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Andrew Kaldas April 10, 2018

Effects of Social Stress and Obesogenic Diet on Prefrontal Cortex, Hippocampus, and Amygdala Structural Development in Juvenile Female Macaques

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Abstract

Effects of Social Stress and Obesogenic Diet on Prefrontal Cortex, Hippocampus and Amygdala Structural Development in Juvenile Female Macaques

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Chronic stress and obesity are modern epidemics, and together they pose a major public health concern by potential synergistic effects predisposing adverse health outcomes including diabetes, cardiovascular disease, and psychopathologies such as anxiety and depression. There is evidence that social stress and highly caloric diets rich in fats and sugars influence both humans and nonhuman primates, producing similar physiological responses and brain structure alterations. This study examined these effects using a highly translational rhesus monkey model of social stress. Rhesus macaques have comparably complicated brain organizations and social structures as those of humans, without confounding factors such as comorbid psychiatric disorders, drug abuse, cognitive awareness or social stigma. The goal of this study was to use an MRI approach to examine the long-term, potentially synergistic effect of postnatal exposure to social stress and to a highly caloric, obesogenic, diet on brain structure of juvenile female macaques. Regions of interest were the prefrontal cortex, hippocampus and amygdala due to their involvement in stress and emotion regulation and their vulnerability to the effects of stress and obesogenic diets. Measures of cortisol levels, calories consumed, and body weights were collected for examination of associations between these potential underlying biological factors and the brain structural outcomes of chronic exposure to stress and obesogenic diet. To minimize potential confounding effects of prenatal environment or heritability, we used a partial cross-fostering design with random assignment of infants to either a high or low ranking foster mother at birth. MRI techniques were used at 16 months to examine the structural effects of chronic

stress and obesogenic diet. This study found increased total brain volume in the obesogenic diet group as well as increased amygdala, hippocampus and prefrontal cortex cerebrospinal fluid volumes in the low ranking group, in comparison to high-ranking animals. These findings suggest that postnatal exposure to a highly caloric diet has long-term global effects on brain size during development while social rank has more region-specific structural effects on the amygdala, hippocampus and prefrontal cortex of female primates.

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Introduction:

Chronic stress is a documented risk factor for a number of adverse health outcomes and psychopathologies, including anxiety, mood and substance abuse disorders, and metabolic syndrome (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Baum & Posluszny, 1999; Gunnar & Quevedo, 2007; Jacobson & Sapolsky, 1991; Juster, McEwen, & Lupien, 2010; Lupien, McEwen, Gunnar, & Heim, 2009; Pervanidou & Chrousos, 2012; Segerstrom & Miller, 2004; Selye, 1955). Obesity, an adverse health outcome associated with chronic stress, contributes to conditions such as diabetes, high blood pressure and cardiovascular disease (NIH, 2017; Scott, McGee, Wells, & Oakley Browne, 2008). Increased Body Mass Index (BMI) in children has also been associated with impaired cognition, mood disorders and psychopathologies including anxiety, particularly among females (Bruehl, Sweat, Tirsi, Shah, & Convit, 2011; Hillman, Dorn, & Bin, 2010; Maayan, Hoogendoorn, Sweat, & Convit, 2011; J. L. Miller et al., 2009). Childhood obesity affects over 12 million children in the United States (CDC, 2017), and gains in adiposity are predicted by childhood risk factors associated with low socioeconomic status, disproportionately affecting demographic minorities (Evans, Fuller-Rowell, & Doan, 2012; NIH, 2017). Altogether, chronic stress and obesity are each modern epidemics, and collectively they pose a major public health concern.

Stressors can be actual or perceived challenges to homeostasis, physical or emotional, that activate autonomic, neuroendocrine and immune systems mediating main metabolic, cognitive and behavioral stress responses (G. P. Chrousos, 2009; G.P. Chrousos & Gold, 1992; E. O. Johnson, Kamilaris, Chrousos, & Gold, 1992; McEwen, 2007; McEwen & Gianaros, 2010; Stratakis & Chrousos, 1995). The neuroendocrine stress response involves activation of two main systems: the Sympathetic Adrenomedullary (SAM) system and Hypothalamic-Pituitary-

Adrenal (HPA) axis (Gazzaniga, Ivry, & Mangun, 2014; Gunnar & Quevedo, 2007). The SAM response is initiated by the autonomic nervous system (ANS), through activation of the sympathetic nervous system and promoting adrenal medullary secretion of epinephrine and norepinephrine to systemic blood circulation. These hormones bind to adrenoreceptors on various organs (e.g. heart) involved in the quick flight/fight stress response.

The HPA axis is activated in parallel to the SAM system in response to threats to the organism, including by signals of homeostatic/systemic disruption (e.g. injury, hemorrhage, infection, extreme cold/heat), or psychogenic stressors (e.g. predator sight, social defeat, exams, public speaking) activating different pathways in the brain that project to and activate neurons in the paraventricular nucleus (PVN) of the hypothalamus to release mainly corticotrophin-releasing hormone (CRH), but also arginine vasopressin (AVP). These hormones stimulate the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary into systemic circulation. ACTH binds to receptors on adrenal cortex cells triggering synthesis and release of glucocorticoids (GCs) such as cortisol (in primates) into circulation (Gunnar & Quevedo, 2007; Herman & Cullinan, 1997). GCs bind glucocorticoid receptors (GRs) acting as ligand-activated transcription factors, causing long-latency and long-acting changes in gene transcription (Ulrich-Lai & Herman, 2009). GCs released by the adrenal cortex also mediate the negative feedback loop that shuts down stress-induced HPA axis activations through GCs binding to GRs in the hypothalamus, pituitary and other brain regions outside the HPA axis, such as the hippocampus and prefrontal cortex, inhibiting synthesis of CRH and ACTH. This GC negative feedback is important to limit damage due to exposure to chronically high levels of GCs, thereby minimizing their catabolic, proteolytic, lipogenic, antireproductive, and immunosuppressive effects (Charmandari, Tsigos, & Chrousos, 2005; Ulrich-Lai & Herman, 2009). Limbic forebrain

regulation of the HPA axis involves structures including 1) the amygdala, which activates the HPA stress response through indirect projections to the PVN, 2) the hippocampus linked to GC-mediated negative feedback, inhibitory action on HPA axis, also through indirect pathways, and 3) the prefrontal cortex (PFC) through direct projections to the hypothalamus, but also through indirect projections to the HPA via interconnections with limbic regions including the amygdala and hippocampus (Herman & Cullinan, 1997; Jacobson & Sapolsky, 1991; Smotherman, Kolp, Coyle, & Levine, 1981; Sullivan et al., 2004; Ulrich-Lai & Herman, 2009).

Although the acute stress response is adaptive, chronic stress can cause detrimental effects, some through attenuation of GC negative feedback on the HPA axis. This GR resistance promoting prolonged GC secretion is associated with HPA axis dysfunction and failure to down-regulate inflammatory responses leading to increased neuroinflammation, cardiovascular disease, diabetes and metabolic syndrome, and brain impacts that cause alterations in neurotransmitter activity affecting emotional regulation, reward processing and behavior (Cohen et al., 2012; Ganzel, Morris, & Wethington, 2010; Haroon, Raison, & Miller, 2012; Makino, Hashimoto, & Gold, 2002; Mora, Segovia, Del Arco, de Blas, & Garrido, 2012; Sanchez, Young, Plotsky, & Insel, 2000; Shekhar, Truitt, Rainnie, & Sajdyk, 2005; Ulrich-Lai & Herman, 2009). Cortico-limbic regions involved in emotional and stress regulation, such as the prefrontal cortex, amygdala and hippocampus are vulnerable to chronic stress (Arnsten, 2009; Buwalda et al., 2005; Gazzaniga et al., 2014; Liston et al., 2006; McEwen, 2016; Radley & Morrison, 2005; Rice & Barone, 2000; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002; Watanabe, Gould, & McEwen, 1992) and have been implicated in stress-related psychopathologies including anxiety and depression (Drevets, Price, & Furey, 2008; Lupien et al., 2009; McEwen, 2007; Shekhar et al., 2005; Shepard, Barron, & Myers, 2000; Vyas et al., 2002).

These limbic and cortical regions seem particularly vulnerable to stress during development, and not just during infancy and early childhood, but also during adolescence which has been attributed to another wave of synaptic remodeling during adolescent development (Bourgeois, Goldman-Rakic, & Rakic, 1994; Chareyron, Lavenex, Amaral, & Lavenex, 2012; Koss, Belden, Hristov, & Juraska, 2013; Rakic & Nowakowski, 1981; Rice & Barone, 2000), and these prolonged developmental processes have been found to increase vulnerability to detrimental environmental factors, including chronic stress and obesogenic diets. The amygdala, for example, undergoes increased dendritic arborization due to chronic stress, and increased amygdala volume has been associated with many stress-related disorders (Buwalda et al., 2005; Drevets et al., 2008; Gogtay et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Lupien et al., 1998; McEwen, 2016; McEwen & Gianaros, 2010; Vyas et al., 2002; Watanabe et al., 1992). Inversely, hippocampal dendritic remodeling under conditions of chronic stress and inflammation is associated with dendritic atrophy and debranching (Magariños, McEwen, Flügge, & Fuchs, 1996; Palin et al., 2004; Vyas et al., 2002) resulting in smaller hippocampal volumes reported in literature in conditions of chronic stress or early life stress (Bruehl et al., 2011). Protracted PFC development increases vulnerability to environmental factors such as chronic stress causing spine loss and decreased PFC dendritic arborization (Ansell et al., 2012; Arnsten, 2009; Bourgeois et al., 1994; Knickmeyer et al., 2010; Liston et al., 2006; McEwen & Gianaros, 2010; Noble, Houston, Kan, & Sowell, 2012; Radley & Morrison, 2005), which as described above for the hippocampus, could explain the smaller PFC volumes previously reported in situations of chronic stress or models of early life stress (Ansell et al., 2012; Arnsten, 2009).

Connections between the PFC and amygdala are extensive, with the central nucleus of the amygdala (CeA) known to project directly to the brainstem and indirectly to the hypothalamus driving behavioral (e.g. fear responses), autonomic (sympathetic and SAM activations), HPA axis and somatomotor responsivity and also projects to the neuromodulatory systems underlying dopamine (DA), acetylcholine, serotonin and norepinephrine function (Gazzaniga et al., 2014; Kim et al., 2011; Pitkänen, Pikkarainen, Nurminen, & Ylinen, 2000; Veinante & Freund-Mercier, 1998). The medial PFC is involved in integration of cognitive emotional information, the orbitofrontal cortex is involved in goal-directed motivational and inhibitory control of behavior, and the ventromedial prefrontal cortex (vmPFC) has been shown to regulate amygdala activity pertinent to stress and emotional responses (Delgado, Nearing, Ledoux, & Phelps, 2008; Gazzaniga et al., 2014; Maayan et al., 2011; Radley & Morrison, 2005; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). The hippocampus is involved in learning and memory processes, including storage of emotional information influencing interpretation and reaction to events with connections to the hypothalamus, amygdala and prefrontal cortex(Gazzaniga et al., 2014; Jacobson & Sapolsky, 1991; Phelps, 2004; Preston & Eichenbaum, 2013). Interactions between hippocampus, amygdala and prefrontal cortex have been documented in stress and emotional regulation (Delgado et al., 2008; Kim et al., 2011; Phelps, 2004; Preston & Eichenbaum, 2013; Wager et al., 2008). Altogether, this evidence suggests that stress-related disruption of amygdala, hippocampus and PFC circuitry can affect emotional, stress and motivational/reward responses that may underlie related disorders and psychopathologies.

Chronic stress is also a documented risk factor for childhood obesity (Evans et al., 2012), and stress may predispose emotional overeating in part by acting on reward circuitry (Epel et al., 2004; Izzo, Sanna, & Koob, 2005; Michopoulos, 2016; Richard, Castro, Difeliceantonio,

Robinson, & Berridge, 2013; Shively, Grant, Ehrenkaufer, Mach, & Nader, 1997). Stress and reward brain circuits are interconnected such that exposure to rewarding stimuli (e.g. consumption of palatable food higher in fats and sugars) has been found to lead to release of CRH and activation of CRH Receptor 1 (CRHR1) which has been shown to increase reward-seeking behavior (Dallman et al., 2003; Michopoulos, 2016; Ulrich-Lai & Herman, 2009). Elevated GC levels and CRHR1 activation due to stressors or consumption of palatable foods may predispose overeating and other mood disorders by altering mesolimbic D2R levels in brain reward circuits (Izzo et al., 2005; P. M. Johnson & Kenny, 2010; Michopoulos, 2016; Russo & Nestler, 2013). The PFC, involved in the meso-corticolimbic pathway, is a key mediator of reward processing through connections with reward areas, such as the ventral striatum, including the nucleus accumbens (Haber, 2016; Hyman, Malenka, & Nestler, 2006; Wise, 2002) and coordinates activity of limbic regions such as the amygdala and hippocampus that are highly interconnected with the mesolimbic DA pathway.

Increased intake of high caloric density foods enhances the stress response and is associated with increased weight-gain shown to elicit hyperresponsiveness of the HPA axis and related increased release of GCs and pro-inflammatory cytokines, adverse health outcomes such as metabolic syndrome associated with high blood pressure, high blood sugar, excess adiposity and abnormal cholesterol levels, and psychopathologies including anxiety and mood disorders (Epel et al., 2004; Hillman et al., 2010; Legendre & Harris, 2006; Pasquali et al., 2002; Scott et al., 2008). Subjects exposed to chronic social stress and a high caloric diet have been shown to display greater caloric intake and reduced glucocorticoid negative feedback associated with increased risk for obesity and psychopathology (Michopoulos, 2016).

Obesity has also been associated with impaired cognition, atrophy of frontal lobes, anterior cingulate gyrus and hippocampus, and disinhibited eating associated with impairments in reward processing, executive function and impulse control. (Bruehl et al., 2011; Contreras-Rodriguez, Martin-Perez, Vilar-Lopez, & Verdejo-Garcia, 2017; Maayan et al., 2011; J. L. Miller et al., 2009; Raji et al., 2010). These regions overlap with regions involved in stress, reward and emotional regulation, such as the PFC and hippocampus, and have been demonstrated to cause downstream effects on interconnected structures such as the amygdala (Adam & Epel, 2007; Ansell et al., 2012; Arnsten, 2009; Hyman et al., 2006; Liston et al., 2006; McEwen & Gianaros, 2010; Radley & Morrison, 2005; Wise, 2002) by acting to suppress or enhance activity depending on contextual information (Kim et al., 2011; Wager et al., 2008). Through overlapping circuitry involved in stress, reward and addiction, over-eating may exacerbate the effects of chronic stress, which may perpetuate further non-homeostatic eating and subsequent weight gain along with comorbid disorders (Adam & Epel, 2007; Lutter & Nestler, 2009; Volkow, Wang, Fowler, & Telang, 2008).

Animal models are useful for disentangling the often comorbid impact of chronic stress and obesity effects reported in human populations and for examining underlying biological mechanisms (Brunner, 1997; Buwalda et al., 2005; Machado & Bachevalier, 2003; Radley & Morrison, 2005; Sapolsky, Uno, Rebert, & Finch, 1990; Uno, Tarara, Else, Suleman, & Sapolsky, 1989; Wilson, 2016). In particular, nonhuman primates (NHPs) are highly translational animal models of social stress not confounded by comorbid conditions typical of human studies (e.g. psychiatric disorders, drug abuse), cognitive awareness or social stigma. NHP species, such as rhesus monkeys, are model organisms with high translational value due to

biological and developmental similarities and comparably complicated brain organizations and social structures with humans (Jovanovic, 2016; Wilson, 2016).

