The Impact of a Mediterranean-based Diet on Cognitive, Inflammatory, and Neurotrophic Impairments Induced by a Chronic Social Defeat Stressor in Male C57BL/6N Mice

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Abstract

Background: Stress-related neuropsychiatric disorders have overlapping impairments in social and non-social cognition. Limited efficacy of treatments targeting these symptoms and the continued increase in prevalence in these disorders has necessitated alternative strategies. The Mediterranean (Med) diet has been shown to improve depression, anxiety, and cognitive deficits in clinical studies. Using a mouse model of chronic social stress, this study investigated the potential of a mouse-adjusted Med-based dietary intervention to mitigate social and non-social cognitive impairments and limit changes in brain neurotrophic and inflammatory factors.

Methods: Male C57BL/6N mice were randomly assigned to a Control or a Med-based diet. After a 14-day acclimatization period to the diets, both groups were either subjected to 10 consecutive days of chronic social defeat stress (CSDS) or to a no stressor control condition. Cognitive tests were conducted 24 hours after the last stressor or control session. The ventral hippocampus was collected 24 hours following the last cognitive test and analyzed for the mRNA expression of pro-inflammatory cytokines, microglial markers, and neurotrophic factors.

Results: The CSDS regimen increased social avoidance behaviours and altered the hippocampal expression of neurotrophin-3 and Tropomyosin receptor kinase B. In CSDS mice, the Med-based diet improved long-term memory and reduced hippocampal tumor necrosis factor alpha but promoted social avoidance behaviours, impaired spatial reference memory, and decreased hippocampal brain-derived neurotrophic factor.

Conclusion: Dietary interventions in male mice may have differential effects on cognitive and hippocampal health in the context of chronic social stress, requiring further investigation into its use as an adjunctive therapy for cognitive deficits in stress-related neuropsychiatric disorders.

Keywords: Anxiety, Cognition, Depression, Hippocampus, Inflammation, Mediterranean diet, Mouse model, Neurotrophic factors, Social stress

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Have courage and be kind.

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List of Abbreviations

ACTH	**Adrenocorticotropic hormone**
BBB	**Blood Brain Barrier**
BW	**Body Weight**
BDNF	**Brain Derived Neurotrophic Factor**
CNS	**Central Nervous System**
CRP	**C-reactive Protein**
CRH	**Corticotropin-releasing Hormone**
CSDS	**Chronic Social Defeat Stress**
CX3CR1	**C-X3-C motif chemokine receptor 1**
DHA	**Docosahexaenoic acid**
DSM-V	**Diagnostic and Statistical Manual of Mental Disorders Five**
EPA	**Eicosapentaenoic acid**
FI	**Food Intake**
GAD	**Generalized Anxiety Disorders**
GI	**Gastrointestinal Tract**
GCs	**Glucocorticoids**
GR	**Glucocorticoid receptor**
HPA	**Hypothalamic Pituitary Adrenal**
Iba-1	**Ionized calcium binding adaptor molecule 1**
IL-6	**Interleukin-6**
IL-1β	**Interleukin-1 Beta**
MDD	**Major Depressive Disorder**
MGBA	**Microbiota-Gut-Brain-Axis**
mRNA	**Messenger ribonucleic acid**
MUFAs	**Monounsaturated fatty acids**
NGF	**Nerve growth factor**
NT-3	**Neurotrophin 3**
NOR	**Novel Object Recognition**
ω-3	**Omega-3**
ω-6	**Omega-6**
PUFAs	**Polyunsaturated fatty acids**
RT-qPCR	**Reverse transcription-quantitative polymerase chain reaction**
SIT	**Social Interaction Test**
SIR	**Social Interaction Ratio**
TLR4	**Toll-like receptor 4**
TrkB	**Tropomyosin receptor kinase B**
TNF-α	**Tumour necrosis factor alpha**
Y-Maze	**Forced alternation y-maze**

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Chapter 1: General Introduction

Neuropsychiatric illnesses have increased in prevalence in Canada with approximately 2.1 million people living with major depressive disorder (MDD) and approximately 1.4 million people living with generalized anxiety disorder (GAD) as of 2022 (Statistics Canada, 2024). These disorders negatively affect quality of life, as symptoms interfere with behaviour, cognitive functioning, and overall health (Kupferberg & Hasler, 2023). Stressor exposure, especially on a chronic basis, has been shown to be a major predisposing, precipitating, and perpetuating factor for these neuropsychiatric conditions (Liu et al., 2024; McGonagle & Kessler, 1990). Chronic stressors of a social nature in particular have been shown to produce long-lasting cognitive and behavioural impairments (Koskinen et al., 2020; Lupien et al., 2009), upregulate pro-inflammatory factors (Bailey et al., 2011; Bharwani et al., 2016; Szyszkowicz et al., 2017), and downregulate neurotrophic factors (Molendijk et al., 2014) in both humans and animal models. These biological and behavioural consequences indicate the importance of chronic social stress in the development of neuropsychiatric cognitive impairments.

Current treatment options for depressive and anxiety disorders include pharmacotherapies, psychotherapies, and/or somatic therapies such as electroconvulsive therapy (Karrouri et al., 2021). For MDD, acute-phase remission rates of medication and psychotherapy vary between 25-37% and 26-43%, respectively, while sustained remission rates respectively are 29% and 41% (Furukawa et al., 2021; Ormel et al., 2022). For GAD outcomes, a medium effect size was observed for evidence-based psychotherapy while a small effect size was observed for medication (Carl et al., 2020). Although current treatment options may improve clinically observed symptoms of depressive and anxiety disorders, individuals with MDD often report persisting cognitive deficits despite clinical recovery, as most treatments fail to address these

impairments (Castaneda et al., 2008; McIntyre et al., 2015; Saragoussi et al., 2018). As a result of the limited effectiveness of pharmacotherapy and psychotherapy in the long-term improvement and recovery of cognitive impairments associated with MDD and GAD, is it important to find novel strategies to target and resolve these symptoms for the improvement of quality of life. In the past few years, evidence has shown that healthy dietary patterns, especially those based on the Mediterranean (Med) diet, were associated with reduced symptoms and incidence of depression and improvements in cognitive functioning (Bizzozero-Peroni et al., 2024; Firth et al., 2019; Jacka et al., 2017; Radd-Vagenas et al., 2018). This thesis aims to examine if a Med-based diet, developed for rodents, could limit cognitive impairments, in addition to neuroinflammatory and neurotrophic changes, in a mouse model of chronic social stress.

Chapter 2: Literature Review

2.1 Neuropsychiatric Disorders

2.1.1 Major Depressive Disorder

According to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), MDD is primarily characterized by symptoms of depressed mood and/or a loss of interest/pleasure that persist for most of the day, daily, for a minimum of two consecutive weeks, with significant impairments in social and/or occupational areas (American Psychiatric Association, 2022). In addition to depressed mood and/or loss of pleasure, individuals must have five or more of the following symptoms to be diagnosed with MDD including: significant unintentional weight loss/gain and/or decrease/increase in appetite, sleep disturbances, psychomotor changes, loss of energy, feelings of worthlessness or excessive/inappropriate guilt, impaired ability to think, concentrate or make decisions, and recurrent thoughts of death, suicidal

ideation or attempts (American Psychiatric Association, 2022). The presentation of MDD can be diverse, given the range of symptoms an individual can exhibit, and can impair their ability to initiate and/or complete daily tasks. Developing MDD is due to a complex interaction of biological and psychosocial factors. One major risk factor for adult MDD includes stressful life events experienced in childhood (e.g., emotional, physical, and/or sexual abuse, death of a family member, domestic violence), with a meta-analysis finding a two-fold increase in risk associated with early-life stress (Infurna et al., 2016). The experience of maltreatment in early life can also increase the likelihood of meeting diagnostic criteria for depression in childhood or adolescence by 2.5 times (LeMoult et al., 2020). The other major risk factor for adult MDD includes chronic stress (Kendler et al., 1999; Kessler, 1997). One of the earliest studies using monozygotic female twins found that traumatic experiences in both childhood and adulthood, as well as acute major life events, and recent difficulties significantly predicted a future episode of major depression (Kendler et al., 1993). Additionally, another study found that certain life events, such as ones involving social rejections, had a 21.6% increase in the risk for onset of MDD (Kendler et al., 2003). Other risk factors for developing depression include parental depression and preferentially engaging in negatively biased behaviour patterns, beliefs, dispositions, traits and cognitive processes towards adversities or daily life events (Hammen, 2018). Individuals with poor coping skills, minimal to no social support, or distorted cognitive perspectives based on their experiences in a negative, neglectful or absent environment, may not be adequately prepared for responding to stressful life events and may be more susceptible to developing MDD (Boyce, 2018; Nelson et al., 2020).

2.1.2 Generalized Anxiety Disorder

GAD is a mental health disorder characterized by persistent, excessive, and unrealistic worry about daily events or activities (American Psychiatric Association, 2022). To be diagnosed with GAD, individuals must be experiencing excessive anxiety and worry more days than not for a minimum of 6 months and have difficulty controlling the worrying (American Psychiatric Association, 2022). The anxiety and worry must also be associated with three or more of the following symptoms, with some being present more days than not, for the past 6 months, with significant impairment in social and/or occupational areas: restlessness, easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbances (American Psychiatric Association, 2022). Risk factors for developing GAD include parental depression and anxiety, stressful life events in childhood and adulthood (e.g., parental divorce or death, sexual, emotional and or physical abuse, neglect), parental characteristics (e.g., harsh discipline, overinvolvement), internalising and externalizing disorders, and behavioural inhibition (Beesdo et al., 2009; Clark et al., 2007; Kagan, 1989; Moreno-Peral et al., 2014).

2.1.3 Cognitive Symptoms in Depression and Anxiety Disorders

MDD and GAD share many overlapping symptoms, notably cognitive impairments related to executive function, cognitive flexibility, sustained attention, visual memory, working memory, and learning (Castaneda et al., 2008; Kim et al., 2019; Luo et al., 2022; Rock et al., 2014). These deficits can significantly impair an individual's ability to function both occupationally and socially in daily life. For instance, a systematic review and meta-analysis conducted in individuals with MDD in both symptomatic and remitted states showed that executive dysfunction and attention deficits persisted during remission in the absence of significant low mood symptoms (Rock et al., 2014). The use of cognitive behavioural therapy

and metacognitive therapy are currently being used to treat GAD cognitive biases, although some individuals may require long-term of ongoing sessions to achieve or maintain recovery (Solem et al., 2021). Intact cognition is crucial for both psychosocial and non-social functioning in daily life. The perception, analysis, and management of everyday situations can be negatively influenced in individuals with MDD or GAD. For example, while having a conversation with a friend, a social cue may be misinterpreted as negative or threatening, resulting in the individual feeling lonelier and avoiding this friend for fear of further judgment. As another example, an individual talks to their sibling about a hockey game. Despite their enjoyment or familiarity with the players or teams involved, an individual may have difficulties remembering the player of topic, have difficulties concentrating on the conversation with their sibling, or not be able to think clearly, for example regarding the performance of the players involved. These difficulties can negatively affect the interaction, with the individual experiencing embarrassment over their lack of relatable or tangible information, potentially affecting future conversations regarding hockey games with this sibling. Additionally, another example in which a co-worker passing by an individual workspace without saying "hello" and making eye contact may be misinterpreted as a catastrophic event, with the individual considering that the interaction was an intentional rejection or a sign of impending job loss. Individuals with these mental disorders may be overwhelmed and have altered perceptions of reality, negative or non-existent coping strategies for managing normal, unpredictable, and uncontrollable stress life events, ultimately reducing their overall quality of life (Compas et al., 2017; Hofmann & Hayes, 2019).

2.2 Non-Social and Social Cognition

Cognition refers to the conscious and unconscious mechanisms involved in acquiring information and developing understanding. This includes reasoning, learning from experience,

and processing sensory input that culminate in knowledge acquisition and comprehension (Chomsky, 1959; Newell et al., 1958; Wells, 1998). Non-social cognition refers to the processes underlying non-social interactions or non-social settings. This includes but is not limited to the speed of processing, verbal learning and memory, visuospatial learning and memory, working memory, attention/vigilance, reasoning and problem solving (Chang et al., 2024). Social cognition refers to the cognitive processes involved in social behaviour, including identifying, comprehending, and responding to both cognitive and emotional characteristics, thoughts and feelings, of oneself and of others (Chang et al., 2024). These processes involve perception, encoding, storage, retrieval, and regulation of information regarding oneself and others (Adolphs, 1999) that when combined, can assist in deriving and predicting the emotional and mental state, behaviours and reactions of our own self and of others (Fiske, 2013). Both non-social and social cognition share similar mechanisms of acquiring and processing information but differ in their utilization of that information (Green et al., 2019). As mentioned earlier, cognitive impairment is a symptom shared by depression and anxiety disorders (Millan et al., 2012). A meta-analysis found moderate cognitive deficits in executive function, memory, and attention in MDD individuals compared to healthy controls (Rock et al., 2014). Another meta-analysis of theory-of-mind abilities in individuals with MDD, a crucial skill that enables one to attribute mental states to others and use that insight to understand and predict their behavior, found significant social cognition deficits in this population, related to the severity of symptoms in affective, cognitive, verbal and visual tasks (Bora & Berk, 2016). In addition, a more recent study found that MDD individuals had impairments in sustained attention, visual memory, working memory, learning, and executive functioning, compared to healthy controls (Luo et al., 2022). Studies investigating GAD individuals have shown impairments in sustained attention,

visual memory, and executive functioning (Luo et al., 2022), difficulties maintaining and updating information regarding social emotions and identity (Xu et al., 2022), as well as poorer performance on complex span tasks and impairments in working memory when performing attentionally demanding tasks (Moran, 2016), ultimately making social interactions difficult and promoting GAD symptoms of worrying and rumination.

2.3 Neuropsychiatric Disorders and Social Stressors

A major risk factor for the development of MDD and GAD is chronic stress (Kendler et al., 1999, 2003; Kessler, 1997). One of the most common sources of chronic stress encountered is from negative social interactions. From an evolutionary perspective, social interactions were optimal for survival as it was necessary to establish and maintain relationships, requiring adaptation (Slavich, 2020). Social animals often form dominance hierarchies, creating inequality in the distribution of resources (Sapolsky, 2005), regardless of quantity and/or availability (Sapolsky, 1994). The social rank of an individual is determined by the interaction between genetic, experiential, and environmental factors (Archer, 1988), in addition to the individuals current hierarchal position, the social setting in which the new rank was obtained, and the individuals personality styles (e.g., vigilant, aggressive, competitive, affiliative) (Sapolsky, 1994). With this, it is reasonable to assume that an individual's position within a hierarchy influences how they cope with social and environmental challenges (Bartolomucci et al., 2005), and can influence their vulnerability to stress-related disease (Sapolsky, 2005). The common pattern occurring indicates that "*the rank that experiences the largest quantity of physical and psychological stressors will also present with the most severe stress-related pathologies*" (Sapolsky, 2005). In stable hierarchies, the actively subjugated individual experiences the most social stress. Subordinates in this context experience lack of social control and predictability,

work harder to obtain food resources, and have an absence of social outlets including grooming or displacing aggression onto a lower ranked subordinate (Sapolsky, 2005). In hierarchies experiencing reform, dominant individuals whom are involved in social conflict, such as losing their current rank in the hierarchy, experience the most social stress (Bartolomucci et al., 2005; Sapolsky, 2005). Social interactions can be positive or negative, depending on the nature of the interaction and individual characteristics such as the perception of the interaction (Wood & Bhatnagar, 2015). With this, the individual experience of negative social relationships can be a source for chronic social stress (Bartolomucci et al., 2005; Nelson et al., 2020). Prolonged social stress can overwhelm adaptive coping mechanisms and may dysregulate hypothalamic-pituitary-adrenal (HPA) axis function (Koss & Gunnar, 2018; Lupien et al., 2009). This can heighten stress sensitivity, social dysfunction, and the development of neuropsychiatric disorders (Murphy et al., 2022). A study found that interpersonal life events predicted the subsequent onset of MDD in two adolescent samples (Vrshek-Schallhorn et al., 2015). Another study found that following an interpersonal social stress event, adolescents with heightened pro-inflammatory cytokine salivary responses were more likely to develop depressive symptoms (Slavich et al., 2020). Additionally, a study found that in individuals who had previously experienced a depressive episode, but did not currently meet diagnostic criteria for MDD, their chronic interpersonal stress predicted depressive episode recurrence (Sheets & Craighead, 2014). Individuals persistently experiencing interpersonal conflicts may become increasingly sensitive to future interactions (Arnett, 2004; Sheets & Craighead, 2014), increasing their risk for developing mental health disorders. Conversely, people with depression were more likely to experience moderate to severe life stressors (Uliaszek et al., 2012), which could lead continued depressive symptoms and future recurrence (Rudolph, 2009). Of note, not everyone that experiences social stress, even in chronic

conditions, will develop stress-related psychopathologies, like MDD or GAD (Bartolomucci et al., 2005). Psychosocial and behavioural factors such as self-perception, personality, cognitive reappraisal, adaptive or passive coping strategies, dietary preferences, and lifestyle habits can modulate an individual's vulnerability versus resilience to stress (Koh, 2018). The individual vulnerability and resilience to chronic social stress can be modeled effectively in animal models of neuropsychiatric conditions to elucidate the underlying mechanisms of action (Wang et al., 2021).

2.4 Chronic Social Defeat Stress: An Animal Model of Chronic Social Stress

To study the impact of chronic social stress on behaviour and physiology and mimic the development of stress-related mental health disorders observed in humans, rodent models have been widely used (Planchez et al., 2019). One such model is chronic social defeat stress (CSDS), a paradigm that simulates chronic psychosocial stress in rodents, allowing researchers to study individual responses to social stressors (Berton et al., 2006). This model involves brief physical interactions between a smaller naïve male mouse that is placed into and cohabitating in the home cage of a new larger resident male mouse daily, for ten consecutive days (Golden et al., 2011). The natural behaviour of male mice is to acquire and defend a territory (Bartolomucci et al., 2001), which results in a dominant winner, typically the resident mouse, and a defeated loser, typically the intruder mouse, of the interactions. Losing or not accessing a resource, such as dominance status or a territory, is an intense event that may result in persistent physiological changes and may promote the development of pathological conditions (McEwen & Wingfield, 2003). The social interactions with another mouse displaying aggressive behavioural traits can also result in persistently avoidant and/or submissive behaviours, eventually leading to social withdrawal, passive coping, fear, and anhedonia, which are features of depressive and anxiety

disorders (Berton et al., 2006; Kudryavtseva et al., 1991). A subset of mice defeated as part of the CSDS model, termed stress-susceptible, typically show social avoidance as well as depressive-like and anxiety-like behaviours (Doney et al., 2023; Hing et al., 2018; Menard et al., 2017; Szyszkowicz et al., 2017). Stress-susceptible mice chronically treated with fluoxetine, imipramine, or venlafaxine, three chemically distinct antidepressants used in humans, exhibited limited social avoidance, anhedonia, helpless behaviour, and anxiety-like behaviours (Berton et al., 2006; Menard et al., 2017; Tsankova et al., 2006; Venzala et al., 2012), indicating that stress-induced behavioural alterations can be reversed with chronic antidepressant treatment. As mentioned earlier, cognitive dysfunction and difficulties with social cognitive processes are features of both depression and anxiety (Moran, 2016; Rock et al., 2014). In addition to classic depressive-like and anxiety-like behaviours, the CSDS model impairs non-social learning and memory functions as well as social cognitive processes required for determining appropriate responses to social threats (Duque et al., 2017). Stress-susceptible defeated mice were also shown to have enhanced fear memory as well as impaired recognition memory, attention, executive dysfunction, and poor decision making (Du Preez et al., 2021; Huang et al., 2013; Jin et al., 2015; Martin et al., 2017; Yu et al., 2011).

2.5 Impact of Chronic Stressors: Dysregulation of the HPA Axis and Immune Responses

Stress is a response to a detected potential or real threat, referred to as a stressor. When an individual perceives a stressor, the body activates a complex series of physiological responses to cope with the stressor, with the end goal of returning to homeostasis (De Kloet et al., 2005). The neuroendocrine response to a stressor is managed by the HPA axis (Smith & Vale, 2006). Upon the confirmation of a stressor, the paraventricular nucleus of the hypothalamus produces corticotropin-releasing hormone (CRH), which signals the anterior pituitary gland to produce

adrenocorticotropin hormone (ACTH) and enter circulation. In response to the circulating ACTH, the adrenal cortex produces glucocorticoids (GCs) such as cortisol (humans) or corticosterone (rodents) which subsequently enters into the bloodstream (Sorrells et al., 2009). The GCs then target glucocorticoid receptors (GRs) in the hypothalamus and the pituitary gland to reduce the production of CRH, ACTH, and GCs, ultimately creating a negative feedback loop to return to homeostasis (De Kloet et al., 2005). In addition, GCs temporarily reduce the expression of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor alpha (TNF-α), while upregulating anti-inflammatory cytokines (e.g., interleukin-10, tumour necrosis factor beta) (Sorrells et al., 2009).

Chronic stressors can be difficult to cope with, as they challenge the body's normal physiological stress responses to appropriately manage an ongoing aversive experience while attempting to return to homeostasis (Harbuz & Lightman, 1992). Chronic stressor exposure results in the elevated production and circulating levels of GCs over an extended period of time, leading to dysregulations in the HPA axis and other systems, including the immune system (Frank et al., 2013; Herman, 2022). Depending on the individual, these dysregulations can be beneficial as it prepares them for future stressors, or could be maladaptive as the adverse consequences of prolonged GC exposure includes immune dysregulation, metabolic dysregulation, and impairments in learning, emotional perception, and mood (Belanoff et al., 2001; Roozendaal, 2002; Russell & Lightman, 2014). Chronic stress has been shown to induce long-lasting cellular and molecular alterations, in both animal models and in humans (Harbuz & Lightman, 1992; Menard et al., 2017; Sapronova et al., 2024; Szyszkowicz et al., 2017). The increased production and circulation of GCs may result in a decreased sensitivity of GRs and mineralocorticoid receptors, creating GC resistance (Miller et al., 2002; Schleimer, 1993). The

GC resistance developed during chronic stress can decrease the anti-inflammatory actions of GCs and impair the negative feedback inhibition of CRH production, resulting in prolonged pro-inflammatory activity and HPA axis hyperactivity (Cohen et al., 2012). To assess systemic peripheral inflammation, C-reactive protein (CRP), an acute phase reactant, is one of the most commonly utilized biomarkers (Fernandes et al., 2016) in addition to IL-1β, IL-6, and TNF-α. Both animal models of chronic social stress and clinical studies of neuropsychiatric patients have found increased circulating levels of these pro-inflammatory factors. Most notably, CSDS can alter both the HPA axis and immune function, which are integral to the development of behavioural and cognitive impairments (Bondar et al., 2018; Merkulov et al., 2017; Sapronova et al., 2024). For example, mice susceptible to the effects of CSDS were shown to have increased circulating levels of IL-1β, IL-6, and TNF-α (Goshen et al., 2008; Hodes et al., 2015). In clinical studies, a meta-analysis found that depressed individuals had higher serum levels of IL-1β, IL-6, TNF-α, CRP and reduced levels of the anti-inflammatory cytokine interleukin-4, compared to non-depressed individuals (Osimo et al., 2020). Additionally, a separate meta-analysis showed that GAD individuals had increased levels of CRP and TNF- α compared with healthy controls (Costello et al., 2019).

