ASSOCIATIONS BETWEEN CUMULATIVE SOCIODEMOGRAPHIC RISK, DAILY STRESS AND ANXIETY SYMPTOMS, AND EXECUTIVE FUNCTION IN FEMALES: THE ROLE OF PROGESTERONE

By

Ania Dorota Pathak

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ABSTRACT

The current study evaluates how the accumulation of sociodemographic risk (CSR) may impact executive function (EF). This work focuses on *accumulation* of risk given the established and supported theories of conceptualizing stress's impacts on physiology and function via allostatic load. Allostatic load is defined as the cost of adapting to stressors and environmental demands, and frames stress as cumulative and systemic. The current work focuses on females given sex differences in stress susceptibility, the documented differential rates of mood and affective disorders in females compared to males, and the historic lack of representation of female subjects in neuroscience research. Daily symptoms of stress and anxious arousal (DS) are considered as mediators of CSR's expected effects on EF. Progesterone is evaluated as a moderator of the relationships between CSR, DS, and EF. Hypotheses include high CSR predicting reduced EF, high CSR predicting high DS, high DS predicting reduced EF, DS mediating the effects of CSR on EF, and progesterone moderating all the direct relationships between CSR, DS, and EF such that the relationships strengthen at high progesterone.

151 natural cycling female participants enrolled for 35 days intended to encompass one menstrual cycle. They completed demographics and psychological interviews, provided daily saliva and affective symptoms, and attended cognitive assessments at four lab visits across the 35 days. Cumulative risk was characterized via a composite CSR score from self-reported race, childhood socioeconomic status, and trauma data. Lab visits included an N-back working memory task with concurrent EEG, from which the P300 Event Related Potential (ERP) and behavioral data was obtained and used to index EF. Evaluating the direct relationships between CSR, DS, and EF was done using multilevel modeling (MLM). DS were tested as potential mediators using Monte Carlo simulations to test for indirect effects. Progesterone levels obtained

from daily saliva samples were tested for moderating effects on the relationships between CSR, DS, and EF using MLM.

Results showed high CSR significantly reduced measures of EF but showed no effects of CSR on DS. DS predicted a subset of EF measures in opposite directions: daily stress increased reaction time (RT) at low and high working memory (WM) load, and anxious arousal symptoms predicted decreased RT at medium WM load. DS did not mediate the effects of CSR on EF. Progesterone did not moderate any of the relationships between CSR, DS, and EF. Instead, it had its own small main effects on EF and anxious arousal when included as a covariate predictor. Findings suggest CSR is a better predictor of EF than DS, that daily measures may be insufficient to mediate the effects of adapting to CSR on EF, and that daily self-reported stress, anxious arousal, and salivary progesterone are interrelated in their impacts on EF.

I dedicate this dissertation to those who came before me, believed in me, and afforded me the opportunity to grow and become who I am today. I would not be who and where I am without every one of you. You've breathed life into this work and into me.

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CHAPTER 1: BACKGROUND

Overview

Biopsychosocial models recognize the interplay between biology, psychology, and social environments in human pathology or dysfunction [1]–[4]. These models underscore how biology is affected by the environment. Cumulative stress associated with minoritized identities, including non-White race and female sex, as well as the presence of other related environmental stressors like lower socioeconomic status and traumatic experiences (henceforth collectively referred to as sociodemographic risk factors) can negatively affect human health and cognitive function [5]–[11]. Allostatic load (AL), a concept in the stress literature, describes the cumulative multi-systemic physiological wear and tear that results from adaptation to such stressors over time [12]. In this way, stress, the psychophysiological response to stressors, impacts human physiology and function. Stress and anxiety may mediate the observed effects of sociodemographic risk on executive function — cognitive skills needed to learn and manage daily life. Moreover, when focusing on females, it is critical to consider the role of ovarian hormones (estrogen and progesterone) because of the documented associations between ovarian hormones, stress systems (e.g., hypothalamic pituitary adrenal axis; HPA axis) and cognitive brain structure and function [13]. Understanding the roles of these factors may help elucidate documented sex differences in stress susceptibility. The current study therefore focuses on how cumulative sociodemographic risk (CSR) impacts executive function in females.

Stress Physiology

Stress is a ubiquitous part of life that, when toxic or in excess, has documented negative effects on both society and individuals– whether that is decreased productivity, increase in stress-related disease, or other decreases in quality of life and reductions in function. Within

individuals, stress has harmful, far-reaching consequences, including widespread effects across multiple organ systems such as the nervous, cardiovascular, gastrointestinal, and reproductive systems.

Defined specifically, a stressor is a stimulus– either internal or external– that evokes a biological response. Within the nervous system, this response is elicited across various domains, including the autonomic nervous system, central neurotransmitter and neuropeptide system, and hypothalamic-pituitary-adrenal (HPA) axis [14].

The two main stress pathways in the nervous system include a rapid response via the autonomic nervous system– specifically the Sympathetic-Adreno-Medullar (SAM) axis, and a longer lasting response via the HPA axis. Activation of the SAM axis primarily results in the secretion of catecholamines from the adrenals and sympathetic neurons (epinephrine and norepinephrine– E and NE, sometimes referred to as adrenalin(e) and noradrenalin(e), respectively). NE is secreted from sympathetic nerves, while both E and NE are secreted from the adrenal medulla. These hormones primarily act in the brain and body via B-adrenergic G-protein coupled membrane receptors to prompt cellular responses via signaling cascades. The systemic rise in E and leads to the physiologic changes associated with the "flight or flight" response– including changes in heart rate and alertness [15].

Meanwhile, the HPA axis primarily results in the release of the glucocorticosteroids– cortisol in humans, and corticosterone in animals. When a physical or psychological stressor is encountered, numerous brain regions act in concert to process the stimulus and bring the hypothalamus online, which then releases corticotropin releasing hormone (CRH) from the paraventricular nucleus (PVN). When CRH reaches the anterior pituitary, the anterior pituitary's corticotrophs synthesize and release adrenocorticotropic hormone (ACTH) into the bloodstream

[16]. Upon reaching the adrenals, ACTH stimulates the middle layer of the adrenal cortex, the fasciculata [17]–[19] to synthesize and release both cortisol and androgens [17].

These steroids act via both nuclear and non-nuclear mechanisms, but this overview will focus on their nuclear effects. Cortisol binds to both mineralocorticoid and glucocorticoid receptors (MR and GR – sometime termed Type 1 and Type 2, respectively). MR have ten times the affinity for cortisol as GR, and given cortisol's diurnal circadian rhythm, this allows for differential effects and differential receptor saturation at high compared to low cortisol levels, including at diurnal cortisol trough vs peak [14].

It is important to note that both the SAM and HPA axes influence one another, with colocalization of B-Adrenergic, MR, and GR on effector tissues, as well as regulatory feedback mechanisms both within each axis, and across the axes [14]. For example, the hippocampus has high colocalization of both MR and GR receptors, and it has been observed that psychological stress and stress-induced levels of glucocorticosteriods disrupt long term potentiation and primed burst potentiation in the hippocampus [20], while lower levels of those same steroids enhance those processes.

It is in this way that stress leads to the production and release of glucocorticosteroids, which by their lipophilic nature can cross the blood-brain barrier, enter the cells, and act via nuclear receptors to exert their long-lasting transcriptional effects in the brain, impacting both brain structure and function– including cognition [14]

Stress and Cognition

Stress has been shown to have both acute and chronic effects on cognition through catecholamines and glucocorticosteroids, respectively [21]. The acute effects are primarily beta-adrenergic consequences, while chronic effects result from changes in gene expression mediated

by steroids [21]. Adrenal glucocorticosteroids have been demonstrated to affect hippocampal function during cognition and memory retrieval in a biphasic manner, where synaptic plasticity is impacted on the order of hours, followed by changes in dendritic structures that last for weeks [21] . Notably, multiple mechanisms have been shown to modulate the association between stress and cognition [21], [22]. And past work has also demonstrated the onset of cognitive disorders following exposure to stress [23]. When stress is chronic, these glucocorticosteroids have been shown to destroy neurons via excitotoxicity [24].

In sum, stress has been shown to cause structural changes, including atrophy, in various brain regions– including the hippocampus, amygdala, and frontal and temporal lobes– which then can then contribute to differences in cognition and memory[25]–[27]. These changes have been shown to scale with the intensity and duration of stressors [14]. The effect of stress on cognition is primarily a reduction in function.

Types of Stressors: Chronic, Early Life, Social, and Maladaptive

Previous work has shown that social inequality and life adversity have neurocognitive consequences. Some consider social inequity and life adversity as chronic or environmental stressors, ones that can aggregate over time into "chronic stress." [11], [28], [29]. These are particularly potent in early life, supported by much of the literature evaluating the impact of early life stress on adult life– across domains of physical health, mental health, and cognition. Early life stress prompts a sustained physiologic stress response at early ages, when the nervous system, along with other systems, is still developing, leading to increased sensitivity to stress over the lifespan, and thus susceptibility to disease and dysfunction [11], [28]–[30] . The "neuro-immune network" hypothesis suggests that early life stress strengthens cortico-amygdala circuitry, thus priming and heightening SAM, HPA, and immune activity [31]–[33].

Over evolutionary time, the stress response adapted to recruit and mobilize physiological, psychological, and behavioral resources to address a resolvable threat or pressure– like running from a predator. This heightened mobilization and utilization of resources is, from an evolutionary perspective, predicated on the pressure, need, or threat being resolvable and transient. These responses are generally beneficial in the moment when the threat is imminent. However, chronic, psychological or extreme stressors that do not resolve lead to extended activation of these stress responses across physiological, behavioral, and psychological systems. This extended activation then leads to dysregulation across all three of these domains [29], [34]

A recent review [29] reports that early life stress (ELS) has lasting negative impacts on prefrontal–hypothalamic–amygdalar circuits and dopaminergic circuits, and that these effects are at least partially mediated by changes in HPA axis function. An additional review by Pechtel and Pizzagalli concludes that complex higher-order cognitive and affective functions associated with brain regions with extensive postnatal development are particularly susceptible to the impacts of ELS; that the amygdala is also highly sensitive to early ELS; and that the deficits that result can persist for years, particularly affective symptoms, and may lead to psychopathology later in life [11].

Foundational work in stress physiology and preclinical work in animal models demonstrates that social stress and stress we lack control over is particularly toxic [35], [36]. This is supported by work in humans[37]–[39]. In animal models comparing stress paradigms, corticosterone and catecholamine responses to laboratory stressors are higher for social stressors (e.g social defeat model) compared to physical stressors (e.g. foot shock) . Animal studies also have shown that the physiologic consequences of stress (e.g. stomach ulcers) are highest when there is no perceived control over the stressor[36] . This is echoed in humans [39]; traumas with

an interpersonal component– like sexual violence– go on to produce higher PTSD symptoms than traumas that are physical in nature, like motor vehicle accidents [40], [41].

Trauma, race, and socioeconomic status are specific sociodemographic risk factors that have all been associated with stress and neurocognitive change, including changes in executive function. Trauma exposures have been linked to decreased measures of working memory (WM). Per Weltz, et al., childhood trauma in the form of emotional abuse was associated with stronger stress-reactivity for anxiety [42] . In another study by Tinajero, trauma measures– specifically childhood abuse– were associated with pre-sleep arousal, difficulties with executive function, and challenges with emotion regulation [43]. Familial trauma has also been associated with a medium effect size to worse performance in executive function composite, which included both working memory, and processing speed tasks [44]. Taken together, these works support trauma exposure being associated with decreased executive function later in life.

Research has shown the impact of racial discrimination on core executive functions. Specifically cognitive flexibility and working memory have been shown to be negatively impacted by recent discrimination, supporting the notion that discrimination may have its effects on executive functioning due to the cognitive demands associated with responding to it [45]. Similarly negative cognitive effects have been seen from both experiencing and observing racial discrimination [46]. In children, belonging to an ethnic minority has been observed to impact working memory [47], [48] and discrimination has been implicated as a key component of racial disparities in human health [49]. Taken together, race may have value as a variable that serves as a proxy for likelihood of experiencing racism as chronic stress.

Socioeconomic status has been linked to changes in brain structure, particularly in areas related to memory, executive control, and emotion– ie, the hippocampus, prefrontal cortex

(PFC), and amygdala [50]. Using structural imagining, Brito and Noble propose a model where stress mediated the impact of socioeconomic status on the aforementioned regions, and thus the observed impacts on memory, socio-emotional processing, and cognitive control and self regulation. Low socioeconomic status (SES) in children, measured by family savings and homeownership, was associated with greater 2-year increases in daily cortisol output in a sample of 50 healthy children [51]. In addition, when performing genome-wide transcriptional profiling in healthy adults who experienced either high or low SES in childhood, low childhood SES adults showed an upregulation of genes associated with pro-inflammatory signaling and resistance to glucocorticoids [52].

Taken together, chronic, early life, and social stressors that individuals lack control over have pronounced stress responses with lasting negative impacts. These impacts include higher order brain regions that underlie important cognitive functions, including executive function.

Executive Function and Working Memory

Executive function (EF) is a term used to describe a suite of cognitive skills needed to learn and manage daily life and regulate behavior, including working memory, attention, planning, metacognition, goal directed behavior, and adaptable thinking [53]. While EF is needed to manage daily life and regulate behavior, studies also suggest EF deficits can be both markers and consequences of psychopathology [53].

EF is characterized as a top-down process, and one that involves effort, and capacity for effort. Importantly, capacity for effort can be impacted by numerous factors. EF is recognized as important for mental and physical health, general success in life and academics, as well as cognitive, social, and psychological development, and overall quality of life [53]. In addition, in being top-down and effortful, it is impacted by social, emotional, and physical health. Stress,

lack of sleep or exercise, and loneliness have all been shown to impair EF. Various social determinants of health have also been shown to impact executive function– including childhood socioeconomic status [54].

One very important and measurable subcomponent of EF is working memory [55]. Working memory describes the ability to both store and manipulate information during tasks [56], [57]. It is needed for daily function and goal-directed behavior by allowing task and goal relevant information to remain available in the face of distraction. This temporary storage allows for teleologic outcomes– permitting information to be manipulated in order to complete a task, or for information to become stored in long term memory for future use [55], [58]–[61]. Working memory has also been associated with other higher order functions, including reasoning, planning, and problem-solving [55], [58]. In addition, working memory correlates with measures of general intelligence [61], [62] and serves as a strong predictor of academic performance compared to other intelligence measures [61], [63]. Past work shows that children with decreased working memory capacity demonstrate cognitive deficits including inattention, distractibility, and challenges with problem solving in academic settings [64]–[66]. Taken collectively, evidence supports conceptualizing working memory as a cornerstone component of executive function, and critical for other general functional outcomes [64].

Working memory often bridges the gap between a stimulus and response that will take place once said stimulus is no longer present. Often, working memory is broken down into two main components: the storage of information, and executive top-down processes that do not retain information themselves. This flexible scaffold biases salience to control what is and is not retained, and therefore acted upon [67]. Early work in fMRI evaluating the neural substrates of working memory identified the prefrontal cortex as the region active when a dual task was

performed (verbal and spatial passive working memory task), implicating it as the central executive system that controls attention and facilitates the flow of information between visual and spatial short term memory buffers [68].

Presently, there is general support for conceptualizing working memory as closely related to attention, and attention allocation [69]. Given that working memory is pivotal to coordinating processing in environments with competing stimuli and multiple goals, and for guiding behavior informed by stimuli not immediately present, it has been studied extensively by neuroscientists and psychologists alike. Research from both fields converges on understanding working memory as information encoding via attention allocation to internal representations. This offers an explanation for why fMRI analyses of working memory processes often include stimulus-relevant regions not typically associated with memory processing. Concurrently, the PFC weights salience, informed by context. Combined, this creates an interplay between stimulus-specific sensory processing regions, the PFC, striatal circuits, and ascending dopaminergic neuromodulatory signaling that emerges as working memory processing [70]. More simply, this can be conceptualized as a division of labor– in which sensory regions encode low-level stimulus details, while prefrontal regions encode abstract, categorical information. This information can generalize across sensory modalities, but additionally include the active processing of sensory input into a form that will impact an impending behavioral response, transforming sensory input into a behavioral response [67].

Various factors have been shown to impact working memory. Studies comparing working memory in high and low anxiety populations demonstrated reductions in both working memory storage and processing capacity for high anxiety individuals. This work concluded that high anxiety reduces both working memory storage and processing capacity [71]. Work evaluating

how and if childhood socioeconomic status impacts executive functioning demonstrated domains of executive function are affected unevenly, with the most pronounced impacts being on working memory and cognitive control [54]. Past work shows that trauma exposure– irrespective of the development of post-traumatic stress disorder symptoms– was linked to decreased working memory compared to non-trauma exposed controls [72]. Socioeconomic disadvantage and ethnic minority status have been associated with differences in working memory in children [47]. And recent work demonstrates that experiencing recent racial discrimination is negatively associated with working memory, consistent with the broader literature describing the negative effects of stress on executive function and working memory [45].

Taken together, these data support working memory as a measurable and functionally significant component of executive function that is impacted by various ecological stressors, including anxiety, childhood socioeconomic status, trauma exposure, as well as ethnic minority status and racial discrimination.

Characterizing Working Memory

The verbal N-Back task was developed to capture and test working memory. It does so by being a dual task, in which attentional and working memory demands increase, with a concurrent and constant matching subtask [73]. It is also a dynamic span task, requiring the participant to attend to and update information continuously– at various levels of cognitive load [74]. Though various forms of the N-back exist across stimulus modalities, our work will focus on the verbal N-back where a participant responds to a letter shown when that same letter had been presented "N" number of letters back.

Electroencephalogram (EEG) can be used during this task to measure brain electrical activity in real time, with millisecond-level precision. These EEG recordings can then be used to

extract event-related potentials (ERPs)– a kind of EEG measure specific to an event, often either a stimulus or a response. ERPs are measured deflections of voltage that occur in response to a given stimulus [75]. The resultant waveform is a visual representation of the brain's electrical activity at a given point spatially and temporally. ERPs are thought to measure the neural responses specific to the chosen event, and are thought to index specific neural, psychological, or physiological processes, acting as their electrical signature in real-time.

ERPs have been used in the N-Back working memory task before. Specifically, there is precedence for using the P300 in the N-back verbal working memory task [73]. The P300 is an EEG ERP waveform that indexes resources available for cognitive processing, including attention allocation and self-referential processes. It peaks 300-500ms after task relevant, salient, or novel stimuli, and is maximal at parietal sites. The P indicates a positive voltage deflection, and the "300" indicates the time at which it occurs, in milliseconds. It is sometimes referred to as the P3, where in this case it is named for being the third positive deflection after a stimulus. This work will refer to it as the P300.

Past work shows that as load ("N") in the N-back increases, the P300's amplitude drops [73], [74], [76], [77]. This smaller P300 amplitude that is both observed and expected in larger N-back loads (3- vs. 0-back), indexes the decrease in cognitive resources available to attend to stimuli when working memory is under load [73], [74], [77]. At higher N-back loads, there is greater reliance on working memory processes as an increasing number of stimuli must be held in working memory, continually updated with each new stimulus presentation, and processed into a behavioral matching task response.

Thus the decreased P300 amplitude observed at higher N-Back loads reflects the reduced cognitive resources available to attend to and process external stimuli, because those resources

are occupied by greater demand on internal working memory processes. Given the impact of aforementioned factors on working memory capacity, it can be expected that individuals with more risk factors previously associated with decreased working memory (such as stress, anxiety, ethnic minority status, experiences of racism, trauma exposure, and low childhood socioeconomic status) may experience a reduction in the cognitive resources the P300 indexes compared to their low-risk counterparts. This might manifest either with lower P300 amplitudes overall, or as greater reductions in the P300 amplitude at lower magnitudes of cognitive load (i.e lower "N-"backs). Put differently, the impact of these risk factors on executive function, either in the form of reduced working memory capacity, or in the form of cognitive resources available to be recruited, would suggest that the P300 would have a smaller amplitude in individuals with a higher number of risk factors.

Larger amplitudes thus indicate more available attentional resources, while smaller amplitudes indicate fewer cognitive and attentional resources available on the electrophysiological level. In this way, the P300 speaks to real-time activity of underlying brain structures (e.g. the anterior cingulate cortex, insula, prefrontal cortex) involved in attention allocation, and serves as an index for executive function.

In addition to having value in itself, the P300 has been associated with other measures of executive function and performance. In patients with temporal lobe temporal lobe epilepsy compared and matched to healthy controls, patients with temporal lobe epilepsy showed decreased P300 amplitude. A correlation between P300 amplitude and working memory was also observed. Taken together, these findings implicate the temporal lobe in executive dysfunction, and the P300 as a marker of this dysfunction [78].

As such, the P300 is a valuable measure speaking to executive function in the form of cognitive resources available for attention allocation, especially contextualized by N-Back behavioral performance measures that speak to working memory capacity. In this context, it can serve as a measure of one's ability to pay attention under stress in the form of cognitive load. It can serve as a metric of those specific attentional cognitive resources, and given its other more global associations supported by literature, could be a reasonable metric to paint a picture of overall executive function. Literature also demonstrates that the P300 is impacted by stress.

Stress As Cumulative: Allostatic Load

In addition to having far-reaching multi-systemic and neurocognitive consequences, stress also aggregates. Allostatic load is defined as the cost of adapting to stressors and maintaining allostasis under demanding pressures [12]. The allostatic load model of stress suggests that stress is best conceptualized as cumulative.