Among NHP models, female rhesus monkeys constitute a valuable model to understand the impact of chronic psychosocial stress on female neurobehavioral development. Female macaques live in troops with matriarchal and matrilineal social structure, establishing complex long-term relationships between family members with influences pertaining to allocation of resources or defense against predation in nature (Silk, 2002). Strict matrilineal social hierarchies wherein female offspring adopt the rank of their mother influence social interactions and the social environment (Suomi, 2005), with social rank strictly enforced by aggression from more dominant to more subordinate families/animals (Bernstein, 1976). Thus, low social status in adult female macaques has been associated with more frequent exposure to social stressors such as aggression and trauma, resulting in elevated levels of GCs due to activations of stress neuroendocrine systems such as the HPA axis (Abbott et al., 2003; Godfrey, Pincus, & Sanchez, 2016; Kohn et al., 2016; Michopoulos, Toufexis, & Wilson, 2012; Sapolsky, 2005). Social subordination in females stress also influences food intake, increasing the preference for highly caloric diets and leading to overeating and the development of an obese phenotype in subordinate compared to dominant animals, at least during adulthood (Arce, Michopoulos, Shepard, Ha, & Wilson, 2010; Godfrey et al., 2016; Michopoulos, 2016; Michopoulos et al., 2012).

It is unclear, though, whether and how social subordination stress and exposure to an obesogenic diet may interact and function synergistically during female development to alter brain structure and function of the corticolimbic circuits reviewed above. Although environmental insults such as exposure to stress and highly caloric diets seem to impact

development of emotional and stress regulatory and reward circuits in the brain, underlying the mechanisms and synergistic effects of stress and obesogenic diet are not fully understood.

Understanding the specific and combined neurodevelopmental effects of chronic social stress and exposure to a high caloric (obesogenic) diet is important clinically, but difficult to study in a prospective and longitudinal way in humans. The main **goal** of the present NHP study is to use an MRI approach to examine the long-term, potentially synergistic effect of stress and the obesogenic diet (and likely increased fat mass) on brain structure once female macaques reach the juvenile, prepubertal, period (16 months of age). We hope to gain a better understanding of mechanisms underlying stress- and obesity-related disorders potentially related to alterations in brain structural development and psychopathologies to ultimately contribute to innovations in healthcare and social policy.

We hypothesize that **1)** animals exposed to social subordination will experience a greater degree of chronic social stress associated with elevated hair cortisol levels and **2)** will show smaller PFC and hippocampus volumes and greater amygdala volume relative to those of dominant subjects, and **3)** exposure to a high caloric density obesogenic diet will result in increased caloric intake and increased body weight, and **4)** will be associated with smaller PFC and hippocampal volumes in comparison to animals in the low caloric dietary condition, with opposite effects expected for amygdala volume, and **5)** subordinates with access to an obesogenic diet (Choice condition) will experience a synergistic effect of stress and diet, exacerbating effects hypothesized above including elevated hair cortisol levels, and increased amygdala volume as well as decreased PFC and hippocampal volumes.

Methods:

Subjects –

Forty-four female rhesus macaques (*Macaca mulatta)* born during spring 2014, 2015 or 2016 were originally assigned to the study. All subjects were born and raised at the Yerkes National Primate Research Center Field Station in Lawrenceville, GA, reared by dams in social groups comprising 1-2 males, 30-60 females and their offspring. Subjects were socially housed in outdoor enclosures three-quarters of an acre in size each with an attached climate-controlled indoor enclosure.

Although data was collected longitudinally in these animals since birth through 16 months of age (juvenile, prepubertal), in this study I focus only on the 16-month structural MRI data. Six subjects were excluded from analyses due to health-related issues (e.g. chronic unthriftiness early in life) that resulted in their release from the study. Therefore, a total number of 38 subjects were included in analyses for this study. All studies were carried out in accordance with the Animal Welfare Act and the U.S. Department of Health and Human Services "Guide for the Care and Use of Laboratory Animals" and were approved by the Emory University Institutional Animal Care and Use Committee (IACUC).

Half of the subjects were reared by their biological mother, and the other half were randomly assigned at birth (or within 48 hours postpartum) to either a low or high-ranking foster mother using a cross-fostering experimental design using well-established procedures (Drury et al., 2017; B.R. Howell, Neigh, & Sanchez, 2016; Pincus, 2018) to disentangle the effect of postnatal social rank experience from that of potential social rank-related heritable factors. This design allows for the examination of the impact of postnatal conditions while controlling for maternal, prenatal conditions and heritable effects (Phelan et al., 2011; Schlotz & Phillips, 2009).

Newborn subjects weighing less than 450g were excluded from the study to avoid effects of prematurity and low birth weight on brain development.

Cross fostered infants assumed the social status of their foster mothers similar to rhesus offspring assuming the social status of their biological mothers (Bernstein, 1976; Kutsukake, 2000; Spencer-Booth, 1968). The final sample size included 19 dominant (high ranking) mother-infant pairs and 19 subordinate (low-ranking pairs), with approximately half of pairs in each group assigned to the low calorie diet (LCD) or Choice diet that included access to a high caloric density (HCD) diet and the LCD option (see details in the feeding section below).

Rank Determination –

Prior to birth of the subjects examined in this study, social status of individuals in each group was determined from formal group checks with outcomes of dyadic agonistic interactions recorded in a matrix and analyzed (Altmann, 1962; Bernstein, 1976). In an interaction, the subordinate animal is identified as the one producing an unequivocal submissive behavior such as a withdrawal or fear grimace in response to another (more dominant) animal's approach or aggressive act. Dam social rank was therefore defined based on the subordinate animal's submissive behavior rather than that of the dominant animal (e.g. contact or non-contact aggression). Dams selected for this study were from families at the extremes of the social hierarchy within their enclosures. Dominant-ranking dams were recruited from families ranking in the top third of the social hierarchy, and subordinate-ranking dams were recruited from families in the bottom third of the hierarchy. Exclusionary criteria for Dam selection included primiparous females and females with histories of infant physical abuse or neglect.

Individual/family rankings within social hierarchies were evaluated each month to monitor and account for group changes in social structure. Relative ranks of infant subjects were calculated as ratios of postnatal dams' rank divided by the number of (female) animals older than three years of age in the female social hierarchy of each enclosure (i.e. if highest rank was 1/100, lowest rank would be 100/100).

Diet Intervention –

Subjects were randomly assigned to either a low calorie diet (LCD) condition or given access to both an LCD and high caloric-density (HCD) diets as part of a "choice" dietary condition (Moore, Michopoulos, Johnson, Toufexis, & Wilson, 2013; Wilson et al., 2008). Prenatal dietary environment was controlled for by maintaining all pregnant females on LCD-only diet during gestation. The LCD used in this study was LabDiet Monkey Diet 503A, a pelleted standard monkey chow from Purina Mills International, St. Louis, MO, containing 3.46 kcals/gram (14% fat, 18% protein and 65% carbohydrate). The HCD pellets used in this study contained 4.25 kcal/gram (30% fat, 20% protein and 50% carbohydrate). It should be noted the HCD chow was comprised of more sugar carbohydrates (29.84% of total calories) relative to the LCD chow (6.11% of total calories). LCD and HCD chows contain similar amounts of vitamins and minerals.

Food pellets were available 24/7 and were dispensed from automated feeders activated with radio-frequency identification (RFID) chips subcutaneously embedded in the subjects' wrists. Dams received RFID chips prior to the onset of this experiment and had access to the LCD feeders prenatally; however, the access to the HCD diet feeders was activated only after they gave birth. All non-subject animals in each social group had access to the LCD but were

restricted from accessing the HCD. Infant subjects received RFID chips at six weeks of age before infants transition to solid food. Prior to weaning, exposure to the HCD during the first six postnatal weeks in infants in the Choice condition was through the mother's milk. Automated feeders were designed to record subjects' RFID, dispense a single pellet of chow at a time and record each subject's caloric intake (Pincus, 2018; Wilson et al., 2008). This design has been shown to provide monkeys the ability to consume food as desired from both a HCD feeding station and three LCD feeding stations, allowing researchers to systematically control access to food types and maintain established experimental diet conditions. Although this set up is not naturalistic for rhesus monkey societies (e.g., lacks resource competition, HCD diet with high fat % composition), the choice (HCD plus LCD) condition offers translational value by modeling common human dietary environment with access to less healthy dietary alternatives to relatively more healthy diet options. Subjects were also weighed at 16 months at the Yerkes National Primate Research Center Field Station. Kcal consumption was calculated as the cumulative amount of kcals (LCD + HCD) consumed since birth.

Hair Cortisol –

High cortisol accumulation in hair can be used as a marker of stress exposure over an extended period of time (Davenport, Tiefenbacher, Lutz, Novak, & Meyer, 2006; Meyer, Novak, Hamel, & Rosenberg, 2014). Approximately one square inch of hair was shaved from the back of subjects' necks at 16 months of age. Samples were stored at -80 degrees Celsius until assayed. Based on previously established protocols (Davenport et al., 2006; Meyer et al., 2014), each sample was weighed, washed twice in isopropanol to remove external contamination, dried, ground into a fine powder using a Retsch ball mill, and then extracted with methanol overnight.

The methanol was evaporated and the residue was redissolved in the assay buffer. Cortisol concentrations in hair were measured as pg/mg hair units using the Salimetrics (Carlsbad, CA) enzyme immunoassay kit (cat. # 1-3002) according to the manufacturer's directions.

Neuroimaging –

Structural MRI scanning took place at the Yerkes National Primate Research Center Imaging Center, requiring each subject to be transported from the Yerkes National Primate Research Center Field Station to the YNPRC Imaging Center the day before image acquisition. MRI was performed at 16 months of age using a 3T Siemens Magnetom TRIO system (Siemens Med. Sol., Malvern, PA, USA) and an 8-channel phase array knee coil. Both T1 and T2-weighted structural MRI scans were acquired during the same scanning session. The T1-weighted structural MRI scans were collected using a 3D magnetization prepared rapid gradient echo (3D-MPRAGE) parallel imaging sequence (TR/TE = 2600/3.46msec, FoV: 116mm, voxel size: $0.5mm^3$ isotropic, 8 averages, GRAPPA, R=2). T2-weighted MRI scans were collected in the same direction as the T1 images (TR/TE = 3200/373msec, FoV: 128mm, voxel size: $0.5mm^3$ isotropic, 3 averages, GRAPPA, R=2) in order to assist in the identification of the brain tissue classes by improving contrast of the borders between gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), and aid in the delineation of the regions of interest (Knickmeyer et al., 2010). Regions of interest (ROIs) include cortico-limbic areas with critical involvement in emotion and stress regulation, executive function, inhibitory control of behavior, reward and social behavior: Prefrontal Cortex (PFC), Hippocampus and Amygdala.

In order to minimize motion artifacts scans were collected under isoflurane anesthesia (1% to effect, inhalation) following induction with telazol (3-4 mg/kg, intramuscular) and

intubation. Animals' physiological parameters were monitored during scanning with an oximeter, electrocardiograph, rectal thermomistor and blood pressure monitor. Dextrose/NaCl (0.45%) was administered intravenously to maintain hydration throughout the scanning session, and subjects were placed on an MRI-compatible heating pad to maintain temperature. Subjects were scanned in the same supine placement and orientation through placement on a custom-made head-holder with ear bars and a mouth piece to prevent head movements. To indicate the right side of the brain, a vitamin E capsule was taped to each subject's right temple during scanning. After scanning, subjects were monitored until full recovery before being returned back to social housing.

MRI Data Processing, Analysis and ROI Volume Computation –

Structural data was analyzed using the AutoSeg (version 3.3.2) software application pipeline – developed by our collaborators at the Neuro Image Research and Analysis Laboratories of University of North Carolina – to perform automatic brain tissue structural segmentation into gray matter (GM), white matter (WM), or cerebrospinal fluid (CSF), as well as parcellation into selected ROIs to compute their volumes (Liu et al., 2015; Shi et al., 2016). Images are registered to population-based T1- and T2-MRI brain atlases (Liu et al., 2015; Shi et al., 2016). AutoSeg corrects image intensity inhomogeneity with N4 bias field correction, accounting and correcting for bias in field signal intensities that result in gradual variations in the image intensities within the same tissue due to radiofrequency (RF) coil imperfections. Then, AutoSeg performs image registration to atlas space using BRAINSFit for rigid body and affine registration (Liu et al., 2015), aligning the subject brain image to age-specific, population-based T1- and T2-MRI atlases using a reference space algorithm (Styner et al., 2007). For this project,

subjects' images were registered to the 12-month UNC-Emory juvenile rhesus brain T1- and T2-MRI atlases which are very close in GM/WM/CSF signal contrast to our 16-month subjects' MRI images (Shi et al., 2016). These 12-month T1 and T2 atlases were built from 48 juveniles scanned at YNPRC, in collaboration with members from UNC using deformable registration tools in the Advanced Normalization Tools (ANTs) software (Liu et al., 2015; Shi et al., 2016).

Once the subject's T1- and T2- MRI images were in atlas space, AutoSeg uses an automatic atlas-based classification (ABC) tissue segmentation for probabilistic tissue class classification of each subject's image into GM, WM and CSF brain tissue or non-brain tissue (e.g. skull, vessels, muscle) and to remove non-brain tissue for analysis (referred to as "skull-stripping"). The program does this by using information on T1 and T2 image signal intensities and by warping the atlas-specific tissue priors (i.e. weight values) from the UNC-Emory Atlas (Fig. 1) into the subject to label each voxel via probabilistic maps for each tissue type (Liu et al., 2015). The first round is done with skull and the 2nd round is done after skull stripping, in which all non-brain tissue is identified and removed from analyses. Skull-stripping is automatically performed by AutoSeg, although this step typically requires manual editing with a program such as ITK-snap to improve results of another round of ABC GM, WM and CSF tissue segmentation with the manually skull-stripped images (Carpenter, 1983; Styner et al., 2007; Yushkevich et al., 2006) and lobar parcellations (described next). The next step is the cortical lobar (PFC) and subcortical ROI parcellations (amygdala, hippocampus) during which AutoSeg uses ANTS registration (Liu et al., 2015) of the ROIs in the skull-stripped version of the brain atlas to the skull-stripped subject image. The tissue class segmentations generated (GM, WM, CSF) are also applied to the cortical parcellations to generate WM, GM and CSF of each cortical region (see Fig. 2). In the final step, AutoSeg computes volumes for all ROIs in this study: volumes of right

and left PFC (GM, WM, CSF and total PFC volume), right and left amygdala, right and left hippocampus. Total Intracranial Volume (ICV) was arithmetically calculated (total GM + total WM + total CSF) as a measure of total brain volume/size. Volumes are reported in cubic millimeters for all regions.

Neuroanatomical Definition of Regions of Interest (ROI) in the Atlas –

The atlas ROIs have been described previously (Knickmeyer et al., 2010; Shi et al., 2016). The amygdala boundary was defined rostrally by the anterior limit of the periamygdaloid cortex, posteriorly by the hippocampus, ventrally by CSF, ventrolaterally by WM (Amaral & Basset, 1989; Price, 1987), and when CSF was not visible due to low contrast, the ventromedial border was defined by the rhinal fissure. The PFC border was defined anteriorly and superiorly by CSF, posteriorly and inferiorly by the Sylvian fissure and the arcuate sulcus also serving as the superior boundary posteriorly, and medially by the interhemispheric fissure. The hippocampal boundaries followed previous anatomical definitions (Rosene & Hoesen, 1987), delineated superiorly by the lateral ventricle and temporal horn, except at the subiculum where the boundary was marked by WM. WM also marks the inferior boundary, separating the hippocampus from the entorhinal cortex. Borders are defined anteriorly by the lateral ventricle, temporal horn and amygdala, posteriorly by the lateral ventricle and WM, and medially by CSF (Knickmeyer et al., 2010).

Statistical Analyses –

SPSS (version 24.0) was used for statistical analyses. The threshold for significance was set at $p < 0.05$, although statistical trends are also reported for $0.1 > p > 0.05$. If the assumption

of homogeneity was violated, the results were presented using the corrected Greenhouse-Geisser values for sphericity not assumed.