2.6 Central Inflammation

Chronic stress can lead to a sustained increase in circulating pro-inflammatory cytokines, which not only heightens susceptibility to stressors and the development of depressive- and anxiety-like behaviours (Hodes et al., 2015), but may also result in systemic inflammation that could indirectly trigger neuroinflammatory processes within the central nervous system (CNS) (Dantzer et al., 2008). In normal conditions, the blood-brain barrier (BBB), which is mainly composed of brain microvascular endothelial cells, manages the exchange of molecules between

the bloodstream and the CNS, preventing pathogens, toxins, and inflammatory factors from passing into the CNS, and ensuring homeostasis and brain functions are maintained (Aburto & Cryan, 2024). In a mouse model of CSDS, BBB permeability was increased due to the downregulation of the endothelial cell tight junction protein claudin-5 and the stress-induced circulatory recruitment of peripheral immune factors, allowing the passage of circulating IL-6 into the CNS and resulting in depressive-like behaviours (Menard et al., 2017). The infiltrating pro-inflammatory cytokines may result in additional cytokine production within the brain, by activating microglia, the resident immune cells within the CNS and important mediator regulating cognition (Dantzer et al., 2008; Maier, 2003; Tynan et al., 2010; Zhou et al., 2024), as well as through neurons and astrocytes (Galic et al., 2012; Liddelow & Barres, 2017). Microglia can detect central and peripheral threat signals, adapting by morphologically transforming into different states with independent functions (Ransohoff & Cardona, 2010). Upon threat activation, microglia will change into its activated phenotype, primarily facilitating pro-inflammatory and neurotoxic activity (Ślusarczyk et al., 2018) while reducing neurogenesis (Bassett et al., 2021), and will synthesize pro-inflammatory cytokines (e.g., IL-1β, TNF-α, and IL-6), nitric oxide, and glutamate to remove the harmful stimuli (Lively & Schlichter, 2018). The other microglia phenotype is induced through the uptake of apoptotic cells and by anti-inflammatory cytokines (e.g., IL-4, IL-10), to promote anti-inflammation, tissue repair, restoration of cellular structures (Tang & Le, 2016), and neurogenesis (Yuan et al., 2017). Chronic stress can promote pro-inflammatory microglial activity (Milior et al., 2016), which can remodel neuronal structures, potentially inducing profound alterations and contributing to neurobehavioural complications, such as depression and cognitive deficits (Norden & Godbout, 2013). Microglia can recruit circulating immune cells to cross the BBB (Ajami et al., 2011; Miller & Raison, 2016; Yamasaki

et al., 2014) and peripheral cytokines can directly cross the BBB through specific transport mechanisms to then act on microglia and other neuromodulators (Hodes et al., 2015).

Animal models utilizing CSDS have shown that the influx of monocytes through the BBB infiltrated brain regions involved in depression and anxiety such as the hippocampus, contributing to increased pro-inflammatory activity in these regions and to the development of depressive- and anxiety-like behaviours (McKim et al., 2018; Sawicki et al., 2015; Wohleb et al., 2012, 2013). In humans, post-mortem brain analyses of individuals that had committed suicide in the context of a major depressive episode have shown increased pro-inflammatory microglia compared to individuals without psychiatric or inflammatory disorders (Torres-Platas et al., 2014). A recent meta-analysis and systematic review investigating central inflammation in post-mortem MDD patients, found increased levels of IL-6 in the brain and increased expression of TNF-α mRNA in post-mortem MDD brains (Enache et al., 2019; Wang & Miller, 2018). They also found increased brain expression of toll-like receptor 3 and 4 (TLR4), which mediates the activation of microglia and increased pro-inflammatory cytokine production, in post-mortem MDD brains (Facci et al., 2014; Pandey et al., 2014). Additionally, from the included studies that used positron emission tomography for investigating brain inflammation, translocator protein, a marker of central inflammation, was shown to be elevated in several brain regions, including the hippocampus (Enache et al., 2019).

2.7 Systemic Inflammation May Impact Neurotrophic Factors

The elevated pro-inflammatory cytokine activity within the CNS can influence key neurobiological processes, including hippocampal neurogenesis and synaptic plasticity, ultimately affecting cognition (Enache et al., 2019; Facci et al., 2014; Pandey et al., 2014; Wang & Miller, 2018). Neurotrophic factors are a group of proteins that support neuronal processes and

are primarily synthesized by neurons and glial cells within the CNS as well as by peripheral nervous system and immune cells (Tian et al., 2012). The most characterized neurotrophic factors are BDNF, nerve growth factor (NGF), and neurotrophin-3 (NT3), which are responsible for the regulation of neurogenesis, the survival and maintenance of neuronal connections, neuroplasticity, cognitive functions, and mood-related behaviours (Aloe, 2004; De Miranda et al., 2020; Miranda et al., 2019). The stress-induced production of GCs, pro-inflammatory cytokines, and additional microglia-mediated neuroinflammatory responses suppresses the production and regulatory actions of neurotrophins, negatively regulating cognitive functions and altering behaviour (Surget & Belzung, 2022; Willner et al., 2013). In a CSDS mouse model, BDNF expression was downregulated in the hippocampus, persisting up to four weeks after the last social defeat interaction (Tsankova et al., 2006). It was also shown that in rodents susceptible to the effects of CSDS, reduced BDNF expression in the hippocampus correlated with both stress-associated anxiety- and depressive-like behaviour changes (Miao et al., 2019). In contrast, overexpression of BDNF in mice prevented hippocampal atrophy induced by chronic stress and had antidepressant effects (Govindarajan et al., 2006). Post-mortem brain analysis of depressed individuals after suicide showed decreased expression of BDNF and its receptor, tropomyosin receptor kinase B (TrkB), in the hippocampus, but their expression was increased in those that received antidepressant treatment before their death (Karege et al., 2005). Studies investigating the peripheral serum levels of neurotrophic factors have found that treatment-naïve depressed individuals had lower serum levels of BDNF, which were linked with impairments in memory and attention compared to healthy controls (Teng et al., 2021), while other studies have found that MDD patients had lower serum levels of NGF (Ogłodek et al., 2016; Wiener et al., 2015), and NT-3, where the concentrations decreased with increasing depression severity (Ogłodek et

al., 2016). A meta-analysis and systematic review found that peripheral protein NGF levels were reduced in patients with MDD (Chen et al., 2015), while a separate study found reduced mRNA expression of NT-3 in the peripheral white blood cells of MDD patients (Otsuki et al., 2008). These results suggest that the changes in neurotrophic factor expression are associated with the pathophysiology of neuropsychiatric disorders.

2.8 Chronic Stress Impairs Hippocampal Function

The hippocampus is an important brain structure with multiple roles in modulating the stress response, cognition, memory, anxiety, and depression (Kim and Diamond, 2002; Fanselow & Dong, 2010; Gulyaeva, 2019). The dorsal and the ventral hippocampus each have unique projections within the brain, contributing to their respective functions (Grigoryan & Segal, 2016). The dorsal (posterior in human) hippocampus is primarily involved in learning, memory, spatial navigation and exploration, while the ventral (anterior in human) hippocampus is mostly involved in emotional behaviour and regulation of the HPA axis (Fanselow & Dong, 2010; Gulyaeva, 2019). Using animal models of hippocampal damage, studies have shown that dorsal hippocampus lesions result in spatial learning impairments, while ventral hippocampus lesions can attenuate innate anxiety behaviours and stress-induced increases in plasma corticosterone, and prevent increased defecation response to an anxiogenic environment (Bannerman et al., 2002, 2003, 2004; Kjelstrup et al., 2002; Moser et al., 1993; Moser et al., 1995; Pentkowski et al., 2006; Pothuizen et al., 2004). The quantity and survival of newborn neurons in the dorsal hippocampus may support new learning and memory processes, in contrast to the ventral hippocampus where neurogenesis can effectively improve emotional impairment (Ramírez-Rodríguez et al., 2021; Toda et al., 2019; Yagi et al., 2020; Yau et al., 2015). Interestingly, studies have emphasized that both dorsal and ventral hippocampus play an overlapping function

on location and spatial memory processes, as well as on affective and emotional behaviours (Almeida et al., 2020; Hartmann et al., 2019; Riaz et al., 2017; Sant'Ana et al., 2019). Throughout the literature, it is mutually agreed upon that the functions of the hippocampus are more complicated than the simple "learning vs emotions" model (Gulyaeva, 2019). Studies have shown that adult hippocampal neurogenesis, which is dependent on C-X3-C motif chemokine receptor 1 (CX3CR1)/CX3C chemokine ligand 1 signalling between microglia and neurons (de Miranda et al., 2017; Delpech et al., 2015), plays a role in the behavioural effects of antidepressant drugs (Fang et al., 2023; Lino de Oliveira et al., 2020). Chronic stress negatively affects hippocampal-dependent learning and memory processes, in addition to structural changes, resulting in impairments regulating episodic and spatial memory (Horchar & Wohleb, 2019; Kim et al., 2015; Smith, 2013; Zhou et al., 2016). In studies using CSDS, susceptible rodents have impaired hippocampal neurogenesis and smaller hippocampal volume (Lee et al., 2009; Rahman et al., 2016). A study using a different model of chronic social stress, known as repeated social defeat, had shown impaired spatial memory recall and increased monocyte recruitment mediated by microglia, which was associated with increased hippocampal mRNA expression of IL-1β, IL-6, and TNF-α (McKim et al., 2016). In clinical studies, meta-analyses of both MDD and GAD individuals have found reductions in hippocampal volumes compared to healthy controls (Kolesar et al., 2019; Madonna et al., 2019; Santos et al., 2018), which may underlie cognitive and behavioural impairments.

2.9 Intestinal Inflammation and the Microbiota-Gut-Brain Axis

While peripheral and central inflammation as well as neurotrophic factors play a critical role in the pathophysiology of depression and anxiety disorders, evidence also highlights the bidirectional communication between the brain and the gut in these conditions (Doney et al.,

2022; Margolis et al., 2021; Reyes-Martínez et al., 2023; Tang et al., 2021). In particular, intestinal inflammation has garnered significant attention as a key contributor to this relationship, with disruptions in the gut microbiota and compromised intestinal integrity potentially exacerbating neuroinflammatory processes (Doney et al., 2023; Leigh et al., 2023). Understanding the interplay between intestinal and central inflammation offers valuable insight into the broader inflammatory mechanisms underlying depression and anxiety. The gastrointestinal (GI) tract is viewed as an avenue that can potentially allow the external environment access to the internal environment of the body (Aburto & Cryan, 2024). To protect the host from external pathogens, there are selectively permeable barriers allowing the translocation of dietary nutrients, amino acids, short-chain fatty acids (SCFAs), water and other selective metabolites from the intestinal lumen into circulation while blocking harmful pathogens from entering (Turner, 2009). The integrity of the intestinal barrier is dependent on the interplay between intestinal cells, immune cells, and neuronal innervations (Suriano et al., 2022). In rodent models, CSDS has been shown to disrupt the regulation of tight junction proteins, such as TLR4 expression on intestinal cells in the colonic gut barrier (Doney et al., 2023; Lauffer et al., 2016; Leigh et al., 2023; Vicario et al., 2012), increasing paracellular permeability across the gut barrier. The increased intestinal permeability can promote pro-inflammatory responses, and allow for the translocation of bacterial by-products into the host (Doney et al., 2023; Wu et al., 2023). The gut microbiota, which is a collection of trillions of microorganisms harboured by the GI host, is involved in the regulation of local and systemic immunity, the HPA axis, GI functions, and systemic homeostasis (Rusch et al., 2023). The gut microbiota can bidirectionally communicate with the brain using the microbiota-gut-brain axis (MGBA). The MGBA connects the brain and the gut using neuro-endocrine-immune mediators, direct neural connections, and

gut-derived metabolites such as SCFAs, thereby influencing neuronal processes and behaviour (Carabotti et al., 2015; Cryan et al., 2019). Studies have shown that male germ-free mice have an overactive HPA axis with exaggerated blood concentrations of corticosterone and ACTH after a stressor (Sudo et al., 2004), increased permeability across the BBB (Braniste et al., 2014), reductions in hippocampal volume (Luczynski et al., 2016), alterations in BDNF expression as well as immature microglia in the hippocampus (Bercik et al., 2011; Erny et al., 2015; Gareau et al., 2011; Heijtz et al., 2011), impaired social behaviour and social cognition, non-spatial, hippocampal-mediated and working memory deficits (Gareau et al., 2011; Lu et al., 2018; Luczynski et al., 2016), and a reduction in anxiety-like and depressive-like behaviours (Heijtz et al., 2011; Zheng et al., 2016). These alterations in mice devoid of microbes suggest the involvement of the gut microbiota in the etiology of stress-related neuropsychiatric disorders (Delgado-Ocaña & Cuesta, 2024). Gut microbiota alterations have been observed in both animal models and in individuals with depression and anxiety disorders (Gao et al., 2023; Nikolova et al., 2021; Szyszkowicz et al., 2017), suggesting that the MGBA may serve as a potential target for improving behavioural and cognitive impairments associated with neuropsychiatric conditions.

2.10 Dietary Interventions in the Context of Mental Health

With no clear etiology and limited effective treatment options in a subset of individuals, depressive and anxiety disorders necessitate additional strategies to improve symptoms and potentially mitigate future occurrences. Research suggests that diet, as a modifiable factor and major determinant of gut microbiota composition, may be a potential therapeutic strategy for supporting cognitive and emotional stability, enhancing resilience to stress, and improving mental health outcomes (Bizzozero-Peroni et al., 2024; Fu et al., 2022; Jacka et al., 2017;

Koelman et al., 2022; Schneider et al., 2024). Both preclinical and clinical evidence supports the intake of healthy dietary components for their positive impact on mood, even in individuals without diagnosed neuropsychiatric conditions (Muscaritoli, 2021). Nutritional components of interest in this context include monounsaturated and polyunsaturated fatty acids (MUFAs and PUFAs, respectively), which metabolize and produce beneficial metabolites, and polyphenols. These components have been shown in animal models to reduce corticosterone levels, protect against circulating and CNS inflammation, improve BBB integrity, promote neuronal survival and differentiation, regulate hippocampal BDNF expression, which may improve cognitive dysfunction as well as anxiety-like and depressive-like behaviours (Calder, 2015; Ferraz et al., 2011; Kołodziej et al., 2023; Rana et al., 2022; Zailani et al., 2024).

Intakes of MUFAs and PUFAs are essential for regulating the structure and functions of neuronal, glial, and endothelial cells in the CNS. While MUFAs can be synthesized from simple precursors within the brain (Bazinet & Layé, 2014), PUFAs are primarily obtained from dietary sources, including marine food products (e.g., salmon, sardines, mackerel, anchovies), nuts (e.g., walnuts), green leafy greens, and flaxseed oil (Fernandes et al., 2017). These PUFAs can also be converted from essential dietary precursors (α-linolenic and linoleic acids), predominantly in the liver, and from there, transported through the blood to their targets, and can cross the BBB (Bazinet & Layé, 2014; Jump, 2002; Liu et al., 2015; Sublette et al., 2024). Individuals with MDD have been shown to have lower circulating levels of omega (ω)-3 and higher ω-6 levels compared to individuals without depression, however, there are mixed results which highlights the need for further investigation (Berger et al., 2017; Lin et al., 2010; Liu et al., 2013; Mongan et al., 2021). Previous literature has also shown that higher circulating levels of ω-3 was associated with improved cognitive function and lower incidence of depression, whereas higher

circulating levels of ω-6 was associated with impaired cognitive function (Preedy & Watson, 2019; Stachowicz, 2021; Wani et al., 2015). Meta-analyses found that ω-3 PUFAs supplements containing ≥60% eicosapentaenoic acid (EPA) showed a therapeutic effect on the improvement of depression (Firth et al., 2019; Liao et al., 2019).

Polyphenols are bioactive phytochemicals that can induce anti-inflammatory and antioxidant effects (Dias et al., 2012). Polyphenols can be found in fruits, vegetables, olive oil, red wine, with flavonoids being the largest group. Dietary polyphenols can exert neuroprotective effects by downregulating the activation of microglia, inhibiting cytokine release from activated glial cells, and downregulate the expression of pro-inflammatory transcription factors (González-Gallego et al., 2010), which can mitigate neuroinflammatory responses. In rodent models, specific polyphenols like resveratrol have been shown to reduce chronic unpredictable mild stress-induced depressive-like behaviours as well as corticosterone and pro-inflammatory cytokine increases (Yang et al., 2017). Randomized controlled trials found that high polyphenol intake improved global cognition and serum BDNF levels (Neshatdoust et al., 2016).

Adherence to different dietary patterns may provide the gut microbiota different nutrient sources for metabolite production. The Western diet is characterized by a high consumption of red and/or processed meat, refined grains, high-fat dairy products, sugar-sweetened beverages, and low intake of fruits and vegetables (Jacka et al., 2010; Zhang et al., 2024). The Western diet contains low concentrations of fibre, micronutrients, and healthy fatty acids, but high concentrations of saturated fats, salts, and sugar (Clemente-Suárez et al., 2023; Cordain et al., 2005). Higher adherence to a Western dietary pattern has been associated with an increased risk of anxiety, depression, and depressive symptoms (Lassale et al., 2019; Zhang et al., 2024). Additionally, children with MDD consume less healthy foods compared to non MDD children

(Korczak et al., 2022), which may negatively impact depression symptom severity and future depressive episodes. In stark contrast, the Mediterranean (Med) diet is composed of whole grains, nuts, legumes, vegetables, and fruits, with moderate consumption of fish and poultry products (Sánchez-Villegas et al., 2009) and has been extensively investigated for its health benefits. The Med diet contains high concentrations of MUFAs, PUFAs, polyphenols, vitamins, and minerals, which can potentially result in anti-inflammatory and neuroprotective effects, and improve both depressive and anxiety symptoms (Bizzozero-Peroni et al., 2024). The Med diet has been correlated with a reduced risk of developing depression in several studies (Bizzozero-Peroni et al., 2024; Firth et al., 2019; Lassale et al., 2019). Additionally, a randomized controlled trial using the Med diet as a dietary intervention for MDD showed significant reductions in depressive symptom severity, independent of body mass index, physical activity, and other lifestyle factors, showing the benefit of the intervention (Jacka et al., 2017). The bioactive compounds found within the Med diet including MUFAs, PUFAs, polyphenols, essential vitamins, and minerals may provide a synergistic effect on reducing intestinal (Deleu et al., 2024) and neuro-inflammatory responses (Almanza-Aguilera et al., 2022; Méndez & Medina, 2021).

2.11 Research Question, Objectives, and Hypotheses

In the present study, our aim was to investigate whether a dietary intervention, based on the human Med diet and designed for mice, could protect against cognitive impairments, in addition to neuroinflammatory and neurotrophic changes, in a mouse model of chronic social stress.

Our first objective was to confirm that male mice subjected to CSDS displayed social and non-social cognitive impairments, as well as inflammatory and neurotrophic changes in the

hippocampus, a brain region implicated in depression, emotional regulation, social and non-social cognition, and the stress response (Anacker & Hen, 2017; McEwen et al., 2016). Our second objective was to determine whether a version of the human Med diet designed for mice could mitigate the cognitive, neuroinflammatory, and neurotrophic changes elicited by CSDS.

We first hypothesized that CSDS mice would show more social avoidance behaviours, impaired working, spatial, short- and long-term memory in both social and non-social contexts, as well as an elevated expression of pro-inflammatory cytokines and microglial markers, but a reduced expression of neurotrophic factors in the hippocampus. We also anticipated that CSDS mice fed the Med-based diet, compared to their counterparts fed a control diet, would show limited cognitive, pro-inflammatory, microglial, and neurotrophic changes. With accumulating evidence supporting the anti-inflammatory and neuroprotective properties of the Med diet (Bizzozero-Peroni et al., 2024; Firth et al., 2019; Koelman et al., 2022), this study will contribute to our understanding of the influence of dietary factors on neuroinflammatory and neurotrophic processes impaired in chronic social stress, thereby offering insights into the potential of a Med-based dietary intervention to enhance resilience to chronic social stress and improve mental health outcomes.

Chapter 3: The Impact of a Mediterranean-based Diet on Cognitive, Inflammatory, and Neurotrophic Impairments Induced by a Chronic Social Defeat Stressor in Male C57BL/6N Mice

Full-Length Research Report

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3.1 Abstract

Background: Stress-related neuropsychiatric disorders continue to increase in prevalence and current treatments do not sufficiently address social and non-social cognitive impairments, requiring alternative approaches. The Mediterranean (Med) diet has been shown to improve depression, anxiety, and cognitive deficits in clinical studies. Using a mouse model of chronic social stress, this study investigated a Med-based diet as a preventative strategy to limit social and non-social cognitive impairments and limit changes in brain inflammatory and neurotrophic factors.

Methods: Male C57BL/6N mice were randomly assigned to a Control or a Med-based diet. After a 14-day acclimatization period to the diets, both groups were either subjected to 10 consecutive days of chronic social defeat stress (CSDS) or to a no stress control condition. Cognitive tests were conducted 24 hours after the last stressor or control session. The ventral hippocampus was collected 24 hours following the last behavioural test and analyzed for the mRNA expression of pro-inflammatory cytokines, microglial markers, and neurotrophic factors.

Results: Mice subject to CSDS exhibited increased social avoidance behaviours and had altered hippocampal expression of neurotrophin-3 and Tropomyosin receptor kinase B. In CSDS mice, the Med-based diet further exacerbated social avoidance behaviours, impaired spatial reference memory, and reduced hippocampal BDNF expression, but improved long-term memory and decreased hippocampal TNF-α expression.

Conclusion: Dietary interventions, in male mice subject to chronic social stress, have varied effects on cognition and hippocampal health, necessitating further investigation into their role as adjunctive therapies for cognitive impairments in stress-related neuropsychiatric disorders.