As described in McEwan (1993) the idea of homeostasis has limited value in describing how chronic stress leads to disease. He proposes instead a model of allostasis. This model proposes that instead of aiming to maintain consistency as would be the case in models of homeostasis, healthy biologic systems adapt and fluctuate to meet the demands of their environments, finding allostasis. The allostatic model of stress allows for the conceptualization of maintaining allostasis over time, revealing allostatic load as the physiologic cost of adapting to aggregating (both in number and duration) or chronic stressors. This emphasizes the importance of conceptualizing stress as cumulative, especially in the context of chronic stressors. The more adaptation to environmental challenges that are experienced as stressful, the higher the physiologic cost of that adaptation. Increased measures of allostatic load have been associated with impacted executive function.

Sex Differences in Stress Susceptibility

It is also well documented that sex differences in stress susceptibility exist, with females displaying increased susceptibility compared to males [79]. Rates of affective and mood disorders, including anxiety and depression, are two-fold in human females compared to males [80], [81].

Animal studies and preclinical work support the idea that females demonstrate a heightened susceptibility to stress as compared to their male counterparts, implicating PFC dysfunction as a result of this stress susceptibility [82]. However, much work focuses on estrogen and testosterone, with very little work evaluating the role of progesterone. Even work informed by the estrous cycle in animals and menstrual cycle in humans primarily focuses on estrogen fluctuations compared to progesterone fluctuations.

Estrogen has been demonstrated to mediate differences in stress-induced prefrontal cortex dysfunction [82], [83] . In rats using a PFC dependent working memory task, female rats were more impaired by stress than male rats while in proestrus (luteal in humans) than estrous (follicular in humans). Ovariectomized rats only showed increased stress susceptibility after estrogen replacement [84]. In contrast, other work in rodents has shown testosterone to have protective effects against stress susceptibility in the development of anhedonic symptoms in both gonadectomized male and female rats, with no effects of estrogen [85].

Progesterone and Sex Steroid Production

The HPA and hypothalamic-pituitary-gonadal (HPG) axes influence one another. Various mechanisms have been proposed including colocalization of cortisol and sex steroid receptors across effector tissue; competitive inhibition or potentiation of sex steroids and cortisol at various effector tissue; direct impacts of sex steroids on the HPA axis itself and vice versa, with

cortisol impacting HPG function (cortisol acting on the ovaries); and also by competition for binding at circulating corticosteroid plasma binding proteins [86]–[88]. Regardless of the mechanism, it is known that HPA-HPG cross talk occurs [89], [90].

Importantly, cortisol and progesterone are chemically related steroids. Cortisol (corticosterone in animals) is synthesized from progestins. The adrenals are also known to release progesterone in addition to cortisol in response to stress, and progesterone and cortisol are positively correlated in humans. However, it remains unclear if one increases in response to the other, in tandem, or if the relationship is bi-directional. In a sample of naturally cycling females, during an experimental stress paradigm– the cold pressor test– both progesterone and cortisol increased. Positive associations between baseline progesterone and baseline cortisol levels were also observed. Of note, during the stress session, the magnitude of change in progesterone was mediated by the magnitude of the change of cortisol. [91].

Importantly, progesterone is a systemically circulating steroid. While it has and is known for its reproductive effects, it also has systemic effects across organ systems, including the nervous system. Progesterone has been shown to affect the brain. Progesterone is neuroactive: progesterone receptor expression has been shown in the amygdala, hippocampus, and frontal cortex, and across glutamatergic, GABA-ergic, dopaminergic, and serotonergic pathways [92]. These regions and pathways are also affected by sociodemographic risk and stress, and are implicated in executive function.

In a study by Arelin, progesterone was found to be associated with connectivity between the dorsolateral PFC and the hippocampus across the menstrual cycle [93]. Animal work has also demonstrated the presence of progesterone receptors in brain regions associated with cognition, but little work has elucidated that further [94], [95]. Progesterone is also known to have

anxiogenic effects, while its metabolites have anxiolytic effects. These impacts are a results of modulating activity at GABA receptors, and including their up and down regulation [89], [90], [94], [95]. These known mechanistic associations suggest that there may be reason to evaluate progesterone's potential to impact both stress processes and executive function on the behavioral level in an ecological context.

The Menstrual Cycle

Progesterone fluctuates cyclically in females, and thus any influence progesterone has would be cycle dependent. The menstrual cycle in humans, also known as the estrous cycle in animals, is a predictable cyclic hormonal fluctuation that allows for reproductive viability in a subset of mammalian species. In humans, the entire cycle lasts approximately 28 days.

The menstrual cycle is primarily divided into two phases that follow naming conventions based on either ovarian or uterine histology– the follicular or proliferative phase, and the luteal or secretory phase. Follicular and luteal refer to the ovarian naming convention, while proliferative and secretory refer to the uterine or endometrial naming convention. This work will utilize the ovarian naming convention.

Cycle lengths can vary from 21 to 35 days in length, with clinical convention dictating that cycles less than 21 days are termed polymenorrheic, while cycles longer than 35 days are termed oligomenorrheic. The luteal phase of the cycle is relatively stable across menstruating individuals with a duration of 14 days, with cycle length variation typically being the result of variation in the length of the follicular phase. Cycles begin with the onset of menstruation– the sloughing of endometrial lining, precipitated by a steep drop in estradiol and progesterone. This begins the follicular phase, which comprises menses, and the time leading up to ovulation. This aptly named phase is characterized by the recruitment and development of ovarian follicles, of

which one will mature and be released at ovulation. Hormonally, estrogen rises steadily over the course of the follicular phase, in tandem with follicle size and development. A modest increase in progesterone is also seen [96].

34-36 hours before ovulation, the preovulatory follicle produces a steep rise in estradiol, prompting a luteinizing hormone (LH) surge. The LH surge peak happens 10-12 hours before ovulation. Estradiol levels drop right before the LH peak, due to either LH downregulation of the LH receptor or due to progesterone inhibiting estradiol synthesis. This LH surge prompts the production of progesterone from ovarian granulosa cells, which leads to the mid cycle follicle stimulating hormone (FSH) surge. Prostaglandins and proteolytic enzymes increase in response to progesterone and LH to digest the collagen in the follicular wall, releasing the oocyte [97]. This begins the luteal phase of the cycle.

Follicular cells that were not released at ovulation begin to enlarge and combine with surrounding ovarian tissue to become the corpus luteum, a transient endocrine organ that secretes progesterone to prepare the endometrium should the oocyte become a fertilized ovum and implant. The luteal phase is when peak serum levels of both progesterone and estradiol are seen. If human chorionic gonadotropin is not produced by a pregnancy, the corpus luteum atrophies, becoming a scar known as the corpus albicans, and progesterone and estrogen levels drop, prompting the sloughing of endometrial tissue, and the cycle then repeats. It is the withdrawal of progesterone that prompts menses [96].

Given that progesterone fluctuates cyclically and predictably in females, any influence progesterone may have on the nervous system, stress, anxiety, or executive function would be cycle dependent. Previous work has shown a distribution of progesterone receptors across brain regions associated with stress and cognition [11], [21], [22], [24], [93], [98], [99], as well as

fluctuating connectivity in response to progesterone fluctuations across the menstrual cycle. Together, this suggests progesterone fluctuations play a role at these brain regions in a way that changes monthly, and the nature of its role would be a valuable line of inquiry.

Rationale

Though the effects of all three components of CSR and our stress measures have been associated with changes in executive function, few associations have been made with the P300 ERP specifically, to ask questions about altered function of attentional networks. The P300 is valuable because it indexes attention allocation involved in critical components of working memory and executive function more broadly. The P300 has also been used as a marker for neuropsychiatric conditions, including PTSD, and implicated in brain-heart coupling— and as such may carry clinical significance. Brain regions thought to be the neural substrates of the P300 include regions also changed by CSR, allostatic load, and progesterone fluctuations across the menstrual cycle (e.g., dorsolateral prefrontal cortex, insula, anterior cingulate cortex). Prior demonstrations of associations in the trauma and PTSD literature show a decreased P300 amplitude following traumatic stress and in PTSD. Importantly, an increased P300 latency was also associated with higher salivary cortisol in disabled workers in a recent pilot study. The authors attributed the increased cortisol levels to alteration of the HPA axis as a result of living with the stresses of a physical disability—a premise similar to this work's proposed conceptual framework.

Relatedly, Letang et. al. (2021) found evidence for stress as partially mediating the pathway from SES to episodic memory, working memory capacity, and executive function in Black Americans compared to non-Hispanic White Americans [48]. They also found stress to partially mediate ethnoracial disparities in working memory for lower SES Black and Hispanic

Americans, compared to non-Hispanic White Americans. These findings similarly share aspects of this work's proposed framework of risk impacting working memory via stress.

The current study tests this framework and aims to establish the presumed mediating role of stress while considering the neuroactive roles of ovarian hormones on attentional networks and the stress response to address female health. The P300 will be used to characterize environmental stressors' impacts on attentional networks and stress psychophysiology in an underrepresented population, in a way that has the potential to impact female health and elucidate the multifactorial etiological mechanisms of environmental determinants of health and function.

AL has been indexed across systems, including stress, immune, cardiovascular and metabolic markers, and some studies include psychological measures as AL indices. AL's multi-level components have been attributed to remodeling from cortisol due to sustained activation of the HPA axis. Perceived stress speaks to the psychological and interpreted stress response. Anxious arousal measures symptoms of autonomic arousal, and the response of the sympathetic nervous system. Together, these measures speak to the emergent psychophysiological symptoms that occur systemically in response to stressors, typically through catecholamines and glucocorticoids—the primary stress hormones. These primary stress hormones have been shown to fluctuate across the menstrual cycle in response to changing levels of progesterone and estrogen, and the HPA axis has been shown to be affected by HPG axis activation, the axis that exerts neural control of over the menstrual cycle. Progesterone's relationship to cortisol has been established, but its relationship to executive function remains underexplored.

Though little has been done to directly examine progesterone's relationship to perceived stress, positive correlations have been found between serum cortisol and perceived stress, and

some work has shown an increase in cortisol during the luteal (progesterone dominated) phase of the menstrual cycle. The relationship between progesterone and anxious arousal is similar, in that little directly defines progesterone's relationship to autonomic arousal, but literature exists connecting the premenstrual (late luteal) and luteal phases of the menstrual cycle with increased autonomic arousal, and literature exists correlating cortisol with increases in sympathetic activation [100]–[102].

Executive function's associations with CSR and indices of the stress response have been characterized using performance measures and neuropsychological testing [11], [103]. This level of testing does not parse apart what networks and functions of the brain are contributing to observed deficits. The neural substrates of attention allocation, given their ubiquitous and critical role in executive function, are a promising substrate for investigation [104]. Little work has been done to understand the aforementioned effects on neural substrates of executive function at the neurophysiological level. Critically, circulating sex steroids have been implicated in observed sex differences in HPA axis response to stressors [86], [87], [105]. Though work has also been done associating stress measures with both CSR and executive function [18], [86], [88], [106], [107], evaluating these relationships in the context of ovarian hormone fluctuations in naturally cycling females has not been examined to date. Despite composing half the world's population, females remain underrepresented in research in both cognitive neuroscience and physiology, and their specific physiology remains not fully characterized.

Historically, female sex steroids are predominantly studied in reproductive contexts [108], despite estrogen and progesterone's physiologically active roles in tissue across all systems, playing a role in everyday functions, including executive function [109]–[111]. This problem and missing knowledge is important because lacking mechanistic understanding of how

CSR impacts executive function ultimately inhibits effective intervention. Poor performance associated with decreased executive function contributes to a host of social and physical consequences and demands attention and intervention [104], [112], [113]. These negative life consequences include limitations in access to social mobility, perpetuation of cycles of poverty, increased burdens on social programs, loss of talent and productive contribution to society, increased mental and physical health burdens, and decreased quality of life for those affected. These burdens in turn contribute to a continued accumulation of AL across the lifespan, and numerous health and social consequences, exacerbating the broader negative impact on society [114]. Filling these gaps by examining the interactive effects of CSR, daily reported stress response and ovarian hormones on attentional networks (as an index of EF) will provide a needed next step in charting the mechanisms involved in the observed effect of CSR on executive function performance decrements.

The current proposal leverages real-time EEG measures of attention allocation to probe associations between CSR, stress, ovarian hormones and neural and behavioral performance measures of executive function. Doing so will enable the characterization of how CSR impacts the female-specific nervous system, with consequences for both daily symptoms and executive function, increasing representation of female-specific physiology in research and knowledge of the human body and cognitive science. This work therefore will broaden science's understanding of how ovarian hormones play roles in female health and function. This is especially important given the under-representation of females in neuroscience and physiology research, as well as the underresearched multi-systemic roles of fluctuating female sex steroids that govern the menstrual cycle. Using this multi-method approach, this work will investigate associations between CSR and both EEG and behavioral measures of executive function, and further explore how that

relationship may be (1) mediated by measures of daily reported stress and anxious arousal, and (2) impacted by fluctuations in ovarian hormones across the menstrual cycle.

This work innovates in four ways: (1.) Examining if neurophysiologic change (indexed by the P300 brain potential) explains the neuropsychologically measured changes in executive function previously observed in response to CSR and the stress response. (2.) Testing a conceptual framework that posits attention allocation as a means by which executive function is decreased due to psychophysiologic stress and CSR. (3.) Evaluating the role of fluctuating female sex steroid hormones across the menstrual cycle in psychophysiologic stress's proposed mediating role in CSR's effects on executive function. (4.) Testing if conceptualizing CSR as cumulative in the form of a composite score can be predictive of stress, anxious arousal, and executive function.

The Current Study

Given the aforementioned gaps in the literature, the current study aims to evaluate how cumulative sociodemographic risk and daily stress and anxious arousal symptoms impact executive function in females. This work will use a biopsychosocial lens to assess stress as cumulative response to accumulated stressors.

Specifically, the project's goals include: (1) confirming the relationships between stress /anxiety measures and executive function in our dataset using a cumulative measure of sociodemographic risk; (2) evaluating if our stress measures mediate the relationship between cumulative sociodemographic risk and executive function; and (3) evaluating how progesterone may interact with these relationships.

This work hypothesizes and aims to test if stress mediates the effect of cumulative sociodemographic risk on executive function, and if each of these aforementioned direct relationships are moderated by progesterone fluctuations across the menstrual cycle.

To do this, this work will address the following Aims:

Aim 1. First, this work will confirm the supported associations between cumulative sociodemographic risk (CSR), daily symptoms (DS) of self-reported stress and anxious arousal, and executive function (EF) as supported by the literature.

Aim 2. Second, stress will be evaluated as mediating the effects of sociodemographic risk on executive function.

Aim 3. Third, the role of progesterone in the relationships between sociodemographic risk, stress, and executive function will be explored.

CHAPTER 2: METHODS

Sample

The study sample was composed of 151 participants recruited from central Michigan and the Greater Lansing and East Lansing area as part of the Brain Cycle Study (BCS) [115]–[117].

The sample age ranged from 18 to 25 years of age (M = 20.71; SD = 1.742). The self-reported racial breakdown was as follows: 50.99% White, 19.87% Black, 5.30% Asian, 5.30% Latinx/Hispanic (Non-White), 8.61% Middle Eastern/North African (Non-White), 7.85% multiracial, 1.99% missing. 52.98% of the sample reported making less than $50,000 per year. 81.46% were students. Please see Table 1 in the appendix for further demographics breakdown.

This study was conducted at Michigan State University to look at ovarian hormones across the menstrual cycle and their effects on anxiety and cognition, as detailed further in other published work [115]–[117].

Participant recruitment strategies included mail, flyers, local media, and online advertisements. Study participants were naturally and regularly menstruating female individuals between 18-25 years of age, recruited between 2017-2022. In addition to being naturally cycling (defined as having a consistent menstrual cycle every 22-35 days), additional study criteria included not taking medication that would impact the nervous, endocrine, or reproductive systems, nor having a medical history or condition that impacts these systems. Exclusion criteria included the use of hormonal contraceptives, psychotropic medication, or steroids within the 8 weeks preceding study participation; as well as any reported thyroid conditions, metabolic disorders, epilepsy, severe psychiatric conditions including bipolar disorder and schizophrenia, or head trauma leading to loss of consciousness lasting for more than 5 minutes in duration. Other exclusion criteria included hearing or visual impairments that would impact data quality

and being a non-native English speaker. Anxiety and depression measures were not measured as inclusion criteria in order to produce a spectrum of symptoms in these dimensions across the community sample.

Procedure

As detailed in other work [115]–[117], BCS study participants enrolled in the longitudinal study for 35 consecutive days, intended to encompass one full menstrual cycle. This was done after completing a phone eligibility screen and providing a menstrual cycle history.

Participants were required to have tracked their most recent 3-5 cycles using either a calendar or a phone application. These cycle lengths were averaged and used to project the next date of menstruation using a hybrid method adapted from Lester et al. (2003), and then used to prospectively delineate four separate menstrual cycle phases characterized by distinct levels of estrogen and progesterone (i.e., early follicular, late follicular, ovulation and mid-luteal). This information was applied to the participant's current cycle for scheduling the participant's first EEG visit date to ensure a similar number of participants began the study in each cycle phase, allowing for variability in ovarian hormones across the sample, and to ensure the majority of the cycle was captured per participant. These projected phases were used for scheduling purposes only and not for analyses because the investigation centered on the direct effects of estrogen and progesterone.

Participants completed an initial visit at study onset composed of an intake and demographic interview, as well as study briefing, explanation, consent, and providing of materials. After their initial visit, participants then provided daily saliva and self-report measures. These included approximately 1.8ml of passive drool upon waking using the materials provided. These samples would be used for ovarian hormone assay. Affective symptom

questionnaires were completed between 5:00pm and 10:00pm each day using Qualtrics, an online portal. These included measures of daily perceived stress as well as mood and anxiety symptoms.

At four time points spread across the 35 days to coincide with 4 different menstrual phases characterized by variations in estrogen and progesterone levels, participants visited Michigan State's Clinical Psychophysiology Laboratory to take part in an N-back working memory task while concurrent electroencephalography (EEG) was taken. Participants then completed a final study visit during which a Structured Diagnostic Clinical Interview (SCID) for the Diagnostic Statistical Manual of Mental Disorders Version 5 (DSM-5) was administered. Participants received $280 as compensation for fully completing the study, and prorated compensation for partial completion. Approval of protocols utilized in this study was granted by the IRB at MSU under approval number LEGACY13-144.

Measures

Cumulative Sociodemographic Risk Measures

Race and Childhood Sociodemographic Status

Upon starting the study, participants underwent an intake visit that included explanation of the study structure, providing the study materials, and a thorough interview that included demographic information. During this intake interview, participants provided both racial information and childhood socioeconomic status. Race was provided as a self-reported self-identification selection among the following categories with the ability to select more than one of the following: Native American/American Indian/Alaska Native/Indigenous; Asian; Black; Latinx/Hispanic (Non-White); Middle Eastern/North African (Non-White); Pacific

Islander/Native Hawaiian; White; Multiracial with free response space to specify further, and Not Listed with free response space to specify further.

Childhood socioeconomic status was provided as a self-reported measure of total household income in childhood across all earners, phrased as: "Growing up, your family's average annual household income (all earners) was:" with the following ranges as options: 0-15,000; 15,001 - 25,000; 25,001-35,000; 35,001-50,000; 50,001-75,000; 75,001-100,000; 100,001-200,000; or more than $200,000. Participants also reported the total number of people who relied on this income, including the participant.

Trauma

At study completion, participants completed the SCID psychological interview. This included the Post Traumatic Stress Disorder (PTSD) screener, which assesses whether or not an individual has experienced trauma as defined by the DSM-5 criteria. The screener includes five main trauma types: (1) life threatening situation (e.g., fire, combat); (2) physical or sexual assault or abuse, (3) witnessing another person being sexually or physically assaulted or abused, (4) seeing another person killed, dead or badly hurt; and (5) being the victim of a serious crime. Of these criteria, participants disclosed all that applied to them, and were able to disclose more than one, or none at all. The SCID also assesses proximity to the traumatic event in the form of these things happening to the participant, if they witnessed it happening to someone else, or if they learned that it happened to someone they were close to.

Cumulative Sociodemographic Risk (CSR) Composite Score

Race, Childhood socioeconomic status, and Trauma were converted into binary 0 and 1 scores based on the criteria described below, and then summed, creating a composite cumulative sociodemographic risk (CSR) score ranging from 0-3.

For Race, Non-white was scored as 1, white scored as 0. Childhood socioeconomic status was computed using total income and total number of individuals relying on that income using 200% of the 2005 federal poverty line (FPL), where at or below 200% of the 2005 FPL was scored as 1, and above was scored a 0. Participant responses to the PTSD screener portion of the SCID were converted such that any trauma disclosures of any proximity were scored as 1, while having no disclosures of any kind was scored as 0. These resultant binary scores were then summed for each individual, providing each participant with a single, 0-3 CSR composite score.

Daily Stress and Anxiety Measures

Participants completed daily questionnaires every evening for 35 days. Responses reflected the frequency of any given symptoms on the day of completion. As part of these daily questionnaires, participants were asked to report what best describes how stressed they felt that day on a Likert scale from 1 (no stress) to 7 (extreme stress). They also completed a 38-item version of the Mood and Anxiety Symptom Questionnaire (MASQ; [119] to assess daily symptoms of mood and anxiety from a scale of 1 (not at all) to 5 (extremely). The anxious arousal component from this version of the MASQ was then appropriately scored, summed, and used to assess daily anxious arousal symptoms.

Executive Function (N-back Working Memory Task Measures)

Both behavioral and neurophysiologic measures of executive function were taken from the N-back verbal working memory task. Participants completed the task as described in [115], [117], [120].

