2023

Modulators of the medial temporal hippocampal system: cardiorespiratory fitness and psychosocial stress in the context of the built and social environment

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Dissertation

MODULATORS OF THE MEDIAL TEMPORAL HIPPOCAMPAL SYSTEM: CARDIORESPIRATORY FITNESS AND PSYCHOSOCIAL STRESS IN THE CONTEXT OF THE BUILT AND SOCIAL ENVIRONMENT

by

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Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

2023

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DEDICATION

I would like to dedicate this work to those in my life who have stuck with me through this whole process. Without them, this work would not have been possible.

ACKNOWLEDGMENTS

I first want to express deep gratitude for the mentorship I have received throughout the entirety of this dissertation. Dr. Karin Schon has been the most supportive and selfless mentor, having been there for me both personally and professionally. You have taught me so much about how to be a scientist, to think critically about what I do and WHY I do it. Over the last six years you have provided me the space to by whole self, and for that I will be forever grateful. I would like to also extend my gratitude to my committee members, Drs. Chantal Stern, Alice Cronin-Golomb, Joseph McGuire, and Negar Fani. Without your critical feedback and support, I would not have been able to complete this dissertation and become the neuroscientist that I currently am.

My cohort. From the moment I joined the Graduate Program for Neuroscience I felt at home in the love and community they provided. Margaret, our lawn lunches at the medical campus are some of my fondest memories. Tom, thank you for helping me to build my confidence as a scientist and for constantly offering me snacks when I'd stop by your office to complain and listen to gossip. Kaitlyn, I've always looked up to you for your passion for teaching and mentorship and deeply appreciate how much you supported me as we finished up our graduate school years together while writing our dissertations. Lucas, you kept me grounded in queerness and fierceness, and Friday night RuPaul's Drag Race would never have happened without you. Luis, I have no words for what your presence meant to me over the last six years. Our time running the Underrepresented Graduate Student Organization, hosting a symposium, applying for grants together, eating your home

cooked meals, and putting up with my affections. I wouldn't have made it to this point without all of you.

I have also been mentored by many people over the last six years. First, none of this would have happened without Dr. Aletha Baumann. Dr. Baumann, you are my first mentor, and I will forever be grateful to you for convincing me one day on St. Croix at the University of the Virgin Islands that I could be a scientist. Dr. Keisha Pollack Porter, through the Health Policy Research Scholars program, you listened to my critiques and let me work together with some fabulous abolitionists (Ashley, Ans, Jason, Stephanie, Demar, and Sireen!) to think critically about health policy and the ways we approach it both inside and outside of legislative systems. Drs. Gina Poe and Carmen Maldonado-Vlaar at the Summer Program in Neuroscience, Education, and Success at the Marine Biological Laboratory, you helped me to feel confident with other scientists of color, realizing that we too have a space in neuroscience. This is most certainly not an exhaustive list, and I would like thank all of you.

Over the years, I have crafted and maintained a chosen family that has been there for me through thick and thin and through copious amounts of desperation during the PhD process. My Crazy Cuatro family, Nikkia, PJ, and Shaun: we've known each other for over 15 years, and you are some of my most stalwart companions, giving me love, support, honesty, and some of the best moments in my life through weddings and babies and trips to new places. Lauren and Travis, when I run away from Boston, the both of you provide one of the few bastions of succor for my heart. Saskia and Tanicia (TTZ), I'm afraid to parse through the six years of memes and pictures we have shared with each other. You've

made me laugh until I've cried and kept me housed in joy. Kathryn, we've known each other since our years in the STaRS program, lived together, cried together, and eaten a lot together. You've always been one of my biggest cheerleaders and I'm so grateful to have met you. Chino, thank you for constantly pushing to be a better version of myself. Colin, you always found a way to bring the kid out of me, and reminded me to chill out (thank you).

Finally, my family. My parents, Wanda and Tony Rosario, and my siblings Kira and Carl and their families have all loved and supported me in ways I can't begin to describe. They've dealt with my flightiness, absences from phone calls and family events, and so much more. I am who I am today because of who you are to me. I am eternally grateful.

Sadly, this can't be an exhaustive list of all the people who have helped me get to the finish line. But this is an unequivocal declaration that I didn't get here alone. Through sweat, tears, frustrations, and joy, it is all because of them. I didn't do this. We did this.

MODULATORS OF THE MEDIAL TEMPORAL HIPPOCAMPAL SYSTEM: CARDIORESPIRATORY FITNESS AND PSYCHOSOCIAL STRESS IN THE CONTEXT OF THE BUILT AND SOCIAL ENVIRONMENT

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ABSTRACT

The medial temporal hippocampal system exhibits high plasticity and is influenced by behavioral and socioenvironmental factors. Animal models have demonstrated the neuroplasticity of this system through environmental enrichment, exercise, and chronic stress. Human studies have replicated these findings, highlighting the positive impact of exercise and cardiorespiratory fitness, as well as the detrimental effect of chronic stress on brain structure. However, limited research has explored the differences between young and older adults in extrahippocampal regions of the medial temporal lobes. Additionally, the impact of psychosocial stressors such as perceived discrimination and moderating factors like sense of control on this brain system remains understudied. Furthermore, there is a lack of investigation into the neurobiological consequences of perceived discrimination as a significant psychosocial stressor on neurocognitive health.

The goals of this dissertation project were to investigate the role of cardiorespiratory fitness and perceived discrimination on medial temporal hippocampal system neurocognitive integrity in humans. I had two hypotheses. First, higher

cardiorespiratory fitness would correlate with higher extrahippocampal cortical thickness in young and older adults. Second, a greater number of experiences of perceived discrimination would correlate with reduced amygdala and anterior hippocampus volume in older adults. Two experiments were conducted to assess the impact of behavioral and socioenvironmental factors on medial temporal hippocampal system structure. In the first experiment, cross-sectional data were collected from two randomized clinical controlled trials (n = 100; 56 young adults and 44 older adults). In the second experiment data were collected from two pilot studies (n = 36). Finally, we discuss how the built and social environment, artificially created or modified areas where individuals live, work, or engage in recreational activities, can facilitate or impede behaviors that benefit brain health such as physical activity to increase cardiorespiratory fitness or social engagement.

Experiment 1 used structural MRI and assessed cardiorespiratory fitness in sedentary young and older adults. The primary objective was to examine the relationship between cardiorespiratory fitness and entorhinal, parahippocampal, and perirhinal cortical thickness. The results indicated a positive association between cardiorespiratory fitness and cortical thickness in these regions, specifically in the left hemisphere of young adults. However, this relationship was not observed in older adults.

Experiment 2 focused on the association between participants' perceived social discrimination experiences and amygdala and anterior hippocampus volume. Additionally, the moderating role of locus of control, a measure of self-efficacy, was examined. The findings revealed that higher levels of perceived social discrimination were associated with reduced amygdala and anterior hippocampus volume. Moreover, higher levels of locus of

control attenuated the relationship between perceived social discrimination and these brain regions.

The third project integrated the aforementioned ideas within the context of the built and social environment. The discussion centered around how systemic barriers within the environment can either support or hinder engagement in health-promoting behaviors like cardiorespiratory fitness. The importance of considering the built and social environment in clinical interventions was highlighted, with a focus on improving translation of research findings to benefit research participants. Factors such as safety, access to green spaces, and social connectedness were explored, particularly in relation to universal design and its potential to enhance healthy aging and accessibility while addressing systemic racism and structural barriers.

These chapters provide evidence to inform policymakers, clinicians, and neuroscientists about the broader implications of clinical research in communities. By considering the impact of clinical interventions on the built and social environment, this work aims to promote health and well-being beyond laboratory settings.

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CHAPTER ONE: INTRODUCTION

Opposing Modulators of the Medial Temporal Hippocampal (MTH) System

The MTH system and its role in memory

One of the most important findings in neuroscience over the last century was the discovery of place cells, neurons that fire selectively when an animal is in a specific location in its environment, in the rodent hippocampus (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971). The hippocampus is a region of the brain that plays a critical role in how individuals process their spatiotemporal context, and is responsible for the encoding and retrieval of memories of specific events, as well as integrating this information within this larger spatiotemporal context (Hasselmo, 2013). The discovery of place cells has had a profound impact on our understanding of learning and memory and has led to a greater appreciation of the role of the hippocampus and related structures in memory and spatial cognition. The hippocampus contains neurons that encode information about an individual's movement and direction (Kropff, Carmichael, Moser, & Moser, 2015), encode information about the timing and sequence of events (Eichenbaum, 2014), encode information about boundaries within a given space (Alexander et al., 2020), and encode information on the direction faced within an environment (Taube, Muller, & Ranck, 1990). Grid cells are yet another type of neuron that contribute to spatiotemporal processing. These neurons fire at regular intervals when an individual moves through space, creating a hexagonal grid-like pattern that enables more accurate spatial mapping (Hafting, Fyhn, Molden, Moser, & Moser, 2005). Grid cells have been observed in the entorhinal cortex, a region that is closely connected to the hippocampus and is a primary pathway for providing

information into the hippocampus via the perforant path (Rolls, 2013; Witter & Amaral, 1991). Beyond the hippocampus and entorhinal cortex, the perirhinal cortex and parahippocampal cortex play a major role in providing spatiotemporal input to the hippocampus. The perirhinal cortex is responsible for processing of objects, whereas the parahippocampal cortex is involved in spatial navigation and the processing of spatial and contextual information (Squire, Stark, & Clark, 2004; Squire & Zola-Morgan, 1991). The parahippocampal place area, located within the posterior parahippocampal cortex in humans, maintains representations of spatial layout (R. Epstein & Kanwisher, 1998) and the perirhinal cortex maintains more general representation of objects within space (Connor & Knierim, 2017). The perirhinal and parahippocampal cortices contain separate, yet slightly overlapping reciprocal connections with the entorhinal cortex (Suzuki & Amaral, 1994), and the entorhinal cortex has direct reciprocal connections with the hippocampus (Witter & Amaral, 1991). Finally, the amygdala is another brain region in the medial temporal lobes that has been implicated in modulating implicit and explicit memory, particularly enhancing emotional memories by modulating the encoding and retrieval of memories based on their emotional salience (Kensinger & Ford, 2020; Phelps, 2004; Phelps & LeDoux, 2005). The hippocampus can also be functionally and structurally delineated along its long-axis, with the anterior portion implicated in affective function (Fanselow & Dong, 2010; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013a), and it is also directly bidirectionally connected to the amygdala (Saunders, Rosene, & Van Hoesen, 1988). Altogether these brain regions work synergistically in memory formation and retrieval within a given spatiotemporal context.

Binding in context model

The binding in context (BIC) model, proposed by Ranganath and colleagues, is a theoretical framework for understanding how the brain encodes and retrieves episodic memories (Diana, Yonelinas, & Ranganath, 2007; Ranganath, 2010). The model proposes that memories are stored as patterns of activity distributed across neural populations, and that the binding of different elements of a memory (such as the time, place, context, and emotional salience in which the memory was formed) is critical for successful retrieval. According to the BIC model, the hippocampus plays a central role in binding the different elements of a memory. Specifically, the model proposes that the hippocampus receives input from sensory and perceptual regions of the brain, and that this input is used to create a spatiotemporal representation that incorporates information about the time, place, and other features of the memory. This contextual representation is then bound to the other features of the memory (such as the objects or events that were experienced) to form a complete memory representation. According to the BIC model, the perirhinal and parahippocampal cortices play critical roles in providing the sensory and contextual information that is used by the hippocampus to create a complete memory representation (Ranganath, 2010). Specifically, the model proposes that the perirhinal cortex creates object representations and the parahippocampal cortex represents spatial and contextual information which is processed in the entorhinal cortex, and then bound to the contextual representation created by the hippocampus to retrieve a memory. Expanding on this framework, Yonelinas and Ritchey (2015) posited that the amygdala functions within the BIC model by binding emotion and item within context, and that this may cause a slower

degrading of the emotional contextual memory over time (Yonelinas & Ritchey, 2015). Overall, the BIC model provides a theoretical framework for understanding how the medial temporal hippocampal (MTH) system encodes and retrieves episodic memories, and provides a conceptual framework for how context, including socioenvironmental factors, such as place, space, social interactions, and navigating within the environment (e.g., via physical activity) may influence MTH system structure and function via modulation of cellular and circuit mechanisms within these brain regions. Next, we discuss the upregulation and downregulation of the MTH system in the context of environmental enrichment and chronic stress, how they have been shown to facilitate or impede MTH system health, and their importance for translation to human participant clinical research.

Upregulation and Downregulation of MTH Neuroplasticity: Environmental Enrichment and Chronic Stress

As stated above, the MTH system is comprised of a series of interrelated structures that support learning and memory. Moreover, regions within the MTH system are also responsible for affective and stress regulation. Importantly, these brain regions have been shown to be exquisitely sensitive to the impact of behavioral and socioenvironmental factors, displaying neuroplasticity as a result of factors such as environmental enrichment and chronic stress. Early neurobiological animal models of environmental enrichment and wheel running (Mohammed et al., 2002) have shown upregulation of neuroplasticity mechanisms. Neuroplasticity is crucial for the functioning of the hippocampus as a whole. Studies have shown that environmental enrichment and wheel running can increase the

number of adult newborn cells in the hippocampus (neurogenesis), as well as enhance the survival and integration of existing cells (Van Praag, Christie, Sejnowski, & Gage, 1999; Van Praag, Shubert, Zhao, & Gage, 2005). Moreover, neuroplasticity is essential for the ability of the hippocampus to adapt to changing environmental demands. For example, the hippocampus can reorganize its cell assemblies to create new representations of the environment, allowing individuals to navigate new and unfamiliar surroundings (Leutgeb, Leutgeb, Treves, Moser, & Moser, 2004). Research centered on how environmental enrichment and physical activity affect the MTH system found that voluntary wheel running leads to an increased expression of biochemical growth factors, which play a pivotal role in the survival and differentiation of existing neurons (Ickes et al., 2000; Pham et al., 1999). Studies by van Praag et al., (1999) found that environmental enrichment and wheel running increased the proliferation of adult-born neurons in the dentate gyrus subfield of the hippocampus (Van Praag, Christie, et al., 1999; Van Praag, Kempermann, & Gage, 1999a). Similarly, Stranahan et al., (2007) observed increased basal dendrite spine density in layer III of the entorhinal cortex (Stranahan, Khalil, & Gould, 2007), and van Praag and colleagues (2005) showed that environmental enrichment promoted proliferation and expansion of existing neurovasculature in young mice (Van Praag et al., 2005). We discuss these ideas in more detail in Chapter 2 in the context of our findings on the relationship between higher cardiorespiratory fitness and greater extrahippocampal MTH cortical thickness in humans.

In an opposing fashion, factors such as aging and chronic stress have been implicated in the downregulation of these neuroplasticity mechanisms. It is well-

established in animal models of stress that these regions of the MTH undergo structural reorganization during stressful events (Fuchs & Flügge, 2003; Fuchs, Flugge, & Czéh, 2006; McEwen, Nasca, & Gray, 2016). Findings in rodent and nonrodent models using foot shocks, chronic restraint, and social stress paradigms have emphasized the plasticity and sensitivity of the MTH system in relation to chronic stress paradigms. Multiple studies have shown that chronic stress has negative effects on the brain. Chronic stress results in dendritic pruning and synapse loss in the amygdala and hippocampus, and apoptosis of adult-born cells in the dentate gyrus subregion of the hippocampus (Anacker et al., 2018; Fuchs et al., 2006; Magariños, McEwen, Flügge, & Fuchs, 1996; McEwen et al., 2016). In a resident-intruder paradigm, exposure to a dominant conspecific tree shrew resulted in dendritic atrophy in the CA3 region of the hippocampus (Magariños et al., 1996). In contrast, Vyas et al. (2002) showed that psychosocial chronic stress induced dendritic expansion in the amygdala(Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). Anacker et al. (2018) reported that chronic stress stimulates apoptosis of newly generated cells in the dentate gyrus subregion of the hippocampus (Anacker et al., 2018). Exposure to psychosocial stress in tree shrews also showed impaired hippocampus-dependent memory and was associated with a reduction in hippocampal volume as measured by MRI (Ohl, Michaelis, Vollmann-Honsdorf, Kirschbaum, & Fuchs, 2000). In non-human primate models of fetal glucocorticoid exposure, increased fetal exposure to glucocorticoids resulted in a reduction of hippocampal volume 20 months after birth in experimental animals compared to controls (Uno et al., 1994). In Chapter 3, we discuss these ideas in

the context of psychosocial stress in humans, showing a relationship between greater perceived social discrimination and a lower amygdala and anterior hippocampal volume.

Aging and Cardiorespiratory Fitness in Humans

Human studies of exercise, physical activity, and cardiorespiratory fitness (CRF) building on neurobiological models of wheel running and environmental enrichment have shown a beneficial impact in aging, ameliorating cortical, archiocortical, and subcortical atrophy and impairments in cognitive function. Studies in humans have investigated the effects of aging on brain structure, with particular attention to the hippocampus and parahippocampal regions. Jack et al. (1997) found that among healthy older adults, older age was associated with greater hippocampal and parahippocampal atrophy (Jack et al., 1997). Complementary longitudinal assessments have revealed age-related entorhinal and parahippocampal structural atrophy in healthy older adults (Daugherty & Raz, 2017; N. Raz, Rodrigue, Head, Kennedy, & Acker, 2004; Naftali Raz et al., 2005; Shaw, Sachdev, Anstey, & Cherbuin, 2016). Over a period of four years, healthy adults showed age-related shrinkage of the entorhinal cortex, which is known to play a key role in memory encoding and retrieval (Naftali Raz et al., 2005). Similarly, Shaw and colleagues (2016) observed significant longitudinal declines in parahippocampal and entorhinal cortical thickness in healthy aging adults (Shaw et al., 2016). Moreover, Daugherty and Raz (2017) found that age-related declines in the structural integrity of the entorhinal cortex are associated with lower scores on tests of episodic memory (Daugherty & Raz, 2017). These findings suggest that aging is associated with significant negative structural changes in brain regions crucial

for learning and memory. In contrast, there is a significant body of evidence suggesting that physical activity and aerobic exercise can help mitigate age-related changes in brain structure and function (Hillman, Erickson, & Kramer, 2008; Voss, Vivar, Kramer, & van Praag, 2013). In humans, aerobic exercise has been shown to increase CRF (Hagberg et al., 1989; Kohrt et al., 1991), which is a measure of one's capacity to support ongoing physical activity through the combined efforts of the respiratory, cardiovascular, and musculoskeletal systems (Dalleck & Tischendorf, 2014). Previous neuroimaging studies in middle-aged and older adults have demonstrated profound positive associations between aerobic exercise, CRF, and the neurocognitive integrity of cortical, archiocortical, and subcortical regions (Colcombe et al., 2003; Kirk I. Erickson, Leckie, & Weinstein, 2014; Hayes, Hayes, Cadden, & Verfaellie, 2013; Voss et al., 2013; V. J. Williams et al., 2017). For instance, in midlife, greater CRF was found to be associated with increased bilateral perirhinal cortex volume (Tian, Studenski, Resnick, Davatzikos, & Ferrucci, 2015). Additionally, in older adults, greater CRF was linked to reduced age-related cortical atrophy across multiple brain regions, including prefrontal, inferior, and middle temporal cortices (Colcombe et al., 2003), and directly related to greater bilateral hippocampal volume (Kirk I. Erickson et al., 2009). A longitudinal study further found that an increase in CRF following a year-long aerobic exercise intervention was significantly associated with attenuation of age-related bilateral hippocampal volume loss in older adults (Kirk I. Erickson et al., 2011). Altogether, in aging, physical activity and cardiorespiratory fitness have been shown to have a beneficial impact on neurocognitive integrity, attenuating age-related declines in cortical structure.

However, in comparison there is a dearth of research investigating the impact of exercise and CRF on young adult neurocognitive integrity. Recent studies have investigated the impact of CRF on brain structure, cognitive function, and MTH-dependent behavior in young adults. A cross-sectional study using voxel-based morphometry found that greater CRF was associated with greater right entorhinal cortex volume in young adults (Whiteman, Young, Budson, Stern, & Schon, 2016). A similar study found that greater CRF was associated with increased hippocampal viscoelasticity, a measure of hippocampal tissue integrity, and that this integrity mediated the relationship between CRF and performance on a spatial relational task (Schwarb et al., 2017). An exercise training study showed that 12 weeks of aerobic exercise training resulted in increased volume of the left anterior hippocampus, specifically in the dentate gyrus/CA3 subfield, in young adults (Nauer, Dunne, Stern, Storer, & Schon, 2020). Complementary work by Thomas et al. (2016) showed that increased CRF following a six-week aerobic exercise training program was associated with increased anterior hippocampal volume in young and middle-aged adults (Thomas et al., 2016). In addition to these structural changes, CRF has also been linked to improvements in cognitive function and MTH-dependent performance. Nauer, Dunne, et al. (2020a) found that increasing CRF through 12 weeks of aerobic exercise training was associated with significant improvement in hippocampal-dependent memory performance in initially lower-fit young adults (Nauer, Dunne, et al., 2020). Kronman, Kern, and colleagues (2020) showed that in young adults, greater CRF predicted increased effective connectivity between the hippocampus and other regions of the default mode network (Kronman et al., 2020). Finally, Stroth et al. (2009) reported that increasing CRF

through aerobic exercise training is associated with a significant improvement in visuospatial memory in young adults (Stroth, Hille, Spitzer, & Reinhardt, 2009). Taken together, these studies suggest that increasing CRF through aerobic exercise training can have a positive impact on brain structure, cognitive function, and MTH-dependent behavior in young adults, outside of age-related declines in neurocognitive integrity. We discuss our findings on the relationship between CRF and neurocognitive integrity in young and older adults in more detail in Chapter 2, filling an important gap in the literature on our understanding of how CRF influences extrahippocampal regions of the MTH system in young adulthood.

Chronic Stress and Perceived Discrimination in Humans

In contrast to cardiorespiratory fitness, the chronic stress has a deleterious impact on brain health. Two mechanisms by which this may occur is via the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), two major physiological systems involved in the body's response to stress (McEwen, 1998a). The HPA axis, consisting of the hypothalamus, pituitary gland, and adrenal gland, is responsible for the release of cortisol, a stress hormone that plays a key role in regulating the body's response to stress. The SNS, on the other hand, is responsible for the acute release of adrenaline and noradrenaline, which trigger the body's fight-or-flight response. The HPA axis and SNS work together to maintain the body's physiological response to stress. Research has shown that chronic stress can lead to dysregulation of the HPA axis and SNS, which can have negative effects on both physical and mental health (McEwen,

2012). One study found that chronic stress can lead to structural and functional changes in the brain, including alterations in the HPA axis and SNS, suggesting that these changes may contribute to the negative health outcomes associated with chronic stress (McEwen & Gianaros, 2011). Although these systems are important for maintaining physiological balance in response to acute stressors, chronic stress can lead to dysregulation of these systems and negative health outcomes (McEwen, 2012). The hippocampus and amygdala are two key structures in the brain that play important roles in the body's response to stress, and they are closely connected with the HPA axis and SNS. The hippocampus and amygdala contain high levels of cortisol receptors, specifically the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which are essential for the regulation of the stress response (Joëls, Pasricha, & Karst, 2013). The MR is highly expressed in the hippocampus and amygdala, and it has a high affinity for cortisol. It is responsible for inhibiting the HPA axis, which leads to a decrease in cortisol release. This mechanism is important for preventing excessive cortisol release in response to stress and protecting the hippocampus from the damaging effects of chronic stress (Joëls et al., 2013). Chronic stress can lead to downregulation of the MR and may contribute to the development of stress-related disorders (McEwen, 2012).

The weathering hypothesis and the allostatic load framework are two theoretical frameworks that help explain the physiological impact of stress on the body (Das, 2013; McEwen, 2012). The weathering hypothesis posits that chronic stress and exposure to socioenvironmental and economic disadvantage lead to accelerated biological aging (Arline T. Geronimus, Hicken, Keene, & Bound, 2006) and an increased risk for chronic

diseases, particularly among minoritized populations. This hypothesis proposes that the repeated activation of stress response systems, such as the HPA axis and SNS, results in wear and tear on the body's systems over time, leading to increased morbidity and mortality. The weathering hypothesis is particularly relevant in the context of health disparities, where marginalized people may experience chronic stress due to discrimination, poverty, and limited access to resources. Complementing this body of work, the allostatic load framework expands upon the weathering hypothesis by providing a neurobiological framework for how chronic stress impacts the body's physiological systems. This framework proposes that repeated or chronic activation of the body's stress response systems results in an accumulation of physiological "wear and tear" over time, known as allostatic load (McEwen, 1998b). Both the allostatic load framework and weathering hypothesis suggest that chronic stress can impact health by disrupting the body's ability to self-regulate. By considering the physiological impact of chronic stress, these frameworks provide insight into the mechanisms by which stress can contribute to health disparities and the development of chronic diseases. Research conducted by Lupien et al. (2018) showed that chronic stress was associated with decreased hippocampal volume and impaired cognitive function (Lupien, Juster, Raymond, & Marin, 2018). Additionally, Gianaros et al. (2007) found that chronic stress was associated with decreased grey matter density in the amygdala and hippocampus (Gianaros et al., 2007). Seminal work corroborating the weathering hypothesis and allostatic load framework showed that Black/African American people showed greater allostatic load compared to White/European Americans. When the groups were broken down by both race and sex,

there was a significant effect of sex and race whereby Black/African American women showed the highest allostatic load across the lifespan, followed by Black/African American men, White/European American women, and White/European American men, respectively. (A. T. Geronimus, 2001; Arline T. Geronimus et al., 2006).