Keywords: Anxiety, Cognition, Depression, Hippocampus, Inflammation, Mediterranean diet, Mouse model, Neurotrophic factors, Social stress

3.2 Introduction

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are among the leading causes of disability burden worldwide (GBD 2019 Diseases and Injuries Collaborators, 2020). While these neuropsychiatric disorders are distinct, they share similar symptoms, notably cognitive impairments including executive dysfunction, cognitive inflexibility, as well as deficits in both social and non-social aspects of cognition (Hammar et al., 2022; Isakulyan & Marachev, 2024; Kim et al., 2019; Luo et al., 2022; Pan et al., 2019). Despite a complex interaction of biological, psychosocial, and genetic factors contributing to their heterogenous etiology, chronic stress has been established as a major predisposing factor in the development of MDD and GAD (Liu et al., 2024; McGonagle & Kessler, 1990), as well as of cognitive impairments (Lupien et al., 2009; Sandi, 2013). Chronic stress has been shown to upregulate peripheral and central inflammatory activity (Costello et al., 2019; Hodes et al., 2015; Menard et al., 2017), and alter neurotrophic factor expression, including brain derived neurotrophic factor (BDNF) (Surget & Belzung, 2022; Tsankova et al., 2006; Willner et al., 2013), which has been associated with both MDD and GAD (Miao et al., 2020; Molendijk et al., 2014; Teng et al., 2021). Current pharmacological treatments have limited efficacy on symptom management (Baldwin et al., 2011; Rush et al., 2006), particularly cognitive symptoms that continue to persist, even during remission (Bora et al., 2013), highlighting the necessity of developing additional strategies for preventing and/or mitigating symptoms. Research has suggested that diet, which is a modifiable lifestyle factor, could be a potential therapeutic target for improving mental health, enhancing resilience to stress, and supporting cognitive stability (Firth et al., 2019; Hardman et al., 2016; Jacka et al., 2017; Parletta et al., 2013; Siervo et al., 2021). A primary source for chronic stress comes from negative social interactions. Prolonged exposure to social stressors can overwhelm

adaptive coping mechanisms, predisposing individuals to heightened stress sensitivity, impaired social relationships and cognitive functioning, and increased risk for developing neuropsychiatric disorders (Murphy et al., 2022; Schlosser et al., 2011). Chronic social stress can dysregulate the hypothalamic-pituitary-adrenal axis (Koss & Gunnar, 2018; Lupien et al., 2009) and alter immune function, which can result in prolonged inflammatory conditions (Cohen et al., 2012; Murphy et al., 2022), behavioural, social and non-social cognitive impairments similar to that observed in MDD and GAD (Bondar et al., 2018; Miao et al., 2020; Molendijk et al., 2014; Teng et al., 2021). Among validated animal models of neuropsychiatric disorders, chronic social defeat stress (CSDS) produces translatable behavioural and cognitive impairments, including social avoidance, anhedonia, impaired short-term and spatial working memory (da Costa et al., 2023; Huang et al., 2013; Menard et al., 2017; Moreira et al., 2016; Szyszkowicz et al., 2017; Yu et al., 2011). Studies utilizing CSDS have shown that chronically defeated mice exhibit upregulated peripheral and central pro-inflammatory cytokine expression, including interleukin (IL)-6, interleukin-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α), in addition to ionized calcium binding adapter molecule 1 (Iba-1) (Enache et al., 2019; Hodes et al., 2016; Menard et al., 2016, 2017; Szyszkowicz et al., 2017), which is a marker for activated microglia (Frick et al., 2013), as well as functional and structural deficits in important brain structures, particularly in the hippocampus (Fanselow & Dong, 2010; Lee et al., 2009; Rahman et al., 2016). Dysfunction of key hippocampal-dependent processes such as synaptic plasticity, cognition, and adult neurogenesis (Huang & Reichardt, 2001; Vilar & Mira, 2016), which is mediated by C-X3-C motif chemokine receptor 1 (CX3CR1)/CX3C chemokine ligand 1 signalling between microglia and neurons (de Miranda et al., 2017; Delpech et al., 2015), can result in learning and memory impairments. Adult hippocampal neurogenesis has been implicated in its involvement

mediated the behavioural effects elicited by antidepressant medications (Fang et al., 2023; Lino de Oliveira et al., 2020). With this, neurotrophic factors, including BDNF and its receptor tropomyosin kinase receptor B (TrkB) (Molendijk et al., 2014), nerve growth factor (NGF), and neurotrophin-3 (NT3) are key mediators of synaptic plasticity and have been shown to be deficient in depressed patients (Karege et al., 2005; Ogłodek et al., 2016; Ray et al., 2014; Teng et al., 2021). The Mediterranean (Med) diet has been extensively investigated for its health benefits. Characterized by the abundant consumption of olive oil as well as of plant-based and minimally processed foods (e.g., fruits, vegetable, pulses, nuts, fish), the Med diet contains several bioactive components, including MUFAs, PUFAs, polyphenols, and other essential nutrients, which have been shown to be anti-inflammatory and neuroprotective (Bizzozero-Peroni et al., 2024; Gamage et al., 2023; Koelman et al., 2022; Kołodziej et al., 2023). Notably, adherence to the Med diet was shown to be associated with a reduced risk for developing depression (Lassale et al., 2019). Interventions based on this diet have also been shown to have positive effects on cognitive functioning (Fu et al., 2022; Loughrey et al., 2017; Radd-Vagenas et al., 2018) and reducing depressive and anxiety symptoms (Bayes et al., 2022; Bizzozero-Peroni et al., 2024; Firth et al., 2019; Jacka et al., 2017), supporting its potential as an intervention treatment for neuropsychiatric disorders with cognitive symptoms.

In this study, we investigated whether a Med-based dietary intervention could mitigate cognitive deficits, in addition to pro-inflammatory and neurotrophic changes elicited by CSDS in male mice. We first evaluated social and non-social aspects of cognition following CSDS. We then evaluated the mRNA expression of pro-inflammatory cytokines, microglial-related markers, and neurotrophic factors within the hippocampus, a stress-sensitive brain region implicated in depression, emotional regulation, social and non-social cognition, and the stress response

(Fanselow & Dong, 2010; Gulyaeva, 2015, 2019). With the robust evidence demonstrating the Med diets anti-inflammatory and neuroprotective efficacy (Almanza-Aguilera et al., 2022; Estruch, 2010; Hornedo-Ortega et al., 2018, 2020), our goal was to further determine the influence of this diet on the regulation of neurotrophic, pro-inflammatory, and microglial markers in the context of chronic social stress. Ultimately, our goal is to elucidate how dietary interventions can modulate neuroinflammatory and neurotrophic processes, which can then be used as a potential adjunctive strategy to enhance resilience to chronic social stress and mitigate symptoms of neuropsychiatric disorders.

3.3 Materials and Methods

3.3.1 Animals

Fifty-eight naïve male C57BL/6N mice (Charles River Laboratories, Montréal, QC), aged 8-9 weeks old, were used as experimental mice (n = 44) or for paired-housing control procedures and as social targets during behavioural testing (n = 14). Thirteen sexually differentiated CD-1 male retired breeders (4-4.5 months old at arrival; Charles River Laboratories, Montréal, QC) were used as aggressive residents for the stressor procedures and as aggressive targets during behavioural testing. At their arrival, all mice were housed in single housing cages made from polypropylene (27 × 21 × 14 cm). Mice had twelve hours of light (from 0800 to 2000 h) and twelve hours of dark (from 2000 to 0800 h) daily, and this cycle was maintained throughout the duration of the experiment. The animal housing area was maintained at a temperature of 22 °C and humidity of 63%. All mice had free access to water and to their respective diet. The experimental procedures of the study were approved by the Animal Care Committee of the University of Ottawa according to the guidelines of the Canadian Council on Animal Care.

3.3.2 Summary of Experimental Procedures

Mice were randomly assigned to their dietary intervention upon arrival. Half of the experimental mice were maintained on a Control diet (n = 22), while the other half were maintained on a Med-based diet (n = 22) for two weeks (Days 1-14), after which approximately half of the mice of each diet group (n = 12 for mice fed the Control diet and n = 12 for mice fed the Med-based diet) were subjected to CSDS while the other half (n = 10 for mice fed the Control diet and n = 10 for mice fed the Med-based diet) were exposed to a no stressor control condition for 10 consecutive days (Days 15-24). Immediately after the last stressor or control session, mice were individually housed for twenty-four hours after which a social interaction test (SIT; Day 25) was performed, followed by the novel object recognition test (NOR; Days 26-28), the forced alternation Y-maze test (Y-maze; Day 29), and the three-chamber sociability test (3C; Day 30). Approximately 16-20 hours after the last behavioural test (Day 31), mice were euthanized, and sections of the brain were obtained. All mice had their food intake (FI), and body weight (BW) measured at five key timepoints during the experiment: on Day 1 (baseline, start of dietary intervention), Day 7 (1-week acclimatization to dietary intervention and housing environment), Day 15 (start of stressor procedures), Day 24 (end of stressor procedures), and Day 30 (before euthanasia). Fresh diets were given to mice at Day 1, Day 7, Day 14 (before start of stressor procedures), and Day 24. Experimental procedures are summarized in Figure 1.

Experimental Timeline

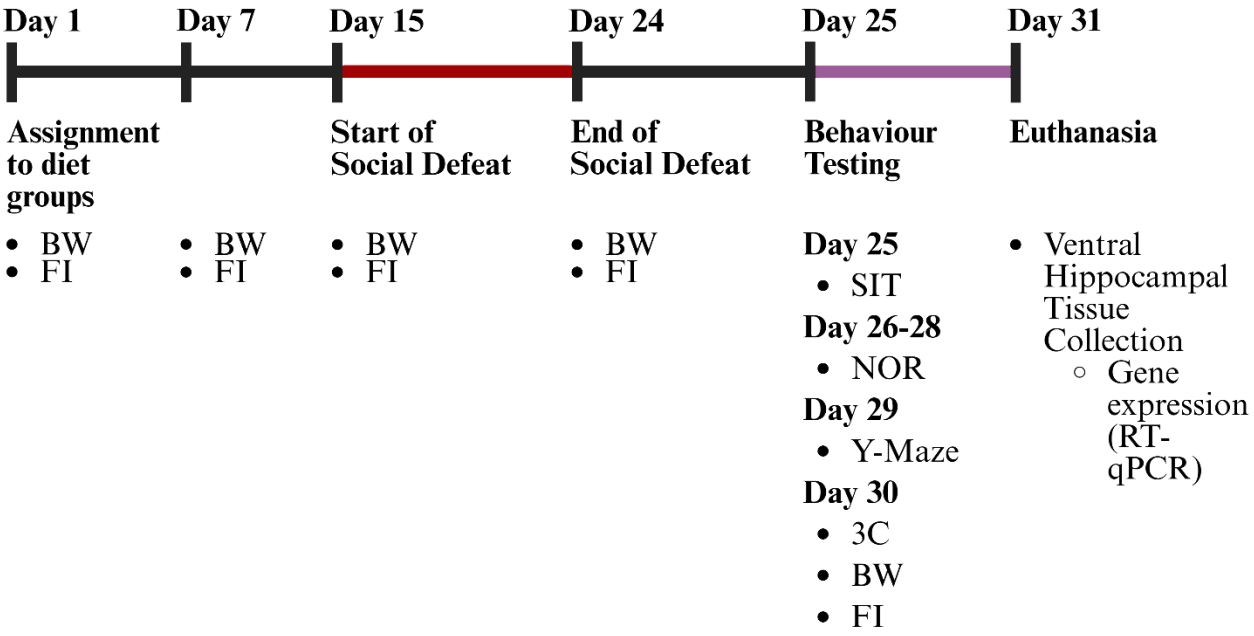

Fig. 1. **Summary of experimental procedures.** Male C57BL/6N mice were assigned to either a Control (*n*=22) or a Med-based diet (*n*=22) from Days 1-31. Approximately half of each diet group (*n*'s=12) were assigned to a Stressor condition (chronic social defeat stress) while the other half (*n*'s=10) were assigned to a No Stressor condition for Days 15-24. Behaviour and cognition were assessed on Days 25-30 (SIT, NOR, Y-Maze, 3C). Brains were collected approximately 16-20 hours after on Day 31 for the determination of inflammatory and neurotrophic factors (RT-qPCR). Abbreviations: FI, Food Intake (24-hour changes); BW, Body Weight; SIT, Social Interaction Test; NOR, Novel Object Recognition Test; RT-qPCR, Reverse transcription-quantitative polymerase chain reaction; Y-Maze, Forced Alternation Y-Maze Test; 3C, Three-Chamber Sociability Test. Created in https://BioRender.com.

3.3.3 Dietary Interventions

The diets mice were assigned to were either a Control diet (modified version of the D12052701M Open Standard Diet; Research Diets Inc) or a Med-based diet (modified version of the D12052702 Med-based dietary formula; Research Diets Inc, Barrington et al., 2018), both developed in our lab. The details of the dietary development are available elsewhere (Udechukwu, 2024). Briefly, the Control diet had a total macronutrient composition of 3654 kcal, with 21.5% protein, 60.5% carbohydrate, and 18% fat. This diet was composed of

ingredients including casein, corn starch, maltodextrin, cellulose, and soybean oil. The Med-based diet was isocaloric to the Control diet (3654 kcal) with variations in macronutrient composition with 17% protein, 44% carbohydrate and 39% fat. In addition to base ingredients like casein, maltodextrin, wheat starch, fish protein isolate, and powdered cooked beef, this diet contained homemade ingredients from the human Med diet, including freeze-dried chickpeas and lentils powders, walnuts, a fruit and veggie blend (apples, peach, strawberries, blueberries, pomegranates, kale, spinach, broccoli, tomatoes, and carrots), trans-resveratrol, beta-glucan powder, and olive oil. The composition of the Control and Med-based diets is presented in Supplementary Table 1.

3.3.4 Food Intake and Body Weight Measurements

Food intake and body weight were assessed at the same five timepoints: at the start of diet exposure (Day 1), after one week of acclimatization to the diets (Day 7), 24 hours prior to the start of social defeat (Day 14; which also corresponded to 2 weeks of acclimatization to the diets), the last day of social defeat (Day 24; before being exposed to the last session), and 24 hours prior to euthanasia (Day 30). Food intake measured the 24-hour changes observed in mice by taking the difference between the weight of the diet provided and the remainder to obtain the amount in grams consumed during that period for each timepoint. The body weight changes at each timepoint relative to the weight at the start of diet exposure were determined by taking the difference between body weight at a given timepoint and body weight at arrival, divided by arrival weight. The body weight changes at each timepoint relative to the previous timepoint were determined by taking the difference between body weight at a given timepoint and body weight at the previous timepoint, divided by the previous timepoints body weight.

3.3.5 Stressor Procedures

Mice were subjected to either CSDS or a paired-housing control condition. As previously described (Golden et al., 2011; Szyszkowicz et al., 2017), for the CSDS regimen, each experimental mouse was put into the home-cage of a CD-1 retired breeder previously tested for aggressive behaviours and engaged socially directly until one mouse was defeated (defeated mice exhibit submissive and/or withdrawal behaviours (e.g., standing on the hind-limbs pushing the opponent with fore-paws with the head pulled far back, rapid escape from opponent, being immobile while opponent is in physical contact but not attacking, lying motionless on back with ventral surface exposed to the opponent) (Bartolomucci et al., 2004) or until 10 minutes had elapsed. A wire-mesh screen was then placed to separate the experimental mouse from the CD-1 aggressor so that no physical interactions occurred, but mice were able to see, hear, and smell each other. After 24 hours, the experimental mouse was removed and placed into a novel CD-1 aggressor home cage (to prevent habituation) and this procedure was repeated daily until each experimental mouse had encountered 10 different CD-1 aggressors. For the paired-housing regimen, experimental mice were subjected to 10 consecutive days of paired-housing with a novel male C57BL/6N mouse every day, with a wire-mesh screen placed to separate them. No physical interactions occurred, but the mice were able to see, hear, and smell each other. Immediately after their last encounter with an aggressor or a social target, all mice were returned to their home cages, individually, for the rest of the study.

3.3.6 Behavioural and Cognitive Tests

3.3.6.1 Social Interaction Test

Twenty-four hours following the last CSDS or control session (Day 25), mice were examined for social avoidance behaviours, typically observed in stress-susceptible mice, as previously described (Berton et al., 2006; Golden et al., 2011; Szyszkowicz et al., 2017). A white

plastic open field (45 × 45 × 45 cm; Canus Plastics, Canada) containing a transparent plastic 5.5 × 9.6 cm rectangular cage with wire mesh at the base (large enough to fit an adult mouse) on one side of the box was used. Each experimental mouse investigated the arena for 2.5 minutes without the presence of other mice. After an intertrial interval of about 1 minute during which the arena was cleaned and the wire-mesh cage was changed, mice were re-introduced into the arena for a second session of 2.5 minutes with an unfamiliar CD-1 aggressor mouse placed into the wire mesh enclosure so that mice cannot directly interact with the aggressor but can still see and smell them. The two sessions were recorded using an overhead camera and mouse movements were tracked and analyzed using the Ethovision XT software from Noldus. This test was performed under red light conditions (mice are nocturnal and more active in dark conditions). Mice habituated under the same red-light conditions as the test in a room adjacent to the testing room for one hour prior to testing. The open field was cleaned with a Quato solution, and wire-mesh cages were changed between each test session to remove smell from previous animals. The time spent in the interaction zone (14.5 × 27 cm surrounding the wire mesh cage) in the absence and presence of the unfamiliar CD-1 aggressor mouse as well as the time spent in the two corner zones (10 × 10 cm) across from the wire mesh cage, and the total distance traveled in the presence of the aggressor were generated by Ethovision. The social interaction ratio was determined by dividing the time spent in the interaction zone with the aggressor mouse present over the time spent in the interaction zone without the aggressor mouse present (Berton et al., 2006; Golden et al., 2011; Szyszkowicz et al., 2017).

3.3.6.2 Novel Object Recognition Test

Twenty-four hours after the SIT, training for the NOR test began (Day 26). The purpose of this test was to investigate non-social cognitive functions, including learning, novelty preference,

as well as short- and long-term memory (Taglialatela et al., 2009), which involve the hippocampus (Goulart et al., 2010; Hammond, 2004; Oliveira et al., 2010; Reger et al., 2009). A white plastic open field arena (45 × 45 × 45 cm), a red plastic solo cup, a white plastic funnel, and a 150 ml orange capped transparent glass bottle were used. On the habituation session (T0), mice were placed in the center of the empty open field for 5 minutes of acclimatation, after which they returned to their home cage for 24 hours. During the training session that occurred 24 hours after on Day 26 (T1), two identical objects, either two red solo cups or two white funnels were placed in diagonally opposite corners of the field and mice were allowed to explore both objects for 5 minutes, after which they returned to their home-cage. After an intertrial interval of approximately 2 hours, the first testing session (T2) occurred to investigate short-term memory. One of the objects used during T1, called the familiar object, and one novel object (one red solo cup and one white plastic funnel), were placed in diagonally opposite corners of the field. Mice were allowed to explore both objects for 5 minutes, after which they returned to their home-cage for 24 hours. During a second testing session that occurred 24 hours after Day 27 (T3), used to investigate long-term memory, a familiar object from T1 and one novel object, different from the one used in T2 (e.g., one red solo cup and one 150 ml orange capped transparent glass bottle), were placed in diagonally opposite corners of the field. Mice were allowed to explore both objects for 5 minutes, after which they returned to their home cages. The three sessions were recorded using an overhead camera and mouse movements were tracked and analyzed by the Ethovision XT software from Noldus. This test was performed under red light conditions. Mice habituated in a room adjacent to the experimental room under red light conditions for 1 h prior to training or testing each day. In between sessions, the open field was cleaned with Quato solution and objects were cleaned with a 70% ethanol solution. The time spent interacting with each object (~2 cm from edge of object) was

generated by the Ethovision XT software. Mice that did not interact with one of the objects (time = 0s), during the sessions were excluded from subsequent analysis. The preference for exploring a novel object, a NOR ratio, was calculated by dividing the time spent with the novel object over the total time spent with both objects at each test session. A ratio above 0.5 indicated preference for the novel object (Cadoret et al., 2023). In the presence of a novel object, mice are more alert and require examination of the object, whereas in the presence of a familiar object, it requires attention and re-evaluation. When both a novel and familiar object are present, mice with an intact hippocampus preferentially spend time with the novel object until it loses its novelty (Antunes & Biala, 2012; Ennaceur, 2010).

3.3.6.3 Forced Alternation Y-Maze

Twenty-four hours after the last NOR session (Day 28), mice were tested in the forced alternation Y-maze test to assess non-social spatial reference memory (Kraeuter et al., 2019), which involves the hippocampus (Conrad et al., 1996; Sarnyai et al., 2000; Swonger & Rech, 1972). The test was conducted using a symmetrical Y-maze made of black plastic with white floor inserts. Each arm of the maze was 38-cm long and 7.6-cm wide, and the three arms were spaced 120 degrees apart to form a Y shape. Removable black opaque plastic inserts were used to block sections of the maze. Extra-maze cues on the walls of the testing room (irregular black cue with squared edges on the left wall and a black triangle on the right wall) and intra-maze cues at the back wall of each arm (Arm 1 has a solid black rectangle, Arm 2 has two thick white horizontal bars, and Arm 3 has two thick white diagonal stripes) helped mice distinguish the otherwise identical arms of the maze. For the first session of the trial (T1), mice were placed at the back of Arm 1, designated the Start arm, and left to explore the maze for 5 minutes, with one of the three arms blocked. The unblocked arm during T1 was referred to as the Familiar arm. After a 30-minute

intertrial interval spent in their home-cage, mice were placed at the back wall of the Start arm for the retrieval trial (T2), during which the insert was removed, allowing free access to the three arms for 5 minutes. The arm that was selected to be blocked alternated between mice. The two sessions used an overhead camera and video recorded mouse movements which was analyzed by the Ethovision XT software from Noldus. This test was performed under a lighting of 60 lux. Mice habituated in a room adjacent to the experimental room under 60 lux conditions for 1 h prior to testing and the maze was cleaned using Quato solution after each mouse. The time spent in each arm was generated by the Ethovision XT software. The percentage of time spent in the Novel arm (the blocked arm in T1) was determined by dividing the time spent in the Novel arm by the time spent in all arms during the first minute of T2. The first minute of this test is important as exploring a novel environment will become 'familiar' to mice within the span of one to two minutes (Anisman, 1975). The forced alternation percentage was determined by the percent of mice that entered their Novel arm first during T2. Mice with preserved cognitive functioning typically enter the arm that was previously blocked first, as it is considered a novel environment (Kraeuter et al., 2019). Mice that did not make a single entry during the first minute of T2 were excluded from the analysis. (Anisman, 1975; Wolf et al., 2016).