For this task, a series of trials of single letters were presented centrally on a screen. Each letter was presented for 1000 ms with a 1100 ms intertrial interval, and participants were given 2000 ms to respond to each stimulus by attempting to correctly indicate if the letter is a target (left button press) or non-target (right button press) based on whether they had seen that same

letter N- trials back (where N = 0-back, 2-back or 3-back). Targets were defined as a letter matching a letter shown N trials ago; all other letters would be considered a non-target. Correctly identifying a target or non-target was considered a correct response, while misidentification would be considered an incorrect, or error, response.

For example, for 0-back trials, participants simply respond to the letter "X" as a target, and respond to all other letters as non-targets; this serves as a simple signal detection task with no load on working memory. However, in 2-back trials, if "A, B, C, B, D, C" are presented on the screen, a participant would respond to the second B in the above sequence as a "target" because it appears 2 trials earlier in the sequence. However, in a 3-back trial, this "B" would be a non-target, as it occurs 2 trials back in the sequence instead of three. In a 3-back trial, the second "C" would be a target.

In this way, working memory load was manipulated across blocks of trials by increasing the number of trials back the letter needed to match (i.e. 0-back = no working memory load, 2-back = medium working memory load, 3-back = high working memory load). These 3 conditions create 3 levels of increasing memory load, as they ask the participant to respond to a letter depending on if they had seen it an increasing "n" number of trials back, requiring the participant to hold and manipulate through comparison an increasingly long string of letters in their working memory as the n-back number increases.

Overall, the N-back Working Memory Task consisted of 16 blocks totalling 320 trials: 160 0-back trials, 80 2-back trials, and 80 3-back trials. Participants completed this task 4 times over the course of the study, at each of their lab visits. As they did so, concurrent EEG was taken.

N-back neuro/electrophysiologic (EEG) measures: P300

As described in Gloe (2019), throughout the N-back verbal working memory task continuous concurrent EEG was taken from 64 Ag-AgCl electrodes using the ActiveTwo Biosemi system (BioSemi, The Netherlands). Electrode ports were distributed across a stretch-lycra cap fitted to the heads of participants based on a 10-20 system, where the electrode port locations are standardized and distributed from one another at a distance of either 10% or 20% of the total front-back and left-right distance of the skull.

Participants' scalps were measured to ensure appropriate cap size and thus electrode distribution. Cap size was determined by measurements taken from the nasion (the depression between the eyes, between the forehead and the nose) and the inion (the lowest point on the posterior aspect of the skull identified by a prominent bump). Caps were then centered by measuring the distance from the tips of each ear over the head in the coronal plane, dividing that measurement in half, and aligning Cz and all other midline electrodes such that they were equidistant from each ear tip. A Velcro chin strap was then used to keep the cap securely in place.

Ports were filled with "Signa Gel," a highly conductive water-based electrolyte electrode gel suitable for biofeedback and neuroimaging. Electrodes were then plugged into the 64 individually labeled ports. Ports are named using letter and digit combinations comprised of capital letters corresponding to the approximate lobes/brain regions of the cerebral cortex the electrode sits superficial to, where F = frontal, T= temporal, C= central, P = parietal, and O = occipital lobes (e.g. Pz, FP1, O1, T8, C3). Sites at transitions are named for the lobes that create the junction (e.g. FP = frontoparietal). The last character indicates distance from midline, where

z = at midline, odd numbers indicate left hemisphere sites, and even numbers indicate right hemisphere sites, with larger numbers indicating more displacement from midline.

To control for electrooculogram (EOG) activity resulting from blinks and eye-movements, additional sensors were placed on the outer canthi of both eyes, at the temporal aspect of the eyes where the upper and lower eyelids meet, and below the left eye in line with and approximately 1cm inferior to the pupil. EOG activity was determined from these three sensors and the FP1 site. To serve as references for later processing, two sensors were placed on the left and right mastoids. The Common Mode Sense (CMS) active electrode and the Driven Right Leg (DRL) passive electrode were used as a ground during data acquisition. Signals were digitally acquired at 1,024Hz, indicating 1,024 samples of data taken per second, allowing for millisecond-level temporal resolution.

BrainVision Analyzer 2 (Brain Products, Gilching, Germany) was used to extract the P300 event related potential (ERP) data from the raw EEG recordings. The P300 is only computed from correct target responses.

Prepping the EEG recording in order to extract the P300 involved removing and interpolating channels with visually obvious noise, band-pass filtering, referencing to the mastoids, removing signals due to ocular activity, segmenting the data into trials and stimulus locking the time window, baseline correction within each trial, and then, lastly, removing any remaining artifacts. This process is explained in further detail below.

Raw EEG data recordings showing electrical activity over time at all 64 channels from the N-Back working memory task were initially visually examined for any problematic aberrations or significant artifactual noise at any recording channel. If five or fewer channels contained significant and obvious noise, they were removed and interpolated based on activity

from the closest surrounding channels. If greater than five channels showed significant noise, those EEG recordings were removed from analyses and considered missing. Channels from which specific ERPs of interest are computed (in this case, Pz for computing the P300) were not removed and interpolated– that data was simply considered missing for a given ERP.

Then, a band-pass filter with cutoffs of 0.1 Hz and 30Hz (12dB/oct roll off) was applied to the EEG data recordings, and data was re-referenced to the numeric mean of the mastoids, which does not sit superficial to excitable tissue and should show no electrical activity and can thus act as a reference.

Ocular correction was then conducted using a common regression method [121] to account for eye movement and blinks measured as EOG activity described above. EOG activity is typically greatest at frontal scalp sites near the eyes, and this specific method includes the calculation of a propagation factor to account for the estimated diffusion of this electrical activity's impact/influence at/on sites across the scalp.

Error trials (trials with incorrect responses) were removed, and the remaining correct trial types were segmented by type: by both working memory cognitive load type (0-back, 2-back, 3-back) and stimulus type (target, nontarget). Though the task also contained lure stimulus trials, they sit outside the scope of this work; they, as well as non-targets, were not included in these analyses. Only correct responses to targets were used to compute the P300.

Segments were then temporally aligned to be relative to stimulus presentation (i.e., "stimulus-locked"). These stimulus-locked segments begin 200ms prior to the letter stimulus and end 1,000ms after stimulus onset.

Artifact correction was then carried out on each set of segments to remove trials that contained any of the following: a voltage step greater than 50 microvolts/ms compared to

preceding and following trials; a difference in voltage of 300 microvolts across a 200ms time window; a voltage difference less than 0.5 microvolts across 100ms; or an amplitude more extreme than 200 microvolts.

Individual channel activity was then averaged across trials of one type to create a single channel average per trial type per participant. The data was recalibrated using the average electrical activity from the 200ms preceding the stimulus as baseline; this 200ms pre-stimulus baseline average was subtracted from all post-stimulus electrical activity data points.

From these data, the P300 waveform was then computed at channel Pz (the scalp location where the P300 ERP reaches its maximum amplitude) as the average voltage amplitude in microvolts (μV) across the 300-500ms time window following the stimulus.

N-back Behavioral Measures: Reaction Time and Accuracy

Reaction times (RT) for correct responses and accuracy were calculated for responses to targets on each trial type (0-, 2-, and 3-back). Accuracy was computed as the number of correctly identified targets out of total presented in a given trial type per participant. These measures were averaged across trials for each participant. To ensure data quality and integrity, correct trials with reaction times less than 200 ms, and any trials where accuracy was less than or equal to 30% across all trial types were excluded from further analysis.

Progesterone

Study participants provided approximately 1.8 ml of saliva daily within 30 minutes of waking using the passive drool method for 35 consecutive days. Participants then stored these samples in provided kits in their home freezers until they could transport them to the lab, where they were then stored in a –80 °F freezer. Saliva samples were then shipped to Salimetrics, LLC (College Park, PA) where they were assayed for estradiol and progesterone using enzyme

immunoassay. Salmetrics' progesterone enzyme immunoassay had an intra-assay coefficient of variation of 6.2%, inter-assay coefficient of variation of 7.6%, and an assay sensitivity of 5 pg/mL. Saliva was used in lieu of blood in order to decrease participant burden given the ease of providing daily saliva compared to blood, informed by past studies demonstrating a high correlation between blood and saliva estradiol and progesterone levels [122], [123]. Blood sampling may also cause acute stress resulting in an increase in cortisol and catecholamines, and thus may not be ideal given naturalistic and daily stress is a prominent subject of this work's interrogation. Estradiol and progesterone z-scores were charted per individual in hormone plots in order to identify anovulatory cycles per Klump et al., 2015. Participant visits occurring during anovulatory cycles were removed from analyses.

Analysis

The main analytic approaches used in this work to achieve the aforementioned aims included multilevel modeling and the Monte Carlo method for assessing mediation.

Overall, this project took advantage of the multi-level nature of the data and explored both mediation and moderation on top of direct associations. The multilevel modeling approach evaluated direct effects between CSR, DS and EF, and then looked at DS (stress and anxiety) as mediators of CSR on EF, and progesterone as a moderator of the relationships between CSR, DS, and EF.

In order to evaluate the relationships between CSR, Stress, Anxiety, EF, and Progesterone, a series of 87 total multilevel models were run using SPSS. Multilevel modeling (MLM), sometimes referred to as hierarchical linear modeling, allows for analysis given the nesting of data that comes with repeated measures within individuals, as is the case in this data structure, where visits are nested within individuals. MLM accommodates for the resultant

violation of the law of independence that repeating measures from a specific participant produces. It also allows for flexibility in missing data, allowing this work to utilize data from all participants even if they were missing a visit.

The current analyses used daily stress, anxious arousal, and progesterone level measures from in-person lab visit days. In all models, predictors were grand mean centered. Outcome variables were not centered. A fixed effects model with compound symmetry with correlation parameterization was utilized. This covariance structure has constant variance and constant covariance. Person-level variables included CSR, while visit-level variables included self-reported stress, anxious arousal symptoms, EF measures, and progesterone.

Aim 1 evaluated direct effects between CSR, DS, and EF, Aim 2 evaluated for mediating variables, and Aim 3 evaluated progesterone as a moderating variable in all the direct effect relationships evaluated in Aim 1. In total, due to the 3x3 nature of the EF measures (P300, reaction time, and accuracy at 0, 2, and 3 back), this came to 29 models for Aim 1, 18 Monte Carlo simulations using Selig and Preacher's (2012) Monte Carlo method for assessing mediation for Aim 2, and 58 models for Aim 3 [125]. For the Monte Carlo Method for Assessing Mediation, the squared standard errors computed for Aim 1 were used for var(a) and var(b) for path a and b, and 20,000 repetitions were run per simulation, which will be detailed further in Chapter 4.

All aims used measures described above. As the aims varied in specific model structure, more aim-specific analytic details are included in their respective chapters.

Please see appendices for breakdown of predictor and outcome variables per model by aim.

CHAPTER 3: AIM 1: DIRECT ASSOCIATIONS BETWEEN RISK, DAILY SYMPTOMS, AND EXECUTIVE FUNCTION

Analytic Method

To confirm the previously observed associations between the CSR composite score, DS measures of stress and anxious arousal, and executive function, univariate multilevel models were utilized.

The modeled relationships can be summed up in the representations below, where EF indicates a suite of nine measures of executive function: the P300, reaction time, and accuracy at 0-, 2-, and 3-Back trials (low, medium, and high working memory load, respectively):

a) $CSR \rightarrow EF$

b) $CSR \rightarrow Stress; CSR \rightarrow AnxiousArousal$

c) $Stress \rightarrow EF; AnxiousArousal \rightarrow EF$

These univariate multilevel models were used to evaluate if a) the CSR score significantly predicts EF measures, b) if CSR significantly predicts DS measures of self-reported stress and anxious arousal, and c) if DS of stress and anxious arousal predict EF.

For a), nine models predicting each EF outcome from CSR were used to evaluate if increased CSR would negatively impact EF.

For b), two univariate models were used to evaluate if CSR predicts increased daily self-reported stress and anxious arousal symptoms.

For c), to evaluate if increased measures of daily stress and anxious arousal would both be associated with decreased measures of executive function eighteen models (2x9) were run. The first nine models used daily stress measures to predict nine executive function measures, and the second nine models evaluated if anxious arousal symptoms predicted the same nine executive function outcome measures.

Decreased EF was defined as decreased P300 amplitude, increased reaction time, and decreased accuracy across all (low, medium, and high working memory– i.e. 0, 2, and 3-Back) trial types.

Results

a) CSR on EF

As can be seen in the table below, models evaluating 0-Back EF measures indicated that during 0-Back target trials at average CSR (*mean* = 1.18), the P300 had an average amplitude at Pz of 8.911 μV. For every one unit increase in CSR, the P300 average amplitude at Pz during 0-Back targets dropped by 1.585 μV (B = -1.585, p = <.001). The model showed that at average CSR the average reaction time at 0-Back Targets was 499.671 ms. Then for every one unit increase in CSR, the predicted reaction time increased by 14.471ms (B = 14.471, p = .024). Not in line with hypotheses, the model assessing CSR's effects on accuracy during the 0-Back task was not significant, with p = .55.

For 2-Back EF measures, all three models showed the expected significant effects. Results showed that at average CSR (*mean* = 1.18), the P300 during 2-Back targets had an average amplitude at Pz of 6.561 μV. For every one unit increase in CSR, the P300 average amplitude at Pz predictably decreased by 0.753 μV (B = -0.753, p = .026). The second model evaluating if CSR significantly predicted reaction time showed that at average CSR, the average reaction time at 2-Back Targets was 622.348 ms. Then for every one unit increase in CSR, the

predicted reaction time increased by 28.137ms ($B = 28.137$, $p = .007$). When modeling CSR's effects on accuracy, results showed that at average CSR, the accuracy averaged .783, or 78.3%. For every one unit increase in CSR, the accuracy significantly decreased by .047, or 4.7% ($B = -.047$, $p = .004$).

Lastly, models were run to evaluate the effects of CSR on the P300, reaction time, and accuracy during high working memory load (3-Back) target trials. Only the P300 and accuracy models showed significant effects. Results showed that at average CSR (*mean* = 1.18), the P300 during 3-Back targets had an average amplitude at PZ of 5.425 μV. And then for every one unit increase in CSR, the P300 average amplitude at PZ was found to significantly decrease by 0.932 μV ($B = -0.932$, $p = .005$). Not in line with expectations, the model predicting CSR's effects on reaction time during 3-Back trials did not reach significance (p = .089). Its results showed that at average CSR, the average reaction time at 3-Back Targets was 663.511 ms, and that for every one unit increase in CSR, the predicted reaction time increased by 20.454ms ($B = 20.454$, $p = .089$). However, the model predicting accuracy showed that at average CSR, the accuracy averaged .653, or 65.3%, and for every one unit increase in CSR, the accuracy significantly decreased by .038, or 3.8% ($B = -.038$, $p = .017$).

Aim 1A. Simple Direct Relationships with **CSR (*n* = 130)** as a Predictor of Measures of Executive Function

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
0-Back					
P300 (µV)	**-1.585**	**0.396**	**< 0.001**	8.911	0.329
Reaction Time (ms)	**14.471**	**6.319**	**0.024**	499.671	5.246
Accuracy (prop.)	-0.006	0.010	0.550	0.865	0.009
2-Back					
P300 (µV)	**-0.753**	**0.334**	**0.026**	6.561	0.278
Reaction Time (ms)	**28.137**	**10.208**	**0.007**	622.348	8.475
Accuracy (prop.)	**-0.047**	**0.016**	**0.004**	0.783	0.013
3-Back					
P300 (µV)	**-0.932**	**0.330**	**-0.005**	5.425	0.274
Reaction Time (ms)	20.454	11.939	0.089	663.511	9.912
Accuracy (prop.)	**-0.038**	**0.016**	**0.017**	0.653	0.013

Table 1. A table depicting direct effects of CSR on measures of EF, calculated using a multilevel model. Significant relationships are bolded. Intercepts were calculated at the average value of the predictor (CSR: *M* = 1.18).

CSR's predictive effects on the P300, reaction time, and accuracy can be seen graphed below:

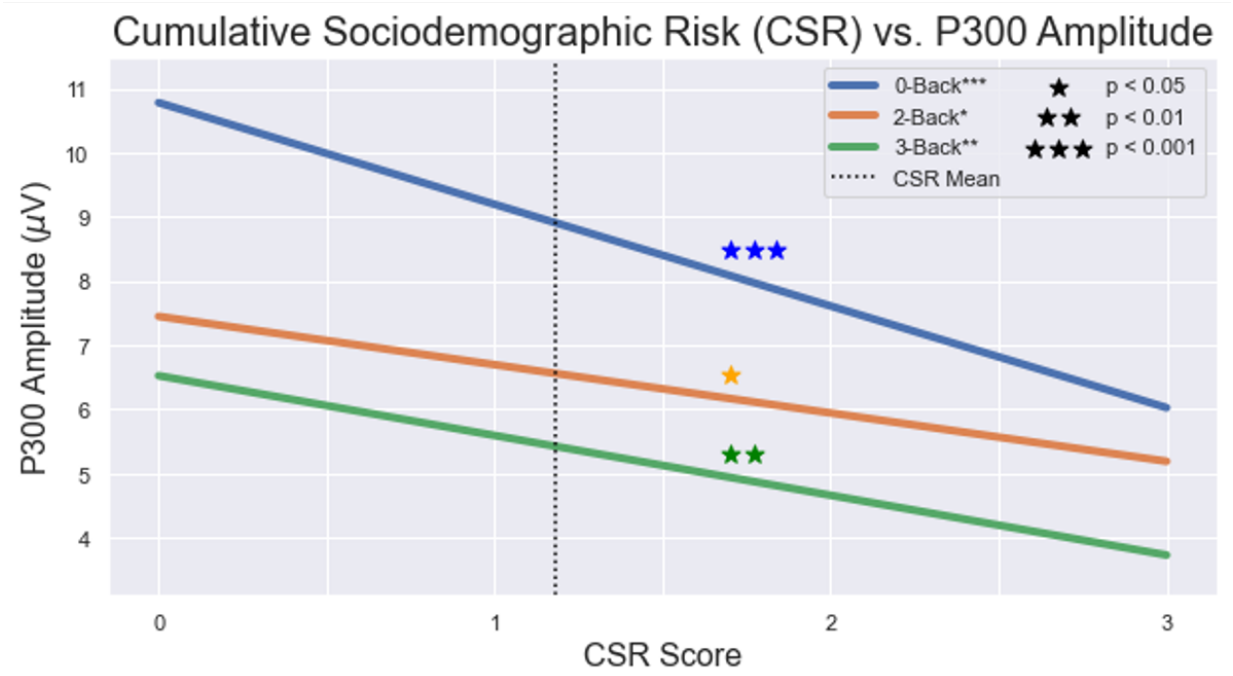

Figure 1. Graph depicting resulting regressions from a multilevel model between CSR and P300 amplitude across levels of cognitive load. Significance is marked with stars. Intercepts were calculated at the average value of the predictor (CSR: *M* = 1.18), depicted by the vertical dotted black line.

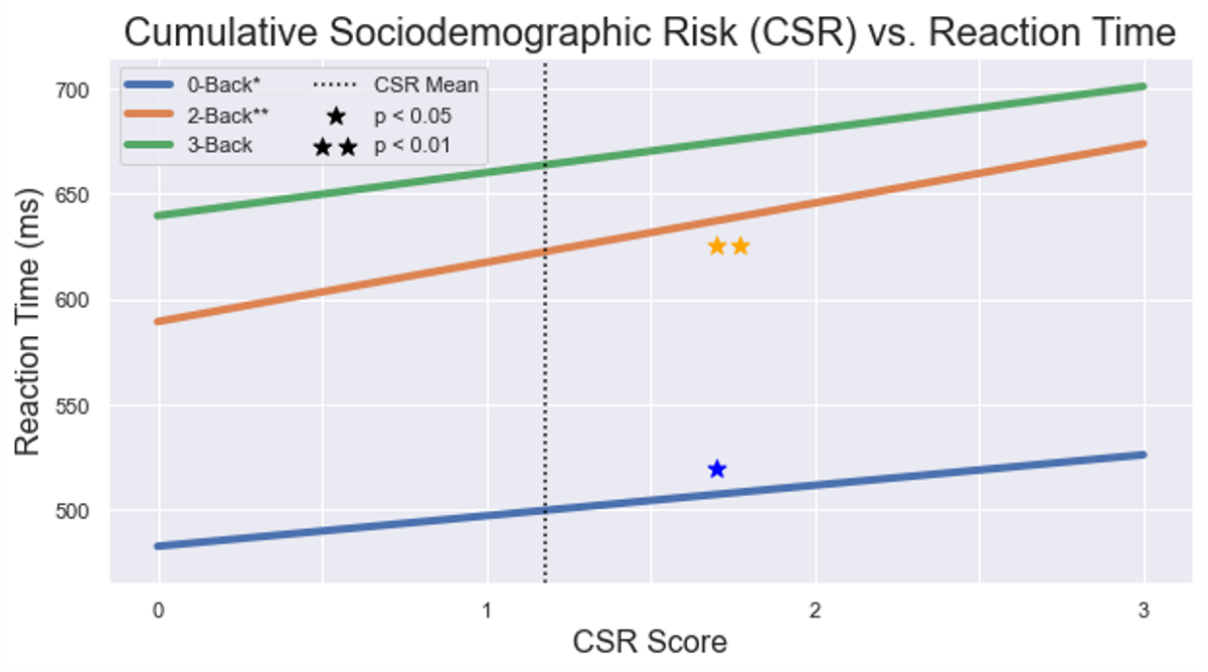

Figure 2. Graph depicting resulting regressions from a multilevel model between CSR and reaction time across levels of cognitive load. Significance is marked with stars. Intercepts were calculated at the average value of the predictor (CSR: $M = 1.18$), depicted by the vertical dotted black line.