A rapidly growing literature has begun to investigate the impact of chronic stress on brain health through the lens of discrimination. As society becomes increasingly diverse and multicultural, with complex and historically influenced social interactions, individuals with marginalized identities are at an elevated risk of experiencing psychosocial stress due to perceived social discrimination. Perceived social discrimination is defined here as the unfair treatment of one group by a dominant social group along singular or intersectional identities, without the agency to respond effectively (Bailey et al., 2017; Dean, Williams, & Fenton, 2013; Krieger, Smith, Naishadham, Hartman, & Barbeau, 2005; Ong, Fuller-Rowell, & Burrow, 2009). Marginalized identities may include those based on race, ethnicity, gender, sexuality, ability, age, socioeconomic status, or their intersections (Crenshaw, 1991). Despite being socially constructed, perceived social discrimination has been associated with negative health consequences, including mental and cognitive health outcomes (Bailey et al., 2017; Barnes et al., 2012; Lewis, Aiello, Leurgans, Kelly, & Barnes, 2010; Zahodne, Manly, Smith, Seeman, & Lachman, 2017a; Zahodne, Sol, & Kraal, 2019). Greater experiences of perceived social discrimination have been linked to increased rates of depression and anxiety (D. R. Williams & Williams-Morris, 2000) as well as higher inflammation (Lewis et al., 2010; Simons et al., 2018b). Within the last decade, perceived social discrimination has been well characterized through both cross-

sectional and longitudinal research to have negative consequences for neurocognitive health (Barnes et al., 2012; Clark, Miller, & Hegde, 2018a; Fani, Carter, Harnett, Ressler, & Bradley, 2021; Fani et al., 2022; Glymour & Manly, 2008; Zahodne et al., 2023). Recent studies have also shown that perceived social discrimination is associated with negative cognitive health outcomes in diverse populations. For instance, research by Barnes and colleagues (2012) found that greater perceived social discrimination was linked to lower global cognition, including episodic memory and perceptual speed, in a sample of healthy Black older adults (Barnes et al., 2012). Longitudinal analyses using the Health and Retirement study demonstrated that greater perceived social discrimination predicted lower executive function, processing speed, and visuospatial construction performance in a diverse, nationally representative sample of older adults (Zahodne et al., 2020). Furthermore, among older Black women, greater self-reported perceived social discrimination predicted later decline in subjective memory for those who experienced more discrimination (Coogan et al., 2020). Perceived social discrimination has also been shown to impact brain function and structure. Clark and colleagues (2018) reported that greater perceived social discrimination was associated with aberrant amygdala functional connectivity in a diverse sample (Clark, Miller, & Hegde, 2018b). In a study assessing neural responses to traumatic emotional images, greater perceived social discrimination predicted greater functional activity in regions important for emotional regulation and attention among Black women (Fani et al., 2021). Additionally, greater experiences of discrimination has been linked to reduced fractional anisotropy, a measure of white matter structural integrity, in several white matter pathways among trauma-exposed Black

women, independent of experiences of trauma, post-traumatic stress disorder, and other social factors (Fani et al., 2022). Finally, recent studies have also demonstrated that greater perceived social discrimination is associated with lower hippocampal volume and greater white matter hyperintensities among older adults (Zahodne et al., 2023). As a salient chronic psychosocial stressor, although social identities that are subjected to chronic discrimination are social constructs, perceived social discrimination has been shown to have dire consequences for health and well-being. Altogether, the above findings provide evidence for the negative impact of perceived social discrimination as a psychosocial stressor on neurocognitive health outcomes. We discuss our own findings on the relationship between higher experiences of perceived social discrimination and lower amygdala and anterior hippocampus volume in Chapter 3.

Place, Space, and Context: How does the built and social environment facilitate or impair our access to "brain health"

Thus far we have discussed the MTH system in the context of environmental enrichment, cardiorespiratory fitness, chronic stress, and perceived discrimination. The ability for individuals to process, embody, and recall these experiences relies on our ability to access the spatiotemporal context we inhabit, and we do this partially via the MTH system. Based on the BIC model, our ability to recall a memory requires the context, features of the environment, the time when the memory happened, and perhaps some emotionally salient factor. Importantly, aspects of the built and social environment modulate MTH plasticity and influence brain health:

> "The structures in the environment—the houses we live in, the areas we play in, the buildings we work in—affect our brains and our brains affect our behavior…The different spaces in which we live and work are changing our brain structures and our behaviors, and this has been going on for a long time."
>
> -Fred Gage (Eberhard, 2009)

In the foreword to Eberhard's book "*Brain Landscape: The Coexistence of Neuroscience and Architecture*", Dr. Fred Gage highlights the importance of how our brains interact with the spaces that we live in, touching upon the idea that the spatiotemporal context of our lived experience matters. Although this passage focuses on the architecture of the built environment, it nevertheless describes a pressing issue of health inequalities and health inequties in relation to our spatiotemporal context. Although perceived social discrimination is typically characterized as sociocultural and interpersonal phenomena, it is essential to consider the systemic ways in which society can reinforce racial, gender, class, and other types of power, privilege, and disadvantage. This includes examining issues such as unequal pay, de facto redlining, housing disparities, educational disparities, employment opportunities, healthcare access, the criminal legal system, and other types of system inequality that shape our biases and affect our ability to promote and sustain human well-being (Bailey, Feldman, & Bassett, 2021; Bailey et al., 2017).

When considering the positive effects of physical activity and cardiorespiratory fitness on human health, it is essential to take into account the structural barriers that limit safety and accessibility to health and well-being. This requires situating these known relationships between brain health and CRF within the spatiotemporal context of the sociopolitical world, to recognize the disparities in access to environments that promote physical activity, enriched (rather than deprived) neighborhoods and communities, and

social connection. The questions we must ask are whether individuals have access to safe physical environments that allow for social connection (such as community centers) or physical activity (such as greenspaces and sidewalks). To expand on this, it is important to recognize that individuals from marginalized communities often face greater obstacles when it comes to accessing safe environments for physical activity and social connection (Bailey et al., 2017; H. Cole & Immergluck, 2021; H. V. S. Cole, Triguero-Mas, Connolly, & Anguelovski, 2019; Cronin-de-Chavez, Islam, & McEachan, 2019; Izenberg, Mujahid, & Yen, 2018; Saunders et al., 2022). These barriers can include the lack of sidewalks or bike paths in their neighborhoods, inadequate public transportation systems, limited availability of affordable recreational facilities, and the absence of safe greenspaces. Additionally, the lack of safe and accessible environments for physical activity and social connection may contribute to feelings of isolation and disconnection from community and society (Hunter et al., 2019). It is only by addressing these structural barriers that we can ensure that all individuals have equitable opportunities to engage in the benefits of the outcomes of neuroscientific research that discusses how we can achieve better brain health through physical activity and social connectedness. In Chapter 4, we discuss these ideas in more detail and introduce the concept of universal design, an architectural and learning paradigm that can be traced back to disability rights and an increase in the aging population (Connell et al., 1997; Ostroff, 2011). The universal design paradigm aims to create a world that is accessible across all ability levels, across all ages (Carr, Weir, Azar, & Azar, 2013; Connell et al., 1997; Mace, 1988). One key feature that sets universal design apart from other inclusive design paradigms for built environments is its emphasis on social

connectedness and sustainability (Connell et al., 1997). In addition to promoting accessibility, creating spaces that foster social connection and community building can lead to stronger social networks and mutual support, reducing barriers to building community resilience and decreasing resource consumption (Krasny & Tidball, 2012; Ridge, 2011). This is particularly important in disadvantaged neighborhoods, where individuals may have limited access to resources and opportunities. By incorporating universal design principles into these communities, we can promote social connection, help individuals feel more supported and engaged in their communities, and reduce brain health disparities. By incorporating the principles of universal design into the built environment, we can create spaces that promote ease of navigation and spatial cognition, reducing cognitive load by simplifying the way we interact with the world. This can have a positive impact on cognitive functioning and the quality of life of individuals of all abilities, enabling access to physical activity and social connectedness. We discuss these ideas in greater detail in Chapter 4, and discuss universal design through the lens of cognitive neuroscience.

Dissertation Overview

Two experiments were conducted to understand the impact of behavioral and socioenvironmental factors on MTH system structure. In the first experiment, we examined how cardiorespiratory fitness correlated with greater cortical thickness of extrahippocampal regions implicated in subjective spatial cognition, building on neurobiological models of environmental enrichment and wheel running. These secondary cross-sectional data were obtained from two randomized clinical controlled trials (n = 100;

56 young adults and 44 older adults). In the second experiment, we examined the relationship between perceived social discrimination and amygdala and anterior hippocampal volume in older adults. These data were collected from two pilot studies (n = 36), investigating the role of racism and discrimination as down-regulators of MTH system neuroplasticity, building on neurobiological animal models of chronic stress.

Experiment 1 used structural MRI and an assessment of cardiorespiratory fitness to investigate the relationship brain structure and cardiorespiratory fitness in healthy, sedentary young and older adults. Our primary objective was to test whether entorhinal, parahippocampal, and perirhinal cortical thickness would be positively modulated by cardiorespiratory fitness. We found that with greater cardiorespiratory fitness, there was corresponding greater cortical thickness of these regions in young adults, and that this was lateralized to the left hemisphere. However, contrary to our hypothesis we found that there were no such relationships in older adults.

In experiment 2, we investigated the relationship between participants' subjectively perceived social experiences of discrimination and anterior hippocampus and amygdala volume. Our primary hypothesis was that greater levels of perceived social discrimination would be associated with smaller amygdala and hippocampal, specifically anterior hippocampal, volume. Additionally, we tested whether sense of control, a measure of self-efficacy, would moderate these relationships. We found that at higher levels of perceived social discrimination there was lower amygdala and anterior hippocampal volume. Moreover, we found that at higher levels of personal mastery, a sub-measure and proxy for the belief that one has agency over an experience or event, the relationship between

perceived social discrimination and amygdala and anterior hippocampal volume was attenuated.

In the third chapter, we sought to integrate the aforementioned ideas in the context of health equity and universal design principles from a cognitive neuroscience perspective. Drawing upon critical race theory, public health, and public policy, we discuss the issue of structural determinants of health in the context of clinical interventions. We discuss structural determinants of health in the context of clinical interventions that are meant to positively influence brain health. We ask questions of the importance of safety, presence of sidewalks, access to green-blue spaces, and more in order to determine whether our interventions can be directly translated to promoting brain health and well-being in everyday life. Moreover, we discuss the potential for using universal design, a design paradigm built to support models of healthy aging and accessibility for those who are disabled, across the lifespan. Importantly, we discuss this within the context of systemic racism and structural barriers to health and well-being. We additionally expand upon one of universal design's tenets of the importance of social connectedness and social sustainability in tandem with the built environment in order to promote brain health and well-being.

Together these cross-sectional findings build upon our understanding of the sensitivity of the medial temporal hippocampal system to socioenvironmental factors. Additionally, these chapters aim to provide motivation to policy makers, clinicians, and other neuroscientists to think critically about the implications of their research beyond the bench, to the communities for whom this work is conducted.

CHAPTER TWO: CARDIORESPIRATORY FITNESS PREDICTS CORTICAL THICKNESS OF MEDIAL TEMPORAL BRAIN AREAS ASSOCIATED WITH SPATIAL COGNITION IN YOUNG BUT NOT OLDER ADULTS

The data for this project was collected Rachel Nauer Wehr, Matthew Dunne, Kathryn Kern, and Razan Alotaibi. I was responsible for conceptualizing the idea behind the project, analyzed the secondary data, and wrote the chapter with feedback from Kathryn Kern, Shiraz Mumtaz, Thomas Storer, and Karin Schon. This chapter exists as a preprint: Rosario, M. A., Kern, K. L., Mumtaz, S., Storer, T. W., & Schon, K. (2021). Cardiorespiratory fitness predicts cortical thickness of medial temporal brain areas associated with spatial cognition in young but not older adults. BioRxiv, 2021-04. doi: 10.1101/2021.04.11.439355.

Introduction

As part of a network essential for learning and memory, the hippocampus, entorhinal cortex (ERC), parahippocampal cortex (PHC), and perirhinal cortex (PRC) work cooperatively within a larger functional and structural extrahippocampal network (Ekstrom, Huffman, & Starrett, 2017; Moffat, Kennedy, Rodrigue, & Raz, 2007; Squire et al., 2004) to support spatial cognition. The PHC and PRC contain separate, yet slightly overlapping reciprocal connections with the ERC (Suzuki & Amaral, 1994), and the ERC has direct reciprocal connections with the hippocampus (Witter & Amaral, 1991). Initial electrophysiological support for the role of the hippocampus in spatial learning and memory was established through the discovery of place cells (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971). These regions were further implicated in spatial navigation through the

discovery of time (Eichenbaum, 2014), grid (Hafting et al., 2005), head direction (Taube et al., 1990), speed (Kropff et al., 2015), and boundary (Lever, Burton, Jeewajee, O'Keefe, & Burgess, 2009) cells. The PHC and PRC have been posited to underlie the representation of context and items, respectively (Squire & Zola-Morgan, 1991), with the parahippocampal place area, located within the posterior PHC, maintaining representations of spatial layout (R. Epstein & Kanwisher, 1998) and the PRC in more general visuospatial binding of objects within space (Connor & Knierim, 2017). These studies and computational models highlight a critical role for the medial temporal lobe (MTL) cortices, which house these brain regions, in spatial cognition.

Along with the aforementioned studies, additional non-human primate, and human studies also support the role of the MTL cortices in spatial navigation. Electrophysiological recordings in monkeys showed place-related neural signals during virtual navigation in the hippocampus (Hori et al., 2005) and PHC (Furuya et al., 2014). Neurotoxic lesioning of the hippocampus in rhesus monkeys impaired spatial relational learning (Lavenex, Amaral, & Lavenex, 2006). Follow-up histological analyses showed that this lesioning also resulted in partial to extensive damage of the human PHC homologue in monkeys (Lavenex et al., 2006), suggesting possible PHC involvement in spatial relational learning. In treatment-resistant epileptic patients, lesions of the PHC resulted in spatial memory impairment (Ploner et al., 2000). Functional magnetic resonance imaging (fMRI) investigations showed hippocampal recruitment during virtual navigation of a town (Maguire et al., 1998) and parahippocampal activation when participants virtually navigated a maze (Aguirre, Detre, Alsop, & D'Esposito, 1996). A more recent fMRI study in human subjects showed

macroscopic grid-cell like signals associated with the ERC during virtual navigation in an open arena (Doeller, Barry, & Burgess, 2010). Collectively, the above literature provides evidence for a role of the hippocampus and extrahippocampal MTL cortical regions in spatial cognition, including spatial navigation.

In addition to the MTLs supporting spatial navigation, these regions are exquisitely sensitive to the effects of aging on brain structure and spatial ability. In humans, older age is associated with greater hippocampal and PHC atrophy (Jack et al., 1997). Further, longitudinal assessments have shown age-related ERC and PHC structural atrophy in healthy adults (Daugherty & Raz, 2017; N. Raz et al., 2004; Naftali Raz et al., 2005; Shaw et al., 2016). In addition, age-related structural atrophy in these MTL regions is heterogeneous, such that the hippocampus atrophies at a faster rate compared to the ERC in healthy aging (Naftali Raz et al., 2005). Aging associated behavioral and functional changes in MTL-dependent spatial navigation and episodic memory also exist (Lester, Moffat, Wiener, Barnes, & Wolbers, 2017; Zhong & Moffat, 2018). Cross-sectional work has demonstrated an age-related decline in spatial mnemonic performance across the lifespan during a virtual route disambiguation task (Nauer, Schon, & Stern, 2020). Furthermore, two functional neuroimaging studies examining spatial navigation showed reduced activation of MTL regions while navigating a virtual environment (Moffat, Elkins, & Resnick, 2006) and encoding of visual cues for goal-directed spatial navigation for older compared to young adults (Antonova et al., 2009). Considered together, these studies show that there are structural, behavioral, and functional age-related differences that are associated with experimental MTL-dependent measures of spatial navigation.

Whereas aging has been associated with reduced brain structural integrity and cognitive function, physical activity and aerobic exercise have been suggested as ways to mitigate age-dependent atrophy and cognitive dysfunction (Hillman et al., 2008; Voss et al., 2013). In humans, aerobic exercise increases cardiorespiratory fitness (CRF) (Hagberg et al., 1989; Kohrt et al., 1991), which is a measure of one's capacity to support ongoing physical activity through the combined efforts of the respiratory, cardiovascular, and musculoskeletal systems (Dalleck & Tischendorf, 2014). In middle-aged and older adults in particular, previous volumetric neuroimaging studies have shown positive associations between aerobic exercise, CRF, and neurocognitive integrity of cortical and subcortical regions (K. I. Erickson & Kramer, 2009; Kirk I. Erickson et al., 2014; Voelcker-Rehage & Niemann, 2013; Voss et al., 2013). In midlife, greater CRF was associated with increased bilateral PRC volume (Tian et al., 2015). Additionally, in older adults, greater CRF was associated with reduced age-related cortical atrophy across multiple brain regions, including prefrontal, inferior, and middle temporal cortices (Colcombe et al., 2003) and directly related to greater bilateral hippocampal volume (Kirk I. Erickson et al., 2009). Accordingly, these cross-sectional findings provide complementary evidence that CRF is related to attenuated age-related decline of neocortical and subcortical neurocognitive integrity.

A growing literature has shown that CRF also modulates cognitive function, MTL-dependent behavior, and brain structure in young adults. Kronman, Kern, and colleagues (2020) showed that in young adults, greater CRF predicted increased effective connectivity between the hippocampus and other regions of the default mode network (Kronman et al.,

2020). Separately, Nauer, Dunne, et al. (2020) showed that in initially lower-fit young adults, increasing CRF through aerobic exercise training was associated with significant improvement in hippocampal-dependent mnemonic disambiguation (Nauer, Dunne, et al., 2020). Consistent with these data, one study showed that increasing CRF through aerobic exercise training is associated with a significant improvement in visuospatial memory in young adults (Stroth et al., 2009). Recent work has also investigated relationships between CRF and MTL structure. In a cross-sectional voxel-based morphometry study, greater CRF was associated with greater right ERC volume in young adults (Whiteman et al., 2016). Schwarb and colleagues (2017) found that greater CRF was associated with greater hippocampal tissue integrity in young adults (Schwarb et al., 2017). In the same study, they found that hippocampal viscoelasticity, a measure of tissue integrity, mediated the relationship between CRF and performance on a spatial relational task (Schwarb et al., 2017). Furthermore, an exercise training study showed that increasing CRF through 12 weeks of aerobic exercise training resulted in increased volume of the left anterior hippocampus that was specific to the dentate gyrus/CA3 subfield in young adults (Nauer, Dunne, et al., 2020). Complementary work by another laboratory showed that increased CRF following a six-week aerobic exercise training program was associated with increased anterior hippocampal volume in young and middle-aged adults (Thomas et al., 2016). These complementary data show that the hippocampal and entorhinal regions are positively influenced by CRF in young adulthood, rather than only in the presence of age-related atrophy, but little is known regarding other MTL neocortical structures implicated in spatial navigation.

The current study was designed to examine the influence of CRF upon left and right extrahippocampal MTL cortical regions implicated in spatial cognition in young and older adults. Here, we take a region of interest approach to the MTL based on the extant functional and structural literature. The primary goal of this study was to investigate the association between CRF and brain structure of MTL cortical regions that, along with the hippocampus, are critical for spatial cognition. Based on the above literature, we hypothesized that greater CRF should positively predict left and right ERC, PHC, and PRC thickness in young and older adulthood. Additionally, we also hypothesized that MTL cortical thickness would be positively associated with greater subjective sense of direction in young and older adults. To test our hypotheses, we used a submaximal treadmill test to estimate CRF in young and older adults and an automatic segmentation protocol using FreeSurfer to measure MTL cortical thickness. We found that greater CRF was associated with greater ERC, PHC, and PRC thickness in young, but not older, adults and that these associations were lateralized to the left hemisphere. We also showed that left PHC thickness differentially predicted sense of direction across age groups, with young adults showing a positive and older adult a negative relationship between left PHC thickness and sense of direction. Our findings extend a growing literature on the impact of CRF on brain structure in young and older adults from the hippocampus to the MTL neocortex, which are brain regions associated with spatial cognition.

Materials and Methods

Participants

Data for this study comes from two larger randomized controlled clinical trials (study 1: Neuroimaging Study of Exercise and Memory Function, ClinicalTrials.gov Identifier: NCT02057354) (Kern, Storer, & Schon, 2020; Kronman et al., 2020; Nauer, Dunne, et al., 2020); (study 2: The Entorhinal Cortex and Aerobic Exercise in Aging, ClinicalTrials.gov Identifier: NCT02775760) (Kern, McMains, Storer, Moffat, & Schon, 2022; Kern et al., 2020) which are both focused on investigating the effects of exercise on MTL structure and function. Baseline data from 56 young adults (18 - 35 years), 20 older adults (55 - 85 years) from study 1, and 24 older adults (60 - 80 years) from study 2 were included for the purposes of the current study. Participants were recruited from the greater Boston area via flyers and advertisements in local papers.

Participants underwent a prescreening process over the phone for inclusion and exclusion criteria. For young adults, exclusion criteria included severe anemia; history or occurrence of musculoskeletal, circulatory, or pulmonary conditions; diagnosis of an electrolyte disorder; acute infection, cancer, obesity as determined by American College of Sports Medicine (ACSM) guidelines (Dalleck & Tischendorf, 2014), diabetes mellitus type 1 or type 2, kidney failure, liver disease, thyroid disorders such as thyrotoxicosis/hyperthyroidism; history or diagnosis of psychiatric or neurological conditions; cardioactive or psychoactive medications; and self-reported drug abuse or alcohol misuse. Young adult women were also excluded if they were pregnant or breast-feeding. In addition to these exclusion criteria for young adults, older adults were also

screened for evidence of cognitive impairment using the Dementia Rating Scale-2 (DRS-2) (Mattis, 1976). Only cognitively intact older adults were included in the study. For study 2, exclusion criteria were identical to those described for study 1 except participants with heart, circulatory, respiratory, or musculoskeletal conditions could receive clearance by their primary care physician to enter the study. Finally, both young and older adult participants were screened for MRI contraindicators (e.g., ferro-magnetic metal in or on the body that could not be removed, claustrophobia).

Inclusion criteria for both young and older adults included being generally healthy, non-smoking, and sedentary, defined as less than 30 minutes three times per week of moderate or higher intensity physical activity over the last three months per ACSM guidelines (Dalleck & Tischendorf, 2014). Additionally, participants were fluent English speakers and had normal or corrected to normal vision. All participants signed a consent form approved by the Boston University Medical Campus Institutional Review Board and this research was conducted under the guidelines of the Declaration of Helsinki. Data is available upon reasonable request and upon establishment of a formal data sharing agreement.

Experimental Overview

Over three study visits, participants gave informed consent and were screened, underwent cardiorespiratory fitness testing, and completed MR imaging and cognitive testing. The visits were completed within a two to three-week period, with MR imaging

occurring no later than a week and not earlier than 24 hours after fitness testing to control for the acute effect of exercise on brain function and structure (Suwabe et al., 2017).

