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Margaret Kyle April 9, 2019

Chronic Social Stress and Consumption of an Obesogenic Diet Alter Neurobehavioral Development in Infant and Juvenile Macaques

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Abstract

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By Margaret Kyle

As the United States faces a pediatric obesity crisis, it is vital that we understand how children with early exposure to highly caloric diets are developmentally impacted. Obesogenic diet consumption is often comorbid with chronic psychosocial stress, which itself poses a cumulative risk factor for obesity and is associated with psychopathology. It is not well understood, though, how neurobehavioral alterations caused by chronic stress emerge during development and interact with consumption of obesogenic diets. This study examined the potential synergistic impact of postnatal exposure to chronic stress and obesogenic diets on infant and juvenile brain development longitudinally, while probing underlying biological mechanisms. We utilized a translational macaque model of social subordination stress, and followed forty-one (n=21 dominant, n=20 subordinate) rhesus monkeys with access to either a low-calorie diet (LCD) only, or to both the LCD and an obesogenic, highly caloric diet (HCD; Choice condition) from birth. Food intake was recorded continuously using automatic feeders and radio-frequency identification (RFID) chips implanted in subjects' wrists. Brain structural MRI data was collected during infancy (2 weeks, 6 months) and in the juvenile period (16 months). Hair cortisol, C-reactive protein (CRP), body weight, and kilocalorie (Kcal) consumption data was analyzed across the same period to examine stress- and diet-induced alterations of physiological markers. Subordinate animals had higher CRP levels, and subjects with access to a HCD consumed an increasing number of HCD Kcals with age and consumed more total Kcals than LCD subjects, but there were no group differences in body weight. Females who consumed the HCD showed larger overall brain (intracranial volume; ICV),

prefrontal cortex (PFC), insula (INS), and amygdala (AMYG) volumes than those on the LCD. Subordinate animals showed larger AMYG, PFC, and hippocampus (HIPP) volumes than dominants, and AMYG growth was predicted by CRP exposure. Total Kcal consumption predicted ICV, HIPP, and PFC growth rates, while HCD Kcal consumption predicted PFC and INS growth rates. Our findings suggest that postnatal exposure to social subordination and an obesogenic diet has both global and region-specific, non-synergistic effects on primate brain development that appear during infancy and are driven by inflammation and Kcal consumption.

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Introduction

The Developmental Impact of Obesogenic Diets and Chronic Social Stress

Childhood obesity in the United States has become an increasingly severe epidemic in recent decades. Surveys from 2015-2016 placed the prevalence of overweight and obesity in US youth at an estimated 35%, 18.5% of which was comprised of obesity alone (Fryar, Carroll, & Ogden, 2018). Rates of obesity have risen dramatically in children and adolescents over the past 30 years (Fryar, Carroll, & Ogden, 2018), and they also increase into adulthood, with the prevalence of adult obesity in the US recently estimated at 36% (Ogden, Carroll, Fryar, & Flegal, 2015). Obese children are significantly more likely to be obese as adults (Whitaker et al., 1997), and they develop obesity-related diseases, such as cancers, type 2 diabetes, cardiovascular disease, and psychological disorders (Hill, 2006; Must & McKeown, 2000; Visscher & Seidell, 2001), earlier and with more severity than their non-obese counterparts (Lim et al., 2012; Dietz, 1998; Freedman et al., 2001; Freedman et al., 2007; Dabelea & Harrod, 2013). Although the high prevalence of childhood obesity indicates an alarming public health concern, the scientific understanding of its etiology and consequences has thus far been limited by its comorbidity with and exacerbation by other health risk factors, including chronic stress.

Obesity has consistently been linked to poverty and low socioeconomic status, which are associated with chronic psychosocial stress and a multitude of chronic health problems (Raphael, 2011; Lipowicz, Koziel, Hulanicka, & Kowalisko, 2007; Brooks-Gunn, 1997; Evans & English, 2002; Evans, Fuller-Rowell, & Doan, 2012). Youth in lower income groups have a significantly higher prevalence of obesity (18.9%) than those in families with the highest incomes (10.9%) (Ogden et al., 2018), and a review of US counties found that poverty-dense counties have obesity rates 145% higher than wealthy ones (Levine, 2011). Beyond comorbidity, chronic stress has

been shown to directly influence eating habits and obesity: it has been linked to emotional eating in youth (Mazur, Dzielska, & Malkowska-Szkutnik, 2011), and poses a cumulative risk factor for childhood obesity (Evans, Fuller-Rowell, & Doan, 2012). Chronic stress has also been shown to promote preference for calorically dense diets and increased calorie consumption in both animal (Hagan et al., 2003; Foster, Solomon, Huhman, & Bartness, 2005; Solomon, Foster, Bartness, & Huhman, 2007; Arce et al., 2010) and human studies (Adam & Epel, 2007; Greeno & Wing, 1994). Girls and women seem to be particularly vulnerable to chronic stress-induced increases in caloric consumption and phenomena like "stress-eating" (Grunberg & Straub, 1992; Greene et al., 2011; Suglia, Duarte, Chambers, & Boynton-Jarrett, 2012; Noll, Zeller, Trickett, & Putnam, 2007).

The evident relationships between chronic stress, eating habits, and obesity may be mediated by stress-induced alterations in brain structure and function. Chronic stress early in life is particularly problematic because it affects brain development, including reports of structural changes in corticolimbic circuits central to stress and emotional regulation and reward processes, such as the amygdala (AMYG), hippocampus (HIPP), prefrontal cortex (PFC), insula (INS), and nucleus accumbens (NAcc) (Tottenham et al., 2010; Noble, Houston, & Sowell, 2012; Noble et al., 2015; Dannlowski et al., 2012; Meaney, Brake, & Gratton, 2002). Generally, chronic stress and stress-related disorders are associated with increased AMYG volumes (Tottenham et al., 2010; Noble, Houston, & Sowell, 2012; McEwen & Gianaros, 2010; Weniger & Lange, 2006; Frodl et al., 2002) and decreased HIPP volumes (McEwen, 2006; Gianaros et al., 2007), although there are also some reports of increased HIPP volumes in children of low socioeconomic status (Noble, Houston, & Sowell, 2012). The PFC, a cortical region highly connected with the AMYG that is believed to exert top-down control over the emotional response of subcortical limbic

structures (Ghashghaei, Hilgetag, & Barbas, 2007; Phillips, Ladouceur, & Drevets, 2008), shows reduced volume in association with chronic stress (Ansell et al., 2012; Arnsten, 2009). Chronic stress has also been linked to smaller volumes in the INS (Ansell et al., 2012; Dannlowski et al., 2012), a cortical region also highly connected with the AMYG that is involved in interoception (i.e. sense of the body's internal state) and processing emotional stimuli and reward (Reynolds & Zahm, 2005; Liberzon et al., 2007). Further, early life stress (ELS) down-regulates dopamine (DA) receptor sensitivity in the NAcc (Meaney, Brake, & Gratton, 2002), compromising its ability to integrate stress and reward information and predisposing individuals to drug or even food addiction (Meaney, Brake, & Gratton, 2002; Volkow, Wang, Fowler, & Telang, 2008). Additionally, specific sub-regions of the PFC, including the dorsolateral PFC (dlPFC), medial PFC (mPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC), which are particularly important for executive functions, including impulse control, reward associations, and emotional regulation (Andersen, 2003; Crews et al., 2007), have been linked to ELS-induced alterations (Liston et al., 2006; Arnsten, 2009; Lu et al., 2013). Importantly, the NAcc, AMYG, INS, and PFC have all been proposed to play a role in non-homeostatic eating (i.e. eating beyond the point of satiety; Ghashghaei, Hilgetag, & Barbas, 2007; Haber & Knutson, 2010; Tomasi & Volkow, 2013; Volkow et al., 2012; Warne, 2009), suggesting that alterations in these structures could provide a neurobiological connection between chronic stress and over-eating.

Obesity and high caloric intake in humans are associated with some structural brain alterations that resemble those of chronic stress. Obesity has been linked to smaller INS volumes in adults (Janowitz et al., 2015) and smaller PFC volumes in adolescents (Bruehl et al., 2011). Reduction in HIPP volumes are also associated with obesity in adolescents (Bruehl et al., 2011), and consumption of a calorically dense, "Western" diet is associated with smaller hippocampi in

adults (Jacka et al., 2015). Increased BMI in children and adolescents was recently linked to enlarged AMYG and NAcc volumes (Perlaki et al., 2018). Obesity has also been associated with structural alterations in the dlPFC, mPFC, OFC, and ACC (Figley, Asem, Levenbaum, & Courtney, 2016; Shott et al., 2015; Yokum & Stice, 2016; Pannacciulli et al., 2006). Further, obesity, like chronic stress, is associated with psychiatric disorders that are related to alterations in these regions, including anxiety disorders, depression, and substance abuse (Dietz, 1998; Boutelle et al., 2010; Carr et al., 2013; Weniger & Lange, 2006; Frodl et al., 2002; Goldstein & Volkow, 2011; Sala et al., 2004; Tomasi & Volkow, 2013).

Although a range of neurobiological evidence exists for the effects of chronic stress early in life on the brain and behavior, there has been less research on the neurodevelopmental impact of obesity, and very limited research on how effects of both factors emerge and interact early in development. Examining chronic psychosocial stress and obesogenic diet consumption together is challenging in human subjects, because the effects are difficult to disentangle and experimental control and random assignment to stress and diet conditions is not feasible or ethical. Additionally, much of the research on ELS and childhood obesity is retrospective, taking place later in life once their effects have already manifested, preventing complete understanding of the early impact of exposures, including the unfolding of effects throughout development and the potential biological mediators (e.g. dysregulation of the stress response and chronic inflammation).

Chronic Activation of the Autonomic and Endocrine Stress Responses

Acute stressors activate two neuroendocrine stress response systems which, under non-chronic conditions, are effective at preparing the body to respond to a threat while maintaining

homeostasis. The sympathetic-adrenomedullary (SAM) response is fast-acting: information related to acute stressors is relayed to the hypothalamus and brainstem, activating preganglionic sympathetic neurons in the spinal cord, which initiate the sympathetic neural response through direct innervation of organs such as the heart and lungs, increasing heart and respiration rates while simultaneously activating the SAM response (Ulrich-Lai & Herman, 2009). The SAM response is initiated by sympathetic innervation of the adrenal glands to release the catecholamines noradrenaline and adrenaline into the blood, which act as stress hormones throughout the body, increasing heart rate and dilating lung and skeletal muscle blood vessels while constricting non-essential organs (Kvetnansky, Sabban, & Palkovits, 2009). Following the threat, the parasympathetic nervous system acts like a brake to reestablish balance.

The slower, longer-lasting hypothalamic-pituitary-adrenal (HPA) axis is activated by stressors concurrently with the SAM response. Information is transmitted to the HPA axis via stressor-specific neural pathways (e.g. through threat assessment by the AMYG, which is one of the structures that projects to and activates the HPA axis) which stimulate parvocellular neurons in the paraventricular nucleus (PVN) of the hypothalamus to release corticotropin-releasing hormone (CRH) to the portal vascular system (Chrousos & Gold, 1992; Johnson, Kamilaris, Chrousos, & Gold, 1992). CRH then binds to receptors in the pituitary, triggering the release of adrenocorticotropic hormone (ACTH) into systemic blood circulation. When ACTH reaches the adrenal glands, it binds to receptors on adrenal cells, activating the synthesis and release of glucocorticoids (GCs; e.g. cortisol in primates, corticosterone in rodents) (Ulrich-Lai & Herman, 2009; Myers, McKlveen, & Herman, 2012). GCs act systemically, binding to glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) to mobilize energy and increase the effect of the SAM response. GRs and MRs are intracellular receptors that translocate to the

nucleus after binding with GCs, where they act as transcription factors and regulate gene expression (Ulrich-Lai & Herman, 2009; Charmandari, Tsigos, & Chrousos, 2005). GCs also act as a negative feedback mechanism for the HPA axis: when they bind to GRs in the hypothalamus and pituitary (and other extrahypothalamic regions, such as the hippocampus and PFC), they inhibit synthesis of ACTH and CRH, shutting down the axis and preventing further GC synthesis (Herman et al., 2012).

The HPA axis and SAM response are adaptive responses to acute stressors that mobilize energy and aid survival. But under conditions of chronic stress, consistent activation may cause these systems to become compromised. The negative feedback mechanism of the HPA axis is particularly vulnerable to impairment as a result of chronic stress, which creates the potential for excessive and prolonged release of GCs (Raadsheer et al., 1994; Makino, Smith, & Gold, 1995; Makino, Hashimoto, & Gold, 2002; Myers, McKlveen, & Herman, 2012). Through their regulation of gene expression in the brain, the GRs and MRs that bind those high GC concentrations are capable of influencing dendritic arborization or atrophy (Fuchs et al., 2001; Lucassen et al., 2014; Arnsten, 2009; McEwen, Nasca, & Gray, 2016; Hall, Moda, & Liston, 2015) and remodeling synapses and myelin (Hall, Moda, & Liston, 2015), allowing elevated GC exposure to enact direct effects on brain structure and function. Indeed, children of lower socioeconomic status have shown increased baseline cortisol levels (Lupien, King, Meaney, & McEwen, 2000), and elevated GC levels under conditions of chronic stress have been linked to increased dendritic arborization in the AMYG (Lucassen et al., 2014), while causing dendritic atrophy in the HIPP (Fuchs et al., 2001) and PFC (Arnsten, 2009; McEwen, Nasca, & Gray, 2016), demonstrating that elevated GCs are a potential chronic stress-related biological mechanism that can affect brain structure. Obesity and increased adipose mass are also

associated with HPA axis over-activation and increased GC production (e.g. hypercortisolemia) (Pasquali et al., 2002; Baudrand & Vaidya, 2015), and sustained consumption of an obesogenic diet has been shown in a number of studies to increase GC secretion in response to stressors (Michopoulos, Toufexis, & Wilson, 2012; Pasquali et al., 2003; Legendre & Harris, 2006), further implicating elevated levels of GCs as a mechanism by which both chronic stress and obesogenic diets may impact the brain.