Total Intracranial Volume (ICV), as well as total GM, total WM and total CSF volumes were analyzed using a Two Way ANOVA with Rank (High – Dominant –, Low – Subordinate –) and Diet condition (LCD, Choice (LCD + HCD)) as fixed factors, to determine main or interaction effects of Rank and Diet on total ICV, GM, WM or CSF volumes. Due to the small sample size of this dataset I was underpowered to examine the additional potential effects of biological mother rank or crossfostering factors in the statistical models. However, the potential confounding effect of these two factors was controlled for by counterbalancing them across all our experimental groups.

Effects of Rank and Diet condition on PFC volumes (GM, WM, CSF and total), as well as on hippocampus and amygdala volumes were analyzed using repeated measures (RM) ANOVA with Rank (High, Low) and Diet condition (LCD, Choice) as fixed factors and Hemisphere laterality (Left, Right) as the repeated measures factor. In cases when a significant interaction effect was detected, post-hoc pairwise comparisons of the means (Tukey's) were used. To ensure that Rank and/or Diet condition regional effects were not due to variation in brain size (defined as ICV here), when an effect of Diet condition or Rank was detected on ICV, RM analysis of covariance (ANCOVA) was utilized entering ICV as a covariate in the statistical models for each of the ROIs (amygdala, hippocampus, PFC).

Hair Cortisol collected at 16 months and accumulated from 12-16 months, total cumulative kcal consumption (LCD + HCD kcals) since infancy, cumulative LCD kcal consumption and HCD kcal consumption, and Body Weight were analyzed using Two Way ANOVAs with Rank and Diet condition as fixed factors to determine main or interaction effects

of Rank and Diet on cortisol, feeding data and body weight. Due to high variance in Dominant subjects' Hair Cortisol as compared to that of Subordinates, Hair Cortisol data was also log 10 transformed and analyses re-ran in the log-transformed data.

Bivariate Pearson correlations were also run between brain and cortisol/calorie intake/body weight measures to examine potential associations between measures. These correlations incorporate analyses using both untransformed and log base 10 transformed hair cortisol data. Correlations were also run with relative rank as a continuous variable.

Results:

Structural MRI Measures –

ICV and total GM, WM and CSF volumes

Two Way ANOVA revealed a main effect of Diet Condition ($F_{1,34}$=7.29, p=0.01, $\eta^2_{partial}$= 0.18) on ICV with the Choice Diet condition (LCD + HCD) showing greater ICV relative to the LCD condition. No other main effects of Rank ($F_{1,34}$=0.01, p=0.94, $\eta^2_{partial}$=2x10^{-4}) or interaction effects of Diet by Rank ($F_{1,34}$=0.17, p=0.69, $\eta^2_{partial}$= 0.01 were detected on total ICV (see Fig. 3). Because a main effect of Diet was detected on ICV, RM ANCOVA adding ICV as a covariate was used to analyze results for the ROI volumes (PFC, amygdala, and hippocampus).

Two Way ANOVA also revealed a main effect of Diet ($F_{1,34}$=4.47, p=0.04, $\eta^2_{partial}$= 0.12) on total WM volume with the Choice Diet condition showing greater average total WM volume relative to the LCD condition. No other main effects of Rank ($F_{1,34}$=0.39, p=0.54, $\eta^2_{partial}$= 0.01) or interaction effects of Diet by Rank ($F_{1,34}$=0.01, p=0.92, $\eta^2_{partial}$= 3x10^{-4}) were detected on total WM volume (see Fig. 4).

An additional main effect of Diet ($F_{1,34}$=7.27, p=0.01, $\eta^2_{partial}$= 0.18) was detected on total GM volume with the Choice Diet condition showing greater average total GM volume relative to the LCD condition. No other main effects of Rank ($F_{1,34}$=4x10^{-3}, p=0.95, $\eta^2_{partial}$= 1x10^{-4},) or interaction effects of Diet by Rank ($F_{1,34}$=0.27, p=0.61, $\eta^2_{partial}$= 8x10^{-3}) were detected on total GM volume (see Fig. 5).

No main effects of Diet ($F_{1,34}$=2.82, p=0.10, $\eta^2_{partial}$= 0.08), Rank ($F_{1,34}$=0.50, p=0.48, $\eta^2_{partial}$= 0.02,) or interaction effects of Diet by Rank ($F_{1,34}$=0.06, p=0.80, $\eta^2_{partial}$= 2x10^{-3}) were detected on total CSF volume (see Fig. 6).

Amygdala Volume

RM ANCOVA (controlling for ICV as a covariate) revealed a main effect of Rank ($F_{1,33}$=6.75, p=0.01, $\eta^2_{partial}$= 0.17) on Amygdala volume with the Low Rank (subordinate) condition showing bilaterally greater (right and left hemisphere) Amygdala volumes relative to the High Rank (dominant) condition. No other main effects of Diet ($F_{1,33}$=2.25, p=0.14, $\eta^2_{partial}$= 0.06), Hemisphere ($F_{1,33}$=1.21, p=0.28, $\eta^2_{partial}$= 0.04), or interaction effects of Diet by Rank ($F_{1,33}$=0.47, p=0.50, $\eta^2_{partial}$= 0.01), Diet by Hemisphere ($F_{1,33}$=1.34, p=0.26, $\eta^2_{partial}$= 0.04), Rank by Hemisphere ($F_{1,33}$=7x10^{-5}, p=0.99, $\eta^2_{partial}$= 2x10^{-6}), or Diet by Rank by Hemisphere ($F_{1,33}$=2.31, p=0.14, $\eta^2_{partial}$= 0.07) were detected on amygdala volume (see Fig. 7).

Hippocampus Volume

RM ANCOVA (controlling for ICV as a covariate) revealed a main effect of Rank ($F_{1,33}$=13.05, p=1x10^{-3}, $\eta^2_{partial}$=0.28) on Hippocampal volume with the Low Rank condition showing bilaterally greater Hippocampal volumes relative to the High Rank condition. No other main effects of Diet ($F_{1,33}$=0.80, p=0.38, $\eta^2_{partial}$= 0.02), Hemisphere ($F_{1,33}$=0.18, p=0.67, $\eta^2_{partial}$= 0.01), or interaction effects of Diet by Rank ($F_{1,33}$=1.51, p=0.23, $\eta^2_{partial}$= 0.04), Diet by Hemisphere ($F_{1,33}$=0.10, p=0.76, $\eta^2_{partial}$=3x10^{-3}), Rank by Hemisphere ($F_{1,33}$=0.37, p=0.55, $\eta^2_{partial}$= 0.01), or Diet by Rank by Hemisphere ($F_{1,33}$=1.85, p=0.18, $\eta^2_{partial}$= 0.05) were detected on hippocampus volume (see Fig. 8).

PFC Volume

RM ANCOVA analyses on total PFC volume (controlling for ICV as a covariate) revealed no main effects of Diet ($F_{1,33}$=0.17, p=0.69, $\eta^2_{partial}$= 0.01), Rank ($F_{1,33}$=0.59, p=0.45,

$\eta^2_{partial}$=0.02), Hemisphere ($F_{1,33}$=2x10^{-4}, p=0.99, $\eta^2_{partial}$= 5x10^{-6}), or interaction effects of Diet by Rank ($F_{1,33}$=0.03, p=0.87, $\eta^2_{partial}$= 8x10^{-4}), Diet by Hemisphere ($F_{1,33}$=0.37, p=0.55, $\eta^2_{partial}$= 0.01), Rank by Hemisphere ($F_{1,33}$=2.56, p=0.12, $\eta^2_{partial}$= 0.07), or Diet by Rank by Hemisphere ($F_{1,33}$=1.82, p=0.19, $\eta^2_{partial}$= 0.05) on PFC Total Volume (see Fig. 9).

A similar RM ANCOVA model for PFC WM volume (controlling for ICV as a covariate) revealed no main effects of Diet ($F_{1,33}$=1x10^{-3}, p=0.97, $\eta^2_{partial}$= 4x10^{-5}), Rank ($F_{1,33}$=0.13, p=0.73, $\eta^2_{partial}$= 4x10^{-3}), Hemisphere ($F_{1,33}$=2.77, p=0.11, $\eta^2_{partial}$= 0.08), or interaction effects of Diet by Rank ($F_{1,33}$=0.52, p=0.48, $\eta^2_{partial}$= 0.02), Diet by Hemisphere ($F_{1,33}$=4x10^{-3}, p=0.95, $\eta^2_{partial}$= 1x10^{-4}), Rank by Hemisphere ($F_{1,33}$=0.01, p=0.95, $\eta^2_{partial}$= 1x10^{-4}), or Diet by Rank by Hemisphere ($F_{1,33}$=0.15, p=0.70, $\eta^2_{partial}$= 0.01) on PFC WM volume (see Fig. 10).

RM ANCOVA analyses for PFC GM volume (controlling for ICV as a covariate) revealed no main effects of Diet ($F_{1,33}$=0.01, p=0.92, $\eta^2_{partial}$= 3x10^{-4}), Rank ($F_{1,33}$=1x10^{-4}, p=0.99, $\eta^2_{partial}$= 4x10^{-6}), Hemisphere ($F_{1,33}$=1.14, p=0.29, $\eta^2_{partial}$= 0.03), or interaction effects of Diet by Rank ($F_{1,33}$=0.22, p=0.88, $\eta^2_{partial}$= 6x10^{-4}), Diet by Hemisphere ($F_{1,33}$=2.58, p=0.12, $\eta^2_{partial}$= 0.07), Rank by Hemisphere ($F_{1,33}$=2.51, p=0.12, $\eta^2_{partial}$= 0.07) or Diet by Rank by Hemisphere ($F_{1,33}$=0.11, p=0.75, $\eta^2_{partial}$= 3x10^{-4}) on PFC GM volume (see Fig. 11).

RM ANCOVA statistical analyses for PFC CSF (controlling for ICV as a covariate) revealed a main effect of Rank ($F_{1,33}$=5.26, p=0.03, $\eta^2_{partial}$= 0.14) on PFC CSF volume with bigger PFC CSF volumes in Dominant than in Subordinate animals. No other main effects of Diet ($F_{1,33}$=0.69, p=0.41, $\eta^2_{partial}$= 0.02), Hemisphere ($F_{1,33}$=0.10, p=0.75, $\eta^2_{partial}$= 3x10^{-3}), or interaction effects of Diet by Rank ($F_{1,33}$=0.25, p=0.62, $\eta^2_{partial}$= 0.01), Diet by Hemisphere ($F_{1,33}$=0.51, p=0.48, $\eta^2_{partial}$= 0.02), or Rank by Hemisphere ($F_{1,33}$=1.02, p=0.32, $\eta^2_{partial}$= 0.03) were detected on PFC CSF volume. However, a trend for a Diet by Rank by Hemisphere

interaction effect was detected ($F_{1,33}$=3.03, p=0.09, $\eta^2_{partial}$= 0.08) with specific effects of Rank in the Choice group observed in the right hemisphere (see Fig. 12).

Hair Cortisol –

Two Way ANOVA revealed no main effects of Diet ($F_{1,34}$=1.41, p=0.24, $\eta^2_{partial}$= 0.04), Rank ($F_{1,34}$=0.18, p=0.67, $\eta^2_{partial}$= $5x10^{-3}$,) or interaction effects of Diet by Rank ($F_{1,34}$=2.02, p=0.16, $\eta^2_{partial}$= 0.06) on hair cortisol levels (see Fig. 13). Following hair cortisol data log10 transformation, Two Way ANOVA revealed no main effects of Diet ($F_{1,34}$=0.48, p=0.49, $\eta^2_{partial}$= 0.01), Rank ($F_{1,34}$=0.48, p=0.49, $\eta^2_{partial}$= 0.01,) or interaction effects of Diet by Rank ($F_{1,34}$=1.06, p=0.31, $\eta^2_{partial}$= 0.03) on hair cortisol levels.

Total kcal Consumption –

Two Way ANOVA revealed main effects of Diet ($F_{1,31}$=9.63, p=$4x10^{-3}$, $\eta^2_{partial}$= 0.24) and Rank ($F_{1,31}$=8.01, p=$8x10^{-3}$, $\eta^2_{partial}$= 0.21) on total kcal consumption, with the animals in the HCD condition consuming more cumulative calories than the LCD group, and Dominant animals consuming more calories than subordinates. No interaction effects of Diet by Rank ($F_{1,31}$=0.04, p=0.85, $\eta^2_{partial}$= $1x10^{-3}$) were detected on kcal consumption (see Fig. 14).

LCD kcal Consumption –

Two Way ANOVA revealed main effects of Diet ($F_{1,31}$=25.63, p=$2x10^{-5}$, $\eta^2_{partial}$= 0.45) and Rank ($F_{1,31}$=5.06, p=0.03, $\eta^2_{partial}$= 0.14) on LCD kcal consumption, with the animals in the LCD condition consuming more cumulative LCD calories than those in the Choice dietary condition, and Dominant animals consuming more LCD calories than subordinates. No

interaction effects of Diet by Rank ($F_{1,31}$=1.64 p=0.21, $\eta^2_{partial}$= 0.05) were detected on LCD kcal consumption (see Fig. 15).

HCD kcal Consumption –

Two Way ANOVA revealed a main effect of Diet Condition ($F_{1,34}$=53.64, p=6x10^{-4}, $\eta^2_{partial}$= 0.61) on HCD kcal consumption, with the animals in the HCD condition consuming more cumulative HCD calories than those in the LCD-only condition. No main effects of Rank ($F_{1,34}$=1.95, p=0.17, $\eta^2_{partial}$= 0.05) or interaction effects of Diet by Rank ($F_{1,34}$=0.65 p=0.43, $\eta^2_{partial}$= 0.02) were detected on HCD kcal consumption (see Fig. 16).

Body Weight –

Two Way ANOVA revealed no main effects of Diet ($F_{1,33}$=0.26, p=0.61, $\eta^2_{partial}$= 8x10^{-3}) or Rank ($F_{1,33}$=0.03, p=0.87, $\eta^2_{partial}$= 1x10^{-3}) or interaction effects of Diet by Rank ($F_{1,33}$=2x10^{-4}, p=0.99, $\eta^2_{partial}$= 7x10^{-6}) on subjects' body weight at 16 months (see Fig. 17).

Correlations Between Brain Measures and Cortisol, Caloric Intake and Body Weight Data –

Results of bivariate Pearson correlations (see Fig. 18) revealed significant positive correlations between: body weight and right and left PFC GM volumes (r=0.33, p=0.05 and r= .36, p=0.03, respectively) and between total kcals consumed and right and left PFC CSF volumes (r=0.40, p=0.02), as well as between body weight and total kcals consumed and total CSF volume (r=0.36, p=0.03 and r= 0.44, p=0.01, respectively). Significant negative correlations were detected between kcal consumption and left hippocampal volume (r= -0.39, p=0.02), hair cortisol and right PFC WM (r= -0.35, p=0.03), and between hair cortisol concentrations and ICV

and total WM volume (r=-0.34, p=0.04 and r=-0.41, p=0.01, respectively). Analyses using log-transformed hair cortisol data revealed significant negative correlations between hair cortisol and Right and Left PFC WM (r=-0.39, p=0.02 and r=-0.32 and p=0.05, respectively), hair cortisol and ICV (r=-0.35, p=0.03), and between hair cortisol and total WM (r=-0.44, p=0.01). Correlational analyses revealed no significant correlation between Relative Rank and Hair Cortisol (r=-0.06, p=0.70).

Further, significant positive correlations were detected between HCD kcal consumption and Total CSF Volume (r=0.40, p=0.01), HCD kcals and total kcal consumption (r=0.78, $p=1x10^{-3}$), and a significant negative correlation was detected between HCD kcals and LCD kcal consumption (r=-0.60, $p=2x10^{-4}$). No significant correlations were detected between HCD kcal consumption and ICV (r=0.22, p=0.19) or between LCD kcal consumption and ICV (r=-0.18, p=0.31).