3.3.6.4 Three-Chamber Sociability Test

On Day 30, the last test conducted was the three-chamber sociability test. The objective of this test was to determine social preference and social novelty, which both involve the hippocampus (Caffé et al., 1987; Eichenbaum et al., 1996; Sutherland & Rudy, 1989; van Wimersma Greidanus & Maigret, 1996). The testing utilized a white plastic box that was open, measuring 45 cm in length, 60 cm in width, and 22 cm in height, divided into 3 equal chambers, each of them measuring 39 × 19 × 22 cm. These chambers were separated by clear plexiglass

dividing walls with small openings allowing for access into each chamber. In the first session (habituation), experimental mice were placed in the center chamber and allowed to freely explore all three chambers for 5 minutes, after which they returned to their home-cage for a 5-minute intertrial interval. In the second session (social preference), an unfamiliar male C57BL/6N mouse was placed in a wire-mesh cage in one of the outer chambers while the second outer chamber contained an empty wire mesh cage, and experimental mice were placed into the center chamber and allowed to explore the apparatus for 10 minutes. After a 5-minute intertrial interval in their home cage, experimental mice were placed again into the center chamber and allowed to explore all chambers for 10 minutes but for this third session (social novelty), a different unfamiliar male C57BL/6N mouse was placed into the wire-mesh cage in the outer chamber that did not previously contain anything in it while the mouse from the second session remained in its wire-mesh cage (now considered the 'familiar' social target). The three sessions used an overhead camera and video recorded mouse movements which is then analyzed by the Ethovision XT software from Noldus. The test was performed under a lighting of 100 lux. Mice habituated in a room adjacent to the experimental room at 100 lux for 1 h prior to testing. The chambers and objects were cleaned with Quato solution between each mouse. The time spent sniffing each wire-mesh cages (~2.5 cm from edge of wire mesh cup), time spent in each chamber, and number of entries into each chamber, of the three sessions were generated by the Ethovision XT software. The preference index for sociability was calculated by taking the time spent sniffing the social target subtracted by the time spent sniffing the non-social stimulus divided by the total time spent sniffing both social and non-social stimuli multiplied by 100. The preference index for social novelty was calculated by takin the time spent sniffing the novel social target subtracted by the time spent sniffing the familiar

stimulus divided by the total time spent sniffing both social targets multiplied by 100 (Rein et al., 2020).

3.3.7 Euthanasia and Sample Collection

Approximately 18-20h after the three-chamber sociability test (Day 31), mice were euthanized by rapid decapitation. Whole brains were quickly removed, placed on a stainless-steel matrix positioned on an ice plate (2.5 x 3.75 × 2.0 cm; slots spaced approximately 500 μm apart), and sectioned coronally using razor blades guided by the matrix slots. The ventral hippocampus was dissected from one of the brain sections based on the Franklin and Paxinos mouse atlas (Franklin & Paxinos, 2019). The ventral hippocampus was placed in nuclease-free cryotubes, flash frozen in liquid nitrogen, and stored at -80°C for the future determination of pro-inflammatory, microglial, and neurotrophic factor mRNA expression.

3.3.8 Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

Ventral hippocampal sections were homogenized using TRIzol and total RNA was extracted according to the manufacturer's instructions (Invitrogen). RNA concentration and purity were assessed using a NanoDrop™ One Spectrophotometer (Thermo Fisher Scientific). Total RNA was then converted into cDNA via reverse transcription using iScript™ Reverse Transcription Supermix (Bio-Rad, Canada) and a T100 Thermal Cycler (Bio-Rad, Canada) and cDNA aliquots were analyzed in simultaneous reverse-transcription quantitative polymerase chain reactions using SsoAdvanced Universal SYBR Green Supermix (Bio-Rad, Canada) and a CFX96 Touch Real-Time PCR Detection System (Bio-Rad, Canada). Hippocampal samples were analyzed in triplicates. Primers that amplified glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and β-Actin (Actb) were used as reference genes and their geometric mean was used to normalize the expression of the genes of interest. Fold changes for the mRNA expression of

genes of interest were calculated using the 2−ΔΔCT method relative to the groups in the Control condition (Livak & Schmittgen, 2001; Schmittgen & Livak, 2008). Primer sequences are listed in Supplementary Table 2.

3.3.9 Statistical Analyses

Data was analyzed using IBM SPSS Statistics version 26 and GraphPad Prism version 10 was used for plotting graphs. All data were tested for normality (Shapiro-Wilk test) and homogeneity of variances (Levene test). One mouse from the Control Diet / No Stressor group was removed from all analyses due to an extreme social interaction ratio result in the SIT. Food intake, body weight changes, behaviours in the SIT, NOR, forced alternation Y-maze, and three-chamber sociability tests, and ventral hippocampal mRNA expression of pro-inflammatory cytokines, microglial factors, and neurotrophic factors were analyzed using two-way analyses of variance (ANOVAs) with Diet (Control versus Med-based) and Stressor (No Stressor versus CSDS) as the between-group factors. Following the 2-way ANOVAs, we examined the main and simple effects using t-tests, with a Bonferroni correction to maintain the family-wise error rate at 0.05. The alpha level was maintained at 0.05 for all analyses.

3.4 Results

3.4.1 Food Intake

As shown in Figure 2, food intake was collected at five timepoints during the experiment. Food intake was significantly increased in mice fed the Med-based diet on the first day of diet exposure (Day 1), $F_{(1,39)} = 147.136$, $p < 0.0001$, after the first week acclimatizing to their assigned diet (Day 8), $F_{(1,39)} = 53.350$, $p < 0.0001$, after the second week acclimatizing to their assigned diet (Day 15; before being exposed to the first social defeat or control session), $F_{(1,39)} = 23.800$, $p < 0.0001$, and on the last day of social defeat (Day 25; before being exposed to the last session),

$F_{(1,39)} = 57.301$, $p < 0.0001$, compared to mice fed the Control diet, irrespective of the stressor condition. Diet, Stressor, and the Diet × Stressor interaction did not significantly impact food intake at the endpoint of the study (Day 31; p's > 0.05).

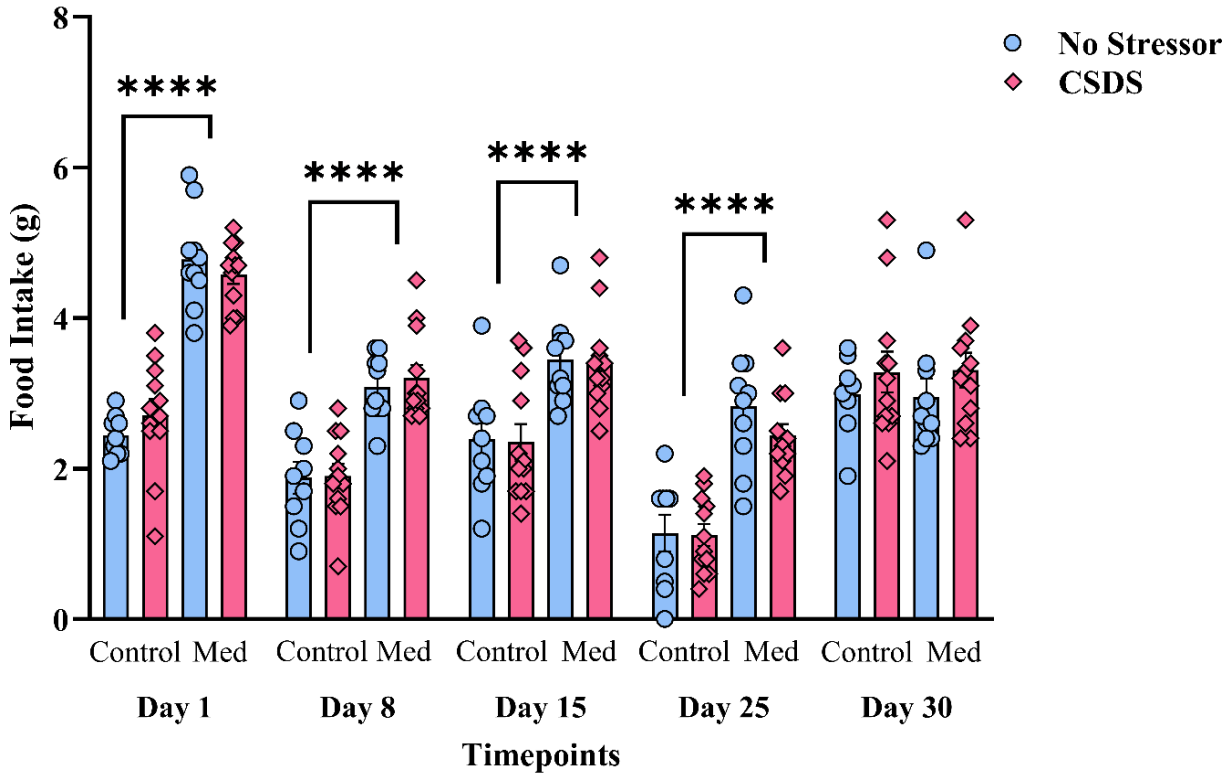

Fig. 2. **24-hour assessment of food intake**. Mice fed the Control and Med-based diets in the No stressor (light blue) and the Chronic Social Defeat Stress (CSDS; pink) conditions during the study period. The average and S.E.M. of each group were assessed, and individual points (dots and diamonds), representing individual mice, were plotted in their respective bars for each timepoint. **** $p < 0.0001$ relative to mice fed the Control diet. n = 9-10 for No Stressor groups and n = 12 for CSDS groups.

3.4.2 Body Weight Changes

3.4.2.1 Relative to Body Weight at Arrival

The body weight of mice was assessed at the same five timepoints where food intake was measured. As shown in Figure 3, body weight gains from the initiation of the diet interventions were more pronounced in mice fed the Med-based diet than in those fed the Control diet throughout the experiment, being higher after the first week of acclimatization to the diets, $F_{(1,39)} = 22.368$, p

< 0.0001, during the period leading to the start of social defeat (which also corresponded to the first 2 weeks of acclimatization to the diets), $F_{(1,39)} = 29.989$, $p < 0.0001$, during the period leading to the end of social defeat, $F_{(1,39)} = 22.461$, $p < 0.0001$, and during the period leading to euthanasia, $F_{(1,39)} = 45.769$, $p < 0.0001$. Mice that were stressed also gained less weight than non-stressed mice during the period leading up to euthanasia, $F_{(1,39)} = 4.541$, $p = 0.039$. The Diet × Stressor interaction did not impact the percentages in body weight change at any measured timepoints (p's > 0.05).

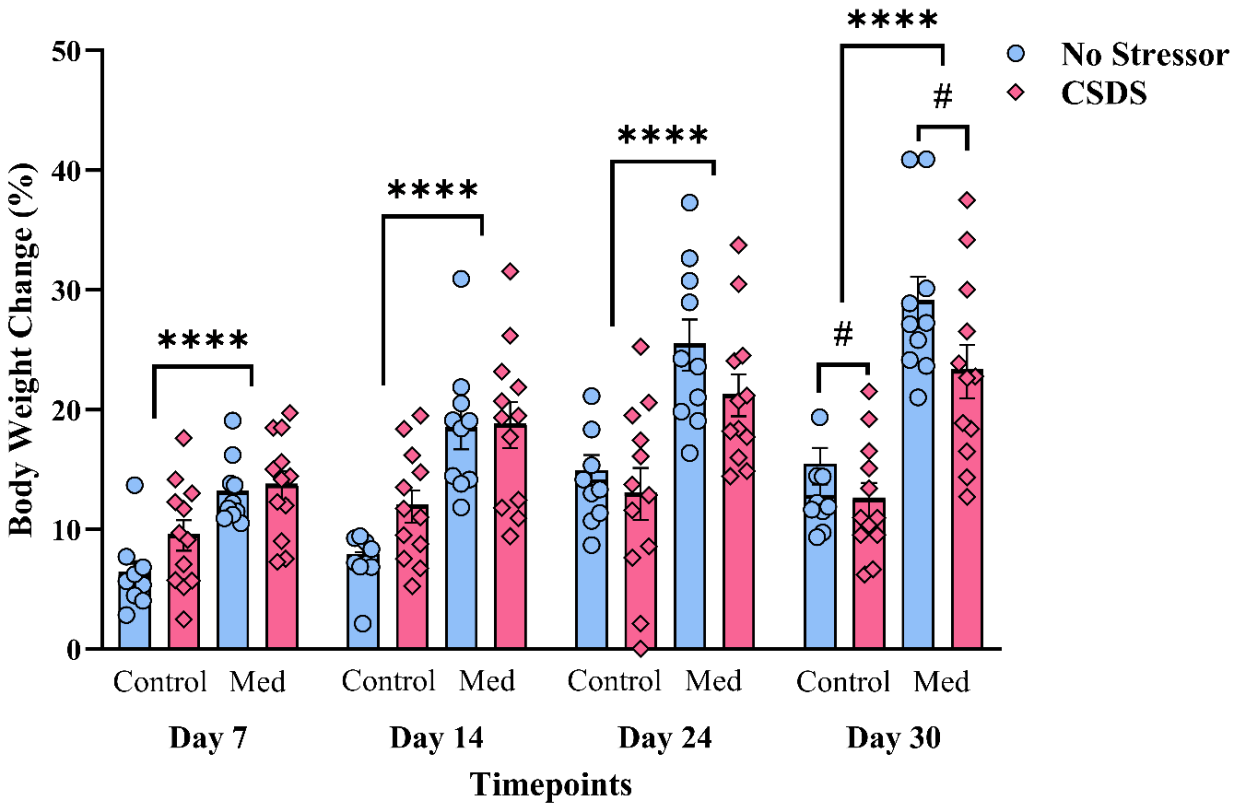

Fig. 3. **Assessment of percentages in body weight changes in mice relative to the start of diet exposure.** Mice fed the Control and Med-based diets in the No stressor (light blue) and CSDS (pink) conditions during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. **** $p < 0.0001$ relative to mice fed the Control diet. # $p < 0.05$ relative to non-stressed mice. $n = 9$-10 for No Stressor groups and $n = 12$ for CSDS groups.

3.4.2.2 Relative to the Immediate Previous Timepoint

To obtain the body weight changes from timepoint to timepoint and better determine the effects of the different manipulations, the body weight at each timepoint relative to the weight at the immediate previous timepoint was used, leading to four timepoints at which a percentage change was assessed. As seen in Figure 4, mice fed the Med-based diet gained more weight than those fed the Control diet after the first week of acclimatization to the diets, $F_{(1,39)} = 22.368$, $p < 0.0001$, as well as during the second week of acclimatization, $F_{(1,39)} = 7.178$, $p = 0.011$, irrespective of the stressor condition. Mice that experienced the chronic social stressor, regardless of diet, had limited weight gains from the start to the end of CSDS and these gains were lower than mice in the No Stressor condition, $F_{(1,39)} = 10.448$, $p = 0.002$. Diet, Stressor, and the Diet × Stressor interaction did not impact the percentages of body weight changes from the end of CSDS to euthanasia (p's > 0.05).

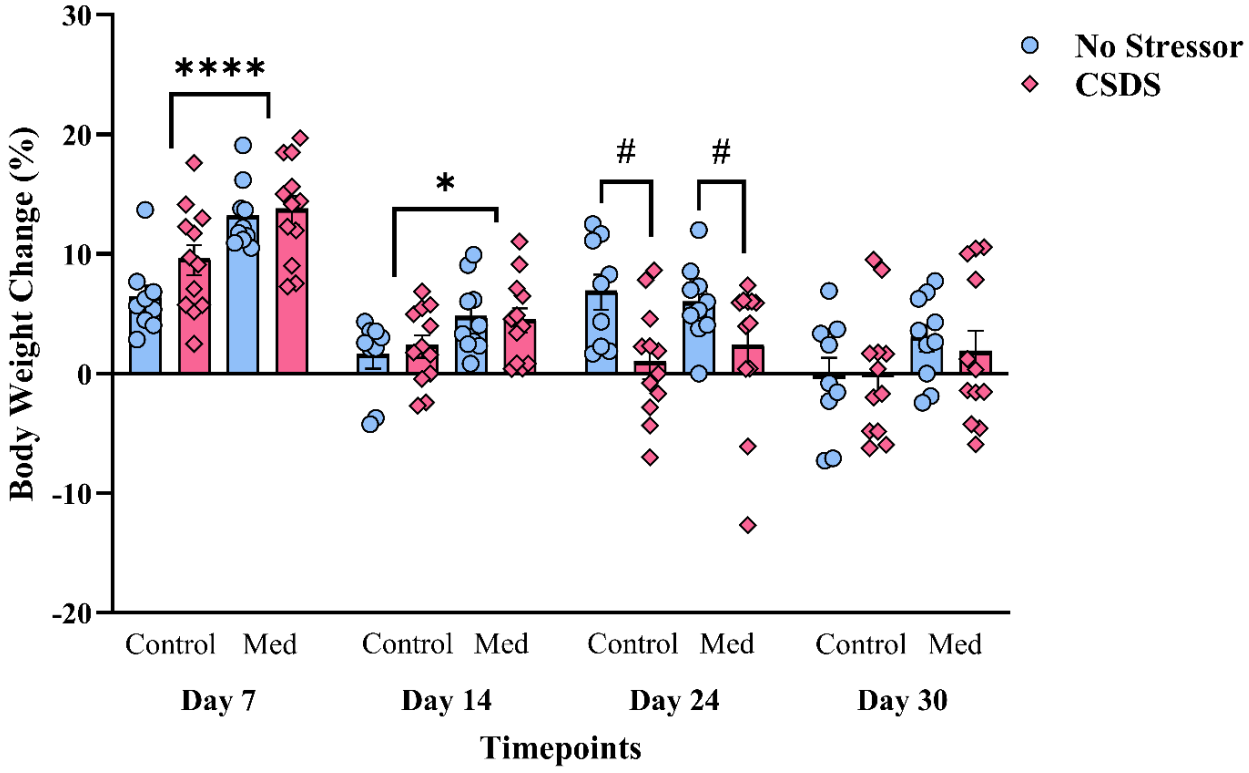

Fig. 4. **Assessment of percentages in body weight changes in mice relative to previous timepoints.** Mice fed the Control and Med-based diets in the No stressor (light blue) and CSDS (pink) conditions during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. **** $p < 0.0001$ and * $p < 0.05$ relative to mice fed the Control diet. # $p < 0.05$ relative to non-stressed mice. n = 9-10 for No Stressor groups and n = 12 for CSDS groups.

3.4.3 Behaviour

3.4.3.1 Social Interaction Test

This test was conducted following CSDS and its control condition to assess the impact of chronic social stress on social avoidance behaviours, a feature of behavioural stress susceptibility (Kudryavtseva et al., 1991; Krishnan et al., 2007; Nestler and Hyman, 2010). As shown in Figure 5A, CSDS mice had lower social interaction ratios than non-stressed mice, $F_{(1,39)} = 22.368$, $p < 0.0001$, irrespective of their diet, although Diet itself significantly influenced these ratios, $F_{(1,39)} = 4.175$, $p = 0.0478$, with mice fed the Med-based diet having lower social interaction ratios than those fed the Control diet. To further confirm the presence of avoidance behaviours, the time spent

in the corner zones in the presence of the aggressor mouse was assessed. As seen in Figure 5B, CSDS mice spent more time in the corner zones, $F_{(1,39)} = 10.382$, $p = 0.003$, whereas Diet and the Diet × Stressor interaction did not impact this measure (p's > 0.05). Finally, as seen in Figure 5C, Diet, Stressor, and the Diet × Stressor interaction did not impact the distance traveled in the presence of an aggressor mouse during the test (p's > 0.05).

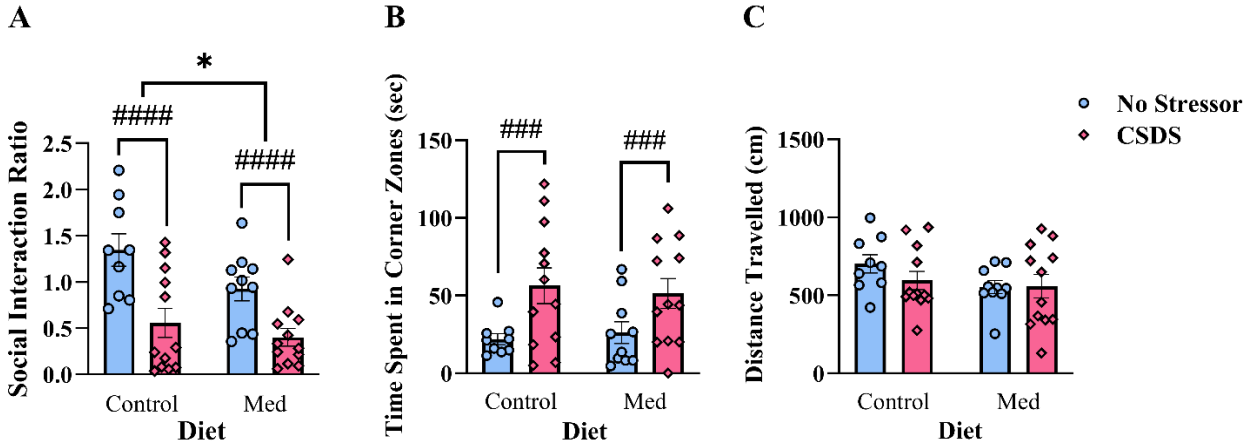

Fig. 5. **Impact of chronic social defeat stress on behaviours in the social interaction test.** (A) Social interaction ratio in the interaction zone. (B) Time spent in the corner zones in the presence of an aggressor mouse. (C) Distance travelled in the apparatus in the presence of an aggressor mouse. Mice fed the Control and Med-based diets in No Stressor (light blue) and in CSDS (pink) groups during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. * $p < 0.05$ relative to mice fed the Control diet, #### $p < 0.0001$ and ### $p < 0.005$ relative to non-stressed mice. n = 9-10 for No Stressor groups and n = 12 for CSDS groups.

3.4.3.2 Novel Object Recognition Test

The novel object recognition test was used to investigate learning and memory based on the natural tendency of mice to explore novelty in their environment (Berlyne, 1950; Ennaceur and Delacour, 1988; Ennaceur, 2010). Figure 6A shows the NOR ratio of mice, when assessed 2 hours after the training session (short-term memory). All groups except for CSDS mice fed the Control diet had a NOR ratio above 0.5, suggesting that the short-term preference for the novel object was impaired by the stressor. However, Diet, Stressor, and the Diet × Stressor interaction did not impact this

ratio (p's > 0.05), indicating that the stressor effect on the short-term NOR was not significant. Twenty-four hours following the first testing session, mice were introduced to a novel object different from the novel object used in this first session, in combination to a familiar object from their training session, to evaluate their long-term memory and preference for a novel object. As seen in Figure 6B, only stressed mice fed the Med-based diet had a long-term NOR ratio above 0.5, suggesting increased long-term preference for the novel object in this group. This was confirmed statistically with the NOR ratio assessing long-term memory being increased in mice fed the Med-based diet, $F_{(1,39)} = 4.778$, $p = 0.035$, regardless of the Stressor or the Diet × Stressor interaction (p's > 0.05).