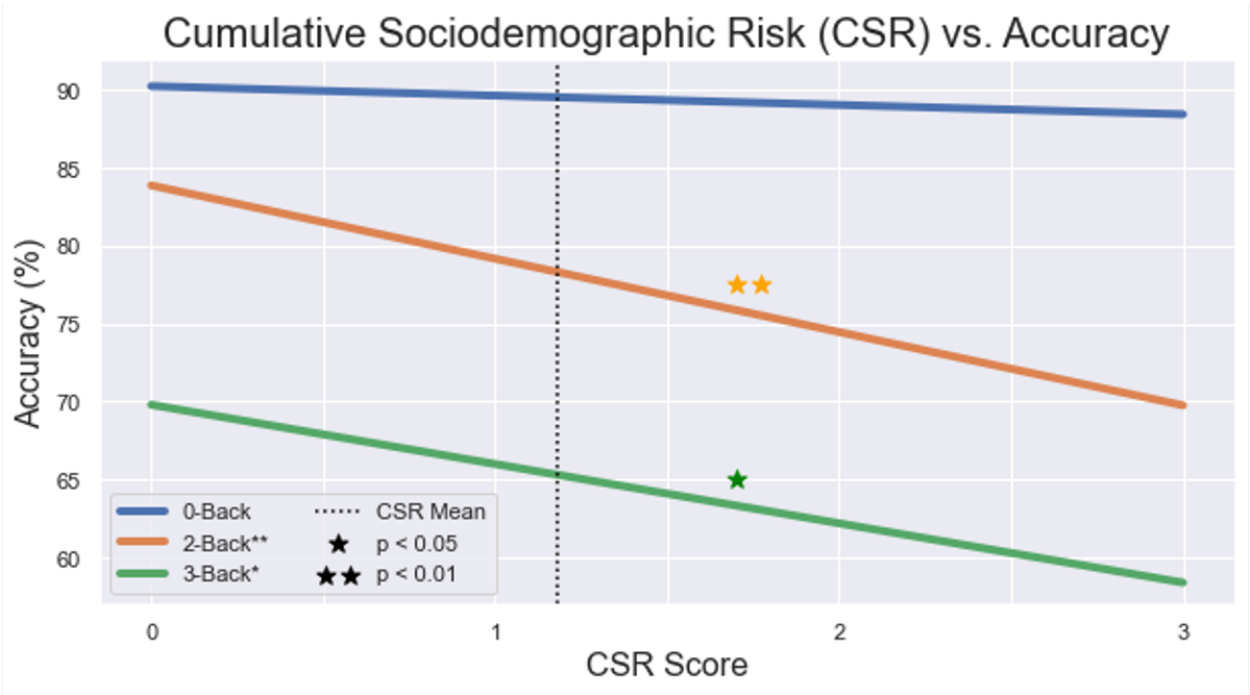

Figure 3. Graph depicting resulting regressions from a multilevel model between CSR and accuracy across levels of cognitive load. Significance is marked with stars. Intercepts were calculated at the average value of the predictor (CSR: $M = 1.18$), depicted by the vertical dotted black line.

The hypothesis was mostly supported. The P300 was found to be significantly impacted by CSR at all levels (0-, 2-, and 3- back) of cognitive load. Meanwhile, CSR's impact on reaction time only reached significance at low (0-back) and medium (2-back) working memory load. In contrast, CSR's impact on accuracy only reached significance at medium (2-back) and high (3-back) working memory loads. Notably, CSR's effects on 3-back reaction time and 0-back accuracy did not reach significance; meaning that at high working memory loads, CSR did not significantly impact reaction time, and at low working memory loads, CSR did not have an impact on accuracy.

b) CSR on DS

Per the table below, results from models examining if high CSR increases DS demonstrated that CSR did not significantly predict either outcome variable. CSR did not significantly predict daily self-reported stress measures (B = -.17, p = .3), nor daily self-reported anxious arousal symptoms (B = -.151, p = .841). These findings are contrary to the hypothesis.

Aim 1B. Simple Direct Relationships with **CSR** as a Predictor of Measures of Daily Stress Scores and Anxious Arousal

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
Stress (n = 101)	-0.170	0.163	0.300	3.441	0.127
Anxious Arousal (n = 130)	-0.151	0.753	0.841	25.472	0.626

Table 2. A table depicting direct effects of CSR on measures of daily stress, calculated using a multilevel model. Significant relationships are bolded. Intercepts were calculated at the average value of the predictor (CSR: M = 1.18).

c) DS on EF

Results from all 18 models can be seen in the table below. The nine models evaluating the effects of DS stress on EF showed that increased levels of daily self-reported stress significantly predicted a longer reaction time at 0- and 3-back (i.e., low and high cognitive load),

but had no significant effects on reaction time at 2-back (i.e., medium cognitive load). Namely, coefficients and p-values for stress's impact on RT at 0- and 3-Back came to B= 3.817, p = .021, and B = 8.275, p = .036, respectively. Meaning that for every one unit increase in stress, a 3.817ms and 8.275ms increase in RT during 0- and 3-back can be expected, respectively. Stress did not significantly predict any other tested executive function measures, including the P300 and accuracy, for any trial types (0-, 2-, or 3-back). The significant findings for stress' impact on reaction time at 0- and 3- back are consistent with this work's hypotheses.

In contrast, of the nine anxious arousal on EF models, anxious arousal only significantly predicted a change in reaction time at 2-back (B= -2.051, p = .005). This change was significant in the opposite direction of expectations: results showed that every one unit increase in anxious arousal predicted a 2.051ms decrease in reaction time, contrary to the slowed reaction time hypothesized. Effects on all other EF measures were insignificant.

The lack of predicted effects on accuracy and P300 across either DS predictor was inconsistent with hypotheses.

Aim 1C. Simple Direct Relationship with **Daily Stress Scores** and **Anxious Arousal** as Predictors of Measures of Executive Function

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
Stress (n = 111) predicting...					
0-Back					
P300 (μV)	-0.119	0.195	0.541	9.240	0.408
Reaction Time (ms)	**3.817**	**1.642**	**0.021**	498.098	5.952
Accuracy (prop.)	0.000	0.003	0.928	0.891	0.011
2-Back					
P300 (μV)	0.028	0.137	0.863	6.520	0.320
Reaction Time (ms)	1.356	3.716	0.715	619.658	9.491
Accuracy (prop.)	0.000	0.005	0.959	0.782	0.015
3-Back					
P300 (μV)	-0.228	0.151	0.132	5.383	0.309
Reaction Time (ms)	**8.275**	**3.938**	**0.036**	660.848	10.849
Accuracy (prop.)	-0.001	0.005	0.845	0.651	0.014
Anxious Arousal (n = 142) predicting...					
0-Back					
P300 (μV)	0.030	0.036	0.397	9.099	0.358
Reaction Time (ms)	-0.497	0.357	0.164	499.101	5.138
Accuracy (prop.)	0.001	0.001	0.142	0.896	0.009
2-Back					
P300 (μV)	0.037	0.027	0.172	6.51	0.278
Reaction Time (ms)	**-2.051**	**0.732**	**0.005**	620.08	8.408
Accuracy (prop.)	0.001	0.001	0.169	0.790	0.013
3-Back					
P300 (μV)	0.048	0.028	0.091	5.484	0.274
Reaction Time (ms)	-1.359	0.781	0.083	661.306	9.522
Accuracy (prop.)	0.001	0.001	0.264	0.659	0.012

Table 3. A table depicting direct effects of measures of daily stress on measures of EF, calculated using a multilevel model. Significant relationships are bolded. Intercepts were calculated at the average value of the predictor (Stress: M = 3.34; Anx. Ars.: M = 25.27).

Discussion

Previously observed associations between CSR, DS, and EF were expected to be demonstrated in this data set, and to be present using the cumulative risk score.

Specifically, this work hypothesized that: **(a)** high sociodemographic risk measured as the CSR composite score would be associated with decreased measures of executive function; **(b)** high socio-demographic risk (CSR) would be associated with increased measures of both daily stress and daily anxious arousal; and **(c)** increased daily measures of stress and anxious arousal would be associated with decreased measures of executive function.

a) CSR on EF

The hypothesis that CSR reduces EF was mostly supported. The P300 was found to be significantly impacted by CSR at all levels (0-, 2-, and 3- back) of cognitive load. Meanwhile, CSR's impact on reaction time only reached significance at low (0-back) and medium (2-back) working memory load. In contrast, CSR's impact on accuracy only reached significance at medium (2-back) and high (3-back) working memory loads. Notably, CSR's effects on 3-back reaction time and 0-back accuracy did not reach significance; meaning that at high working memory loads, CSR did not significantly impact reaction time, and at low working memory loads, CSR did not have an impact on accuracy.

Overall, the results of 1a paint a picture of CSR having a significant overall negative impact on executive function, with notable and informative exceptions during high and low working memory tasks. High working memory load was sufficiently difficult that regardless of CSR everyone's reactions slowed. Meanwhile, in the case of accuracy under low working memory load, the task was sufficiently easy - merely a signal detection - that accuracy was unaffected by CSR. However, it is important to note that in both the 0-Back and 3-Back cases, the other two executive function markers (P300 and reaction time in the case of 0-Back, and P300 and accuracy in the case of 3-Back) were nonetheless significantly affected by CSR. For 0-back, though accuracy may not be affected as CSR increases, deficits appear elsewhere and may

be compensatory. This suggests that to maintain accuracy under high CSR even during signal detection, reaction time may lengthen. In reverse in the 3 back (high working memory load) condition, slowing of reaction time at lower CSR may maintain higher accuracy, while it does not in individuals with a higher CSR score. Significant results at 2-back however, may be most telling by showing effects across all EF markers. In medium-load tasks, all markers are affected.

The P300 was impacted across all WM load trial types. P300 acts as an index of available attentional resources under cognitive stress, showing that even for simple signal detection, the addition of a single CSR factor significantly negatively impacts cognitive resources available for attentional processes. The P300 being significantly affected across all task difficulties may be telling of underlying neuroelectrophysiological deficits– where the neural substrates of cognitive resources available for attention allocation under cognitive load are impacted, and that those deficits manifest differently under different task pressures, as in the case of 0-Back and 3-Back showing opposite significant impacts for reaction time and accuracy. In conclusion, though underlying P300 deficits may exist with higher CSR, this work provides additional insight into how these deficits may manifest behaviorally: depending on load, individuals with EF deficits predicted from high CSR can perform as fast as individuals with low CSR but with a drop in accuracy, or they can perform as accurately but with more time.

b) CSR on DS

Models predicting DS measures from CSR found no associations. This is contrary to hypotheses, given that literature suggests sociodemographic stressors alter nervous system reactivity, and it was expected that this altered nervous system would manifest in DS. However, it is possible that DS reflects ecological factors that cannot be accounted for and are too temporally constrained to reflect larger patterns in the nervous system's responsivity.

c) DS on EF

In models testing for DS's impacts on EF, mixed results were seen. Of the nine measures of executive function, DS measures only impacted RT. Stress only significantly predicted decreased EF as increased RT at 0- and 3- back, and anxious arousal only significantly predicted a decreased reaction time at 2-back. Anxious arousal's change was significant in the opposite direction of expectations: results showed that every one unit increase in anxious arousal predicted a decreased (faster) reaction time, contrary to the slowed reaction time hypothesized. The lack of predicted effects on accuracy and P300 were surprising. Unexpectedly, results only indicated impacts on reaction time, and that reaction time was not only differentially affected by stress compared to anxious arousal, but that these differential impacts happened at different and complementary levels of cognitive load, where stress impacted 0- and 3-Back and anxious arousal impacted 2-back.

Considering these findings, self-reported daily measures of either stress or anxious arousal could be seen as impacting processing speed (indexed by reaction time), without having any impact on available cognitive resources (P300), or accuracy of performance.

Summary

Overall, findings exploring the direct relationships between CSR, DS, and EF revealed that CSR impacts EF, DS have some small and mixed impacts on EF, and CSR does not significantly predict DS. Notably, CSR's impact on EF is much greater than DS's, in line with other work demonstrating that distant factors like early life stress often have greater effects on functional outcomes than proximal daily factors [126], [127].

CHAPTER 4: AIM 2: DAILY SYMPTOMS MEDIATING THE RELATIONSHIPS BETWEEN RISK AND EXECUTIVE FUNCTION

Analytic Method

To evaluate the overarching hypothesis that stress mediates the effect of cumulative sociodemographic risk on executive function, findings from the models run in Aim 1 were used to assess for mediation. Effect sizes from all Aim 1 findings were used in 18 (2x9) Monte Carlo simulations testing for indirect effects predicting the nine executive function measures from CSR, with the first nine using daily stress self-report as a mediator and the second 9 using daily anxious arousal symptoms. These computations were structured such that they evaluated the effects of 1 predictor (CSR), 2 mediators (Stress and Anxious Arousal), and 9 outcome measures (the 9 EF measures).

The 18 Monte Carlo computations used Selig and Preacher's (2012) Monte Carlo simulation for assessing mediation. For the Monte Carlo Method for Assessing Mediation, the squared standard errors computed for Aim 1 were used for var(*a*) and var(*b*) for path *a* and *b* (seen in the diagram below), and 20,000 repetitions were run per simulation using an open-source web utility [128], [129].

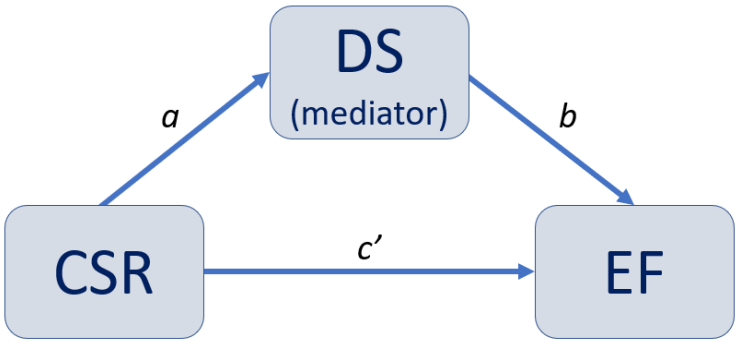

Figure 4. Diagram representing paths *a* and *b* in the Monte Carlo simulations testing for indirect effects of CSR on 3-Back EF outcomes (P300, RT, and Acc.) with daily stress scores as a mediator.

The first nine simulations evaluated daily self-reported stress as a mediator in the relationships between CSR and each EF measure. Resultant histograms are shown for each simulation below, followed by a summary table of lower and upper 95% confidence interval (CI) limits. If zero is contained within the limits, there is no significant finding.

The second nine simulations evaluated daily self-reported anxious arousal symptoms in lieu of daily self-reported stress. Similarly, resultant histograms can be seen below, followed by a summary table of lower and upper 95% CI limits.

Stress Mediation Monte Carlo Simulation Inputs

As depicted in figure 5, *a* is the unstandardized regression coefficient of CSR's association with stress and *b* is the unstandardized regression coefficient of stress' association with measures of executive function; var(*a*) and var(*b*) are the sampling variances of *a* and *b*, respectively.

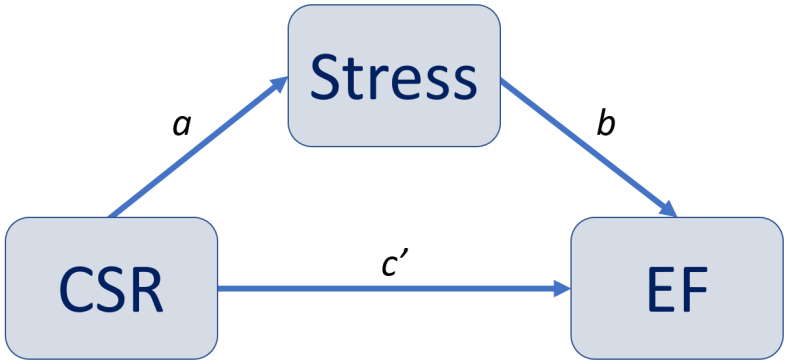

Figure 5. Diagram representing paths *a* and *b* in the Monte Carlo simulations testing for indirect effects of CSR on 3-Back EF outcomes (P300, RT, and Acc.) with stress as a mediator.

Aim 2. Monte Carlo Simulation using **Stress** as a Mediator in the Relationship Between CSR and Executive Function

Model Outcome	*a*	*Var(a)*	*b*	*Var(b)*
0-Back				
P300 (μV)	-0.17	0.026569	-0.119	0.038025
Reaction Time (ms)	-0.17	0.026569	3.817	2.696164
Accuracy (prop.)	-0.17	0.026569	0.000	0.000009
2-Back				
P300 (μV)	-0.17	0.026569	0.028	0.018769
Reaction Time (ms)	-0.17	0.026569	1.356	13.808656
Accuracy (prop.)	-0.17	0.026569	0.000	0.000025
3-Back				
P300 (μV)	-0.17	0.026569	-0.228	0.022801
Reaction Time (ms)	-0.17	0.026569	8.275	15.507844
Accuracy (prop.)	-0.17	0.026569	-0.001	0.000025

Table 4. A table depicting inputs of the Monte Carlo Simulation for assessing the mediation of stress in the relationship between CSR and measures of EF. Variables *a* and *b* represent the unstandardized regression coefficients from CSR to stress and from stress to EF, respectively. Var(*a*) and var(*b*) are the asymptotic sampling variances of *a* and *b*, respectively.

Anxious Arousal Mediation Monte Carlo Simulation Inputs

As depicted in figure 6, *a* is the unstandardized regression coefficient of CSR's association with anxious arousal and *b* is the unstandardized regression coefficient of anxious arousal's association with measures of executive function; var(*a*) and var(*b*) are the sampling variances of *a* and *b*, respectively.

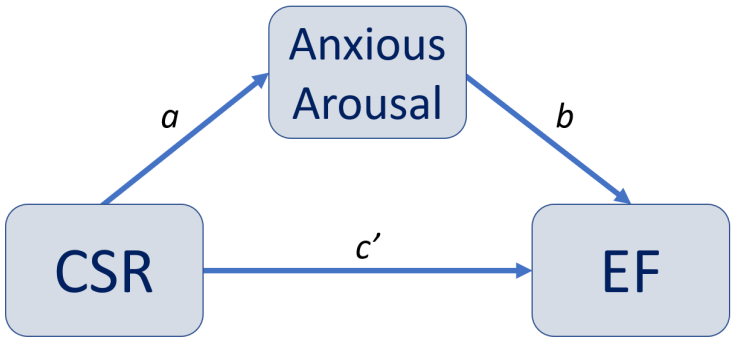

Figure 6. Diagram representing paths *a* and *b* in the Monte Carlo simulations testing for indirect effects of CSR on 3-Back EF outcomes (P300, RT, and Acc.) with anxious arousal as a mediator.

Aim 2. Monte Carlo Simulation using **Anxious Arousal** as a Mediator in the Relationship Between CSR and Executive Function

Model Outcome	*a*	*Var(a)*	*b*	*Var(b)*
0-Back				
P300 (μV)	-0.151	0.567009	0.030	0.001296
Reaction Time (ms)	-0.151	0.567009	-0.497	0.127449
Accuracy (prop.)	-0.151	0.567009	0.001	0.000001
2-Back				
P300 (μV)	-0.151	0.567009	0.037	0.000729
Reaction Time (ms)	-0.151	0.567009	-2.051	0.535824
Accuracy (prop.)	-0.151	0.567009	0.001	0.000001
3-Back				
P300 (μV)	-0.151	0.567009	0.048	0.000784
Reaction Time (ms)	-0.151	0.567009	-1.359	0.609961
Accuracy (prop.)	-0.151	0.567009	0.001	0.000001

Table 5. A table depicting inputs of the Monte Carlo Simulation for assessing the mediation of anxious arousal in the relationship between CSR and measures of EF. Variables *a* and *b* represent the unstandardized regression coefficients from CSR to anxious arousal and from anxious arousal to EF, respectively. Var(*a*) and var(*b*) are the asymptotic sampling variances of *a* and *b*, respectively.

Results

Stress as Mediator

0-Back: Low Working Memory Load (Signal Detection)

Simulations predicting indirect effects on executive function measures taken during low working memory load trials all showed null findings, indicating that measures of daily self-reported stress do not mediate the effects of CSR on the P300, RT, or accuracy under low working memory load conditions. This finding is contrary to the overarching hypothesis.

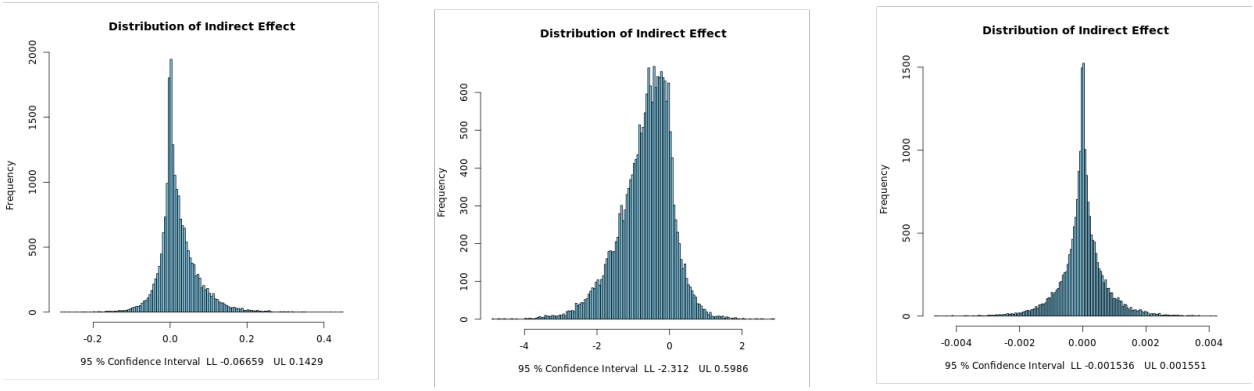

Figure 7. Histograms demonstrating results from Monte Carlo simulations testing for indirect effects of CSR on 0-Back EF outcomes (P300, RT, and Acc, respectively) with stress as a mediator.