Discussion:

The goal of this study was to use a structural MRI approach to examine the long-term, potentially synergistic effect of stress and the obesogenic diet (and likely increased fat mass) on brain structural development of female macaques during the juvenile, prepubertal, period. For this, in addition to investigating potential effects on global brain size, we focused on specific structural impact on the prefrontal cortex, hippocampus and amygdala due to their critical involvement in stress and emotion regulation as well as reward processing and social behavior. These regions also show vulnerability to environmental factors (e.g. stress and diet) during their protracted development into the juvenile period. We utilized a naturalistic model of social stress in rhesus monkeys comparing volumetric long-term structural impact of social rank and postnatal exposure to a highly caloric diet. Overall significantly greater total brain volume (measured as ICV) and total WM and GM volumes were detected by MRI for subjects in the Choice (HCD + LCD) dietary condition, relative to subjects eating LCD diet. Although this could be related to the higher total Kcal consumption observed in the Choice diet group, the correlational analyses only confirmed a positive association between Kcals and body weights with bigger total brain CSF and PFC GM and CSF volumes, while they did not predict the main finding of bigger ICV volumes in the Choice group. These findings suggest that the differences in ICV, and total GM and WM volumes between the Choice and LCD diet juveniles may be better explained by qualitative differences in the nutrient composition between both diets. Regarding the effects of social rank, bigger amygdala and hippocampal volumes were detected in Low Ranking (subordinate) animals than in the High Ranking (dominant) group. These findings suggest that both postnatal social rank and diet exposure influence neurodevelopment affecting brain volume

growth as well as region-specific effects before puberty, but that the effects of diet and social subordination on brain development seem distinct.

Social subordination in adult females is considered a chronic psychosocial stress, however, it is unclear when this phenotype emerges during development. Previous studies show subordinate juveniles have higher morning baseline plasma cortisol compared to dominant females at ~18 months of age (Buwalda et al., 2005; B. R. Howell et al., 2014; Michopoulos, 2016; Shively et al., 1997), although hair cortisol analyses from the current study did not differentiate dominant versus subordinate females. This said, chronic and psychosocial stress have been found to influence neurobehavioral development in humans (Ansell et al., 2012; Drevets et al., 2008; Lupien et al., 2009), as well as to increase consumption of highly caloric diets, which has also been documented to influence physiology and neurodevelopmental trajectories in humans (Bruehl et al., 2011; Maayan et al., 2011; J. L. Miller et al., 2009; Raji et al., 2010). Additional findings show childhood gains in adiposity have been associated with low socioeconomic status (SES) in humans, an effect largely accounted for by deteriorated self-regulatory abilities (Evans et al., 2012), although these findings should not be equated to social subordination. To our knowledge, only two studies (Embree et al., 2013; B. R. Howell et al., 2014) have previously examined the relationship between social subordination stress and brain development in juvenile peripubertal female macaques, demonstrating that effects of social rank on brain serotonin function and structural connectivity are already present in the juvenile, prepubertal period. A potential mechanism for these effects involves activation of the HPA axis, resulting in increased release of GCs (e.g. cortisol in primates). GCs can, indeed, affect structural and functional connectivity in the brain, capable of remodeling dendritic length and branching as well as synapses and myelin through genomic effects on gene expression (Hall, Moda, & Liston,

2015). And, based on this literature, I proposed the hypothesis that stress-induced increases in GCs (cortisol) would explain the expected bigger amygdala volumes in the subordinate females. The findings of bigger amygdala volumes in low ranking females partially supported my hypotheses, but I did not find either higher hair cortisol accumulation in subordinate than dominant animals, nor a positive correlation between cortisol and amygdala volumes. Therefore, additional studies will need to address the biological mechanism mediating the bigger amygdala sizes of low ranking animals, which were already detected in the same animals during infancy (Kyle et al., 2017).

Another potential mechanism underlying these organizational effects of stress involves Corticotropin-Releasing Hormone (CRH) released from the hypothalamus and amygdala, activating the HPA axis. Pharmacologically antagonizing CRH Receptor 1 (CRHR1) has been shown to inhibit effects related to the stress response, one of which involves dopamine (DA) neurotransmission (Michopoulos, 2016). Chronic stress associated with a hypodopaminergic state wherein mesolimbic DA Receptor 2 (D2R) levels are diminished (Hall et al., 2015; Michopoulos, 2016). This impaired DA neurotransmission is associated with dysregulated reward circuitry in areas such as the PFC, amygdala, Nucleus Accumbens (NAcc), suggesting an effect of HPA axis activation on reward circuitry. Amygdala and Orbitofrontal Cortex (OFC) neurons have also been shown in primates to respond to stress as well as taste, texture, sight and smell of food (Kadohisa, Verhagen, & Rolls, 2005; Rolls, 2015a, 2015b). Further, the amygdala and OFC project to the hypothalamus involved in the orexigenic-satiety network, which could explain an alternative pathway through which these regions may affect feeding behavior (Rolls, 2015a). Research on adult female macaques (Michopoulos et al., 2012) has also shown chronic social subordination stress results in altered leptin satiety signals predisposing overeating or

"emotional eating," which can lead to insulin insensitivity associated with developing diabetes. Based on all this evidence, I proposed the hypothesis that chronic social subordination stress would also lead to overeating of the HCD in the low ranking juveniles in my study. However, the findings that, instead, the Dominant group consumed more Kcals than the subordinate females, did not support my hypothesis of increased emotional eating of the HCD diet in the low-ranking females. This may have been due to competition for food at the HCD feeders, with subordinates having reduced access to the one feeder with HCD because of the presence of more dominant females.

ICV was significantly bigger in juveniles exposed to a Choice diet comprised of both Low Caloric Density (LCD) and High Caloric Density (HCD) options. In addition, subjects in the Choice diet condition also had bigger total volumes of WM and GM. In humans, ICV growth follows a parabolic inverted U shape trajectory, first increasing during childhood and peaking at 10 ½ years of age in females and 14 ½ years in males and decreasing thereafter (Giedd & Rapoport, 2010), although it has also been documented in rats that an obesogenic diet can accelerate pubertal timing and influence hormonal activity affecting neurodevelopment (Sloboda, Howie, Pleasants, Gluckman, & Vickers, 2009). Although we found that the Choice condition was associated with bigger ICV, we did not detect effects of dietary condition on Body Weight despite finding the Choice and high-ranking conditions to consume more cumulative kcals. We found this increased consumption of kcals to be related to an increased intake of HCD kcals, which was also inversely correlated with LCD kcal consumption. Thus, it is possible that a high fat and sugar diet influenced physiology as well as neurodevelopmental tempo resulting in accelerated brain structural growth that resulted in bigger ICV and total GM and WM volumes in the juveniles in the Choice diet in comparison to those maintained on LCD since infancy.

Observed differences in ICV are driven by diet differences in total GM and total WM, and caloric intake of HCD kcals was also related to greater total CSF volumes, although consumption of neither HCD nor LCD kcals was significantly correlated with ICV. A recent study showed GM to decrease in volume relatively earlier during development in monkeys (around 10 months), than in humans (at 10.5 years in females), indicating a potential accelerated maturation during macaque development, which can be further accelerated by environmental/exogenous factors (Liu et al., 2015). Although these findings of bigger ICV associated with the Choice diet condition contrast with other reports in the literature (Janowitz et al., 2015), the findings are inconsistent, and other studies show contrasting brain structural development effects seen in children as compared to adults (Giedd & Rapoport, 2010; Knickmeyer et al., 2010; Tottenham & Sheridan, 2009). It is possible that obese-like phenotype changes do not emerge until later, which has been previously supported by findings showing that as females go through puberty the Choice dietary condition starts showing greater body weights and increased fat mass (determined by DEXA) than subjects in the LCD-only dietary condition. These effects of HCD exposure may also occur neonatally through programming by factors such as increased fat in the milk of the Choice dietary condition mother-infant pairs, as shown previously in rats and suggested by recent data in rhesus macaques (Pincus, 2018; Wright, Fone, Langley-Evans, & Voigt, 2011). Thus, the effect of diet condition on ICV may be more related to composition than quantity of diet with the Choice condition exposed to foods of higher caloric density, sugar and fat content, including proinflammatory lipids, which has been shown to affect neuroinflammation and brain development (Simopoulos, 2013), and may also be due to obesity/obesogenic diet-related factors that may develop during early adolescence and will potentially emerge later (Sasaki, de Vega, St-Cyr, Pan, & McGowan, 2013; Tottenham & Sheridan, 2009; Vasconcelos, Cabral-Costa,

Mazucanti, Scavone, & Kawamoto, 2016). Future studies on these subjects should be carried out to assess longitudinal brain development in association with a high fat and sugar diet.

Significant main effects of social rank were detected for the amygdala, showing a region-specific impact on neurodevelopment. Low-ranking (subordinate) subjects were found to have significantly greater amygdala volumes relative to those of their high-ranking (dominant) peers. This is consistent with previous literature on humans finding low SES to be associated with greater amygdala volumes in children (Noble et al., 2015; Noble et al., 2012). A potential explanation for social rank-related increases in amygdala volume could be related to social stress, as stress has been found to enhance dendritic arborization in neurons of the basolateral amygdala (McEwen & Gianaros, 2010; Vyas et al., 2002). However, our failure to detect higher levels of cortisol exposure in the hair of Subordinate animals would not support this hypothesis. An alternative explanation is that early life, associated with rapid amygdala development followed by slowed, protracted development, provides enhanced amygdalar functional development opportunities (Tottenham & Sheridan, 2009) that may reflect neuroadaptation to prepare infant and juvenile subordinates for rank-related social stressors that they are able to perceive by observing their mothers as infants while they are still experiencing limited exposure to direct aggression (Kawai, 1958).

Our findings are inconsistent with research showing subordinate status and stress related to decreased amygdala volume (McEwen & Gianaros, 2010; Noonan et al., 2014). Because the animals in our study were juvenile, prepubertal females, it is possible that once these animals reach puberty similar chronic activation of the amygdala associated with stress that once led to increased amygdala activation and structural volumetric increases may lead to synaptic and dendritic damage, instead, causing a reduction in spine density in areas such as the medial

amygdala neurons, an effect that may be observable at a later age (B. R. Howell et al., 2014; McEwen & Gianaros, 2010). Further anatomical delineation between nuclei of the Amygdala (e.g. basolateral, medial, etc.) may elucidate findings, although this is not currently possible with the limited MRI image resolution provided by the 3T scanner neuroanatomical definitions of the atlases used in this study.

Significant main effects of social rank were also detected for the hippocampus, with subordinate subjects having bigger hippocampal volumes relative to dominant peers. This finding is in context of studies showing greater hippocampus volumes associated with low SES in children (Noble et al., 2015; Noble et al., 2012). However, if social subordination is interpreted to be associated with increased chronic stressor exposure, these findings contrast with those of numerous studies in humans, rats, and NHPs that have found stress to cause hippocampal neuronal death and atrophy (Lupien et al., 1998; McEwen & Gianaros, 2010; Uno et al., 1989; Watanabe et al., 1992) through GC and glutamate excitotoxicity dendritic shrinkage (McEwen, 2016; Popoli, Yan, McEwen, & Sanacora, 2011). Our findings did not support the hypothesis that subordinate animals had smaller hippocampal volumes (but the contrary), or elevated cortisol levels, and the correlational analyses did not show a negative correlation between hair cortisol and hippocampal volumes. It is possible that bigger hippocampal volumes in Subordinates are an adaptive response to increase the storage of valuable information (e.g. spatial or emotional memories) and may be related to increased amygdala volumes as both limbic regions are strongly connected (McEwen, 2016; Phelps, 2004; Preston & Eichenbaum, 2013; Sasaki et al., 2013; Tottenham & Sheridan, 2009). Further studies are necessary to explain the biological mechanisms that led to bigger hippocampal volumes in subordinate relative to dominant animals.

Our hypotheses that the subordinate animals would also show smaller PFC volumes relative to the dominant group due to greater levels of stress exposure in the subordinate subjects (Abbott et al., 2003; Ansell et al., 2012; Arnsten, 2009; Godfrey et al., 2016; Kohn et al., 2016; Michopoulos et al., 2012; Sapolsky, 2005) was not supported by our results, either. Instead we found no significant effect of rank or diet condition on total PFC volume, which could be interpreted in accordance with reports of protracted PFC volume development into adulthood (Knickmeyer et al., 2010; Lupien et al., 2009), and may limit observable effects associated with impaired PFC function (Ansell et al., 2012; Liston et al., 2006; Wager et al., 2008) until later ages, past adolescence. Although no significant effects were detected for total PFC volume, some local effects of social rank were detected for PFC CSF volume with subordinate subjects having significantly bigger PFC CSF volumes relative to dominant subjects. A potential explanation of this effect of rank on PFC CSF may be described by an association discovered between increased lateral ventricle volume and impaired emotional regulation related to psychopathologies in humans (Stoll, Renshaw, Yurgelun-Todd, & Cohen, 2000). A large portion of the CSF volume in the PFC is accounted for the lateral ventricles (Knickmeyer et al., 2010; Shi et al., 2016), implicating these structures as sources of variance in PFC CSF volume between rank conditions.

Chronic stress and obesity have also been shown to promote a pro-inflammatory state (Cohen et al., 2012), with cytokines influencing neurogenesis, differentiation, migration, neural plasticity and synapse formation during development (Boulanger, 2009; Garay & McAllister, 2010). Cytokines alter neurotransmitter levels, influence synaptic transmission, and functional connectivity, with elevated levels shown to activate microglia in the PFC (Felger, Hernandez, & Miller, 2015; Felger et al., 2016; Marsland et al., 2017; Yang et al., 2005), associated with stress-related disorders (Setiawan et al., 2015). Chronic inflammation associated with increased levels

of inflammatory cytokines is also associated with obesity (Gregor & Hotamisligil, 2011; A. A. Miller & Spencer, 2014), and consumption of an obesogenic diet has been documented to increase inflammation levels before obesity is apparent (Vasconcelos et al., 2016). Further, exogenous administration of cytokines also influences activation of reward systems (Eisenberger et al., 2010; Harrison et al., 2009) through cytokine-induced DA release reductions in critical reward regions such as the ventral striatum (Felger et al., 2015). Altogether, numerous explanations can describe effects of social subordination status and postnatal diet on brain structural development.

A main limitation of this study is the sample size of 38 animals leading to group sizes of 9-10, which both 1) may not be representative of the general population, and 2) is underpowered to address the potential effect of heritability factors related to the social rank of the biological mother or crossfostering effects. However, for this study potential confounding effects of crossfostering and biological mother social rank were controlled for by counterbalancing across all rank and diet conditions. Future studies should also include the full longitudinal data from birth in the statistical analysis in order to better address questions related to brain developmental effects over time and across groups as subjects progress from infancy through puberty and transition into to adult neurodevelopment. Additional analyses of potential biological signals that could mediate the reported Diet and Rank effects on juvenile brain structure should also include proinflammatory cytokines (C-reactive protein, CRP & Interleukin-6, IL-6).

In summary, the findings of this study suggest that postnatal diet and social rank have long-term effects on female primate brain structure. We found overall greater ICV in subjects exposed to a high caloric density diet in comparison to animals exposed to a low caloric diet. We also found that lower rank resulted in bigger amygdalae, hippocampi and PFC CSF volumes.

Further structural effects of rank and diet are expected to emerge as the animals progress through puberty into early adulthood and as animals in the Choice dietary condition continue to experience physiologic effects of caloric intake including increased adiposity and related metabolic and neurologic outcomes. Additional studies with these animals as well as future longitudinal studies are necessary to expand our understanding of the mechanisms and organizational effects of social rank and dietary exposure on neurodevelopment.