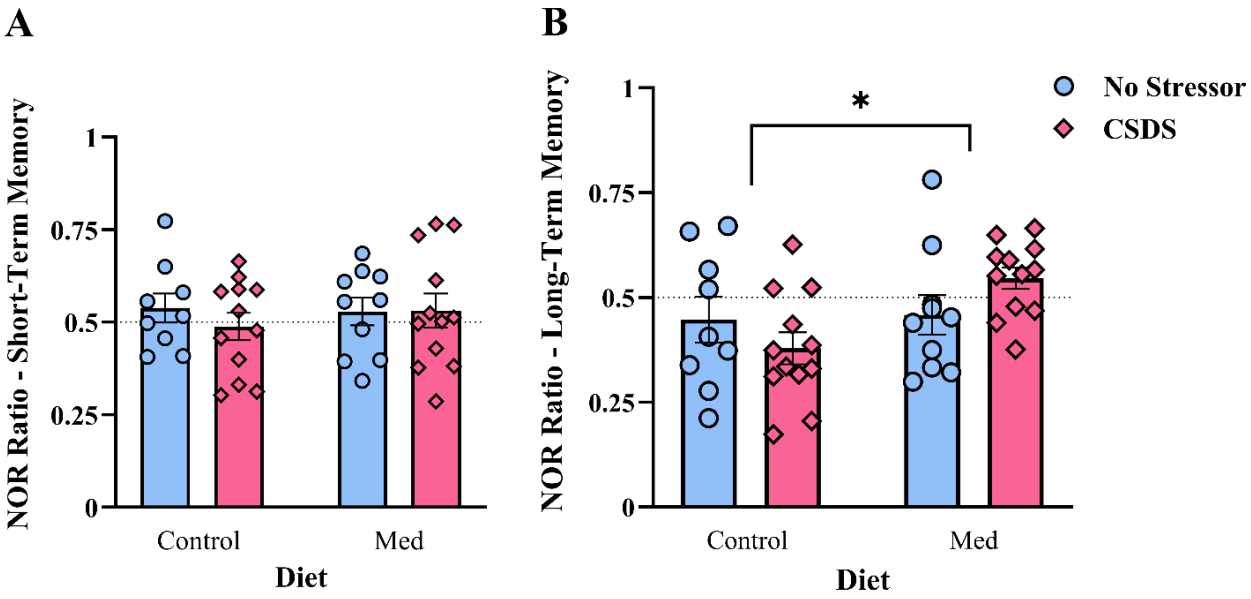

Fig. 6. **Evaluation of non-social learning and memory in mice using the novel object recognition (NOR) test**. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. (A) NOR ratio assessing short-term memory and preference for a novel object. (B) NOR ratio assessing long-term memory and preference for a novel object. Mice fed the Control and Med-based diets in the No Stressor (light blue) and CSDS (pink) groups during the study period. * $p < 0.05$ relative to mice fed the Control diet. n = 9-10 for No Stressor groups and n = 12 for CSDS groups.

3.4.3.3 Forced Alternation Y-Maze

This test was used to assess spatial reference memory (Kraeuter et al., 2019). Using the criteria from a validated protocol that excluded mice with less than three entries into arms during the first minute of the test sessions (Wolf et al., 2016), we obtained only 11 mice for the subsequent analyses, which was insufficient. Thus, we modified the protocol to exclude mice that did not move out of the start arm in the first minute. Using this modified exclusion criteria, 36 mice were included in the subsequent analyses out of 44, and thus the degrees of freedom for this test differ from the other tests. In Figure 7A, Stressor and the Diet × Stressor interaction did not impact the time spent in the novel arm during the first minute of the retrieval trial (p's > 0.05), however Diet was just shy of significance ($F_{(1,32)} = 3.046$, $p = 0.091$). Although the interaction between these two factors was not significant, based on the *a priori* predictions that the non-social short-term spatial and working memory impairments would be mitigated or improved in mice fed the Med-based diet, follow-up comparisons of the simple effects comprising the interaction were conducted and revealed that CSDS mice fed the Med-based diet spent less time exploring the novel arm compared to their control diet counterparts ($p = 0.0221$). In Figure 7B, the forced alternation percentage was determined by whether mice entered the novel arm first. Diet, Stressor, and the Diet × Stressor interaction did not impact the forced alternation percentage (p's > 0.05). Of note, although groups did not differ on this measure, all mice fed the Control diet correctly entered the novel arm first, which was not the case in mice fed the Med-based diet (Fig. 7B).

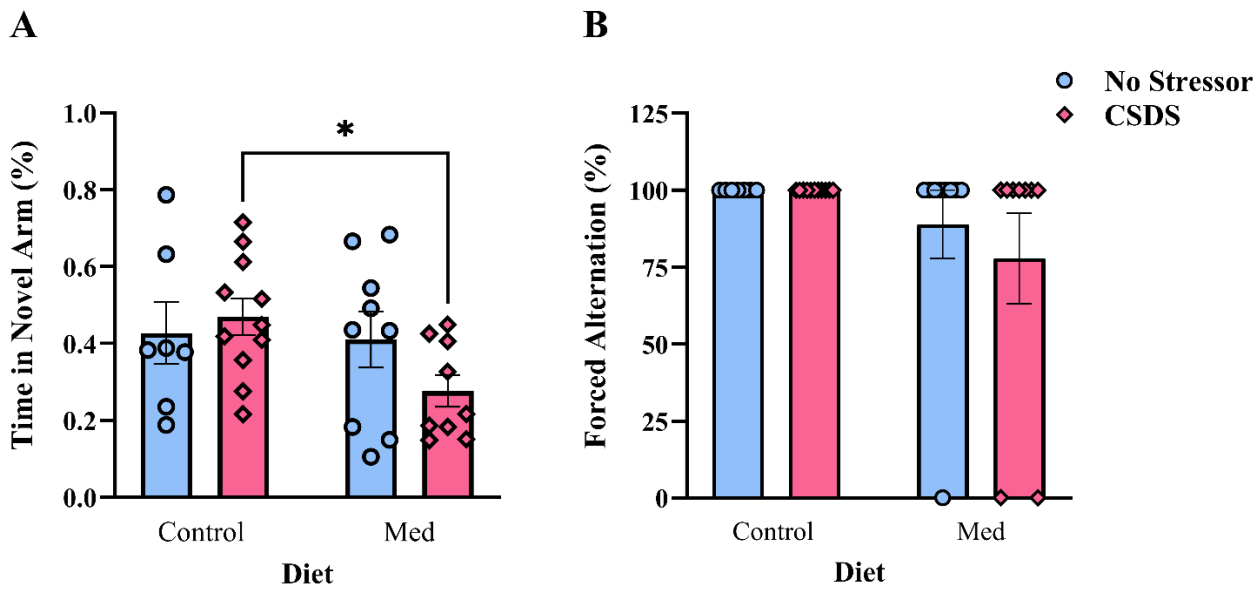

Fig. 7. **Assessment of working and spatial memory in the forced alternation Y-maze.** (A) Time spent in the novel arm during first minute of the retrieval trial. (B) Percentage of mice that correctly chose to first enter the novel arm which was previously blocked. Mice fed the Control and Med-based diets in the No Stressor (light blue) and CSDS (pink) groups during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. * p = 0.0221, relative to CSDS mice fed the Med-based diet. n = 9-10 for No Stressor groups and n = 12 for CSDS groups.

3.4.3.4 Three-Chamber Sociability Test

Mice are social animals by nature (Bailey & Crawley, 2009) and this test assessed their social approach, social novelty, and social memory (Leblanc & Ramirez, 2020; Okuyama, 2018; Rein et al., 2020) with mouse targets of the same age, sex, and species. As shown in Figures 8A and 8B, during the second session where mice were allowed to investigate either an unfamiliar object versus an unfamiliar social target, CSDS mice spent more time in the chamber that contained an object, $F_{(1,39)}$ = 12.276, p = 0.001, but less time in the chamber that contained a social target, $F_{(1,39)}$ = 21.045, p < 0.0001, than non-stressed mice, regardless of diet. In Figures 8C and D depicting the third session where mice were allowed to investigate either a familiar social target or a novel social target, Diet, Stressor, and the Diet × Stressor interaction did not impact the time spent in the chambers containing a familiar (C) or a novel (D) social target (p's > 0.05).

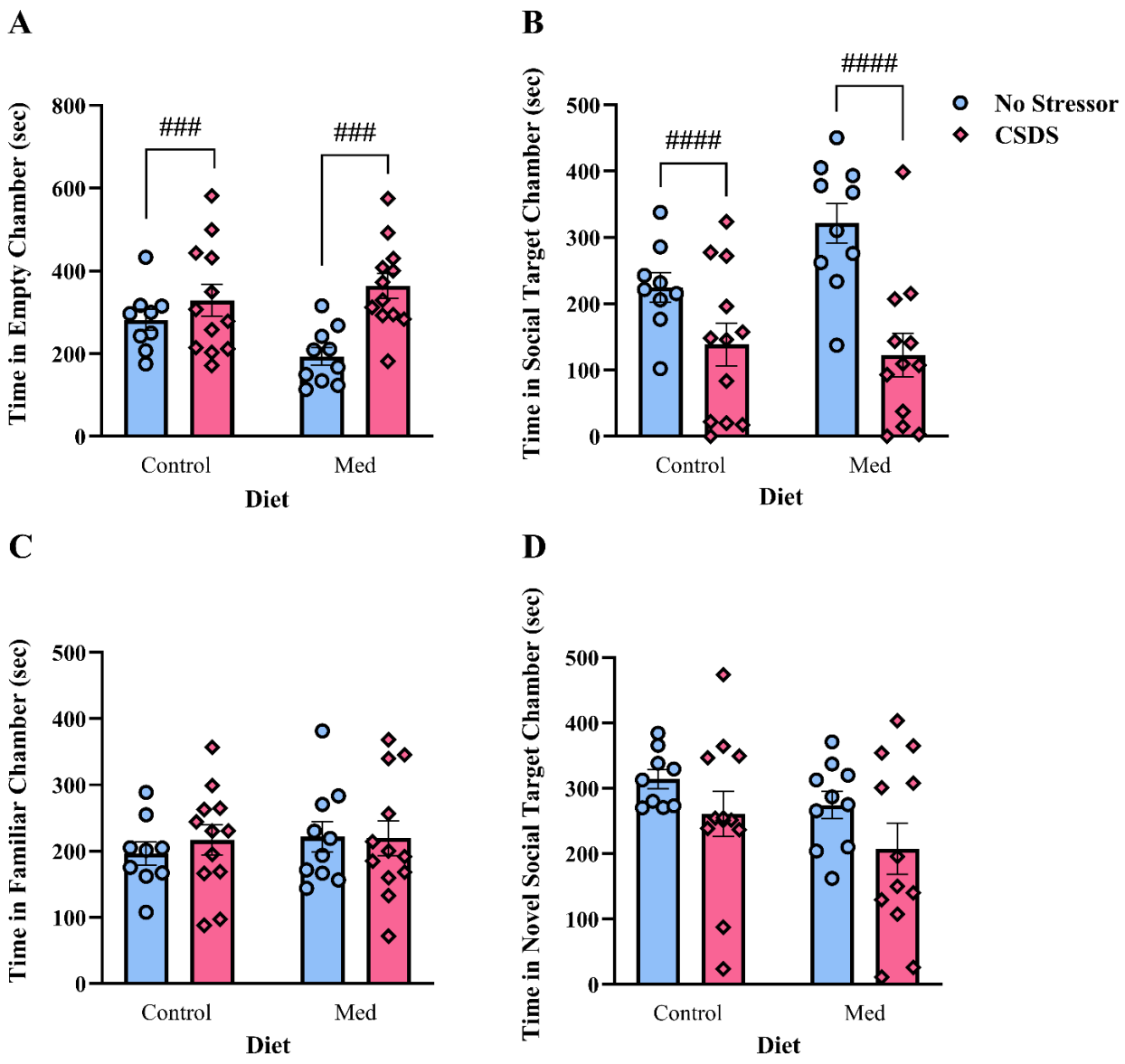

Fig. 8. **Cumulative time spent in chambers of the three-chamber sociability test**. Time spent in the chamber that contained an unfamiliar object (A) versus the chamber with a social target (B) during the second session. Time spent in the chamber containing the familiar social target (C) versus the chamber containing a novel social target (D) during the third session. Mice fed the Control and Med-based diets in the No Stressor (light blue) and CSDS (pink) groups during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. #### $p < 0.0001$ and ### $p < 0.005$ relative to non-stressed mice. n = 9-10 for No Stressor groups and n = 12 for CSDS groups.

As shown in Figure 9, during the second session Diet, Stressor, and the Diet × Stressor interaction did not impact the number of entries into the chamber containing an unfamiliar object *(p*'s > 0.05; Fig 9A), but CSDS mice entered the chamber containing a social target less often than non-stressed mice, $F_{(1,39)} = 4.298$, $p = 0.045$, irrespective of Diet or the Diet × Stressor interaction *(p'*s > 0.05; Fig 9B). During the third session, mice fed the Med-based diet entered the chamber containing a familiar social target less often than mice fed the Control diet, $F_{(1,39)} = 5.880$, $p = 0.020$, irrespective of Stressor or the Diet × Stressor interaction *(p'*s > 0.05; Fig. 9C). In contrast, CSDS mice entered the chamber containing a novel social target less often than non-stressed mice, $F_{(1,39)} = 4.651$, $p = 0.037$, independently of Diet or the Diet × Stressor interaction *(p*'s > 0.05; Fig. 9D).

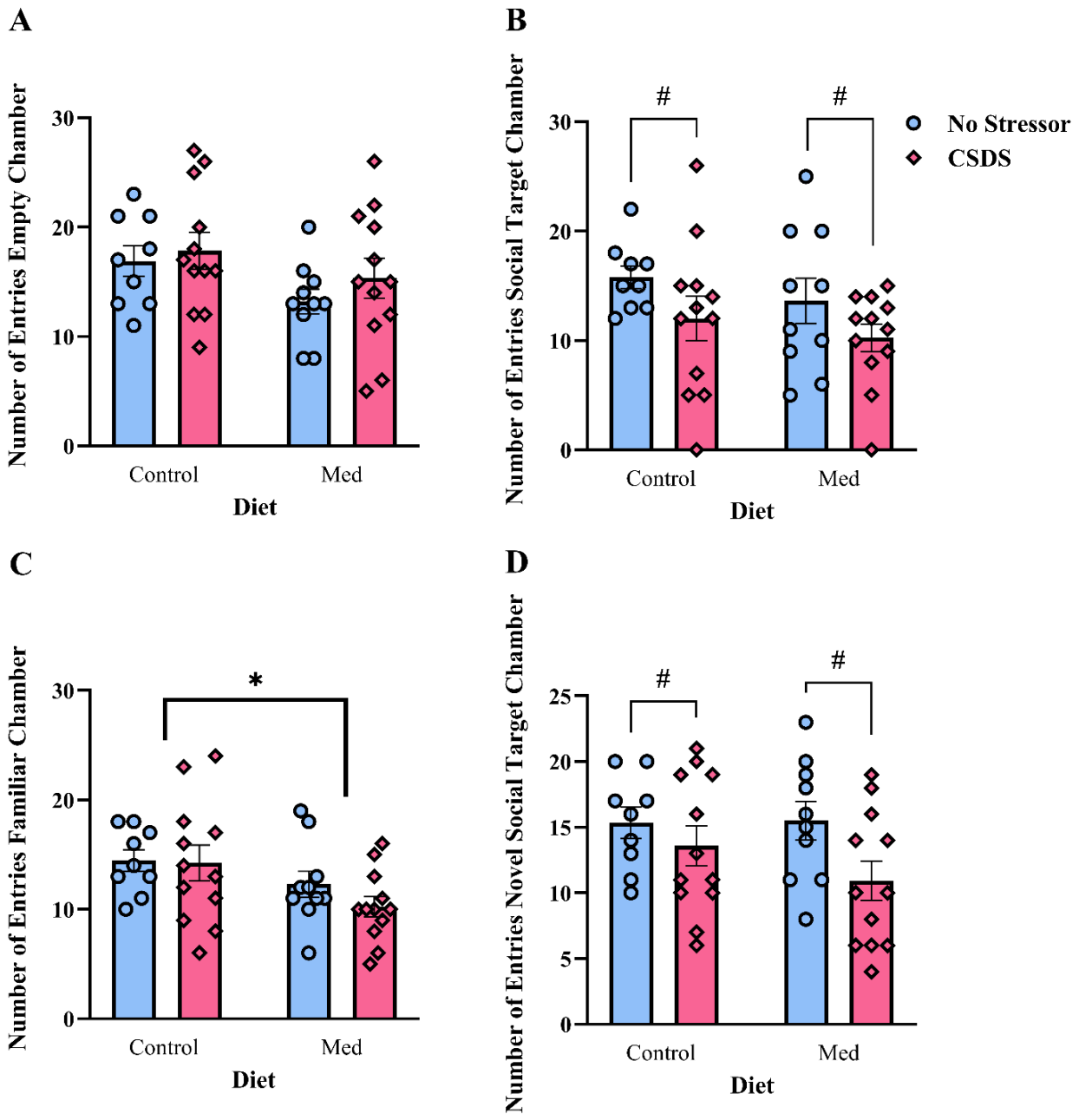

Fig. 9. **Number of entries into the chambers of the three-chamber sociability test**. Number of entries into the chamber that had no social target (A) versus a social target (B) during the second session. Number of entries into the chamber that contained the familiar social target (C) versus the novel social target (D) during the third session. Mice fed the Control and Med-based diets in the No Stressor (light blue) and CSDS (pink) groups during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. # $p < 0.05$, relative to non-stressed mice and * $p < 0.05$, relative to mice fed the Control diet. n = 9-10 for No Stressor groups and n = 12 for CSDS groups.

As shown in Figure 10A, CSDS mice had a reduced preference for a social target compared to non-stressed mice, preferring to spend less time interacting with a social target compared to a non-social stimulus, $F_{(1,39)} = 14.371$, $p = 0.001$. This was not modulated by the Diet or the Diet × Stressor interaction (p's > 0.05). In Figure 10B, Diet, Stressor, and the Diet × Stressor interaction did not impact the preference for social novelty (p's > 0.05).

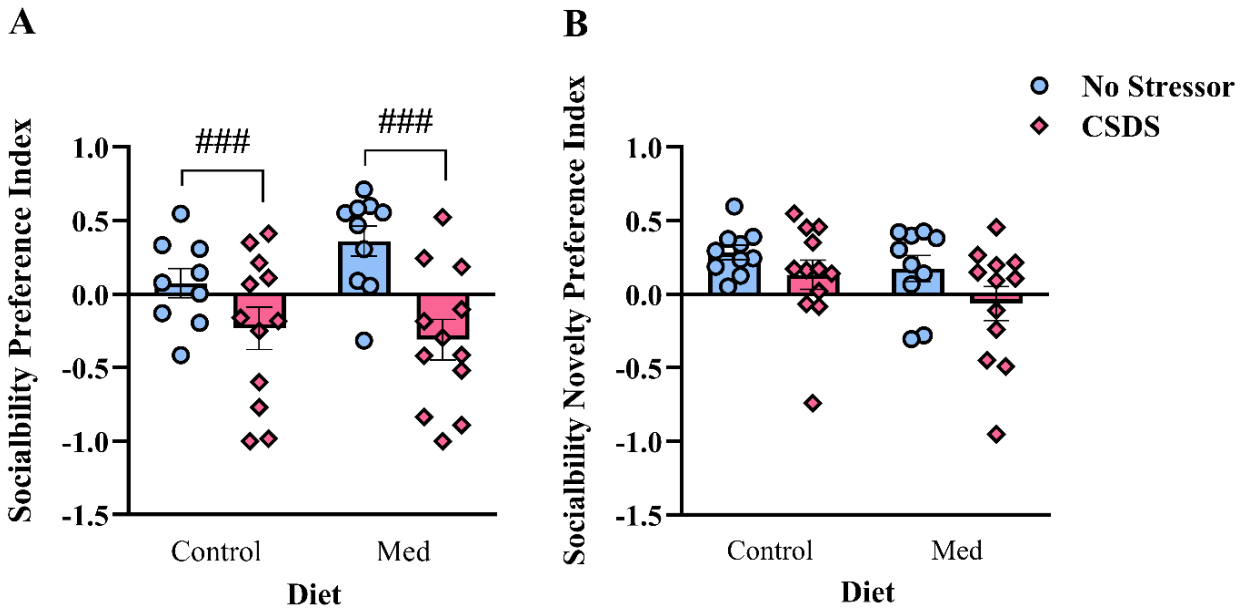

Fig. 10. **Preference index for sociability and social novelty in the three-chamber sociability test**. (A) Preference for a social target compared to a non-social target during the second session (B) Preference for new social target compared to a familiar social target during the third session. Mice fed the Control and Med-based diets in the No Stressor (light blue) and CSDS (pink) groups during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. ### $p < 0.005$, relative to non-stressed mice. n = 9-10 for No Stressor groups and n = 12 for CSDS groups.

3.4.4 Gene Expression Analysis

A total of 9 genes of interest were analyzed in the ventral hippocampus of experimental mice. The pro-inflammatory cytokines IL-6, IL-1β, and TNF-α, were assessed for their roles in signalling the production of pro-inflammatory immune components, coordinating pro-inflammatory processes, interactions with neuronal plasticity and neuroendocrine function, in

addition to their reliability as peripheral biomarkers for the assessment of human neuropsychiatric disorders (Dantzer et al., 2008; Miller et al., 2009; Mössner et al., 2007; Raison et al., 2006; Zorrilla et al., 2001). The microglial marker Iba-1 was assessed, as it is a specific indication of microglial cells (Frick et al., 2013), and has been shown to be upregulated in studies using chronic psychosocial stress (Calcia et al., 2016). The microglial factor CX3CR1 was assessed, as adult hippocampal neurogenesis depends on CX3CR1/CX3C chemokine ligand 1 signalling between microglia and neurons (de Miranda et al., 2017; Delpech et al., 2015). Neurotrophic factors BDNF and TrkB were assessed for their neuroprotective and antidepressant roles, where BDNF binds to TrkB to exert its biological functions including mediating synaptic plasticity, neuronal regulation, and mediating neurogenesis (Bekinschtein et al., 2014; Leal et al., 2017; Lu et al., 2014; Zhang et al., 2022). The neurotrophic factors NGF and NT-3 were assessed for their roles in neuronal survival and maintenance, in addition to regulating neurogenesis and facilitating hippocampal plasticity (Banerjee et al., 2013; De Miranda et al., 2020; Shimazu et al., 2006; Vilar & Mira, 2016). The RT-qPCR analyses of these genes in the ventral hippocampus of non-stressed and CSDS mice fed the Control, or the Med-based diets yielded detectable significance in 3 of the genes investigated.

In terms of pro-inflammatory cytokines, although Diet, Stressor, and the Diet × Stressor interaction did not impact the hippocampal expression of IL-6 or IL-1β (p's > 0.05; Figs 11 A and B), fold changes in TNF-α varied as a function of the Diet × Stressor interaction, $F_{(1,29)} = 5.358$, $p = 0.05$, with the effect of CSDS in control mice ($p = 0.016$) and the effect of the Med-based diet in non-stressed mice ($p = 0.010$).