Assessment of Cardiorespiratory Fitness

We operationally defined CRF as aerobic capacity determined by maximal oxygen uptake ($\dot{V}O_{2max}$). Following previous work (Kern et al., 2022, 2020; Kronman et al., 2020; Nauer, Dunne, et al., 2020) we used a submaximal graded treadmill exercise test following a modified Balke protocol (Dalleck & Tischendorf, 2014) at the Boston University Fitness and Recreation Center in Boston, MA. This test protocol includes a 3-minute warm up followed by 8-12 minutes of data collection, followed by a 3-minute cool down. This protocol required participants to walk at their pre-determined fastest comfortable walking pace with an incrementally increasing grade. We monitored heart rate continuously using a heart rate monitor affixed to a chest strap (Polar, model H1) that wirelessly paired to a heart rate watch (study 1: Polar, model FT7; study 2: Polar, model A300). Using this heart rate monitor, we recorded heart rate observed in the last five seconds of every minute of testing. We measured blood pressure and recorded participants' rating of their perceived exertion, RPE, (Borg, 1982) every 3 minutes during the exercise test in line with established guidelines (Dalleck & Tischendorf, 2014). We terminated testing when the participant reached 85% of their age-predicted maximum heart rate (Tanaka, Monahan, & Seals, 2001). Oxygen uptake ($\dot{V}O_2$) was estimated from treadmill speed and grade using standard equations which take advantage of the known linear relationship between heart

rate and oxygen uptake (Wasserman, 2012) and the oxygen cost associated with walking at increasing grade, based on ACSM guidelines (Equation (1)):

$$\dot{V}O_2(est.) = (0.1\,mL/kg/\text{min} * S) + (1.8\,mL/kg/\,\text{min} * S * G) + (3.5\ mL/kg/\text{min}) \quad (1)$$

which has previously been described in detail (Kern et al., 2022, 2020; Kronman et al., 2020). In brief, $\dot{V}O_2$ is predicted from gross oxygen uptake (mL/kg/min), treadmill speed (*S*; m/min), percent treadmill grade (*G*; treadmill grade/100), and $\dot{V}O_2$ at rest (3.5 mL/kg/min), respectively (Dalleck & Tischendorf, 2014). Finally, we used linear regression to predict $\dot{V}O_{2max}$ based on the known relationship between heart rate and $\dot{V}O_2$ determined from work rate and the participant's age-predicted maximum heart rate. Participants were asked not to perform any strenuous activities 24 hours prior to the test and not to consume any caffeine three hours prior to fitness testing. This exercise protocol allowed us to safely and accurately estimate $\dot{V}O_{2max}$ for both young and older adults (Hagberg, 1994).

Magnetic Resonance Image Acquisition and Image Analysis

Study 1

Participants from Study 1 were scanned at the Boston University Aram V. Chobanian & Edward Avedisian School of Medicine Center for Biomedical Imaging using a 3 T Philips Achieva scanner with an 8-channel head coil. We collected high-resolution T1-weighted structural scans (multi-planar rapidly acquired gradient echo images; SENSitivity Encoding P reduction: 1.5, S reduction: 2; TR = 6.7 ms, TE = 3.1 ms, flip

angle = 9°, field of view = 25 cm, Matrix Size = 256 × 254, 150 slices, resolution = 0.98 mm × 0.98 mm × 1.22 mm).

Study 2

Participants from Study 2 were scanned at Boston University Cognitive Neuroimaging Center using a 3 Tesla Siemens MAGNETOM Prisma MRI scanner equipped with a stock 64-channel head coil. Since data acquisition for Study 1 happened before data acquisition of Study 2, and the Siemens Prisma scanner was not available yet for Study 1, data for the two studies were acquired using two different MRI scanners. Data from young adults were not collected for Study 2. For Study 2, we collected a high-resolution whole-brain structural T1-weighted magnetization-prepared rapid acquisition gradient multi-echo (multi-echo MPRAGE volume (slices (sagittal) = 176, TR = 2200 ms, TE = 1.67 ms, TI = 1100 ms, flip angle = 7°, field of view = 230 x 230 mm, acquisition matrix = 230 x 230, voxel resolution = 1.0 mm x 1.0 mm x 1.0 mm, GRAPPA acceleration = 4).

Regions of Interest

We conducted all automatic segmentations using FreeSurfer 6.0, a well-documented and free software available for download online (http://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012). FreeSurfer is a standardized, automatic segmentation tool that constructs surface-based representations of cortical thickness calculated as the closest distance from the gray/white matter boundary to the gray/CSF boundary (Fischl & Dale, 2000). All analyses were conducted on Boston University's Shared Computing Cluster, a Linux-based cluster with over 9,000 CPU cores.

All measures of cortical thickness for our regions of interest (ROIs), constructed using FreeSurfer's *recon-all* command, were extracted separately for the ERC (Desikan et al., 2006), PHC (Desikan et al., 2006), and PRC (Augustinack et al., 2013), for our *a priori* hypotheses detailed above. We also extracted cortical volumes for these ROIs and hippocampal volume for comparison with previous work. To decrease the likelihood of a Type 1 error, we restricted our analyses to a limited set of extrahippocampal cortical regions in the MTL that support spatial cognition constructed using FreeSurfer's anatomical demarcation (Augustinack et al., 2013; Desikan et al., 2006). For each participant, we visually inspected white matter and pial surface boundaries to assure proper ROI segmentation (Dale, Fischl, & Sereno, 1999).

Santa Barbara Sense of Direction Scale

We used the Santa Barbara Sense of Direction (SBSOD) scale (Hegarty, Richardson, Montello, Lovelace, & Subbiah, 2002) to investigate potential relationships between MTL cortex thickness and subjective spatial navigation. The SBSOD scale is a 15-item self-report questionnaire of one's ability to accurately navigate an environment. Participants were asked to select how much they agreed with a statement using a 7-point Likert scale ranging from *Strongly Agree* to *Strongly Disagree*. Some example questions include: "*My "sense of direction" is very good"; "I can usually remember a new route after I have traveled it only once"*. SBSOD scale scores were calculated as the averaged sum of all items after reverse-scoring positively phrased items. Higher scores indicate better subjective spatial ability. Three participants (1 young adult and 2 older adults from

Study 1) had missing SBSOD questionnaire data and were excluded from these analyses (final sample size: young adults n = 55; older adults n = 42).

Statistical Analyses

Statistical analyses were conducted using R (4.0.0) and RStudio (1.2.5042). We tested our primary outcome variables for normality using the Shapiro-Wilk test. All variables were normally distributed in the overall sample and within the young and older adult samples separately. Demographic characteristics were calculated using independent sample's t-tests. Continuous variables were summarized by mean, range, and standard deviation. Sex was summarized by percentage. In order to account for differences in scanner type between studies in our statistical analyses, we statistically controlled for scanner, and this is further discussed below. We conducted additional analyses without participants from Study 2 (Siemens Prisma), which is discussed in more detail below.

First, we conducted young and older adult group comparisons using an analysis of covariance (ANCOVA) method controlling for sex, education, and scanner type to establish if there was a differential impact of age group on ROI thickness. Next, we used multiple regression analyses that included a CRF (operationalized as estimated $\dot{V}O_{2max}$) by age group interaction term to determine whether CRF predicted left or right ERC, PHC, and PRC thickness differentially between young and older adults, controlling for sex, education, and for scanner type. Subsequently, we used ordinary least squares multiple regression models to test our primary hypothesis that greater CRF would predict greater left or right MTL ROI thickness in our young and older adults, separately, holding sex,

chronological age, education, and scanner type constant. We also ran the aforementioned analyses with just the Study 1 participants (n = 20 older adults, n = 56 young adults) controlling for sex and education. Moreover, taking advantage of FreeSurfer's output of cortical volume and hippocampal volume, we ran these same analyses with measures of ERC, PHC, PRC, and hippocampal volume as our primary outcome measures These secondary analyses allowed for comparison with the existing CRF and aging literature. We additionally controlled for estimated intracranial volume, provided by FreeSurfer's *recon-all* function.

In our analyses investigating sense of direction, we included an age group by ROI interaction term to determine whether cortical thickness of our ROIs predicted SBSOD scores differentially between age groups. We then separated our analyses by age group to investigate SBSOD scores from our primary ROIs in separate models, holding sex, chronological age, education, and scanner type constant, and included a ROI x estimated $\dot{V}O_{2max}$ interaction term to determine if CRF had any appreciable impact on the relationship between ROI and sense of direction. A significant interaction effect signified that estimated $\dot{V}O_{2max}$ moderated the ROI slope on sense of direction beyond the solitary influence of either estimated $\dot{V}O_{2max}$ or ROI thickness, in the statistical model.

Continuous predictor variables were standardized by mean-centering and scaling by 2 standard deviations (Gelman, 2008). ΔR^2, calculated using the *getDeltaRsquare* function in R, was used as a measure of effect size to determine the variance explained by the interaction effect and the inclusion of estimated $\dot{V}O_{2max}$ in our models. We corrected for multiple comparisons with the False Discovery Rate (FDR) method in R using the *p*-

adjust function, and statistical significance was considered at the corrected level of $p_{FDR} < .05$.

Results

Participant Characteristics

Participant characteristics for the overall sample are described in Table 2.1. DRS-2 raw memory and total scores are provided to show that our older adult sample is cognitively healthy compared with normative data (Johnson-Greene, 2004), and are not included in further analyses. We additionally provided a visual representation of the distribution of estimated $\dot{V}O_{2max}$ and SBSOD scores by age group and sex (see Figure 2.1). Subsequent analyses within the older adult sample were conducted and showed a significant difference in age and education between the older adults in Study 1 and Study 2 (see Supplemental Table 2.1).

Association between cardiorespiratory fitness and cortical thickness differs between young and older adults.

To understand our findings within the context of the existing CRF, aging, and brain structure literature, we first assessed whether there were mean differences in our primary ROI measures of cortical thickness, independent of CRF, by age group. Using an ANCOVA controlling for sex, education, and scanner type we compared young and older adults and found that there was no effect of age group on the thickness of the left ERC ($F(4,95) = .32$, $p = .57$), right ERC ($F(4,95) = 1.18$, $p = .28$), or left PRC ($F(4,95) = 2.33$,

p = .13). However, there was a significant effect of age group on thickness of the left PHC (F(4,95) = 10.15, p < .01), right PHC (F(4,95) = 9.03, p < .01), and right PRC (F(4,95) = 4.25, p = .04). These significant differences demonstrated that young adults had significantly greater mean cortical thickness than older adults (see Figure 2.2). Additionally, our exploratory examination of the hippocampus showed differences in left and right hippocampal volume between young and older adults. There was an effect of age group on left (F(4,95) = 21.45, p < .001) and right (F(4,95) = 20.80, p < .001) hippocampal volume, whereby young adults had significantly greater hippocampal volume compared to older adults.

Subsequently, using ordinary least squares regression, controlling for sex, education, and scanner, we tested for a CRF x Age Group interaction effect on left and right ERC, PHC, and PRC thickness. Although we predicted similar relationships for young and older adults, we conducted these analyses in order to determine if CRF would modulate extrahippocampal MTL cortical thickness differently in young and older adults as seen in previous work (V. J. Williams et al., 2017). We found no significant CRF x Age Group interaction effects on the thickness of the left ERC (ß = -.25 CI[-.53,.03], t(94) = -1.877, p_{FDR} = .12, ΔR^2 = .03; model: F(6,93) = 1.78, R^2 = .10), right ERC (ß = -.11 CI[-.43,.20], t(94) = -.70, p_{FDR} = .49, ΔR^2 < .01 ; model: F(6,93) = .67, R^2 = .04), left PHC (ß = -.32, CI[-.57,-.07], t(94) = -2.55, p_{FDR} = .07, ΔR^2 = .06; model: F(6,93) = 3.36, R^2 = .18), right PHC (ß = -.27, CI[-.51,-.03], t(94) = -2.20, p_{FDR} = .09, ΔR^2 = .04; model: F(6,93) = 2.78, R^2 = .15), left PRC (ß = -.29, CI[-.56,-.01], t(94) = -2.04, p_{FDR} = .09, ΔR^2 = .04; model: F(6,93) = 3.50, R^2 = .18), nor right PRC (ß = -.19, CI[-.52,.13], t(94) = -1.20, p_{FDR} = .28,

ΔR^2 = .01; model: $F(6,93)$ = 1.41, R^2 = .08) after correction for multiple comparisons. Similar to our findings in the overall sample, when we focused our analyses on Study 1, when controlling for sex and education, we found no significant interaction between CRF and age group (see Supplemental Table 2.2).

Next, in our overall sample, we investigated whether CRF predicted left or right ERC, PHC, or PRC thickness separately in young and older adults, first without the inclusion of CRF (model 1) and then with the inclusion of CRF (model 2). In order to do so, we separated our dataset by age group and controlled for chronological age, sex, and education within our models. Furthermore, in our older adult sample, we also statistically controlled for scanner type. In contrast to our hypothesis that greater CRF would predict increased cortical integrity in older adults, there were no significant relationships between greater CRF and left nor right ERC, PHC, or PRC thickness for older adults (see Table 2.2 for statistics). However, in agreement with our hypothesis for our young adult sample, greater CRF was positively correlated with greater left ERC, left PHC, and left PRC thickness (see Table 2.2 for statistics; Figure 2.3). CRF explained an additional 17%, 9%, and 11% of the variance for left ERC, left PHC, and left PRC thickness, respectively, beyond chronological age, sex, and education, in these statistical models. These analyses confirmed a positive association between greater CRF and increased MTL ROI thickness within the young adult group, and this was specific to the left hemisphere. There was no significant association between CRF and right ERC, right PHC, and right PRC thickness in young adults (see Table .2 for statistics). To confirm that the findings in our older adult sample were not confounded by scanner parameters, we further broke our older adult

sample into two groups by scanner, and found that there were no significant relationships between CRF and our ROIs, when controlling for chronological age, sex, and education (see Supplemental Table 2.3).

Next, for comparison with our analyses of the measures of cortical thickness, we extracted measures of cortical volume for our cortical ROIs. Data were tested for normality. Left ERC volume and left PRC volume in the overall sample (across age groups), and left ERC volume in the young adult sample were moderately to highly positively skewed and were log transformed for normality before subsequent analyses were completed. Using an ANCOVA controlling for sex, education, scanner, and estimated intracranial volume, we found no significant age group differences in left ($F(4,96) = .17$ $p = 0.68$) and right ($F(4,96) = .65$ $p = 0.42$) ERC and left ($F(4,96) = 2.78$, $p = 0.10$) and right ($F(4,96) = .19$, $p = 0.66$) PRC volume. However, there was a significant effect of age group on left ($F(4,96) = 26.14$ $p < .001$) and right ($F(4,96) = 12.68$ $p < 0.001$) PHC volume. These differences showed that young adults demonstrated significantly greater left and right PHC volume compared to older adults.

Using a multiple regression, controlling for sex, education, scanner, and estimated intracranial volume, we tested for a CRF x Age Group interaction effect on left and right ERC, PHC, and PRC volume. Similar to our previous analyses on cortical thickness, we found no significant CRF x Age Group interaction effect on these ROIs (see Supplemental Table 2.4 for statistics). Our volumetric analyses additionally showed no significant CRF x Age Group interaction effect on the volume of the left ($ß = -43.10$, CI[-344.41,258.20], $t(93) = -.28$, $p = .77$, $\Delta R^2 < .001$; model: $F(7,92) = 10.67$, $R^2 = .45$;) nor right ($ß = 31.56$,

CI[-.284.19,347.30], $t(93) = .20$, $p = .84$, $\Delta R^2 < .001$; model: $F(7,92) = 10.31$, $R^2 = .45$) hippocampus after controlling for sex, education, scanner, and intracranial volume. Next, following our analyses above, we stratified our analyses by age group and tested whether CRF predicted left or right ERC, PHC, or PRC volume separately in young or older adults, first without the inclusion of CRF (model 1) and then with the inclusion of CRF (model 2). In contrast to our findings on cortical thickness above, there was no relationship between CRF and volumetric measures of our ROIs in our young adult sample after correcting for multiple comparisons. In addition, similar to our previous results in older adults, we found no relationship between CRF and volume in our ROIs (see Supplemental Table 2.5). Moreover, when we conducted further analyses within age group, we found no significant association between CRF and left nor right hippocampal volume, when controlling for sex, education, age, scanner, and intracranial volume (see Supplemental Table 2.5).

Left parahippocampal cortical thickness sense of direction for young and older adults.

Based on our above finding that there was a significant difference in SBSOD scores by age group whereby older adults self-rated greater sense of direction compared to young adults ($t(95) = -3.64$, $p < .001$), we first investigated whether age group interacted with left and right ERC, PHC, and PRC thickness or CRF to predict sense of direction. Thus, we included a CRF x Age Group interaction term controlling for sex and education, and a ROI x Age Group interaction term in separate models, controlling for sex, education, and scanner. There was no significant CRF x Age Group interaction effect on SBSOD scores

(ß = -.17, CI[-1.15,.82], $t(97) = -.34$, $p_{FDR} = .78$), thus we excluded CRF from all further analyses.

There was a significant Left PHC thickness x Age Group interaction effect on SBSOD scores (ß = -1.30, CI[-2.16,-.44], $t(96) = -2.99$, $p_{FDR} = .03$, $\Delta R^2 = .08$; model: $F(6,90) = 4.21$, $R^2 = .22$). We focused our subsequent analyses on the left PHC in order to determine whether the significant Left PHC thickness x Age Group interaction was driven by young and/or older adults, using multiple regression analyses within separate age group models. We found a significant positive relationship between greater left PHC thickness and greater SBSOD scores (ß = .59, CI[.001,1.18], $t(52) = 2.01$, $p = .05$, $\Delta R^2 = .07$; model: $F(3,51) = 2.0$, $R^2 = .11$), controlling for sex and education, in young adults (see Figure 2.4A). Contrary to our prediction, in older adults there was a significant negative relationship between greater left PHC thickness and lower SBSOD scores (ß = -.66, CI[-1.23,-.09], $t(38) = -2.35$, $p = .02$, $\Delta R^2 = .13$; model: $F(4,37) = 1.76$, $R^2 = .16$), controlling for sex, education, and scanner (see Figure 2.4B). Hence, our Left PHC thickness x Age Group interaction effect shows that greater sense of direction was associated with lower left PHC thickness in older adults and greater left PHC thickness in young adults.

For comparison with our above findings, we also tested whether age group interacted with left and right ERC, PHC, PRC, and hippocampal volume to predict sense of direction using a ROI x Age Group interaction term in separate models, controlling for sex, education, scanner, and estimated intracranial volume. In contrast to our cortical thickness results, we found a significant left (ß = -1.30, CI[-2.16,-.44], $t(96) = -2.99$, $p_{FDR} = .04$, $\Delta R^2 = .06$; model: $F(6,90) = 4.21$, $R^2 = .22$) and right (ß = -1.40, CI[-2.25,-.54], $t(95)$

= -3.25, p_{FDR} = .01, ΔR^2 = .09; model: $F(7,90) = 4.27$, R^2 = .25) ERC x Age Group and right (ß = -1.25, CI[-2.03,-.22], $t(95) = -2.46$, p_{FDR} = .04, ΔR^2 = .05; model: $F(7,90) = 3.49$, R^2 = .21) PRC x Age Group interaction effect on sense of direction. Neither left (ß = .03, CI[-.62,.67], $t(96) = .09$, p_{FDR} = .93, $\Delta R^2 < .001$; model: $F(6,90) = 2.46$, R^2 = .14) nor right (ß = .05, CI[-.63,.73], $t(96) = .15$, p_{FDR} = .93, $\Delta R^2 < .001$; model: $F(6,90) = 2.50$, R^2 = .14) hippocampus predicted sense of direction.

When stratified by age group, we found that left ERC (ß = .69, CI[3.53, 4.88], $t(51)$ = 2.22, p_{FDR} = .04, ΔR^2 = .09; model: $F(4,50) = 1.83$, R^2 = .13) and right ERC (ß = .74, CI[.11,1.36], $t(51) = 2.37$, p_{FDR} = .04, ΔR^2 = .10; model: $F(4,50) = 2.00$, R^2 = .14), but not right PRC volume (ß = .66, CI[-.02,1.33], $t(51) = 1.96$, p_{FDR} = .03, ΔR^2 = .07; model: $F(4,50) = 1.55$, R^2 = .11) significantly positively predicted sense of direction in young adults, controlling for sex, education, and estimated intracranial volume. In our older adult sample we found no significant relationships between left ERC (ß = -.42, CI[-.99,.16], $t(37)$ = -1.47, p_{FDR} = .21, ΔR^2 = .05; model: $F(5,37) = 1.39$, R^2 = .16), right ERC (ß = -.62, CI[-1.17,.06], $t(37) = -2.23$, p_{FDR} = .10, ΔR^2 = .11; model: $F(5,37) = 2.02$, R^2 = .21), nor right PRC volume (ß = -.38, CI[-.98,.22], $t(37) = -1.29$, p_{FDR} = .21, ΔR^2 = .04; model: $F(5,37)$ = 1.27, R^2 = .15) and sense of direction, when controlling for sex, education, scanner, and estimated intracranial volume.

Discussion

The goal of the current study was to investigate the relationship between CRF and structural integrity of MTL regions that subserve spatial cognition using a cortical surface-based structural analysis of cortical thickness. We tested the hypothesis that CRF would

positively predict left and right ERC, PHC, and PRC thickness in young and older adults. First, we investigated whether there was a significant difference in MTL neocortical thickness in young compared to older adults. We found that there was a significant difference in left PHC, right PHC, and right PRC thickness between young and older adults, such that young adults had greater cortical thickness in these regions compared to older adults. In line with our primary hypothesis for our young adult sample, at higher CRF, ERC, PHC, and PRC thickness was greater, but unexpectedly, these cortical thickness results were lateralized to the left hemisphere. Contrary to our hypothesis for our older adult sample, CRF was not correlated with MTL ROI cortical thickness. We then investigated whether a subjective assessment of sense of direction was related to CRF and to cortical thickness of our ROIs. We found that age group and left PHC thickness significantly interacted statistically to predict sense of direction. Ensuing analyses stratified by age group specific to the left PHC showed that young adults displayed a positive relationship and older adults a negative relationship between left PHC thickness and sense of direction. These findings extend a growing body of literature on the association between CRF and brain structure in young adults, by focusing on extrahippocampal MTL regions.

Cardiorespiratory fitness is positively associated with neocortical thickness in the MTL in young but not older adults

The primary objective of this study was to investigate the modulating role of CRF on extrahippocampal neocortical thickness of MTL regions implicated in spatial cognition in both young and older adults. Although we hypothesized a positive association between

CRF and MTL ROI thickness in both young and older adults, we first conducted analyses investigating whether age and CRF would interact to differentially predict left or right ERC, PHC, and PRC thickness similarly to previous work (V. J. Williams et al., 2017). There were no significant interactions between CRF and age group on left or right ERC, PHC, or PRC thickness. We then tested our primary *a priori* hypotheses by stratifying our following analyses by young and older adult groups to determine if CRF predicted cortical thickness of MTL ROI volumes within each age group.

Contrary to our hypothesis, there were no significant relationships CRF and MTL neocortical thickness nor between CRF and hippocampal volume in our older adult sample. In addition, when we separated our older adult participants by study, we found that our results on were consistent with our overall sample findings on cortical thickness. Considering the previously published literature, recent studies in older adults have investigated the effects of exercise on brain structural integrity and have largely focused on hippocampal volume. This body of work has demonstrated that greater CRF (Kirk I. Erickson et al., 2009), greater physical activity (K. I. Erickson et al., 2010), and aerobic exercise training that increases CRF (Kirk I. Erickson et al., 2011) are associated with increased or greater hippocampal volume and/or attenuation of age-related hippocampal atrophy. Additionally, in older adults increased CRF after a three-month exercise intervention was associated with increased hippocampal perfusion and hippocampal head volume (A. Maass et al., 2015). A recently published study focused on the relationship between CRF and hippocampal subfield volume in healthy older adults, showed that CRF was significantly related to bilateral hippocampal subiculum volume, and that this effect

was driven by the women in this sample (Kern et al., 2020). This finding could potentially explain this lack of relationship in our data, both in cortical thickness and cortical volume, given that previous findings showed that increased left anterior dentate gyrus volume following twelve weeks of exercise training was dependent on being initially lower fit and was specific to the dentate gyrus subfield of the left hippocampal head (Nauer, Dunne, et al., 2020). Although we recruited participants who identified as sedentary (Dalleck & Tischendorf, 2014), the participants in our older adult sample were generally more fit in comparison to national fitness norms (Myers et al., 2017) and we did not examine hippocampal subfield specificity. We also found no relationship between MTL cortical volume and CRF. The above literature suggests this lack of associations between CRF and hippocampal and MTL cortical thickness and volume identified for the older adults in our study may be due to either a sex-specific or hippocampal subfield-specific impact of CRF in aging. Moreover, the biggest benefit of CRF may be conferred to initially lower-fit individuals who have the capacity to increase fitness levels.

Our results in young adults complement a growing body of literature on the positive relationships between CRF and MTL structure in young adults (Nauer, Dunne, et al., 2020; Schwarb et al., 2017; Whiteman et al., 2016). Our analyses showed that greater CRF had a moderate to large effect on left ERC, left PHC, and left PRC thickness in young adults. Previously, using a voxel intensity-based morphometry method, greater CRF was shown to predict greater right ERC volume in a sample of young adults (Whiteman et al., 2016). When we examined the relationship between CRF and ROI volume, we found that there were no significant relationships. This suggests a potential preferential impact of CRF on

cortical thickness in our sample. We extended our understanding of the relationship between CRF and MTL ROI thickness to the left ERC, PHC and PRC. As in our older adult sample, these cross-sectional analyses in our young adult sample found no relationship between CRF and left nor right hippocampal volume. In conjunction with our null findings reported above, these data in young adulthood suggest that the ERC, and other regions of the MTL including the PHC and PRC, may be associated with CRF in the absence of age-related structural atrophy. Thus, our data builds on and complements a growing literature on the relationship between CRF and MTL structure beyond the hippocampus to the left ERC, left PHC, and left PRC in young adulthood.