2-Back: Medium Working Memory Load

Similar to our findings predicting executive function measures during 0-Back trials, simulations predicting indirect effects on executive function measures taken during medium (2-Back) working memory load trials all showed null findings. This indicates that measures of daily self-reported stress do not mediate the effects of CSR on the P300, RT, or accuracy under medium working memory load conditions, contrary to our overarching hypothesis.

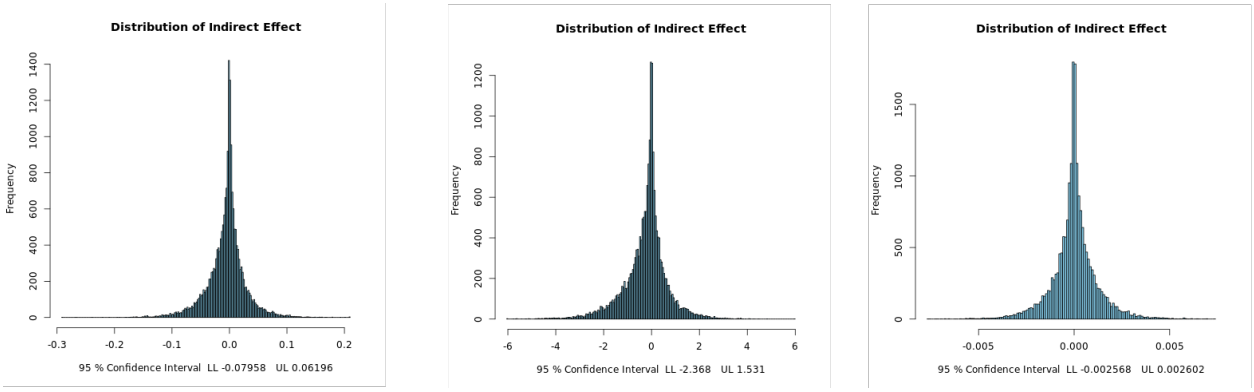

Figure 8. Histograms demonstrating results from Monte Carlo simulations testing for indirect effects of CSR on 2-Back EF outcomes (P300, RT, and Acc, respectively) with stress as a mediator.

3-Back: High Working Memory Load

As with our findings from simulations assessing for indirect effects on executive function measures during 0-Back and 2-Back trials, findings predicting indirect effects on executive function measures during 3-Back trials all showed null findings. This indicates that measures of daily self-reported stress do not mediate the effects of CSR on the P300, RT, or accuracy under high working memory load conditions. This finding is contrary to our overarching hypothesis.

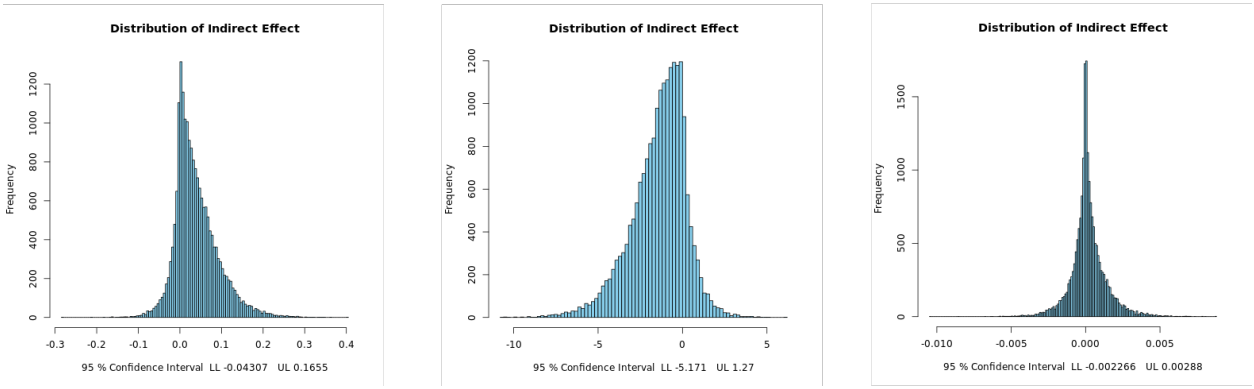

Figure 9. Histograms demonstrating results from Monte Carlo simulations testing for indirect effects of CSR on 3-Back EF outcomes (P300, RT, and Acc, respectively) with stress as a mediator.

Stress Mediation Confidence Interval Summary

In sum, confidence intervals for all models testing daily stress as a mediating the effects of CSR on EF contained zero. This indicates that the daily stress measure does not mediate the effect of CSR on EF.

95% Confidence Intervals for the Total Indirect Effect CSR on EF outcomes with **Stress** as a Mediator

Model Outcome	*LL*	*UL*
0-Back		
P300	-0.06659	0.1429
Reaction Time	-2.312	0.5986
Accuracy	-0.001536	0.001551
2-Back		
P300	-0.07958	0.06196
Reaction Time	-2.368	1.531
Accuracy	-0.002568	0.002602
3-Back		
P300	-0.04307	0.1655
Reaction Time	-5.171	1.270
Accuracy	-0.002266	0.00288

Table 6. A table depicting results of the Monte Carlo Simulation for assessing the mediation of stress in the relationship between CSR and measures of EF, providing the lower and upper bounds of the 95% confidence interval of the estimated mediation effect.

Anxious Arousal as Mediator

0-Back: Low Working Memory Load (Signal Detection)

Simulations predicting indirect effects on executive function measures taken during low working memory load trials all reveal no indirect effects, indicating that measures of daily self-reported anxious arousal symptoms do not mediate the effects of CSR on the P300, RT, or accuracy under low working memory load conditions. This finding is contrary to our overarching hypothesis.

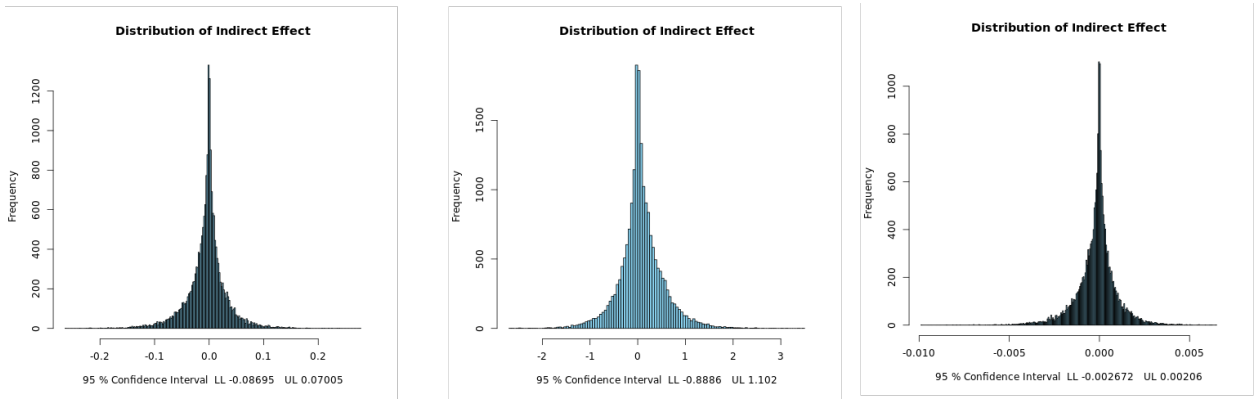

Figure 10. Histograms demonstrating results from Monte Carlo simulations testing for indirect effects of CSR on 0-Back EF outcomes (P300, RT, and Acc, respectively) with anxious arousal as a mediator.

2-Back: Medium Working Memory Load

Similar to findings from 0-Back trials, simulations predicting indirect effects on executive function measures taken during medium (2-Back) working memory load trials all showed null findings. This indicates that measures of daily self-reported anxious arousal symptoms do not mediate the effects of CSR on the P300, RT, or accuracy under medium working memory load conditions. This is contrary to expectations.

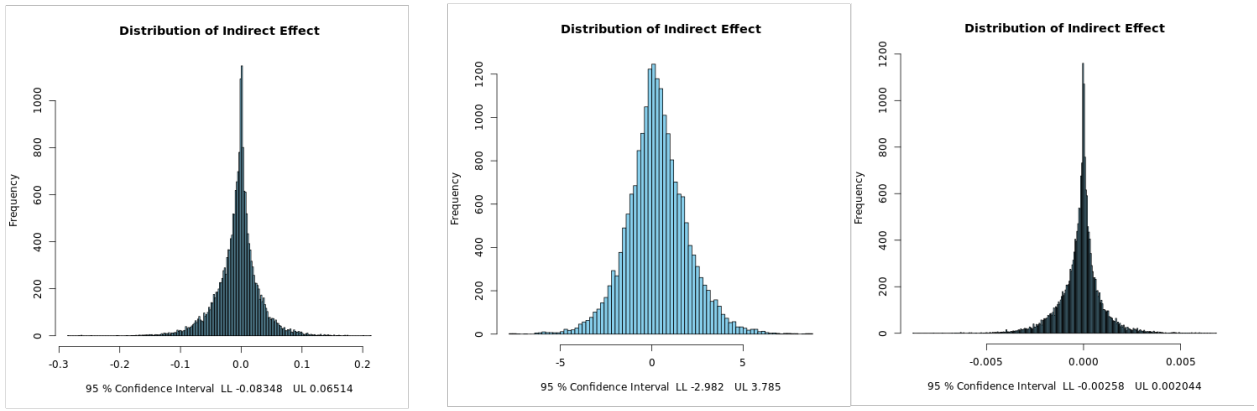

Figure 11. Histograms demonstrating results from Monte Carlo simulations testing for indirect effects of CSR on 2-Back EF outcomes (P300, RT, and Acc, respectively) with anxious arousal as a mediator.

3-Back: High Working Memory Load

Consistent with the results from simulations assessing for indirect effects on executive function measures during 0-Back and 2-Back trials, simulations predicting indirect effects on executive function measures during 3-Back trials all showed no indirect effects. This indicates that measures of daily anxious arousal symptoms do not mediate the effects of CSR on the P300, RT, or accuracy under high working memory load conditions. This finding is contrary to our overarching hypothesis.

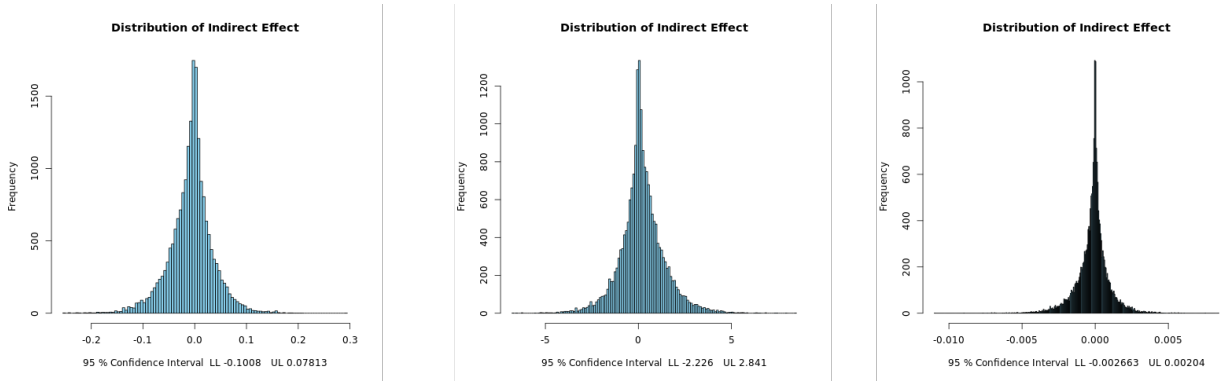

Figure 12. Histograms demonstrating results from Monte Carlo simulations testing for indirect effects of CSR on 3-Back EF outcomes (P300, RT, and Acc, respectively) with anxious arousal as a mediator.

Anxious Arousal Mediation Confidence Intervals Summary

Similarly, confidence intervals for all models testing daily self-reported anxious arousal symptoms as mediating the effects of CSR on EF contained zero. This indicates that the daily anxious arousal symptoms do not mediate the effect of CSR on EF.

95% Confidence Intervals for the Total Indirect Effect CSR on EF outcomes with **Anxious Arousal** as a Mediator

Model Outcome	*LL*	*UL*
0-Back		
P300	-0.08695	0.07005
Reaction Time	-0.8886	1.102
Accuracy	-0.002672	0.00206
2-Back		
P300	-0.08348	0.06514
Reaction Time	-2.982	3.785
Accuracy	-0.00258	0.002044
3-Back		
P300	-0.1008	0.07813
Reaction Time	-2.226	2.841
Accuracy	-0.002663	0.00204

Table 7. A table depicting results of the Monte Carlo Simulation for assessing the mediation of stress in the relationship between CSR and measures of EF, providing the lower and upper bounds of the 95% confidence interval of the estimated mediation effect.

Discussion

This work aimed to evaluate if daily symptoms – specifically, daily self-reported stress and anxious arousal – mediated the effects of CSR on EF. It was hypothesized that this would be the case.

To evaluate this, Monte Carlo simulations as described by Selig and Preacher tested for indirect effects [128]. The first group of simulations tested for stress as a mediator, and the second tested for anxious arousal as a mediator. All nine EF outcomes were tested with each mediator, totaling 18 simulations. None showed any significant mediating effects of either daily stress or daily anxious arousal.

This finding was unexpected. Based on allostatic load literature, this work expected that the physiologic response to CSR would mediate the impact of CSR on EF. It was expected that the physiologic response to CSR, whether that response was via organizational or activational

effects on the nervous system and stress systems, would be measurable and reflected in daily self-reported symptoms. It is possible that daily symptoms better reflect, or are more strongly impacted by, factors that cannot be controlled for or anticipated – specifically the events of a given day – than nervous system structure. Thus, other measures might be better suited to comprehensively speak to the state of the nervous system. It might be possible that measures of trait or baseline anxiety and nervous system stress susceptibility would better reflect AL and nervous system changes, and thus may be better measures than daily symptoms to characterize what mediates the effects of CSR on EF.

It is also possible that CSR impacts EF through nervous system changes that are completely independent of daily stress and anxious arousal symptoms. It may be possible - though unlikely based on past work [130] - that CSR's impacts are primarily cognitive instead of affective, impacting more prefrontal and cortical structures as compared to midbrain, affective, and amygdalar structures. It is also possible not that these regions are differently affected, but that their connectivity may be altered. Or alternatively, DS may simply not be the best characterization of CSR's sensitization of the nervous system's stress response.

As mentioned above, it may also be that daily measures index variation that is sufficiently constrained temporally (from day to day) such that daily impacts on EF are small in comparison to something on the individual level, such as CSR. Put differently, an individual level characteristic or risk factor may have an influence on EF so large that day to day variation would be insufficient to mediate its effects. Claiming an individual level factor's effects are mediated by a day-to-day variable may be inherently limited.

Moving forward, there would be value in better characterizing allostatic load or the stress response, and then reassessing the proposed mediation model. Namely, daily symptoms may not

be the best representation of how an individual's nervous system adapts to and carries the allostatic load of CSR. Notably, allostatic load may also be a separate construct from DS and may both affect and be affected by DS. Instead, a monthly DS average might be a better predictor, or individual trait-level (as opposed to situational state-level, or symptom-based) assessments. Similarly, looking at monthly DS variability may speak to both the nervous system's responsivity or lack thereof and could provide valuable insight. Additional physiologic measures would undoubtedly be of value to characterize the state of an individual's nervous system and individual stress response: cortisol, heart rate, heart rate variability, and skin conductance would provide insight into HPA and SMA activity. Similarly, testing nervous system responsivity and flexibility outright with various stressor tasks, including cold pressor tasks and social stress paradigms while measuring the physiologic markers above would likely provide deeper insight and a more robust characterization of the nervous system than daily self-reported symptoms alone. Daily self-reported symptoms carry ecological and translational weight, while experimentally controlled variables might provide more mechanistic insight. Redefined with this better characterization, stress may well be found to mediate the relationship between CSR and EF. Put differently, allostatic load may still mediate the effects of CSR on EF, but the characterization of allostatic load would benefit from encompassing more than daily measures.

Additionally, McEwen mentions 4 types of physiologic responses that result from allostatic load that future work might benefit from exploring, seen in the diagram below [131]. Response heterogeneity may be seen in how individuals respond to CSR, leading to subgroups with varied DS and varied response to DS, making DS unreliable as mediators. Using a metric

that better characterizes a nervous system's stress response under more controlled conditions than a daily self-report could even offer the opportunity to identify these subgroups.

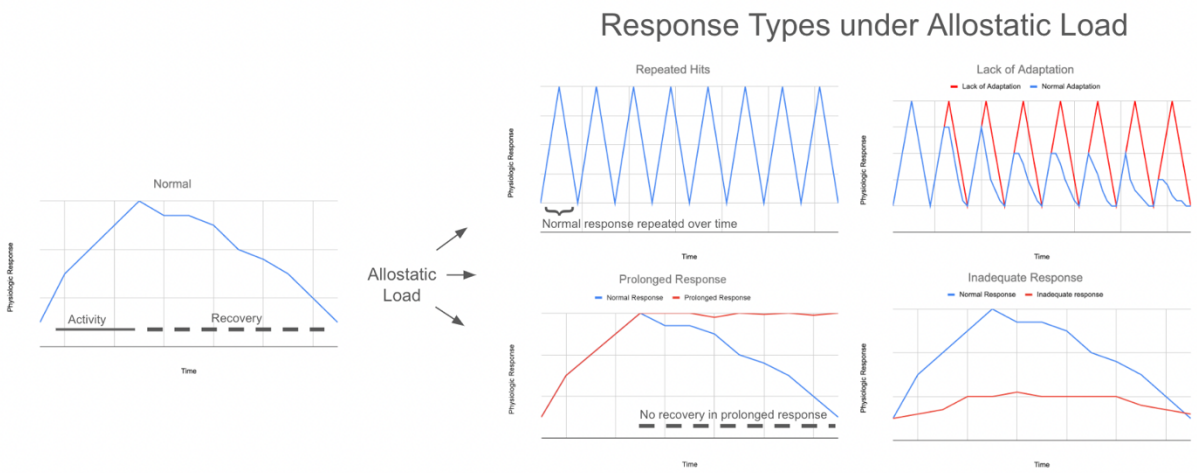

Figure 13. Adapted from McEwen, (2000), a depiction of four types of physiologic responses resulting from allostatic load, including: repeated normal response, lack of adaptation, prolonged response, and inadequate response [131].

Given that Aim 1 showed that DS had limited and differential effects on the reaction time component of EF and that CSR had no significant predictive effects on DS, it was not surprising that DS did not mediate the effects of CSR on EF in this dataset. All in all, though DS were not found to mediate the effects of CSR on EF, allostatic load, which DS was intended to partially index, DS may still be candidate mediators for CSR on EF. Future work exploring AL as mediating the relationship between CSR and EF would benefit from a more thorough characterization of AL.

CHAPTER 5: AIM 3: PROGESTERONE MODERATING ASSOCIATIONS BETWEEN RISK, DAILY SYMPTOMS, AND EXECUTIVE FUNCTION

Finally, this work evaluated the role of progesterone as a moderator in the relationships between sociodemographic risk, stress, and executive function given the differences in stress susceptibility between sexes and the close relationship between progesterone and cortisol.

Analytic Method

In order to evaluate if progesterone moderates the direct effects between CSR, DS, and EF, multilevel main effects and interaction models were utilized. Specifically, for each of the previous univariate models evaluated in Aim 1, first progesterone was added as a covariate, resulting in a bivariate main effects model. Then, an interaction variable including progesterone was added to evaluate for any interaction progesterone may have with the original predictors up and above each of their main effects. This was done for each direct relationship tested in Aim 1: a) CSR's effects on EF, b) CSR's effects on DS, and c) DS's effects on EF.

a) CSR on EF

First, models explored how and if progesterone impacts the strength of the relationship between sociodemographic risk and measures of executive function. Based on literature, it was hypothesized that when progesterone is increased, high sociodemographic risk would be more strongly associated with decreased measures of executive function (decreased P300, increased reaction time, and decreased accuracy) across all trial types (0, 2, and 3-Back). To evaluate this, eighteen models were run. First, a main effects model structure that accounted for progesterone as its own predictive covariate alongside CSR was run for all nine EF outcome measures.

First, a bivariate model was run, seen below:

$$CSRSum\_C + Pro\_C \rightarrow EF$$

This model structure evaluates the predictive effects of both CSR and progesterone on EF when both CSR and progesterone (Pro) are included and accounted for in the same model. This illustrates the effects of CSR on EF with progesterone held constant, and the effects of progesterone on EF with CSR held constant.

Subsequently, an interaction term was added to the models to see if the interaction between CSR and progesterone predicts any of the EF measures.

$$CSRSum\_C + Pro\_C + CSRSum\_C * Pro\_C \rightarrow EF$$

This model structure allows testing for the predictive effects of the interaction between the two predictors, while holding constant the main direct and independent effects of the predictors. This allows one to test for moderation by seeing if there is a significant interaction effect between the predictors on the outcome. If so, a simple slopes analysis is conducted to follow up on and characterize the significant interaction.

b) CSR on DS

Next, this work explored how and if progesterone impacts the strength of the relationship between sociodemographic risk and daily measures of stress and anxious arousal. This builds on aim 1b by running 2 additional models based on the CSR predicting daily stress model, as well as 2 additional models based on the CSR predicting anxious arousal model. Main effects models

added in progesterone as a main effect covariate predictor to both the stress predicting EF model as well as the anxious arousal predicting EF model. Interaction models then added in an interaction CSR by progesterone variable as a covariate predictor. This came to 4 models total, with a main effects model using CSR and progesterone as covariate predictors of daily stress and daily anxious arousal, and interaction models that include a CSR by progesterone interaction term predicting daily stress and anxious arousal.