In addition to obesogenic diets and chronic stress both causing over-activation of the HPA axis and elevation of GC levels, both factors are also associated with chronic inflammation. Stress, indeed, activates the acute inflammatory response through SAM activation (Raison & Miller, 2011). The release of adrenaline and noradrenaline to the blood activates pro-inflammatory pathways in monocytes, mediating the release of pro-inflammatory cytokines, including Interleukin-6 (IL-6) (Dinarello, 2010). The rise in the blood concentration of IL-6 under conditions of acute or chronic inflammation triggers the synthesis of C-reactive protein (CRP), primarily in the liver, which magnifies inflammation by activating the pro-inflammatory complement system, a part of the innate immune system that acts to remove damaged cells during injury or infection (Thompson, Pepys, & Wood, 1999). During the acute stress response, the GCs released by the HPA axis have an anti-inflammatory effect that maintains homeostasis (McEwen et al., 1997; Sapolsky, Romero, & Munck, 2000; Silverman & Sternberg, 2012). However, conditions of chronic stress with prolonged GC exposure can affect HPA axis negative feedback, and can cause innate immune cells to develop GC resistance through alterations in GR functioning and expression (Barnes, 2006; De Bosscher, Vanden Berghe, & Haegeman, 2006; Pace, Hu, & Miller, 2007), impairing the ability of GCs to suppress inflammation (Reader et al., 2015; Silverman & Sternberg, 2012). In addition, chronic stress leads to hypersecretion of

adrenaline and noradrenaline, further stimulating monocytes to produce pro-inflammatory cytokines (Wurtman, 2002). Higher levels of CRP and IL-6 have been found in humans of low socioeconomic status (Pollitt et al., 2008; Loucks et al., 2010), and obesity has also been linked to chronic inflammation by way of excess macronutrients in adipose tissue that induce enlargement of adipocytes and subsequent decreased blood supply, or hypoxia, to these cells, stimulating the release of pro-inflammatory mediators (Ellulu et al., 2017). Importantly, peripheral inflammation has been found to activate microglia in the brain, prompting their release of local inflammatory cytokines which results in neuroinflammation (Brooke et al., 1994). Further, over-activation of microglia can cause alterations in synaptic pruning and impact myelination and white matter brain structure (Mottahedin et al., 2017; Kucharova et al., 2011), affecting brain structure and function. Microgliosis in the PFC has been linked to stress-related psychopathology, including depression (Steiner et al., 2008; Setiawan et al., 2015). Clearly, both chronic stress and obesogenic diets can result in elevated levels of GCs and a pro-inflammatory state, biological signals which have the potential to be important mediators between stress- and diet-induced structural brain alterations and neurobehavioral outcomes.

Rhesus Macaque Model of Social Subordination Stress

Non-human primate (NHP) models are very useful to disentangle the neurobehavioral effects and underlying biological mechanisms of postnatal exposure to obesogenic diets and chronic stress, considering the difficulties and ethical concerns inherent to the experimental control of such factors in children. Macaque species provide a particularly translatable model due to their neurodevelopmental, behavioral and physiological similarities with humans, including reciprocal connections between the PFC and the AMYG, INS, and NAcc (Ghashghaei & Barbas,

2002; Augustine, 1996), protracted PFC development (Knickmeyer et al., 2010), and complex maternal and social behaviors (Byrne & Whiten, 1988). Protracted PFC development in children and macaques allows sculpting of brain regions by early experience, including by environmental insults like chronic stress (Hertzman & Wiens, 1996; Hertzman, 1999; McEwen, 2012). Naturalistically-occurring social subordination in female rhesus macaques is a well-validated translational model for chronic psychosocial stress in humans (Michopoulos, Higgins, Toufexis, & Wilson, 2012; Shively & Willard, 2012), allowing research on the effects of chronic social stress during this highly plastic window of early neurodevelopment. As part of matrilineal rhesus macaque dominance hierarchies, infants assume the relative group and familial social ranks of their mothers (Bernstein, 1976). Subordinate ranking monkeys receive significantly more aggression and harassment from high-ranking animals, and fewer affiliative behaviors from groupmates (Sapolsky, 2005; Silk, 2002; Abbott et al., 2003; Michopoulos, Higgins, Toufexis, & Wilson, 2012). The often unprovoked, unpredictable aggression from dominant animals (Abbott et al., 2003) reliably induces HPA axis over-activation and chronic-stress-related phenotypes in subordinate monkeys, including anxiety-like behaviors and emotional dysregulation (Shively, 1998; Shively et al., 2005; Kaplan et al., 1996; Gust et al., 1991; Snyder-Mackler et al., 2016; Zehr, Van Meter, & Wallen, 2005; Kaplan & Manuck, 2004; Wilson & Kinkead, 2008; Morgan et al., 2002). Subordinate female rhesus macaques have also shown higher expression of genes involved in chemokine and cytokine inflammation (Snyder-Mackler et al., 2016; Tung et al., 2012). Low-ranking animals may begin to receive aggression even during infancy (Spencer-Booth, 1968), and effects of social subordination are communicated at an early age through perceived harassment directed towards family members as well as immunological and hormonal signals present in breastmilk from mothers, including cytokines and GCs (Casabiell et al., 1997;

Hart et al., 2004; Innis, 2007). By the time they are juveniles, at pre-puberty, subordinate animals already show neurodevelopmental outcomes related to chronic stress, including elevated cortisol and alterations in structural brain development as evidenced by measures of white matter integrity (Howell, Godfrey et al., 2014). Further, subordinate rhesus monkeys have shown susceptibility to stress-induced overeating of high fat, high sugar diets (Michopoulos, Toufexis, & Wilson, 2012; Arce et al., 2010), and adult subordinate animals were found to eat nearly twice as many calories in the presence of an obesogenic diet (Arce et al., 2010). The naturalistic model of chronic psychosocial stress provided by rhesus macaque social subordination can thus be coupled with experimental control of diet condition, an approach which allows for systematic study of the potentially synergistic neurodevelopmental effects of obesogenic diets and chronic social stress and their underlying biological mechanisms, as well as an understanding of how alterations unfold early in development.

Aims and Hypotheses

In this study, we fed dominant (DOM) and subordinate (SUB) rhesus monkeys different postnatal diets to investigate how social subordination stress interacts with consumption of an obesogenic diet to impact the structural development of corticolimbic regions involved in stress and emotional regulation and reward processing, as well as biological mechanisms that may underlie structural brain alterations. To probe biological mechanisms, we examined effects of diet and stress on markers of chronic HPA axis activation (hair cortisol), and markers of inflammation (CRP), as well as on kilocalories (Kcals) consumed of the different diets, and examined whether these variables predicted structural brain effects of diet and subordination. We followed subjects from infancy through the juvenile, pre-pubertal period (i.e. up to 16 months of

age), and fed animals either a low-calorie-only diet (LCD), or both the LCD and an obesogenic diet higher in calories, fat, and sugars (HCD) that could be chosen ad libitum (Choice condition). During the lactational period, roughly from birth through 6 months of age, the dietary condition of the mothers matched that of the infants. We hypothesized that social subordination would promote hypercaloric consumption in the Choice condition, an outcome which would emerge by 6 months of age, after the weaning period, and become most pronounced by 16 months of age. We also hypothesized that social subordination and consumption of an obesogenic diet would synergize to alter the structural developmental trajectory of corticolimbic regions, producing increases in AMYG and decreases in hippocampal, PFC, and INS volumes. For corticolimbic outcomes, we hypothesized that all experimental groups would show similar brain volumes at the earliest 2 week time point, but that volumetric differences by group would emerge by 6 months and be most evident at 16 months of age. We further hypothesized that subordination status and consumption of an obesogenic diet would synergize to increase levels of cortisol and inflammatory markers. For hair cortisol, we hypothesized that levels would be highest at birth but not significantly different by experimental group, before decreasing across development while becoming increasingly elevated in subordinate compared to dominant animals, and in animals consuming the HCD compared to those consuming only the LCD. For CRP levels, we hypothesized that group differences (subordinate>dominant, Choice>LCD) would emerge across development while overall CRP levels increased, becoming most distinct by group at the pre-pubertal period. Finally, we hypothesized that cumulative exposure to hair cortisol, CRP, and consumption of HCD kilocalories would predict alterations in the overall rate of growth of corticolimbic regions between the 2 week and 16 month time points.

Methods

Subjects

Subjects were 41 female rhesus macaques (*Macaca mulatta*) born across three different birth seasons (Spring of 2014, 2015, or 2016) at the Yerkes National Primate Research Center (YNPRC) Field Station in Lawrenceville, GA. They were reared by dams in large social groups composed of approximately 2-3 males, 30-60 adult females, and their offspring. The animals lived in outdoor enclosures with access to climate-controlled indoor areas attached. Data were collected longitudinally during the first 16 months of life, from infancy through the juvenile, pre-pubertal period (Figure 1: at birth for baseline assessments; at 2 weeks to assess potential early effects of social rank and diet through the mother's milk; at 6 months for measures during weaning, when infants eat solid food and are more independent from dams; and at 16 months to assess effects during the juvenile period). All procedures were approved by the Emory University Institutional Animal Care and Use Committee (IACUC), 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."

Dam Selection and Prenatal Diet Conditions

Multiparous dams were selected for the study prior to infant birth based on their relative rank in the social hierarchy. Macaque social groups form a dominance hierarchy in which lower-ranking animals emit visibly submissive behaviors in response to approach or aggression from a dominant animal (Bernstein, 1976). These types of dyadic agonistic interactions were recorded via group dominance observations to determine the social status of individuals in the social groups. The dams assigned to the study were from families at the extreme ends of their group's

social hierarchy: dominant dams were selected from families ranked in the top third of the group, and subordinate dams were selected from families ranked in the bottom third. Primiparous females as well as females with a history of infant physical abuse or neglect were excluded. Since a focus of this study was on the developmental effects of postnatal exposure to an obesogenic diet, all pregnant females were on the chow-based, low-calorie-only diet (LCD) before conception and through gestation to control for previously reported neurobehavioral effects of the prenatal dietary environment (Sullivan et al., 2010; Teegarden, Scott, & Bale, 2009; Reyes, 2012). To avoid the effects of prematurity and/or low birth weight on brain development (Scott et al., 2015), dam-infant pairs were excluded from the study if infant birth weight was <450g.

Infant Assignment to Experimental Group and Cross-Fostering

The specific developmental effects of postnatal diet were examined through our experimental control of automated feeders that allow subject access to only the LCD or to both the LCD and the obesogenic, high calorie (HCD) diets (Choice condition). Given the potential effects of heritable/prenatal factors related to social rank, including genetic or epigenetic transmission of traits, or exposure to prenatal maternal stress in the subordinate mothers (Phelan et al., 2011; Schlotz & Phillips, 2009), we used a cross-fostering design with random assignment at birth to social rank group to further disentangle the effects of postnatal exposure to subordination stress from heritable or prenatal effects related to social rank. Thus, as shown in Table 1, approximately half (n=21) of the newborns were randomly selected to be cross-fostered to dams of the same or different social status as their biological mother. Infants were cross-fostered within 48 hours of birth using well-established procedures (Howell et al., 2016; Drury et

al., 2017) and the effect of biological mother's rank (and cross-fostering status) were later assessed in the statistical models. The remaining subjects were reared by their biological mother. Because all rhesus offspring assume the social status of their mothers (Bernstein, 1976), cross-fostered infants assumed the social status of their foster mothers. A total of 21 dominant-ranking and 20 subordinate-ranking mother-infant pairs were followed postnatally. Ranks were assessed each month to monitor potential (albeit rare) changes in hierarchy in the groups. The relative rank of each subject was calculated as the ratio of its postnatal dam's social status divided by the total number of animals older than 3 years of age in the group, excluding adult males (i.e. a dam with a rank of 30 out of 100 animals was assigned a relative rank of 0.30, and this rank was assumed by her infant; Howell, Godfrey et al., 2014).

Diet Intervention

Table 1 summarizes the distribution of subjects across diet, rank, and cross-fostering groups. The Choice condition, which includes access to both a LCD and a HCD, closely models the "Western" human diet and has been shown to allow for stress-induced, emotional feeding in animal models (Michopoulos, Moore, & Wilson, 2013; Moore et al., 2013; Warne, 2009; Wilson et al., 2008) as well as to promote obesity more effectively than a HCD alone (Moore et al., 2013). The LCD was LabDiet Monkey Diet 503A, a pelleted version of the standard, low caloric, LabDiet Monkey Diet 5038 (Purina Mills International, St. Louis, MO). The LCD diet contained 3.45 kilocalories (Kcals)/gram, distributed as 12% fat, 4.14% sugar, 65.9% starch, and 18% protein (Table 2). The HCD pellets (D14051502B, Research Diets, Inc.) contained more Kcals per gram (4.25 Kcals/gram), distributed as 30% fat, 29.8% sugar, 20.2% starch, and 20% protein. LCD and HCD pellets provided comparable amounts of vitamins and minerals.

Food (as well as water) was provided *ad libitum*. Subjects could access the feeders at any time, via radio-frequency identification (RFID) chips subcutaneously implanted in their wrists that were programmed to allow them access to only LCD feeders or to both the LCD and HCD feeders in their compound, depending on their diet group assignment. Dams had RFID chips implanted at the outset of the experiment, and infants received RFID chips at 6 weeks of age, before weaning and the transition to eating solid food (Stroud et al., 2006). Feeders were automated and had radio-frequency antenna that scanned subject RFID chips, dispensing a single pellet at a time and quantifying each subject's caloric intake. This feeding system has been previously validated to allow monkeys to consume food as desired while allowing researchers systematic control over subject access to the two experimental diets and accurate recording of the Kcal consumption from each diet (Arce et al., 2010; Wilson et al., 2008). The validation of this system has also shown that subjects almost always consume a pellet of food once they have taken it from the feeder (Wilson et al., 2008). LCD and HCD calorie intake was recorded continuously for the first 16 months of life to determine the effects of diet condition and social status on Kcal intake (measured as Kcals/day, which was computed into cumulative Kcals consumed of the LCD, HCD, or Total (LCD+HCD) through 6 months and between 6 and 16 months of age).