Because we had no *a priori* hypotheses regarding laterality, we did not conduct analyses directly comparing hemispheres. However, it is of note that the relationships observed in young adults between CRF and MTL cortical thickness were found in the left, not right, hemisphere. In studies of physical activity in older adults, longitudinal and prospective research has shown a specific effect of physical activity (where CRF was not measured) on left lateralized brain structures, specifically in the left hippocampus (K. I. Erickson et al., 2010; Rosano et al., 2017). A meta-analysis of randomized controlled trials of CRF-induced changes following exercise training across the adult lifespan also reported a specific effect of aerobic exercise on left, but not right, hippocampus volume (Firth et al., 2018). Longitudinal work in young adults showed that a 12-week exercise intervention resulted in a volume increase in the left dentate gyrus/CA3 of the hippocampal head (Nauer, Dunne, et al., 2020). In contrast to these studies, an exploratory cross-sectional study investigating the relationship between CRF and cortical thickness in healthy young

vs. older adults found a more global association of CRF with brain structures in both the left and right hemispheres (V. J. Williams et al., 2017). Additionally, as mentioned previously, Whiteman and colleagues (2016) found a relationship between CRF and right ERC volume (Whiteman et al., 2016). These differences may relate in part to sample composition or analysis method, and future studies are necessary to examine whether CRF-brain relationships are lateralized. Our current findings on the relationships between CRF and left ERC, left PHC, and left PRC thickness add to our growing understanding of the impact of exercise and fitness on brain structure, and in the context of the extant literature, suggest that there may be a preferential impact on the left hemisphere, for reason as of yet unknown.

Our understanding of the underlying neurobiological mechanisms modulated by CRF in humans is still limited. Research in rodents provide suitable theoretical grounding on the impact of exercise, and by inference, CRF on brain structure and function, and suggest that growth and genetic factors may underlie the current study's observed associations between CRF and MTL cortices. For example, in rodents, the hippocampus and ERC showed greater expression of growth factors after wheel running which, in turn, were involved in the survival and differentiation of existing neurons (Ickes et al., 2000; Pham et al., 1999). In addition, independent of exercise effects, rodents from strains that engaged in more voluntary wheel running showed higher levels of brain-derived neurotrophic factor (BDNF), a growth factor important for neuronal survival and synaptic plasticity, in the MTL system, at rest (R. A. Johnson, Rhodes, Jeffrey, Garland, & Mitchell, 2003; Rebecca A. Johnson & Mitchell, 2003). Complementary to this research, a recent

human neuroimaging study in male adolescents investigated whether individual differences in BDNF genotype would moderate the impact of CRF on brain structures. They found such a moderation effect whereby participants with a BDNF genotype that facilitates greater BDNF expression showed a significant positive relationship between CRF and bilateral medial precuneus surface area (Herting, Keenan, & Nagel, 2016). This suggests the need for future studies to control for genetic factors in order to distinguish between exercise effects and genetic effects of CRF-related plasticity.

In addition to the research in rodents suggesting that growth and genetic factors may be modulated by CRF, work focused on morphological changes in both rodents and humans have proposed that neurogenesis, myelination, and vascularization may similarly be targets of increased exercise, and hence CRF. Early research on wheel-running in rodents showed a preferential impact of exercise on neurogenesis in the dentate gyrus subfield of the hippocampus (Van Praag, Christie, et al., 1999; Van Praag, Kempermann, & Gage, 1999b). More recent work using diffusion tensor imaging has shown an exercise-induced change in hippocampal myelination in both humans and rodents (Islam et al., 2020; Thomas et al., 2016). Separately, in a study focusing on the impact of exercise training on the MTLs, Pereira and colleagues (2007) found increased blood flow to the dentate gyrus subregion of the hippocampus in young mice after two weeks of voluntary wheel running (Pereira et al., 2007). In the same study, they found a corresponding increase in cerebral blood flow to the dentate gyrus in a small sample of young to middle-aged adults, as well as a non-significant positive impact of exercise training on increased cerebral blood flow to the ERC, after a three-month exercise intervention (Pereira et al., 2007). Altogether,

these neurobiological mechanisms provide different targets that may be modulated by CRF and necessitate additional multimodal and concurrent cross-species investigations to determine whether the observed changes associated with CRF are indeed conserved across species.

Left parahippocampal cortex thickness is differentially associated with sense of direction in young and older adults

We next investigated the relationship between CRF and our ROIs with sense of direction. We found that there was a significant interaction between age group and left PHC thickness predicting subjective sense of direction, and we thus limited our analyses on this relationship to left PHC thickness. The PHC has been implicated in both allocentric and egocentric navigation (Colombo et al., 2017; R. A. Epstein, 2008; R. A. Epstein, Patai, Julian, & Spiers, 2017), and is also related to subjective sense of direction (Hao et al., 2016). Thus, we asked whether left PHC thickness predicted sense of direction in our sample and found that in young adults, greater left PHC thickness predicted better sense of direction, whereas in older adults, greater left PHC thickness predicted poorer sense of direction. Moreover, in our supplementary analyses including cortical volume, we additionally found that in young adults left and right ERC volumes were directly related to sense of direction.

These results in our young adult sample extend previous work, which showed that greater bilateral ERC and PHC volume was positively correlated with higher SBSOD scores in a large sample of young adults (Hao et al., 2016). In contrast to our findings in young adults, our results in older adults are generally inconsistent with previous research

in spatial navigation and aging. First, using the SBSOD we found that older adults scored higher than young adults, and that within the older adult sample, men scored higher than women. Secondly, based on our hypothesis, we predicted that similar to our observation in the young adult sample we might see a positive relationship between greater cortical thickness and greater sense of direction in our older adult sample, which would reflect preservation of sense of direction with greater cortical thickness. However, in this analysis, we found no positive relationship. Additionally, in our supplementary analyses investigating the relationship between cortical volumes and sense of direction in older adults, we found no relationships. In a study investigating spatial memory in young and older adults, Rosenbaum and colleagues (2012) found that older adults rated themselves higher on subjective spatial ability compared to young adults, but performed worse on tests of spatial memory (Rosenbaum, Winocur, Binns, & Moscovitch, 2012). In the context of this literature, our results on the difference of self-rated navigational ability suggest that young adults may better approximate subjective sense of direction compared to older adults. Moreover, it is possible that self-rated sense of direction may not rely on the integrity of the MTL. A previous study in older adults showed that reduced parahippocampal gyrus volume predicted reduced signal in this region during encoding of virtual cues in an allocentric spatial navigation task (Antonova et al., 2009), suggesting that structural integrity of the PHC may underlie successful navigational performance in older adults. We found no significant interaction between CRF and age group on sense of direction in our study. One study in young adults that did investigate the influence of CRF on spatial performance found that a sensitive measure of hippocampal integrity, its

viscoelasticity, a measure of tissue integrity, mediated the relationship between CRF and performance on a spatial relational task (Schwarb et al., 2017). This suggests that CRF may be related to objective but not subjective measurements of spatial navigation. Further neuroimaging studies that examine both brain structure and function are needed to determine whether CRF modulates brain function and the underlying neural correlates that support spatial navigation ability in young and older adults. Further empirical research is also needed to investigate whether CRF may rescue functional and behavioral impairment in navigation ability in older, relative to young, adults.

Limitations

A major strength of the study is the large sample size compared to similar work investigating relationships between CRF and structural integrity within young and older adults. Our data were collected from two randomized controlled clinical trials. One major limitation of note is that we did not collect the MRI data on the same scanner. In order to maintain statistical power while addressing the potential for scanner effect (Chen et al., 2022) for our cross-sectional data, we statistically controlled for scanner type. Moreover, we additionally mitigated this concern by examining our older adult sample separately by scanner type. Although a limitation of our study is that we estimated rather than measured $\dot{V}O_{2max}$ with a submaximal test, this method was used because it has been established as a safe way to reliably estimate $\dot{V}O_{2max}$, compared to high-intensity maximal exercise tests, to ensure safety of populations with different mobility needs (Dalleck & Tischendorf, 2014; Hagberg, 1994). We chose this protocol to ensure the safety of our older participants during

exercise testing, and used the same protocol for our young adults to maintain concordance between age groups.

Although we cannot determine causality within our cross-sectional analyses, we showed that CRF was positively associated with left hemispheric MTL neocortical thickness in young adults. Randomized controlled trials that measure the change in extrahippocampal cortical thickness and change in CRF across multiple time points are needed to examine the nature of causal influence among our correlational findings.

Our current study lacked an objective measure of virtual navigation performance to supplement our measure of subjective spatial cognition. Thus, our results should be interpreted with caution, because subjective measures of spatial navigation may incorrectly approximate navigation ability in older adults (Rosenbaum et al., 2012). Future studies should collect objective measures of spatial navigation ability to understand how brain-CRF relationships support performance on spatial navigation tasks, and whether CRF mitigates age-related and neuropathological decline in spatial cognition (Anne Maass & Shine, 2019).

Conclusion

The current study extends the extant literature by providing additional evidence on the association between CRF and cortical thickness in the MTL of young adults. More specifically, these data extend previous work on the relationship between CRF and volume of the ERC in young adults, to left ERC, left PHC, and left PRC thickness, suggesting that these regions may be amenable to experience-dependent structural plasticity outside of age-related or neurodegeneration-related change. Additionally, although there is a rich

literature supporting the positive effect of exercise and CRF in older adults, our results observed in young adults did not extend to our older adult sample. Our findings on subjective sense of direction showed that left PHC was positively associated with sense of direction in young, but negatively associated with sense of direction in older adults. These paradoxical results in older adults require further investigation with objective measures of spatial navigation ability, and these measures are necessary to further investigate the relationship between CRF and spatial navigation ability. Our results suggest that across the lifespan there may be different neurobiological mechanisms by which CRF could influence brain plasticity at different time period in the adult lifespan.

Tables

Table 2.1

Demographics	$Range_{YA}$	$Mean_{YA}$	$Range_{OA}$	$Mean_{OA}$
N = 100		*N* = 56 M(SD)		*N* = 44 M(SD)
Age (years)	20 - 35	26 (3.5)	55 - 85	66 (7.3) *
Sex	-	71% female	-	58% female
Education (years)	12 - 20	17 (2.6)	12 - 20	17 (2.2)
Estimated $\dot{V}O_{2max}$ (ml/kg/min)	25.1 - 57.5	36.7 (6.8)	17.7 - 42.7	30.4 (5.9) *
Estimated $\dot{V}O_{2max}$ Percentile	3 - 90	41.7 (22.64)	27 - 99	78.3 (21.13)
SBSOD	1.7 - 6.3	4.4(1.1)	2.8 - 6.7	5.1 (.87) ***
DRS-2 Total Raw Score	-	-	133 - 144	140.97 (2.26)
DRS-2 Memory Raw Score	-	-	22 - 25	24.18 (.99)

Table 2.1. Participant Characteristics. Parametric data are presented as Mean (SD). Categorical data are presented using percentages. Differences between age groups statistically significant at $p < .05$ * or $p < .001$ ***. YA: Young adults; OA: Older Adults; $\dot{V}O_{2max}$ (ml/kg/min): maximal oxygen uptake; SBSOD: Santa Barbara Sense of Direction Scale; DRS-2: Dementia Rating Scale 2.

Table 2.2

	Cortical Thickness							
	ROI	*ß*	*95%CI*	*t(52)*	p_{FDR}	ΔR^2	*F*(4,51)	*Model* R^2
YA	Left ERC	**.25****	.10 - .41	3.30	**.01****	.17	2.39	.20
n = 56	Left PHC	**.18***	.03 - .33	2.36	**.04***	.09	2.18	.15
	Left PRC	**.23***	.02 - .44	2.64	**.03***	.11	2.50	.16
	Right ERC	.07	-.13 - .28	.70	.56	.01	.47	.04
	Right PHC	.10	-.06 - .26	1.29	.30	.03	.89	.07
	Right PRC	.06	-.14 - .25	.58	.56	<.01	.36	.03
	ROI	*ß*	*95%CI*	*t(39)*	p_{FDR}	ΔR^2	*F*(5,40)	*Model* R^2
OA	Left ERC	-.02	-.27 - .21	-.23	.82	<.01	.63	.08
n = 44	Left PHC	-.10	-.28 - .09	-1.02	.82	.02	1.21	.14
	Left PRC	-.03	-.28 - .22	-.23	.82	<.01	2.21	.23
	Right ERC	.04	-.20 - .28	.31	.82	<.01	.64	.08
	Right PHC	-.09	-.26 - .07	-1.12	.82	.03	2.45	.24
	Right PRC	-.04	-.28 - .21	-.29	.82	<.01	1.19	.14

Table Hierarchical multiple linear regression results for CRF and cortical thickness by age group. Table 2.2 details the change in variance explained by CRF (estimated $\dot{V}O_{2max}$) in separate models for young and older adults by ROI, controlling for chronological age, education, and sex. Significant results are bolded. OA: Older Adults; YA: Young Adults; ROI: region of interest, CI: confidence interval, ERC: entorhinal cortex, PHC: parahippocampal cortex, PRC: perirhinal cortex. ***** $p < .05$, ****** $p < .01$

Supplemental Tables

Supplemental Table 2.1

OA Demographics	$Range_{Study1}$	$Mean_{Study1}$	$Range_{Study2}$	$Mean_{Study2}$
N = 44		*N* = 20 M(SD)		*N* = 24 M(SD)
Age (years)	55 - 85	61.8 (6.9)	60 - 80	68.3 (5.7) **
Sex	-	45% female	-	71% female
Education (years)	12 - 20	15.9 (2.5)	12 - 20	17.5 (2.6) *
Estimated $\dot{V}O_{2max}$ (ml/kg/min)	19.9 - 42.7	30.21 (5.2)	17.7 - 41	30.1 (6.3)
Estimated $\dot{V}O_{2max}$ Percentile	27 - 99	69 (22.9)	43 - 99	86 (16.3) *
SBSOD	2.8 - 6.5	5.3(1)	3.4 - 6.7	5 (.8)
DRS-2 Total Raw Score	133 - 144	140.7 (2.6)	136 - 144	141.2 (2)
DRS-2 Memory Raw Score	22 - 25	24.2 (1.1)	22 - 25	24.17 (.96)

Supplemental Table 2.1. Older Adult Participant Characteristics. Parametric data are presented as Mean (SD). Categorical data are presented using percentages. Differences between age groups statistically significant at $p < .05$ * or $p < .01$ **. OA: Older Adults; $\dot{V}O_{2max}$ (ml/kg/min): maximal oxygen uptake; SBSOD: Santa Barbara Sense of Direction Scale; DRS-2: Dementia Rating Scale 2.

Supplemental Table 2.2

	Cortical Thickness							
	ROI	*ß*	*95%CI*	*t(71)*	p_{FDR}	ΔR^2	*F*(5,70)	*Model* R^2
	Left ERC	-.33	-.74 - .06	-1.69	.24	.03	2.20	.13
n = 76	Left PHC	-.27	-.65 - .11	-1.42	.24	.02	2.90	.17
	Left PRC	-.14	-.55 - .28	-.66	.57	<.01	3.70	.21
	Right ERC	-.15	-.65 - .36	-.57	.57	<.01	.58	.04
	Right PHC	-.27	-.66 - .11	-1.41	.24	.03	2.20	.14
	Right PRC	-.33	-.81 - .14	-1.42	.24	.03	1.81	.11

Supplemental Table 2.2. Multiple linear regression results for CRF by age group interaction. Supplemental Table 2.2 details the change in variance explained by the CRF (estimated $\dot{V}O_{2max}$) x Age Group interaction, controlling for sex and education in Study 1 (OA n = 20; YA n = 56). OA: Older Adults; YA: Young Adults; ROI: region of interest, CI: confidence interval, ERC: entorhinal cortex, PHC: parahippocampal cortex, PRC: perirhinal cortex.

Supplemental Table 2.3

	Cortical Thickness							
	ROI	*ß*	*95%CI*	*t(16)*	p_{FDR}	ΔR^2	*F*(4,15)	*Model* R^2
OA_{study1}	Left ERC	-.1	-.45 - .25	-.62	.97	.02	1.85	.33
n = 20	Left PHC	.04	-.30 - .38	.24	.97	<.01	.79	.18
	Left PRC	.18	-.26 - 62	.86	.97	.03	1.71	.31
	Right ERC	-.01	-.49 - .47	-.03	.97	<.01	.57	.13
	Right PHC	-.01	-.32 - .30	-.06	.97	<.01	1.45	.28
	Right PRC	-.07	-.46 - .32	-.40	.97	.01	1.90	.34
	ROI	*ß*	*95%CI*	*t(20)*	p_{FDR}	ΔR^2	*F*(4,19)	*Model* R^2
OA_{study2}	Left ERC	.03	-.33 - .40	.17	.86	<.01	.29	.57
n = 24	Left PHC	-.23	-.48 - .02	-1.92	.35	.15	1.34	.22
	Left PRC	-.22	-.54 - .10	-1.43	.35	.08	1.50	.24
	Right ERC	.08	-.19 - .36	.62	.81	.02	.32	.06
	Right PHC	-.15	-.37 - .07	-1.42	.35	.08	1.33	.22
	Right PRC	-.04	-.42 - .34	-.21	.86	<.01	.11	.02

Supplemental Table 2.3. Hierarchical multiple linear regression results for CRF and cortical volume by age group. Supplemental Table 2.3 details the change in variance explained by CRF (estimated $\dot{V}O_{2max}$) in separate models for older adults in Study 1 and Study 2, by ROI thickness, controlling for chronological age, sex, and education. OA: Older Adults; ROI: region of interest, CI: confidence interval, ERC: entorhinal cortex, PHC: parahippocampal cortex, PRC: perirhinal cortex.

Supplemental Table 2.4

	Cortical Volume							
	ROI	*ß*	*95%CI*	*t(93)*	p_{FDR}	ΔR^2	*F*(7,92)	*Model* R^2
	Left ERC	-.08	-.15 - -.001	-2.02	.09	.04	2.74	.17
n = 100	Left PHC	-135.23	-380.61 - 110.16	-1.10	.33	<.01	6.98	.35
	Left PRC	-.04	-.10 - .02	-1.48	.22	.02	3.24	.20
	Right ERC	-356.09	-687.04 - -25.14	-2.14	.09	.04	2.60	.17
	Right PHC	-72.25	-317.68 - 173.18	-.59	.56	<.01	3.34	.20
	Right PRC	-321.20	-582.01 - -60.39	-2.45	.09	.06	2.72	.17

Supplemental Table 2.4. Multiple linear regression results for CRF by age group interaction. Supplemental Table 2.4 details the change in variance explained by the CRF (estimated $\dot{V}O_{2max}$) x Age Group interaction, controlling for chronological age, sex, education, scanner, and estimated intracranial volume. OA: Older Adults; YA: Young Adults; ROI: region of interest, CI: confidence interval, ERC: entorhinal cortex, PHC: parahippocampal cortex, PRC: perirhinal cortex.

Supplemental Table 2.5

	Cortical Volume							
	ROI	*ß*	*95%CI*	*t(51)*	p_{FDR}	ΔR^2	*F*(5,50)	*Model* R^2
YA	Left ERC	.04	-.01 - .09	1.62	.20	.04	2.49	.20
n = 56	Left PHC	54.28	-92.55 - 201.11	.74	.62	<.01	4.65	.32
	Left PRC	167.70	2.27 - 333.12	2.04	.19	.06	2.92	.23
	Left HPC	92.47	-64.73 - 249.68	1.18	.38	.01	13.11	.57
	Right ERC	193.83	-21.20 - 408.86	1.81	.20	.05	2.69	.21
	Right PHC	2.19	-160.53 - 164.91	.03	.98	<.01	2.27	.19
	Right PRC	189.19	29.74 - 348.63	2.38	.17	.08	4.94	.33
	Right HPC	29.19	127.79 - 186.17	.37	.81	<.01	13.38	.57
	ROI	*ß*	*95%CI*	*t(38)*	p_{FDR}	ΔR^2	*F*(6,37)	*Model* R^2
OA	Left ERC	-83.23	-313.03 - 146.58	-.73	.98	.01	1.07	.15
n = 44	Left PHC	12.30	-168.72 - 193.32	.14	.98	<.01	2.33	.27
	Left PRC	-8.41	-180.27 - 163.46	-.10	.98	<.01	1.32	.18
	Left HPC	86.74	-136.59 - 310.06	.79	.98	.01	4.05	.40
	Right ERC	-91.59	-331.13 - 147.94	-.78	.98	.01	1.39	.18
	Right PHC	-2.36	-170.60 - 175.32	.03	.98	<.01	.65	.10
	Right PRC	-35.94	-223.51 - 151.62	-.39	.98	<.01	1.21	.16
	Right HPC	83.03	-161.89 - 327.95	.69	.98	<.01	4.44	.42

Supplemental Table 2.5. Hierarchical multiple linear regression results for CRF and cortical volume by age group. Table 2.5 details the change in variance explained by CRF (estimated $\dot{V}O_{2max}$) in separate models for young and older adults by ROI volume, controlling for chronological age, sex, education, scanner, and estimated intracranial volume. OA: Older Adults; YA: Young Adults; ROI: region of interest, CI: confidence interval, ERC: entorhinal cortex, PHC: parahippocampal cortex, PRC: perirhinal cortex, HPC: hippocampus.

Figures

Figure 2.1

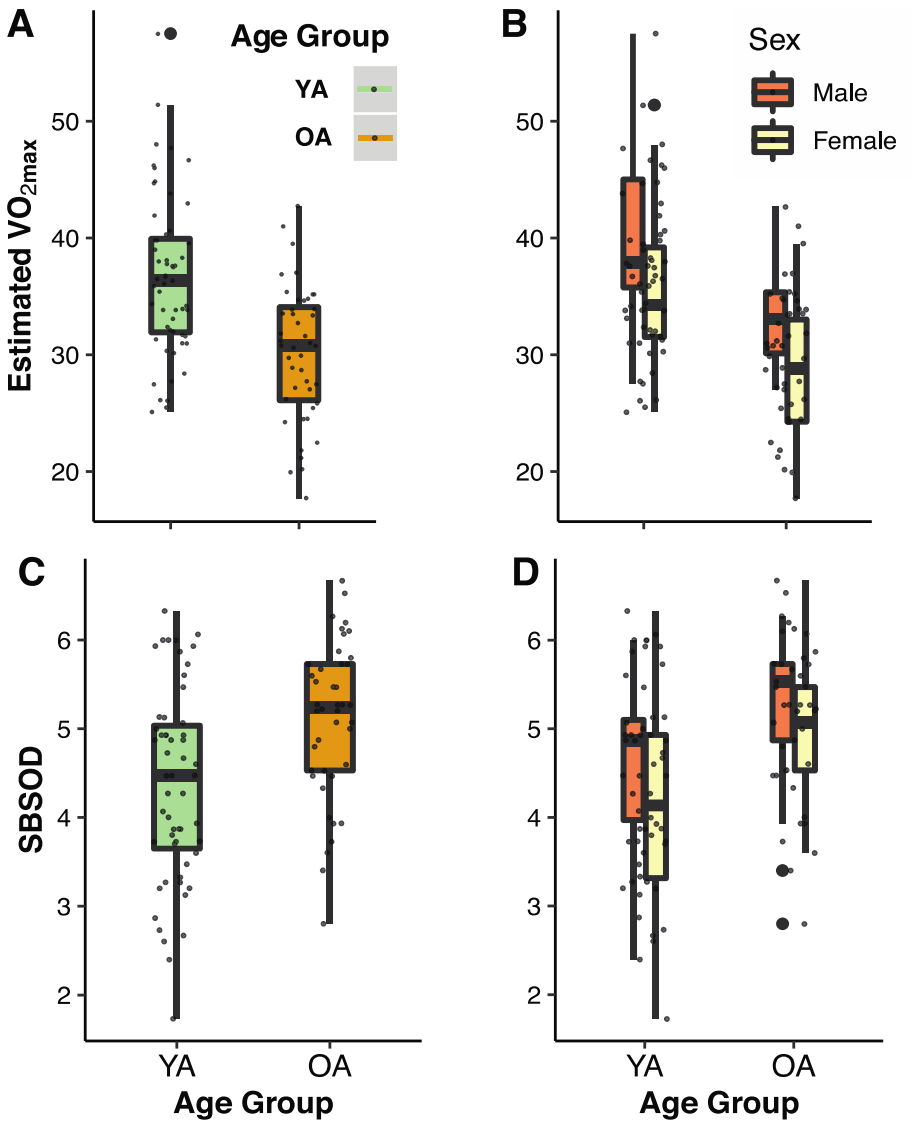

Figure 2.1. Boxplots of distributions by age group and sex for CRF and SBSOD. Distribution of estimated $\dot{V}O_{2max}$ by A) age group and by B) age group and sex. Distribution of subjective sense of direction scores by C) age group and by D) age group and sex. SBSOD: Santa Barbara Sense of Direction, YA: Young Adult, OA: Older Adult: Estimated $\dot{V}O_{2max}$: cardiorespiratory fitness operationalized.

