and anhedonia symptoms of depression (Bekhbat et al., 2022), which is related to numbing symptoms in PTSD (within the negative thoughts cluster) (APA 2013; Orsillo et al., 2007). For example, previous work from our lab with non-pregnant women found that CRP was associated with less functional connectivity between the ventromedial prefrontal cortex (vmPFC) and ventral striatum, which was in turn associated with symptoms of anhedonia (Mehta et al., 2020). Thus, subsequent studies should aim to understand the relationships between CRP, avoidance, and negative thoughts in PTSD within pregnant persons.

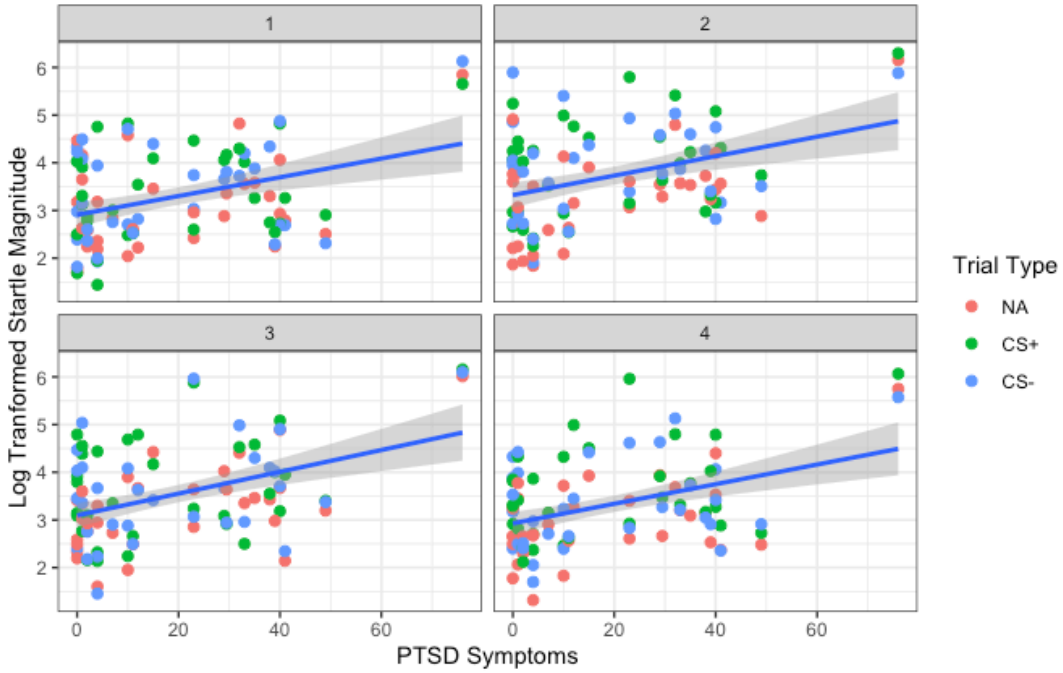
Lastly, we found that PTSD symptoms are associated with greater startle magnitude during the FPS task, which is in line with previous work. One hallmark symptom of PTSD is increased startle magnitude in the FPS paradigm. In the current study, results may have been driven by one individual with particularly high symptoms. Several participants in the present study had low symptoms, and future studies are needed with larger sample sizes that include more individuals with higher symptoms to better understand the relationship between PTSD and FPS in pregnancy. Our low sample size could also explain the non-significant interactions

between trial type, block, and/or PTSD symptoms. We also saw that CRP concentrations interacted with block in predicting startle magnitude, with an emerging relationship between CRP concentrations and startle magnitude in late acquisition, as evidenced by the positive correlations between CRP and startle magnitude in blocks 3 and 4. However, despite the significant interaction in our mixed-effects model, the correlations between CRP concentration and startle magnitude were not significant in blocks 3 and 4, likely due to very low sample size. Although our findings on the relationships between PTSD symptoms, CRP concentration, and startle magnitude among a pregnant sample provides a good initial step, future studies with significantly larger sample sizes are needed to better understand the neurobiological underpinnings of PTSD in pregnancy.

Our study had several strengths, including the focus on a group historically excluded from biomedical research and the specificity of looking at a particular time point in pregnancy for our analyses on PTSD, FPS, and CRP, which is important given significant biological changes during pregnancy that may influence these relationships. Despite these strengths, there are several limitations. First, we used a cross-sectional sample, where a longitudinal study may better explain how environmental and biological factors impact PTSD symptoms over the course of pregnancy. For our analyses on neighborhood poverty, we had an acceptable sample size, though our previous studies on the role of neighborhood poverty on PTSD symptoms used much larger sample sizes (Chapters 2 and 3, N>250), so future studies on the relationship between neighborhood poverty and PTSD symptoms may need to be replicated with even larger sample sizes. Our analyses with FPS and CRP were under-powered due to a very low sample size resulting from COVID-19 study delays and impacts. Future studies are needed with larger sample sizes that include more individuals with higher PTSD symptoms to assess the