Body Weight Measurements

Body weights (in kg) were collected at birth, 2 weeks, 6 months, and 16 months of age.

Physiology Measures

Inflammatory marker: C-reactive Protein

C-reactive protein (CRP) was measured as a peripheral inflammatory marker from baseline blood plasma samples collected at sunrise at 2 weeks, 6 months, and 16 months of age. CRP concentrations were measured using Meso Scale Discovery electrochemiluminescent (ECL) immunoassay V-PLEX human panels on the MSD SECTOR Imager 2400-A (Meso Scale Diagnostics, LLC, Rockville MD). Samples were diluted by a factor of 1000 and run in duplicate. The assay includes conversion of the ECL signal to pg/mL values based on standard curves of calibrator proteins. All samples included in the analysis had coefficient of variation (CV) values <10%.

Stress marker: Hair Cortisol Accumulation

High accumulation of cortisol in hair is an indicator of chronic stress in primates (Davenport et al., 2008; Davenport et al., 2006). To examine potential exposure to prenatal stress (particularly in infants with socially subordinate dams) hair samples were shaved from the nuccal area at birth to assay cortisol hair concentrations. Additional postnatal hair samples were shaved from the same area at 6, 11.5, and 16 months of age to examine accumulation of the stress hormone in the hair that grew between those ages. Hair cortisol levels were analyzed based on previously established protocols (Davenport et al., 2006; Meyer, Novak, Hamel, & Rosenberg, 2014). Each sample was weighed, washed twice in isopropanol to remove external contamination, ground to a fine powder, and then extracted with methanol overnight. The methanol was evaporated, the residue was re-dissolved in the assay buffer, and cortisol was then measured using the Salimetrics (Carlsbad, CA) enzyme immunoassay kit (cat. # 1-3002) according to the manufacturer's directions. Intra- and inter-assay CV were <10%.

Structural MRI

MR Image Acquisition

Structural MRI scans were collected at 2 weeks, 6 months, and 16 months of age. One day prior to each scan, infant subjects (2 weeks and 6 months) were transported with their mothers from the YNPRC Field Station to the Imaging Center. At 16 months, the juveniles were transported alone. Using a 3T Siemens Magnetom TRIO system (Siemens Med. Sol., Malvern, PA, USA), and an 8-channel phase array coil, T1 and T2-weighted structural MRI scans were collected in the same session. T1-weighted scans were acquired 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 scans were collected in the same direction as the T1-weighted scans (TR/TE = 3200/373msec, FoV: 128mm, voxel size: $0.5mm^3$ isotropic, 3 averages, GRAPPA, R=2) to aid with delineation of regions of interest (ROIs) by improving the contrast of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) borders (Rapisarda et al. 1983; Knickmeyer et al., 2010).

To prevent motion artifacts, subjects were scanned under isoflurane anesthesia (1% to effect, inhalation) following induction with telazol (2-4 mg/kg body weight, i.m.) and intratracheal intubation. Physiological parameters were monitored throughout the scan with an oximeter, electrocardiograph, rectal thermometer, and blood pressure monitor. Hydration was maintained with dextrose/NaCl (0.45%) administered through an I.V. catheter, and body temperature was stabilized with an MRI-compatible heating pad. All subjects were scanned in the same supine position and orientation, using a custom-made head holder with ear bars and a mouth piece. A vitamin E capsule was taped to the right temple to mark the right side of the

head. Upon full anesthesia recovery at the end of the scanning session, infants were immediately returned to their mothers in shared housing, and the pair (or juvenile) was returned to their social group the following day. Three infants could not be scanned at 2 weeks because either the infant or mother was sick, but they were retained in the study because they did not have missing data at the other two ages.

sMRI Processing

Structural data was processed and analyzed using AutoSeg (version 3.3.2) and NeoSeg (version 1.0.7; for specific steps only applicable to the 2 week time point), which are open-source pipelines developed by the Neuro Image Research and Analysis Laboratories of the University of North Carolina (NIRAL; Wang et al., 2014). The atlas-based software pipelines use an automatic segmentation approach to segment brain images into probabilistic tissue maps, cortical lobar parcellations, and subcortical regions of interest (ROIs). NeoSeg (for 2 week subjects) and AutoSeg (for 6 and 16 month subjects) were used to automatically segment the brain into tissue classes (WM, GM, and CSF), and AutoSeg was used for all subjects to generate parcellations of cortical lobes (for this study: the prefrontal cortex (PFC) and insula (INS)), and subcortical structures (amygdala (AMYG) and hippocampus (HIPP)) to compute their respective volumes in subjects.

Volume computations were achieved by registering each subject's native space images into population-based, age-specific T1- and T2-MRI brain atlases (Figure 2A) using the BRAINSFit tool, a module in the Slicer program (developed by MIT and Surgical Planning Lab; Liu et al., 2015; Shi et al., 2016; Fedorov et al., 2012; Styner et al., 2007). Inhomogeneity was corrected with N4-ITK bias field correction, which accounts for variations in MRI image

intensity within each tissue class resulting from imperfections in the radiofrequency (RF) coil (Tustison et al., 2010). Atlas Based Classification (ABC) then used the ANTS (Advanced Normalization Tools) registration tool and intensities from both T1 and T2 images and atlas-specific tissue priors to assign a tissue label to each voxel in the subject's image, which enabled automatic classification of subject images into brain tissue (WM, GM, CSF) or non-brain tissue (e.g. skull, vessels, muscle) (Tustison & Avants, 2013; Liu et al., 2015). This step allowed for removal of non-brain tissue from the image (skull stripping), which was manually edited by researchers blind to group. A second round of ABC was performed after skull stripping to register the images to skull-stripped versions of the atlases, and warp fields were generated for each of the cortical and subcortical parcellations and applied to generate cortical and subcortical parcellations in the subject. Cortical parcellations were merged with tissue segmentations, which allowed AutoSeg to compute volumes for cortical ROIs subdivided by WM, GM, and CSF, as well as total volumes of tissue classes. Volumes were calculated for intracranial volume (ICV), defined as total WM + GM + CSF (Figure 2B), as well as right and left ROIs: PFC (total PFC, PFC GM, PFC WM), INS (total INS, INS GM, INS WM), AMYG, and HIPP.

Cortical and subcortical parcellations generated automatically by AutoSeg were manually adjusted to ensure accurate anatomical delineation of structures following published definitions (Figure 2C; Amaral & Bassett, 1989; Paxinos et al., 2000; Sallem & Logothetis, 2006). The AMYG was defined following macaque anatomical landmarks (Price, Russchen, & Amaral, 1987; Amaral & Bassett, 1989) with WM (including the internal capsule, optic and auditory radiations, and the anterior commissure) as the superior boundary; the lateral ventricle/temporal horn as the as the posterior inferior boundary, including the AMG-HIPP transition area as part of the AMYG ROI; the HIPP as the posterior boundary; the rostral periamygdaloid cortex as the

anterior boundary; and the meninges as the medial boundary (Howell, Grand et al., 2014; Knickmeyer et al., 2010; Payne et al., 2010; Saleem & Logothetis, 2012). The horn of the lateral ventricle was the dorsal and lateral boundary of the HIPP, and the WM separating the HIPP from the entorhinal cortex was the ventral border (Knickmeyer et al., 2010; Saleem & Logethetis, 2012). The PFC was defined using CSF at the surface of the brain as the lateral and anterior boundaries, the interhemispheric fissure as the medial boundary and the arcuate sulcus as the posterior boundary (Knickmeyer et al., 2010; Saleem & Logothetis, 2012). The inferior boundary, which changed moving rostral to caudal, was defined by the CSF, the sylvian fissure, and the arcuate sulcus (Saleem & Logothetis, 2012; Seltzer & Pandya, 1978). The INS was defined laterally and inferiorly by the lateral sulcus, and medially and superiorly by WM. It included the granular, dysgranular, agranular, and insular proisocortex subdivisions (Knickmeyer et al., 2010; Saleem & Logothetis, 2012; Seltzer & Pandya, 1978; Stephani et al., 2011).

Statistical Analysis

Analyses were performed using SPSS (Version 25; developed by IBM Corp.), and a p-value ≤ 0.05 was considered significant. Variables were summarized as mean ± standard error of the mean (SEM). Kolmogorov-Smirnov tests were used to assess the normality of all variables, and non-normally distributed variables were log10-transformed. We used linear mixed modeling (LMM) analyses to examine the longitudinal effects of postnatal experience of social subordination and obesogenic diets on structural brain development (ICV and volumes of AMYG, HIPP, PFC and INS; Aim 1), as well as on biological measures of caloric intake, growth, stress activation (cortisol) and inflammation (CRP; Aim 2). Using hierarchical linear regression, we examined the biological signals that predicted growth of ROIs and ICV (Aim 3).

We also examined the effects of potential confounding variables such as social group (compound), birth year (cohort), cross-fostering, and biological mother's rank (for cross-fostered animals) on our outcome measures, using hierarchical linear regression analyses. Confounding variables that significantly contributed to the variance were included as a covariate in the final LMM for that measure.

LMM for sMRI Data

All sMRI variables were normally distributed. As described above, we first performed hierarchical linear regression to examine whether any potentially confounding variables (cross-fostering, cohort, compound, and biological mother's rank) explained a significant amount of the variance in any of the sMRI measures, by examining the R-squared-change value when removing each confounder from the regression model for each brain measure. None of the potential confounders accounted for significantly more variance than the effects of age in the analyses, and were therefore excluded from the final LMMs.

LMM was used to longitudinally examine the fixed effects of diet condition (LCD vs. choice), social status (DOM vs. SUB), age (2 weeks, 6 months, 16 months), and their interactions on ICV and ROI volumes over the first 16 months of life. For ROIs (AMYG, HIPP, PFC, PFC WM and GM, INS, and INS WM and GM), Laterality (brain hemisphere: right vs. left) was also included in the model as an additional repeated measure and fixed factor to account for hemispheric differences in ROI volumes. Subject was entered as a random effect in each model in order to account for individual variation across subjects.

As shown in detail below (see Results), effects of diet were detected on total brain size (ICV); thus, LMM analyses were repeated for each ROI with ICV as a covariate (random effect)

in the model to account for differences in overall brain size when assessing effects on ROI volumes. Notably, the AutoSeg pipeline does not calculate ICV in each hemisphere, which is instead measured across the whole brain. As a result, analyses of the effects on ROIs with ICV were only assessed on the total ROI (left + right) and differences in ROIs across hemispheres were not assessed.

LMM for Biological Signal Data

Outliers, defined as above or below three standard deviations (SD) from the mean, were removed from the analyses. CRP and hair cortisol were log10-transformed for normality. As described for sMRI data, a hierarchical regression model was used to examine potential effects of confounding variables on outcome measures (Total and HCD kcals consumed; body weight; CRP; hair cortisol). As before, confounders that significantly contributed to the explained variance in the model were included as a covariate (fixed factor) in the subsequent LMM analysis.

LMM was used to examine the fixed effects of diet condition, social status, age (2 weeks, 6 months, 16 months), and their interactions on CRP levels during the first 16 months of life. Hierarchical regression analyses revealed a confounding effect of cross-fostering on CRP levels; thus, this variable was entered into the LMM as a covariate (fixed factor). In order to characterize the effects of cross-fostering, post-hoc analyses were conducted separately for animals that were cross-fostered and those that were not.

For hair cortisol, a similar statistical approach was used. Consistent with previous findings in human and nonhuman primates (Grant et al., 2016; Jerker, Frostell, Theodorsson, & Faresjö, 2013), our data showed that hair cortisol levels at birth are considerably higher than

levels at later ages. Since this difference represents a measure of prenatal cortisol exposure, it was excluded from the overall LMM cortisol model. We focused instead on the postnatal 6, 11.5 and 16 month time-points as repeated measures. Effects of birth hair cortisol levels were accounted for in the LMM by including it as a covariate (random factor). Cohort was also included as a covariate (fixed factor) based on its significant confounding effects on cortisol. As with cross-fostering, post-hoc analyses were conducted separately for each cohort.

Both cohort and biological mother's rank (in cross-fostered subjects) had confounding effects on body weight, requiring multiple stages of analysis. The ages of interest for body weight were birth, 2 weeks, 6 months, and 16 months. The first LMM included cohort as a covariate (fixed factor). As a post-hoc analysis to this test, results were separated by cohort group. Given that biological mother's rank is only relevant to cross-fostered animals, we analyzed a third model that excluded non-cross-fostered subjects, and included both cohort and biological mother's rank as covariates (fixed factors). Results were not further separated in post-hoc analyses, because there would have been small sample size and insufficient power for each group.

There were no effects of potential confounders on cumulative HCD Kcals consumed or total cumulative Kcals consumed; thus, no covariates were added to the LMM for Kcal measures. The HCD and total Kcals LMM analyses used the 6 month (cumulative Kcals consumed to 6 months) and 16 month (cumulative Kcals consumed between 6 and 16 months) time-points, because subjects do not consume sufficient solid food at earlier ages. Fixed effects of diet condition, social status, age, and their interactions on HCD and total Kcal consumption were assessed. As in the other linear mixed models, the random effect of individual subject was accounted for.

Results

Structural MRI Linear Mixed Models (LMM)

No significant effects of potential confounding factors were detected on any of the sMRI measures using hierarchical regression analyses, so they were not included in the final LMM results reported in this section.

Intracranial Volume (ICV)

Intracranial volumes increased with age (Figure 3; $F(2, 68.85)=481.94$, $p<.001$), and subjects that consumed the HCD showed significantly larger ICV across ages ($F(1, 100)=19.73$, $p<.001$). There was no significant main effect of Social Status, and there was no significant Age x Diet interaction or any other interaction effect on ICV.