Figure 2.2

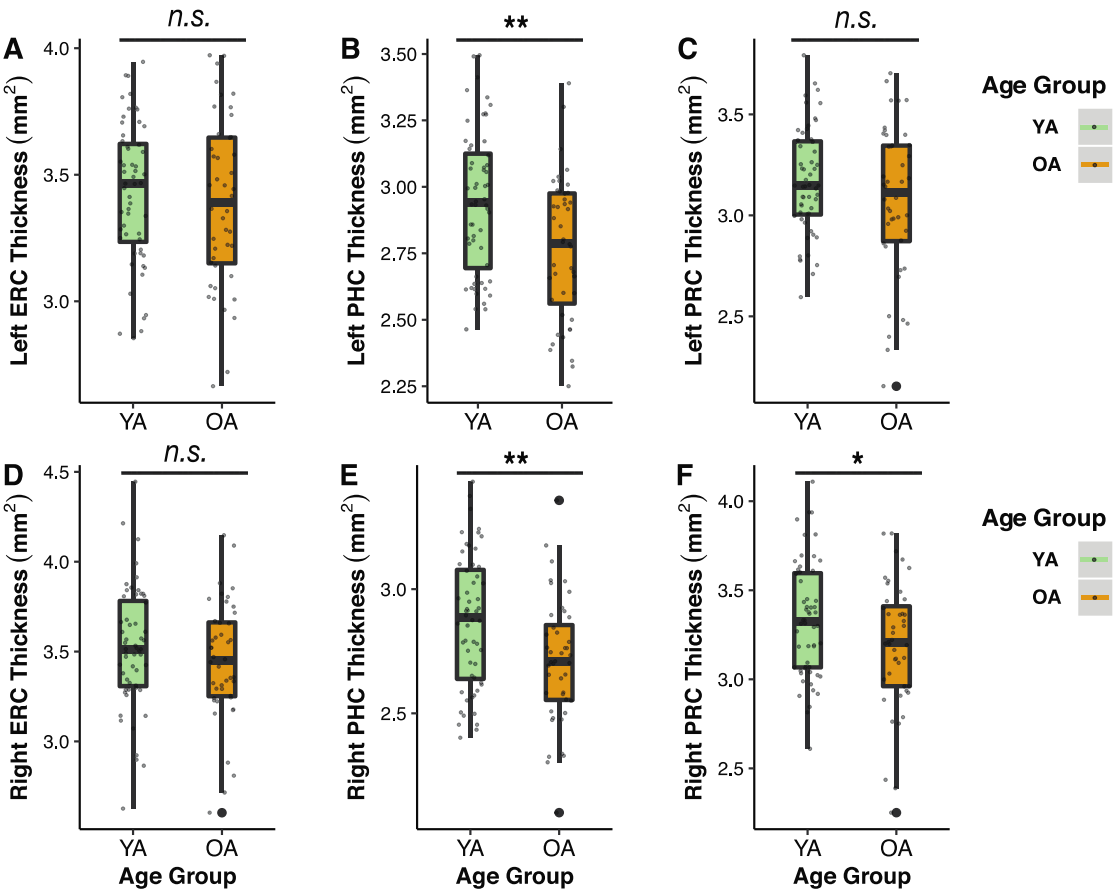

Figure 2.2. Box plots displaying significant mean differences between young and older adults by ROI. Top row presents left hemisphere ROIs: A) ERC, B) PHC, C) PRC; bottom row presents right hemisphere ROIs: D) ERC, E) PHC, and F) PRC, by age group, independent of the effect of cardiorespiratory fitness. ERC: entorhinal cortex, PHC: parahippocampal cortex; PRC: perirhinal cortex; YA: Young Adult; OA: Older Adult. * $p < .05$, ** $p < .01$.

Figure 2.3

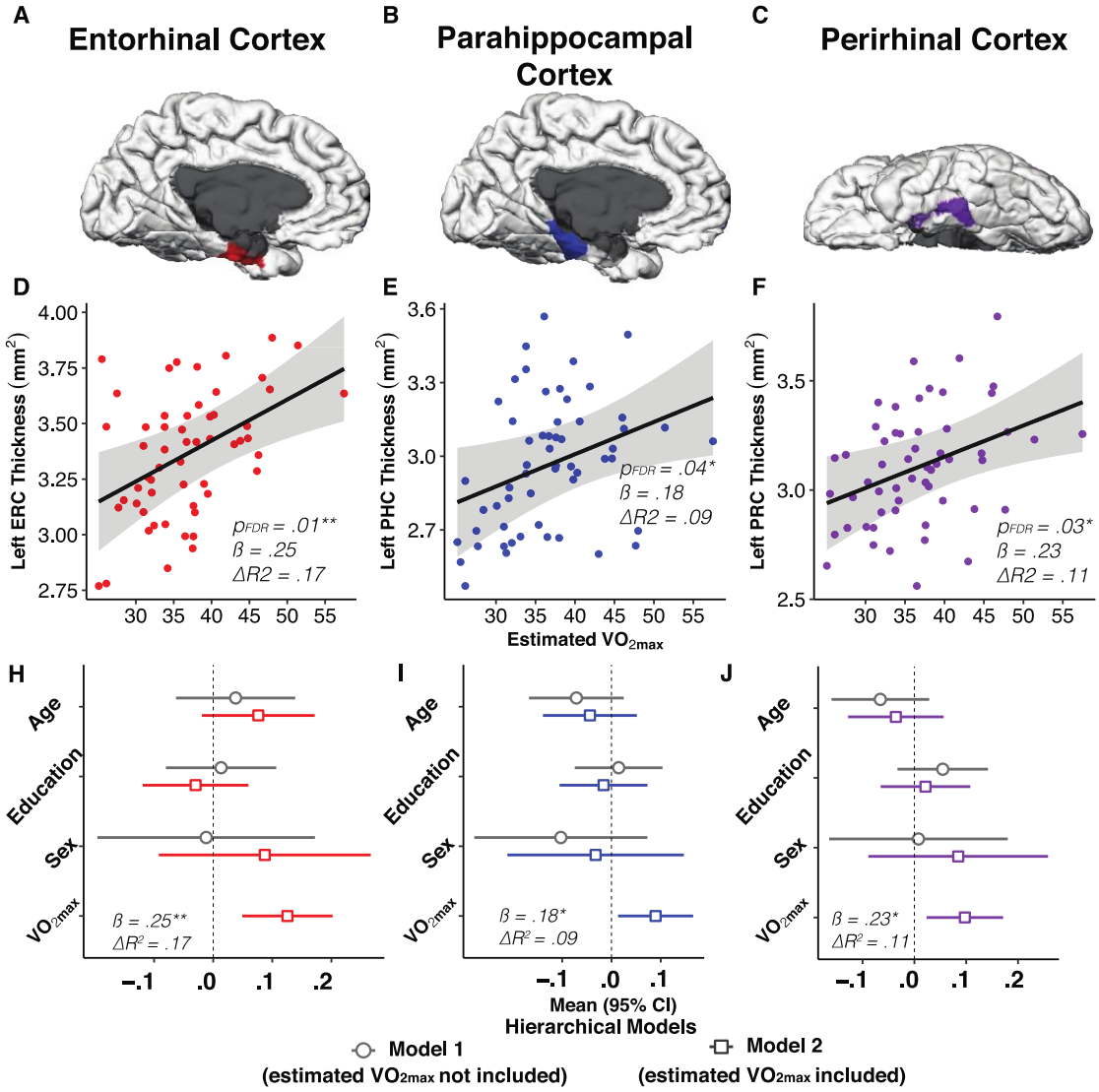

Figure 2.3. Greater CRF is associated with left ROI thickness in young adults. Figures within the top row present a graphical view of the region of interest from a representative participant for each corresponding scatterplot: A) entorhinal cortex (red), B) parahippocampal cortex (blue), C) perirhinal cortex (purple). Partial residual plots displaying the regression results for left D) ERC, E) PHC, and F) PRC thickness are presented in the second row, respectively, controlling for chronological age, education, and sex. For each corresponding scatterplot, we used a forest plot to display the overall results of the hierarchical linear model for each ROI, including covariates. Model 1, without the inclusion of estimated $\dot{V}O_{2max}$, is represented with an open circle, and model 2, with the

inclusion of estimated $\dot{V}O_{2max}$, is represented by an open square. The p_{FDR}, beta coefficient, and ΔR^2 are presented for each significant model.

Figure 2.4

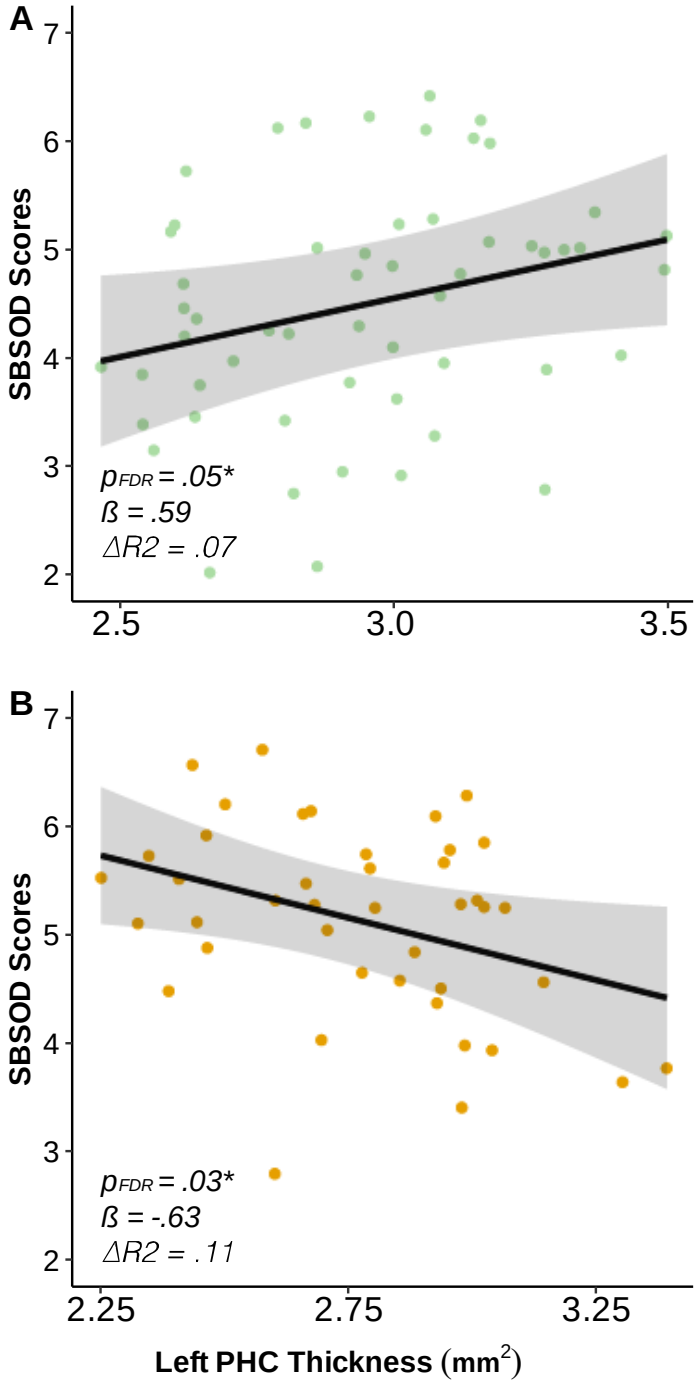

Figure 2.4. Santa Barbara Sense of Direction Scale Scores and Left Parahippocampal Cortical Thickness. There was a significant Left PHC Thickness x Age Group interaction

effect on subjective sense of direction. A) Subjective sense of direction was positively associated with greater left PHC thickness in young adults, controlling for sex and education. B) In older adults, subjective sense of direction was negatively associated with left PHC thickness, controlling for sex and education. PHC: Parahippocampal Cortex. SBSOD: Santa Barbara Sense of Direction.

CHAPTER THREE: GREATER PERSONAL MASTERY MODERATES THE ASSOCIATION BETWEEN GREATER PERCEIVED DISCRIMINATION AND LOWER AMYGDALA AND ANTERIOR HIPPOCAMPAL VOLUME IN A DIVERSE SAMPLE OF OLDER ADULTS

Data for this project were collected from two studies. I was responsible for data collection for Study 1 and Razan Alotaibi was responsible for data collection for study 2, collected via the Boston University Alzheimer's Disease Center Health Outreach Program for the Elderly. I conceptualized the project, analyzed the data for the project, and was responsible for writing this chapter in full. I was assisted by Amara Ayoub and Alan Espinal in data collection.

Introduction

The hippocampus and amygdala are part of the medial temporal lobe (MTL) system and have been well-established for their role in learning and memory. These regions have also been shown to be exquisitely sensitive to the impact of chronic psychosocial and physical stress (Magariños et al., 1996; McEwen, 2012; McEwen et al., 2016). The hippocampus can be functionally and structurally delineated along its long-axis, with the posterior portion shown to play a role in spatio-cognitive tasks and the anterior portion implicated in affective function (Fanselow & Dong, 2010; Poppenk et al., 2013a). The hippocampus is also bi-directionally structurally connected to the amygdala (Saunders et al., 1988). Together, these two brain regions work together within a larger structural and functional network including the prefrontal cortex to regulate stress and emotions (McEwen et al., 2016; Phelps, 2004; Phelps & LeDoux, 2005). Recent research has shown

that greater psychosocial stress negatively modulates hippocampal and amygdala volume in humans (Lupien et al., 2018; McEwen, 2012). Parallel findings in rodent and nonrodent models using foot shocks, chronic restraint, and social stress paradigms have emphasized the sensitivity of these two brain regions to chronic stress. Chronic stress, in turn, results in dendritic pruning and synapse loss in the amygdala and hippocampus, as well as apoptosis of adult-born neurons in the dentate gyrus subregion of the hippocampus (Anacker et al., 2018; Fuchs et al., 2006; Gianaros et al., 2007; Lupien et al., 2018; Magariños et al., 1996; McEwen et al., 2016; Phelps, 2004). Of particular importance and currently understudied is the role that sociocultural stress, namely perceived discrimination, has on amygdala and hippocampal structure and its implications for and translation to human health and well-being.

In an increasingly diverse and multicultural nation, with complex and complicated historically influenced social interactions, the potential for experiencing some form of psychosocial stress due to perceived discrimination associated with marginalized identities is elevated. Here, we define perceived discrimination as the unfair treatment of one group by a dominant social group along both singular and intersectional identities, with limited or no agency to respond to the event (Bailey et al., 2017; Krieger et al., 2005; Ong et al., 2009). This can be defined along many social axes, including race, sex, gender, sexual orientation, disability, age, or class and their intersections. As a salient chronic psychosocial stressor, although social identities that are subjected to chronic discrimination are social constructs perceived discrimination has been shown to have dire consequences for health and well-being (Bailey et al., 2017; Lewis et al., 2010; Zahodne, Manly, Smith,

Seeman, & Lachman, 2017b; Zahodne, Sol, et al., 2019). Greater experiences of discrimination have been associated with increased depression and anxiety (D. R. Williams & Williams-Morris, 2000) and higher inflammation (Lewis et al., 2010; Simons et al., 2018a).

Within the last decade, perceived discrimination has been well characterized through both cross-sectional and longitudinal research to have negative consequences for neurocognitive health (Barnes et al., 2012; Clark et al., 2018a; Fani et al., 2021, 2022; Glymour & Manly, 2008; Zahodne et al., 2023). In a sample of healthy Black older adults, research conducted by Barnes and colleagues (2012) found that greater perceived discrimination was associated with reductions in global cognition, including performance on episodic memory and perceptual speed assessments (Barnes et al., 2012). Longitudinal analyses conducted using the Health and Retirement study in a diverse, nationally representative sample of older adults found that greater perceived discrimination was associated with reductions in executive function, processing speed, and visuospatial construction performance (Zahodne et al., 2020). Research conducted through the Black Women's Health Study found that among older Black women, greater self-reported perceived discrimination predicted lower subjective memory for those who experienced more perceived discrimination (Coogan et al., 2020).

Recently, a rapidly growing literature has begun to focus on investigating the association between perceived discrimination and brain function and structure. In a cross-sectional lifespan study, Clark and colleagues (2018) showed that greater perceived discrimination was associated with aberrant amygdala functional connectivity among a

diverse sample (Clark et al., 2018a). During a task designed to assess neural responses to traumatic emotional images, greater racial discrimination predicted greater functional activity in regions important for emotional regulation and attention among Black women (Fani et al., 2021). Structurally, independent of experiences of trauma and post-traumatic stress disorder, greater perceived discrimination was associated with reduced fractional anisotropy, a measure of white matter structural integrity, in a number of white matter pathways among trauma-exposed Black women (Fani et al., 2022). More recently, greater perceived discrimination has been shown to be associated with lower hippocampal volume and greater white matter hyperintensities among older adults (Zahodne et al., 2023). This growing literature stresses the importance of characterizing and describing the impact that perceived discrimination has on brain structure and function in order to determine how the sociocultural environment may "get under the skin" to influence brain health. Altogether, the above findings provide evidence for the negative impact of perceived discrimination as a psychosocial stressor on neurocognitive health outcomes.

Complementing these research studies, exploring possible moderators of these relationships are also important and necessary to understand potential targets for intervention. Sense of control, a correlate of self-efficacy, has been shown to moderate physical and psychological health (Gore, Griffin, & McNierney, 2016; Lachman & Firth, 2004; Lachman & Weaver, 1998). Sense of control, measured using the MIDI Sense of Control scale, can be divided into two independent constructs, perceived constraints and personal mastery (Lachman & Firth, 2004). Personal mastery, internally perceived control over an event, and perceived constraints, externally perceived imposed obstacles, have

been shown to be predictors of well-being (Gore et al., 2016; Lachman & Firth, 2004). Across the lifespan, sense of control has predicted health and well-being with greater sense of control predicting better health outcomes. Research conducted by Pruessner and colleagues (2005), showed that among both young and older adults, sense of control was directly related to hippocampal volume (Pruessner et al., 2005). Moreover, in older adults, sense of control moderated the negative impact of physiological stress on both global brain volume and cognitive decline (Pruessner et al., 2005). Here, we focus on personal mastery and expand on its definition to define it as the self-perception of the agency an individual has in decision making in their everyday life. Greater personal mastery has been shown to enable individuals to extricate themselves from unsolvable tasks compared to those with lower personal mastery (Aspinwall & Richter, 1999). In a sample of older African American and Afro-Caribbean adults, personal mastery partially mediated the relationship between perceived discrimination and psychological distress, and suggest that interventions focused on increasing personal mastery may help in attenuating the negative impact of perceived discrimination on psychological distress (Muruthi et al., 2022). Considered altogether, the perceived discrimination and sense of control literature provide evidence for a direct impact of psychosocial stress on brain health and suggests a moderating role of personal mastery on the influence of psychosocial stress on brain structural outcomes.

The goal of the current study was to fill the gap in our understanding of the relationship between psychosocial stress, namely perceived discrimination, and brain structures of the medial temporal lobe both vulnerable to chronic stress and important for

stress and emotional regulation and processing. Thus, based on the extant literature, we had two primary hypotheses. First, we hypothesized that greater perceived discrimination would predict lower amygdala and anterior, but not posterior, hippocampal volume due to their role in both stress regulation and affective processing. Second, we hypothesized that greater personal mastery would attenuate the negative relationship between perceived discrimination and our regions of interest volume. In order to test these hypotheses, we assessed perceived discrimination using the Williams-Krieger Experiences of Discrimination (EOD) scale and personal mastery using the MIDI Sense of Control scale. We used FreeSurfer, an automatic segmentation software tool, to obtain amygdala and hippocampal volumes. Our results showed that greater perceived discrimination predicted lower amygdala and anterior, but not posterior, hippocampal volume. We additionally show that personal mastery attenuated these relationships, whereby at greater levels of personal mastery the relationship between perceived discrimination and our regions of interest was weakened. We conducted a number of exploratory analyses. First, we explored whether perceived discrimination was associated with anterior hippocampal subfield volumes, and found that perceived discrimination was associated with reduced anterior CA1 and subiculum volume. Second, we investigated whether perceived constraints would inversely moderate the relationship between perceived discrimination and amygdala and anterior hippocampal volume, and we found that there was no significant effect of perceived constraints on the relationships. Finally, although we report cross-sectional findings, we discuss potential mechanisms that might underlie our findings. Here, we provide evidence for the relationship between psychosocial stress, perceived

discrimination, and reduced brain structural volume, and a moderating role of personal mastery on these relationships, complementing a quickly growing literature on the relationships between perceived discrimination and neurocognitive health.

Materials and Methods

Participants

Data for this study were compiled from two pilot projects (study 1: Alzheimer's Association Research Grant Chronic Stress and Aging Study; study 2: Boston University Alzheimer's Disease Center (ADC) Pilot Grant) investigating the impact of experiences of perceived interpersonal social discrimination on brain structure in older adults (n = 36, 55 – 86 years). Participants from Study 1 were recruited from the greater Boston area via flyers and advertisements in local papers. Participants from Study 2 were recruited through the Boston University Alzheimer's Disease Center (ADC) Health Outreach Program for the Elderly (HOPE) Study. Data collection began in 2018 and was ended in March 2020 due to COVID-19 pandemic.

Study 1: Inclusion criteria included being between 50 to 80 years of age, identifying as non-Latinx Black/African American or White/European American, fluent in English, a non-smoker, and a resident of the Greater Boston Area. Participants were excluded if they had any major signs or symptoms suggestive of neurological or psychiatric symptoms, conditions, or disorders that are to known to affect medial temporal hippocampal system (e.g., epilepsy, diagnosis of depression, post-traumatic stress disorder, etc.), and conditions that affect HPA axis function (e.g., Cushing's disease).

Study 2: Inclusion criteria included being between 50 and 85 years of age, identify as non-Hispanic Black/African American or White/European American, an ADC research diagnosis of "Control" (i.e., cognitively unimpaired), available MRI data (a T1-weighted structural scan), and fluent in English. Eligible participants were contacted by the ADC staff to determine interest in this research. Similar to Study 1, participants were excluded if they had any major signs or symptoms suggestive of neurological or psychiatric symptoms, conditions, or disorders that are to known to affect medial temporal hippocampal system (e.g., epilepsy, diagnosis of depression, post-traumatic stress disorder, etc.), and conditions that affect HPA axis function (e.g., Cushing's disease).

All participants signed a consent form approved by the Boston University Chobanian & Avedisian School of Medicine Institutional Review Board, and this research was conducted under the guidelines of the Declaration of Helsinki. Data is available upon reasonable request and upon establishment of a formal data sharing agreement.

Experiences of Discrimination

The Williams Major Discrimination questionnaire is a survey tool that has been extensively used in epidemiological studies to assess subjective interpersonal, perceived social discrimination (Krieger et al., 2005). Respondents are posed a series of 9 questions related to everyday situations and asked to indicate whether they experienced discrimination and subsequently assign the reason for which they were discriminated against (e.g., sexism, racism, nationality, class, sexual orientation, etc.). Sample questions include: *At any time in your life, have you ever been unfairly fired; Have you ever been*

unfairly stopped, searched, questioned, physically threatened or abused by the police? Following the work of Barnes and colleagues (2012), scores were summed for a minimum score of 0 and a maximum score of 9 (Barnes et al., 2012). Higher scores reflect more experiences of discrimination.

Perceived Stress Scale

We used the Perceived Stress Scale (PSS) to control for potential confounds of everyday life stress, separate from stress due to perceived social discrimination. The PSS is a 10-item questionnaire that assesses how stressful an individual perceived their life to be over the course of the previous month. Participants were asked to select how much they agreed with a statement using a 5-point Likert scale ranging from *Never* to *Very Often*. Some example questions include: "In the last month, how often have you been upset because of something that happened unexpectedly?*";* "In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?*"*. PSS scores were calculated as the averaged sum of all items after reverse-scoring positively phrased items. Higher scores indicate greater perceived stress.

Sense of Control

We used the MIDI Sense of Control questionnaire, a 12-item scale, to investigate the moderating influence of sense of control (Lachman & Firth, 2004; Lachman & Weaver, 1998). Specifically, we used the personal mastery subscale to determine whether respondents perceived that they were in control of responding to their experiences.

Questions included items such as: *I can do just about anything I set my mind to, Other people determine most of what I can and cannot do*. Personal mastery was used as a proxy for greater belief in agency over responding to an event. Higher scores reflect greater personal mastery.

Magnetic Resonance Image Acquisition and Image Analysis

MRI Acquisition

Participants from both projects were scanned at the Boston University Chobanian & Avedisian School of Medicine Center for Biomedical Imaging using the same Alzheimer's Disease Neuroimaging Initiative imaging protocol, collected on a 3T Philips Achieva scanner with an 8-channel head coil. We obtained high-resolution T1-weighted structural scans (multi-planar rapidly acquired gradient echo images; SENSitivity Encoding P reduction: 1.5, S reduction: 2; TR = 6.7 ms, TE = 3.1 ms, flip angle = 9°, field of view = 25 cm, Matrix Size = 256 × 254, 150 slices, resolution = 0.98 mm × 0.98 mm × 1.22 mm).