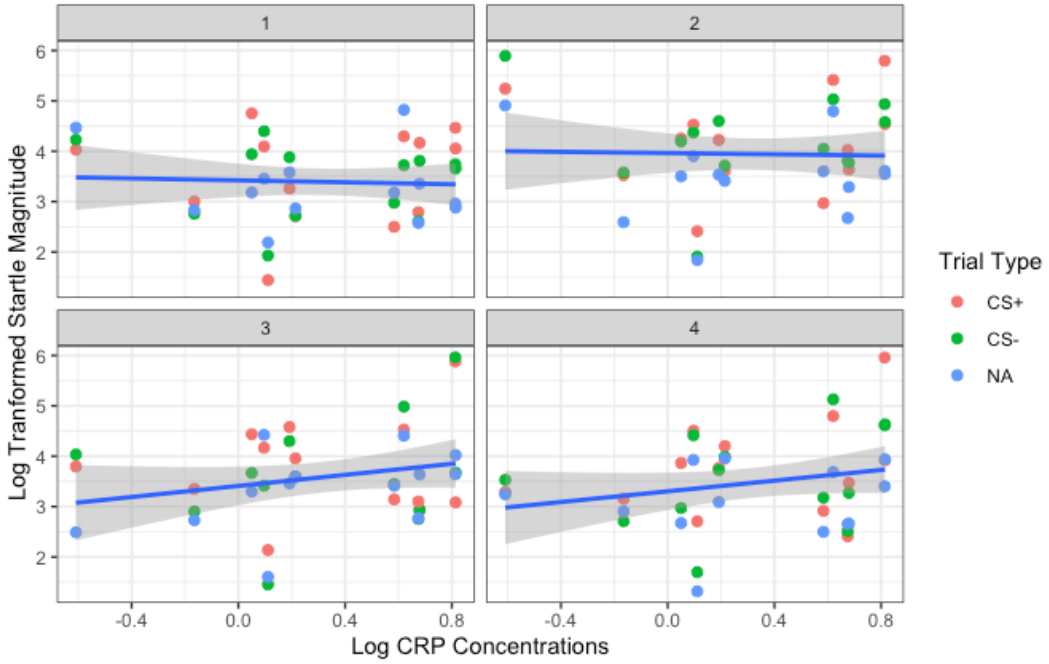
relationships between FPS, PTSD, and inflammation. Finally, our measure for PTSD symptoms used the self-report PCL-5 instead of the gold-standard Clinician Administered PTSD Scale (CAPS), though the PCL-5 shows high consistency with the CAPS, so we are confident that our measure of PTSD symptoms is accurate. Despite these limitations, the findings in this study are a good first step and provide initial insight into the relationships between environmental and biological factors with PTSD and fear psychophysiology in pregnant persons.

Figure 4.1: PTSD Symptoms and Startle Magnitude



*Panel number denotes block
NA: Noise Alone trials
CS+: Conditioned Stimulus without reinforcement, Danger Signal
CS-: Conditioned Stimulus without reinforcement, Safety Signal
Relationship between PTSD symptoms and startle magnitude did not differ by block or cue type (N=33)

Figure 4.2: CRP Concentration and Startle Magnitude



*Panel number denotes block
NA: Noise Alone trials
CS+: Conditioned Stimulus without reinforcement, Danger Signal
CS-: Conditioned Stimulus without reinforcement, Safety Signal
Correlations between CRP concentration and startle magnitude were not significant in any block (N=13)

Table 4.1: Sample Demographics (N=270)

Demographic	**Mean (SD); Percent**
Age (years)	27.26 (5.50)
Total Trauma (Witnessed or Experienced)	5.05 (3.81)
Monthly Household Income	
$0-$249	15.5%
$250-$499	6.6%
$500-$999	15.5%
$1000-$1999	25.8%
$2000 or more	36%
Education	
Less than 12th grade	15.9%
12th Grade/High School Graduate	40%
GED	3.7%
Some College or Technical School	23.7%
Technical School Graduate	3.7%
College Graduate	11.5%
Graduate School	1.5%
Employment	
Currently Unemployed	54.6%

Table 4.2: Correlations Between Neighborhood Poverty and PTSD Symptoms (N=147)

Variable	1	2	3	4	5	6	7
1. Neighborhood poverty rate (census tract)	-	*r*=.503 *p*<.001	*r*=.031 *p*=.744	*r*=.006 *p*=.949	*r*=.039 *p*=.681	*r*=.053 *p*=.580	*r*=.005 *p*=.961
2. Neighborhood poverty rate (zip code)		-	*r*=.123 *p*=.140	*r*=.182 *p*=.027	*r*=.022 *p*=.796	*r*=.115 *p*=.166	*r*=.056 *p*=.503
3. Total PTSD Symptoms			-	*r*=.849 *p*<.001	*r*=.722 *p*<.001	*r*=.924 *p*<.001	*r*=.885 *p*<.001
4. Re-experiencing/ Intrusive Symptoms				-	*r*=.595 *p*<.001	*r*=.677 *p*<.001	*r*=.637 *p*<.001
5. Avoidance/Numbing Symptoms					-	*r*=.572 *p*<.001	*r*=.537 *p*<.001
6. Negative Changes in Mood/Cognition						-	*r*=.778 *p*<.001
7. Hyperarousal Symptoms							-

Table 4.3: CRP and PTSD Symptoms Regression Results (N=21)

Dependent Variable		R^2	F	Standardized Beta	t	p
Total PTSD Symptoms						
	Step 1	.169	3.864			.064
	Constant				.829	.418
	CRP			.411	1.966	.064
	Step 2	.189	2.099			.152
	Constant				-.164	.872
	CRP			.360	1.596	.128
	BMI			.151	.668	.512
Re-experiencing/ Intrusive Symptoms						
	Step 1	.086	1.789			.197
	Constant				.659	.518
	CRP			.293	1.338	.197
	Step 2	.086	.849			.444
	Constant				.285	.779
	CRP			.290	1.209	.242
	BMI			.011	.046	.963
Avoidance/Numbing Symptoms						
	Step 1	.206	4.928			.039
	Constant				.088	.931
	CRP			.454	2.220	.039
	Step 2	.230	2.682			.096
	Constant				-.597	.558
	CRP			.398	1.812	.087
	BMI			.163	.743	.467
Negative Alterations in Mood/Cognitions						
	Step 1	.206	4.918			.039
	Constant				.203	.841
	CRP			.453	2.218	.039
	Step 2	.223	2.585			.103
	Constant				-.448	.659
	CRP			.406	1.838	.083
	BMI			.141	.637	.532
Hyperarousal Symptoms						
	Step 1	.098	2.054			.168
	Constant				1.760	.094
	CRP			.312	1.433	.168
	Step 2	.151	1.602			.229
	Constant				-.025	.980
	CRP			.229	.992	.334
	BMI			.246	1.066	.301

Table 4.4: Trauma Exposure and CRP Regression Results (N=23)