Amygdala

AMYG volumes increased with age (Figure 4; $F(1, 158)=4133.06$, $p<.001$), and there was a significant main effect of Hemisphere ($F(1, 158)=32.76$, $p<.001$; L>R). Subjects that consumed the HCD exhibited larger AMYG volumes ($F(1, 158)=22.70$, $p<.001$), an effect which seems magnified with increasing age, as shown by an Age x Diet interaction effect ($F(1, 120)=4.82$, $p=.010$). Even after accounting for the effects of ICV (proxy for brain size and entered as a covariate in the LMM model), the main effect of Diet ($F(2, 106)=7.72$, $p=.006$) and Diet x Age interaction ($F(2, 50)=7.12$, $p=.002$) were both retained.

Main effects of Social Status were also detected, with subordinate subjects showing significantly larger AMYG volumes than dominant subjects ($F(1, 158)=41.83$, $p<.001$). This

effect was also retained when accounting for ICV ($F(1, 106)=11.22$, $p=.001$). No interaction effects involving Social Status were observed in the AMYG.

Hippocampus

The HIPP increased with age (Figure 5; $F(1, 108)=4375.39$, $p<.001$), and a main effect of Hemisphere was detected ($F(1, 142)=14.69$, $p<.001$; R>L). A main effect of Social Status was observed, with subordinate animals showing significantly larger HIPP volumes than dominant animals ($F(1, 142)=53.84$, $p<.001$). An Age x Social Status interaction was also found ($F(2, 108)=3.88$, $p=.024$) with social status effects seeming to increase with age. When effects of ICV were accounted for, the Social Status effect ($F(1, 7964)=8.65$, $p=.003$) and Age x Social Status interaction ($F(2, 52)=6.74$, $p=.002$) on HIPP volumes remained significant. No other main or interaction effects were detected.

Prefrontal cortex

PFC volumes increased with subject age (Figure 6; $F(2, 135)=1876.94$, $p<.001$). A main effect of Diet was also found ($F(1, 179)=26.52$, $p<.001$), with subjects that consumed the HCD showing larger total PFC volumes across ages. No other main or interaction effects were found for total PFC volumes. The effect of Diet was not significant when the effects of ICV were accounted for. After controlling for ICV, though, a main effect of Social Status emerged in the total PFC, with subordinate animals showing significantly larger PFC volumes than dominant animals ($F(1, 75)=6.34$, $p=.014$). There was also an Age x Social Status interaction after accounting for ICV ($F(2, 32)=3.91$, $p=.030$), where effects of social status seem to become stronger with age.

Results for PFC GM indicate volumetric growth with age (Figure 7; $F(2, 127)=861.93$, $p<.001$). A main effect of Diet was also found, with subjects that consumed the HCD showing significantly larger volumes than those on the LCD alone ($F(1, 184)=31.15$, $p<.001$). This effect remained significant when ICV was accounted for ($F(1, 38)=5.45$, $p=.025$).

A main effect of age was also seen in PFC WM, with volumes decreasing slightly to 6 months before increasing to 16 months (Figure 8; $F(2, 128)=56.89$, $p<.001$). Subjects that consumed the HCD exhibited larger PFC WM volumes across ages ($F(1, 197)= 16.63$, $p<.001$), which remained significant when effects of ICV were accounted for ($F(1, 38)=4.43$, $p=.042$). No other main or interaction effects were detected for PFC GM or PFC WM development across groups.

Insular cortex

Total INS volumes increased with age (Figure 9; $F(2, 138)=648.98$, $p<.001$). Subjects that consumed the HCD showed significantly larger overall volumes in the INS ($F(1, 193)=60.80$, $p<.001$). Total INS volumes also exhibited a main effect of Social Status, with subordinate animals showing larger volumes than dominant animals across ages ($F(1, 193)=5.70$, $p=.018$). The effect of Diet remained significant when controlling for the effects of ICV ($F(1, 38)=12.27$, $p=.001$), and an Age x Diet interaction emerged when ICV effects were accounted for ($F(2, 45)=4.83$, $p=.013$). The Social Status effect on INS volume was not consistent when the effects of ICV were accounted for.

INS GM also increased with age (Figure 10; $F(2, 142)=1076.61$, $p<.001$), and a main effect of hemisphere was detected $F(1, 186)=14.20$, $p<.001$). INS GM was larger in subjects that consumed the HCD than those that consumed the LCD only ($F(1, 186)=52.29$, $p<.001$), and an

Age x Diet interaction (F(2, 142)=3.09, p=.049) indicated that this effect became more pronounced with age. Both the main effect of Diet (F(1, 38)=9.81, p=.003) and the Age x Diet interaction (F(2, 48)=8.41, p=.001) on INS GM were sustained when the effects of ICV were controlled for.

There was a main effect of age on INS WM (Figure 11; F(2, 143)=803.30, p<.001); INS WM volumes decreased to 6 months before increasing to 16 months. There was also a main effect of Hemisphere (F(1, 149)=479.93, p<.001; R>L). Subjects that consumed the HCD exhibited larger INS WM volumes than LCD-only subjects (F(1, 149)=19.19, p<.001). A main effect of Social Status was also detected, with subordinate animals having larger INS WM volumes (F(1, 149)=5.73, p=.018). In addition to main Diet and Social Status effects, there was a significant Diet x Social Status interaction on INS WM: subordinate animals who consumed the HCD exhibited the largest volumes (F(1, 149)=4.32, p=.039). However, only the main effect of Diet on INS WM remained significant once the effects of ICV were accounted for (F(1, 53)=6.57, p=.013).

Biological Signals LMM

Inflammatory marker: C-reactive Protein

Cross-fostering explained a significant amount of the variance in the hierarchical regression analysis of confounding variables for CRP (F(1, 111)=5.52, p=.021), so it was entered as a covariate in the LMM analysis. CRP levels increased with subject age (Figure 12A; F(2, 58)=75.95, p<.001). A main effect of Social Status was detected such that across ages, subordinate animals showed higher levels of CRP than dominant animals (F(1, 87)=5.06, p=.027). No main effect of Diet or interaction effects of Age x Social Status or Diet x Social

Status were detected. Since cross-fostering had a significant effect on CRP levels as a covariate (Figure 12B; $F(1, 90)=6.61$, $p=.012$), a secondary LMM analysis was conducted separately for cross-fostered and non-cross-fostered animals. This analysis showed that for animals that were cross-fostered, CRP levels were higher in subordinate animals than in dominant subjects ($F(1, 34)=4.54$, $p=.040$). No significant effects of Social Status were observed in non-cross-fostered animals.

Stress marker: Hair Cortisol Accumulation

In the confounding variables assessment, Cohort explained a significant amount of the variance in hair cortisol ($F(1, 114)=4.94$, $p=.028$), so it was included as a covariate in the linear mixed model. Hair cortisol levels decreased with age (Figure 13A,B; $F(3, 54)=2715.59$, $p<.001$), and birth hair cortisol had a significant effect on hair cortisol levels as a covariate ($F(1, 34)=1.64$, $p<.001$). No main or interaction effects of Cohort, Diet, or Social Status on hair cortisol were observed.

Body Weight

A significant amount of the variance in body weight was explained by including Cohort in the assessment of confounders ($F(1, 158)=16.73$, $p<.001$). For cross-fostered subjects, including biological mother's rank in the confounders regression model also explained a significant amount of the variance in body weight ($F(1, 80)=8.12$, $p=.006$). Body weight increased significantly with age in both the model including Cohort as a covariate (Figure 14; $F(3, 47)=1181.10$, $p<.001$), as well as the model for cross-fostered subjects including Cohort and

biological mother's rank as covariates ($F(3, 21)=595.11$, $p<.001$). However, there were no significant main or interaction effects of Diet or Social Status on body weight in either model.

Kcal Consumption

None of the potential confounders explained a significant amount of variance in HCD or total Kcal consumption. Total Kcal consumption increased with age (Figure 15; $F(1, 37)=304.56$, $p<.001$). Subjects with access to the HCD consumed significantly more total Kcals than those with access to LCD only ($F(1, 37)=11.74$, $p=.002$). Dominant animals also consumed more total Kcals than subordinate animals ($F(1, 37)=12.53$, $p=.001$). Diet and Social Status effects became enhanced with age: significant Age x Diet ($F(1, 37)=6.43$, $p=.016$) and Age x Social Status ($F(1, 37)=7.38$, $p=.010$) interaction effects were observed.

When specifically analyzing consumption of HCD Kcals by subjects on the Choice diet, consumption also increased with age (Figure 14; $F(1, 37)=80.52$, $p<.001$), but there were no significant main or interaction effects involving Social Status.

Hierarchical Regression Model: Biological Predictors of Brain Growth

Based on the LMM analysis, CRP and Kcals consumed were identified as biological signal measures with significant main or interaction effects of Diet or Social Status to be tested as predictors of structural brain growth for ICV and ROIs. Our aim was to examine whether cumulative exposure to biological signals affected by diet and/or social status predicted volumetric brain growth rates, calculated for ICV and each ROI as the difference between the subject's 2 week and 16 month sMRI measures. To assess cumulative exposure to CRP, the area under the curve (AUC) was calculated for CRP levels. For Kcals, the cumulative measures from

each time point (6 and 16 months) were summed to represent total cumulative exposure to HCD Kcals vs. total Kcals. To account for the effects of ICV on regional brain volumes, ICV and age were entered as the first block of the regression for ROIs. Potential predictor variables were added to the model in the following order:

ROI growth rate = (ICV + Age) + CRP AUC + cumulative total or HCD Kcal exposure + social status + diet

Predictors of ICV growth were examined in a separate model that did not include the block accounting for ICV. Additionally, because INS WM volumes decreased substantially between 2 weeks and 6 months before increasing between 6 months and 16 months, INS WM was analyzed with two separate models: one that used the differences between the 2 week and 6 month measures, and one that used the overall difference between the 2 week and 16 month measures. For all models, R-squared-change values were examined with the addition of each variable to determine its explanation of the amount of variance in volumetric growth. To assess effects of total Kcal exposure against exposure to HCD Kcals (i.e. to probe whether the quality or the quantity of calories consumed is a better predictor of volumetric brain changes), the analysis was completed first with cumulative total Kcals, and then it was repeated with cumulative HCD Kcals.

Results: Biological Predictors of Brain Growth

Models are reported here for ROIs (as well as ICV) whose growth was significantly predicted by cumulative CRP exposure, total cumulative Kcals consumed, or cumulative HCD Kcals consumed. In the first model, which was used to examine ICV growth, CRP AUC, Social Status, and Diet were not significant predictors of ICV growth, whereas total Kcals consumed

was a significant predictor (Table 3; $F(1, 117)=8.81$, $p=.004$). In the model for ICV growth that incorporated HCD Kcal exposure, CRP AUC, HCD Kcals consumed, Social Status, and Diet were not significant predictors.

For AMYG growth, total Kcals consumed and Social Status were not significant predictors (Table 4). However, Age and ICV ($F(2, 113)=5.58$, $p=.005$), cumulative exposure to CRP ($F(1, 112)=13.49$, $p<.001$), and Diet ($F(1, 109)=16.60$, $p<.001$) were significant predictors of AMYG growth. In the second model that included HCD Kcal exposure, HCD Kcals consumed was not a significant predictor (Table 5).

For the HIPP, Age, ICV, CRP AUC, and Diet were not significant predictors (Table 4). Total Kcal consumption ($F(1, 111)=5.62$, $p=.019$) and social status ($F(1, 110)=14.88$, $p<.001$) were significant predictors of HIPP growth. In the second model, HIPP growth was not predicted by HCD Kcals consumed.

For total PFC growth, CRP AUC, Social Status, and Diet were not significant predictors (Table 4). Age and ICV ($F(2, 113)=6.07$, $p=.003$), and total Kcal consumption ($F(1, 111)=8.88$, $p=.004$) significantly predicted PFC growth. In the second model, cumulative HCD Kcal consumption was a significant predictor of PFC growth (Table 5; $F(1, 111)=5.87$, $p=.017$), but the model with total Kcal consumption predicted PFC growth better than the model with HCD Kcal consumption.

Total INS growth was not predicted by biological exposure variables (CRP AUC or total Kcals consumed) in the first model. In the second model, however, HCD Kcal consumption was a significant predictor of INS growth (Table 5; $F(1, 111)=5.64$, $p=.019$). Age, ICV, CRP AUC, and Social Status were not significant predictors in this model, but Diet did significantly predict INS growth ($F(1, 109)=8.71$, $p=.004$).

For INS GM growth, the biological exposure variables were also not significant predictors in the first model. In the second model, Age/ICV (Table 5; $F(2, 113)=3.61$, $p=.030$), HCD Kcals consumed ($F(1, 111)=13.03$, $p<.001$), and Diet ($F(1, 109)=11.00$, $p=.001$) were significant predictors of INS GM growth. CRP AUC and Social Status were not significant predictors.

Biological exposure variables did not predict INS WM growth to 6 months in the first model. In the second model, Age, ICV, CRP AUC, and Diet were not significant predictors (Table 5), however, HCD Kcals consumed ($F(1, 111)=25.94$, $p<.001$) and Social Status ($F(1, 110)=8.08$, $p=.005$) were predictors of INS WM growth to 6 months. For overall INS WM growth, biological exposure variables were also not significant predictors in the first model. In the second model, Age, ICV, CRP AUC, Social Status, and Diet were not significant predictors (Table 5), but cumulative HCD Kcal consumption was a significant predictor of overall growth of INS WM ($F (1, 111)=16.42$, $p<.001$).