Regions of Interest

We conducted all automatic segmentations using FreeSurfer 7.1.0, a well-documented and free software available for download online (http://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012). FreeSurfer is a standardized, automatic segmentation tool that uses a probabilistic approximation of subcortical and archicortical volumes based on postmortem analyses of brain structure (Fischl & Dale, 2000). Pre-processing includes motion correction and averaging (Reuter, Rosas, & Fischl, 2010), removal of non-brain tissue (Ségonne et al., 2004), intensity normalization (Sled, Zijdenbos, & Evans, 1998) (Sled et al., 1998), tessellation of the gray matter white matter boundary, automated Talairach

transformation, and segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl, 2012; Fischl et al., 2002) Using the *recon-all* command, measures of cortical volume were extracted for the hippocampus and amygdala for our *a priori* hypotheses detailed above. Moreover, FreeSurfer also provides measures of hippocampal subfield volume. Hippocampal subfields were generated using a probabilistic tool based on ultra-high resolution based on *ex vivo* MRI data, providing delineations of anterior and posterior hippocampus, as well as subfields within the anterior and posterior hippocampus (Iglesias et al., 2015). Finally, we collected estimated intracranial volume (EICV), which was automatically calculated by FreeSurfer based on the transformation of each individual participant brain image to the atlas template space for brain normalization (Buckner et al., 2004).

Statistical Analyses

Statistical analyses were conducted using R (4.0.0) and RStudio (1.2.5042). We tested our primary outcome variables for normality using the Shapiro-Wilk test. All were normally distributed in the overall sample. Continuous variables were summarized by mean, range, and standard deviation. Sex was summarized by percentage. Demographic characteristics grouped by sex (men and women) and race (Black/African American and White/European American) were calculated using the Wilcoxon rank sum test due to unequal sample sizes.

We used multiple regression analyses to test our primary hypothesis that a greater number of perceived discrimination would predict lower amygdala and anterior hippocampal volume, controlling for sex, education, current stress, and EICV. Continuous predictor variables were standardized by mean-centering and scaling by 2 standard deviations (Gelman, 2008). Next, we conducted moderation analyses with personal mastery and perceived constraints as our moderating variables using the Interact package in R. Personal mastery and perceived constraints were broken down as the mean ± 1 standard deviation. Statistical significance of p-values was considered at the level of $p_{FDR} < .05$, using the false discovery rate for correction for multiple comparisons. We did not correct for multiple comparisons in our exploratory analyses, but provide measures of confidence intervals, *F* statistics, and adjusted-R^2 for comparison in addition to *p* values (Rubin, 2017).

Results

Participant Characteristics

Participant characteristics for the overall sample are described in Table 3.1. The participant characteristics are also broken down by study group and by sex. Black participants were younger, had fewer years of education, and had greater perceived discrimination. Black participants endorsed slightly higher perceived stress. Among men and women, there was a slight difference in personal mastery with women endorsing greater personal mastery. Men and women did not differ in age, education, perceived stress, nor perceived discrimination.

Association between perceived discrimination and amygdala and anterior but not posterior hippocampal volume

Using a multiple regression analysis, we investigated the relationship between perceived discrimination and amygdala and anterior hippocampal volume, controlling for current stress, sex, education, age, and EICV. We found that higher perceived discrimination was associated with lower amygdala (ß = -180.43, CI [-323.21, -37.66], $t(30) = -2.59$, $p_{FDR} = .03$; model: $F(6,29) = 3.22$, $R^2_{adj} = .28$) and anterior hippocampal (ß = -148.93, CI [-297.85, -0.0006], $t(30) = -2.05$, $p_{FDR} = .05$; model: $F(6,29) = 2.22$, $R^2_{adj} = .17$) volume. We also tested for the relationship between perceived discrimination and hippocampal body volume and found no association (ß = -60.80, CI [-147.81, 22.20], $t(30) = -1.51$, $p = .14$; model: $F(6,29) = 3.14$, $R^2_{adj} = .27$). We additionally investigated whether there were any associations between perceived discrimination and volume in our regions of interest by racial group and by sex. We found no significant interaction between perceived discrimination and racial group nor sex (see Supplementary Table 3.1).

Exploratory analyses by hemisphere and hippocampal subfield

We additionally explored the relationship between perceived discrimination and amygdala and anterior hippocampal volume by hemisphere. These exploratory analyses showed that perceived discrimination was associated with lower left (ß = -199.46, CI [-344.69, -54.23, $t(30) = -2.81$, $p < .01$; model: $F(6,29) = 3.56$, $R^2_{adj} = .31$), but not right (ß = -161.41, CI [-337.11, 14.29, $t(30) = -1.88$, $p = .07$; model: $F(6,29) = 1.92$, $R^2_{adj} = .14$) amygdala volume. Additionally, perceived discrimination was not associated with lower left (ß = -170.77, CI [-355.00, 13.47, $t(30) = -1.90$, $p = .07$; model: $F(6,29) = 2.40$, $R^2_{adj} =$

.19) nor right (ß = -127.0838, CI [-285.68, 31.52, t(30) = -1.64, p = .11; model: F(6,29) = 1.15, R^2_{adj} = .03) anterior hippocampal volume.

We further tested for the association between perceived discrimination and overall hippocampal subfield volume. We combined the DG/CA3/CA4 subregions due to voxel size resolution and tested for associations between perceived discrimination and subfield volumes (DG/CA3/CA4, CA1, subiculum in anterior vs. posterior hippocampus, combining left and right ROI volumes). We found that greater perceived discrimination was associated with lower anterior (ß = -57.32, CI [-109.34, -5.30] t(31) = -2.25, p = .03; model: F(5,30) = 2.06, R^2_{adj} = .13), but not posterior (ß = -5.28, CI [-21.17, 10.60], t(31) = -.68, p = .50; model: F(5,30) = 1.49, R^2_{adj} = .07), CA1 volume. Additionally, there was no association between perceived discrimination and anterior (ß = -21.72, CI [-62.67, 19.23], t(31) = -1.08, p = .29, model: F(5,30) = 1.79, R^2_{adj} = .10) nor posterior (ß = -7.75, CI [-38.29, 22.79], t(31) = -.52, p = .61, model: F(5,30) = 1.90, R^2_{adj} = .11) DG/CA3/CA4 volume. Finally, we found that perceived discrimination negatively predicted anterior (ß = -21.95, CI [-37.71, -6.19], t(31) = -2.84, p < .01, model: F(5,30) = 2.29, R^2_{adj} = .16) but not posterior (ß = -10.73, CI [-25.96, 4.49], t(31) = -1.44, p = .16, model: F(5,30) = 4.50, R^2_{adj} = .33) subiculum.

We next investigated the relationship between perceived discrimination and the anterior hippocampal subfield regions by hemisphere due to our previous significant associations in the anterior hippocampus. There was a significant association between perceived discrimination and left anterior CA1 volume (ß = -65.79, CI [-130.12, -1.45], t(31) = -2.09, p = .05, model: F(5,30) = 1.95, R^2_{adj} = .12) and left anterior subiculum

volume (ß = -29.00 , CI [-51.13, -6.88], $t(31) = -2.68$, $p = .01$, model: $F(5,30) = 2.15$, $R^2_{adj} = .14$). There were no significant associations between perceived discrimination and right anterior CA1, right anterior subiculum, nor anterior left or right DG/CA3/CA4 volume (see Supplemental Table 3.2).

Personal mastery moderates the relationship between perceived discrimination and anterior hippocampal and amygdala volumes

Next, to understand whether personal mastery influences the relationship between perceived discrimination and amygdala and anterior hippocampal volume in our sample, we ran a series of moderation analyses separately by personal mastery and perceived constraints since they are purported to test independent effects of sense of control (Gore et al., 2016). We found that personal mastery, but not perceived constraints (see Supplemental Table 3.3), interacted with perceived discrimination to predict amygdala (ß = 450.96, CI [5.43, 896.48], $t(29) = 2.07$, $p = .05$; model: $F(7,28) = 3.55$, , $R^2_{adj} = .34$) and anterior hippocampus (ß = 498.20, CI [27.38, 969.02], $t(29) = 2.17$, $p = .04$; model: $F(7,28) = 2.44$, , $R^2_{adj} = .22$) volume, such that as personal mastery increased the negative relationship between perceived discrimination and our regions of interest were attenuated (see Figures 3.1 and 3.2). We provide results for a test of simple slopes for each region of interest (see Table 3.2).

Discussion

The primary objective of this study was to investigate whether perceived discrimination, a salient modern psychosocial stressor, predicts amygdala and anterior

hippocampal volume among older adults. Additionally, we sought to understand the moderating role of sense of control on these relationships. We tested the hypothesis that higher perceived discrimination would correlate with lower amygdala and anterior, but not posterior, hippocampal volume. Moreover, we posited that higher levels of personal mastery, a subscale of sense of control, would attenuate the aforementioned relationships. First, we found that a higher number of experiences of perceived discrimination correlated with lower amygdala and anterior, but not posterior hippocampal volume. Second, we found that within the sample, higher levels of personal mastery attenuated the relationship between both amygdala and anterior hippocampal volume and perceived discrimination. We also conducted exploratory analyses examining these regions by hemisphere and within hippocampal subfields. We found that greater perceived discrimination was associated with left but not right amygdala volume, and was not associated with neither left nor right hippocampal volume. When examining the relationship between perceived discrimination and hippocampal subfield volumes, we found that greater perceived discrimination correlated with smaller anterior CA1and subiculum volume. Moreover, when we explored these associations by hemisphere, we found that these associations were lateralized to the left hemisphere.

Perceived discrimination is correlated with amygdala and anterior, but not posterior, hippocampal volume

The amygdala and hippocampus have been well characterized in their role in emotional and stress regulation (Herman & Cullinan, 1997; McEwen et al., 2016). Due to

this, we hypothesized that these regions of the medial temporal lobe may be particularly sensitive to the impact of perceived discrimination, a chronic psychosocial stressor. We specifically limited our focus to the amygdala and anterior hippocampus given their roles in modulating hypothalamic-pituitary-adrenal axis function, which is responsible for the stress response, and their recruitment in emotional regulation (McEwen & Gianaros, 2011; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013b). Although longitudinal research is needed to measure causality or directionality between perceived discrimination and brain structure or function in humans, it is possible to build on our understanding of the impact of perceived discrimination on brain structure using neurobiological animal models of psychosocial stress. It is well-established in animal models of stress that these regions of the brain undergo structural reorganization during stressful events (Fuchs & Flügge, 2003; McEwen et al., 2016). Fuchs and colleagues found that in tree shrews, exposure to a dominant conspecific resulted in dendritic atrophy in the CA3 region of the hippocampus (Magariños et al., 1996). Moreover, exposure to psychosocial stress impaired hippocampus-dependent memory and was associated with a reduction in hippocampal volume (Ohl et al., 2000). In non-human primates, fetal exposure to increased glucocorticoids, a physiological marker of increased stress, resulted in a reduction of hippocampal volume at 20 months compared to controls (Uno et al., 1994). In humans, general stress has been associated with reductions in hippocampal volume (Gianaros et al., 2007). More recent research has found that perceived discrimination was associated with aberrant amygdala functional connectivity (Clark et al., 2018a) and reductions in hippocampal volume (Zahodne et al., 2023).

Complementing this literature, in our current study, we found that perceived discrimination was negatively correlated with both amygdala and anterior, but not posterior hippocampus volume, such that as perceived discrimination increased we found a corresponding decrease in amygdala and anterior hippocampus volume in our older adult sample. Inflammation provides one potential neurobiological pathway by which we may see a deleterious impact of perceived discrimination on neurocognitive health, including changes to underlying neural architecture and emergent cognitive ability dependent on these structures. Greater perceived discrimination has been shown to predict greater inflammation in humans (Cuevas et al., 2020; Lewis et al., 2010; Paalani, Lee, Haddad, & Tonstad, 2011; Stepanikova, Bateman, & Oates, 2017; Yaffe et al., 2003; Zahodne, Kraal, Sharifian, Zaheed, & Sol, 2019). Greater inflammation, in turn, has also been shown to compromise cognition in older adults (Boots et al., 2020; Zahodne, Kraal, et al., 2019). Complementing this research, in rodents, inducing an inflammatory response in the hippocampus has been shown to impair hippocampal-dependent function (Czerniawski & Guzowski, 2014; Czerniawski, Miyashita, Lewandowski, & Guzowski, 2015). Together, this suggests a role for inflammation as a neurobiological mechanism underlying the link between perceived discrimination and neurocognitive health.

When we investigated the relationship between perceived discrimination and amygdala and anterior hippocampal volume by racial group and by sex, we found no significant associations, despite differences in the stress response by sex (McEwen et al., 2016; McLaughlin, Baran, & Conrad, 2009). However, we found no sex effect of perceived discrimination in our current sample. Our small and unequal sample size by both sex and

race may have obfuscated some of the potential sex and race-dependent effects of perceived discrimination on our regions of interest. Seminal work conducted by Geronimus and colleagues (2006) found that Black/African American people showed greater allostatic load, a composite measure of biological dysregulation, compared to White/European Americans. Moreover, when the groups were broken down by both race and sex, there was a significant difference by sex and race whereby Black/African American women showed the highest allostatic load across the lifespan, followed by Black/African American men, White/European American women, and White/European American men, respectively. Allostatic load has been consistently examined as a mechanism underlying the impact of chronic stress on health, including its influence on the plasticity of the human brain (McEwen, 1998b, 2012). Future research should collect physiological measures of the stress response and other markers of allostatic load including measures of inflammation in order to determine whether allostatic load may mediate the relationship between perceived discrimination and brain structural integrity in aging. Finally, for our exploratory analyses, we had anticipated that there would be a primary effect of perceived discrimination on the DG/CA3/CA4 region of interest due to its neuroplastic role in the production of adult-born neurons and its sensitivity to stress (Anacker et al., 2018; Belarbi & Rosi, 2013). However, we found that greater perceived discrimination was correlated with lower CA1 and subiculum volume, but not with DG/CA3/CA4 volume. Both the CA1 and subiculum hippocampal subregions have been implicated in the encoding and retrieval of episodic memories (Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Ledergerber & Moser, 2017). In healthy aging we also see a reduction of both volume and neurons in the

CA1 and subiculum in humans, and this effect is increased in Alzheimer's disease (Šimić, Kostović, Winblad, & Bogdanović, 1997). Our exploratory results suggest that the CA1 and subiculum subregions may be negatively impacted by experiences of discrimination outside of healthy aging, and this may impair episodic memory performance. However, research conducted within the context of perceived discrimination should use tasks that tax these dissociable regions in order to confirm these conjectures.

Personal mastery attenuates the relationship between perceived discrimination and amygdala and anterior hippocampal volume

Allostatic load, and components that influence it such as inflammatory biomarkers, has been consistently examined as a mechanism underlying the impact of chronic stress on brain health, (McEwen, 1998b, 2012). Greater perceived discrimination has been shown to predict greater inflammation in humans (Cuevas et al., 2020; Lewis et al., 2010; Paalani et al., 2011; Stepanikova et al., 2017; Yaffe et al., 2003; Zahodne, Kraal, et al., 2019) and compromise cognition in older adults (Boots et al., 2020; Zahodne, Kraal, et al., 2019). Although these neurobiological mechanisms play a part in explaining the harmful effects of perceived discrimination, it does not fully explain individual differences in how an individual may respond to an event, or whether they feel they have the agency to respond to that event. A framework developed by Fani and Khalsa (2022), may explain, in part, some of these differences (Fani & Khalsa, 2022). They hypothesize, in those experiencing racial discrimination, that there may be a disruption of somatic and perseverative function as a result of experiencing and perceiving discrimination. Here, we found that personal mastery attenuated the negative relationship between perceived discrimination and

amygdala and anterior hippocampus volume, such that as personal mastery increased, the relationships observed were attenuated. The amygdala and hippocampus are implicated in a number of disease states, including depression and may be disrupted as a result of perseverative cognition, or rumination (Belzung, Willner, & Philippot, 2015; Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010). Based on our findings, we propose that personal mastery may function as a way to interrupt increased perseverative cognition as a result of perceiving discrimination via belief in greater agency in responding to the event. Although we found that personal mastery attenuated the relationship between perceived discrimination and amygdala and anterior hippocampal volume, the role of personal mastery may be more complicated depending on previous life experience (Infurna, Rivers, Reich, & Zautra, 2015). In a study of childhood trauma and emotional reactivity to daily events, for participants who experienced childhood trauma, greater personal mastery was associated with reductions in perceived overall sense of well-being (Infurna et al., 2015). Finally, although we conducted an exploratory analysis of perceived constraints, we found no moderating effect of perceived constraints. In contrast to personal mastery, we expected to see an inverse relationship such that at lower levels of perceived constraints, perceived discrimination would have a negligible influence on amygdala and anterior hippocampus volume. However, it is possible that perceived constraints and perceived discrimination may interact in other ways to influence neurocognitive integrity. Altogether, these results suggest a more intricate model of the impact of personal mastery on brain health, and this may be complicated by experiences earlier in life.

Limitations of the Study

This study sought to understand the relationship between perceived discrimination and the structural integrity of regions of the medial temporal lobe important for stress and emotional processing and regulation in older adults. A potential limitation of the study, and a subject for future investigation, is to study regions of interest outside of the medial temporal lobe additionally recruited in stress and emotion, such as the prefrontal cortex (McEwen et al., 2016). One such region is the ventromedial prefrontal cortex, which has been posited to inhibit amygdala function in stress and emotional dysregulation (Andrewes & Jenkins, 2019; Hanson, Knodt, Brigidi, & Hariri, 2015; Myers-Schulz & Koenigs, 2012). Although we were able to investigate the relationship between perceived discrimination and amygdala and anterior hippocampal volume, due to our smaller sample size, we were unable to parse out differences related to different identities (e.g., race, class, gender) or their intersection (Crenshaw, 1991) which may individually or interactively contribute to our findings. Moreover, our approach to understanding perceived discrimination is coarse in that we ask participants to retrospectively report experiences of discrimination which may induce bias into our study. Future studies should use strategies such as ecological momentary assessment which may provide a better metric to evaluate experiences of discrimination (Shiffman, Stone, & Hufford, 2008), or group-specific studies that focus on experiences of discriminatory factors such as sexism or racism with a larger sample size. Finally, although we attempt to characterize the relationship between perceived discrimination and brain structure of the medial temporal lobe, it is also critical to assess cognitive function dependent on these brain regions to determine whether there is a

corresponding negative impact of perceived discrimination on cognitive function, such as learning and memory, as has been seen more globally (Barnes et al., 2012).

Conclusions

Characterizing how perceived discrimination impacts brain health is imperative to health equity. Without an understanding of how the sociocultural environment "gets under the skin" to influence brain health we are unable to create interventions that may help ameliorate the impact of perceived discrimination, including interventions through health and public policy. In the current project we determined that perceived discrimination was correlated with lower amygdala and anterior hippocampus volume. Moreover, we show that personal mastery, a measure of internal sense of control, attenuated these relationships, suggesting a potential avenue for future intervention studies.

Tables

Table 3.1

Variables	**Overall**	**Black**	**White**	**Male**	**Female**
	N = 36	N = 11	N = 25	N = 15	N = 21
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Age (years)	70.8 (6.8)	66.23 (8.3)	72.8 (5.0) *	69.2 (8.5)	72.0 (5.3)
Education	16.4 (2.1)	14.8 (1.7)	17.1 (2.0) **	16.4 (2.1)	16.4 (2.2)
Personal Mastery	22.1 (5.7)	20.1 (6.6)	23.0 (5.2)	20.7 (5.2)	23.0 (6.0) †
Perceived Constraints	46.6 (10.1)	45.6 (8.2)	47.0 (10.9)	45.5 (7.5)	47.3 (11.7)
Perceived Stress	11.4 (8.3)	16.6 (10.5)	9.1 (6.0) †	11.3 (8.1)	11.5 (8.6)
Perceived Discrimination	1.8 (1.8)	2.8 (2.0)	1.3 (1.5) *	2.1 (2.3)	1.5 (1.3)

Table 3.1. Participant Demographics († < .10, * < .05, ** < .01)

Table 3.2

Bilateral Amygdala	β	*p*	95% CI
-1 *SD*	**-114.11**	< .01**	-186.16, -42.05
At the mean	**-50.58**	.01**	-89.17, -11.99
+1 *SD*	12.95	.73	-62.32, 88.22
Bilateral Anterior Hippocampus	β	*p*	95% CI
-1 *SD*	**-111.65**	.01**	-187.80, -35.51
At the mean	**-41.47**	.05*	-82.25, -.69
+1 *SD*	28.72	.47	-50.82, 108.26

Table 3.2. A test of simple slopes showed that the relationship between perceived discrimination and our regions of interest was attenuated at one standard deviation below (score of 16.35) and at the mean (22.08) of personal mastery. *$p \leq .05$, **$p \leq .01$

Supplemental Tables

Supplemental Table 3.1

	Amygdala	Anterior Hippocampus	Posterior Hippocampus
PD*Sex	13.24	-41.36	-25.14
	[-130.48, 156.97]	[-190.52, 107.79]	[-110.21, 59.93]
N	36	36	36
R^2	0.40	0.32	0.40
PD*Group	-58.96	-51.03	-4.18
	[-196.13, 78.20]	[-183.01, 80.95]	[-85.21, 76.84]
N	36	36	36
R^2	0.56	0.57	0.56

Supplemental Table 3.1. Interaction analysis of perceived discrimination and sex. (Beta estimate [CI]; PD: perceived discrimination)

Supplemental Table 3.2.

	Left CA1	Right CA1	Left DG/CA3/CA4	Right DG/CA3/CA4	Right Subiculum
PD	**-32.89 ***	-24.43	-9.04	-12.68	-7.45
	CI[-65.06, -0.73]	CI[-53.42, 4.56]	CI[-32.59, 14.50]	CI[-34.75, 9.40]	CI[-15.45, .56]
N	36	36	36	36	36
R^2	0.25	0.17	0.20	0.20	.14

Supplemental Table 3.2. Perceived discrimination and anterior hippocampal subfield by hemisphere, uncorrected. (Beta estimate [CI]; PD: perceived discrimination; *$p \leq .05$)

Supplemental Table 3.3

	Amygdala	Anterior Hippocampus
PD*Perceived Constraints	-12.52	-49.03
	CI [-88.34, 63.31]	CI [-128.00, 29.94]
N	36	36
R^2	0.39	0.31

Supplemental Table 3.3. Perceived constraint does not interact with PD to predict amygdala nor anterior hippocampal volume, uncorrected. (Beta estimate [CI]; PD: perceived discrimination)

Figures

Figure 3.1

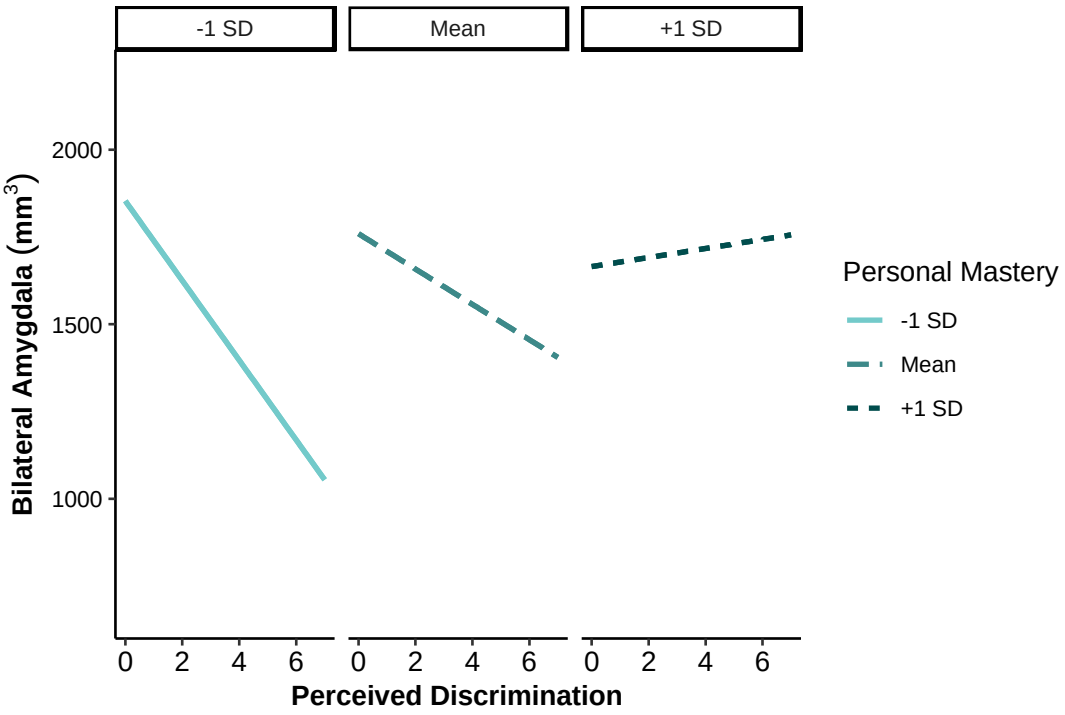

Figure 3.1. Perceived discrimination and personal mastery interacted to predict bilateral amygdala volume such that as personal mastery increased, the relationship between perceived discrimination and bilateral amygdala volume was attenuated.