	R^2	*F*	Standardized Beta	*t*	*p*
Step 1	.006	.135			.717
Constant				4.928	<.001
Trauma Exposure			.080	.368	.717
Step 2	.182	2.229			.134
Constant				.156	.877
Trauma Exposure			.107	.527	.604
BMI			.420	2.074	.051

CHAPTER 5: INDIRECT EFFECT OF NEGATIVE EVALUATIONS OF THERAPY ON THE ASSOCIATION BETWEEN RACIAL STRESS AND PTSD SYMPTOMS IN PREGNANT BLACK PERSONS

5.1 Context, Authors' Contribution, And Acknowledgement Of Reproduction

The following Chapter focuses on the indirect relationship between racial stress and PTSD symptoms through a negative evaluation of therapy. The dissertation author contributed to data collection, conceptualization, data analysis, and writing the manuscript under the guidance of Drs. Vasiliki Michopoulos. Drs. Emma Lathan, Cecilia Hinojosa, and Abigail Lott contributed to conceptualization and editing the manuscript. Ms. Shimarith Wallace, Ms. Dominique Jones, Ms. Jamie Villalobos, and Ms. Sriya Karra contributed to data collection and editing the manuscript. This Chapter is reproduced from Ravi M., Lathan, E., Wallace, S., Hinojosa, C., Jones, D., Villalobos, J., Karra, S., Powers, A., Michopoulos, V. Indirect Effect of Negative Evaluations of Therapy on the Association between Racial Stress and PTSD Symptoms in Pregnant Black Persons. Psychological Trauma: Theory, Research, Practice, and Policy (Under Revision).

5.2 Abstract

Black pregnant individuals are at disproportionate risk for posttraumatic stress disorder (PTSD) compared to other groups. A wealth of literature suggests racial stress contributes to this inequity, but cultural and structural mechanisms, such as perceived barriers to mental health treatment, underlying the relationship between racial stress and PTSD symptoms remain understudied. Negative evaluations of psychotherapy and stigma represent potential mechanisms, though no previous studies have examined these associations. To address this gap, we tested an indirect effect of racial stress on PTSD symptoms through perceived barriers to mental health treatment in pregnant Black individuals. Mediation analyses were used to assess an indirect relationship between racial stress and PTSD symptoms through perceived barriers to mental health treatment. At the bivariate level, racial stress was significantly associated with PTSD symptoms (r=.20, p=.03) and negative evaluations of therapy (r=.22, p=.02), but not with

stigma (r=.140, p=.147). Negative evaluations of therapy were also associated with PTSD symptoms (r=.43, p<.001). There was an indirect effect of racial stress on PTSD symptoms through a negative evaluation of therapy (β=.08, SE=.04, CI[.01, .18]). More specifically, racial stress was associated with a more negative evaluation of therapy, which was in turn associated with more PTSD symptoms. Results highlight the need for accessible and culturally competent mental health care for pregnant Black individuals.

5.3 Introduction

Posttraumatic stress disorder (PTSD) is a debilitating and heterogenous disorder that can develop after experiencing a traumatic event. PTSD is characterized by a number of symptoms, including intrusions/re-experiencing, avoidance, negative changes in cognition and mood, and alterations in arousal and reactivity (APA, 2013). Black individuals are disproportionately affected by PTSD as compared to other racial groups; while rates of lifetime PTSD are approximately 7% in the general population (Keane et al., 2009), rates in Black communities with few economic resources are as high as 46% (Gillespie et al., 2009). Pregnant individuals in these communities are at even higher risk for PTSD (Seng et al., 2011), as evidenced by lifetime PTSD rates as high as 56% (Powers et al., 2020). Therefore, a better understanding of factors contributing to PTSD within pregnant Black persons with few economic resources is necessary to provide effective care and to reduce symptom burden.

One factor that could help explain the disparity in rates of PTSD between pregnant Black persons and other groups is racism. Racism is a complex and multifaceted oppressive system designed to uphold white supremacy at the expense of other racial groups (Braham et al., 1992; Corneau & Stergiopoulos, 2012). Racism occurs at the individual, cultural, institutional levels and can therefore negatively impact Black individuals in a multitude of ways (Jones, 1991).

Individual racism consists of behaviors and attitudes (intentional or unintentional) where members of a marginalized race are treated differently due to their race (Jones, 2000). Individual racism can manifest in many ways, including a lack of respect, suspicion of committing crime, or hate crimes/police brutality against racially marginalized individuals (Jones, 2000). Institutional racism consists of policies and procedures that deny marginalized racial groups access to opportunities and resources, which prevents upward mobility (Jones, 2000). Finally, cultural racism refers to the widespread belief that White ideologies and values are superior to other racial groups, and where the culture and values of other racial groups are perceived negatively (Oliver, 2001; Utsey, 1999).

Because the pervasive nature of racism is inherently traumatizing, it can lead to racial stress, or psychological distress caused by racism (Plummer & Slane, 1996). Racial stress can negatively impact overall mental health for Black individuals (Comas-Díaz et al., 2019; Kirkinis et al., 2021; Mekawi, Carter, et al., 2021). For example, racism is associated with reduced life satisfaction in Black adults (Broman, 1997), and with more symptoms of depression and anxiety (Williams & Mohammed, 2009). In the context of PTSD, experiencing racism is associated with a future PTSD diagnosis among Black and Latinx adults (Bird et al., 2021; Sibrava et al., 2019). Racial stress is also associated with PTSD symptoms among Black individuals with few economic resources, even while controlling for confounding factors like distress levels, crime rates, and perceived safety (Brooks Holliday et al., 2020; Mekawi, Carter, et al., 2021).