First, stress as an outcome was evaluated. The two models that were run predicting daily stress as an outcome included a main effects model and an interaction model. Both models use CSR and progesterone as predictors, with the latter including an interaction of CSR by progesterone.

To assess how and if progesterone moderates the effects of CSR on daily self-reported stress, a model of CSR predicting daily stress while accounting for progesterone was run, represented by the equation below:

$$CSRSum\_C + Proc\_C \rightarrow Stress$$

This model evaluates the predictive effects of both CSR and progesterone on EF when both CSR and progesterone are included and accounted for in the same model.

Next, an interaction model was run, represented below:

$$CSRSUM\_C + Pro\_C + CSRSum\_C * Pro\_C \rightarrow Stress$$

This model evaluates if the interaction between CSR and progesterone significantly predicts stress, while accounting for both CSR's and progesterone's main direct and independent effects on stress.

Next, anxious arousal was evaluated as an outcome. Similar to the model structures predicting stress, in order to evaluate progesterone as moderating the effects of CSR on daily self-reported anxious arousal symptoms, a model of CSR predicting anxious arousal while accounting for progesterone was run. This model evaluates the independent main effects of progesterone and CSR on anxious arousal. It is represented by the equation below:

$$CSRSum\_C + Pro\_C \rightarrow ANXAROUS$$

Just as in the case of stress as an outcome, a subsequent interaction model was run including a CSR by progesterone interaction term. This was used to assess if an interaction between CSR and progesterone predicts any anxious arousal symptoms while accounting for CSR's and progesterone's independent main effects. It is represented in the equation below:

$$CSRSum\_C + Pro\_C + CSRSum\_C * Pro\_C \rightarrow ANXAROUS$$

c) DS on EF

Lastly, the effects of DS on EF were evaluated. This built on aim 1c by running two additional types of models on all the stress predicting EF models, as well as the anxious arousal predicting EF models. The two additional types of models included a main effects model and an interaction model. The main effects models add in progesterone as a main effect covariate

predictor, and the interaction models add in an interaction variable: stress by progesterone and anxious arousal by progesterone, respectively. This came to 36 models total.

Models evaluating stress as a predictor included a main effects model structure evaluating for all 9 executive function measures (P300, reaction time, and accuracy at 0-, 2-, and 3-Back trial types) adding progesterone in as a covariate. This evaluates the independent main effects of daily stress and progesterone on our executive function measures. The model can be seen represented below:

$$Stress\_C + Pro\_C \rightarrow EF$$

Next, a stress by progesterone interaction term was added to the main effects models for all 9 executive function measures (P300, reaction time, and accuracy at 0-, 2-, and 3-Back trial types). This model evaluated if the interaction between stress and progesterone predicts any executive function measures up and above the independent main effects of daily stress and progesterone. The model can be seen represented below:

$$Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow EF$$

The same was done for anxious arousal as a predictor.

To begin assessing for the moderating effects of progesterone on the association between anxious arousal and the nine measures of executive function, main effects models adding progesterone in as a covariate were run, represented below.

$$ANXAROUS\_C + Pro\_C \rightarrow EF$$

Next, an anxious arousal by progesterone interaction term was added to the model, to evaluate if the interaction between anxious arousal and progesterone predict any measures of executive function up and above the main effects of either anxious arousal or progesterone. The model is represented below:

$$ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow EF$$

Results

a) CSR on EF

Results from models evaluating the main and independent effects of CSR and progesterone on EF can be seen in Table 9, below.

For this first model, where CSR and Progesterone independently predict EF results show that at low working memory load (0-Back), CSR significantly predicted a decrease in the P300 (B = -1.607, p < .001), and an increase in reaction time (B = 14.704, p = 0.025); while progesterone significantly predicted a small but significant decrease in the P300 (B = -0.003, p = 0.022). CSR had no significant effect on accuracy at 0-Back (p = .421), and progesterone did not significantly predict either reaction time or accuracy at 0-back, with p-values of .334 and .3, respectively.

At medium working memory load (2-Back), CSR significantly predicted changes in EF across all EF measures – electrophysiological (P300, B = -0.853, p = .014) and behavioral (reaction time and accuracy, B = 28.723, p = .006 and B = -.054, p <.001, respectively). All of these relationships were similar to when CSR was assessed as the only predictor. Specifically, in the bivariate model accounting for progesterone, a one unit increase in CSR predicted a .853 μV

decrease in the P300, a 28.723 ms increase in reaction time, and a 5.4% decrease in accuracy. In contrast, progesterone did not have any significant predictive effects on any of our EF measures at 2-Back (p = 0.584, 0.905, 0.285 for P300, RT, and Acc, respectively).

At high working memory load (3-back), a one unit increase in CSR significantly predicted a .998 μV decrease in the P300 amplitude (p = .004), and a 4.2% decrease in accuracy (p = .009). In this bivariate model holding progesterone constant, CSR's impact on reaction time under high load (3-Back) trials approached but did not reach significance (B = 22.362, p = .067). Progesterone predicted a small but statistically significant .003μV decrease in the P300 (p = .04). Progesterone did not significantly predict either reaction time or accuracy during 3-Back trials (p = 0.903 and p = .633, respectively).

In sum, these results for CSR predicting EF mimic the results seen in aim 1a, where CSR predicted EF. Adding progesterone into this model as a covariate tested for the effects of progesterone holding the effects of CSR on EF constant, and vice versa: testing for the effects of CSR holding progesterone constant. Put differently, this method tests for the main direct and independent effects of each predictor (termed covariate) on the outcome. Results indicated very small but significant predictive effects of progesterone on executive function only for the P300 at 0-Back and 3-Back (low and high working memory load) trial types, and at no other measures of executive function at any other trial type.

Aim 3A. Main Effects Model with **CSR and Progesterone (n = 130)** as Predictors of Measures of Executive Function ($CSR + Prog. \rightarrow EF$)

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
0-Back					
P300 (μV)					
from CSR	**-1.601**	**0.415**	**< 0.001**	8.932	0.645
from Prog.	**-0.003**	**0.001**	**0.022**	8.932	0.645
Reaction Time (ms)					
from CSR	**14.704**	**6.477**	**0.025**	500.238	5.381
from Prog.	0.016	0.017	0.334	500.238	5.381
Accuracy (prop.)					
from CSR	-0.009	0.011	0.421	0.897	0.009
from Prog.	-3.24 E-5	3.13 E-5	0.300	0.897	0.009
2-Back					
P300 (μV)					
from CSR	**-0.853**	**0.344**	**0.014**	6.526	0.286
from Prog.	-0.001	0.001	0.560	6.526	0.286
Reaction Time (ms)					
from CSR	**28.723**	**10.324**	**0.006**	621.290	8.581
from Prog.	0.004	0.037	0.906	621.290	8.581
Accuracy (prop.)					
from CSR	**-0.054**	**0.016**	**< 0.001**	0.783	0.013
from Prog.	-6.17 E-5	5.37 E-5	0.251	0.783	0.013
3-Back					
P300 (μV)					
from CSR	**-0.998**	**0.340**	**0.004**	5.377	0.284
from Prog.	**-0.003**	**0.001**	**0.040**	5.377	0.284
Reaction Time (ms)					
from CSR	22.362	12.100	0.067	662.598	10.054
from Prog.	0.005	0.038	0.903	662.598	10.054
Accuracy (prop.)					
from CSR	**-0.042**	**0.016**	**0.009**	0.650	0.013
from Prog.	2.48 E-5	5.20 E-5	0.633	0.650	0.013

Table 8. A table depicting results from the multilevel model using CSR and progesterone both as predictors of measures of EF. Significant results are bolded.

For the model where CSR, Progesterone, and the interaction between CSR and progesterone predict EF results indicated that the same relationships observed in the main effects model remained: controlling for progesterone, CSR continued to predict 0-back P300 and RT (*B*

= -1.606, p = <.001; B = 14.838, p = 0.024, respectively); 2 back P300, RT, and accuracy (B = -.863, p = 0.014; B = 28.706, p = 0.006; B = -.055, p = <.001, respectively), and 3-back P300 and accuracy (B = -.974, p = .005; B = -.042, p = .009, respectively). Controlling for CSR, progesterone significantly predicted reduced P300 amplitudes at 0- and 3- back (B = -.003, p = .022; B = -.003, p = .033, respectively).

The interaction of CSR and progesterone did not predict any of the EF outcomes, contrary to hypotheses. The effect of the interaction term did not reach significance for any EF measure.

Aim 3A. Interaction Model with **CSR, Progesterone, and CSR*Progesterone Interaction (n = 130)** as Predictors of Measures of Executive Function ($CSR + Prog. + CSR * Prog. \rightarrow EF$)

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
0-Back					
P300 (μV)					
from CSR	**-1.606**	**0.416**	**< 0.001**	8.932	0.345
from Prog.	**-0.003**	**0.001**	**0.022**		
from CSR*Prog.	-6.17 E-5	0.001	0.964		
Reaction Time (ms)					
from CSR	**14.838**	**6.493**	**0.024**	500.166	5.389
from Prog.	0.016	0.017	0.350		
from CSR*Prog.	-0.007	0.018	0.703		
Accuracy (prop.)					
from CSR	-0.008	0.011	0.434	0.897	0.009
from Prog.	-3.33 E-5	3.14 E-5	0.289		
from CSR*Prog.	-1.17 E-5	3.47 E-5	0.737		
2-Back					
P300 (μV)					
from CSR	**-0.863**	**0.346**	**0.014**	6.534	0.287
from Prog.	-0.001	0.001	0.584		
from CSR*Prog.	0.001	0.002	0.734		
Reaction Time (ms)					
from CSR	**28.706**	**10.358**	**0.006**	621.297	8.596
from Prog.	0.004	0.037	0.905		
from CSR*Prog.	0.001	0.041	0.983		
Accuracy (prop.)					
from CSR	**-0.055**	**0.016**	**< 0.001**	0.783	0.013
from Prog.	-5.78 E-5	5.39 E-5	0.285		
from CSR*Prog.	4.64 E-5	5.97 E-6	0.438		
3-Back					
P300 (μV)					
from CSR	**-0.974**	**0.343**	**0.005**	5.366	0.285
from Prog.	**-0.003**	**0.001**	**0.033**		
from CSR*Prog.	-0.001	0.002	0.435		
Reaction Time (ms)					
from CSR	22.077	12.139	0.071	662.749	10.074
from Prog.	0.006	0.038	0.879		
from CSR*Prog.	0.015	0.042	0.721		
Accuracy (prop.)					
from CSR	**-0.042**	**0.06**	**0.009**	0.650	0.013
from Prog.	2.59 E-5	5.23 E-5	0.620		
from CSR*Prog.	1.33 E-5	5.78 E-5	0.818		

Table 9. A table depicting results from the multilevel model using CSR, progesterone, and the interaction of CSR and progesterone as predictors of measures of EF. Significant results are bolded.

b) CSR on DS

As can be seen in the two tables below, results from both the main effects and interaction models predicting daily stress showed no significant results. However, though results from the main effects predicting anxious arousal showed no significant effect of CSR on daily anxious arousal symptoms, a small significant effect of progesterone on anxious arousal (B = -0.008, p < .001) was observed. This indicates that for every one unit increase in progesterone, a .008 point increase in self-reported daily anxious arousal symptoms can be expected. Results from the interaction model similarly showed no effect of CSR on anxious arousal, but a small significant effect of progesterone on anxious arousal (B = -0.007, p < .001), and no significant effect of the interaction between CSR and progesterone on anxious arousal (p = 0.484).

Aim 3B. Main Effects Model with **CSR and Progesterone** as Predictors of Measures of Daily Stress ($CSR + Prog. \rightarrow DS$)

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
Stress (n = 101)					
from CSR	-0.184	0.164	0.265	3.446	0.19
from Prog.	0.000	0.001	0.652	3.446	0.19
Anxious Arousal (n = 130)					
from CSR	-0.296	0.739	0.689	25.468	0.614
from Prog.	**-0.008**	**0.002**	**< 0.001**	25.468	0.614

Table 10. A table depicting results from the multilevel model using CSR and progesterone both as predictors of measures of daily stress. Significant results are bolded.

Aim 3B. Interaction Model with **CSR, Progesterone, and CSR*Progesterone Interaction** as Predictors of Daily Stress ($CSR + Prog. + CSR * Prog. \rightarrow DS$)

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
Stress (n = 101)					
from CSR	-0.201	0.163	0.220	3.449	0.127
from Prog.	0.000	0.001	0.681	3.449	0.127
from CSR*Prog.	0.001	0.001	0.189	3.449	0.127
Anxious Arousal (n = 130)					
from CSR	-0.328	0.739	0.658	25.484	0.613
from Prog.	**-0.007**	**0.002**	**< 0.001**	25.484	0.613
from CSR*Prog.	0.002	0.002	0.484	25.484	0.613

Table 11. A table depicting results from the multilevel model using CSR, progesterone, and the interaction of CSR and progesterone as predictors of measures of daily stress. Significant results are bolded.

c) DS on EF

Models were run to explore how and if progesterone impacts the strength of the relationships between daily measures of stress and anxious arousal with measures of executive function.

Results from models evaluating the main effects of stress and progesterone on EF revealed a significant effect of stress on reaction time at 0-Back (B = 3.622, p = .03). Notably, when holding progesterone constant, stress's effects on reaction time at 3-back no longer reached significance (B = 7.677, p = .055). Results also revealed a small but significant impact of progesterone on the P300 at 0-Back (B = -0.005, p = .039) and at 3-Back (B= -0.004, p = .05). All other findings were insignificant.

Aim 3C. Main Effects Model with **Stress and Progesterone (n = 111)** as Predictors of Measures of Executive Function ($Stress + Prog. \rightarrow EF$)

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
0-Back					
P300 (μV)					
from Stress	-0.120	0.198	0.544	9.238	0.410
from Prog.	**-0.005**	**0.002**	**0.039**	9.238	0.410
Reaction Time (ms)					
from Stress	**3.622**	**1.661**	**0.030**	498.100	6.001
from Prog.	0.005	0.020	0.788	498.100	6.001
Accuracy (prop.)					
from Stress	-0.001	0.003	0.760	0.892	0.011
from Prog.	-3.58 E-5	3.92 E-5	0.361	0.892	0.011
2-Back					
P300 (μV)					
from Stress	0.030	0.139	0.830	6.534	0.324
from Prog.	-0.003	0.002	0.097	6.534	0.324
Reaction Time (ms)					
from Stress	1.210	3.769	0.748	618.970	9.542
from Prog.	0.040	0.047	0.394	618.970	9.542
Accuracy (prop.)					
from Stress	0.000	0.006	0.936	0.780	0.015
from Prog.	-3.58 E-5	6.89 E-5	0.604	0.780	0.015
3-Back					
P300 (μV)					
from Stress	-0.215	0.152	0.160	5.373	0.309
from Prog.	**-00.004**	**0.002**	**0.050**	5.373	0.309
Reaction Time (ms)					
from Stress	7.677	3.989	0.055	660.833	10.853
from Prog.	0.045	0.049	0.361	660.833	10.853
Accuracy (prop.)					
from Stress	0.000	0.005	0.956	0.650	0.014
from Prog.	-4.96 E-6	6.40 E-5	0.938	0.650	0.014

Table 12. A table depicting results from the multilevel model using stress and progesterone both as predictors of measures of EF. Significant results are bolded.

Aim 3C. Interaction Model with **Stress, Progesterone, and Stress*Progesterone Interaction (n = 111)** as Predictors of Measures of Executive Function ($Stress + Prog. + Stress * Prog. \rightarrow EF$)

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
0-Back					
P300 (μV)					
from Stress	-0.120	0.198	0.544	9.238	0.411
from Prog.	**-0.005**	**0.003**	**0.041**	9.238	0.411
from Stress *Prog.	-3.68 E-5	0.001	0.980	9.238	0.411
Reaction Time (ms)					
from Stress	**3.622**	**1.663**	**0.030**	498.023	5.996
from Prog.	0.007	0.021	0.721	498.023	5.996
from Stress *Prog.	-0.009	0.012	0.456	498.023	5.996
Accuracy (prop.)					
from Stress	-0.001	0.003	0.756	0.891	0.011
from Prog.	-3.15 E-5	3.95 E-5	0.426	0.891	0.011
from Stress *Prog.	-2.09 E-5	2.27 E-5	0.358	0.891	0.011
2-Back					
P300 (μV)					
from Stress	0.028	0.139	0.840	6.525	0.325
from Prog.	-0.003	0.002	0.127	6.525	0.325
from Stress *Prog.	-0.001	0.001	0.288	6.525	0.325
Reaction Time (ms)					
from Stress	1.185	3.773	0.754	618.839	9.549
from Prog.	0.043	0.047	0.358	618.839	9.549
from Stress *Prog.	-0.017	0.027	0.529	618.839	9.549
Accuracy (prop.)					
from Stress	0.001	0.006	0.923	0.780	0.015
from Prog.	-5.03 E-5	6.91 E-5	0.467	0.780	0.015
from Stress *Prog.	7.20 E-5	3.99 E-5	0.072	0.780	0.015
3-Back					
P300 (μV)					
from Stress	-0.215	0.153	0.161	5.372	0.310
from Prog.	-0.004	0.002	0.052	5.372	0.310
from Stress *Prog.	-7.52 E-5	0.001	0.947	5.372	0.310
Reaction Time (ms)					
from Stress	7.720	3.988	0.054	661.066	10.891
from Prog.	0.039	0.050	0.430	661.066	10.891
from Stress *Prog.	0.028	0.029	0.324	661.066	10.891
Accuracy (prop.)					
from Stress	0.000	0.005	0.965	0.651	0.014
from Prog.	-1.53 E-5	6.44 E-5	0.813	0.651	0.014
from Stress *Prog.	5.06 E-5	3.71 E-5	0.174	0.651	0.014

Table 13. A table depicting results from the multilevel model using stress, progesterone, and the interaction of stress and progesterone as predictors of measures of EF. Significant results are bolded.

Aim 3C. Main Effects Model with **Anxious Arousal and Progesterone (n = 142)** as Predictors of Measures of Executive Function ($Anx.Ars + Prog. \rightarrow EF$)

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
0-Back					
P300 (μV)					
from Anx. Ars.	0.018	0.037	0.622	9.132	0.362
from Prog.	-0.003	0.002	0.121	9.132	0.362
Reaction Time (ms)					
from Anx. Ars.	-0.511	0.367	0.164	499.172	5.169
from Prog.	0.004	0.017	0.807	499.172	5.169
Accuracy (prop.)					
from Anx. Ars.	0.001	0.001	0.153	0.896	0.009
from Prog.	-1.48 E-5	3.06 E-5	0.630	0.896	0.009
2-Back					
P300 (μV)					
from Anx. Ars.	0.037	0.027	0.182	6.536	0.282
from Prog.	0.000	0.001	0.839	6.536	0.282
Reaction Time (ms)					
from Anx. Ars.	**-2.149**	**0.755**	**0.005**	619.566	8.481
from Prog.	-0.021	0.037	0.580	619.566	8.481
Accuracy (prop.)					
from Anx. Ars.	0.001	0.001	0.233	0.788	0.013
from Prog.	-3.98 E-5	5.46 E-5	0.467	0.788	0.013
3-Back					
P300 (μV)					
from Anx. Ars.	0.039	0.029	0.184	5.481	0.278
from Prog.	-0.002	0.002	0.154	5.481	0.278
Reaction Time (ms)					
from Anx. Ars.	-1.401	0.803	0.082	660.800	9.581
from Prog.	-0.012	0.039	0.763	660.800	9.581
Accuracy (prop.)					
from Anx. Ars.	0.001	0.001	0.346	0.658	0.013
from Prog.	-1.05 E-6	5.32 E-5	0.984	0.658	0.013

Table 14. A table depicting results from the multilevel model using anxious arousal and progesterone both as predictors of measures of EF. Significant results are bolded.