Appendix:

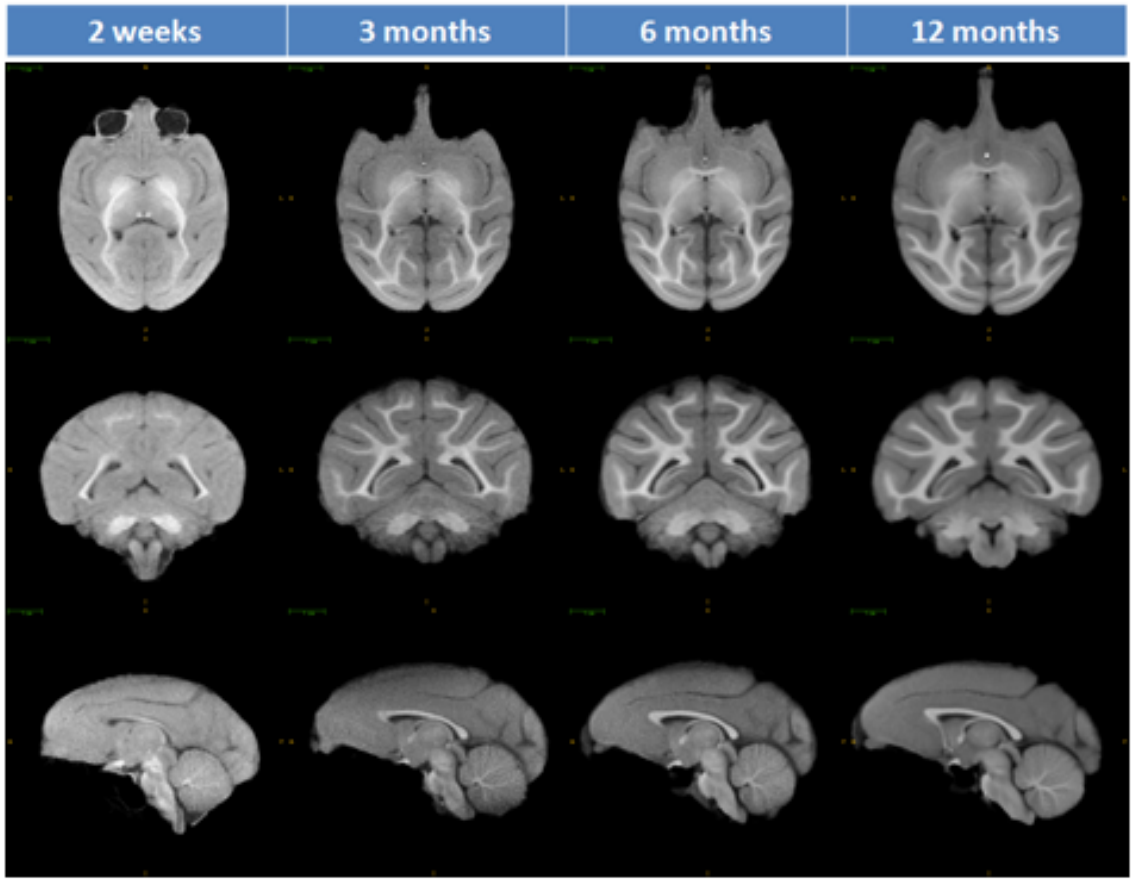

Fig. 1 – AutoSeg UNC-Emory rhesus structural MRI brain atlases. This study used the 12 months atlas as it was structurally and volumetrically most similar to the 16 month brain images examined in this project.

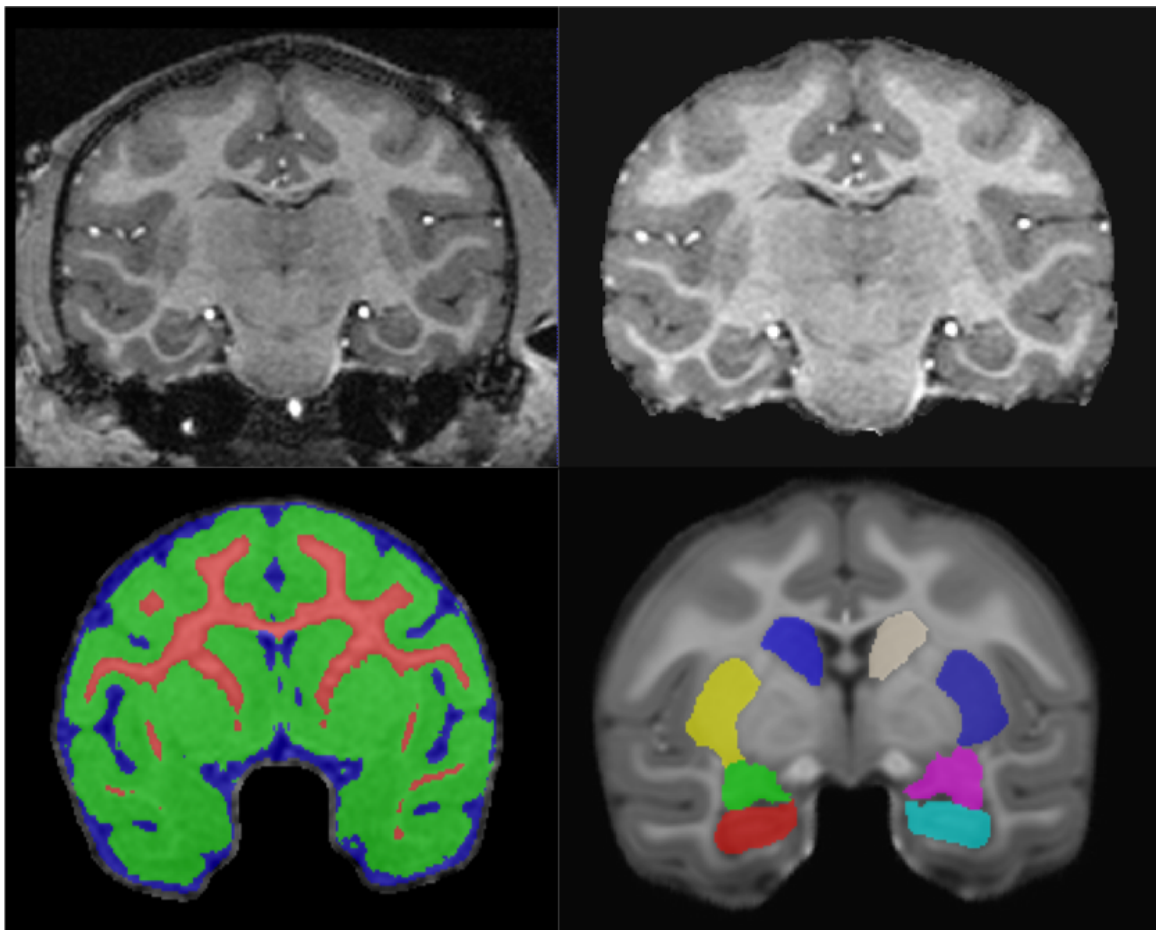

Fig. 2 – Images from AutoSeg showing brain with skull (top left), brain after skull-stripping has been applied (top right), brain segmented into white matter (red), gray matter (green), and CSF (blue) (bottom left), and example subcortical ROI parcellations (bottom right).

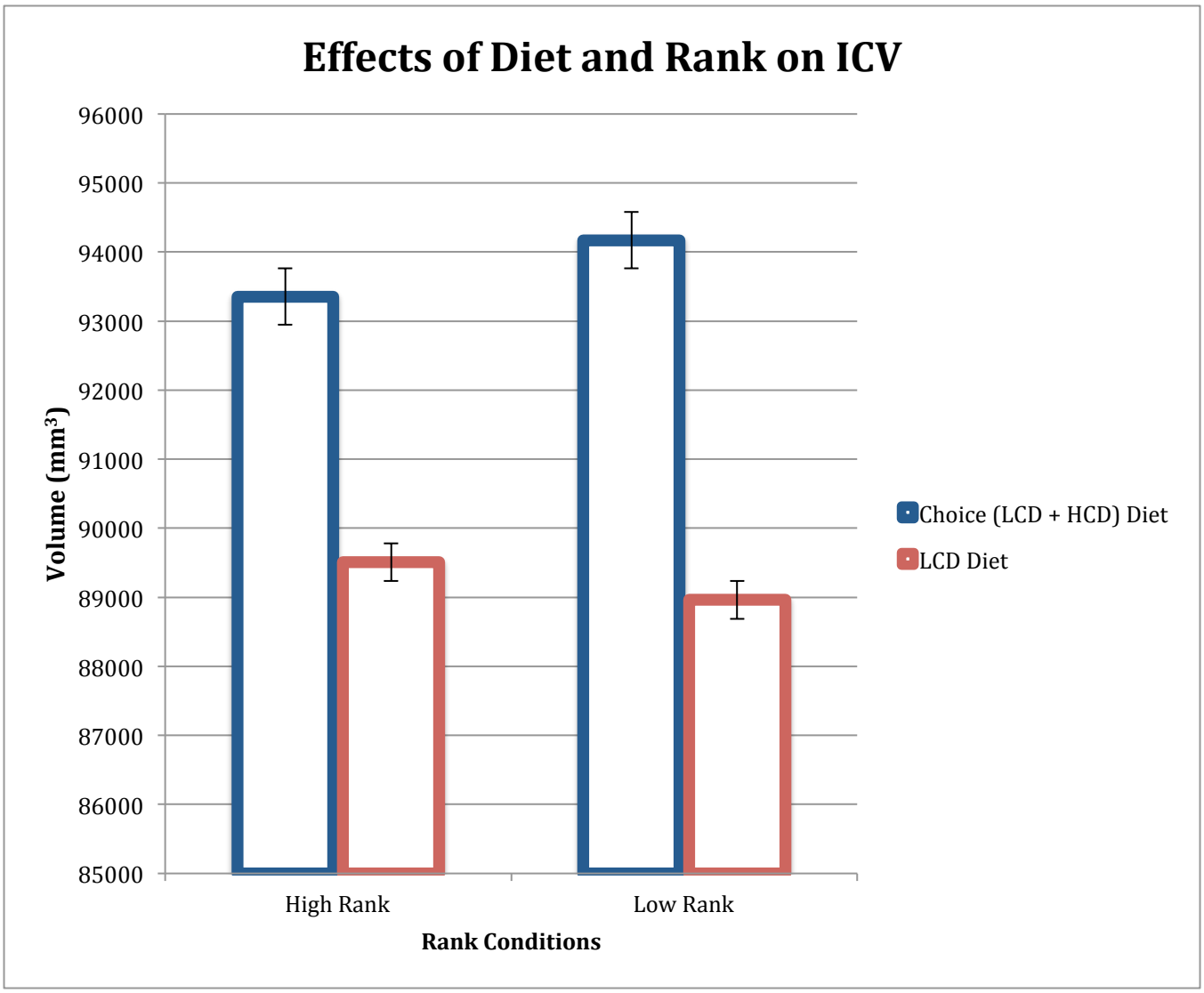

Fig. 3 – Effects of Diet and Rank on ICV. The Choice Diet condition (LCD + HCD) groups were found to have greater ICV relative to the LCD Diet condition groups. Data is represented as mean±standard error of the mean (SEM).

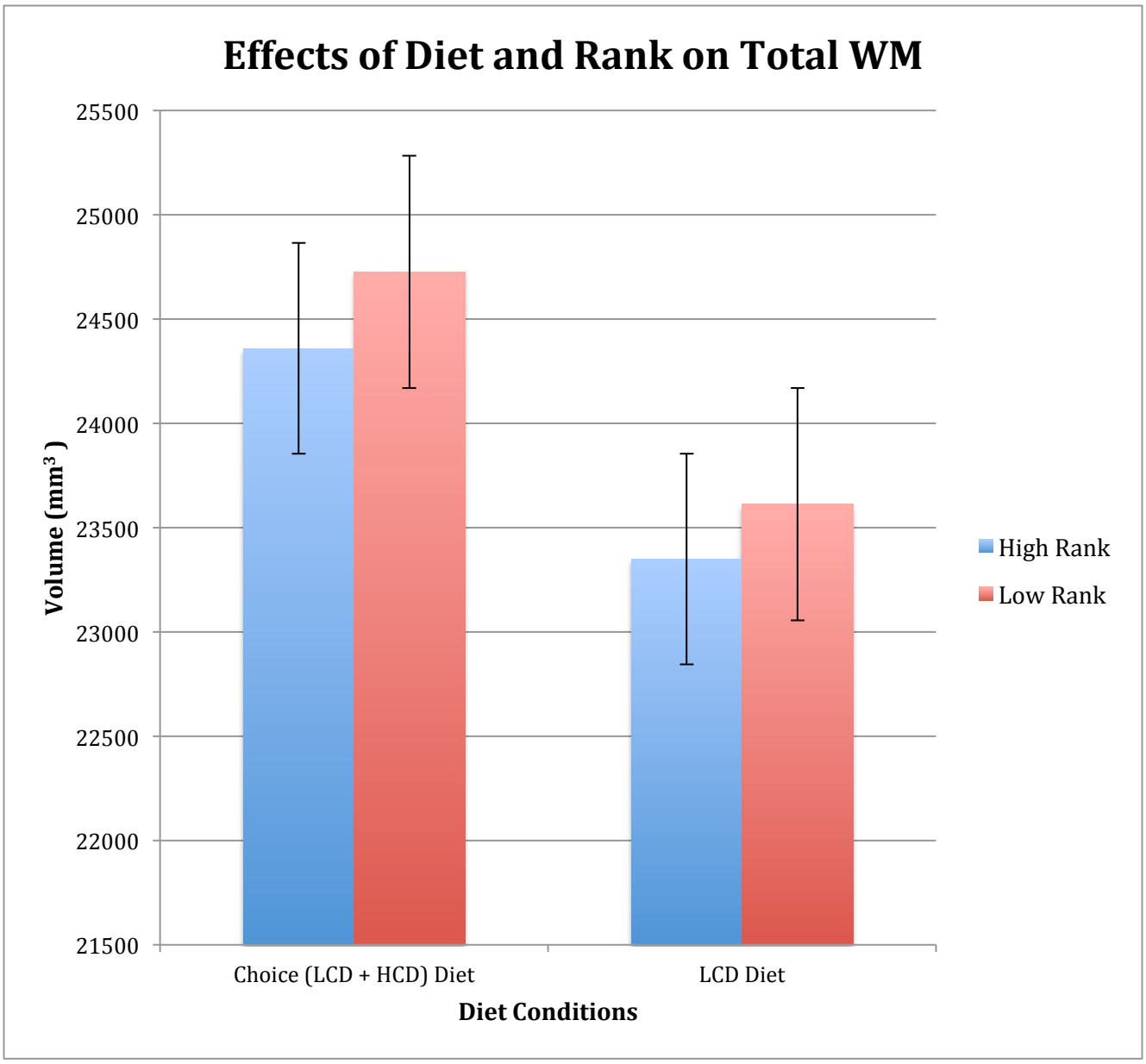

Fig. 4 – Effects of Diet and Rank on Total WM Volume. Data is represented as mean±SEM.