While existing literature demonstrates that racial stress exacerbates PTSD symptoms in non-pregnant Black individuals, studies focusing on pregnant Black individuals are lacking. Importantly, pregnant Black persons are disproportionately affected by negative pregnancy outcomes like pre-term birth and preeclampsia (Purisch & Gyamfi-Bannerman, 2017; Ross,

Dunkel Schetter, et al., 2019). Psychopathology during pregnancy, including PTSD, can increase risk for these negative pregnancy outcomes (Shaw et al., 2017; Yonkers et al., 2014). Black individuals might be at particularly high risk for racial stress when they are pregnant due to increased contact with the health care system, which is steeped in racism (Hoberman, 2012; King, 1996). Pregnant Black individuals' increased risk for both PTSD and experiences of racism highlight the need to understand the role of racial stress in their PTSD symptomology to increase clinicians' ability to provide high quality maternal care, and thus, the likelihood of a healthy pregnancy.

Although the link between racial stress and PTSD is well-established, little is known about mechanisms underlying the association between racism and PTSD. The complex and all-encompassing nature of racism suggests multiple pathways by which racial stress might worsen PTSD outcomes. One mechanism through which racial stress could negatively impact PTSD symptoms is perceived barriers to mental health treatment, which could prevent recovery after experiencing a traumatic event and prolong persistence of PTSD symptoms. Indeed, a systematic review found that negative attitudes towards mental health services and stigma around mental illness prevents trauma survivors from seeking mental health care, and that these relationships are exacerbated in ethnically minoritized individuals (Kantor et al., 2017). Additionally, in a qualitative study with elderly Black adults with depression, barriers like stigma around mental illness and mistrust of the mental health care system (i.e., lack of confidence in mental health care, a mistrust of providers) prevented participants from seeking mental health care (Conner et al., 2010). Participants also felt that stigmatizing attitudes around mental illness were exacerbated for Black individuals with depression as compared to other racial groups (Conner et al., 2010). Participants with PTSD from a community sample of Black adults with few economic

resources endorsed high levels of stigma around seeking mental health services (Powers et al., 2022). In regard to treatment adherence, one study found that Black veterans with PTSD maintained pharmacological treatment for PTSD based on their perception of their provider but maintained talk-based psychotherapy based on what their therapist focused on during sessions (Spoont et al., 2017). Barriers to care are also associated with worse mental health; for example, impediments to mental health treatment, including stigma and negative beliefs about mental health care, predicted more depressive and PTSD symptoms among combat veterans (Wright et al., 2014).

Importantly, experiences of racial discrimination within the health care system predict lower utilization of preventative health services (Trivedi & Ayanian, 2006), underutilization of medical services (Klassen et al., 2002), and less engagement with mental health care among Black Americans (Burgess et al., 2008). Relationships between racial stress and reduced health care engagement could be explained through increased stigma about mental illness (Krill Williston et al., 2019) or a mistrust of the health care system (Hausmann et al., 2013). While existing literature suggests that racial stress within the health care system can lead to negative beliefs and mistrust of the overall health care system, less research has been conducted on the impacts of general racial stress on stigma and perceptions of mental health care.

Given the negative effects of racial stress on mental health, it is important to understand whether stigma and perceptions of mental health care help to explain the relation between racial stress and PTSD symptoms in pregnant Black persons. Thus, to address gaps in research in this area, the current study examined associations between racial stress and PTSD symptoms and two perceived barriers to psychological treatment: negative evaluations of therapy and stigma surrounding mental illness. We conducted follow-up mediation analyses on significant

associations to determine the existence of an indirect association between racial stress and PTSD symptoms through perceived barriers to psychological treatment. We hypothesized that racial stress would be associated with more negative evaluations of therapy and greater stigma, which would in turn be associated with more PTSD symptoms.

5.4 Methods

5.4.1 Procedure

Participants (N=109) seeking prenatal care at a publicly funded hospital (primarily serving minoritized communities with few economic resources) were recruited for involvement in an ongoing study assessing the impact of maternal trauma exposure and responses on perinatal and obstetric outcomes within an urban population. Participants were enrolled between 2018 and 2022. As part of the study, trained interns approached patients in the obstetrics clinics regarding potential participation. During COVID-19, hospital patients were invited to participate via telephone. Eligibility criteria included pregnancy, self-identified Black race, age between 18 and 40 years old, no active psychosis, and ability to provide informed consent. If participants agreed to participate, they gave informed consent and underwent an interview administered by a trained research assistant that assessed PTSD symptomatology, perceived barriers to psychological treatment, and racial stress. Participants were compensated $40 for their time in the study, and all procedures were approved by the Emory University Institutional Review Board and Grady Research Oversight Committee. Only participants who had experienced at least one traumatic event were included in the current analyses.

5.4.2 Measures

Perceived Barriers to Psychological Treatment Scale (PBPT) (Mohr et al., 2010)

The PBPT scale is a 27-item questionnaire that determines potential barriers to mental health treatment. Each item asks about a potential problem that might prevent someone from seeking therapy. Participants are asked to answer on a scale of 1 (not difficult at all) to 5 (impossible) in determining how much each problem would prevent them from seeking therapy. Items are scored for a total score as well as subscales that comprise specific types of barriers to treatment. For this study, we focused on two subscales: negative evaluations of therapy and stigma. The Cronbach's α for negative evaluations of therapy was .76, and the Cronbach's α for stigma was .80.

Index for Race-Related Stress (Brief) (Utsey, 1999)

The IRRS is a 22-item scale that assesses for racial stress across various domains. For each question, participants are asked to answer on a Likert scale ranging from 0 (this event never happened to me) to 4 (this event happened to me, and I was extremely bothered by it). The scale has three subscales, each respectively measuring individual racial stress, institutional racial stress, and cultural racial stress. Total racial stress was determined by taking the mean score of all the items on the scale to ensure each subscale had equal weight for the total racial stress score. The Cronbach's α for the sample was .94.

PTSD Checklist for DSM-5 (PCL-5) (Blevins et al., 2015)

The PCL-5 is a well-validated, 20-item scale assessing PTSD symptoms across four symptoms clusters as defined by the DSM-5: intrusions/re-experiencing symptoms, avoidance, and negative changes in cognitions and mood, and alterations in arousal and reactivity. For each item, participants respond on a Likert scale from 0 (*not at all*) to 4 (*extremely*). Overall PTSD symptoms were defined as the total sum across symptom clusters. The Cronbach's α for the sample was .936.