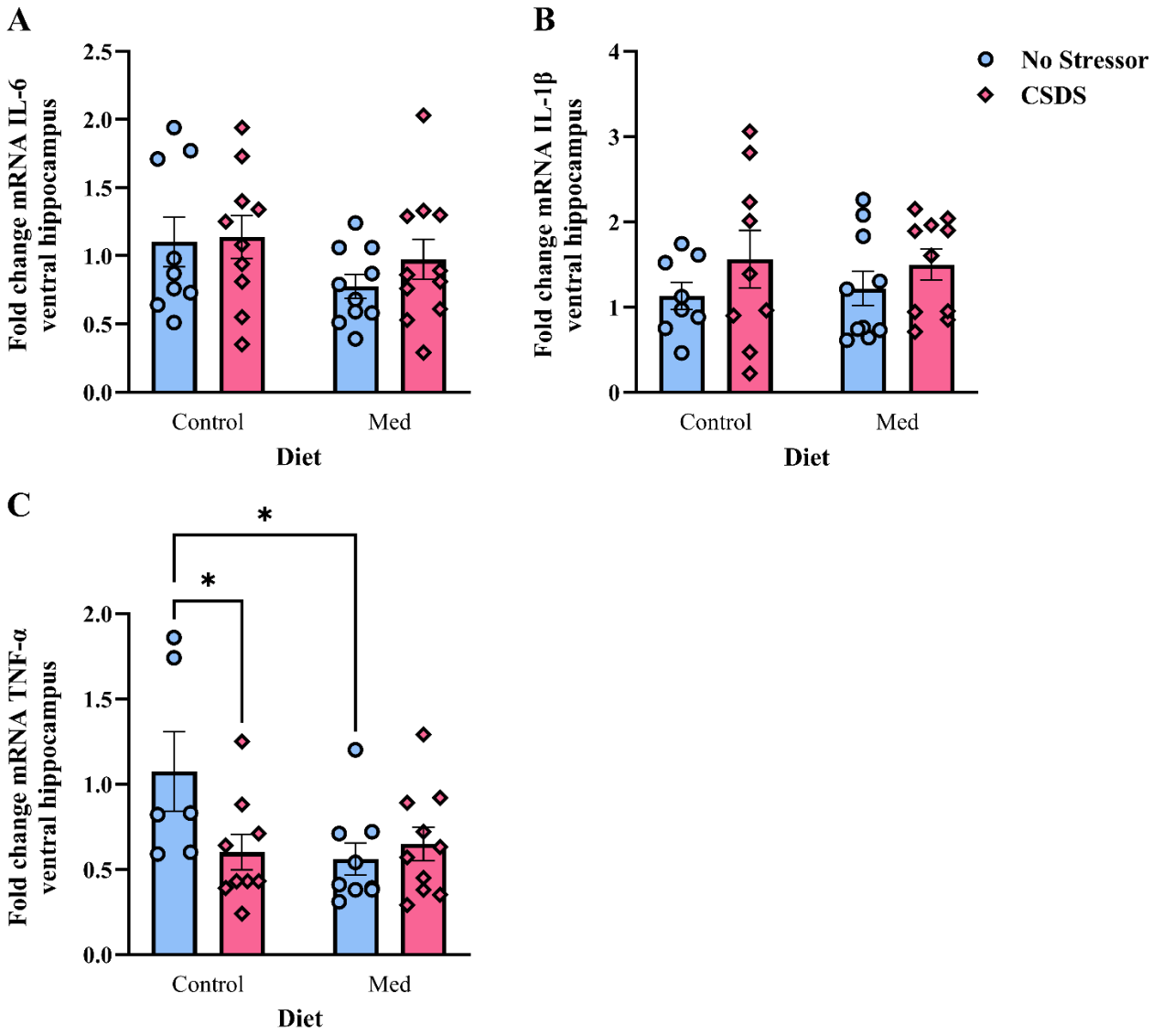

Fig. 11. **Fold changes for pro-inflammatory cytokines in the ventral hippocampus.** (A) IL-6 (B) IL-1β and (C) TNF-α. Mice fed the Control and Med-based diets in the No Stressor (light blue) and CSDS (pink) groups during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. * $p = 0.016$, relative to CSDS mice fed the control diet, and * $p = 0.010$, relative to non-stressed mice fed the Med-based diet. n = 6-9 for No Stressor groups and n = 9-11 for CSDS groups.

In Figure 12A and 12B, Diet, Stressor, and the Diet × Stressor interaction did not impact fold changes for the mRNA expression of the microglial factors CX3CR1 or Iba-1 (p's > 0.05).

17

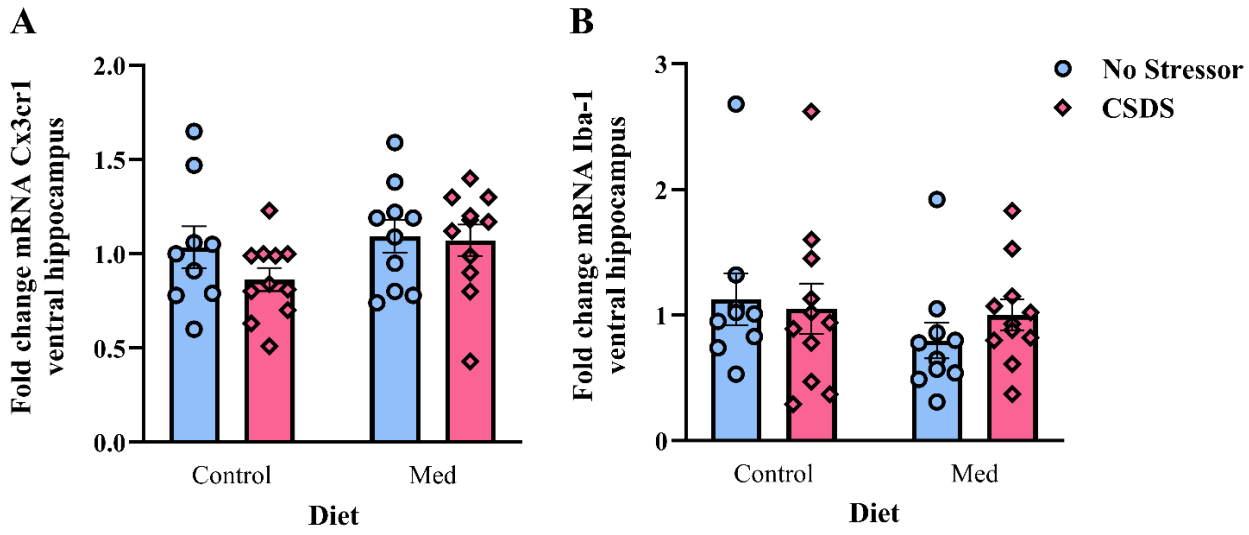

Fig. 12. **Fold changes for microglial markers in the ventral hippocampus.** (A) CX3CR1 and (B) Iba-1. Mice fed the Control and Med-based diets in the No Stressor (light blue) and CSDS (pink) groups during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. n = 9-10 for No Stressor groups and n = 11 for CSDS groups.

In Figure 13A, Diet and Stressor did not impact fold change expression of BDNF (p > 0.05), however the Diet × Stressor interaction was just shy of significance ($F_{(1,36)}$ = 3.840, p = 0.058). Although the interaction between these two factors was not significant, based on the *a priori* predictions that BDNF expression would be mitigated or increased in the Med-based diet groups, follow-up comparisons of the simple effects comprising the interaction were conducted and revealed that non-stressed mice fed the Med-based diet has reduced ventral hippocampal mRNA expression of BDNF compared to their control diet counterparts (p = 0.030). As seen in Figure 13B, CSDS mice had a significant decrease in the BDNF receptor TrkB, $F_{(1,37)}$ = 5.248, p = 0.028, which was independent of Diet (p > 0.05). In Figure 13C, Diet, Stressor, and the Diet × Stressor interaction did not impact fold change expression of NGF (p's > 0.05). As seen in Figure 13D, CSDS mice had a significant increase in NT-3 expression, $F_{(1,39)}$ = 5.4.589, p = 0.05, which again was irrespective of Diet (p > 0.05).

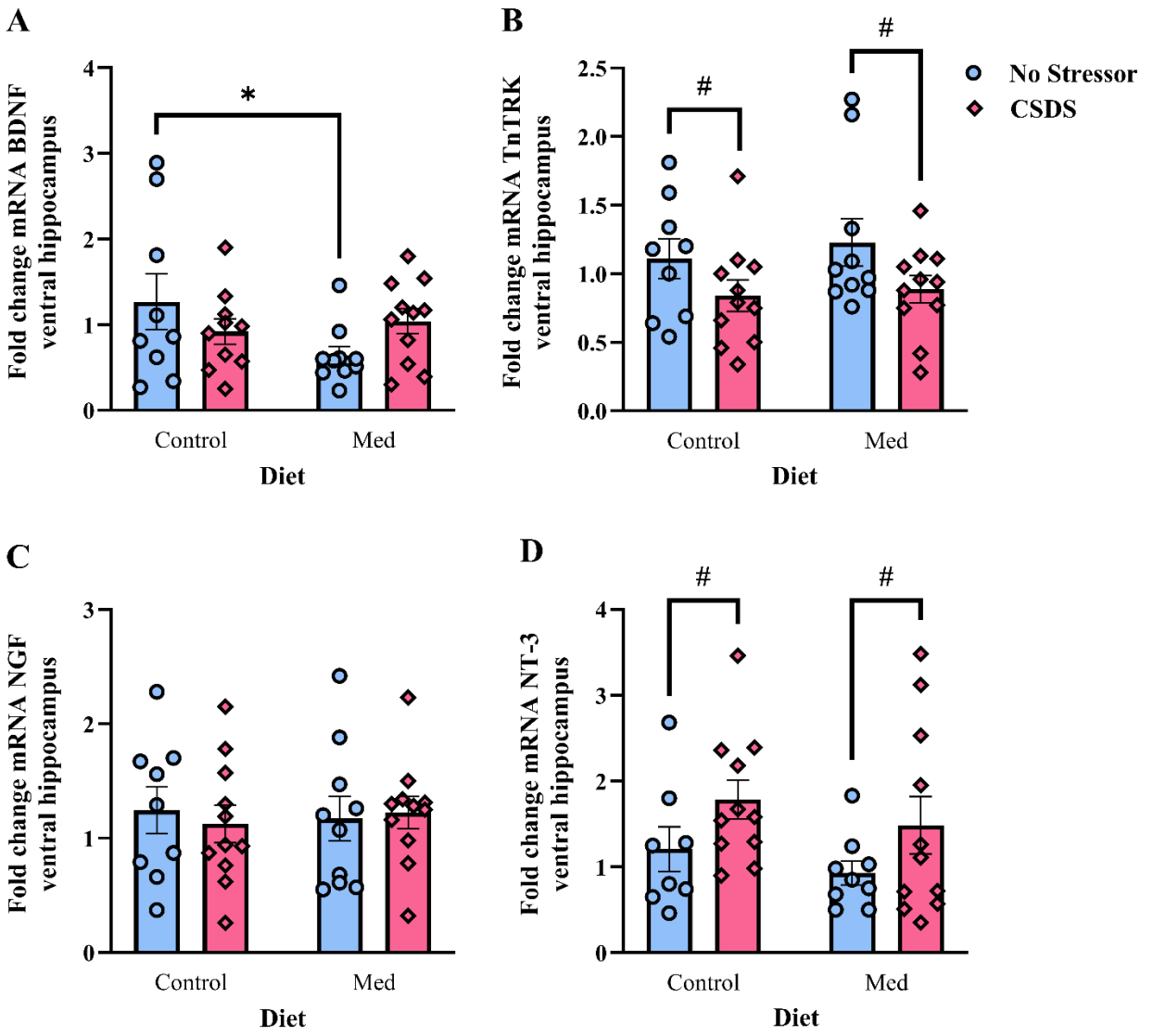

Fig. 13. **Fold changes for neurotrophic factors in the ventral hippocampus.** (A) BDNF (B) TrkB (C) NGF, and (D) NT-3. Mice fed the Control and Med-based diets in the No Stressor (light blue) and CSDS (pink) groups during the study period. The average of each group was assessed, and individual points were plotted in their respective bars for each timepoint. * $p = 0.030$, relative to non-stressed mice fed the Med-based diet. # $p < 0.05$, relative to non-stressed mice. $n = 9$-10 for No Stressor groups and $n = 11$ for CSDS groups.

3.5 Discussion

The rising prevalence of MDD and GAD, along with the limited efficacy of current treatment options, has necessitated the exploration of additional interventions aimed at mitigating symptom burden. Although the precise biological mechanisms underlying the mental health benefits of dietary interventions are not yet fully elucidated, the Med diet has been shown to reduce peripheral circulation of inflammatory markers (Koelman et al., 2022), reducing depressive symptoms (Bizzozero-Peroni et al., 2024), decrease cognitive decline (Solfrizzi et al., 2017), and reducing the risk for developing depression (Gianfredi et al., 2023). The Med diet contains high concentrations of foods with bioactive components that have been independently shown to exert antidepressant and anxiolytic effects (Chen et al., 2023; Jia et al., 2023; Liao et al., 2019; Sarris et al., 2022), reduce risk for cognitive impairment (Mottaghi et al., 2018; Solfrizzi et al., 2017), and incidence for depression and anxiety (Li et al., 2022). This study represents, to our knowledge, the first investigation into the effects of a whole-food dietary intervention on CSDS-induced social and non-social cognitive impairments. The primary aim of this study was to evaluate whether a mouse-adapted Med-based diet could ameliorate the cognitive deficits associated with CSDS through the modulation of pro-inflammatory and neurotrophic factors within the ventral hippocampus. Contrary to the initial hypothesis, the Med-based diet did not attenuate the impairments in social avoidance and preference, the impairments in working and spatial memory, the reduced expression of TNF-α and TrkB, or the increased expression of NT-3 in the ventral hippocampus, induced by CSDS. Although the Med-based diet was associated with increased social avoidance behaviours, decreased TNF-α and BDNF expression in non-stressed mice, it was shown to improve long-term object recognition memory.

Throughout the experimental period, mice maintained on the Med-based diet exhibited higher body weight changes throughout the experimental period and a higher overall food intake relative to those receiving the Control diet. This observation is likely attributable to the Med-based diet's higher fat content and its more complex composition, which includes whole-food sources, thereby enhancing its palatability and perceived energy density. Existing literature indicates that healthy male mice discriminate between foods based on energy density, texture, ingredient composition, with a marked preference for energy-dense diets irrespective of ingredient quality (Rainwater & Güler, 2022). In addition, the specific dietary components of the Med-based diet, primarily MUFAs and PUFAs, have been implicated in appetite regulation, potentially influencing feeding behaviours (Simopoulos, 2016). From the beginning to the end of CSDS exposure, stressed mice demonstrated a reduction in weight gain, irrespective of their diet conditions. These findings align with previous reports of decreased body weight or attenuated weight gain following social defeat (Buwalda et al., 2005; Chaouloff, 2013; Koolhaas et al., 1997; Korte et al., 2005; Krishnan et al., 2007; Savignac et al., 2011), although contrasting studies have reported either no change or increases in body weight (Bartolomucci et al., 2005; Bartolomucci & Leopardi, 2009). Following CSDS, both diet groups consumed similar quantities of their respective diets and had no or limited weight gains. This observation could be explained by the reduction in stressor intensity, as during this time, only behavioural tests were being conducted. Together, these data suggest that stress-induced alterations in body weight are regulated by a complex interplay between stressor intensity, coping mechanisms, and the nutritional composition of the diet.

Socially stressful encounters are differentially experienced based on individual characteristics, which partly explains the heterogeneity in the development of pathological

symptoms (Krishnan et al., 2007). In the current study, CSDS induced marked social avoidance behaviours, as measured by the social interaction test and the three-chamber sociability test, consistent with previous literature (Berton et al., 2006; Doney et al., 2023; Guo et al., 2020; Krishnan et al., 2007; Menard et al., 2017; Szyszkowicz et al., 2017). Mice consuming the Med-based diet, irrespective of stressor conditions, exhibited lower social interaction ratios in the social interaction test and had less entries into the chamber of a familiar conspecific in the three-chamber sociability test. These observations suggest that the dietary intervention may have inadvertently promoted social avoidance behaviours, which is noteworthy given that C57BL/6N mice are typically characterized by high levels of sociability and investigatory behaviour toward both social and non-social cues (Arakawa, 2023; Bolivar et al., 2007; Moy et al., 2007, 2008; Yang et al., 2011). The observed reduction in social interaction, independent of locomotor deficits, contrasts with existing studies reporting that individual components of the Med-based diet, such as polyphenols (e.g., resveratrol), MUFAs, PUFAs, biotin, beta-glucans, inulin, and olive oil, can modulate signaling pathways involved in social cognition, immunity, and mood regulation (Carlson et al., 2019; Sandhu et al., 2017). Instead, our results resemble those of previous studies that employed high-fat diets or dietary interventions low in MUFA and PUFA content (Larrieu et al., 2014, 2016; Takase et al., 2016), potentially suggesting that the bioactive lipids generated from MUFAs and/or PUFAs are unable to initiate anti-inflammatory control under chronic social stress conditions. Interestingly, recent evidence suggests that the pathological conditions associated with altered specialized pro-resolving lipid mediators metabolism and function can contribute to chronicity and magnitude of persistent inflammatory conditions (Chiurchiù et al., 2018). The bioactive lipid family known as the specialized pro-resolving lipid mediators (SPMs) are generated from ω-6 or ω-3 essential PUFA precursors and

are responsible for resolving inflammatory processes. Recent evidence has implied that in addition to the resolution of the innate immune response, SPMs can impact the balance between pathogenic and tolerogenic adaptive immune cells (Chiurchiù et al., 2016), supporting the view that SPMs may prevent chronicity of inflammation and link resolution to adaptive immune cell responses (Chiurchiù et al., 2018). In fact, recent studies have observed insufficient resolution of inflammatory processes in mouse models or in human plasma samples of chronic inflammatory and/or autoimmune diseases, including obesity (Clària et al., 2012), inflammatory bowel disease (Bento et al., 2011; Schwanke et al., 2016), which has high comorbidity with depression and anxiety disorders (Barberio et al., 2021; Byrne et al., 2017; Karpin et al., 2021) and neurodegenerative diseases charactered by chronic inflammation, including as multiple sclerosis, Alzheimer's disease, and amyotrophic lateral sclerosis (Wang et al., 2015; Zhu et al., 2016). Ultimately, the impaired resolution of inflammatory processes by SPMs could have contributed to the lack of observed anti-inflammatory benefits conferred by MUFAs and PUFAs, potentially contributing to the impaired social approach-avoidance behaviours.

Depressive and anxiety disorders are accompanied by cognitive deficits in both social and non-social domains (Knight et al., 2018; Knight & Baune, 2018; Maron & Nutt, 2017; Moran, 2016; Rock et al., 2014; Snyder, 2013). While the Med-based diet did not confer improvements in short-term object recognition, spatial and working memory as assessed by the NOR and forced alternation Y-maze tests, it enhanced long-term object recognition memory in the NOR test. In the current study, we utilized a modified version of the NOR test to assess long-term recognition memory in mice (Cadoret et al., 2023). To our knowledge, this is the first study to use this modified NOR test to assess long-term recognition memory in a mouse model of depression and in a dietary intervention context. While limited rodent studies on dietary interventions and non-

social cognitive processes exist, evidence supports both Med-based diets and their individual components in the reduction of mild to severe cognitive impairments, particularly relating to improvements in short- and long-term working memory, global cognition, and executive functioning in humans (Hardman et al., 2016; Marti Del Moral & Fortique, 2019; Mottaghi et al., 2018; Radd-Vagenas et al., 2018; Solfrizzi et al., 2017; Zhang et al., 2016). The enhancement of long-term recognition memory in mice may be attributed, at least in part, to the presence of ω-3 fatty acids and polyphenolic compounds (e.g., resveratrol and olive oil) within the Med-based diet. Both preclinical and clinical studies have shown that these compounds and their metabolites can prevent learning, recall and spatial memory deficits induced by stressors (Ferraz et al., 2011; Kołodziej et al., 2023; Marx et al., 2018). In this study, CSDS did not impair short-term recognition memory, contrasting with available literature (da Costa et al., 2023; Martin et al., 2017; Moreira et al., 2016). The non-significant impact of CSDS on recognition memory may have been influenced by the objects used in the current study. During the NOR test, the investigation of an object was based on the nose-point of the mice and their position relative to the object. One of the objects used was a funnel affixed to the arena floor, which mice were able to climb onto, potentially influencing the results as they were not deemed to be interacting with the object (Antunes & Biala, 2012; Ennaceur & Delacour, 1988). Another potential explanation may be related to the other involved brain regions, particularly the perirhinal cortex for its involvement in recognition memory after short-retention intervals and the dorsal hippocampus for its specific role in obtaining spatial and contextual information (Goulart et al., 2010; Hammond, 2004; Reger et al., 2009). The perirhinal cortex may not be as susceptible to stress-induced alterations, unlike the hippocampus, potentially contributing to the limited memory alterations conferred by CSDS.

At the neurobiological level, the hippocampus is particularly susceptible to stress-induced changes, including alterations in pro-inflammatory cytokines (Köhler et al., 2017; O'Leary & Cryan, 2014). While the current study did not observe significant effects of CSDS or the Med-based diet in the majority of pro-inflammatory and microglial markers, a significant interaction between diet and stress was noted for TNF-α expression. Specifically, CSDS reduced TNF-α mRNA expression in mice fed the Control diet as did the Med-based diet in non-stressed mice, independently from each other. Our observations are in line with the current literature regarding our dietary components and pro-inflammatory cytokine expression. A recent systematic review and meta-analysis have highlighted that in humans, adherence to a Med-type diet significantly reduces peripheral plasma and/or serum TNF-α, IL-1β, and IL-6 concentrations (Koelman et al., 2022). Rodent studies have also shown that components within the Med diet, for example polyphenols, can inhibit pro-inflammatory pathway activation and microglial activity within the CNS (Hornedo-Ortega et al., 2018), potentially mediating pro-inflammatory cytokine production. Additionally, of omega (ω)-3 PUFAs and their derivatives have been shown to regulate neuroinflammation and the production of pro-inflammatory cytokines within the brain (Caughey et al., 1996; Liao et al., 2019; Su et al., 2015). In fact, a recent collaboration between the World Federation of Societies of Biological Psychiatry (WFSBP) and the Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce released clinician guidelines for the recommended use of ω-3 fatty acids as an adjunctive treatment for MDD (Sarris et al., 2022). In contrast, our observations regarding CSDS and pro-inflammatory cytokine expression do not align with available literature. Current literature using chronic social stress has been shown to elevate TNF-α, in addition to IL-1β, and IL-6 within the hippocampus (Audet et al., 2010, 2011; McQuaid et al., 2013; Szyszkowicz et al., 2017). Moreover, the current study found no

significant impact of CSDS or the Med-based diet on microglial factors CX3CR1 and Iba-1, a result that deviates from reports of reduced anti-inflammatory regulation of CX3CR1 and increased Iba-1 expression after CSDS in stress-susceptible brain regions (Ramirez et al., 2016; Wohleb et al., 2011, 2013, 2014). These findings are interesting, as studies that use a chronic social stressor find disruptions in glucocorticoid production, increased pro-inflammatory cytokine expression and increased microglial activation in the hippocampus, which further recruits more pro-inflammatory monocytes (Sorrells et al., 2009; Ulrich-Lai & Herman, 2009). It is possible that the intake of the Med-diet was considered a natural reward and could buffered the effects of stressors in HPA activity. The reward system and stress processing have a reciprocal relationship, with the nucleus accumbens, the medial prefrontal cortex and the basolateral amygdala playing a crucial role in mediating responses to natural rewards and drugs of abuse (Berridge & Robinson, 1998; Hyman et al., 2006; Wise, 2002). The Med-based diet could be considered a palatable food choice, thereby interacting with the reward system and related key factors including dopaminergic and serotonergic neurotransmission (Hammels et al., 2015), potentially limiting the impact of CSDS-induced increases in hippocampal pro-inflammatory cytokine expression. It is also plausible that the individual differences of the C57BL/6N mice to CSDS limited the significant effects that are typically observed in social defeat studies. The response to social defeat is heterogeneous, with the susceptibility and resilience of each individual mouse varying based on a various factors, including pre-existing differences in sensitivity of the peripheral immune response (Hodes et al., 2014), individual personality and behavioural styles, and the degree of sensitivity to social setting in which a social rank can change (Bartolomucci et al., 2005; Sapolsky, 1994). While the majority of CSDS mice fed the Med-based diet were classified as susceptible, based on their social interaction ratio,

subordination by itself is not detrimental to health (Bartolomucci et al., 2005). In terms of neurotrophic factors, CSDS was associated with a decrease in TrkB and an increase in NT-3 in the ventral hippocampus, while the Med-based diet significantly decreased BDNF expression in non-stressed mice. Although these findings are in line with some repeated stressor studies (Barfield et al., 2017; Nibuya et al., 1995, 1999; Ray et al., 2014; Serra et al., 2017; Smith et al., 1995) they contrast with studies that report an increase in hippocampal BDNF levels following supplementation with polyphenols and PUFAs (Dias et al., 2012; Valente et al., 2009). The pronounced vulnerability of the ventral hippocampus to stress-induced impairments in neurogenesis (Hawley & Leasure, 2012; Larsen et al., 2010; Tanti et al., 2012, 2013) may partially account for the limited neurotrophic benefits observed in the current dietary intervention.