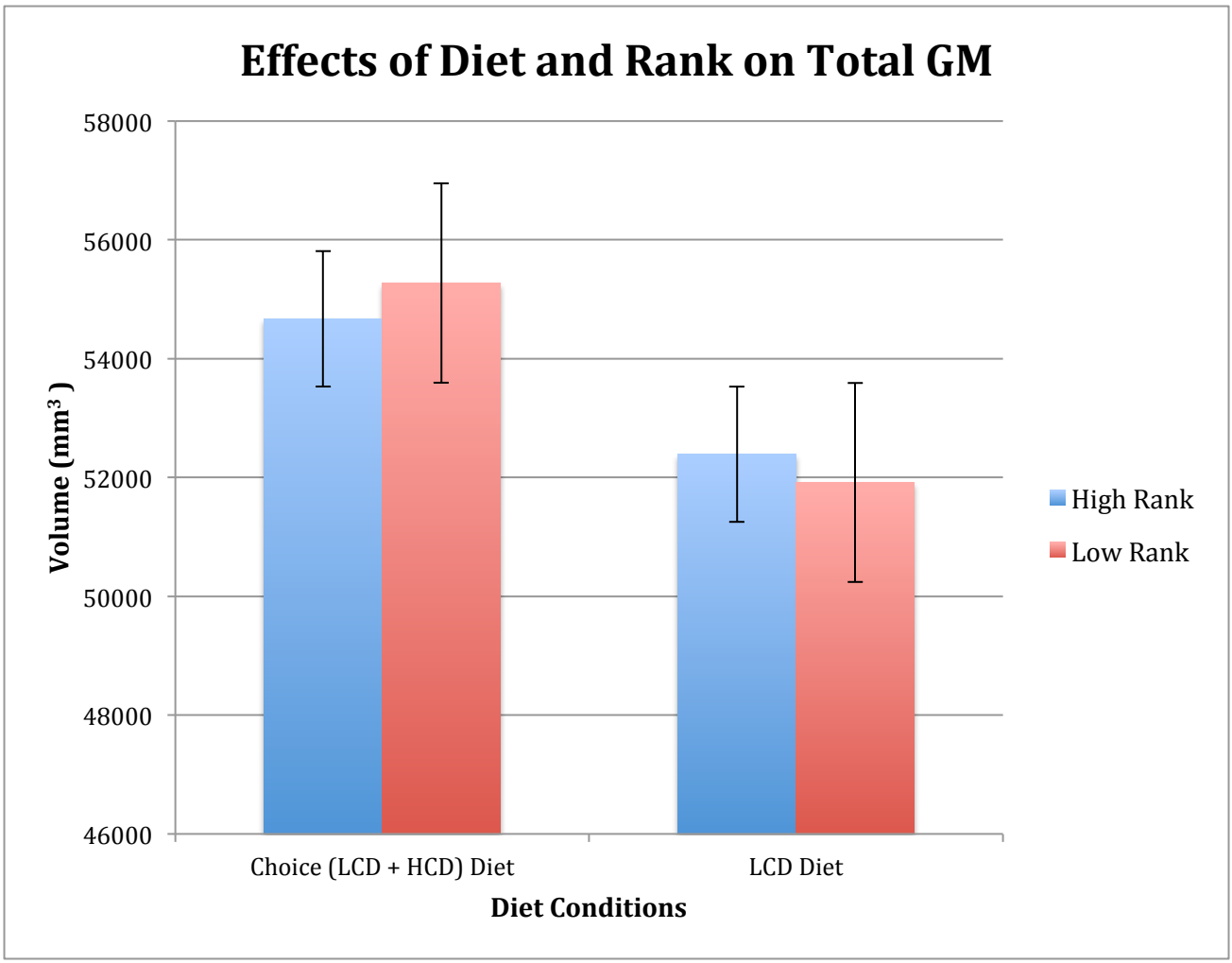

Fig. 5 – Effects of Diet and Rank on Total GM Volume. Data is represented as mean±SEM.

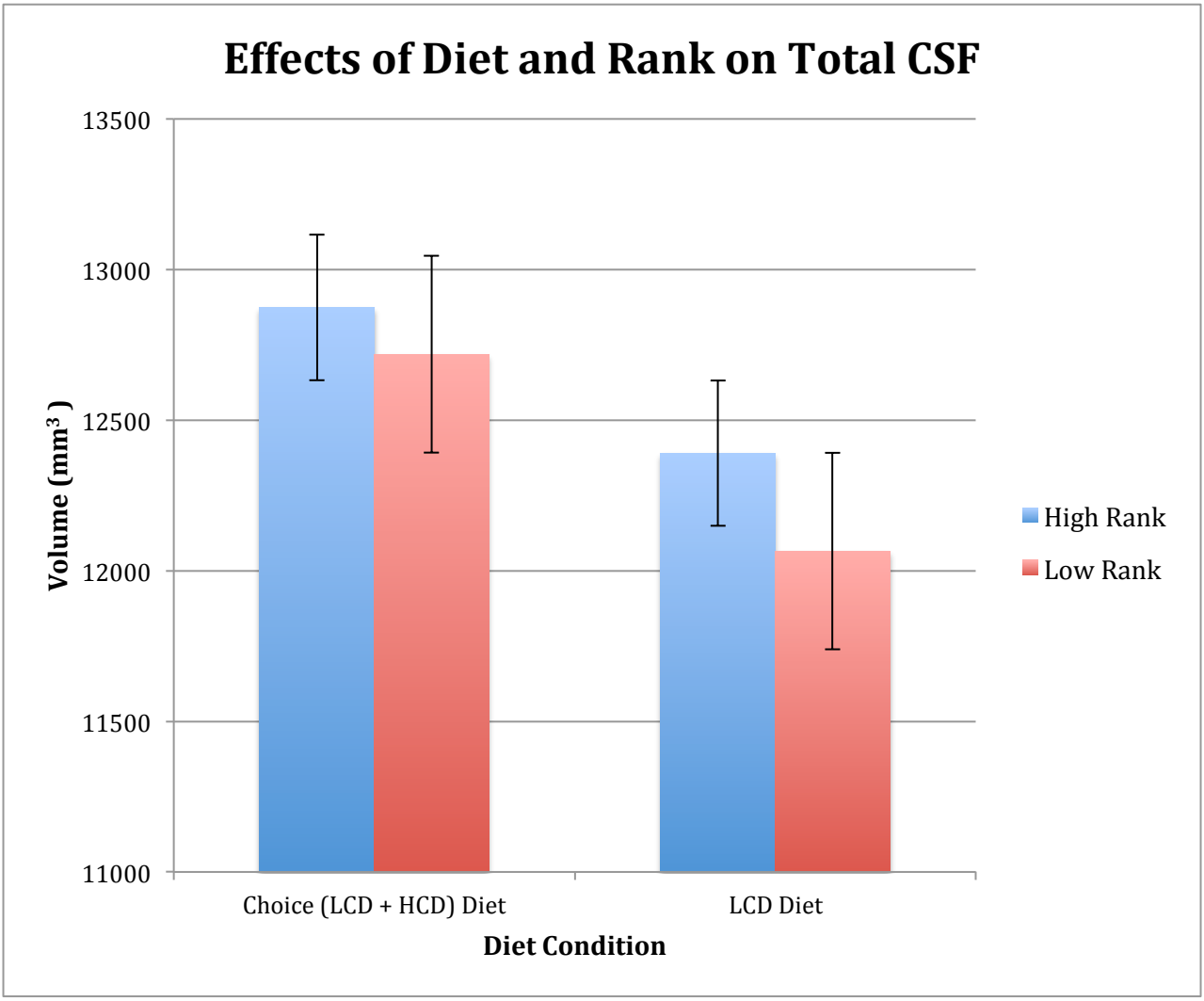

Fig. 6 – No significant effects of Diet or Rank were detected for Total CSF Volume. Data is represented as mean±SEM.

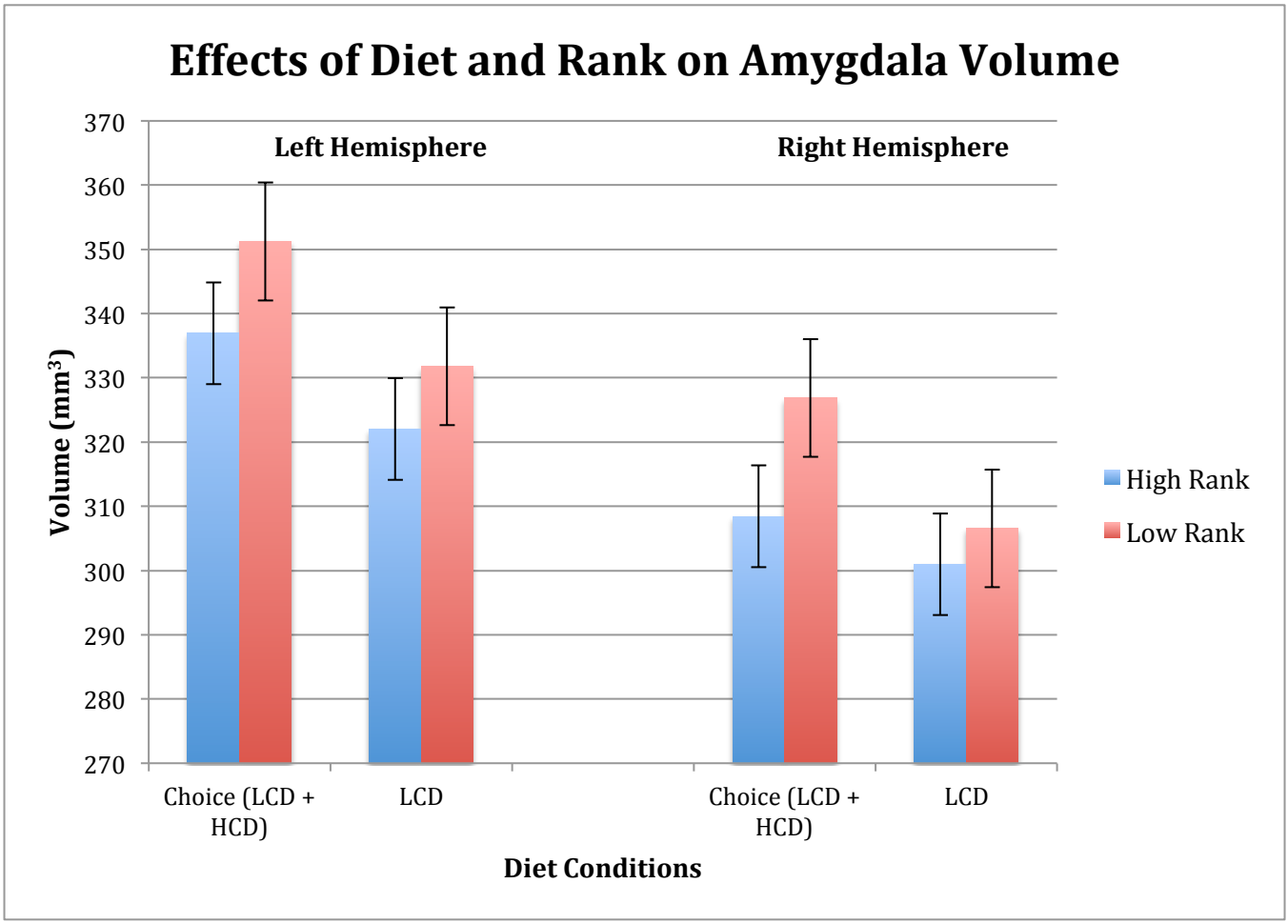

Fig. 7 – Effects of Diet and Rank on Amygdala Volume. The Low Rank condition groups were found to have greater amygdala volume relative to the High Rank condition groups. Data is represented as mean±SEM.

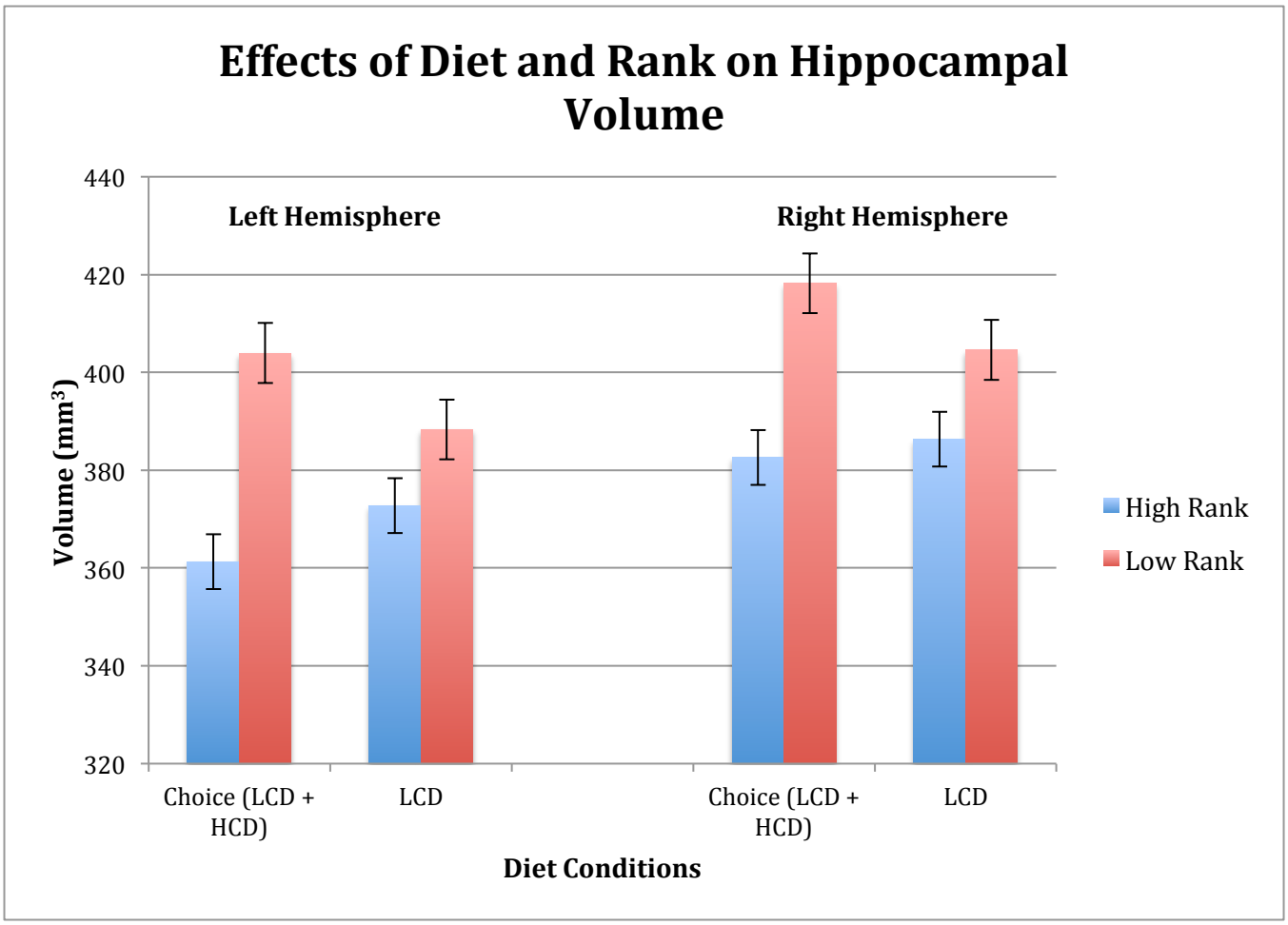

Fig. 8 – Effects of Diet and Rank on Hippocampal Volume. The Low Rank condition groups were found to have bigger hippocampal volume relative to the High Rank condition groups. Data is represented as mean±SEM.