Traumatic Events Inventory (TEI) (Gillespie et al., 2009)

Lifetime trauma history was assessed using the TEI, which determines exposure to different types of traumatic events. This measure shows construct-validity with trauma-related psychological symptoms in primarily Black individuals with few economic resources (Mekawi, Kuzyk, et al., 2021).

5.4.3 Data Analytic Plan

We first checked the distribution of each measure and found that the IRRS and PCL-5 fell within normal range. The two perceived barriers to psychological treatment (negative evaluations of therapy and stigma) were positively skewed, so the data were transformed by taking the natural log of the raw values to normalize the distribution. All subsequent analyses were conducted using the transformed values for negative evaluations of therapy and stigma. We initially ran bivariate correlation analyses between negative evaluations of therapy, stigma, total racial stress, and PTSD symptoms. We conducted follow-up tests on significant correlations ($p < .05$) using simple mediation analyses with PROCESS macro in SPSS Version 28 (Hayes et al., 2017). Through the mediation analyses, we examined whether racial stress (X) impacted PTSD symptoms (Y) through each perceived barrier to therapy (M). In the mediation analysis, the *a* path represented the effect of racial stress on a perceived barrier to therapy, and the *b* path represented the effect of the perceived barrier on PTSD symptoms. The indirect effect (calculated by multiplying the a and b coefficients together; *ab*) represents racial stress' relation to PTSD symptoms through a perceived barrier to therapy. Five-thousand bootstrapped samples were generated to determine a 95% confidence interval for the indirect effect. The indirect effect was considered significant if the bootstrapped confidence interval did not contain zero.

5.5 Results

5.5.1 Participants

On average, participants were 28.17 years old (*SD*=5.49) and experienced 5.56 traumatic events in their lifetime (*SD*= 3.28). Almost half of the participants reported being currently unemployed (49.1%), and most were experiencing significant economic disadvantage (i.e., a monthly household income of less than $2,000; 57.3%). Sample demographics can be found in Table 5.1.

5.5.2 Correlational Analyses

Zero-order correlations can be seen in Table 5.2. Racial stress was associated with PTSD symptoms (r=.185, p=.041) and negative evaluations of therapy (r=.239, p=.013), but not stigma (r=.135, p=.165). Negative evaluations of therapy and stigma were each significantly associated with PTSD symptoms (r's = .439-.553, p's <.001).

5.5.3 Mediation Model

Based on significant results in the correlation analyses, we conducted one mediation analysis to test the indirect association between racial stress and PTSD symptoms through negative evaluations of therapy. Results revealed that more racial stress was associated with a more negative evaluation of therapy (path *a*, β= .217, p=.024), which was in turn associated with more PTSD symptoms (path *b*, β=.349, p<.001). A confidence interval using 5,000 samples was generated to determine the indirect effect of racial stress on PTSD symptoms through negative evaluations of therapy. Altogether, we found a significant indirect effect of racial stress on PTSD symptoms through negative evaluations of therapy (β=.076, SE=.042, CI: [.010-.176) (Figure 1).

5.6 Discussion

In the current study, we aimed to determine potential pathways linking racial stress and PTSD symptoms in a sample of Black pregnant persons. We found an indirect effect of racial stress on

PTSD symptoms through a negative evaluation of therapy; in other words, experiencing more racial stress predicted a more negative evaluation of therapy, which in turn predicted higher PTSD symptoms. Our findings support previous work demonstrating a link between racial stress and negative perceptions of the health care system, and literature showing that mistrust of the health care system mediates a relationship between racial stress and reduced health care engagement. Overall, the current study results add to the literature on the impact of racism on PTSD symptoms and provide additional information on mechanisms underlying this relationship, namely negative evaluations of therapy. Importantly, the current study focused on Black and pregnant individuals, who are at disproportionate risk for PTSD (Powers et al., 2020; Seng et al., 2011) and negative pregnancy outcomes (Purisch & Gyamfi-Bannerman, 2017; Ross, Dunkel Schetter, et al., 2019).

Experiencing racism at any level can lead to negative evaluations of and a mistrust of the health care system, including the mental health care system (Alang, 2019). In terms of racism experienced at the individual level, more negative experiences with police (a form of racism) is associated with medical mistrust (Alang et al., 2020), and both major and everyday discrimination (i.e. disrespect in everyday settings) outside of the health care system are associated with reduced engagement with the mental health care system (Burgess et al., 2008). In addition to individual racism, a legacy of historically racist practices has harmed Black communities, leading to mistrust of mainstream systems that are intended to be helpful (Alsan & Wanamaker, 2018; Williamson & Bigman, 2018). This mistrust of systems also translates to the mental health care system (Castro-Ramirez et al., 2021), which has caused harm to Black communities. For example, 53% of racially minoritized individuals report racist microaggressions from their therapist (Owen et al., 2014), and Black persons are also

disproportionately diagnosed with psychotic disorders (Schwartz & Blankenship, 2014). The mental health care system also often criminalizes the behavior of Black individuals, sometimes leading to involuntary hospitalization or involvement of law enforcement when unnecessary, all of which leads to further mistrust of mental health care (Alang, 2019).

The mistrust of the mental health care system is especially problematic in pregnant Black persons, who are at increased risk for mental illness compared to other groups (Seng et al., 2010). Pregnancy is associated with profound biological and social changes that might negatively impact mental health (Ravi et al., 2022; Smith, 1999). Mental illness during pregnancy not only impacts the pregnant person's well-being, but is also associated with negative pregnancy outcomes like pre-term birth (Cappelletti et al., 2016; Shapiro et al., 2013) and can impact offspring development (Cao-Lei et al., 2016). It is therefore critical to understand how racial stress impacts PTSD symptoms in Black pregnant persons specifically, since Black pregnant individuals are disproportionately impacted by negative pregnancy outcomes. Importantly, previous work from our group has found that PTSD is underdiagnosed in pregnant Black persons (Powers et al., 2020), highlighting an opportunity for intervention for many individuals. Addressing mental illness and other stressors during pregnancy may help address health inequities in pregnancy outcomes, and so it is important to provide adequate, culturally-informed mental health care for Black pregnant individuals.