Discussion

The aim of this study was to examine the effects of postnatal exposure to an obesogenic diet and social subordination stress on the structural development of brain regions associated with stress and emotional regulation, feeding control, and reward processing. We also sought to identify the biological mechanisms underlying obesogenic diet- and social subordination-related structural alterations. To accomplish this, we collected structural MRI, hair cortisol, C-reactive protein (CRP), body weight, and feeding data longitudinally during the first 16 months of life (i.e. from birth through the juvenile, pre-pubertal period) in female rhesus monkeys. We utilized a naturalistic model of chronic psychosocial stress experienced by subordinate rhesus monkeys,

where our subjects were selected from the extreme dominant and subordinate matrilines and had access to two postnatal diet conditions; one diet group had access to low-calorie feeders only (LCD), and the Choice group had access to both LCD feeders and to an obesogenic, higher calorie diet (HCD). Our main findings (summarized in Table 6) showed that animals on the Choice diet consumed more total Kcals than animals on the LCD diet by 6 months of age (i.e. weaning), and that these effects became more apparent at the 16-month time-point, when the consumption of HCD kcals was higher than LCD Kcals. However, the findings did not support the hypothesis that access to the HCD would promote hypercaloric consumption and increased body weight specifically in subordinate subjects; it was, in fact, the dominant animals that ate more Kcals throughout development. Further, we did not find diet or social status differences in body weight at any age, or significant effects of subordination or HCD consumption on hair cortisol levels, although we did find higher CRP levels in subordinate than dominant animals, supporting our hypothesis of increased inflammation in low ranking animals. However, rather than emerging at 6 months of age and becoming exacerbated with time, which is what we had hypothesized, effects of subordination on CRP levels emerged at the earliest, 2-week time-point and were maintained across ages. Our sMRI findings supported our hypothesis that postnatal exposure to an obesogenic diet and subordination would cause significant, long-term effects on structural brain development, but most of our outcome measures did not demonstrate a synergistic effect of consumption of the obesogenic diet and subordination. Rather, obesogenic diet consumption and social subordination seemed to have insult-specific effects, apart from a small number of common effects (e.g. both factors led to bigger amygdalae).

Subjects with access to the HCD showed larger overall brain (intracranial volume; ICV), prefrontal cortex (PFC), insula (INS), and amygdala (AMYG) volumes. Subordinate subjects

showed larger AMYG and hippocampus (HIPP) volumes. Interestingly, several of the structural brain effects of diet or social status were already present at 2 weeks, suggesting potential transmission through maternal biological signals (e.g. milk). Regarding biological predictors of rates of volumetric brain growth, cumulative CRP exposure predicted AMYG growth, total Kcal consumption predicted ICV, HIPP, and PFC growth, and HCD Kcal consumption, specifically, predicted PFC and INS growth. Altogether, our findings suggest that postnatal exposure to social subordination and obesogenic diets have significant and insult-specific effects on structural brain development, which emerge during infancy and seem to become exacerbated with age (or prolonged exposure). They further suggest that elevated inflammation is an important underlying biological mechanism of some of these structural effects, in addition to the cumulative Kcals consumed of the HCD.

Several findings in this study did not support our hypotheses. One discrepancy was that dominant subjects consumed more total Kcals than subordinates, and not the reverse. Further, when we focused on HCD Kcals consumed, there was no effect of social status. These findings are inconsistent with well-documented stress-induced hyper-consumption of obesogenic diets in subordinate animals (Moore et al., 2013; Arce et al., 2010; Michopoulos, Toufexis, & Wilson, 2012; Michopoulos, Moore, & Wilson, 2013). However, these studies have all followed adult animals in small social groups. It is possible that the dominant juveniles in our large social groups were able to control access to the HCD feeders, thereby limiting excess consumption in subordinates. In fact, we found that by 16 months some dominant animals in the LCD group had learned how to "steal" HCD pellets by holding open the gate to the HCD feeder after another animal had used it, but this was a small Kcal contribution to their diets. Subjects with access to the HCD did consume significantly more of the HCD than the LCD, particularly by the 16-

month time point, indicating that access to an obesogenic diet promotes a preference for calorically dense diets over lower calorie ones that becomes stronger with exposure, consistent with previous reports (Moore et al., 2013; Arce et al., 2010; Michopoulos, Toufexis, & Wilson, 2012; Michopoulos, Moore, & Wilson, 2013). Surprisingly, we did not observe significant group differences in body weight, despite higher caloric consumption in subjects with access to the HCD. Therefore, contrary to our hypotheses but consistent with other reports in the literature, the neurobehavioral effects of obesogenic diets seem to emerge before fat mass increases and the obesogenic phenotype itself emerges (Sullivan et al., 2010; Sasaki et al., 2013; Myles, 2014; Vasconcelos et al., 2016). It is possible that body weight differences instead begin to emerge during puberty, when female rhesus macaques undergo a growth spurt (Tanner, Wilson, & Rudman, 1990). We also did not find significant differences by diet or social status in hair cortisol levels. Although this is inconsistent with a range of studies that have shown stress- and diet-induced alterations in cortisol levels, including in the macaque social subordination model (Makino, Smith, & Gold, 1995; Lupien, King, Meaney, & McEwen, 2000; Pasquali et al., 2002; Baudrand & Vaidya, 2015; Michopoulos, Toufexis, & Wilson, Pasquali et al., 2003; Legendre & Harris, 2006; Howell, Godfrey et al., 2014), measures of hair cortisol are not always correlated with blood cortisol levels (Sharpley, McFarlane, & Slominski, 2011). Further, some studies have reported divergences in the effects of chronic stress on hair cortisol (reviewed in Sharpley, McFarlane, & Slominski, 2011). Thus, peripheral measures of cortisol must be analyzed to conclusively determine whether subordination or obesogenic diet exposure affects HPA axis activation in this study.

We did observe a significant effect of social status on CRP levels, with subordinate subjects showing higher levels of CRP than dominant subjects. This is consistent with literature

showing increased inflammation following chronic stress exposure (Wurtman, 2002; Pollitt et al., 2008; Loucks et al., 2010), as well as with previous reports of a pro-inflammatory state in this female macaque social subordination model (Snyder-Mackler et al., 2016; Snyder-Mackler et al., 2019; Tung et al., 2012). The effect of social status on CRP levels was present at 2 weeks of age, suggesting potential transmission through maternal biological signals, such as milk. Cross-fostering resulted in lower CRP levels, and subordination effects were stronger in cross-fostered than non-cross-fostered animals, suggesting a potential "mismatch" effect between the postnatal and ancestral environment (Del Giudice et al, 2011; Gluckman et al, 2005) on inflammation, at least at early ages. There was no effect of diet exposure on CRP levels, but this, along with the lack of diet effect in hair cortisol, could be explained by the absence of an obese phenotype in subjects with access to the HCD. Much of the literature linking obesogenic diets to hypercortisolemia and inflammation has focused on obese subjects and has related these effects to inflammation induced by increased fat mass, as a result of excess nutrients in adipose tissue producing enlargement and hypoxia in adipocytes and triggering the release of pro-inflammatory mediators (Pasquali et al., 2002; Baudrand & Vaidya, 2015; Ellulu et al., 2017). Other pro-inflammatory markers that have been linked to obesogenic diet consumption, such as interleukin-1, interleukin-6, and tumor necrosis factor (Kiecolt-Glaser, 2010), should be tested in future studies.

One of the major findings of this study was that postnatal consumption of the HCD resulted in significant and long-term increases in brain size throughout development (measured as ICV which was computed as the sum of total brain gray and white matter and CSF). The literature on obesogenic diets and overall brain volumes is mixed: although adult obesity is typically associated with smaller brain volumes (Hamer & Batty, 2019; Taki et al., 2008), and

this effect has been replicated in children and adolescents (Alosco et al., 2014), larger overall white matter (Ball et al., 2012) and larger regional brain volumes have also been reported in obese children (Bauer et al., 2015; Moreno-López et al., 2012). One study also found that children who consumed foods higher in glycemic index showed larger white matter volumes (Taki et al., 2010). Notably, effects of diet on ICV in our study were already present at 2 weeks of age (when infants are nursing), rather than emerging at weaning, when infants start eating solid foods from the feeders. Because all dams were maintained on the LCD until infant birth, this finding suggests that postpartum maternal consumption of an obesogenic diet may have immediate effects on infant structural brain development that are potentially transmitted through maternal milk. Studies in rodents support the existence of milk-transmitted neurobehavioral effects of maternal HCD consumption in offspring (Franco et al., 2012; Sun et al., 2012; Sasaki et al., 2013). As mentioned, there were no effects of diet condition on body weight in our subjects, ruling out that the effect of the HCD diet was mediated by biological signals related to obese phenotypes or increased fat mass. ICV increases in the animals that consumed obesogenic diets were predicted by total (but not HCD) Kcals consumed, suggesting that the amount, not the specific nutritional composition, of the diet consumed produced alterations in ICV volumes. It is possible that the higher energy intake by subjects on the HCD initially leads to increased dendritic arborization and/or myelination that results in larger brain volumes, and that the overall brain shrinkage effects that have been previously reported do not manifest until the obese phenotype emerges, with excess adiposity and its associated excess production of stress hormones and pro-inflammatory cytokines (Pasquali et al., 2002; Baudrand & Vaidya, 2015; Ellulu et al., 2017). Interestingly, some rodent models have shown increases in the number of microglia and astrocytes in the HIPP after consumption of a HCD in rats (Graham et al., 2016;

Kang et al., 2016), linking HCD exposure to inflammation-induced cellular mechanisms that may predict structural brain growth. Although CRP exposure did not predict ICV growth, the increase in structural brain growth could be mediated by one of the diet-influenced pro-inflammatory markers that were not tested in this study. While further studies are necessary to elucidate its exact mechanisms, the finding of increased ICV across ages in subjects that consumed the HCD indicates that exposure to an obesogenic diet postnatally, even through maternal milk, has immediate, global effects on structural brain growth.

We found a significant main effect of social subordination, as well as a diet by age interaction, on AMYG development. Subordinate subjects showed larger AMYG volumes than dominant subjects across ages, whereas the increased AMYG volumes in subjects that consumed the HCD emerged at the later ages. Although there was no interaction between social status and diet, subordinate females on the Choice diet had larger AMYG volumes at 16 months compared to the other groups, suggesting that subordination and consumption of obesogenic diets could have a potential additive effect later in development. These findings are consistent with previous reports of larger AMYG volumes in children and developing macaques exposed to early life stress (Tottenham et al., 2010; Noble, Houston, & Sowell, 2012; Lyons-Ruth et al., 2016; Vyas et al., 2004), including other cohorts of peripubertal subordinate female macaques (Howell, Grand et al., 2014), as well as positive associations between body mass index (BMI) and AMYG volumes in children and adolescents (Perlaki et al., 2018), despite reports of the opposite effect in adults (Janowitz et al., 2015). Cumulative exposure to CRP during infancy and the juvenile period predicted AMYG growth, and social rank did not further explain the variance in AMYG growth beyond the contribution of CRP exposure, suggesting that the subordination effect on AMYG volumes can be mainly explained by CRP exposure. Notably, a recent human study

found increased AMYG volumes in infants whose mothers showed higher than normal peripheral levels of interleukin-6 during pregnancy (Graham et al., 2018). Because subordinate females already showed higher CRP levels and bigger AMYG volumes at 2 weeks, it is possible that these structural alterations are maternally-transmitted or –programmed subordination stress-induced inflammation effects (e.g. during pregnancy; through the milk). Inflammation has been shown to activate microglia in the brain (Brooke et al., 1994), and stress-related microgliosis has been linked to alterations in synaptic pruning and myelination (Mottahedin et al., 2017; Kucharova et al., 2011), which may provide a cellular mechanism for inflammation-induced growth in the AMYG under subordination stress. In contrast, the effect of obesogenic diet consumption on AMYG volumes did not emerge until the later ages, suggesting its unfolding after subjects began to consume the HCD (at weaning). The diet effect on AMYG volumes, however, was not predicted by consumption of HCD or total Kcals, and adding Diet to the regression models with CRP still explained a significant percent of the variance, leaving the mechanism of diet-induced growth unclear (although it could be due to qualitative differences in diets, or to milk-programming effects). The finding of both social subordination and obesogenic diet-induced increases in AMYG volumes is striking, considering previous studies linking greater AMYG volumes to increased emotional/stress reactivity and anxiety, and poorer emotional regulation in both animal models and children (Vyas et al., 2002; Vyas et al., 2004; Tottenham et al., 2010; Howell, Grand et al, 2014). Our results suggest that, very early in development, social subordination (via increased inflammation) and obesogenic diet consumption have the potential to structurally alter the AMYG to predispose individuals to psychopathology and poor emotional regulation.

An effect of social rank unfolded across time in the HIPP, with subordinate animals showing larger volumes than dominants as juveniles. This finding is not consistent with extensive literature relating chronic stress to neuronal atrophy and reduced volumes in the HIPP (Fuchs et al., 2001; Noble et al., 2015; Dannlowski et al., 2012; Sapolsky, Uno, Rebert, & Finch, 1990). However, some studies have found larger HIPP volumes in children of lower socioeconomic status (Noble, Houston, & Sowell, 2012), and a recent study found differences in the growth trajectory of HIPP volumes in adolescent girls of low socioeconomic status, who exhibited a slight reduction in HIPP volumes during teenage years, followed by growth into early adulthood, in contrast to the more linear growth pattern shown by middle-income girls (Ellwood-Lowe et al., 2018), suggesting that factors related to social stress can alter the typical HIPP growth trajectory. A potentially contributing factor to be considered regarding the increase in HIPP volumes is the documented high connectivity between the AMYG and the HIPP (McEwen, 2016; Phelps, 2004; Sasaki et al., 2013; Tottenham & Sheridan, 2009), since our study found that both of these limbic structures showed bigger volumes in subordinate than in dominant animals. Perhaps chronic-stress-induced growth in the AMYG early in life, followed by HIPP growth that emerges by the juvenile period, is an adaptive mechanism for the processing and storage of emotional experiences. Volumetric growth in the AMYG could allow for enhanced processing of emotional stimuli early on (e.g. through heightened arousal; Radley, Morilak, Viau, & Campeau, 2015), then, as subjects have an increasing number of threatening social experiences, HIPP growth into the juvenile period could allow for the memory storage of emotional and/or threatening information, further facilitating the emotional response of subordinate animals. Eventually, however, this constant emotional responsivity could lead to wear and tear on both structures, and produce the hypo-emotionality, anxiety phenotypes, and further increased AMYG

volumes, alongside memory deficiencies and decreased hippocampal volumes, that are typically seen in chronically stressed individuals (Radley, Morilak, Viau, & Campeau, 2015). Further time-points of sMRI collection would be necessary to explore this hypothesis. Additionally, although there was no main effect of diet in the HIPP, total Kcals consumed did negatively predict HIPP growth, suggesting that the quantity of calories consumed impacts early hippocampal development, even in the absence of a clear effect of obesogenic diet exposure.