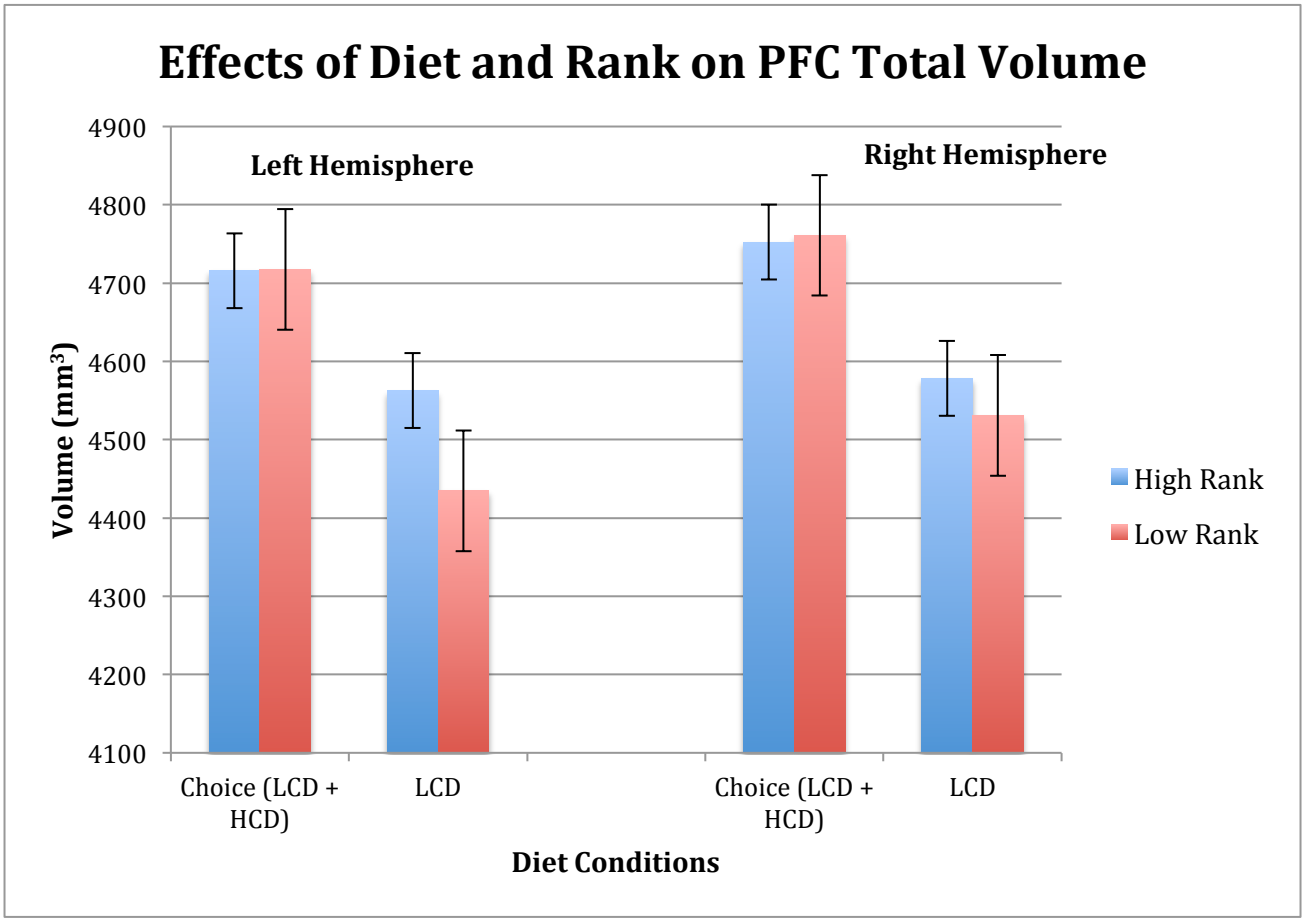

Fig. 9 – Effects of Diet and Rank on PFC Total Volume. Data is represented as mean±SEM.

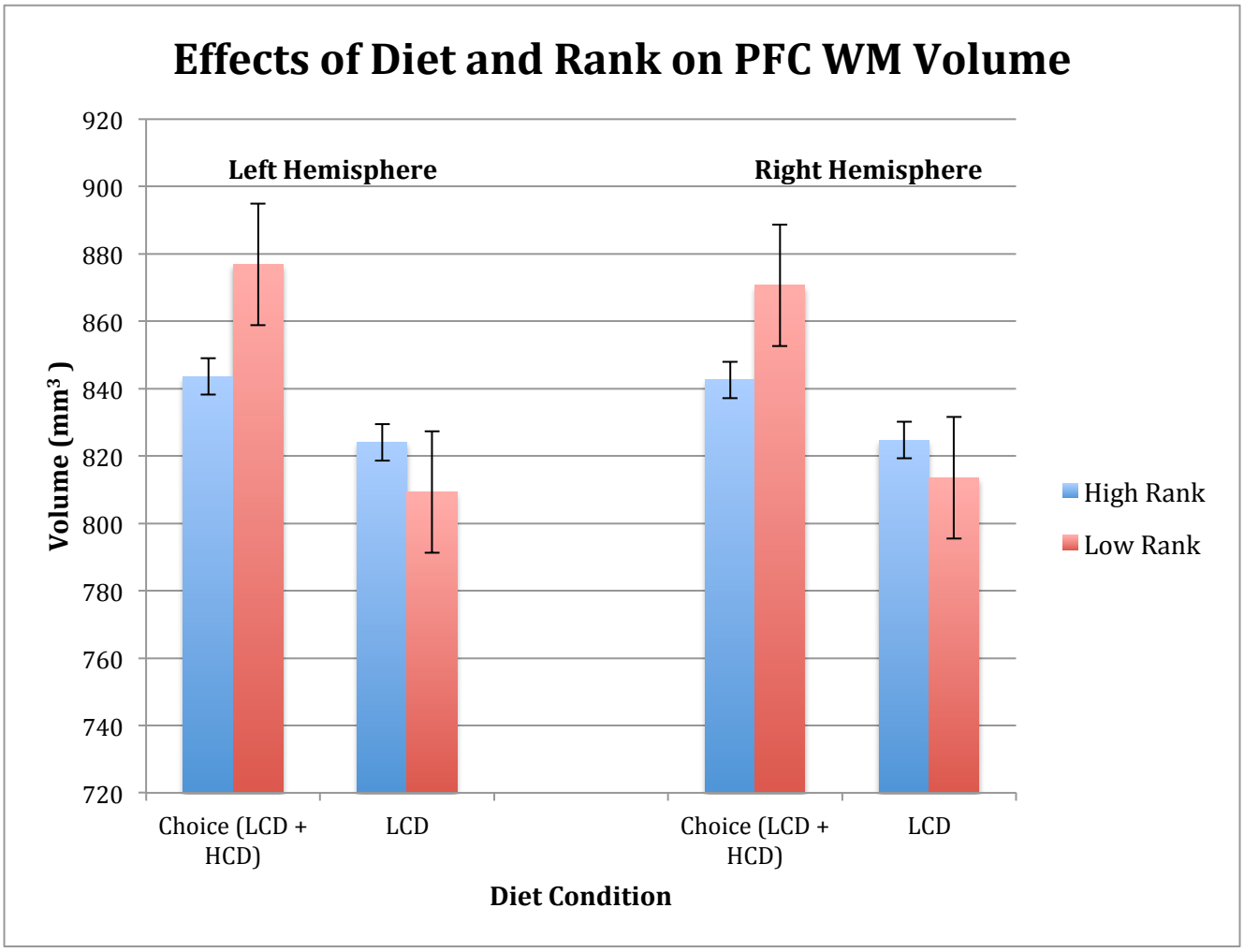

Fig. 10 – Effects of Diet and Rank on PFC WM Volume. Data is represented as mean±SEM.

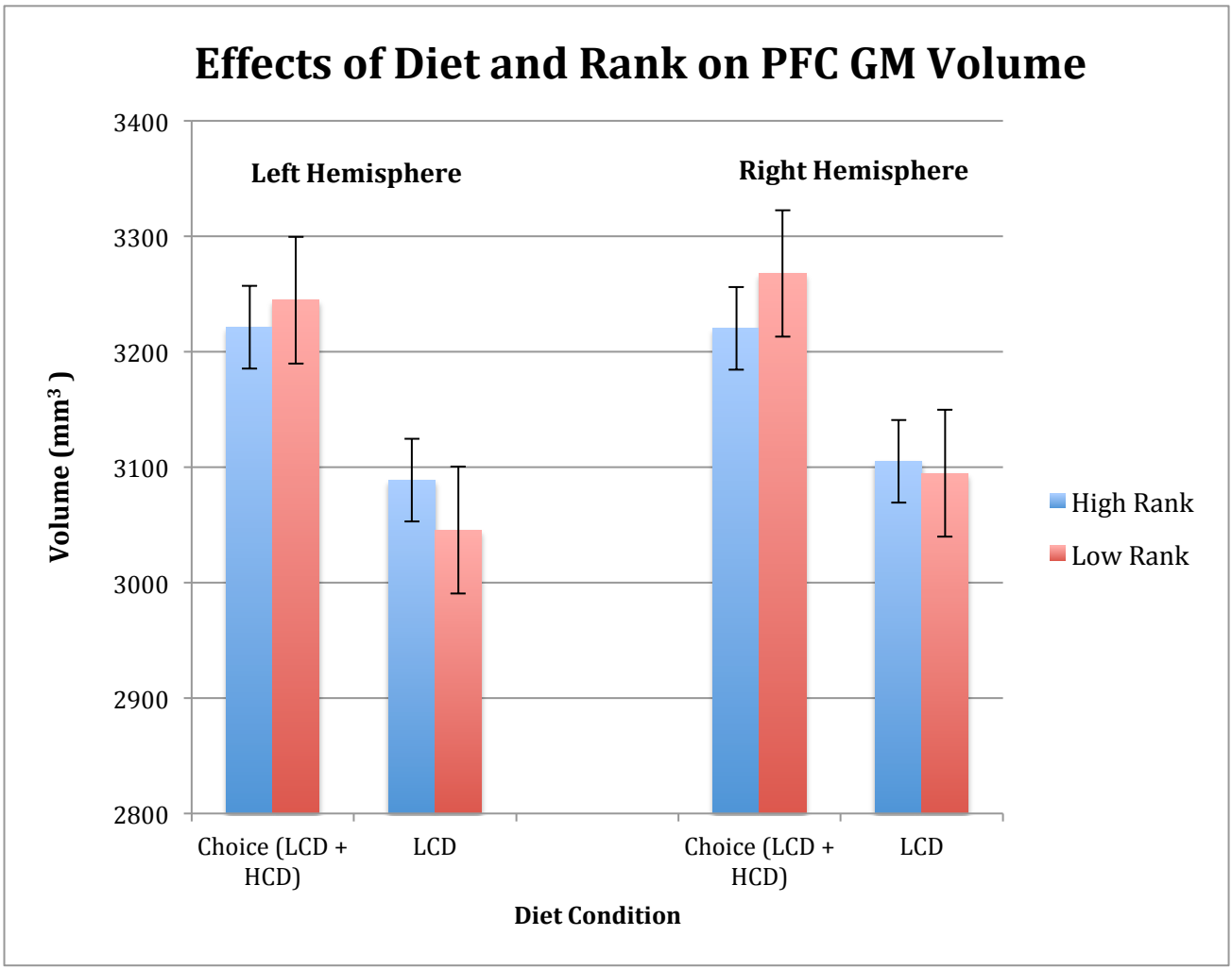

Fig. 11 – Effects of Diet and Rank on PFC GM Volume. Data is represented as mean±SEM.

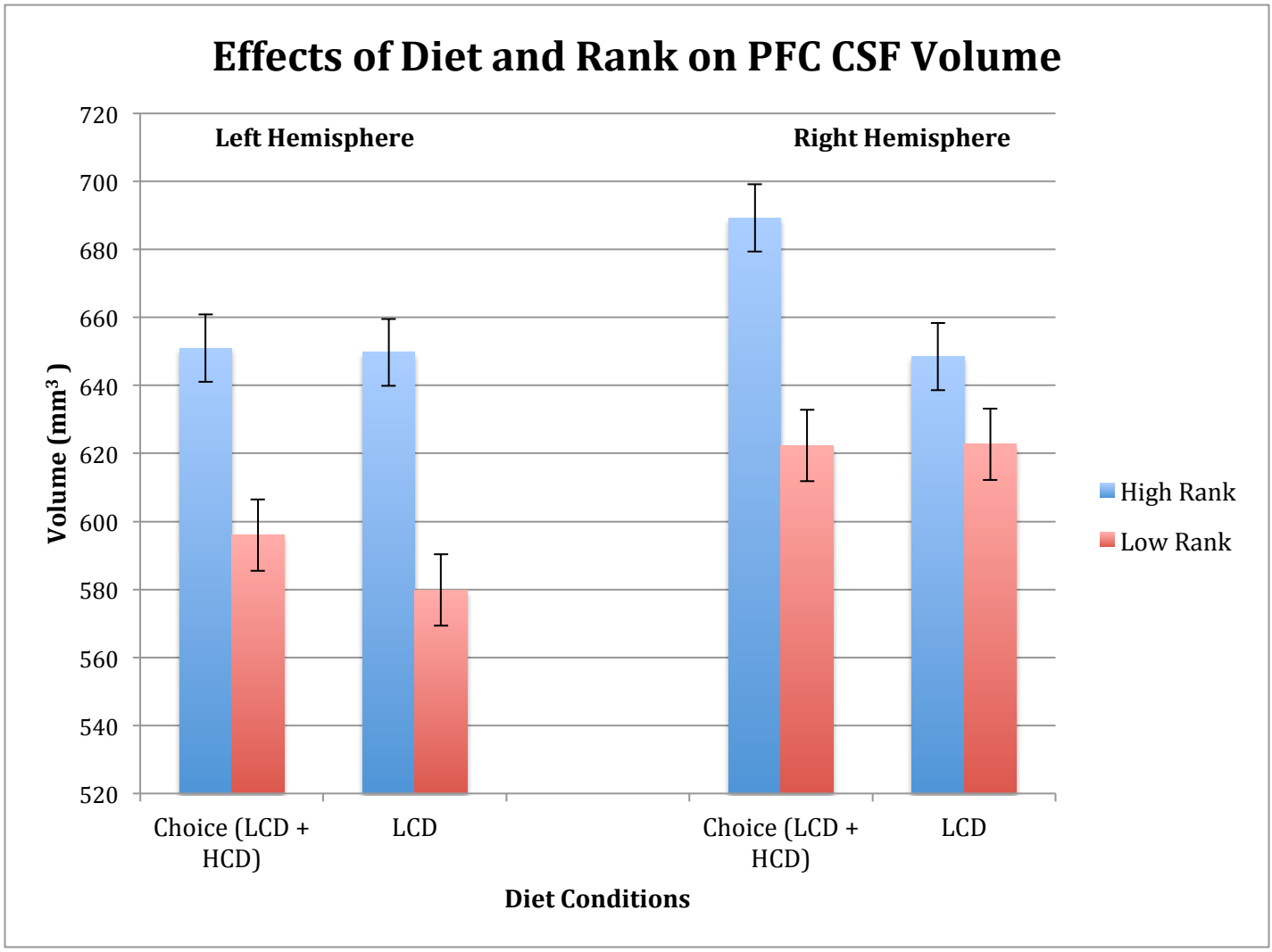

Fig. 12 – Effects of Diet and Rank on PFC CSF Volume. The High Rank condition groups were found to have bigger PFC CSF volumes relative to the Low Rank condition groups. Data is represented as mean±SEM.

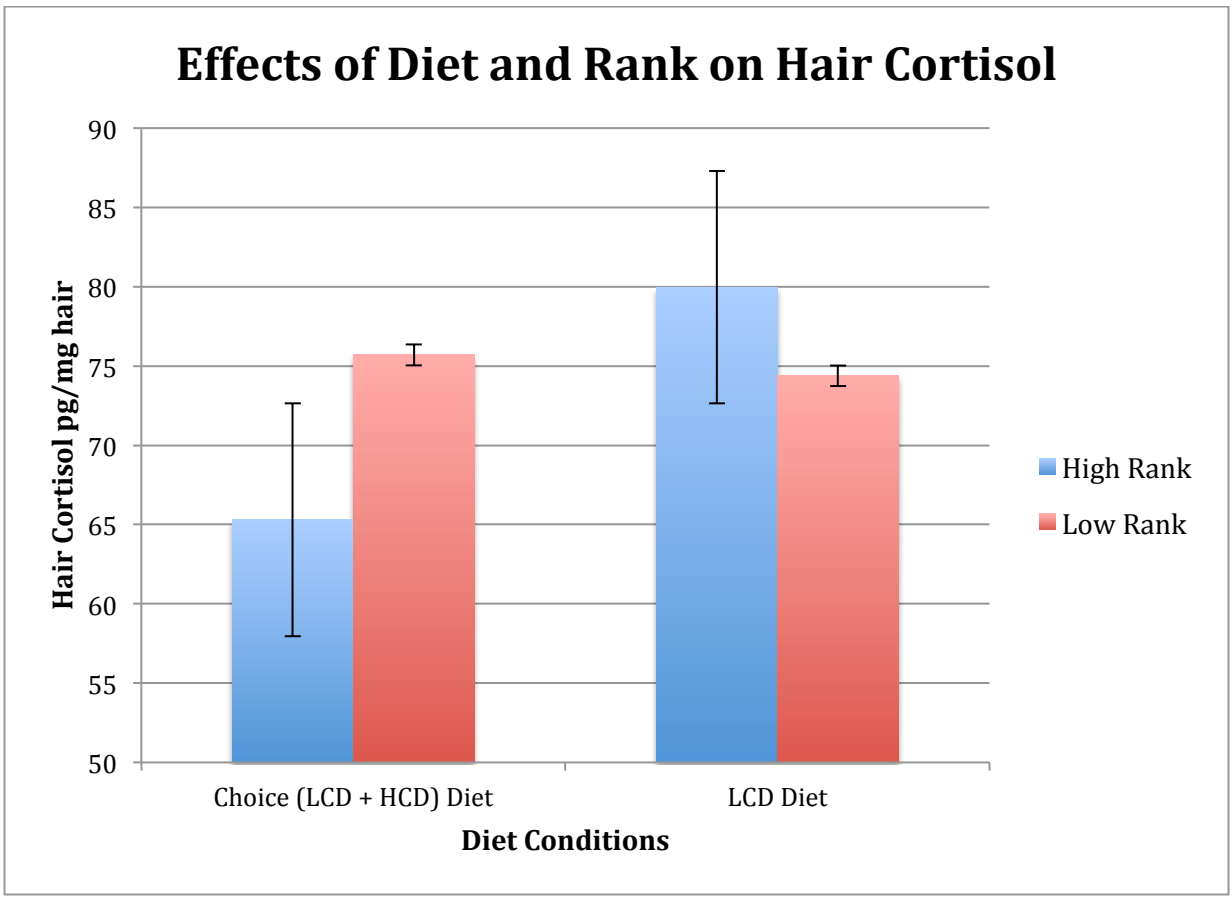

Fig. 13 – Effects of Diet and Rank on Hair Cortisol. Data is represented as mean±SEM.