The current study helps address a gap in understanding how racial stress in everyday life is associated with perceptions of the mental health care system, and how this in turn impacts PTSD symptoms in a high-risk, understudied group. Despite this strength, there are also limitations that must be considered. First, the study was cross-sectional in design, which makes it difficult to assess causality among racial stress, negative evaluations of therapy, and PTSD

symptoms. Future studies could focus on how perceived barriers to therapy change with racial stress exposure over time to better understand relationships between racial stress, perceived barriers to psychological treatment, and PTSD symptoms. Second, our study design did not assess the effects of other oppressive systems that participants may also be experiencing, such as sexism, homophobia, or classism. Future studies should aim to understand how the intersection of multiple marginalized identities are related to perceived barriers to psychological treatment and PTSD symptoms. Third, in the current study we used a self-report scale for PTSD as opposed to a clinician diagnosis. Despite this limitation, the PCL-5 has been well-validated with the gold-standard, clinician administered PTSD scale (Blevins et al., 2015). Finally, the current study included a sample of Black pregnant individuals, primarily with few economic resources, which could limit generalizability to other groups. Nevertheless, Black pregnant persons have historically been excluded from psychiatric research despite disproportionate risk for PTSD, so the current study is well warranted as it addresses needs for a group that experiences greater health inequities.

Our results highlight the need for mental health care providers to be actively anti-racist and address implicit racial biases (Greenwald & Krieger, 2006; Naz et al., 2019), since microaggressions at the hand of therapists and institutionally racist practices lead to mistrust of the mental health care system (Alang, 2019; Owen et al., 2014; Trivedi & Ayanian, 2006). Clinicians must also actively engage clients in determining the best treatment course, as clients who feel pressured into treatments that they may not trust hold more negative beliefs about mental health care (Conner et al., 2010). Training programs for mental health care providers must also remove barriers and make it easier for Black individuals to become clinicians, as some clients may find it easier to build rapport with a therapist with a firsthand understanding of the

negative effects of racism (Chang & Yoon, 2011; Conner et al., 2010). Overall, active efforts to provide accessible, culturally competent care are required to reduce PTSD symptom burden in Black pregnant individuals.

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Figure 5.1: Indirect Relationship of Racial Stress on PTSD Symptoms Through Negative Evaluations of Therapy

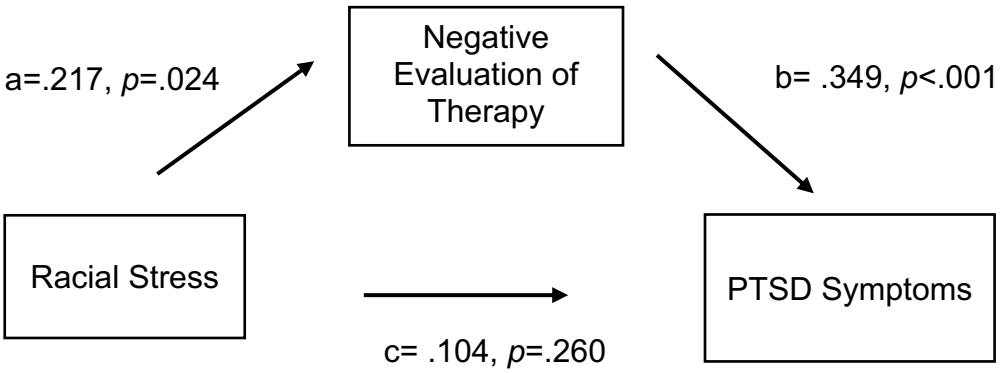

Table 5.1: Sample Demographics

Demographic	M	SD	%
Age (years)	28.17	5.49	
Total types of trauma (witnessed or experienced)	5.56	3.28	
Monthly household income			
$0-$249			6.7
$250-$499			5.6
$500-$999			12.4
$1000-$1999			32.6
$2000 or more			42.7
Education			
Less than 12th grade			9.3
12th grade/high school graduate			37
GED			3.7
Some college or technical school			29.6
Technical school graduate			4.6
College graduate			15.7
Employment			
Currently unemployed			49.1

Table 5.2: Means, Standard Deviations, and Correlations Among Variables of Interest

Variable	M	SD	1	2	3	4
1. Average racial stress	2.538	.926	-	.199*	.217*	.140
2. PTSD Symptoms	24.527	18.348		-	.425**	.569**
3. Negative Evaluations of Therapy	5.343	2.442			-	.635**
4. Stigma	10.750	4.456				-

*p<.05, **p<.001

CHAPTER 6: CONCLUSIONS AND FUTURE DIRECTIONS

6.1 Summary of Findings

In the current dissertation, we have shown that neighborhood poverty is associated with total PTSD symptoms in non-pregnant Black women with few economic resources (Chapter 2) and with future PTSD symptoms in a sample with varying race, sex, and socioeconomic status (Chapter 3), though not with PTSD symptoms in a pregnant Black sample (Chapter 4). We have also demonstrated that racial stress is associated with more PTSD symptoms in both pregnant and non-pregnant persons (Chapters 2, 4, and 5). Finally, we found that PTSD symptoms were associated with greater startle magnitude and had a trending association with CRP concentrations within a pregnant sample. Taken together, our findings suggest that social factors at both individual and structural levels affect risk for PTSD in both pregnant and non-pregnant persons.