Significant effects of both diet and social status were found in the PFC. The larger total PFC volumes in the Choice than the LCD groups seemed to be driven by overall bigger brain sizes in the animals exposed to obesogenic diets. However, even after accounting for differences in ICV, subjects that consumed the HCD showed larger PFC GM and WM volumes than animals on the LCD. This finding was not consistent with our initial hypothesis, based on the PFC atrophy previously reported in obese adolescent (Bruehl et al., 2011; Yokum, Ng, & Stice, 2011) and adult humans (Pannacciulli et al., 2006; Walter, Birdsill, Glisky, & Ryan, 2010), and rats fed a high fat diet (Bocarsly et al., 2015). This inconsistency may stem from a similar mechanism as those suggested for ICV: subjects may be showing an initial increase in PFC volumes as a function of high energy intake at these early developmental time points, but the more commonly reported effects of obesogenic diet consumption on PFC volumes (e.g. dendritic atrophy; Bocarsly et al., 2015) may not develop until the obesogenic phenotype emerges after puberty. Further, because the reciprocal AMYG-PFC circuitry is involved in regulating food reward (Baxter & Murray, 2002), the observed increase in both AMYG and PFC volumes may represent initial over-activity in this circuit as a result of HCD consumption. Diet effects in the PFC were present by 2 weeks of infant age, suggesting immediate effects of HCD exposure, which may have been mediated through maternal milk. Separately, subordinate subjects showed larger PFC

volumes than dominants, which also seems inconsistent with literature in humans and animals showing an association between chronic stress and smaller PFC volumes (Dannlowski et al., 2012; Arnsten, 2009; McEwen, Nasca, & Gray, 2016; Sapolsky, 2005; Radley et al., 2005). Perhaps the increased PFC volumes, alongside increased AMYG volumes, represent another initially over-active circuit that facilitates emotional processing in subordinate animals, as the PFC shows dense reciprocal connections with the AMYG (Ghashghaei & Barbas, 2005) and is thought to exert top-down control over the emotional response of limbic structures (Ghashghaei, Hilgetag, & Barbas, 2007; Phillips, Ladouceur, & Drevets, 2008). Interestingly, as seen in the HIPP, although there was no significant, retained effect of diet, total PFC growth was predicted by total Kcals consumed. In the PFC, unlike in the HIPP, total Kcals positively predicted total growth, but both exhibited effects of general caloric consumption in the absence of obesogenic diet effects. Additionally, the dorsolateral PFC (dlPFC), medial PFC (mPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) will be analyzed in the future to determine whether obesogenic diet consumption and/or chronic stress have larger or more specific impacts on these PFC sub-regions.

The INS seemed to be the region most strongly affected by postnatal HCD consumption. Subjects that consumed the obesogenic diet showed significantly larger total INS, INS GM, and INS WM volumes. For INS WM volumes, effects appeared similar across ages, further implicating maternal milk as a potential pathway for HCD exposure effects, while the effect on the total INS and INS GM seemed to become augmented with age as subjects consumed more of the HCD on their own after weaning. Effects of diet in all measures were preserved after accounting for the effects of ICV. Further, the growth rate of INS volumes was predicted by cumulative HCD Kcals consumed, suggesting that higher caloric consumption of this high fat,

high sugar obesogenic diet was the factor that predicted growth in INS volumes, rather than the total quantity of Kcals consumed. In contrast to our results, the INS has been reported to show smaller volumes in obese subjects (Janowitz et al., 2015; Shott et al., 2015), and a recent study linked smaller newborn INS GM volumes to early life gains in adiposity, a risk factor for obesity (Rasmussen et al., 2017). Importantly, unlike other regions of the rhesus brain, the rate of early macaque INS growth does not match that of humans. In fact, it is one of the fastest-growing regions of the macaque brain during infancy (Scott et al., 2016), whereas it shows a relatively flat growth rate in humans during the first five years of life (Gilmore et al., 2012). This may make the INS more vulnerable to environmental insults in macaque infants than in humans, and its rapid early growth rate may explain both the strong effects of HCD consumption and the discrepancies between our results and the literature. In rodents, consumption of a HCD has been associated with increased neuronal complexity in some cortical areas, with diet-induced pruning dysfunction suggested as a potential mechanism (Sarfert, Knabe, Gunawansa, & Blythe, 2019). Perhaps, similarly, pruning was impaired as a result of obesogenic diet exposure in our Choice animals, a hypothesis supported by the increasing differences by diet in INS GM that we observed with age, as synaptic pruning is thought to account for losses in GM (Selemon, 2013). Over-eating in adolescent girls has been linked to increased INS activity (Carnell et al., 2012), which may represent an outcome of early diet-induced alterations to INS structure.

There are several limitations of the present study that should be noted. The sample size of 41 animals, although big for nonhuman primate studies, was relatively small (n=10-11 per group) in comparison to human studies, and limited the power to detect complex interactions between factors. Future studies will be necessary to replicate these findings with a larger sample size and address the new hypotheses proposed in the Discussion. The aforementioned limitation

of our feeding design, whereby some dominant animals on the LCD managed to "steal" some HCD pellets, did not seem to impact our results, since the number of HCD Kcals consumed by these animals was small. Nonetheless, future studies should improve the technical restrictions on access to HCD feeders by LCD subjects. Additionally, time constraints left us unable to include regions of the brain that are central to reward processing and emotional regulation, including sub-regions of the PFC (dlPFC, mPFC, OFC, and ACC) and the NAcc, but these regions are currently being analyzed for the final study. A further limitation is that only female subjects were used, and sex differences have previously been reported in humans whereby obese women but not men show some structural brain alterations (Horstmann et al., 2011), thus, we did not account for potential differential effects across male rhesus development. Future studies should include both males and females to assess whether stress- and diet-induced effects are more pronounced in either gender. Finally, future studies should include measures of peripheral cortisol and additional inflammatory markers (interleukin-1, interleukin-6, tumor necrosis factor) to probe more completely the potential biological mediators of the effects that we have reported.

Despite these limitations, the findings of this study clearly demonstrate that postnatal exposures to obesogenic diets and chronic stress have a significant impact on both global and regional structural brain development. Most of these effects appear very early in development, perhaps mediated by maternal factors (e.g. milk), and they are long-lasting, through infancy and up to the pre-pubertal period in macaques. Generally, we saw volumetric increases in ICV and ROIs as a result of obesogenic diet consumption and, separately, exposure to social subordination stress, even in regions where HCD consumption and chronic stress are typically associated with volumetric decreases. Combined, the sMRI results suggest the possibility of initial structural growth in response to environmental insults early in development, which may be

followed by later atrophy. Volumetric increases may occur as an initial adaptive strengthening of emotional response and food processing circuitry, they may be a result of deficiencies in pruning, or they may simply represent differential growth trajectories due to the early developmental time-point. Our findings suggest a range of differential biological predictors of these effects, including CRP and total versus HCD Kcals consumed. Additional studies are warranted to further clarify the mechanisms underlying the structural brain changes observed, and should include later time-points of data collection to track brain and physiological growth into the pubertal period of macaque development. Nonetheless, our findings underscore the profound vulnerability of the developing brain to the commonly experienced insults of social stress and obesogenic diet exposure, demonstrating early, long-lasting effects of these factors in regions whose alterations are associated with a range of psychopathologies (Weniger & Lange, 2006; Frodl et al., 2002; Goldstein & Volkow, 2011; Sala et al., 2004; Tomasi & Volkow, 2013). Altogether, these findings present early infant development as a time in which the neurological basis of eventual obesity and chronic-stress-induced psychopathology may be heavily influenced, making them an essential component of understanding and preventing such illnesses.

Table 1. Experimental Groups. Breakdown of subject group assignment by postnatal social status, diet condition, as well as biological mother's rank in cross-fostered subjects (shown in row: Dam's Prenatal Rank).

	Foster Mom				***Biological Mom***	
Dam's Prenatal Rank	**SUB**	**DOM**	**DOM**	**SUB**	**DOM**	**SUB**
Infant's Postnatal Rank	**DOM**	**SUB**	**DOM**	**SUB**	**DOM**	**SUB**
LCD-only	4	1	2	3	5	6
Choice (LCD + HCD)	4	2	2	3	4	5

Table 2. Percent Nutrient Composition of Experimental Diets.

	Experimental Diets				
Diet	**Kcal/g/pellet**	**% Fat**	**% Sugar**	**% Starch**	**% Protein**
LCD	3.45	12	4.14	65.9	18
HCD	4.25	30	29.8	20.2	20

Table 3: Hierarchical Regression of ICV Growth. Models I & II: ICV predicted by total kilocalories consumed vs. HCD kilocalories consumed. Steps which significantly contributed to explaining the variance of the overall model are highlighted. **Bold font** indicates p-values ≤0.05.

ICV Growth								
	Model I (total kcals consumed)					Model II (HCD kcals consumed)		
	R^2	*b*	*t*	*p*		R^2	*b*	*t*	*p*
Step 1					**Step 1**				
Overall model	0.005				Overall model	0.005			
CRP AUC		-0.071	-0.777	0.439	CRP AUC		-0.071	-0.777	-0.439
Step 2					**Step 3**				
Overall model	0.075				Overall model	0.033			
CRP AUC		-0.050	-0.560	0.577	CRP AUC		-0.105	-1.131	-0.260
Total kcals consumed		0.265	2.968	**0.004**	HCD kcals consumed		0.170	1.834	0.069
Step 3					**Step 4**				
Overall model	0.085				Overall model	0.072			
CRP AUC		-0.005	-0.053	0.958	CRP AUC		-0.013	-0.133	0.895
Total kcals consumed		0.204	1.965	0.052	HCD kcals consumed		0.138	1.494	0.138
Social status		0.127	1.127	0.262	Social status		0.218	2.215	**0.029**
Step 4					**Step 5**				
Overall model	0.109				Overall model	0.118			
CRP AUC		-0.027	-0.275	0.784	CRP AUC		-0.001	-0.012	0.990
Total kcals consumed		0.091	0.749	0.456	HCD kcals consumed		-0.221	-1.276	0.204
Social status		0.185	1.593	0.114	Social status		0.266	2.707	**0.008**
Diet condition		0.188	1.786	0.077	Diet condition		0.415	2.435	**0.016**

Table 4: ROI Growth Hierarchical Regression Model I. AMYG, Hippocampus, and PFC growth predicted by CRP AUC and/or accumulative total kilocalories consumed. Steps which significantly contributed to explaining the variance of the overall model are highlighted. **Bold font** indicates p-values ≤0.05.

ROI Growth Model I: CRP AUC & Total Kcals Consumed as Predictors

	AMYG Growth				Hippocampus Growth				PFC Growth			
Step 1	R^2	*b*	*t*	*p*	R^2	*b*	*t*	*p*	R^2	*b*	*t*	*p*
Overall model	0.090				0.037				0.097			
Age		-0.3	-2.42	**0.017**		-0.209	-1.634	0.105		-0.33	-2.672	**0.009**
ICV		0.414	3.338	**0.001**		0.263	2.06	**0.042**		0.428	3.462	**0.001**
Step 2												
Overall model	0.188				0.037				0.098			
Age		-0.262	-2.213	**0.029**		-0.21	-1.629	0.106		-0.327	-2.62	**0.01**
ICV		0.36	3.034	**0.003**		0.264	2.046	**0.043**		0.423	3.378	**0.001**
CRP AUC		0.315	3.672	**<0.001**		-0.008	-0.088	0.93		0.032	0.355	0.723
Step 3												
Overall model	0.189				0.083				0.165			
Age		-0.26	-2.186	**0.031**		-0.224	-1.772	0.079		-0.31	-2.567	**0.012**
ICV		0.357	2.985	**0.003**		0.289	2.271	**0.025**		0.394	3.245	**0.002**
CRP AUC		0.318	3.674	**<0.001**		-0.026	-0.281	0.779		0.053	0.607	0.545
Total kcals consumed		0.03	0.344	0.732		-0.217	-2.371	**0.019**		0.26	2.98	**0.004**
Step 4												
Overall model	0.198				0.193				0.166			
Age		-0.249	-2.094	**0.039**		-0.189	-1.581	0.117		-0.307	-2.526	**0.013**
ICV		0.341	2.835	**0.005**		0.235	1.945	0.054		0.389	3.174	**0.002**
CRP AUC		0.273	2.896	**0.005**		-0.174	-1.832	0.07		0.041	0.427	0.67
Total kcals consumed		0.09	0.894	0.373		-0.017	-0.165	0.87		0.276	2.703	**0.008**
Social status		-0.126	-1.161	0.248		-0.421	-3.858	**<0.001**		-0.034	-0.31	0.757
Step 5												
Overall model	0.304				0.193				0.185			
Age		-0.202	-1.808	0.073		-0.188	-1.557	0.122		-0.287	-2.365	**0.02**
ICV		0.264	2.314	**0.023**		0.233	1.897	0.06		0.356	2.886	**0.005**
CRP AUC		0.233	2.619	**0.01**		-0.174	-1.821	0.071		0.024	0.247	0.806
Total kcals consumed		-0.131	-1.21	0.229		-0.021	-0.181	0.857		0.182	1.548	0.124
Social status		-0.012	-0.117	0.907		-0.419	-3.682	**<0.001**		0.015	0.128	0.898
Diet condition		0.392	4.074	**<0.001**		0.008	0.078	0.938		0.168	1.618	0.108

Table 5: ROI Growth Hierarchical Regression Model II. AMYG, PFC, INS, INS GM, INS WM to 6mo, and INS WM growth predicted by CRP AUC and/or accumulative HCD kilocalories consumed. Steps which significantly contributed to explaining the variance of the overall model are highlighted. **Bold font** indicates p-values ≤0.05.