Aim 3C. Interaction Model with **Anxious Arousal, Progesterone, and Anx. Ars.*Progesterone Interaction ($n = 142$)** as Predictors of Measures of Executive Function ($Anx.Ars. + Prog. + Anx.Ars. * Prog. \rightarrow EF$)

Model Outcome	*Effect Size Unstandardized Coefficient*	*Effect Size Std. Error*	*Effect Size Significance (p)*	*Intercept*	*Intercept Std. Error*
0-Back					
P300 (μV)					
from Anx. Ars.	0.015	0.038	0.688	9.110	0.367
from Prog.	-0.003	0.002	0.120	9.110	0.367
from Anx. Ars.*Prog.	0.000	0.000	0.721	9.110	0.367
Reaction Time (ms)					
from Anx. Ars.	-0.627	0.376	0.096	498.413	5.204
from Prog.	-0.007	0.019	0.713	498.413	5.204
from Anx. Ars.*Prog.	-0.004	0.003	0.168	498.413	5.204
Accuracy (prop.)					
from Anx. Ars.	0.001	0.001	0.204	0.896	0.009
from Prog.	-2.27 E-5	3.38 E-5	0.502	0.896	0.009
from Anx. Ars.*Prog.	-2.60 E-6	4.70 E-6	0.581	0.896	0.009
2-Back					
P300 (μV)					
from Anx. Ars.	0.031	0.029	0.286	6.489	0.286
from Prog.	-0.001	0.002	0.539	6.489	0.286
from Anx. Ars.*Prog.	0.000	0.000	0.311	6.489	0.286
Reaction Time (ms)					
from Anx. Ars.	**-2.302**	**0.774**	**0.003**	618.445	8.585
from Prog.	-0.036	0.041	0.380	618.445	8.585
from Anx. Ars.*Prog.	-0.005	0.006	0.372	618.445	8.585
Accuracy (prop.)					
from Anx. Ars.	0.001	0.001	0.271	0.787	0.013
from Prog.	-4.68 E-5	6.03 E-5	0.438	0.787	0.013
from Anx. Ars.*Prog.	-2.33 E-6	8.42 E-6	0.782	0.787	0.013
3-Back					
P300 (μV)					
from Anx. Ars.	0.038	0.030	0.213	5.470	0.283
from Prog.	-0.002	0.002	0.167	5.470	0.283
from Anx. Ars.*Prog.	-5.30 E-5	0.000	0.827	5.470	0.283
Reaction Time (ms)					
from Anx. Ars.	-1.207	0.823	0.143	662.208	9.671
from Prog.	0.008	0.043	0.855	662.208	9.671
from Anx. Ars.*Prog.	0.006	0.006	0.282	662.208	9.671
Accuracy (prop.)					
from Anx. Ars.	0.001	0.001	0.392	0.658	0.013
from Prog.	-8.19 E-6	5.88 E-5	0.889	0.658	0.013
from Anx. Ars.*Prog.	-2.37 E-6	8.20 E-6	0.773	0.658	0.013

Table 15. A table depicting results from the multilevel model using anxious arousal, progesterone, and the interaction of anxious arousal and progesterone as predictors of measures of EF. Significant results are bolded.

Discussion

This work aimed to evaluate the effects of progesterone on the relationships between CSR, DS, and EF, hypothesizing that at high progesterone the strength of relationships would increase.

a) CSR on EF

First, progesterone's influence on the relationship between CSR and EF was evaluated.

Findings from the bivariate model testing for the independent and main effects of progesterone and CSR indicated that CSR negatively impacts EF at 0-Back P300 and reaction time; 2-back P300, RT, and accuracy, and 3-Back P300 and accuracy when controlling for progesterone. When controlling for CSR, progesterone was found to predict a reduction in P300 amplitude and 0- and 3-back. These results held constant when the interaction term was added, and results from that interaction model indicated that the interaction between progesterone and CSR did not predict any effects on EF. Had the interaction term significantly predicted any of the EF measures, a follow-up simple slopes analysis would have been conducted to determine how strength of the predictive effect of CSR on EF changes at high and low progesterone, or how the strength of the predictive effect of progesterone on our EF measures differs at high and low CSR.

These results are not consistent with the hypothesis that when progesterone is increased, high sociodemographic risk will be more strongly associated with decreased measures of executive function (decreased P300, increased reaction time, and decreased accuracy) across all trial types (0, 2, and 3-Back). Rather, there is no significant interaction between progesterone and CSR predicting EF, and progesterone has no effect on the strength of the association between CSR and EF. Instead, progesterone has its own small but significant and predictive main effect

on a subset of EF measures (P300 measures at low and high working memory load) when CSR is held constant.

b) CSR on DF

Next, progesterone's influence on the relationships between CSR and DS was evaluated. Bivariate main effects models predicting stress and anxious arousal indicated that CSR had no predictive effects on either DS when progesterone was held constant, and that progesterone had no effect on stress with CSR held constant. However, progesterone had a small significant effect on anxious arousal. This effect was such that, with CSR held constant, higher progesterone predicts a decrease in anxious arousal symptoms. Interaction models indicated no effects of the interaction between progesterone and CSR on either DS.

Overall, contrary to hypotheses, these results indicate that progesterone did not moderate the effects of CSR on either daily self-reported stress or anxious arousal symptoms. Instead, progesterone had its own small but significant independent effect on anxious arousal symptoms. This effect was negative, meaning that an increase in progesterone predicted a decrease in anxious arousal symptoms, which is in the opposite direction of expectations.

c) DS on EF

It was hypothesized that when progesterone is increased, increased measures of DS would be more strongly associated with decreased measures of executive function. It was predicted that the interaction variable would be significant, and that a follow up simple slopes analysis would reveal a stronger reduction in EF (greater reduction in P300 amplitude, greater increase in reaction time, and greater reduction in accuracy across all trials) at higher levels of progesterone.

Adding progesterone as a covariate with stress revealed a small but significant independent effect of progesterone on the P300 at 0-back, but not 2 or 3-Back. This indicates that

while holding stress constant, increased progesterone will predict a reduced P300 at low working memory load. Results from this same model showed that holding progesterone constant, higher stress predicts increased reaction time at 0-back, with no other significant impacts on the other EF measures. In this model, progesterone also did not significantly predict any other EF measure aside from P300 at 0-back. Namely, it had no effect on behavioral EF measures reaction time or accuracy at any trial type. The interaction model showed no significant impact of the interaction between progesterone and stress on EF, suggesting that their effects on EF do not moderate one another.

Similar to hypotheses with stress as a predictor, this work hypothesized that when progesterone is increased, increased anxious arousal will more strongly predict decreased P300, increased reaction time, decreased accuracy, across all trial types (0, 2, and 3-Back).

Instead, no effects of progesterone were seen – as a covariate or an interaction term - in both the bivariate main effects or interaction model. This indicates that at constant anxious arousal, progesterone has no effects on EF, nor does the interaction of progesterone with anxious arousal have any effects on EF. However, when holding progesterone constant, increased anxious arousal was found to predict decreased (faster) reaction time at 2-back. This finding was contrary to expectations given literature on the impact of anxiety on EF. However, it is consistent with work that parsed anxious arousal apart from other components of anxiety and found increased reaction time during a working memory task [132].

Summary

As a covariate in models with either CSR or stress, high progesterone significantly predicted small reductions in the P300 at 0- and 3- back. However, as a covariate with anxious arousal, these effects were no longer significant (p = .120 at 0-back and p= .213 at 3-back). This

indicates that at constant anxious arousal, progesterone does not predict these components of EF. Meanwhile, progesterone does predict these components when CSR is held constant, as well as when stress is held constant. These findings of progesterone predicting EF when CSR is held constant and when stress is held constant but not when anxious arousal is held constant warrants further evaluation.

Additionally, the finding that progesterone independently predicts a reduction in anxious arousal when controlling for CSR was surprising. This finding was particularly surprising given that high progesterone predicted a small decrease in anxious arousal symptoms. Though expectations were in the opposite direction and would have been supported by progesterone's reported anxiogenic effects, these results might be attributed to the anxiolytic effects of progesterone's metabolites, namely allopregnanolone [133]. Future work might consider a univariate analysis of the predictive effects of progesterone on anxious arousal symptoms, as well as assaying for progesterone's metabolites.

Contrary to hypotheses and expectations, progesterone did not act as a moderator for any of the associations between CSR, Stress and Anxious Arousal, and Executive Function. It did however demonstrate its own small main direct effects as a covariate in models of the effects of CSR on EF, the effects of CSR on Anxious Arousal, and the effects of Stress on EF. It did not show any effect as a covariate in models of the relationship between Anxious Arousal and EF, and CSR and Stress. These results offer preliminary findings to warrant further exploration and better characterization of progesterone's impacts on EF and anxious arousal, both independently and in the context of other factors like CSR and Stress.

Given the ubiquity of contraceptive use in reproductive age female individuals as well as the steep increase of progesterone during pregnancy, continued evaluation of progesterone's role in the female stress system would be beneficial.

CHAPTER 6: GENERAL DISCUSSION

Overall, this work aimed to evaluate how cumulative sociodemographic risk (CSR) impacts executive function in females. The tested hypotheses were as follows: (1) a) increased CSR would decrease EF, b) increased CSR would increase measures of daily stress and anxious arousal, and c) increased measures of daily stress and anxious arousal would predict decreased EF; (2) that daily measures of stress and anxious arousal mediate the relationship between CSR and EF; and (3) that progesterone moderates all the direct relationships between CSR, daily stress and anxious arousal, and EF, such that higher progesterone levels would strengthen those relationships.

Neither the mediation nor moderation components of the overarching framework were supported, though some of the direct associations between CSR, DS, and EF were, with additional main effects findings for progesterone as a predictor.

High CSR was found to decrease measures of EF. Contrary to expectations, CSR did not significantly impact daily measures of self-reported stress or anxious arousal. Consistent with hypotheses, increased daily self-reported stress increased reaction time at low and high working memory loads but impacted no other EF measures. Not consistent with expectations, increased daily self-reported anxious arousal significantly predicted decreased (faster) reaction time at medium working memory loads, with no other effects on other EF measures. Neither daily stress nor anxious arousal were found to mediate the effects of CSR on EF. And contrary to hypotheses progesterone was not found to moderate any of the relationships between CSR, daily self-reported stress and anxious arousal, and EF. Instead, progesterone was found to have small but significant independent main effects on EF when included as a covariate in models predicting EF from CSR and predicting EF from daily stress, as well as a small significant effect reducing daily

anxious arousal when included as a covariate with CSR. Its effect as a covariate did not reach significance in bivariate models with anxious arousal predicting EF, and with CSR predicting Stress.

Findings in line with hypotheses included CSR's negative impact on EF measures and daily stress predicting increased RT. Data that disproved hypotheses included MLM results indicating no predictive effect of CSR on either daily stress or anxious arousal, Monte Carlo simulations showing no indirect mediating effects via either daily stress or anxious arousal measures of CSR's effects on EF, and MLM main effects and interaction models demonstrating no moderating effects of progesterone on any of the direct effects between CSR, daily stress and anxious arousal, and EF. Finally, findings contrary to hypothesis include the significant effects of anxious arousal on EF, where RT was reduced (sped up) during medium working memory load trials.

Though it was hypothesized that progesterone would have numerous interaction effects with CSR, DS, anxious arousal, and EF when predicting outcomes such as anxious arousal and EF, progesterone only had small main effects when tested as a covariate. Specifically, when tested as a covariate with CSR predicting EF, increased progesterone had a small negative effect on P300 amplitude at 0- and 3- back (low and high working memory load, $B = -0.003$; $p = 0.022$ and $B = -0.003$, $p = 0.040$, respectively). When tested as a covariate with daily stress predicting EF, increased progesterone similarly predicted decreased P300 amplitude at 0- and 3- back. And surprisingly, when tested as a covariate with CSR predicting anxious arousal, increased progesterone predicted a small but significant decrease in daily self-reported anxious arousal symptoms ($B = -0.008$; $p = <.001$). Interestingly, in models predicting EF from anxious arousal and progesterone, progesterone's effects on the P300 at 0- and 3-Back did not reach significance,

which can be interpreted that when anxious arousal is held constant, progesterone's effects on the P300 no longer reach significance. And lastly, progesterone also did not show any significant main effects as a covariate in models predicting stress from CSR.

Interpretations of findings are addressed below.

a) CSR on EF

Across the study, this work evaluated the effects of CSR on EF, both independently and contextualized by progesterone. It was hypothesized that high CSR would negatively impact EF measures, and that these effects would be moderated by progesterone such that at high progesterone, the effects of CSR on EF would be greater.

Results from these models showed that as CSR increases, a decrease in EF measures can be expected. These findings show that as the number of sociodemographic risk factors a given person has increases, their executive function will likely decrease. This is consistent with past literature suggesting that the impact of chronic stressors is cumulative [15], [134]. Given that EF is a suite of cognitive skills that are necessary for navigating and managing daily life, and that EF deficits have been associated with decreased overall quality of life [53], these results emphasize the role sociodemographic risk factors have as they aggregate and confirm that their effects on EF are in fact cumulative, with deleterious impacts on daily function.

Bivariate modeling looking at CSR and Progesterone's impacts on EF revealed that CSR negatively affects EF when progesterone is held constant, and that progesterone was associated with decreased electrophysiologic EF measures (the P300) when CSR was held constant. As above, CSR's effects on EF are consistent with literature suggesting that the functional impact of stressors is cumulative. This work shows that this relationship holds at constant levels of progesterone. Given past work implicating the involvement of the temporal lobe in the

generation of the P300 ERP [78], [135], and the amplitude of the P300 being associated with increased attention [136], [137], increased progesterone predicting a decreased P300 amplitude suggests that at higher progesterone levels, there may be effects seen in the temporal lobe and in attention. Interestingly, per Taylor, progesterone was observed to alter medial temporal lobe volume across the menstrual cycle [138]. Progesterone increased medial temporal lobe volume, while in the present study, progesterone decreased the P300 amplitude. More work will be needed to determine whether there is a relationship between P300 amplitude and medial temporal lobe size specifically in the context of progesterone.

Work by Leeners, et. al. demonstrates that associations between progesterone, attention, and working memory did not replicate across menstrual cycles, and suggests interpreting positive findings with caution [139]. Given this, this work's findings in the context of running multiple analyses should be interpreted with the caution suggested.

Additionally, in Arelin, progesterone was found to increase functional connectivity in areas associated with contextual memory regulation– specifically the hippocampus, dorsolateral PFC, and bilateral sensorimotor cortex [140]. This might lead one to expect a higher P300 amplitude at high progesterone, which is contrary to this work's findings.

Lastly, cumulative sociodemographic risk is associated with increased allostatic load and cortisol levels, as well as decreased executive function. Cortisol and progesterone are secreted in tandem. This served as the basis used to hypothesize that high progesterone would moderate the relationship between CSR and EF, where the negative effects of CSR on EF would be greater at higher levels of progesterone. However, this study's results showed null findings for the interaction between CSR and progesterone on EF. However, the results showing that higher progesterone decreases electrophysiologic measures of EF while CSR is constant suggests that

progesterone may have a small negative effect on executive function at the electrophysiologic level, specifically up and above any of the negative effects of CSR on EF.

Given that progesterone fluctuates across the menstrual cycle and that there are natural variations in progesterone levels across individuals, especially including those on oral contraceptives, more work is needed to home in on how progesterone might play into EF in community contexts given that EF is so fundamental to daily function.

Lastly, when interpreting these findings, it is important to note that the CSR composite score has inherent limitations. First, it only takes into account race, CSES, and trauma. A more thorough investigation of other factors would be desirable. Second, by creating a binary score for each variable, variance and nuance is lost. Third, this strategy frames factors as providing an equal additional amount of risk, which may not be the case. Even so, this strategy does characterize the aggregation of risk while being easily clinically applicable. Though limited, its value is affirmed by the significance of its impacts on EF. The use of risk scores is common clinically, and it is exciting to see this one have predictive value. Follow up work might benefit from including additional factors that have known impacts on EF such as subjective CSES, caregiver education, or metrics of childhood neglect.

b) CSR on DS

Between Aims 1b and 3b, this study also aimed to determine if CSR impacts DS, and to determine if progesterone moderates the strength of that impact. DS as an outcome included both daily self-reported stress as an outcome, and daily self-reported symptoms of anxious arousal as an outcome. These were tested as separate outcomes.

Results from the univariate models evaluating CSR's impact on DS showed that CSR does not predict either daily symptoms of self-reported stress, nor daily self-reported symptoms

of anxious arousal. This finding suggests that regardless of the number of sociodemographic risk factors an individual may have, this does not increase the likelihood of that individual predictably reporting either increased or decreased daily stress level nor symptoms of anxious arousal. This can also be interpreted as reported daily symptoms of stress and anxious arousal are not attributable to CSR levels in this sample.

This is not consistent with hypotheses or expectations. Past literature supports the connection between past stressors, traumatic events, and racism as risk factors for anxiety and daily life stress [141]–[149]. It also supports the accumulation of stressors as leading to greater negative outcomes and symptoms [150], which would be consistent with the proposed mechanistic basis of this work's hypothesis: that the accumulation of sociodemographic risk factors gradually increases allostatic load, which predisposes the nervous system to higher stress sensitivity and reactivity, and thus increased daily symptoms of stress and anxious arousal. Given that various sociodemographic risk factors have been associated with daily affective symptoms and cortisol levels [130], [151], [152] and that early life stress has been shown to sensitize central nervous system circuits involved in the regulation of emotion, stress, and anxious response to novel stimuli [42], [153], [154], it was expected that high CSR would predict both an increase in daily stress and anxious arousal symptoms. More work unpacking these relationships is warranted given inconsistent findings.

Though findings were contrary to expectations, it is both possible and probable that daily self-reported symptom measures may be insufficient to characterize the effects of CSR on the nervous system. Daily self-reported symptoms may not be the most reliable measure of increased stress reactivity and nervous system sensitization. These measures are inherently influenced by factors that cannot be controlled. Namely, a given individual's activities and

experiences on any given day cannot be controlled for and may serve as unknown precipitating factors for the self-reported symptoms. It is possible that these uncontrolled-for influences may have a greater influence on reported symptoms than CSR. These findings echo the results of similar work evaluating associations between childhood trauma, daily stress, and cortisol levels, where childhood trauma was associated with altered cortisol profiles, but not daily stress, and daily stress was not associated with cortisol levels [151].

It's possible that a monthly symptom average would better characterize an individual's nervous system's tendency toward stress or anxious arousal, and that this monthly average and improved characterization might be more directly related to the cost of adapting to CSR. Evaluating symptom variability over that same timespan might index nervous system responsiveness and reactivity.

To better contextualize the daily symptoms, the addition of autonomic and health outcome measures like vagal tone, skin conductance, heart rate, blood pressure, and heart rate variability should be considered. Heart rate variability is used to index cardiac vagal tone, and vagal tone has been considered a physiologic marker of both stress and stress vulnerability [155]–[160]. Measuring cortisol would directly index HPA activity and types of dysregulation. These metrics would provide physiologic insight in addition to symptoms.

As was the case with self-reported symptoms, a monthly average may be more telling of the individual's overall state compared to daily measures. However, daily measures have the benefit of indexing both daily experience and response to said experience and can provide the opportunity to conduct within in addition to between person analyses.

Progesterone's impact on the relationships between CSR and DS was also evaluated. These models indicated that CSR had no predictive effects on either daily stress or anxious

arousal symptoms when progesterone was held constant, and that progesterone had no effect on stress with CSR held constant. These findings are consistent with the univariate model findings that indicated that CSR does not predict either daily symptoms of stress or anxious arousal and shows that CSR's lack of effect on DS holds when progesterone is controlled for.

Progesterone lacking any predictive effect on daily stress when CSR is controlled suggests that variations in progesterone do not impact daily stress levels when the potential effects of CSR are accounted for. Data from this sample provide support for deprioritizing the role of these specific predictors in contributing to daily stress.

Similar to these findings, in work investigating the impact of childhood trauma on stress-responsive systems using an ambulatory assessment of depressed, healthy, and somatic symptom disorder patients, multilevel models indicated that childhood trauma was not associated with higher self-reported daily stress levels in any group [161].

As described in [162] proposed transdisciplinary model of stress, cumulative stressors (measured in this work as CSR), shape habitual processes that influence both psychological and physiological responses to daily stressors. While the daily perceived stress self report was intended to capture the psychological response to daily stressors, it is possible that the daily stress measure self-report was a more accurate measure of daily stressors, as opposed to indexing the stress response itself. If this were the case, daily stressors would be better conceptualized as an independent variable rather than a dependent outcome predicted or influenced by sensitization due to CSR.

Progesterone's lack of association with daily stress might be similarly accounted for: the daily stress measure might act more like an index of daily stressors as opposed to the response that they elicit. While progesterone's previously observed direct correlation with cortisol was

proposed as justification for progesterone's association with stress-related systems, this association may not generalize onto daily self-reported stress.

However, this may not be the case for measures of daily symptoms of anxious arousal. Results showed that progesterone had a small significant effect on anxious arousal when CSR was held constant. This effect was such that, with CSR held constant, higher progesterone predicts a decrease in anxious arousal symptoms.

This finding is contrary to hypotheses, which focused on the expected tandem rise in cortisol and progesterone, with the prediction that higher cortisol would lead to greater sympathetic arousal [163] and thus a higher anxious arousal symptom score. However, additional literature supports these findings.

Though progesterone gets converted to cortisol under stress [164], progesterone has other metabolites with anxiolytic properties [165]. Namely, allopregnenolone has been shown to have biphasic effects at the GABA receptor, where at lower levels it can have anxiogenic effects, while at higher levels it demonstrates anxyolytic effects attributed to positive modulation of the GABA receptor in the form of neural potentiation of GABAergic neurons and downregulation of amygdalar activity [166]–[171]. Given this, the results showing that increased progesterone is associated with a decrease in anxious arousal symptoms may be mediated through the effects of allopregenolone via GABA receptors and provide support for progesterone's anxyolytic effects. It is possible that there may be individual variation within this work's sample in progesterone sensitivity, and future work might break the group up by variables that have been shown to impact progesterone sensitivity, such as environmental factors including childhood stress and maltreatment, genetics, or DSM symptom criteria for premenstrual dysphoric disorder [164], [172].

Contrary to hypotheses, interaction models indicated no effects of the interaction between progesterone and CSR on either DS. This indicates that there is, per the models, no effect on either daily self reported stress or anxious arousal symptoms that can be attributed to an interaction between CSR and progesterone.

Overall, contrary to hypotheses, these results indicate that progesterone did not moderate the effects of CSR on either daily self-reported stress or anxious arousal symptoms. Instead, progesterone had its own small but significant independent effect on anxious arousal symptoms. This effect was negative, meaning that an increase in progesterone predicted a decrease in anxious arousal symptoms, which is in the opposite direction of expectations, but is an effect that can be explained and is supported by literature.

c) DS on EF

The last relationship this work aimed to better characterize was the relationship between DS including self-reported stress and anxious arousal symptoms, and executive function. It also aimed to further elucidate if progesterone strengthened these relationships.