6.2 Contributions to the Field

In Chapters 2 and 3, we found that neighborhood poverty is associated with greater PTSD symptoms. These are some of the first studies that use an objective measure of neighborhood poverty in determining risk for PTSD in adults. In Chapter 3, we utilized a longitudinal study design to determine risk for future PTSD symptoms immediately after experiencing a traumatic event, which is one of few studies of its kind and contributes to our understanding of how and in whom PTSD develops. Neighborhood poverty is a pervasive stressor and is associated with HPA axis dysregulation (Janusek et al., 2017; Karb et al., 2012) and immune system functioning (Finegood et al., 2020; Janusek et al., 2017), both of which can impact risk for PTSD (Michopoulos et al., 2016; Rasmusson et al., 2017). Neighborhood poverty also impacts brain structure (Webb et al., 2021). Specifically, neighborhood disadvantage is associated with smaller hippocampal and ventromedial prefrontal cortex (vmPFC) volumes (Webb et al., 2021), both of which are associated with PTSD (Kühn & Gallinat, 2013; van Rooij et al., 2015). Despite the

links between neighborhood poverty and physiological processes implicated in PTSD, little work has explicitly looked at the relationship between neighborhood poverty and PTSD symptoms. Previous work has found that subjective ratings on neighborhood disorder are associated with worse PTSD symptoms (Gapen et al., 2011), and that living in areas with high rates of poverty in childhood predicts higher PTSD symptoms in adulthood (Schuck & Widom, 2019). Our findings extend this existing work and show that living in an area with high rates of poverty as an adult can also negatively impact PTSD outcomes. Our results suggest that immediate interventions to improve under-resourced neighborhoods could be beneficial in reducing rates of mental illness in marginalized communities (Castillo et al., 2018; Castillo et al., 2019).

We also found that racial stress is associated with PTSD symptoms, which adds to a growing literature that demonstrates the negative effect of racism on mental health outcomes. Racism is a chronic and unpredictable stressor (Lewis et al., 2015; Utsey et al., 2000) that has repeatedly been shown to negatively impact mental health outcomes, including PTSD symptoms (Brooks Holliday et al., 2020; Kirkinis et al., 2021; Mekawi, Carter, et al., 2021; Sibrava et al., 2019). Racial discrimination is linked to altered white matter structure within the cingulum bundle among Black women who have experienced trauma (Fani, Harnett, et al., 2022). The cingulum bundle is a prominent white matter tract within the limbic system, and includes connections between the cingulate gyrus, prefrontal cortices, amygdala, and hippocampus (Bubb et al., 2018). Reduced cingulum bundle integrity is associated with PTSD symptoms (Bubb et al., 2018; Kim et al., 2006), suggesting that racial discrimination may exacerbate PTSD symptoms through its effects on the cingulum. Reduced integrity in the cingulum is also associated with more FPS during extinction, highlighting that the cingulum bundle is important for fear extinction processes (Fani et al., 2015) that are dysregulated in PTSD (Milad et al., 2009;

Norrholm et al., 2011), thereby suggesting a specific mechanism by which racial discrimination may result in greater PTSD symptoms. Racial discrimination is also associated with less thickness in the cingulate cortex (Fani, Eghbalzad, et al., 2022) (Shin & Liberzon, 2010). Lower cingulate volume (of which one component is thickness) is associated with PTSD (Wang et al., 2021). The rostral anterior cingulate cortex (rACC) is part of the vmPFC, and is important for inhibition of the amygdala during extinction (Selemon et al., 2019), which suggests that racial discrimination may lead to greater PTSD symptoms through impaired rACC structure. As far as brain activity, experiences of discrimination broadly are associated with increased spontaneous activity in the amygdala (an important area for the expression of fear) and with altered functional connectivity between the amygdala and regions including rACC and the thalamus, which plays a role in relaying sensory information to the amygdala (Clark et al., 2018). Although the study by Clark and colleagues suggests alterations in amygdalar circuits with more exposure to discrimination, it is not clear how these circuits are altered in function during tasks, such as fear conditioning or fear extinction (Clark et al., 2018). Greater connectivity between the amygdala and the thalamus is also associated with racial discrimination specifically (Webb et al., 2022). Overall, several studies indicate that racial discrimination and other types of psychosocial stress exposure are linked with altered brain structure and function (Grasser & Jovanovic, 2022), which could help explain the association between racial stress and PTSD symptoms. In Chapter 5, we provide one additional mechanism by which racial stress exacerbates PTSD symptoms among pregnant Black persons, where racial stress is associated with more negative evaluations of therapy, which in turn predicts more PTSD symptoms, likely due to a persistence of symptoms through a lack of treatment. Overall, our work contributes to the existing literature highlighting

that racism can impact individuals at multiple levels, and therefore impact PTSD symptoms in a multitude of ways.

6.3 Future Directions

Our findings set up several future directions to better understand environmental and biological factors that contribute to PTSD symptoms in minoritized individuals. For example, in Chapter 4, we did not find a significant relationship between neighborhood poverty at either the census tract or zip code level and total PTSD symptoms. One potential reason for this lack of association could be a relatively low sample size, at least compared to our other studies on neighborhood poverty and PTSD symptoms. A similar analysis with a larger sample size might reveal a relationship between neighborhood poverty and PTSD symptoms within pregnancy. However, in Chapters 2 and 3, we only looked at neighborhood poverty at the zip code level and not at the census tract level, which might be very different constructs. In Chapter 4, the associations between PTSD symptoms and neighborhood poverty at the census tract level were considerably smaller than the same associations with neighborhood poverty at the zip code level. An individual's census tract represents a very small spatial area, and people likely spend significant time in their daily lives outside of their census tract (for example, for work, school, or the grocery store). Thus, the characteristics of an individual's zip code may better capture a person's daily life better than just their census tract, where they physically live. Future work should focus on rates of poverty in an individual's census tract and its relationship to PTSD symptoms in diverse samples to better tease apart how neighborhood poverty at various geographic levels impacts PTSD symptoms. Additionally, in our studies, we used only one factor to assess neighborhood context (rates of poverty). Future analyses should consider multiple factors at the neighborhood level, such as education levels, housing vacancy, exposure to toxins, availability of

green space, and/or number of grocery stores to assess neighborhood context. One database that considers multiple factors is the Area Deprivation Index, which determines how disadvantaged a neighborhood is compared to others (Kind & Buckingham, 2018). Future studies could determine how Area Deprivation Index score is associated with PTSD symptoms, in both pregnant and non-pregnant samples.