ROI Growth Model II: CRP AUC & HCD Kcals Consumed as Predictors

	AMYG Growth				PFC Growth				INS Growth			
Step 1	R^2	*b*	*t*	*p*	R^2	*b*	*t*	*p*	R^2	*b*	*t*	*p*
Overall model	0.090				0.097				0.051			
Age		-0.3	-2.42	**0.017**		-0.33	-2.672	**0.009**		-0.242	-1.906	0.059
ICV		0.414	3.338	**0.001**		0.428	3.462	**0.001**		0.311	2.453	**0.016**
Step 2												
Overall model	0.188				0.098				0.051			
Age		-0.262	-2.213	**0.029**		**-0.327**	**-2.62**	**0.01**		-0.242	-1.896	0.061
ICV		0.36	3.034	**0.003**		**0.423**	**3.378**	**0.001**		0.312	2.43	**0.017**
CRP AUC		0.315	3.672	**<0.001**		0.032	0.355	0.723		-0.005	-0.058	0.954
Step 3												
Overall model	0.199				0.143				0.097			
Age		-0.247	-2.084	**0.039**		-0.297	-2.422	**0.017**		-0.213	-1.688	0.094
ICV		0.334	2.775	**0.006**		0.369	2.967	**0.004**		0.258	2.021	**0.046**
CRP AUC		0.295	3.378	**0.001**		-0.01	-0.106	0.916		-0.047	-0.511	0.61
HCD kcals consumed		0.109	1.234	0.22		0.221	2.423	**0.017**		0.223	2.374	**0.019**
Step 4												
Overall model	0.207				0.149				0.108			
Age		-0.24	-2.019	**0.046**		-0.303	-2.464	**0.015**		-0.204	-1.619	0.108
ICV		0.322	2.67	**0.009**		0.379	3.027	**0.003**		0.245	1.911	0.059
CRP AUC		0.253	2.641	**0.009**		0.025	0.252	0.802		-0.097	-0.953	0.343
HCD kcals consumed		0.126	1.4	0.164		0.208	2.235	**0.027**		0.242	2.547	**0.012**
Social status		-0.099	-1.054	0.294		0.082	0.842	0.401		-0.117	-1.176	0.242
Step 5												
Overall model	0.376				0.167				0.174			
Age		-0.2	-1.884	0.062		**-0.29**	**-2.366**	**0.02**		-0.179	-1.466	0.146
ICV		0.271	2.509	**0.014**		**0.362**	**2.898**	**0.005**		0.212	1.71	0.09
CRP AUC		0.287	3.357	**0.001**		0.036	0.367	0.714		-0.075	-0.766	0.445
HCD kcals consumed		-0.566	-3.773	**<0.001**		-0.021	-0.121	0.904		-0.189	-1.095	0.276
Social status		0.008	0.096	0.923		0.118	1.182	0.24		-0.05	-0.508	0.612
Diet condition		0.806	5.447	**<0.001**		0.267	1.558	0.122		0.503	2.952	**0.004**

ROI Growth Model II (cont.): CRP AUC & HCD Kcals Consumed as Predictors

	INS GM Growth				INS WM to 6mo Growth				INS WM Growth			
Step 1	R^2	*b*	*t*	*p*	R^2	*b*	*t*	*p*	R^2	*b*	*t*	*p*
Overall model	0.06				0.023				0.005			
Age		-0.254	-2.011	**0.047**		0.108	0.843	0.401		0.031	0.242	0.809
ICV		0.338	2.679	**0.008**		-0.206	-1.599	0.113		-0.085	-0.654	0.514
Step 2												
Overall model	0.06				0.03				0.005			
Age		-0.255	-2.004	**0.047**		0.118	0.916	0.362		0.035	0.266	0.79
ICV		0.34	2.66	**0.009**		-0.22	-1.692	0.093		-0.09	-0.684	0.496
CRP AUC		-0.01	-0.11	0.912		0.081	0.863	0.39		0.028	0.3	0.765
Step 3												
Overall model	0.159				0.213				0.133			
Age		-0.211	-1.739	0.085		0.059	0.5	0.618		-0.015	-0.121	0.904
ICV		0.261	2.117	**0.036**		-0.112	-0.94	0.349		0.000	-0.001	0.999
CRP AUC		-0.072	-0.803	0.424		0.165	1.908	0.059		0.099	1.087	0.279
HCD kcals consumed		0.327	3.611	**<0.001**		-0.446	-5.093	**<0.001**		-0.372	-4.052	**<0.001**
Step 4												
Overall model	0.167				0.267				0.156			
Age		-0.204	-1.676	0.097		0.04	0.347	0.729		-0.027	-0.222	0.825
ICV		0.25	2.018	**0.046**		-0.082	-0.71	0.479		0.019	0.152	0.88
CRP AUC		-0.113	-1.15	0.253		0.273	2.967	0.004		0.168	1.701	0.092
HCD kcals consumed		0.343	3.732	**<0.001**		-0.489	-5.67	**<0.001**		-0.4	-4.321	**<0.001**
Social status		-0.098	-1.013	0.313		0.257	2.842	**0.005**		0.165	1.7	0.092
Step 5												
Overall model	0.243				0.268				0.157			
Age		-0.177	-1.516	0.132		0.041	0.357	0.722		-0.024	-0.192	0.848
ICV		0.215	1.808	0.073		-0.084	-0.72	0.473		0.014	0.114	0.91
CRP AUC		-0.09	-0.955	0.342		0.274	2.96	**0.004**		0.171	1.721	0.088
HCD kcals consumed		-0.121	-0.731	0.466		-0.514	-3.16	**0.002**		-0.462	-2.648	**0.009**
Social status		-0.026	-0.27	0.787		0.261	2.796	**0.006**		0.175	1.744	0.084
Diet condition		0.541	3.316	**0.001**		0.029	0.182	0.856		0.072	0.419	0.676

Table 6. Summary of Significant Findings. Directionality of significant alterations in outcome measures is indicated with arrows. For ROIs, only findings that were significant after controlling for the effects of ICV are included here.

Summary of Significant Findings

Outcome Measure	Consumption of HCD	Subordinate Status	Biological Signals That Predict Growth Rates:
ICV	↑		Total Kcals consumed
AMYG Volume	↑	↑	Exposure to CRP
HIPP Volume		↑	Total Kcals consumed
PFC Volumes			
Total		↑	Total Kcals consumed (> HCD Kcals consumed)
GM	↑		
WM	↑		
INS Volumes			
Total	↑		HCD Kcals consumed
GM	↑		HCD Kcals consumed
WM	↑		HCD Kcals consumed
CRP		↑	
Total Kcals consumed	↑	↓	

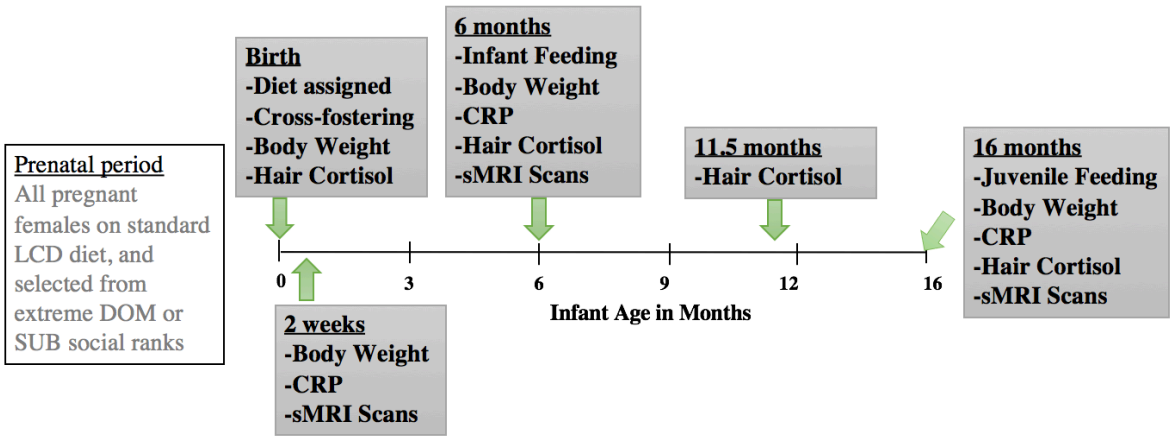


Figure 1. Experimental Design. Diet condition assignment and cross-fostering occurred at infant birth. Body weight measurements were taken at birth, 2 weeks, 6 months, and 16 months of subject age. Hair cortisol samples were collected at birth, and 6, 11.5, and 16 months. CRP measurements and sMRI scans were collected at 2 weeks, 6 months, and 16 months. Cumulative Kcal consumption was calculated from birth through 6 months, and 6 to 16 months of age.

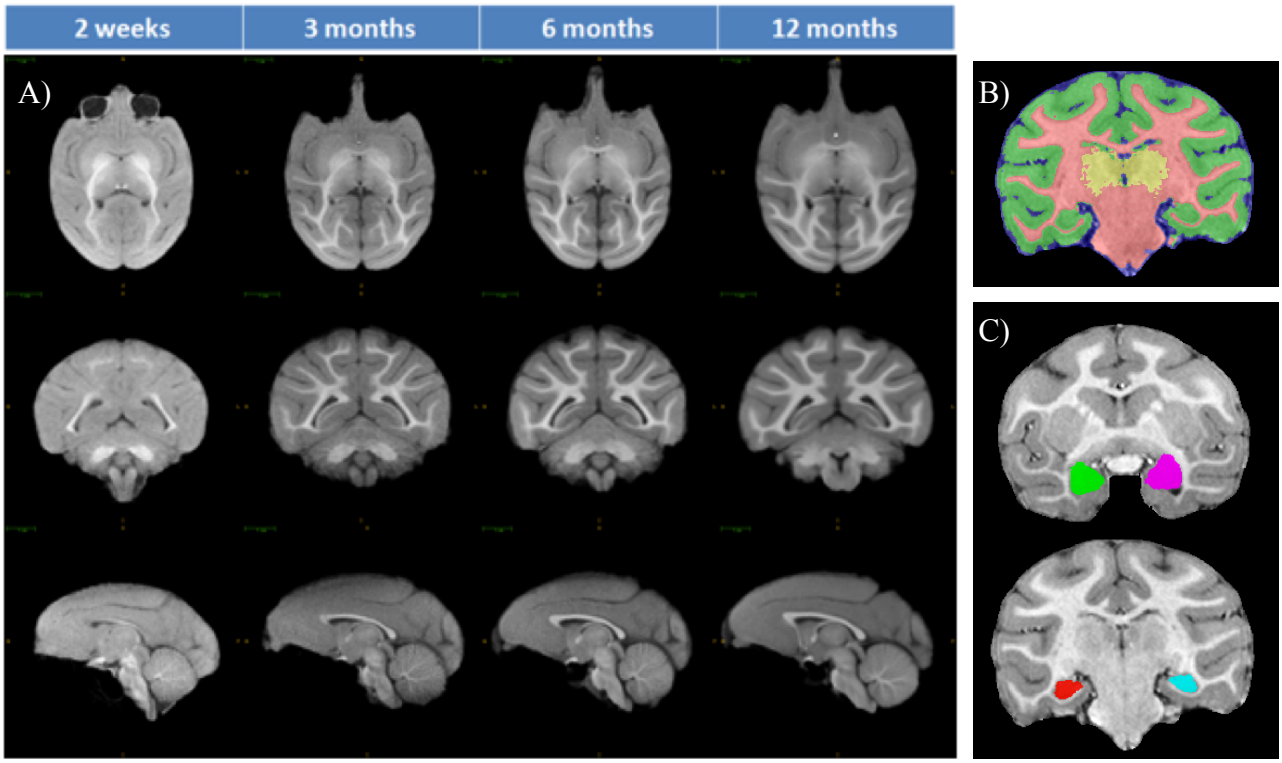


Figure 2. Atlas, Tissue Segmentation, and Subcortical ROIs Used in the AutoSeg Pipeline. A) Infant and juvenile standard brain atlases used for AutoSeg; B) Atlas-Based Classification (ABC) tissue segmentation example in a 16 month subject; C) Examples of single-atlas subcortical ROI parcellations for AMYG and HIPP in a 16 month subject.

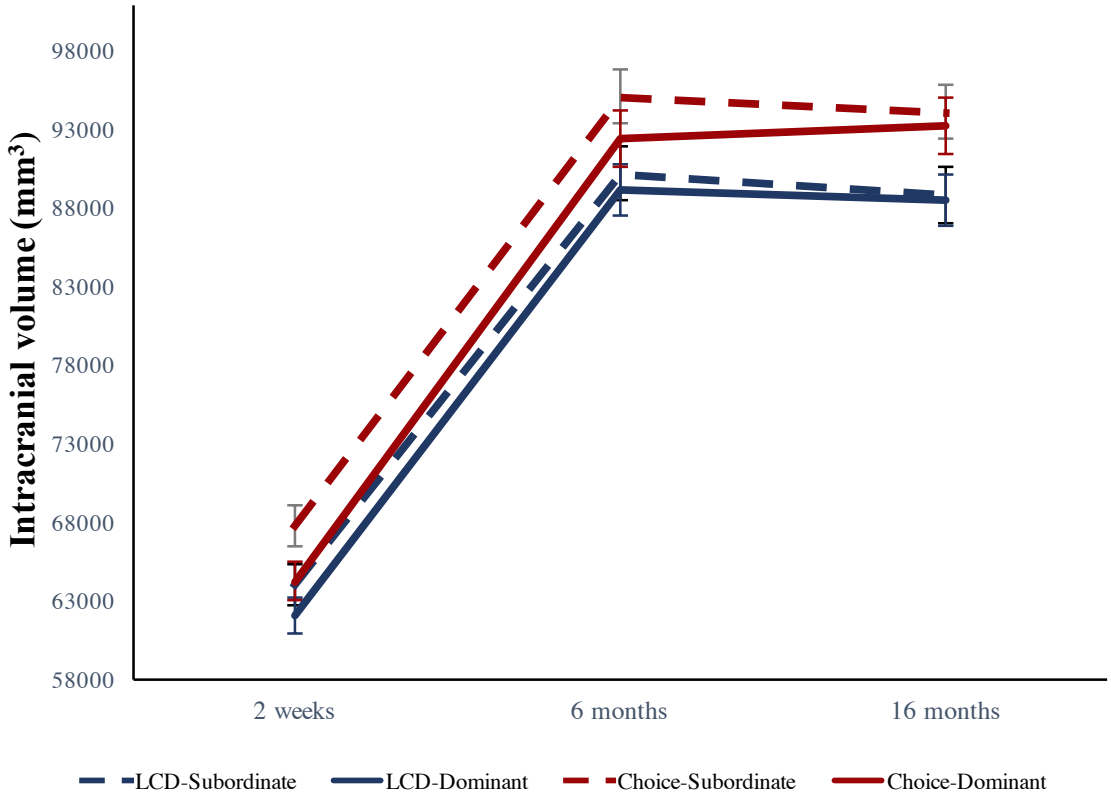


Figure 3. Effects of diet on ICV development. Mean (± SEM) intracranial volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. ICV grew with age ($F(2, 68.85)=481.94$, $p<.001$), and there was a main effect of Diet ($F(1, 100)=19.73$, $p<.001$; HCD>LCD).