Figure 3.2

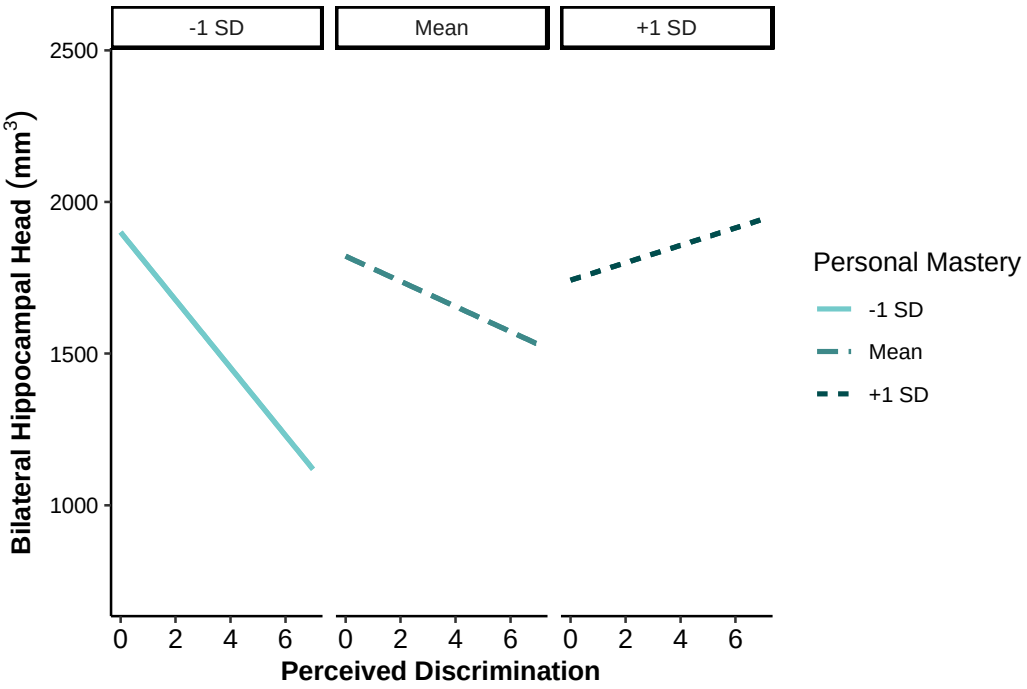

Figure 3.2. Perceived discrimination and personal mastery interacted to predict bilateral anterior hippocampal volume such that as personal mastery increased, the relationship between perceived discrimination and bilateral amygdala volume was attenuated.

CHAPTER 4: COGNITIVE NEUROSCIENCE AND HEALTH INEQUALITIES: A UNIVERSAL DESIGN APPROACH

> "The structures in the environment—the houses we live in, the areas we play in, the buildings we work in—affect our brains and our brains affect our behavior…The different spaces in which we live and work are changing our brain structures and our behaviors, and this has been going on for a long time."
>
> -Fred Gage (Eberhard, 2009)

A major theme in our understanding of the birth of new cells, neurogenesis, in the adult hippocampus is how the environment within which an individual lives influences the plasticity and integration of newborn cells into existing neural architecture to support cognitive function and behavior (Gage, 2002). Adult neurogenesis has also been extensively studied in the context of environmental enrichment, exercise fitness, and chronic stress, and how these environmental factors act as opposing up- and down-regulators of neurogenesis that may positively or negatively impact cognition and behavior, respectively (Klempin & Kempermann, 2007; Mirescu & Gould, 2006; Mohammed et al., 2002; Van Praag, Kempermann, et al., 1999a). Additionally, it has been difficult to contextualize these neurobiological models in their translation to human brain health and well-being. This limited understanding of how these models translate to human health inhibits our ability to introduce effective interventions and preventative health and social policies to support brain health. Here, we attempt to bridge these neurobiological models of environmental enrichment, exercise fitness, and chronic stress with studies in humans. These translation studies investigated relationships between cardiorespiratory fitness and chronic stress with hippocampal and surrounding brain regions of the medial temporal

hippocampal (MTH) system in the context of social and structural barriers to health (Bailey et al., 2017; Cronin-de-Chavez et al., 2019; A. T. Geronimus, 2001). This is imperative for discussing a potential avenue for policy makers and scientists to work synergistically with foundation and governmental funders, community partners, and citizen scientists, to promote health policies that benefit human brain health and well-being. We describe these impacts within the context of the built and social environment to provide a discussion on equitable access to the built environment (artificially created or modified areas where individuals live, work, or engage in recreational activities) in terms of social and structural determinants of health and barriers to health access (Gardner, Marpillero-Colomina, & Begault, 2018; Plough, 2015). We also discuss a potential avenue for scientists and policy makers to work towards health equity by merging concepts from neuroscience of spatial navigation and cognition and universal design, an architectural and learning paradigm that can be traced back to disability rights and an increase in the aging population (Connell et al., 1997; Ostroff, 2011). Studies, funders, organizations, and consortiums who conduct research towards human health and well-being should engage critically with how research conducted for human health may translate post-study. Likewise, funders should encourage and enable scientists to provide briefs on outcomes to policy makers, urban planners, architects, and others to assist in creating a just and equitable world based on evidence-based interpretations of research in order to directly benefit society. Finally, as scientists and researchers investigating factors that influence health, we must work together with community partners, research participants, and citizens for whom our research outcomes provide benefit to understand the material implications of our work.

The neurobiological basis of human health: Animal models of environmental enrichment and chronic stress in the medial temporal hippocampal system

The MTH system is a heterogenous region of the brain that is well-established in its role in learning and memory and is composed of interconnected anatomical structures, including the hippocampus, entorhinal cortex, parahippocampal cortex, perirhinal cortex, and amygdala (Phelps & LeDoux, 2005; Squire et al., 2004). The MTH system is exquisitely sensitive to the impact of chronic psychosocial and physical stress (Magariños et al., 1996; McEwen, 2012; McEwen et al., 2016) and the favorable impact of environmental enrichment (Mohammed et al., 2002).

Altogether, environmental enrichment (in comparison to deprived environments) and chronic stress have been shown to have a direct impact on the plasticity and neurobiological integrity of the MTH system. Environmental enrichment refers to how changes in the environment, such as the introduction of running wheels and sensory items, may be biologically beneficial (Newberry, 1995a). Early rodent model paradigms of environmental enrichment have showed profound beneficial changes in the adult rodent brain induced by the introduction of novel sensory items and running wheels (Mohammed et al., 2002). Research focused on the effect of environmental enrichment and physical activity on the MTH system showed that voluntary wheel running resulted in greater expression of biochemical growth factors involved in the survival and differentiation of existing neurons (Ickes et al., 2000; Pham et al., 1999). Additionally, these paradigms showed that there was an effect of environmental enrichment on proliferation of adult-born

neurons in the dentate gyrus subfield of the hippocampus in rodents (Van Praag, Kempermann, et al., 1999a), increased basal dendrite spine density in layer III of the entorhinal cortex (Stranahan et al., 2007), and proliferation and expansion of existing neurovasculature in young mice (Van Praag et al., 2005). In contrast, chronic stress is known to downregulate neuroplasticity mechanisms in the brain. Stressful events lead to structural reorganization in the MTH in animal models (Fuchs & Flügge, 2003; Fuchs et al., 2006; McEwen et al., 2016). Studies using foot shocks, chronic restraint, and social stress paradigms have emphasized the sensitivity of the MTH system to chronic stress. Chronic stress results in dendritic pruning and synapse loss in the amygdala and hippocampus, and apoptosis of adult-born cells in the dentate gyrus subregion of the hippocampus (Anacker et al., 2018; Fuchs et al., 2006; Magariños et al., 1996; Mirescu & Gould, 2006). Exposure to dominant conspecifics in a resident-intruder paradigm or psychosocial stress in animal models also results in dendritic atrophy and retraction in the hippocampus and amygdala, respectively (Fuchs et al., 2006; Magariños et al., 1996). These studies have also shown that chronic stress impairs hippocampus-dependent memory and reduces hippocampal volume (Ohl et al., 2000; Uno et al., 1994). Acting as opposing modulators of the MTH system in animal models, chronic stress and environmental enrichment provide two separate avenues for our understanding of the neurobiological basis of human health from the environments where we live. Next, we discuss studies and clinical interventions of exercise and physical activit, translated from animal models of environmental enrichment and wheel running, and their impact on the adult human brain.

Physical activity, exercise, and cardiorespiratory fitness and their impact on human brain health

Targets from *Healthy People 2030* call for an increase in physical activity across the lifespan, including calls for improved living environments that provide community access to activity and social connectedness (Office of Disease Prevention and Promotion, n.d.). In humans, the MTH system is modifiable by features of the environment. The hippocampus has been extensively studied in the context of physical activity and exercise, navigation of the environment, and learning and memory. London taxi drivers were found to have greater hippocampal gray matter compared to controls (Maguire et al., 2000), and unlicensed London taxi drivers showed an increase in hippocampal gray matter after training for taxi licensure (Woollett & Maguire, 2011). Building upon animal models of environmental enrichment and wheel running described in the previous section is a vast literature of both cross-sectional studies and longitudinal clinical trials investigating the beneficial impact of exercise, physical activity, and cardiorespiratory fitness on brain health (Aghjayan et al., 2022; Kirk I. Erickson et al., 2011; M. L. Erickson et al., 2022; Zhang, Paul, Winkler, Bogdan, & Bijsterbosch, 2022). In humans, aerobic exercise and physical activity can increase cardiorespiratory fitness (Hagberg et al., 1989; Kohrt et al., 1991), which is a measure of one's capacity to support ongoing physical activity via the interaction of the respiratory, cardiovascular, and musculoskeletal systems. There is substantial evidence of reduction in age-related structural and functional decline among cognitively healthy older adults (Aghjayan et al., 2022; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011), attenuation of cognitive impairment among individuals with mild

cognitive impairment and Alzheimer's disease and related dementias (ADRD) (Demurtas et al., 2020; Pisani, Mueller, Huntley, Aarsland, & Kempton, 2021), associations with better learning and memory (Bernstein & McNally, 2019; Callow, Pena, Stark, & Smith, 2022; Haverkamp et al., 2020; Nauer, Schon, et al., 2020), and greater cortical thickness and cortical volume among young adults (Whiteman et al., 2016; V. J. Williams et al., 2017). Altogether, there is ample evidence for a beneficial impact of exercise, physical activity, and aerobic fitness on brain health and the MTH system. As part of our own cross-sectional and longitudinal clinical trial research on the influence of exercise and cardiorespiratory fitness on brain health (Kronman et al., 2020; Nauer, Schon, et al., 2020; Nauer, Whiteman, Dunne, Stern, & Schon, 2015; Whiteman et al., 2016, 2014), one issue that we continue to tackle is the question of who has access to the built environments, communities, and neighborhoods that encourage and allow individuals to engage in health-promoting behaviors such as building cardiorespiratory fitness through physical exercise with the presence of built features in the environment such as sidewalks or parks. For example, racialized residential segregation has contributed to neighborhood deprivation by limiting access to resources and opportunities (Massey & Tannen, 2016), such as access to greenspaces, places for walking and exercise, and for community engagement. We must ask ourselves, as scientists working towards the benefit of human health in society, what role do we play in supporting policy makers or providing feedback to funders in making sure that the communities and neighborhoods from which we recruit our participants have access to the interventions and benefits of our research outcomes? If we can directly benefit individuals by intervention, avenues for increasing health through exercise should be

created for communities participating in research at the community level to challenge structural or social barriers to healthy living.

Social and structural barriers to brain health and their relation to the built and social environment

More commonly, discrimination as a salient psychosocial chronic stressor, has often been explained along a sociocultural and interpersonal axis and is often defined as the ongoing, unfair treatment of one group by a dominant social group on the basis of some difference in identity (e.g., race, class, gender or their intersection (Crenshaw, 1991)) where there is a decreased agency to respond to the event. (Ong et al., 2009; D. R. Williams & Williams-Morris, 2000). However, when we discuss issues of structural inequalities and barriers to engaging in behaviors for improving brain health, it is important to discuss the ways society could be structured to promote racial, gender, class, and other forms of discrimination. This includes pay inequality, de facto redlining (denying financial services to certain neighborhoods based on their racial or ethnic composition), housing inequality, education inequality, employment, health care, the criminal legal system, and other forms of structural inequalities that contribute to our biases and how we allocate material resources to develop and maintain human health (Bailey et al., 2021, 2017; Plough, 2015). There are a limited number of studies determining how discriminatory societal practices or perceived discrimination impact the brain and physiological markers of chronic stress and well-being. One study by Simons and colleagues found that experiencing segregation and discrimination during adolescence was predictive of increased inflammatory biomarkers

during later life and had a deleterious impact on health (Simons et al., 2018a). By contrast, there has been greater focus placed on investigating how interpersonal perceived discrimination may influence brain health. Perceived discrimination functions as a chronic psychosocial stressor and is associated with negative mental and physical health outcomes (Krieger, 2019; Krieger et al., 2005; Shankar & Hinds, 2017; D. R. Williams, 1997). Preliminary findings from our laboratory have shown that greater perceived discrimination is associated with lower amygdala volume and is moderated by greater personal mastery, a proxy for self-perceived agency (Rosario, Ayoub, Alotaibi, Clark, & Schon, 2020). Perceived discrimination, however, is not the sole contributor to health inequities. Expanding on this idea, perceived racial discrimination is one type of social discrimination and is defined here as the perceived unfair treatment of one group by a dominant social group on the basis of skin color (Ong et al., 2009; D. R. Williams & Williams-Morris, 2000). We focus on racism, the implicit and explicit values and biases that perpetuate racial discrimination, as a case study to directly link structural barriers on the allocation of material resources in neighborhoods. This includes access to/availability of sidewalks, parks, community centers, and greenspaces due to issues such as de facto redlining and housing inequality (Bailey et al., 2017). Ongoing racial discrimination threatens health and results in physiological changes to the body's ability to self-regulate and results in a cumulative toll of chronic stress on the body (Das, 2013; McEwen, 1998b; Shonkoff, Boyce, & McEwen, 2009). Longitudinal and cross-sectional studies have established a link between perceived chronic racism and negative physical and mental health outcomes (Das, 2013; Schmeer & Tarrence, 2018). Moreover, discriminatory experiences negatively

impact hippocampal structure (Zahodne et al., 2023), impair cognition across adulthood in Black Americans (Zahodne et al., 2017b), and impair episodic memory performance, which is reliant on MTH structure and function, in older Black Americans (Barnes et al., 2012),

When we combine our understanding of the beneficial impact of physical activity and aerobic fitness with the knowledge of structural barriers in safety and accessibility on brain health and well-being, it is important to situate how access to health promoting behaviors are affected within the context of the sociopolitical world (Barber, Ferreira, Gripper, & Jahn, 2022; A. T. Geronimus, 2001; Krieger, 1994; Miller, 2005; Plough, 2015). We provide this context in order to acknowledge inequitable access to a built environment conducive to health and well-being related to physical activity, enriched (rather than deprived) environments, and social connection and social sustainability within communities that have been deprived of the material resources outlined above (Barber et al., 2022; Butler, Gripper, & Linos, 2022; Gripper, 2023; Gripper et al., 2022). However, there has been little within the neuroscience literature critically questioning the problem of translation from bench to public health initiatives. It is not sufficient to create public health recommendations around physical activity and social and material sustainability if vulnerable populations do not have access to an environment conducive to positive health behaviors: do research participants or the general public have access to safe physical environments that allow social connection (e.g., community centers), physical activity (e.g., sidewalks), or healthy food (Gripper, 2023; Gripper et al., 2022)? Do we consider issues of inequalities in access to safe living conditions, facilities for community access

and social connection (that are affordable or free), and access to greenspaces (Cronin-de-Chavez et al., 2019; Wang & Lan, 2019)? Next, we discuss possible reasons for these disparities in access to public spaces and a paradigmatic shift that could instill equitable access to brain health and well-being.

Neighborhood disadvantage and deprivation are critical public health issues that affect many communities across the United States (Massey & Tannen, 2016; Ribeiro, Amaro, Lisi, & Fraga, 2018). Neighborhood disadvantage and deprivation are two related but distinct concepts that describe the various economic, social, and environmental factors that negatively impact the quality of life of individuals living in a particular area including factors such as poverty, unemployment, crime, inadequate housing, poor access to resources and services, and low social capital (Leventhal & Brooks-Gunn, 2000; Weinstein, Geller, Negussie, & Baciu, 2017). Historical instances of structural racism such as redlining and segregation have had a profound, and ongoing, impact on neighborhood disadvantage. These practices instill limited access to resources and opportunities, contributing to disparities in health outcomes (Bailey et al., 2017; Weinstein et al., 2017). Redlining refers to the discriminatory practices of denying financial services to certain neighborhoods based on their racial or ethnic composition, and has been shown to, at least in part, still negatively impact Black American health outcomes compared to White Americans (Graetz & Esposito, 2022). As scientists we need to think beyond our hypotheses and findings to the material access and benefits for our participants, without whom our studies and clinical research would be impossible. We suggest asking, “Are communities and neighborhoods safe for everyone?”; “What are the issues of

gentrification?", which have a negative impact on health (H. V. S. Cole et al., 2019; Izenberg et al., 2018); "Is there equitable access to green-blue public spaces and are there subsequent issues of greenspace gentrification (H. Cole & Immergluck, 2021)"? These questions point towards whether participants live in neighborhoods that enable them to translate our findings into practice.

Greenspace use has been shown to have positive impacts on mental and physical health outcomes (Gascon et al., 2015). A recent meta-narrative review by Hunter and colleagues reported how urban greenspace access has a beneficial impact on health, and posits that this pathway to health and well-being is facilitated by increasing physical activity and promoting social interaction (Hunter et al., 2019). It is important to note that other studies have found issues regarding equity-based outcomes among minoritized populations, whereby those from lower socioeconomic statuses or educational backgrounds benefit less from more urban green space development (H. V. S. Cole et al., 2019; Izenberg et al., 2018). Recent research investigating differences in access to greenspace, presence of dilapidated housing, and lack of public infrastructure has also provided evidence of disparities in the built environment compared to more affluent areas in access to the aforementioned built environment, with Black Americans and other minoritized/marginalized people living in areas that are not conducive to developing and maintaining physical health (Yang, Cho, Nguyen, & Nsoesie, 2023). Moreover, individuals living in neighborhoods with greater greenspace had better cognitive functioning than those living in areas with less greenspace (Beyer et al., 2014) and living in areas with high levels of air pollution negatively impacted cognitive function, particularly among older adults

(Weuve et al., 2021). Through the introduction of health and social policies providing access to greenspace, communities can promote physical activity, reduce stress, increase social connection, and improve mental health outcomes. One noteworthy study that reflects the potential for this type of intervention was introduced through qualitative research investigating how access to community gardens and urban agriculture was associated with greater feelings of body-mind wellness, greater community connection, and social interdependence among Black Americans (Gripper, 2023). However, greenspace gentrification, the resulting displacement of people in communities after the introduction of greenspace improvement policies (H. Cole & Immergluck, 2021), disparately limits access to greenspace or result in displacement for certain groups of people, particularly low-income residents and people of color. How then can we design spaces that provide equitable accessibility to brain health and well-being?

Universal design and the built and social environment

Universal design is a paradigmatic approach that works towards creating products, built and social environments, and systems that are accessible to everyone to the greatest possible extent, irrespective of ability status (Carr et al., 2013; Connell et al., 1997; Mace, 1988). A central tenet of universal design that is argued to separate it from other forms of inclusive design paradigms for built environments is its focus on social connectedness and social sustainability (Connell et al., 1997). Social connection refers to the feeling of being connected to and having meaningful relationships with others, which has been shown to be associated with both subjective well-being and reduced risk for chronic diseases (Berkman,

Glass, Brissette, & Seeman, 2000, 2013; Holt-Lunstad, Smith, & Layton, 2010). Creating spaces that promote social connection and community building leads to stronger social networks and mutual support (Krasny & Tidball, 2012; Ridge, 2011). This is particularly important in neighborhoods experiencing disadvantage where individuals may have limited access to resources and opportunities. By promoting social connection through the implementation of universal design in these communities, we can help individuals to feel more connected, supported, and engaged in their communities. The integration of social connection and physical activity in communal spaces like parks and greenspaces has been well-characterized, whereby social connection helps to support people in engaging in more physical activity. For example, it has been shown that social support in physical activity leads to more instances of physical activity (King et al., 2000; Kritz, Thøgersen-Ntoumani, Mullan, Stathi, & Ntoumanis, 2021; Sallis, Prochaska, & Taylor, 2000). In addition, Smith and colleagues (2023) also showed that as social support increased there was a corresponding increase in physical activity (Smith, Moyle, & Burton, 2023). Unfortunately, neighborhoods that experience disadvantage and lack resources may have limited access to universal design features such as accessible buildings, transportation, public spaces, or areas to walk and exercise (Dean et al., 2013). The lack of access to universal design features also contributes to social isolation and reduced quality of life for individuals in these neighborhoods by increasing physical barriers to social engagement (Iwarsson & Ståhl, 2003). This has the potential to further exclude and marginalize people with disabilities, our rapidly aging population, and other marginalized groups.

Research has shown that racial and ethnic minorities experience disability at higher rates than White men and women (Warner & Brown, 2011), potentially leading to barriers to accessing universal design features in their neighborhoods and communities. This disparity can be attributed to systemic and structural inequities, including discrimination and lack of access to resources and opportunities. For example, individuals living in neighborhoods with higher levels of disadvantage may be more likely to have limited access to healthcare which can result in untreated medical conditions and increased risk for disability. Furthermore, promoting social connection in these communities is essential to improving health outcomes, overall quality of life, and lead to greater social sustainability, or the ability of a community to "meet the needs of the present without compromising the ability of future generations to meet their own needs" (Dempsey, Bramley, Power, & Brown, 2011). Creating spaces that promote physical activity, social interaction, and social sustainability increases the chance of creating and maintaining stronger social networks, mutual support, and greater physical activity. By promoting social connection and building on social sustainability inherent to universal design, we can help individuals feel more connected, supported, and engaged in their communities.

Universal design is not a cure-all and has both advantages and disadvantages. The implementation of universal design within a social determinants of health framework (Dean et al., 2013; Plough, 2015) may lead to long-term cost savings by reducing the need for future costly retrofits and accommodations. This is particularly important for disadvantaged and economically deprived neighborhoods, where residents lack the financial resources to make changes to their homes or environments to improve

accessibility. By making neighborhoods and communities more accessible and walkable, we can promote physical and economic activity through increased foot traffic and patronage of local businesses, which can help to support local economic development. By acting as a preventative measure in health and well-being, universal design may also help reduce healthcare costs associated with chronic conditions, injuries, and resulting chronic stress. However, a potential barrier to incorporating universal design features into buildings and public spaces from the outset is expense in the short term which may introduce challenges for policy makers and urban planners. This can be particularly challenging in disadvantaged neighborhoods, where financial resources may be limited. Additionally, improvements in the built environment, such as the incorporation of universal design features, can lead to increased property values and potential gentrification. This can displace existing residents and exacerbate social and economic inequalities. The implementation of universal design features in disadvantaged neighborhoods must be done with care to ensure that these and other unintended consequences do not arise. For example, designers need to keep in mind how the installation of ramps and other accessibility features may inadvertently create barriers for individuals with visual impairments or other disabilities. Although universal design in disadvantaged neighborhoods has the potential to promote economic development and improve health outcomes, it must be approached with care to ensure that unintended consequences are minimized and that the economic benefits outweigh the costs.

The neuroscience of spatial cognition and universal design

To this point, we have discussed the built environment and bridging access to physical activity, greenspace, and social connectedness and sustainability, as well as the potential for displacement and structural discrimination. We have also discussed the importance of universal design in navigating our social and built environment. Importantly, our ability to learn, remember, and navigate is dependent on the spatiotemporal context within which we exist and is dependent on the MTH system (Eichenbaum, 2014; Eichenbaum & Cohen, 2014; Hasselmo & Stern, 2014; Jeffery, 2018; Maguire et al., 1998). The hippocampus working synergistically with other regions of the brain helps to create a cognitive map of space (Alexander et al., 2020; Brown, Hasselmo, & Stern, 2014; Carstensen, Alexander, Chapman, Lee, & Hasselmo, 2021; Eichenbaum & Cohen, 2014; Hafting et al., 2005; Hasselmo & Stern, 2014; Kropff et al., 2015; O'Keefe & Dostrovsky, 1971), but the way that we interact with our environments is also socially and emotionally mapped (Bower, Tucker, & Enticott, 2019). For example, the MTH system has been primarily implicated in creating a cognitive map of structural space for navigation. Tavares and colleagues conducted research showing that individuals also map social structure along the lines of social power and group membership (Tavares et al., 2015). In his commentary on the work of Tavares and colleagues, Eichenbaum (2015) states, "Importantly, just as the dimensions of geographic space are defined in terms of continuous metrics of physical distance, power and affiliation are defined in terms of continuous metrics of social distance…" (Eichenbaum, 2015). That is to say, the way that our brain represents the social

and physical world is reliant on how we perceive and interact with the world and that this may be partially reliant on the MTH system.