While it is possible that we may see a relationship between neighborhood poverty and PTSD symptoms in pregnancy with a larger sample size, it is also possible that pregnancy itself is protective and acts as a buffer against the negative effects of neighborhood poverty. For example, concentrations of steroid hormones estradiol and progesterone increase over the course of pregnancy, and higher or increasing concentrations may be protective against trauma related symptoms (Ravi et al., 2019). The amygdala, hippocampus, and prefrontal cortex, all of which have been implicated in PTSD, have several estradiol receptors and membrane progesterone receptors (Ostlund et al., 2003), suggesting that higher concentrations of estradiol and progesterone during pregnancy may impact functioning in these brain regions. Hippocampal volume is also increased the mid-follicular phase of the menstrual cycle (when estradiol concentrations are high) as compared to the late luteal phase (when estradiol concentrations are low) (Protopopescu et al., 2008), and similar effects on the hippocampus could occur during pregnancy, which might be protective against PTSD symptoms. Estradiol concentrations are also associated with greater vmPFC and hippocampal activity and with greater functional connectivity between vmPFC, hippocampus, and amygdala, which could suggest greater modulatory influences of vmPFC and hippocampus on the amygdala (Ravi et al., 2019). In addition to the potential protective biological changes of pregnancy, social programs aimed at pregnant individuals may also help buffer the effects of neighborhood poverty on PTSD

symptoms in pregnancy. For example, in the state of Georgia, pregnant persons are eligible for the Supplemental Nutrition Program for Women, Infants, and Children (WIC) (Georgia Deparment of Public Health, 2023). This increased access to nutritious food, as well as referrals to other health and social services, may mitigate the effects of living in under-resourced areas and therefore help protect against PTSD symptoms.

In the studies presented in the current dissertation, we focused on relationships between neighborhood poverty and PTSD symptoms, but not on its relationship with biological factors associated with PTSD. Like other chronic stressors, neighborhood poverty likely impacts biological functioning as well as mental health outcomes. Chronic stressors often increase systemic inflammation (Ravi et al., 2021)(Chapter 1), and so although we were not powered to do so in the present studies due to our small sample size, future work should determine how social stressors like neighborhood poverty are associated with inflammatory markers like CRP. Future well-powered could also determine how neighborhood poverty is associated with biological markers of PTSD like FPS, to identify additional neural mechanisms by which neighborhood poverty contributes to PTSD symptoms. If neighborhood poverty is indeed associated with higher concentrations of CRP, results would provide an additional mechanism by which neighborhood poverty negatively impact mental and physical health outcomes. In that case, directly addressing high levels of inflammation may reduce the impact of neighborhood poverty on PTSD symptoms. Potential interventions that address high levels of inflammation in pregnancy should also consider an individual's environment and make sure treatments are accessible for those living in under-resourced areas.

In Chapter 4, we assessed systemic inflammation using concentrations of CRP. Future studies could use more nuanced methods to understand the relationships between stressors and

systemic inflammation. For example, the effects of chronic stress on systemic inflammation are thought to be mediated by glucocorticoid resistance (Ravi et al., 2021)(Chapter 1). Previous studies have determined glucocorticoid resistance by seeing if there was an association between cortisol and a pro-to-anti-inflammatory cytokine ratio, with non-significant associations indicating glucocorticoid resistance (Corwin et al., 2013). Thus, future studies could determine how PTSD symptoms, trauma, and chronic stressors like racism or neighborhood poverty are associated with glucocorticoid resistance within pregnant samples. These findings could be particularly insightful, as glucocorticoid resistance naturally increases at the end of healthy pregnancies (Katz et al., 2012; Ravi et al., 2022), and so understanding how stress and trauma exposure impacts glucocorticoid resistance during pregnancy might shed light on how stress impacts pregnancy outcomes beyond mental health. Futures studies could also focus on inflammatory markers other than CRP, such as IL-18 or IFN-gamma, which might be responsible for exaggerated pro-inflammatory responses to stressors in pregnancy (Ravi et al., 2022; Sacks et al., 2003; Sargent et al., 2006). Furthermore, the results in Chapter 4 are from a cross-sectional study, which while informative, do not indicate how inflammatory changes over the course of pregnancy are related to trauma and PTSD. Because inflammatory profiles vary significantly with pregnancy stage (Mor & Cardenas, 2010; Ravi et al., 2022), future studies should aim to understand how trauma and PTSD influence pregnancy-related changes in inflammation.

Additionally, in Chapter 4, we examined the relationship between PTSD symptoms and fear learning during the acquisition phase of FPS. Extinction processes are impaired in PTSD (Milad et al., 2009), and previous studies have shown differences in extinction learning between individuals with and without PTSD (Norrholm et al., 2011). Subsequent work could focus not

only on the relationships between PTSD symptoms and extinction in pregnancy, but also between racial stress and extinction, as we know greater FPS during extinction is associated with reduced cingulum bundle integrity (Fani et al., 2015). Because racial discrimination is also associated with reduced cingulum bundle integrity (Fani, Harnett, et al., 2022), racial stress may cause impaired extinction during FPS, potentially via its effects on the cingulum bundle.

Overall, the results presented in the current dissertation highlight that two social factors, racism and neighborhood poverty, negatively impact PTSD symptoms across race, sex, and individual socioeconomic status. Importantly, structurally racist policies like red-lining and racial segregation have made Black communities more likely to live in areas with high rates of poverty, and even though these policies have since been outlawed, their effects remain (Appel & Nickerson, 2016; Lynch et al., 2021). New policies should be developed and implemented with members of marginalized communities in order to address the effects of neighborhood poverty and racism on mental health outcomes, with the end goal of eradicating neighborhood and racial inequality and preventing health inequities at their source.

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