Daily self-reported stress and anxious arousal were analyzed individually. The models included DS predicting EF, DS and Progesterone predicting EF, and a model with DS, Progesterone, and the interaction between DS and Progesterone predicting EF. Adding progesterone as a covariate accounted for its independent effects on EF with DS constant. The interaction model evaluated if the interaction between DS and progesterone had any predictive value on EF.

Univariate models revealed that self-reported stress and anxious arousal have opposing effects on reaction time at complementary working memory loads. Namely, high stress was found to significantly increase reaction time at low and high working memory load (0- and 3-

back) trials; high anxious arousal decreased reaction time at medium working memory loads (2-back). Neither stress nor anxious arousal had significant effects on the P300 or on accuracy.

The finding for stress predicting decreased reaction time is consistent with hypotheses, expectations, and literature. In addition to work supporting the negative impact of stress on memory processes more broadly [173], past work has demonstrated that recent stress exposure is associated with decreases in working memory [174] and that experimentally induced psychosocial stress decreased reaction time and accuracy in 2- and 3-Back N-back trials [175]. Past work supporting the association between anxiety and impacts on working memory drove predictions that EF during a WM task would be negatively impacted by anxious arousal [176].

However, this work's findings demonstrated the opposite: decreased reaction time at 2-back with no impact on any other tested EF dimension. Though contrary to expectations, the finding that anxious arousal decreases reaction time has been shown in some past literature. Namely, in work looking at functional connectivity during a working memory task, anxious arousal was treated as a sub-component of anxiety compared to anxious apprehension, and results showed that anxious arousal was associated with increased processing speed and resulted in faster response times in a working memory task [132]. The findings offered by the present work build on the aforementioned findings by including effects stratified by working memory load. If anxious arousal indexes a more sympathetic and peripheral component of anxiety, as compared to dimensions of anxiety that have cognitive components such as worry or anxious apprehension, that may explain the difference in findings compared to expectations. Future directions might consider evaluating trait anxiety's impact on EF and the integration of physiologic markers of sympathetic arousal. To maintain naturalistic measurement, wearables tracking daily heart rate variability might be considered.

Limitations include the self-reported nature of daily symptoms, as well as limitations from being constrained to a specific day. Critiques of DS's temporal constraints are detailed above, though a benefit of daily measures is that they allow for interrogating within person differences, and also serve as an ecological measure. The great value of self-report is that it mimics what would be seen clinically and what may have the greatest impact on disease burden and quality of life. Nonetheless, the insight, reflection, and interpretation required may introduce individual difference, variability, and error that either cannot be or is not accounted for. Engaging in a multimethod approach where symptoms are characterized by both self-report, physiologic measures, controlled experimental testing, and biomarkers would provide a more multidimensional and thorough characterization of daily symptoms and nervous system state. With this improved characterization, subsequent effects on EF might be more readily captured.

This work also added progesterone into these models to evaluate its effects on the relationship between DS and EF. In bivariate models predicting executive function from daily stress and progesterone, stress predicted an increase in reaction time at 0-Back with progesterone held constant. This is consistent with findings from the univariate model of stress's effects on executive function, which also showed slowed reaction time. Holding daily stress constant, progesterone predicted a decreased P300 at 0- and 3-Back. This indicates that with stress held constant, fewer attentional resources may be available at low and high working memory load when progesterone is high.

Past work has shown sex differences in P300 amplitude between females and males, where females demonstrate a smaller P300 [177]. It is possible that transient elevated progesterone levels contribute to these decreased P300 levels. Work by [178] suggests that higher progesterone reallocates attentional resources toward social stimuli and social information

processing, concluding that high progesterone optimizes attention allocation. While this could be interpreted that progesterone would optimize attention allocation and thus result in a larger P300 amplitude, the stimuli used in the N-back did not have social significance. It is possible that that decreased P300 might be the result of a stimulus that is perceived as less relevant at high progesterone levels. It would be interesting to see if the P300 would remain decreased at high progesterone if a task using human faces as stimuli were used instead. It is also interesting that in the present work's findings, the P300 was unaffected at 2-Back, suggesting that attentional resources are not compromised at medium working memory load.

In the case of anxious arousal, when progesterone is held constant the results are consistent with univariate models predicting EF from anxious arousal: anxious arousal predicts decreased reaction time. When anxious arousal is held constant, progesterone does not predict any of the executive function measures.

This is in contrast to progesterone predicting decreased electrophysiologic EF measures (the P300) when either CSR or daily stress are held constant. This suggests that when the effects of stressors on EF are accounted for, be those cumulative or daily stressors, progesterone has a predictable negative electrophysiologic effect on EF, and that this effect on EF is independent and up and above the effects of CSR and daily stress. The fact that these effects of progesterone on EF are seen when stressors are accounted for suggests that the effects of stressors may confound the effects of progesterone if not accounted for.

As mentioned, this is not the case for anxious arousal. In the presence of anxious arousal, progesterone showed no effect on EF, indicating that anxious arousal is not a confounder in any impact progesterone may have on EF. This is supported by this work's findings showing that the interaction between progesterone and anxious arousal had no predictive effects on EF.

The difference in stress potentially confounding the effects of progesterone on EF contrasted with anxious arousal not confounding those effects may be explained by the progesterone's multiple metabolic pathways. These include the conversion of progesterone into cortisol under stress, but also progesterone metabolizing into allopregnanolone, and allopregnanolone's paradox anxiogenic and anxiolytic effects at different concentrations and in different populations via GABA potentiation[164], [169], [171], [179]–[183]. It is possible that stress might reroute progesterone metabolism toward cortisol, and given that cortisol has documented effects on EF, thus confound the effects of progesterone on EF when stress is not accounted for.

Progesterone

Overall, one of the main aims of the work was to characterize how progesterone might influence relationships between CSR, DS, and EF. While moderating effects were hypothesized, direct effects emerged. High progesterone predicted reduced EF measures (decreased P300 at 0- and 3-Back) when included as a covariate with CSR, and also when included as a covariate with stress. However, including progesterone in the bivariate model with stress resulted in stress' effects on the P300 at 3-back to become marginal, suggesting that both variables may be accounting for the same variance in the P300 at 3-Back. In a bivariate model with anxious arousal predicting EF, progesterone no longer had significant effects on any EF measure. These findings support a subtle interplay between progesterone and the nervous system's stress responses as they manifest in daily symptoms, but indicate that said interplay is not in the form of an interaction.

Surprisingly, high progesterone significantly predicted a reduction in anxious arousal symptoms in bivariate models accounting for CSR. Literature suggests this may be attributable to

the anxiolytic effects of progesterone's metabolite allopregnanolone via GABA[183], [184]. Future work might evaluate if the effect remains in univariate follow up analyses and include assaying for allopregnanolone. Future analyses might also evaluate the univariate effects of progesterone on executive function to see if the observed effects of progesterone on executive function are contingent on stress and CSR being held constant. Taken together, it seems that progesterone may influence EF through an interplay between progesterone, stress, and anxious arousal. This would be supported by limited and inconsistent literature reporting higher baseline progesterone association with higher baselines of free cortisol and bioavailable cortisol in response to stressors [91], and work demonstrating that during N-back and stroop tests faster reaction time were seen with higher levels of progesterone [185].

Overall Impressions

Across this work, CSR only significantly predicted EF. No significant effects of CSR were found on DS. Meanwhile, EF was found to be impacted by CSR, Stress, Anxious Arousal, and progesterone. None of the variables evaluated predicted stress, but stress did predict CSR. And lastly, anxious arousal was predicted by progesterone, and also impacted CSR. Overall, the greatest effects on EF were seen from CSR: CSR impacted the most EF measures. This is consistent with other work evaluating proximal and distal factors on behavior, psychopathology, and function: individual level early life experiences and traumas have been found to have more predictive effects than more proximal factors, like daily measures [151]. These effects might be through more long-standing structural changes than susceptibility to daily influences. In addition to affecting more EF components, rerunning analyses with standardized (sample-specific Z-score) measures would allow for the comparison of CSR vs DS vs progesterone effect sizes on EF in ways that reflect changes in standard deviation as opposed to original units.

Limitations to these findings include sample size and age limitations. Though methodologically justified as detailed in Gloe, 2021, 18-25 years of age is a very narrow window in the human life course [115]. Unfortunately, it is possible that these findings may only generalize to and replicate within that group. This is also true for the geographic and cultural limitations of recruiting from Mid-Michigan. Reproducing this work in additional age ranges and locations would amplify its generalizability.

Additionally, while progesterone was assayed, it was nonetheless a salivary measure. Though this method decreases participant burden and increases adherence, serum progesterone may provide a more precise measurement. Additionally, assaying for cortisol or progesterone's psycho- and neuroactive metabolites could offer more mechanistic and physiologically grounded insight into the role of glucocorticoids on the impact of CSR on EF in females, provide deeper understanding into sex differences in stress susceptibility, and evaluate their implications for function and possibilities for intervention.

The DS measure is simultaneously both valuable and limited. A better characterization of daily effects on or daily responses of the nervous system might include cortisol, skin conductance, heart rate variability in addition to reported symptoms. However, the strength of DS is in its clinical relevance and value as an ecological measure. Better mechanistic understanding may come from in vivo or in situ lab paradigms. Thus, a multimethod characterization would be ideal.

In addition to addressing the aforementioned limitations, future work would benefit from expanding the sample to include the impact of oral contraceptives. Oral contraceptives are very common, create supraphysiologic levels of progesterone, and little work evaluates the neuro- and psycho-active effects of doing so or impacts on stress susceptibility. Given the fact that

prevalence of affective and mood disorders in the female population is twice that of males, better characterizing the role exogenous progesterone plays when it is used with regularity in reproductive age females can inform both mechanistic understanding and clinical decision-making. Expanding the work in this way may also offer insight into individual differences, informing which contraceptive choices are appropriate for whom. Results would immediately inform clinical practice and be relevant to clinical populations across specialties including psychology, primary care, gynecology, obstetrics, and endocrinology.

Relatedly, postpartum is a time rife with risk of psychopathology, colloquially often attributed to drops in the neuroactive effects of "pregnancy hormones"-- namely, progesterone. Evaluating the impact on affect, attention, stress susceptibility, and cognitive function in this clinical population would carry great potential therapeutic impact and mechanistic insight.

Future work may be better able to characterize how, if, and when progesterone has its effects by evaluating it in the context of menstrual phase, and by considering change in progesterone in addition to static absolute values. Past work demonstrating phase dependent effects of stressors on cortisol secretion suggest greater cortisol output in the luteal phase [186]. The luteal phase is characterized by increased progesterone. A more thorough investigation might also control for and explore the impacts of testosterone, estrogen, and progesterone's metabolites. Human tissue studies may also offer insight by characterizing the effects of progesterone at various levels at glucocorticoid and mineralocorticoid receptors (GR and MR, respectively), especially given that the distribution of GR and MR in the human brain include both the prefrontal cortex and hippocampal regions [14], [24], [187].

Additionally, more robust measures of allostatic load, including inflammatory markers, could allow this work to integrate more fully with present literature and paradigms that

interrogate the mechanisms underlying CSR's effects on both health and functional outcomes via immune modulation.

Reproducing this work in males would build on past literature that identifies differences in stress reactivity between the sexes. Namely, past work looking at HPA and SAM activation reports that during suppression of either system, females demonstrate an elevated baseline tonicity (with dampened reactivity to stress) of the unsuppressed system, while males in contrast demonstrate increased reactivity of the unsuppressed system. The increased reactivity was not associated with changes in mood, while the increased baseline tonicity was [188]. Meanwhile, preclinical literature regarding sex differences in stress reactivity in arousal and attention systems indicate an increased vulnerability in females to stress-induced hyperarousal, while being more resilient to stress-induced attention deficits than males ([189] Reproducing the current paradigm in males might offer additional insight into sex differences in both attention and arousal.

In addition to sex differences, further exploration might characterize within versus between person effects of DS, AL markers, and circulating glucocorticosteroids including progesterone. Various individual difference measures could also be explored in addition to CSR to characterize different responses to CSR and identify groups either at higher risk or prone to resilience.

Overall, this work was conducted to better understand the impact of cumulative stressors and daily symptoms on the female stress systems, and their downstream functional consequences. It also was intended to identify individuals at risk due to social factors in order to justify and mobilize interventions to address these systemic issues through social infrastructure, education, or individual intervention. Results have confirmed the impact of CSR on EF in females, identifying and confirming the cumulative element of risk as one worth exploring, and

one worth paying attention to clinically. It also offers some preliminary mechanistic understanding of the not-yet-fully-characterized relationships between progesterone, daily symptoms of stress and anxious arousal, and executive function, and sets the groundwork for further exploration.

CONCLUSION

The current study found that a composite cumulative sociodemographic risk (CSR) score of race, childhood socioeconomic status, and trauma exposure significantly predicted both electrophysiological (P300) and behavioral measures of executive function (EF) in females during an N-Back working memory (WM) task. Findings were such that having more risk factors reduced EF. Daily symptoms (DS)-- namely self-reported stress and anxious arousal symptoms, were evaluated as predictors of EF as well as outcomes of CSR. CSR did not predict DS, but DS did have effects on EF: high stress increased reaction time (RT) at low and high WM load, and anxious arousal predicted decreased RT at medium working memory load. Anxious arousal predicting improved reaction time was unexpected, though there is support for this finding in the literature specific to anxious arousal compared to anxiety as a broader construct. The expectation that CSR's effects on EF would be mediated by DS was not supported for any EF measure or either DS mediator. Analyses were done using multilevel modeling (MLM) in SPSS and Monte Carlo simulations to test for indirect effects.

The sample consisted of 151 naturally cycling females aged 18-25 followed over 35 days, with four lab visits for cognitive testing spaced throughout alongside daily measures. In addition to daily affective symptoms, daily saliva samples allowed for salivary progesterone assay. The above findings were evaluated in the context of progesterone, with the expectation that progesterone would moderate any relationships between CSR, DS, and EF. Progesterone was not found to moderate any relationship. Instead, progesterone was found to have its own direct effects on EF when included as a covariate in bivariate models with daily stress and CSR. When included as a covariate with anxious arousal, progesterone did not predict EF. Interestingly, progesterone predicted anxious arousal in the opposite direction of expectations when included

in a bivariate model alongside CSR. In a follow up univariate analysis, progesterone had no significant effects on EF, but did have a significant effect on anxious arousal in the opposite direction of expectations. Taken together, these results suggest an interplay between anxious arousal, stress, and progesterone that results in impacts on EF. More work would do well to better characterize these interrelationships.

Overall, the idea that accumulation of sociodemographic risk impacts EF was supported. This is consistent with allostatic load (AL) literature reporting the impact of social factors on health and function, attributing the cost of adapting to stressors and environmental demands as the potential mechanism by which these social factors lead to deficits in health and function. However, the DS measures did not seem to characterize AL, and were not found to be mediators. Despite not being able to characterize the stress response as expected, this work nonetheless supports framing the impacts of stressors as cumulative and systemic, while offering additional preliminary insight into the role of progesterone in female stress susceptibility and EF outcomes.

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APPENDIX A: DEMOGRAPHICS

Demographics Breakdown		
Category	*N*	*%*
Income		
$0 - $15,000	46	30.46%
$15,001 - $25,000	17	11.26%
$25,001 - $35,000	8	5.30%
$35,001 - $50,000	9	5.96%
$50,001 - $75,000	13	8.61%
$75,001 - $100,000	16	10.60%
$100,000 - $200,000	31	20.53%
More than $200,000	10	6.62%
Missing	1	0.66%
Ethnicity		
Non-Hispanic	133	88.08%
Hispanic	11	7.28%
Missing	7	4.64%
Racial Identification		
White	77	50.99%
Black	30	19.87%
Asian	8	5.30%
Latinx/Hispanic (Non-White)	8	5.30%
Middle Eastern/North African (Non-white)	13	9.61%
Multiracial	12	7.85%
Missing	3	1.99%
Student Status		
Full-Time Status	113	74.83%
Partial Student	10	6.62%
Not a Student	28	18.54%
Education Level		
Grad School	3	1.99%
College Education	39	25.83%
Partial College (at least one year)	91	60.26%
High School	18	11.92%

Table 16. A table showing the demographics of the participants in the study (n = 151).

APPENDIX B: MLM SHORTHAND FORMULAS FOR ALL MODELS

Key and Notes:

CSRSUM indicates CSR

DS indicates DS, within which:

Stress indicates Daily self-reported stress

ANXAROUS indicates Daily self-reported anxious arousal

EF indicates EF, within which:

For 0-Back

PzBC_0backT indicates P300 at 0-Back

ZeroTRT indicates RT at 0-Back

ZeroTAcc indicates Accuracy at 0-Back

For 2-Back

PzBC_2backT indicates P300 at 2-Back

TwoTRT indicates RT at 2-Back

TwoTAcc indicates Accuracy at 2-Back

For 3-Back

PzBC_3backT indicates P300 at 3-Back

ThreeTRT indicates RT at 3-Back

ThreeTAcc indicates Accuracy at 3-Back

Pro indicates progesterone

The suffix "_C" indicates a grand mean centered variable

All predictors in all models were centered.

Aim 1. Univariate Models

Aim 1a)

$CSRSUM\_C \rightarrow EF$

- $CSRSUM\_C \rightarrow 0Back$
    - $CSRSUM\_C \rightarrow PzBC\_0backT$
    - $CSRSUM\_C \rightarrow ZeroTRT$
    - $CSRSUM\_C \rightarrow ZeroTAcc$
- $CSRSUM\_C \rightarrow 2Back$
    - $CSRSUM\_C \rightarrow PzBC\_2backT$
    - $CSRSUM\_C \rightarrow TwoTRT$
    - $CSRSUM\_C \rightarrow TwoTAcc$
- $CSRSUM\_C \rightarrow 3Back$
    - $CSRSUM\_C \rightarrow PzBC\_3backT$
    - $CSRSUM\_C \rightarrow ThreeTRT$
    - $CSRSUM\_C \rightarrow ThreeTAcc$

Aim 1b)

- $CSRSUM\_C \rightarrow DS$
    - $CSRSUM\_C \rightarrow Stress$
    - $CSRSUM\_C \rightarrow ANXAROUS$

Aim 1c)

- $Stress\_C \rightarrow EF$
    - $Stress\_C \rightarrow 0Back$
        - $Stress\_C \rightarrow PzBC\_0backT$

        - $Stress \rightarrow ZeroTRT$
        - $Stress \rightarrow ZeroTAcc$
    - $Stress \rightarrow 2Back$
        - $Stress \rightarrow PzBC\_2backT$
        - $Stress \rightarrow TwoTRT$
        - $Stress \rightarrow TwoTAcc$
    - $Stress \rightarrow 3Back$
        - $Stress \rightarrow PzBC\_3backT$
        - $Stress \rightarrow ThreeTRT$
        - $Stress \rightarrow ThreeTAcc$
- $ANXAROUS\_C \rightarrow EF$
    - $ANXAROUS\_C \rightarrow 0Back$
        - $ANXAROUS\_C \rightarrow PzBC\_0backT$
        - $ANXAROUS\_C \rightarrow ZeroTRT$
        - $ANXAROUS\_C \rightarrow ZeroTAcc$
    - $ANXAROUS\_C \rightarrow 2Back$
        - $ANXAROUS\_C \rightarrow PzBC\_2backT$
        - $ANXAROUS\_C \rightarrow TwoTRT$
        - $ANXAROUS\_C \rightarrow TwoTAcc$
    - $ANXAROUS\_C \rightarrow 3Back$
        - $ANXAROUS\_C \rightarrow PzBC\_3backT$
        - $ANXAROUS\_C \rightarrow ThreeTRT$
        - $ANXAROUS\_C + Pro\_C \rightarrow ThreeTAcc$

Aim 3. Interaction Models

Aim 3a)

$CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow EF$

- $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow 0Back$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow PzBC\_0backT$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow ZeroTRT$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow ZeroTAcc$
- $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow 2Back$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow PzBC\_2backT$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow TwoTRT$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow TwoTAcc$
- $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow 3Back$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow PzBC\_3backT$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow ThreeTRT$
    - $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow ThreeTAcc$

Aim 3b)

$CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow DS$

- $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow Stress$
- $CSRSUM\_C + Pro\_C + CSRSUM\_C * Pro\_C \rightarrow ANXAROUS$

Aim 3c)

$Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow EF$

- $Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow 0Back$
    - $Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow PzBC\_0backT$

- $Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow ZeroTRT$
- $Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow ZeroTAcc$

- $Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow 2Back$
  - $Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow PzBC\_2backT$
  - $Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow TwoTRT$
  - $Stress\_C + Pro\_C + Stress\_C * Pro\_C \rightarrow TwoTAcc$
- $Stress + Pro\_C + Stress\_C * Pro\_C \rightarrow 3Back$
  - $Stress + Pro\_C + Stress\_C * Pro\_C \rightarrow PzBC\_3backT$
  - $Stress + Pro\_C + Stress\_C * Pro\_C \rightarrow ThreeTRT$
  - $Stress + Pro\_C + Stress\_C * Pro\_C \rightarrow ThreeTAcc$

$ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow EF$

- $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow 0Back$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow PzBC\_0backT$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow ZeroTRT$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow ZeroTAcc$
- $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow 2Back$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow PzBC\_2backT$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow TwoTRT$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow TwoTAcc$
- $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow 3Back$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow PzBC\_3backT$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow ThreeTRT$
  - $ANXAROUS\_C + Pro\_C + ANXAROUS\_C * Pro\_C \rightarrow ThreeTAcc$