A limitation of the current study is the investigation of male mice exclusively. The CSDS model was initially developed for male mice due to their territorial and aggressive behaviour (Berton et al., 2006; Golden et al., 2011), despite the increased prevalence of depressive and anxiety disorders in women. Recent studies have modified CSDS protocols for female mice (Harris et al., 2018; Logan, 2019; van Doeselaar et al., 2021), although the use of male urine, male aggressor mice, or using female mice during pregnancy to simulate aggressive behaviours are not effectively translatable to the human experience. Future research should consider dietary interventions using stress models applicable to both sexes, such as unpredictable chronic mild stress or a modified crowding/social instability stress (Frisbee et al., 2015; Furman et al., 2022). In addition, previous work conducted using the same Med-based diet have shown significant effects in limiting chronic restraint stress-induced increases in anxiety-like behaviours, hippocampal pro-inflammatory cytokine expression and limited hippocampal BDNF expression

decreases in female C57BL/6N mice, potentially explaining why limited significant effects were observed in the current study, due to sex differences (Udechukwu, 2024). With this, future studies should consider extending the duration of dietary intervention post-stress to assess long-term effects on behavioural recovery and further investigate the bioavailability and mechanistic pathways through which dietary components interact with the microbiota-gut-brain axis under chronic stress conditions. Additionally, delineating the differential roles of the dorsal and ventral hippocampus in response to dietary and stress-related challenges may offer further clarity on the neurobiological substrates underlying stress-induced cognitive deficits.

3.6 Conclusion

In summary, the present study provides novel insights into the effects of a Med-based dietary intervention in a mouse model of depression induced by CSDS. Although the intervention did not ameliorate behavioural, cognitive, and hippocampal markers of stress, the findings underscore the complex interplay between dietary composition, stress exposure, appetite regulation, nutrient and energy utilization, in addition to cognitive outcomes. The increased palatability and energy density of the Med-based diet appear to modulate feeding behaviour under baseline conditions, while its impact on social behaviour and long-term memory may be mediated by the specific nutrient composition, including MUFAs, PUFAs, and polyphenolic compounds.

Author contributions

M.C.A designed the experiment. A.M.S. performed the experiment, including all the stressor, dietary, behavioural, and molecular analyses, performed data analysis, and prepared the figures; A.M.S. and M.C.A. collected samples and interpreted the data. A.M.S. wrote the first

drafts of the manuscript, which were revised by M.C.A. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Chapter 4: General Discussion

4.1 General Discussion

The increasing rates of MDD and GAD, coupled with the limited effectiveness of existing treatment options, have prompted the need for alternative interventions. Most pharmacotherapies are not suitable for targeting cognitive symptoms, which interfere with daily functioning in social and occupational environments, further contributing to the burden of these neuropsychiatric diseases. Accumulating evidence has posited that dietary patterns and specific food items may be a plausible adjunctive therapeutic treatment option to improve depressive and anxiety symptoms, enhance resilience to stress, and support both cognitive and emotional functioning (Firth et al., 2020; Jacka, 2019; Jacka et al., 2017). In particular, the Med dietary pattern, which is composed of whole grains, nuts, legumes, vegetables, and fruits, with moderate consumption of fish and poultry products (Sánchez-Villegas et al., 2009), has been shown to reduce depressive and anxiety symptoms (Bizzozero-Peroni et al., 2024), peripheral circulation of pro-inflammatory markers (Koelman et al., 2022), and can slow the progression of cognitive decline (Solfrizzi et al., 2017). With this, individual food items found in the Med diet are rich in bioactive components and have been independently shown to reduce depressive and anxiety symptoms (Chen et al., 2023; Jia et al., 2023; Liao et al., 2019; Sarris et al., 2022), further supporting its potential as an intervention treatment for neuropsychiatric disorders. The current study was conducted to determine whether a Med-based diet, adapted for mice, could prevent the cognitive deficits as well as the hippocampal inflammatory and neurotrophic changes, induced by CSDS. Our first objective was to confirm that CSDS elicited social and non-social cognitive impairments, in addition to inflammatory and neurotrophic alterations in the ventral hippocampus of male C57BL/6N mice. Our second objective was to establish whether a Med-

based diet could limit these cognitive, inflammatory, and neurotrophic changes induced by CSDS. To achieve this, we fed individually housed male C57BL/6N mice to either a Med-based or a control diet. Half of each dietary group was then subjected to CSDS or paired-housed with a conspecific, which was the control stressor condition. Following this, both social and non-social cognitive functions were assessed. Following cognitive testing, we collected the ventral hippocampus from mice for the subsequent determination of pro-inflammatory, microglial and neurotrophic factor mRNA expression. Our initial hypothesis proposed that the cognitive, inflammatory, and neurotrophic alterations elicited by CSDS would be attenuated in mice fed the Med-based diet. In this experimental context, our study found that the Med-based diet could not significantly alleviate the impairments in social avoidance and preference as well as in working and spatial memory in CSDS mice. Additionally, the Med-based diet could not mitigate the reduced expression of TrkB or the increased expression of NT-3 in the ventral hippocampus, elicited by CSDS. Finally, the Med-based diet itself improved long-term object recognition memory but was found to increase social avoidance behaviours, impair working and spatial memory, and decrease expression of TNF-α, and BDNF.

Social behaviour in mice can be characterized by approach and avoidance behaviours, interaction, recognition, and creation of memories associated with a social target. Rodents are physiologically driven to socially approach and interact with a new target, outweighing the fear of a novel interaction (Desbonnet et al., 2012). Our study found that in the context of CSDS, mice exhibited marked social avoidance behaviours, independent of locomotor deficits and diminished sociability preference with conspecifics. Our observations are consistent with previous literature assessing social behaviours with the social interaction test in the context of CSDS (Berton et al., 2006; Doney et al., 2023; Krishnan et al., 2007; Menard et al., 2017;

Szyszkowicz et al., 2017). Contrary to our hypothesis, stressed mice fed our Med-based diet not only failed to show resilience against CSDS-induced deficits but, in fact, demonstrated exacerbated avoidance behaviours when compared against their control-diet counterparts. The current study utilized the C57BL/6N strain due to its innate and high expression of sociability and investigatory behaviour towards social and non-social signals (Arakawa, 2023; Bolivar et al., 2007; Moy et al., 2007, 2008; Yang et al., 2011). Social avoidance towards both CD-1 and C57BL/6N mice strains (aggressor and experiment strain respectively) were significant findings observed in our study, as previous literature has shown that CSDS-defeated mice avoided interacting with an aggressor mouse of the CD-1 strain, whereas no social avoidance behaviours were observed towards a conspecific C57BL/6N mouse (Desbonnet et al., 2012). Rodents have been shown to display sociability preferences, preferring to spend time with a social target rather than have no social interaction (Gheusi et al., 1994; Moy et al., 2004). They also have social novelty preferences, preferring to spend time with new social targets than a familiar one (Gheusi et al., 1994; Moy et al., 2004). The fear of novel social interactions that, under normal circumstances, would have been rewarding, may have been due to a dysregulated HPA axis-induced prolonged corticosterone exposure and the complex adverse effects of glucocorticoid receptor-mediated signalling. Although elevated blood corticosterone is found in both socially avoidant and non-avoidant mice, higher expression of CRH in the hypothalamus, which relies on glucocorticoid receptor-mediated signalling in the hypothalamus and hippocampus, was found specifically in social avoidant animals (Elliott et al., 2010; Han et al., 2017). Supporting this, studies have shown that through the systemic inhibition of glucocorticoid receptors during CSDS, social avoidance behaviours were prevented in adult mice (Mouri et al., 2018). While the current study did not assess the blood or plasma levels for peripheral corticosterone or

glucocorticoid receptor expression in the hypothalamus, dorsal or ventral hippocampus, it would be beneficial for future studies to investigate these factors in the context of whole-food dietary interventions.

Several brain regions are involved in the regulation of social behaviours and social cognition, including the nucleus accumbens, the amygdala, and the hypothalamus (Ernst & Fudge, 2009; Ko, 2017). While the current study did not investigate these brain regions, it may be of value to investigate cellular and molecular changes that occur from a chronic social stressor, and in the context of whole-food dietary intervention. Based on our observations, it may be plausible to suggest that ventral hippocampal neurogenesis did not occur in the context of our dietary intervention, which could have otherwise contributed to stress resilience and antidepressant effects (O'Leary & Cryan, 2014; Winkler et al., 2017). Reduced BDNF/TrkB signalling in the ventral hippocampus may contribute to the pronounced vulnerability to stress-induced depression effects (Serra et al., 2017), although the current study did not significantly observe BDNF deficits in CSDS mice. Future studies should investigate alterations in TrkB/BDNF signalling, with specific measures identifying truncated TrkB and inactive BDNF (Serra et al., 2017), which have been shown to be preferentially upregulated in expression, within the ventral hippocampus, in rodents that exhibit excess corticosterone levels (Barfield et al., 2017). Another direction for future studies could be to test whether dietary interventions could improve social cognition using extinction sessions, particularly in conditions where social avoidance generalizes to all social stimuli (Meduri et al., 2013). Extinction training has been shown to reverse social avoidance behaviours through emotional activation (Ayash et al., 2020), which could be utilized as an experimental condition to assess the potential benefits of a dietary intervention on social behaviour.

The increased social avoidance in mice fed the Med-based diet was a surprising observation, given that the human Med diet has been shown to positively influence emotional regulation (Holt et al., 2014). Components of the Med-based diet have also been shown independently to influence HPA axis regulation, regulate pro-inflammatory responses, and improve mental health outcomes (Carlson et al., 2019; Fernandes et al., 2020; Mocking et al., 2016; Sandhu et al., 2017; Schwingshackl et al., 2015). For example, long chain ω-3 PUFAs, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and their metabolites have been shown to regulate the HPA-axis, inflammatory and neuroinflammatory responses, and influences mood and behaviour in both animal and clinical studies (Ferraz et al., 2011; Firth et al., 2019; Jahangard et al., 2018; Larrieu et al., 2014, 2016; Layé et al., 2018; Liao et al., 2019). Recently, ω-3 fatty acids have been recommended for the adjunctive treatment for MDD by the World Federation of Societies of Biological Psychiatry (WFSBP) and the Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce (Sarris et al., 2022). Preclinical studies have also found that a diet enriched with EPA, DHA, long chain PUFAs, and vitamin A improved performance in emotional and reference memory tests (Provensi et al., 2019), while a different study found that supplementing the AIN-93 diet with fish oil containing DHA/EPA 40 mg/g enhanced resilience to social defeat stress, improving but not completely recovering from induced social avoidance and anxiety behaviours (Otsuka et al., 2022). Despite the Med-based diet's high concentration in MUFAs and PUFAs, the social avoidance behaviours observed in the current study are similar to studies that use high-fat diets or diets low in MUFA and PUFA concentration (Larrieu et al., 2014, 2016; Takase et al., 2016). It is plausible that dysregulated fatty acid signalling, independent of the stressor, may have limited the capacity of the Med-based diet-derived MUFAs and PUFAs to exert their regulatory effects on neurogenesis and the HPA

axis, thereby not attenuating the social and cognitive deficits observed in the current study. Although the current study did not investigate this factor, impaired fatty acid signalling has been implicated in mood disorders and cognition (Bazinet & Layé, 2014), potentially contributing to the observed outcomes. Specialized pro-resolving lipid mediators are bioactive lipids that resolve pro-inflammatory responses and are generated from ω-6 or ω-3 essential PUFA precursors. Recent studies have observed insufficient resolution in mouse models or in human plasma samples of chronic inflammatory and/or autoimmune diseases, including obesity (Clària et al., 2012) and inflammatory bowel disease (Bento et al., 2011; Schwanke et al., 2016), which has high comorbidity with depression and anxiety disorders (Barberio et al., 2021; Byrne et al., 2017; Karpin et al., 2021), suggesting that alterations in resolution lipid mediators may contribute to the chronicity and magnitude of chronic inflammatory illnesses (Chiurchiù et al., 2018). Although the current study did not observe increases in central inflammation or assess peripheral markers of inflammation, persistent inflammatory responses may impair crucial metabolic and immune mechanisms of MUFAs and PUFAs, thereby limiting anti-inflammatory effects and potentially impacting social approach-avoidance behaviours. Future studies should measure the central and peripheral expression of MUFA and PUFA metabolites, and specialized pro-resolving lipid mediators to determine if chronic social stress impairs resolution mechanisms conferring an anti-inflammatory effect. In addition to MUFAs and PUFAs, polyphenols have been shown to exhibit anti-inflammatory and antioxidant properties (Bastianetto et al., 2015; Dias et al., 2012; González-Gallego et al., 2010) and improve cognition and serum levels of BDNF in clinical studies (Neshatdoust et al., 2016). Specific polyphenols, such as resveratrol, have been shown to reduce social stress-induced depressive behaviour, pro-inflammatory activity (Finnell et al., 2017; Ge et al., 2013; Yang et al., 2017) and upregulate hippocampal expression of BDNF in

animal models (Abd El-Fattah et al., 2018; Li et al., 2018). Resveratrol is lipophilic and can passively diffuse through the intestinal barrier into circulation, however, it is subject to extensive metabolism and removal showing poor bioavailability (Walle et al., 2004; Wenzel & Somoza, 2005). Limited literature exists on resveratrol's impact on social cognitive functions in depression animal models, however, in a mouse model of autism, resveratrol has been shown to alleviate impaired social behaviour (Bambini-Junior et al., 2014). It is plausible to suggest that the bioavailability of resveratrol or other polyphenolic components found in our Med-based diet, at least in these experimental conditions, may have been limited by the bioaccessibility, absorption or the transformation stages (McClements et al., 2015) in the context of the CSDS conditions, potentially limiting the health benefits exerted by the nutraceutical.

Despite the beneficial effects of bioactive factors in dietary components, limited literature exists regarding whole-food dietary interventions in mouse models of depression. Our Med-based diet primarily contained whole-food and relative concentrations of food items found in the human Med diet, appropriate for a mouse model. Chronic stress has been shown to induce changes in feeding and metabolic mechanisms, such as increased food intake and the utilization of carbohydrates over fat to manage the energy demands of the stressor (Kumar et al., 2013; Lutter et al., 2008; Patterson, Khazall, et al., 2013). In our study, mice maintained on the Med-based diet exhibited a higher overall food intake and increased body weight relative to those receiving the control diet. Although mice maintained on the Med-based diet ate similar quantities of food before and after the stressor, mice did not gain any weight in these experimental conditions. This may indicate that due to the severity and/or intensity of CSDS, the quantity of the dietary intervention and its beneficial bioactive components were insufficient, thereby limiting significant improvement in sociability and/or social cognitive functioning. With this,

CSDS may have significantly promoted intestinal pro-inflammatory responses, limiting the capacity for effective nutrient assimilation and subsequently, their beneficial effects on target regions. Observational studies further support these ideas, as low levels of specific nutrients were related to higher levels of depressive symptoms (Sarris et al., 2016). Obtaining the benefits of nutraceuticals depends on the oral bioavailability of the bioactive compound, which is limited by the bioaccessibility, absorption, and transformation of the dietary component (McClements et al., 2015).

Although the current study did not assess markers of bioactive components and/or their metabolites, it would be beneficial to understand the capacity of whole-food dietary interventions, and the bioactive component efficacy, in the context of chronic social stress. In addition to this, another consequence of CSDS is altered ghrelin expression, which is particularly relevant in the context of a dietary intervention. Ghrelin is a gut peptide and orexigenic hormone that is known to increase appetite, promote adiposity, and has been shown to be secreted in response to stressors (Patterson, Khazall, et al., 2013; Patterson, Parno, et al., 2013). It has been shown that CSDS increases active ghrelin in plasma, increase caloric intake, increase body weight, and alter metabolism to utilize carbohydrates, promoting the storage of fats (Davies et al., 2009; Kumar et al., 2013; Patterson, Khazall, et al., 2013; Raspopow et al., 2010). Studies also showed that blocking the ghrelin receptor in the paraventricular nucleus of the hypothalamus increased consumption of high-fat diets during CSDS (Patterson, Parno, et al., 2013). It may be plausible that CSDS induced alterations in ghrelin signalling, thereby promoting the storage of MUFAs and PUFAs, and limiting their ability to exert beneficial effects. Future studies should investigate ghrelin expression and adipose tissues in the context of a healthy whole-food dietary intervention during CSDS.

The current study did not investigate the gut microbiota and intestinal integrity, although alterations in the gut microbiota and the loss of intestinal barrier integrity may be associated with the severity of social avoidance behaviours induced by CSDS, which has been previously shown in the literature (Doney et al., 2023; Szyszkowicz et al., 2017). While the current study did not examine HPA axis activity directly, a dysregulated HPA axis may have increased general anxiety-like behaviours following CSDS and/or CSDS-induced alterations in reward-seeking behaviour and regulatory mechanisms (Bromberg-Martin et al., 2010; Lukas & de Jong, 2017). In particular, the ventral hippocampus projects emotionally relevant contextual information to the mesolimbic dopamine system, informing and remembering the importance onto the incoming stimuli (Blaha et al., 1997). Although our study did not observe any significant effects indicating neuroinflammation was occurring, at least in the ventral hippocampus, CSDS may have impaired the processing of social stimuli in other brain regions involved in social behaviour.

Non-social cognitive impairments, which are defined as the psychological processes involved in non-social interactions or settings, are shared between MDD and GAD, including deficits in executive function, cognitive flexibility, sustained attention, visual memory, working memory, and learning (Castaneda et al., 2008; Kim et al., 2019; Luo et al., 2022; Rock et al., 2014). Our study found that although our Med-based diet did not improve short-term object recognition or mitigate impairments in short-term working and spatial memory in CSDS mice, at least in the current experiment conditions, it positively enhanced long-term object recognition memory overall. The Med-based diet improvement of long-term object recognition memory in these experimental conditions, with mice showing preference for a novel object irrespective of the stressor condition, may have been influenced by MUFAs, PUFAs, polyphenolic compounds, and their metabolites, obtained from the Med-based diet. These nutrients are essential for

maintaining healthy brain structure and function (Parletta et al., 2019) and may exert synergistic effects through the inhibition of pro-inflammatory pathways and/or the modulation of circulating corticosterone levels (Donoso et al., 2020; Hornedo-Ortega et al., 2018; Lee et al., 2018). Our results regarding long-term memory align with the literature that supports the Med diet's beneficial effects improving global cognition, visuospatial and executive function domains, delayed recognition, visual, and long-term memory (Anastasiou et al., 2017; Hardman et al., 2016; Parletta et al., 2013; Radd-Vagenas et al., 2018). Although the current study did not assess BBB permeability markers or reactive oxygen species in the ventral hippocampus, components within the Med-based diet may have mediated CSDS-induced increases in oxidative stress, the production of free radicals, the promotion of repair processes, and reinforce BBB integrity (Parletta et al., 2013). The current study found that the Med-based diet, at least in the current experimental conditions, did not improve short-term object recognition, or spatial and working memory. However, based on *a priori* predictions that impairments in this spatial and working memory would be mitigated by mice fed the Med-based diet, follow-up comparisons of the simple effects were conducted, revealing that in our specific experimental conditions, CSDS mice fed the Med-based diet showed significant spatial and working memory impairments, relative to their control diet counterparts. This finding contrasts with studies that demonstrate the positive effects of the Med diet and bioactive components found in the Med-based diet on short-term and spatial memory deficits (Ferraz et al., 2011; Fu et al., 2022; Murphy et al., 2014; Pitozzi et al., 2012; Radd-Vagenas et al., 2018). While the current study did not investigate the dorsal hippocampus, alterations in pro-inflammatory, microglial and/or neurotrophic factor expression in this dorsal hippocampus region could have mediated CSDS-induced effects on non-social cognition in mice fed the Med-based diet. With respect to short-term memory, our study found

that CSDS did not significantly impair short-term object recognition memory and short-term working and spatial memory, which is in stark contrast with chronic social stress literature (da Costa et al., 2023; Martin et al., 2017; Moreira et al., 2016). With respect to CSDS, the preserved short-term object recognition memory may have been influence in part by the objects used in the NOR test. To determine object recognition and preference, a mouse was investigating an object when its nose-point was in relative proximity (~2 cm from edge of object) of the object. From the three objects used in our study (red solo cup, white funnel, 150 ml orange cap transparent glass bottle), some mice were observed to climb onto the white funnel, which was affixed to the arena floor. This behaviour was not considered to be an interaction and was not tracked, potentially influencing our overall result (Antunes & Biala, 2012; Ennaceur & Delacour, 1988). The improvements observed may also be related to the non-significant expression of pro-inflammatory cytokines and microglial activation that would indicate neuroinflammation is occurring in the ventral hippocampus. Although our observations found no significant impact of CSDS or dietary intervention on the expression of CX3CR1, hippocampal neurogenesis may be occurring in the dorsal hippocampus, which is involved more in learning, memory, and spatial navigation, thereby preferentially regulating non-social cognitive functions (Fanselow & Dong, 2010; Gulyaeva, 2019). In addition, studies have shown that in non-stress conditions, the dorsal hippocampus is mainly involved in memory retrieval, and during stress conditions, the ventral hippocampus is mainly involved, due to impairments in the dorsal hippocampus (Dorey et al., 2012; Pierard et al., 2017). Another potential factor contributing to the preserved short-term object recognition memory may be the involvement of the dorsal hippocampus and perirhinal cortex. The perirhinal cortex is involved in recognition memory following short-term intervals and may be resilient to the effects of CSDS (Goulart et al., 2010; Hammond, 2004; Reger et al.,

2009). Further investigation should be conducted using CSDS to investigate the timing and activity of both the dorsal and ventral hippocampal involvement, and a dietary intervention. Additionally, future studies would benefit from investigating the structural integrity, functional capacity, and relative expression of neuroinflammatory and neuroprotective factors, as well as pathways of the dorsal and ventral hippocampus, in the context of whole-food dietary interventions during chronic social stress.