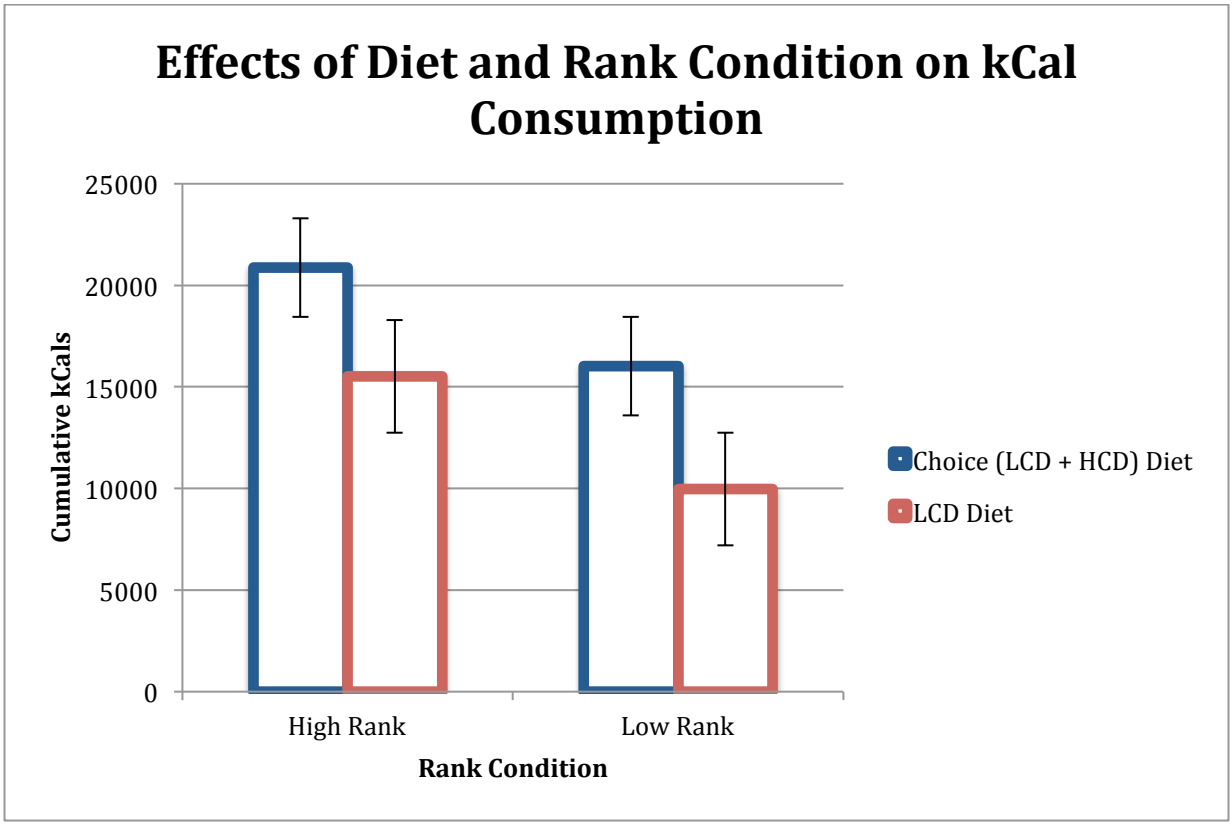

Fig. 14 – Effects of Diet and Rank on cumulative kcal consumption. Both a main effect of Diet and Rank were detected, with animals in the HCD condition and High ranks consuming more cumulative calories than those in the LCD condition and the Lower rank. Data is represented as mean±SEM.

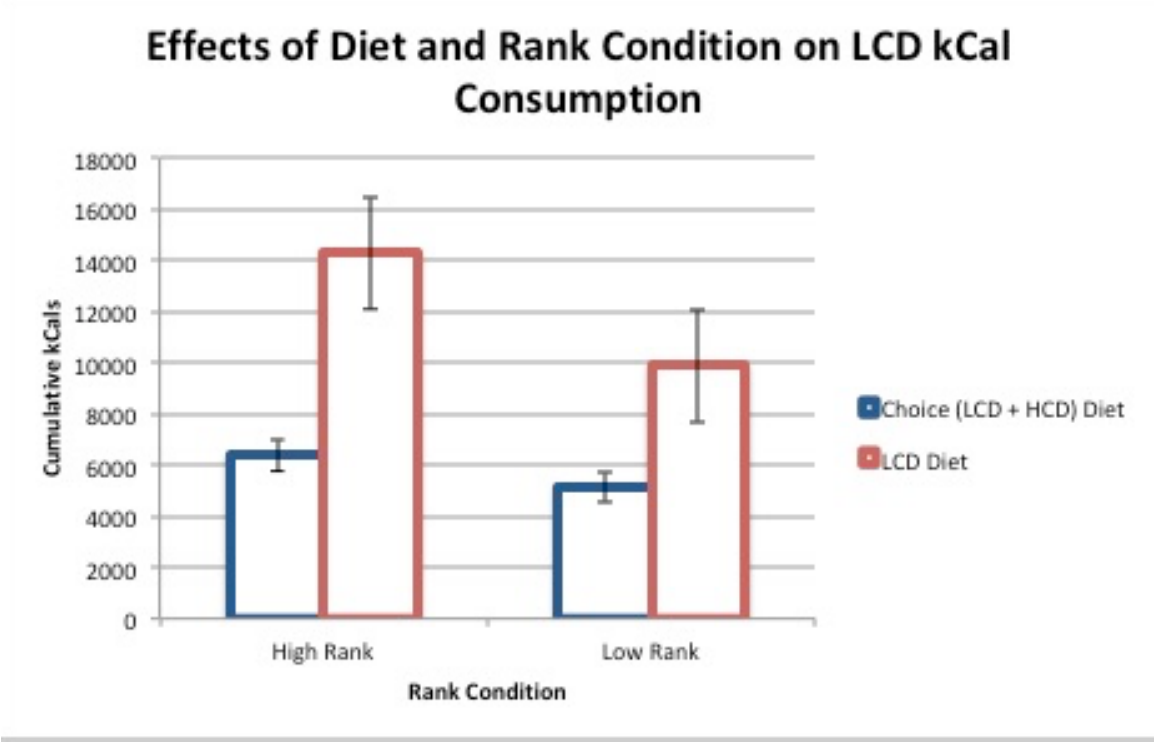

Fig. 15 – Effects of Diet and Rank on cumulative LCD kcal consumption. Both a main effect of Diet and Rank were detected, with animals in the LCD condition and High ranks consuming more cumulative LCD calories than those in the HCD condition and the lower rank. Data is represented as mean±SEM.

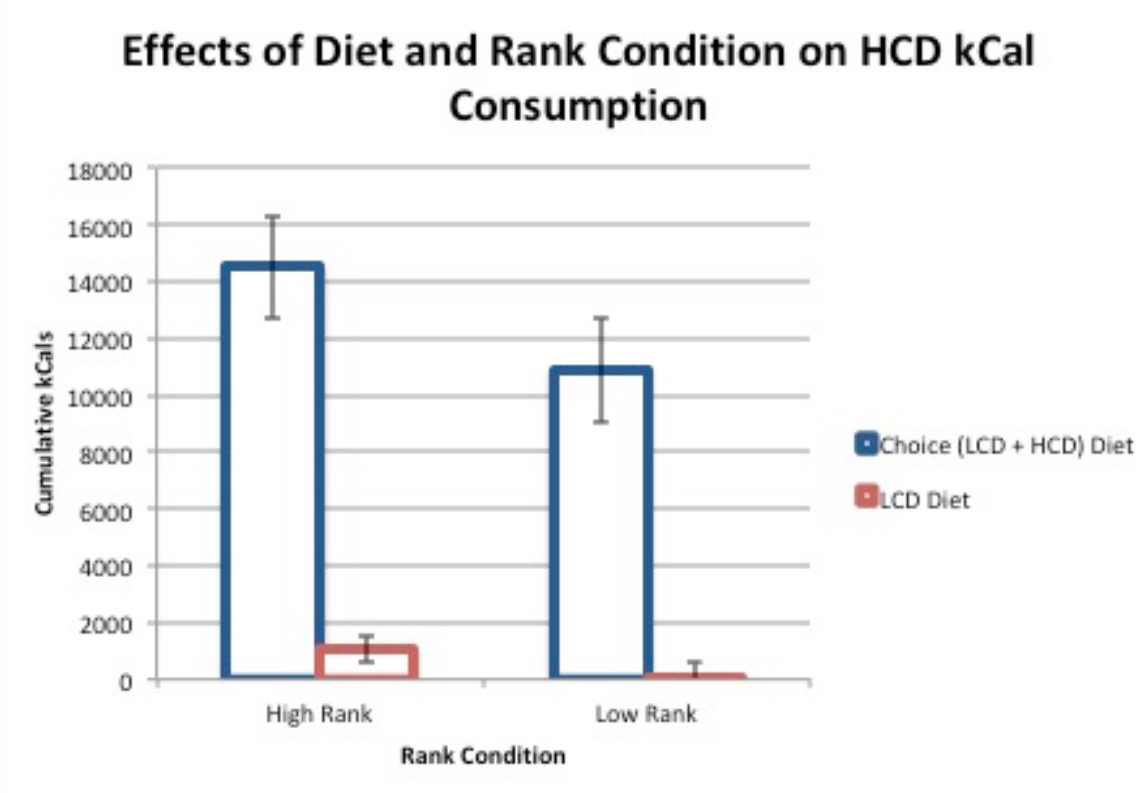

Fig. 16 – Effects of Diet and Rank on Cumulative HCD kcal consumption. A main effect of diet was detected, with animals in the Choice dietary condition consuming more cumulative HCD calories than those in the LCD condition. Data is represented as mean±SEM.

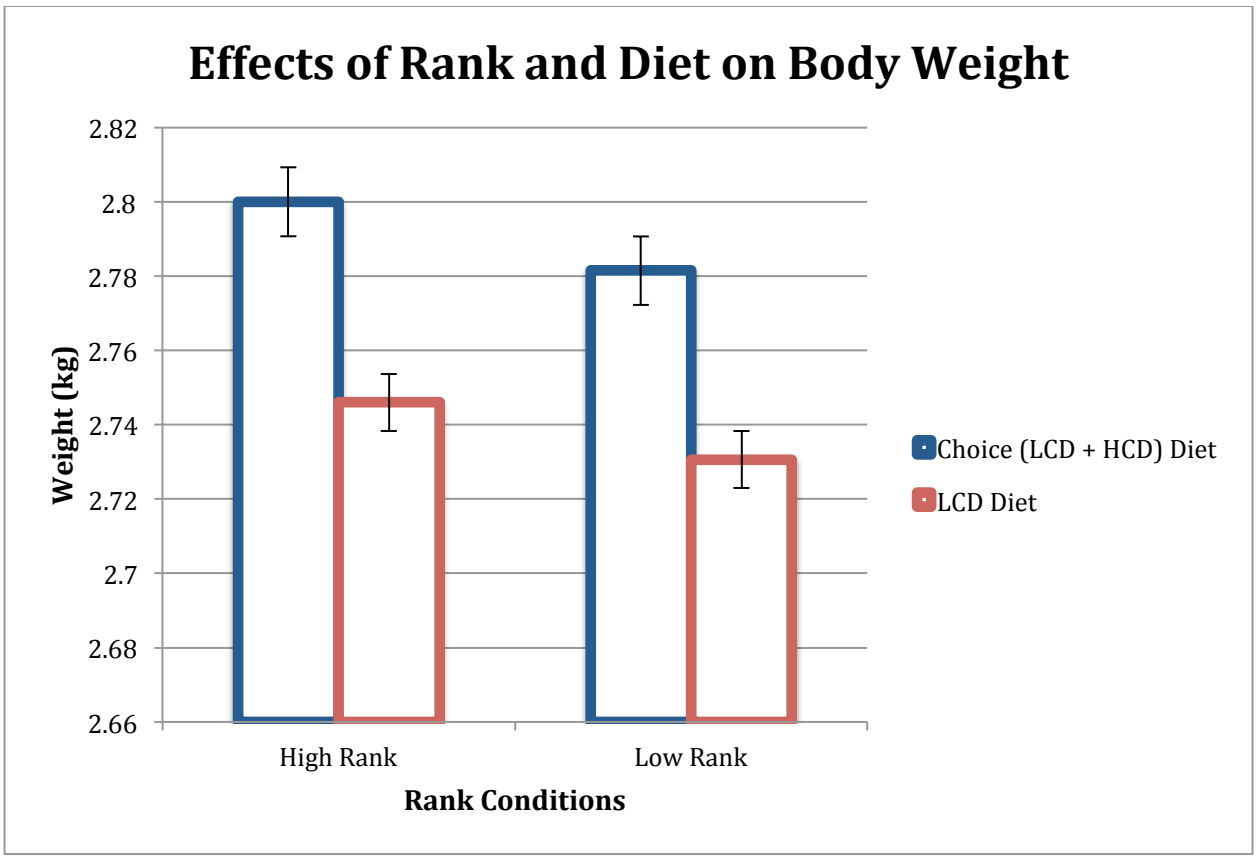

Fig. 17 – Effects of Diet and Rank on Body Weight. Data is represented as mean±SEM.

Measure	ROI (volumes)/ measures	Pearson Correlation Coefficient	P-Value
Body Weight	R&L PFC GM	r = 0.33, 0.36	p = 0.05, 0.03
Kcals Consumed	R&L PFC CSF	r = 0.40	p = 0.02
Body Weight	Total CSF	r = 0.36	p = 0.03
Kcals consumed	Total CSF	r = 0.44	p = 0.01
Kcals consumed	Left Hippocampus	r = -0.39	p = 0.02
Kcals consumed	Total Hippocampus	r = -0.36	p = 0.03
Hair Cortisol	Right PFC WM	r = -0.35	p = 0.03
Hair Cortisol	Total WM	r = -0.41	p = 0.01
Hair Cortisol	ICV	r = -0.34	p = 0.04
Hair Cortisol Log Transformed	R & L PFC WM	r = -0.39, -0.32	p = 0.02, 0.05
Hair Cortisol Log Transformed	ICV	r = -0.35	p = 0.03
Hair Cortisol Log Transformed	Total WM	r = -0.44	p = 0.01
HCD Kcals consumed	Total CSF	r = 0.40	p = 0.01
HCD Kcals consumed	Total Kcals consumed	r = 0.78	p = 0.00
HCD Kcals consumed	LCD Kcals consumed	r = -0.60	p = 0.00

Fig. 18 – Table of Correlations

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