Combining the principles of universal design with the neuroscience domains of spatial cognition has the potential to create environments that promote ease of navigation and how we think about space, reducing cognitive load through simplifying the ways in which we navigate the world (Carr et al., 2013). In healthy aging and in neurodegenerative diseases such as Alzheimer's disease and related dementias (ADRD), we see degradation of the MTH system as well as our ability to navigate (Colombo et al., 2017; Lester et al., 2017; Parizkova et al., 2018; Rosenbaum et al., 2012). By designing spaces that are inclusive and accessible, individuals of all abilities across the lifespan can engage with their environment more easily, which may improve their cognitive functioning and quality of life (e.g., those with mild cognitive impairment or ADRD (Mitchell et al., 2003)).

A relatively new field of neuroscientific inquiry is neuroarchitecture, which attempts to use what we know about spatial cognition and perception to design the built environment (Karakas & Yildiz, 2020). A recent call to action based in disability rights discusses the importance of neuroarchitecture in design for those with both physical and intellectual disabilities, a factor often left out of discussions on universal design (Gillen, 2015). One cognitive architecture framework developed by Sussman and Hollander (2015) for urban design focuses on how we perceive and navigate the world, focusing on edges, shapes (symmetry vs. asymmetry), patterns within the cityscape, greenspace, and emotional salience of the space (Sussman & Hollander, 2021). These factors coincide with research conducted with individuals with cognitive impairment and dementia. One study

conducted using virtual navigation of a town center by participants with dementia found that better delineation between motorways and walkways and clear signage that supported wayfinding and identification of objects helped with ease of navigation (Blackman, van Schaik, & Martyr, 2007). A recent review of interventions in the built environment for people living with Alzheimer's disease and related dementias also noted deficits in the built environment: they promoted reductions in factors that would cause sensory overload, increase physical accessibility through the minimization of physical barriers, and inviting people living with dementia into the decision-making processes of how we design the environments within which they live (Gan, Chaudhury, Mann, & Wister, 2022). Cognitive neuroscience allows us to test and characterize how we perceive, investigate, and navigate the world. Universal design would benefit greatly from insights gleaned from cognitive neuroscience on how our perception of the world influences how we engage with and navigate the built environment.

Conclusion

Currently, there is a need for research combining elements of universal design within cognitive neuroscience. This provides a novel area of scientific inquiry that can support health policies that prevent or mitigate health inequities by informing how we map structural and social space. This line of inquiry should also consider how navigation through these built and social spaces may be beneficial for brain health. Overall, the integration of universal design principles and cognitive neuroscience has the potential to create healthier and more equitable communities for all, across the lifespan. By designing

spaces that are accessible, usable, and reduce cognitive load, individuals of all abilities can engage with their environment more easily and improve their cognitive functioning and overall well-being. We argue that it is essential to prioritize and promote universal design features in neighborhoods and communities experiencing disadvantage and to address systemic and structural inequities that limit access to these features. This can involve community engagement, policy change, and investments in infrastructure and services that promote accessibility and health equity. Novel research approaches such as *Steps for Change* (King et al., 2021) and *Our Voice* (King et al., 2021, 2020) highlights these connections and access to physical activity and social connection, when working in tandem with community-engaged partners and citizen scientists to describe and characterize their environments in terms of barriers and access to health, as well as train community partners in how to advocate to policy makers for the needed changes in their own communities. Thus, we posit that perhaps an improved neuroarchitecturally-informed universal design may be beneficial for neural architecture. By promoting universal design through the lens of cognitive neuroscience and health equity in neighborhoods and communities experiencing disadvantage, we can create more inclusive, sustainable, and resilient communities, working towards making communities happier and healthier.

CHAPTER 5: SUMMARY AND DISCUSSION

Summary of Key Findings

The primary aim of this dissertation was to investigate the modulating role of cardiorespiratory fitness and perceived discrimination in medial temporal hippocampal (MTH) system structure, and to integrate and expand these findings into how we perceive and experience the built and social environment through the combination of the cognitive neuroscience of spatial cognition and universal design. In two separate experiments we tested the hypotheses that cardiorespiratory fitness would positively correlate, and perceived discrimination would negatively correlate, with MTH system structure. In aging, there are dissociable structural volumetric trajectories of different brain regions, including the MTH system (Fjell et al., 2009; N. Raz et al., 2004; Naftali Raz et al., 2005). Importantly, the MTH system shows neurodegeneration in Alzheimer's disease and related dementias (ADRD) and is implicated in depression, anxiety, epilepsy, and other disease states. Additionally, the MTH system provides a sensitive target for understanding the impact of long-term socioenvironmental changes, and potential targets for mitigation and prevention. Building on neurobiological models of environmental enrichment, wheel running, and chronic stress model paradigms, we found that perceived discrimination, acting as a chronic psychosocial stressor, and cardiorespiratory fitness, as a proxy for wheel running and environmental enrichment, correlate as opposing modulators of the MTH system in young and older adults.

In our first experiment, we tested the hypothesis that greater cardiorespiratory fitness, operationalized as estimated $\dot{V}O_{2max}$, would positively correlate with

extrahippocampal regions of the MTH system important for subjective spatial cognition, which included the entorhinal, parahippocampal, and perirhinal cortices, in young and older adults. Additionally, we tested whether these brain regions would positively correlate with subjective sense of direction. In line with our hypotheses, in young adults we found that cardiorespiratory fitness was associated with greater cortical thickness of the left entorhinal, parahippocampal, and perirhinal cortices. Moreover, we found that parahippocampal cortical thickness was associated with greater subjective sense of direction in young adults. Contrary to our hypothesis and different from the extant literature (Colcombe et al., 2003; Kirk I. Erickson et al., 2011; Voss et al., 2011), in older adults we found that there were no significant relationships between cardiorespiratory fitness and these brain regions. However, we found that greater parahippocampal cortical thickness was negatively correlated with subjective sense of direction, contrary to our hypotheses. In order to make sense of these contradictory findings in older adults, we speculated that one underlying reason may be due to an overestimation of subjective spatial navigation ability in older adults (Rosenbaum et al., 2012), which is discussed in more detail in Chapter 2.

In our second experiment, we tested the hypothesis that greater perceived discrimination would negatively correlate with amygdala and anterior, but not posterior, hippocampal volume due to their roles in stress regulation and affective processing. We found that with greater perceived discrimination there was a corresponding decrease in amygdala and anterior, but not posterior, hippocampal volume. Our results suggest that when controlling for potential confounders (e.g., age, sex, education), perceived discrimination was an appreciable correlate of smaller amygdala and anterior hippocampal

volume, outside of age-related decline (Naftali Raz et al., 2005). Moreover, we examined personal mastery, a proxy for self-efficacy, as a potential moderator of these relationships. We conceptualized personal mastery as a measure of perceived agency, working as an opposing factor against perceived discrimination as a social factor that imposes a lack of agency in responding to a discriminatory event (Ong et al., 2009). We found that as personal mastery increased for our participants, there was a corresponding attenuation of the negative correlation between perceived discrimination and amygdala and anterior hippocampus volume.

In Chapter 4, we took an approach building from animal models of environmental enrichment, wheel-running, and chronic physical and psychosocial stress to human studies of the effect of exercise, physical activity, and forms of perceived social and structural discrimination and racism on the medial temporal hippocampal (MTH) system. This region of the brain shows plasticity in response to socioenvironmental factors (Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2012; Glymour & Manly, 2008; Harnett, 2020; McEwen et al., 2016; Zahodne et al., 2023), and is important for stress and emotional regulation. We integrate these ideas in order to further our understanding of how factors in the built and social environment can be modulated through policy changes associated with universal design. We do this in order to leverage our understanding of design approaches of the built and social environment from a framework based on a cognitive neuroscience of spatial cognition approach to universal design, a paradigmatic framework focused on increasing accessibility and social sustainability across all levels of ability and ages (Connell et al., 1997; Ostroff, 2011).

Cardiorespiratory fitness and MTH system structure

In our second chapter, we showed that cardiorespiratory fitness positively correlated with left entorhinal, parahippocampal, and perirhinal cortical thickness and this was specific to young adults. This suggests that in young adults extrahippocampal regions of the MTH system may be amenable to the influence of cardiorespiratory-induced changes in plasticity during interventions focused on increasing cardiorespiratory fitness via exercise such as in work conducted by Nauer and colleagues (Nauer, Dunne, et al., 2020). Much of the extant literature has focused on the role of cardiorespiratory fitness and exercise-induced changes in cardiorespiratory fitness in older adulthood. Region-of-interest studies of the MTH system have shown positive associations between higher CRF and larger hippocampi in healthy older adults (Kirk I. Erickson et al., 2009), and a year-long exercise intervention revealed hippocampal volume maintenance for older participants in the aerobic exercise arm of the study compared to normal volume loss during healthy aging in the stretching comparison group (Kirk I. Erickson et al., 2011). In comparison, in adolescents, CRF modulated cortical surface area (Herting et al., 2016), whereas older adults had a positive relationship between cardiorespiratory fitness and cortical thickness (V. J. Williams et al., 2017). Our group previously found that cardiorespiratory fitness was volumetrically correlated with voxels within the right entorhinal cortex in young adults (Whiteman et al., 2016). Here, we reported left lateralized associations between regions of the MTH and cardiorespiratory fitness. Differences in automatic processing analyses might also explain the asymmetrical differences that we

report in our two studies, on two different cohorts of healthy young adults. Our current findings present insight on the role of the potential impact of CRF as a modulator of cortical thickness in healthy young adults. These results, although cross-sectional, also continue to help bridge our current understanding of the impact of CRF on neuroplasticity in humans (Voss et al., 2013). Combined with our current findings and the extant literature, we believe that these findings present the potential for specific outcome targets across the lifespan in relation to interventions that targets increases in cardiorespiratory fitness, and based on our findings and other research outcomes from our group (Nauer, Dunne, et al., 2020) that this can occur as early as young adulthood. In a later section, we discuss potential neurobiological mechanisms that may influence the relationship between CRF and brain structural outcomes.

Perceived discrimination and amygdala and anterior hippocampal volume in older adults

In Chapter 3 we determined that greater perceived discrimination significantly correlated with reduction in amygdala and anterior hippocampal volume, suggesting that perceived discrimination has some appreciable influence on volumetric outcomes outside of what is seen in healthy aging (Naftali Raz et al., 2005). The amygdala and hippocampus have been well characterized in their role in emotional and stress regulation (Herman & Cullinan, 1997; McEwen et al., 2016), with the anterior hippocampus being more implicated in affective processing (Poppenk et al., 2013b). Due to this, we hypothesized that these regions of the MTH system may be particularly sensitive to the impact of

perceived discrimination, a chronic psychosocial stressor with high emotional salience. We specifically limited our focus to the amygdala and anterior hippocampus given their roles in modulating hypothalamic-pituitary-adrenal axis function and the sympathetic nervous system, responsible in part for different timing of the stress response (Fink, 2016), and their recruitment in emotional regulation (McEwen & Gianaros, 2011; Poppenk et al., 2013b). In humans, general stress has been associated with reductions in hippocampal volume (Gianaros et al., 2007). Expanding upon this, studies investigating the role of perceived discrimination as a psychosocial stressor has shown associations with aberrant amygdala functional connectivity (Clark et al., 2018a) and reductions in hippocampal volume (Zahodne et al., 2023). Complementing this literature, in our current study, we found that perceived discrimination was negatively correlated with both amygdala and anterior, but not posterior hippocampus volume. Adding to the current literature, we also showed that greater personal mastery, a measure of self-efficacy, abolished the negative relationship between perceived discrimination and amygdala and anterior hippocampus volume. Although perceived discrimination may "get under the skin" through mechanisms such as a stress-induced inflammatory response (Das, 2013; McEwen, 2012), we show a potential target for intervention or prevention by focusing on personal mastery as a moderator of these relationships.

Allostatic load has been consistently examined as a mechanism underlying the impact of chronic stress on brain health, including changes to the plasticity of the human brain (McEwen, 1998b, 2012). As mentioned above, inflammation provides one potential neurobiological pathway inherent to dysregulation of allostatic processes by which we may

see a deleterious impact of perceived discrimination on neurocognitive health (Das, 2013), including changes to underlying neural architecture and emergent cognitive ability dependent on these structures (McEwen et al., 2016). Greater perceived discrimination has been shown to predict greater inflammation in humans (Cuevas et al., 2020; Lewis et al., 2010; Paalani et al., 2011; Stepanikova et al., 2017; Yaffe et al., 2003; Zahodne, Kraal, et al., 2019). Greater inflammation has also been shown to compromise cognition in older adults (Boots et al., 2020; Zahodne, Kraal, et al., 2019), and has also been shown to be associated with ADRD and other physical and psychological disorders (Akiyama et al., 2000; Haan, Aiello, West, & Jagust, 2008; Joseph & Golden, 2017; Kim, Na, Myint, & Leonard, 2016; Liu, Wang, & Jiang, 2017; Marsland, Walsh, Lockwood, & John-Henderson, 2017; Metti & Cauley, 2012; Steptoe & Kivimäki, 2012). In addition, there is a striking health inequity in ADRD, with Black Americans having a higher incidence of ADRD compared to white Americans, independent of socioeconomic status, education, and genetic risk factors (Alzheimer's Association, 2018; Tang et al., 1998), suggesting a possible role of a racial discrimination-induced inflammatory stress response mediating this higher incidence of ADRD among Black Americans.

Considered together, this suggests a role for an aberrant inflammatory response as a consequence of chronic stress as a neurobiological mechanism underlying the link between perceived discrimination and neurocognitive health. Future research should collect physiological measures of the stress response and other markers of allostatic load including measures of inflammation in order to determine whether allostatic load may mediate the relationship between perceived discrimination and brain structural integrity in aging.

Although longitudinal research is needed to determine causality or directionality between perceived discrimination and brain structure or function in humans, it is possible to build on our understanding of the impact of perceived discrimination on brain structure using neurobiological animal models of psychosocial stress and inflammation. We describe this in more detail below in our section on neuroplastic mechanisms.

Potential neurobiological mechanisms underlying structural changes in relation to cardiorespiratory fitness and perceived discrimination

Currently still under ongoing investigation is how CRF and chronic psychosocial stress (e.g., perceived discrimination) influences cortical outcome measures (Cabral et al., 2019; McEwen et al., 2016). In this thesis we present cross-sectional experiments, but it remains pertinent to describe potential neuroplasticity mechanisms that may influence the relationships observed in our first and second experiment. It is well-established in animal models of stress and environmental enrichment that regions of the MTH system undergo structural changes (Fuchs & Flügge, 2003; Ickes et al., 2000; McEwen et al., 2016; Mohammed et al., 2002). One way we can interpret these findings is by first asking about the makeup of cortical volume, thickness, and surface area. Cortical volume of a given region is a composite measure determined by both its cortical surface area and cortical thickness. Cortical thickness is defined as the distance between the pial surface and the white matter layer (Fischl, 2012; Rakic, 1995). Cortical surface area is the area of exposed cortical surface and the area of cortex hidden in sulci (Raznahan et al., 2011). Both morphometric components have separate genetic etiologies (Rimol et al., 2010), resulting

from different corticogenetic developmental trajectories (Rakic, 1995). The origin of the cortical surface area is the result of the total number of radial columns determined during development whereas cortical thickness is determined by the number of cells in each column. Cortical surface area is also influenced by input from subcortical areas during development whereas cortical thickness may be influenced by genomic and growth factors within a given region (Rakic, 1995). These differential etiologies are potentially related to socioenvironmental intrinsic versus extrinsic factors during structural development of the cortex and present potential differential outcomes in relation to experiential factors such as CRF and perceived discrimination.

Aside from these different corticogenetic trajectories are a host of factors including neurotrophins, CRF-induced changes in neurovasculature and myelination (Cabral et al., 2019), as well as inflammation-induced changes associated with chronic stress (Belarbi & Rosi, 2013; Fuchs et al., 2006; Gianaros et al., 2012; Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008; Monje, Toda, & Palmer, 2003) which may play significant roles in modulating the MTH system structurally. In this thesis, we did not test hypotheses related to these trophic factors or inflammatory biomarkers and how they may mediate changes in brain structure. Our understanding of the underlying neurobiological mechanisms modulated by CRF and perceived discrimination in humans is still limited. However, research in animal models provide suitable theoretical grounding on the impact of CRF and chronic stress on the brain, and suggest that growth and genetic factors, as well as stress-induced inflammation may underlie the current study's observed associations between CRF and perceived discrimination and the MTH system. In the MTH we see

greater expression of growth factors after wheel running which influenced survival and maintenance of existing neurons in rodents (Ickes et al., 2000; Pham et al., 1999). Independent of the impact of wheel running, rodents from strains that engaged in more voluntary wheel running showed higher levels of brain derived neurotrophic factor, which is important for synaptic plasticity and neuronal health (R. A. Johnson et al., 2003; Rebecca A. Johnson & Mitchell, 2003). Further research focused on morphological changes have proposed that neurogenesis, myelination, and vascularization may constitute other targets underlying plasticity in neural architecture. Wheel running has been shown to increase neurogenesis in the dentate gyrus subfield of the hippocampus (Van Praag, Christie, et al., 1999; Van Praag, Kempermann, et al., 1999b). Using diffusion tensor imaging, Islam and colleagues (2020) showed an exercise-induced change in hippocampal myelination in rodents (Islam et al., 2020). Finally, a study focused on the impact of voluntary wheel running in young mice showed an increase in blood flow in the dentate gyrus subfield (Pereira et al., 2007).

Complementarily, it is well-established in animal models of stress that these regions of the brain undergo structural reorganization during stressful events (Fuchs & Flügge, 2003; McEwen et al., 2016). In tree shrews, exposure to a dominant conspecific resulted in dendritic atrophy in the CA3 region of the hippocampus (Magariños et al., 1996), and there was a reduction in hippocampus-dependent memory and hippocampal volume after exposure to psychosocial stress (Ohl et al., 2000). Fetal glucocorticoid exposure resulted in a reduction of hippocampal volume at 20 months in non-human primates (Uno et al., 1994). Finally, the induction of an inflammatory response impaired hippocampal

dependent function in rodents (Czerniawski & Guzowski, 2014; Czerniawski et al., 2015). Altogether, these neurobiological mechanisms provide different targets that may be modulated by CRF and chronic stress (e.g., perceived discrimination) and necessitate additional multimodal and concurrent cross-species investigations to determine whether the observed changes associated with CRF are indeed conserved across species.

Conclusion: How should the world be designed? Integrating ideas from cognitive neuroscience and universal design to support brain health equity and challenge health inequalities

During the process of completing this thesis, I had to ask myself what roles a neuroscientist can play in society with niche expertise when wanting to challenge health inequalities. Brain health is an oftentimes unconsidered component of health disparities and health equity research and is somewhat absent from our understanding of what a Culture of Health, the belief that everyone has "a fair and just opportunity to live the healthiest life possible" (Chandra et al., 2016; Plough, 2015), can look like. Investigating real world socioenvironmental stressors and identifying modifiable risk factors such as physical activity and personal mastery is critical to more rigorous research that is translatable to health policy intervention and prevention. These ideas were influenced by my participation in a number of organizations geared towards the support of underrepresented graduate students including the Robert Wood Johnson Foundation Health Policy Research Scholars program (HPRS) (Chandra et al., 2016), the Summer Program in Neuroscience, Excellence, and Success at the Marine Biological Laboratory (ongoing since

1989) (Trujillo, Quiñones-Hinojosa, & Thompson, 2020), the Society for Neuroscience's Neuroscience Scholars Program (ongoing since 1982), and the National Institutes of Health Blueprint Diversity Specialized Predoctoral to Postdoctoral Advancement in Neuroscience F99/K00 funding mechanism to support underrepresented graduate students from predoctoral to postdoctoral positions (Jones-London, 2020). Moreover, as a graduate student I had what I considered both opportunities and detriments to my success as a graduate student. I was vice-president of Boston University's cross-campus Underrepresented Graduate Students Organization that sought to bring together graduate students from the arts, humanities, sciences, engineering, and math who were underrepresented in their fields to share fellowship and collaborate on ideas. We successfully hosted symposia and student events to create spaces where we felt empowered. Additionally, I sat on advisory committees for Diversity, Equity, Inclusion, and Justice in departments and programs with which I was affiliated, sat on panels to speak with undergraduate and high school students, and engaged in outreach at the Annual Biomedical Research Conference for Minority Students through Boston University to those who were also marginalized and minoritized by society but were interested in science, and much more. I felt highly successful and proud of the work I did. However, two central questions have followed me throughout these years, and are central to the question of "How should the world be designed?" which are "For whom is this world designed?" and "On whom is the onus to fix these societal issues placed for the minoritized and marginalized?", which is why I mention the word 'detriment' above. The experiments discussed in this thesis is inseparable from these questions because they follow what I believe is a faulty

approach in scientific research-society interactions. Do we ask ourselves in what ways systemic issues need to be addressed and fixed or do we place the burden on individuals through using phrases such as “building resilience” in order to place a band-aid on health issues?

My dissertation project took a brain health equity and antiracist approach, meaning that I asked my research questions within the context of historical and contemporary social and structural determinants of health (Bailey et al., 2017; Cronin-de-Chavez et al., 2019; Weinstein et al., 2017), encapsulated within racist, misogynistic, homophobic, ableist, transphobic ideologies and policies, or as bell hooks would say, the “imperialist white supremacist heteropatriarchy” (hooks, 2012), and how this impacts brain health. Importantly, my experience working with other scholars in organizing an abolitionist workshop, focused on educating fellow scholars on how to challenge unjust and oppressive systemic barriers to health and well-being beyond policy implementation (Clare, 2015; Davis, 2003; hooks, 2012; “The collected poems of Audre Lorde,” 1998; Wasson & Munoz, 2001), my experience in Summer 2021 highlighted how removed neuroscience is from discussions of brain health inequalities, and the importance of bringing ideas of health inequity and critical race theory into neuroscience, an inherently interdisciplinary field. In Chapter 4 we integrated the literature of neurobiological models of environmental enrichment (Mohammed et al., 2002; Newberry, 1995b) and chronic stress (McEwen, 1998b), the cognitive neuroscience of spatial cognition (along structural and social domains (Eichenbaum, 2015; R. A. Epstein et al., 2017; Tavares et al., 2015)) which is dependent, in part, on the MTH system (Brown et al., 2014; Burgess, Maguire, & O’Keefe,

2002), and public health through the lens of critical race theory (Crenshaw, 1991) and systemic inequalities including structural racism (Bailey et al., 2017; Davis, 2003; Gripper et al., 2022; Harnett, 2020; hooks, 2012; Neely, Ivey, Duarte, Poe, & Irsheid, 2020). We used this background to introduce and build upon universal design. This framework is centered on accessibility and social sustainability across all levels of ability and ages (Connell et al., 1997; Ostroff, 2011). This is critical in order to discuss the ways in which we perceive, experience, remember, and navigate the world can be changed to benefit as many people as possible. As we integrate our understanding of the extant literature described above (and in more detail in Chapter 4) with the knowledge of structural barriers in safety and accessibility to brain health and well-being, it is critical that these ideas are placed within a larger spatiotemporal context of the sociopolitical world (Barber et al., 2022; A. T. Geronimus, 2001; Krieger, 1994; Miller, 2005; Plough, 2015). If disadvantaged communities lack a setting that promotes healthy behaviors, then creating public health guidelines solely based on physical activity and social and material sustainability is inadequate without considering the place and space for engaging in those behaviors. We further argue that through the introduction of health and social policies providing residents with access to material resources in the built and social environment -- including greenspace development, space for social connection, and neighborhood safety -- communities can promote physical activity, reduce stress, increase social connection, and improve mental health outcomes (King et al., 2000; Kritz et al., 2021; Sallis et al., 2000). Integrating universal design principles with findings from studies on the cognitive

neuroscience of spatial cognition and navigation, we can facilitate the development of environments that support easy navigation and reduce cognitive load (Carr et al., 2013).

As an activist-scientist, I hope that a positive, yet idealistic, outcome of my dissertation research will highlight the negative impact of perceived discrimination and beneficial impact of cardiorespiratory fitness on neurocognitive integrity and provide evidence to policy makers to direct funding to underserved and under-resourced communities for mitigating systemic inequalities. It is crucial to not only prioritize universal design features but also address the underlying systemic and structural inequities that restrict access to such features in neighborhoods and communities experiencing disadvantage and deprivation. Achieving this objective requires active community participation, policy changes, and investments in infrastructure and services that facilitate accessibility and promote health equity. In this way, when we ask “How should the world be designed?”, we provide a simple answer whereby we respond that everyone should have the potential to live happy, healthy lives in a world designed for all of us.

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