The hippocampus has been regarded as a stress-sensitive region, due to its involvement in the negative feedback inhibition of the HPA axis. Prolonged stress can increase the production of and blood circulating levels of glucocorticoids and pro-inflammatory cytokines, dysregulate anti-inflammatory immune mechanisms, and impair emotional and cognitive regulatory mechanisms (Frank et al., 2013; Herman, 2022; Köhler et al., 2017; O'Leary & Cryan, 2014; Roozendaal, 2002; Russell & Lightman, 2014; Sorrells et al., 2009). The current study did not find alterations in the expression of IL-1β and IL-6, however, we did observe an interaction between the dietary intervention and the stressor on TNF-α expression in the ventral hippocampus. We found that CSDS reduced TNF-α mRNA expression in mice fed the Control diet as did the Med-based diet in non-stressed mice, independently from each other. With respect to TNF-α, our findings align with available preclinical and clinical literature, showing that adhering to a Med-type diet or the components within our Med-based diet, including polyphenols and ω-3 PUFAs, can reduce peripheral plasma and/or serum TNF-α concentrations, (Koelman et al., 2022), regulate neuroinflammatory responses, and mediate pro-inflammatory cytokine production (Caughey et al., 1996; Hornedo-Ortega et al., 2018; Liao et al., 2019; Su et al., 2015). Our findings, at least in the current experimental conditions, are in stark contrast to the majority of preclinical and clinical literature regarding the effects of a dietary intervention on IL-1β and IL-6 expression

(Hornedo-Ortega et al., 2020; Koelman et al., 2022; Liao et al., 2019; Su et al., 2015), and the effects of CSDS on IL-1β, IL-6, and TNF-α expression in the hippocampus (Audet et al., 2010, 2011; McQuaid et al., 2013; Szyszkowicz et al., 2017). Additionally, the current study did not observe effects of the dietary intervention or stressor on microglial factors CX3CR1, which has been shown to be downregulated following CSDS and Iba-1, which has been shown to be increased following CSDS (Ramirez et al., 2016; Wohleb et al., 2011, 2013, 2014). Taken together, the mostly unchanged expression of pro-inflammatory cytokines and microglial markers suggests that the dietary intervention, at least in the current experimental conditions, could not exert considerable influence on cytokine production in the ventral hippocampus. The dietary intervention may have alternatively been utilized for the reduction of peripheral and/or intestinal inflammatory responses and potentially promoting barrier integrity. For example, chronic social stress has been shown to increase permeability of the BBB and the intestinal epithelial barrier (Doney et al., 2023; Lauffer et al., 2016; Leigh et al., 2023; Machorro-Rojas et al., 2019; Menard et al., 2017; Nozu et al., 2017; Yu et al., 2013). A study also found that chronic variable stress and sub-chronic variable stress-induced alterations in tight junction gene expression in the jejunum may potentially allow gut-related inflammatory mediators to pass into the bloodstream (Doney et al., 2023). In fact, Doney et al. identified circulating lipopolysaccharide-binding protein as a gut leakiness potential biomarker, and found elevated serum levels of lipopolysaccharide-binding protein in stress-susceptible mice (Doney et al., 2023). Additionally, a previous study found that exposure to repeated stress altered the relative abundance of bacterial populations and that microbiota are necessary for stressor-induced increases in circulating cytokines (Bailey et al., 2011). Another study found that microbial alterations were associated with social avoidance severity, despite limited pro-inflammatory

cytokine changes in the hippocampus (Szyszkowicz et al., 2017). While the current study did not assess plasma or blood biomarkers of inflammation, the Med diet has been shown to improve serum, plasma, and blood markers of inflammation in clinical populations (Chrysohoou et al., 2004; Fung et al., 2005; Schwingshackl & Hoffmann, 2014). Future studies should investigate and compare the differences in the regulation of intestinal, peripheral circulation, and central inflammatory responses during CSDS, in the context of a dietary intervention.

It is also plausible that the Med-based diet, at least in the current experimental conditions, influenced neuroimmune factors or brain regions not directly assessed in the present study, such as the reward system. The Med-based diet may be perceived as palatable and rewarding (Hammels et al., 2015), and its interaction with the reward system and related pathways could constitute a mechanism through which diet influences stress-related processes and pro-inflammatory activity. Another potential explanation may be related to the individual differences in mice. Despite the majority of stress studies showing biological and behavioural alterations, each mouse can respond to chronic stressors differently (Hodes et al., 2014), which is similarly observed in humans (Krishnan & Nestler, 2008). The experience of social defeat stress may not be experienced or perceived as negative by mice who lose the interaction. Subordinate mice may instead be acclimated to the experience of social defeat, conferring resilience to subsequent sessions. Studies have shown that performing CSDS on mice that were initially housed in groups, with an established social hierarchy, had significant impact on high-ranking, dominant mice (Larrieu et al., 2017; Larrieu & Sandi, 2018). The experience of losing control over territory and on social interactions due to the CSDS can significantly challenge the homeostatic functioning in dominant mice. Future studies may benefit from assessing the impact of dietary

interventions on social behaviour, in single and/or group housing conditions with a suitable chronic social stressor.

Neurotrophic factors are important mediators preserving structural integrity of the CNS, and mediating processes involved in memory and emotional regulation. The current study found that CSDS decreased the expression of TrkB and increased the expression of NT-3 in the ventral hippocampus, independent of the dietary intervention. Unexpectedly, non-stressed mice fed the Med-based diet had reduced expression of BDNF, in the ventral hippocampus. Our findings, with respect to NT-3 and TrkB align with available literature using repeated stressors (Barfield et al., 2017; Nibuya et al., 1995, 1999; Ray et al., 2014; Serra et al., 2017; Smith et al., 1995), and in animal models of depression, particularly relating to neurogenesis rather than neuronal survival, within the ventral hippocampus (Gulyaeva, 2019; Hawley & Leasure, 2012; Larsen et al., 2010; Tanti et al., 2012, 2013; Tanti & Belzung, 2013). The decreased BDNF expression in non-stressed mice fed the Med-based diet, however, do not align with available literature showing increases in hippocampal BDNF levels following polyphenol and PUFA supplementation (Dias et al., 2012; Valente et al., 2009). Taken together, these results highlight a context-dependent effect that differs from previous polyphenol and PUFA supplementation studies.

Future research should investigate the limiting factors in the bioavailability of dietary interventions, in the context of chronic social stressors, and potentially use alternative methods to facilitate improve nutrient assimilation. While the current study aimed to distinguish the role of the ventral hippocampus in CSDS-induced social and non-social cognitive impairments, future studies should investigate the activity of both dorsal and ventral hippocampus, furthering our understanding of the affected regions that respond to chronic social stress, and whether dietary interventions can adequately target these regions during these conditions. With this, the limbic

system should be investigated in the context of dietary interventions and compared against highly palatable and standard diets to further our knowledge of emotional eating behaviours and metabolic alterations during chronic social stress. These future directions will help clarify the intricate mechanisms involved in nutrient assimilation, immune response management, metabolism, chronic social stressor conditions, and the MGBA facilitating these interactions.

4.2 Limitations

4.2.1 Sex Differences

Our study is not without its limitations, as we investigated exclusively male mice. The CSDS model is a well-established mouse model for depression, but was designed and validated based on the territorial and aggressive behaviours exhibited by male mice (Berton et al., 2006; Golden et al., 2011). Our decision to investigate a dietary intervention in the context of CSDS exclusively in males limits the translatability of our study. A recent systematic review found that females are more likely to suffer from MDD than males, with the global prevalence rate being 3.0% in females compared to 1.8% in males (GBD 2019 Diseases and Injuries Collaborators, 2020). Recent studies have modified the CSDS protocol to include female mice, applying male urine on female mice to trigger resident male aggressive behaviours or using female mice during lactation to simulate aggressive behaviours, as neither male nor female residents attack intruder females (Harris et al., 2018; Logan, 2019; van Doeselaar et al., 2021). Male and female mice respond differently to social stressors (van Doeselaar et al., 2021), for example, in response to CSDS, female mice do not exhibit pronounced social avoidance behaviour (van Doeselaar et al., 2021). Therefore, further investigation should be done to create a female-to-female protocol for CSDS that is translatable to the female experience of chronic social stress. There are stress models that are applicable to both sexes, including the unpredictable chronic mild stress and a

modified crowding/social instability stress (Frisbee et al., 2015; Furman et al., 2022), which could be utilized in future studies to investigate the potential benefits of dietary interventions in the context of chronic stress. Notably, recent studies in our laboratory utilizing the same dietary intervention found that our Med-based diet increased self-care behaviour, reduced pro-inflammatory cytokines, and increased BDNF in the hippocampus of postpartum dams, while limiting the increase in anxiety-like behaviours and hippocampal pro-inflammatory cytokines, and mitigating the reductions in hippocampal BDNF in prenatally stressed C57BL/6N mice, particularly in females (Udechukwu, 2024). Males and females also differ in their neuroendocrine and immune systems, which can impact the expression of neuroinflammatory and neurotrophic factors both at baseline and in response to stressors (Derry et al., 2015; Rubinow & Schmidt, 2019). As male and female mice were shown to differ in their response to dietary interventions (Casimiro et al., 2021; de Souza et al., 2022; Maric et al., 2022; Rodríguez-Iglesias et al., 2022), this could lead to immune, neuroendocrine, and metabolic changes that differ between sexes (Asarian & Geary, 2013; Braga Tibaes et al., 2024; Fransen et al., 2017; Kim et al., 2020). Combined, these findings potentially explain why the current study did not observe significant effects of the Med-based diet in males, due to sex differences.

4.2.2 Developmental Stages

In addition to sex differences, CSDS has been validated primarily in adult mice (Berton et al., 2006; Golden et al., 2011) and the tests assessing vulnerability to stressors were developed using adult rodents (Johnston & File, 1991; McCormick & Green, 2013; Palanza, 2001), despite the commonly observed emergence of neuropsychiatric disorders during adolescence (Kessler et al., 2007; Merikangas et al., 2009; Paus et al., 2008). Compared to the established adult brain, the adolescent brain experiences significant dynamic changes in neural development, which can

influence stress reactivity, reasoning, interpersonal interactions, cognitive control of emotions, motivation, and risk-reward appraisal differently than in adults (Andersen, 2003; Romeo & McEwen, 2006; Schneider, 2013). While dietary interventions in adolescence could have mitigated the effects of chronic stress, the goal of the current study was to evaluate the potential of a dietary intervention to enhance resilience to chronic social stress-induced cognitive impairments in a developed adult brain. With that said, future studies should investigate whether early-life exposure to a Med-based diet, prior to or during the onset of a chronic social stressor, could more effectively modulate neurotrophic and neuroinflammatory pathways, thereby potentially promoting resilience to stress-induced cognitive impairments.

4.2.3 Behavioural and Neuroanatomical Considerations

Our study investigated social and non-social cognitive functions, as there is limited literature reporting on cognitive aspects of neuropsychiatric disorders and currently available treatment options are not entirely effective for cognitive impairments (Baldwin et al., 2011; Rush et al., 2006). It is possible that by including depressive- and anxiety-like behaviours in our behavioural outcomes, the current study could have more comprehensively characterized the Med-based diets influence on both cognitive and stress-related affective responses, ultimately providing a more complete assessment of its therapeutic potential. Another limitation of the study is that we investigated only the ventral hippocampus. While the ventral hippocampus has been elucidated as a primary region involved in emotional behaviour and HPA axis regulation, both the dorsal and ventral hippocampus contribute to non-social cognition and emotional behaviours (Almeida et al., 2020; Gulyaeva, 2019b; Hartmann et al., 2019; Riaz et al., 2017; Sant'Ana et al., 2019). Other brain regions, including the prefrontal cortex, nucleus accumbens, amygdala, and the hypothalamus, similarly were not investigated, but participate in the stress

response, as well as in social and non-social cognitive functions (Bossert et al., 2012; Croxson et al., 2011; Ernst & Fudge, 2009; Grossmann, 2013; Ko, 2017; Spencer et al., 2005).

4.2.4 Other Potential Biological Markers Involved

Other important components specifically relating to dietary interventions in the context of mental health, including biomarkers relating to intestinal and blood brain barrier permeability, composition of the gut microbiota, adiposity, circulating levels of corticosterone, pro-inflammatory cytokines or anti-inflammatory cytokines, in addition to ghrelin, were not investigated in the current study but would contribute to our understanding of the complex interactions involved in stress, diet and the MGBA.

4.2.5 Duration of the Dietary Intervention

Experimental mice in the current study had relatively short-term exposure to the dietary intervention prior to social defeat. However, based on previous studies conducted in our lab (Udechukwu, 2024), it was found that a 14-day exposure to the same Med-based diet was sufficient for changing gut microbiota composition. Mice in the current study continued to be fed their dietary intervention throughout social defeat and cognitive testing. Increasing the duration of exposure to the dietary intervention prior to CSDS would further contribute to our knowledge on long-term dietary intervention adherence and mental health.

4.2.6 Baseline Conditions

The CSDS protocol was used to induce alterations in physiology and immunity (Audet et al., 2014; Doney et al., 2023; Szyszkowicz et al., 2017) in the current study. Individuals with neuropsychiatric disorders, however, often present with subclinical inflammation or microbiota imbalances (Cryan et al., 2019; Foster et al., 2021). Future studies could benefit from investigating multi-hit social and non-social stressors, in the context of a Med-based dietary

intervention, for example, combining CSDS with early-life adversity or prior immune stimulation to prime the immune system. These pre-existing challenges could yield a model more reflective of clinical neuropsychiatric conditions, where stress and immune dysfunction are often co-morbid (Hodes et al., 2015; Ménard et al., 2017; Warren et al., 2024), and would allow for a clearer evaluation of whether a Med-based diet can mitigate compounded stress–immune–microbiota interactions and promote resilience to stress-induced cognitive impairments.

4.2.7 Differences in Macronutrient Composition

A potential confounding factor in the current study is the difference in macronutrient composition between the Control and Med-based diets, which may have influenced metabolic, inflammatory, and behavioural outcomes. The Med-based diet was designed based on human dietary patterns and proportionally adapted for mice. The Control diet consisted of 21.5% protein, 60.5% carbohydrates, and 18% fat, whereas the Med-based diet contained 17% protein, 44% carbohydrates, and 39% fat. This distinction is relevant given the contrasting macronutrient profiles, which may differentially affect mouse metabolism and inflammatory responses. Mice are granivores (Kerley & Erasmus, 1991) and tend to have diets higher in carbohydrates and lower in fat (González-Blázquez et al., 2020). The macronutrient proportions of the Med-based diet may thus not have been ideal for mouse metabolic mechanisms, inadvertently compounding the effects of the dietary intervention on metabolic or inflammatory responses. With that said, although the Med-based diet had higher fat and lower carbohydrate proportions, the type of fats derived from the diet were from healthy sources, including olive oil, menhaden oil, and flaxseed oil, which contain high quantities of MUFA's and PUFA's that have been shown to reduce inflammation, not perpetuate it (Fernandes et al., 2020; Méndez & Medina, 2021; Parletta et al., 2019; Rahimlou et al., 2019).

4.2.8 Resveratrol Dosage and Bioavailability

Another limitation of the current study is the dosage of resveratrol. Resveratrol exerts biphasic effects (Calabrese et al., 2010), with low doses promoting positive benefits, including neuroprotection and anti-inflammation (Gambini et al., 2015), while higher doses will negatively promote oxidative stress and cytotoxic effects (Cottart et al., 2010; Shaito et al., 2020). The current study used 0.045 grams of 50% trans-resveratrol for the Med-based diet, which was designed to model dietary supplemental intake rather than a pharmacological dosage, given resveratrol's low oral bioavailability (Walle et al., 2004). Available preclinical literature on resveratrol administration primarily utilize oral gavage or intravenous administration, compared to our dietary-derived trans-resveratrol. One preclinical study done in middle aged C57BL.6NIA mice utilized a standard purified mouse diet (AIN-93G) plus 0.04% of ≥ 98% resveratrol that was mixed to homogeneity during diet manufacturing. In this study, two different concentrations of resveratrol provided mice with an average of 5.2 ± 0.1 and 22.4 ± 0.4 mg kg^{-1} day^{-1}, which correspond to doses considered translatable to humans, and had no significant adverse effects (Baur et al., 2006). In the current study, mice fed the Med-based diet would consume ~2-4 mg/kg/day of resveratrol, which was determined from the quantity of pellets consumed, which is lower than the dosages used in the previous study. Additionally, toxicity studies done in B6C3F1/N mice where 625, 1250, or 2500 mg/kg of resveratrol was administered either through a single intravenous dose or gavage administration found no adverse effects (Mutlu et al., 2020) and had low bioavailability between ~3-6%. In comparison, the European Commission Regulation 2017/2470 specified the maximum daily dose of trans-resveratrol in dietary supplements for adults as 150 mg ("Implementing Regulation - 2017/2470 - EN - EUR-Lex," n.d.). While the Med-based diet contained 0.045 g of trans-resveratrol, the dietary intervention

contained several ingredients with high polyphenolic content. The bioactivity of all polyphenols obtained from the Med-based diet may have positively or negatively influenced cognitive and/or biological outcomes, depending on factors including absorption, competition of polyphenol and fatty acid metabolization (Gabriel & Chinenye, 2023). Future studies should assess the absorption of resveratrol with other polyphenolic compounds, in addition to other bioactive compounds and their derivates to determine their efficacy within dietary interventions.

4.3 General Conclusion

The present study investigated whether a mouse-adapted Med-based dietary intervention could mitigate CSDS-induced cognitive impairments, in addition alterations in pro-inflammatory and neurotrophic factors in the ventral hippocampus. Our study answered our research question, which was that a Med-based dietary intervention could not mitigate the CSDS-induced impairments in social avoidance and preference behaviours. In contrast, although it improved long-term object recognition memory, the Med-based diet increased social avoidance and impaired working and spatial memory in CSDS mice, at least in the current experimental context. In addition, the Med-based dietary intervention, reduced TNF-α and BDFN in the ventral hippocampus of non-stressed mice, without mitigating the stressor-induced increase in NT-3 and reduction in TrkB. Overall, our study demonstrates that a Med-based dietary intervention, at least as developed by our laboratory and in the specific conditions of the current experiment, has limited beneficial effects on social avoidance and preference impairments as well as on neurotrophic alterations in the ventral hippocampus, induced by CSDS in male C57BL/6N mice. These findings indicate that a dietary intervention may influence cognition and hippocampal health differently under chronic social stress, highlighting the need for further

investigation on their potential as adjunctive treatments for cognitive deficits in stress-relate neuropsychiatric disorders.

Supplementary Table 1:

Ingredients (g)	Control	Mediterranean
Casein	223	80
Fish protein isolate	0	18
Egg white	0	9
Beef, cooked	0	40
L-Cystine	3	3
Corn starch	467.4	0
Maltodextrin (for pelleting)	150	125
Wheat starch	0	198.5
Potato starch	0	0
Chickpeas, cooked, dried	0	36
Lentils, cooked, dried	0	36
Sucrose	0	0
Fructose	0	0
Cellulose, BW200	75	14
Inulin	0	5
Pectin	0	0
Beta-glucans	0	5
Soybean oil	70	0
Corn oil	0	0
Menhaden oil	0	9
Butter, Anhydrous	0	5
Flaxseed oil	0	6.5
Olive oil	0	105
Walnuts, dried, powdered	0	20

t-BHQ (antioxidant)	0.0049	0.005
Mineral Mix S10026	10	10
Dicalcium phosphate	13	13
Calcium carbonate	5.5	5.5
Potassium citrate, 1 H_{2O}	16.5	16.5
Vitamin Mix V10001	10	10
Biotin (1%)	0	0.014
Choline Bitartrate	2	2
Cholesterol	0	0
Fruit and Veggie Blend	0	100
Resveratrol (50% trans)	0	0.045
Total	1045.405	872.064
Macronutrient + Fiber composition (g)		
Protein	197	156.4
Carbohydrate	552.9	402.1
Fat	72.7	157.8
Cholesterol	0	0.06
Total fiber	75	55
Insoluble fiber	75	37.8
Soluble fiber	0	18.4
Macronutrient + fiber composition (g%)		
Protein	18.28	17.9
Carbohydrate	52.9	46.1
Fat	7	18.1
Cholesterol	0	0.007
Total fiber	7.2	6.3

Insoluble fiber	7.2	4.3
Soluble fiber	0	2.1
Macronutrient composition (kcal)		
Protein	788	626
Carbohydrate	2212	1608
Fat	654	1420
Total	3654	3654
Macronutrient composition (kcal%)		
Protein	21.5	17
Carbohydrate	60.5	44
Fat	18	39

Supplementary Table 2:

Gene	Gene sequence/Assay ID
Mus GAPDH	Forward: 5'- GGT CGG TGT GAA CGG ATT TG -3'
	Reverse: 5'- TGC CGT GAG TGG AGT CAT ACT G -3'
Mus Actb	Forward: 5'- GAA CCC TAA GGC CAA CCG TG -3'
	Reverse: 5'- GGT ACG ACC AGA GGC ATA CAG G -3'
Mus IL-6	Forward: 5'- ACG GCC TTC CCT ACT TCA CA -3'
	Reverse: 5'- TGC CAT TGC ACA ACT CTT TTC TC -3'
Mus IL-1β	Forward: 5'- TGC CAC CTT TTG ACA GTG ATG -3'
	Reverse: 5'- GTG CTG CTG CGA GAT TTG AA -3'
Mus TNF-α	Forward: 5'- CTC AGC CTC TTC TCA TTC CTG C -3'
	Reverse: 5'- GGC CAT AGA ACT GAT GAG AGG G -3'
Mus BDNF	Forward: 5'- GTC TCC AGG ACA GCA AAG CCA C -3'
	Reverse: 5'- CCT TGT CCG TGG ACG TTT ACT TC -3'
Mus NGF	Forward: 5'- CCA GTG AAA TTA GGC TCC CTG -3'
	Reverse: 5'- CCT TGG CAA AAC CTT TAT TGG G -3'
	Forward: 5'- GGA GTT TGC CGG AAG ACT CTC -3'

Mus NT3	Reverse: 5’- GGG TGC TCT GGT AAT TTT CCT TA -3’
Mus Ntrk2 (TrkB)	Forward: 5’- CAA CCT GCG GCA CAT AAA TTT C -3’
	Reverse: 5’- CAG GAG CAC GTG AAC GGA TTA C -3’
Mus Aif1 (Iba1)	Bio-Rad PrimePCR™ SYBR® Green Assay: qMmuCED0025128
Mus Cx3cr1	Bio-Rad PrimePCR™ SYBR® Green Assay: qMmuCEP0058111

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