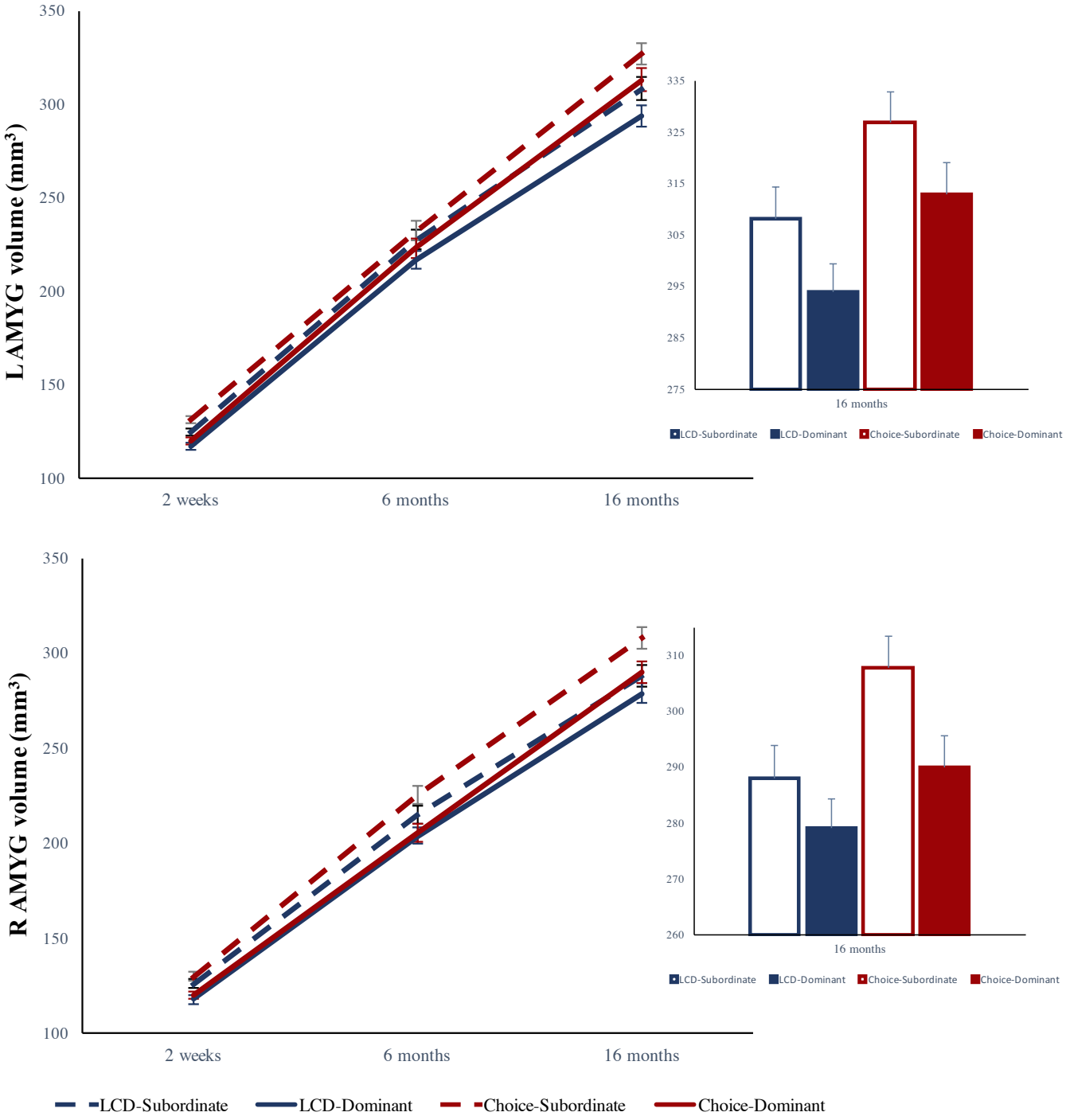


Figure 4. Effects of diet and social status on AMYG development. Mean (± SEM) AMYG volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. There were main effects of Age ($F(1, 158)=4133.06$, $p<.001$; increasing) and Hemisphere ($F(1, 158)=32.76$, $p<.001$; L>R). After controlling for the effects of ICV, there were significant main effects of Diet ($F(2, 106)=7.72$, $p=.006$; HCD>LCD), and Social Status ($F(1, 106)=11.22$, $p=.001$; SUB>DOM), and an Age x Diet interaction ($F(2, 50)=7.12$, $p=.002$).

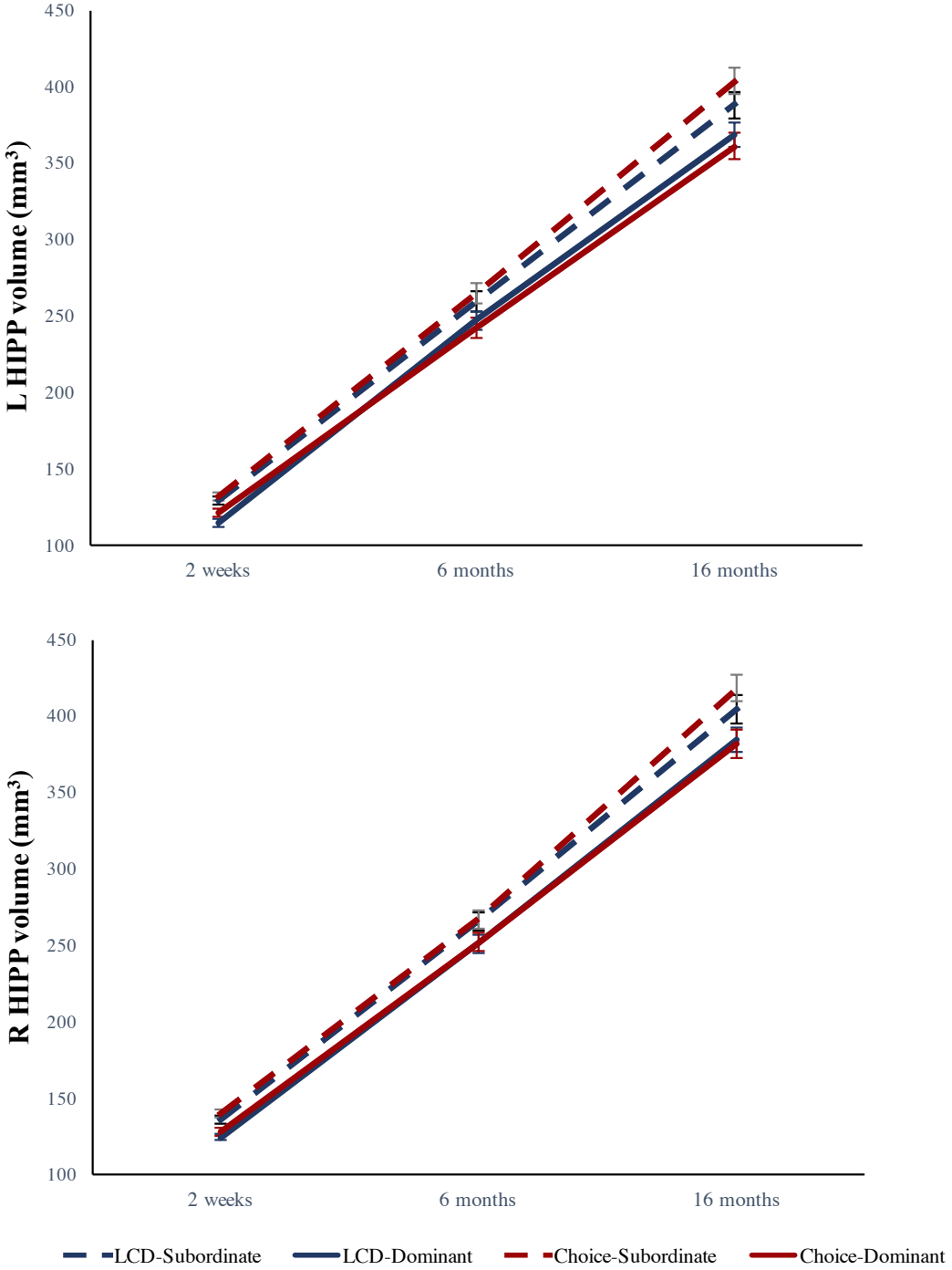


Figure 5. Effects of social status on HIPP development. Mean (± SEM) HIPP volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. There were main effects of Age F(1, 108)=4375.39, p<.001; increasing) and Hemisphere (F(1, 142)=14.69, p<.001; R>L). After controlling for the effects of ICV, there was a main effect of Social Status (F(1, 7964)=8.65, p=.003; SUB>DOM), and an Age x Social Status interaction (F(2, 52)=6.74, p=.002).

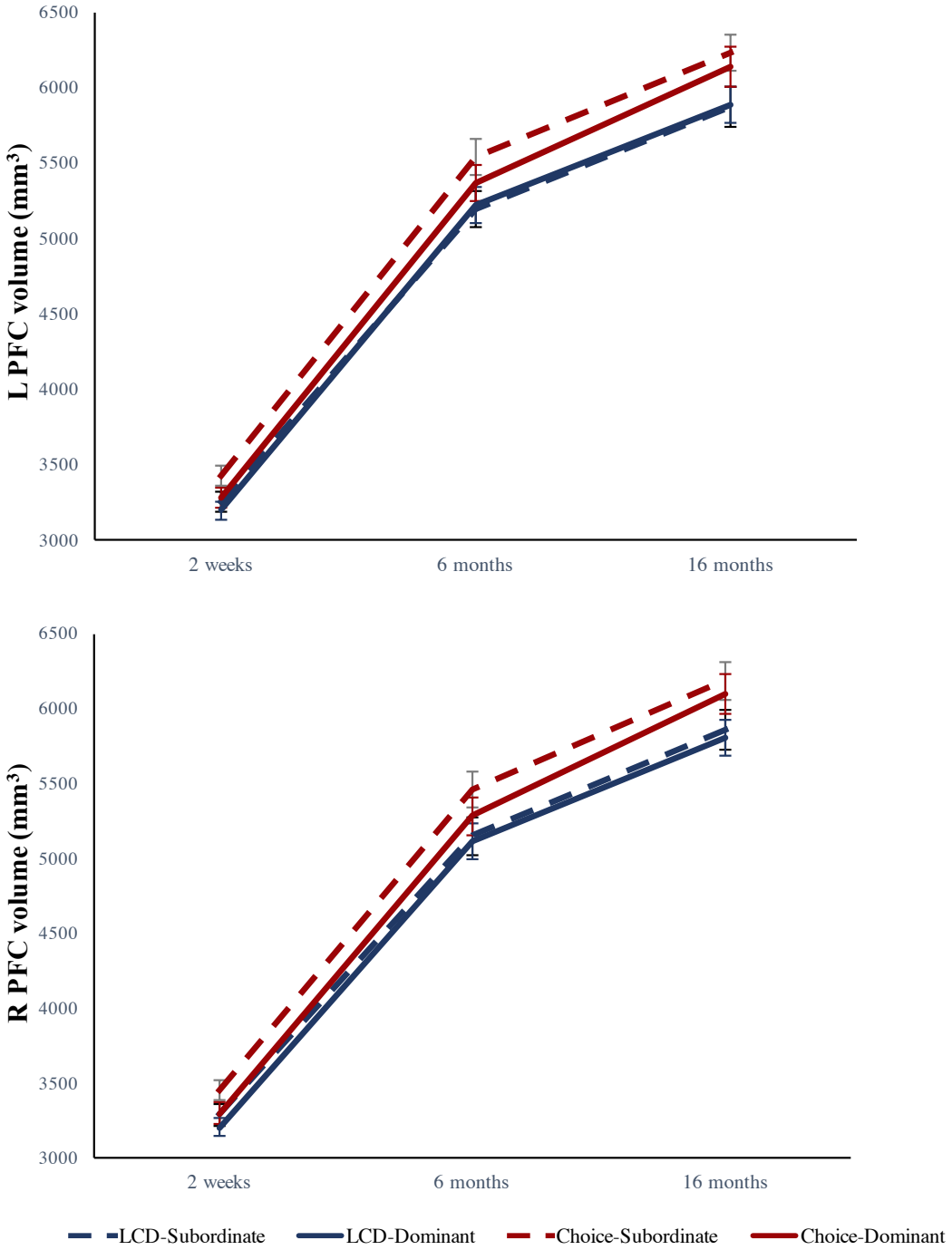


Figure 6. Effects of diet and social status on total PFC development. Mean (± SEM) total PFC volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. There was a main effect of Age ($F(2, 135)=1876.94$, $p<.001$; increasing). A main effect of Diet was significant before controlling for ICV ($F(1, 179)=26.52$, $p<.001$; HCD>LCD). After controlling for the effects of ICV, there was a main effect of Social Status ($F(1, 75)=6.34$, $p=.014$; SUB>DOM), and an Age x Social Status interaction ($F(2, 32)=3.91$, $p=.030$).

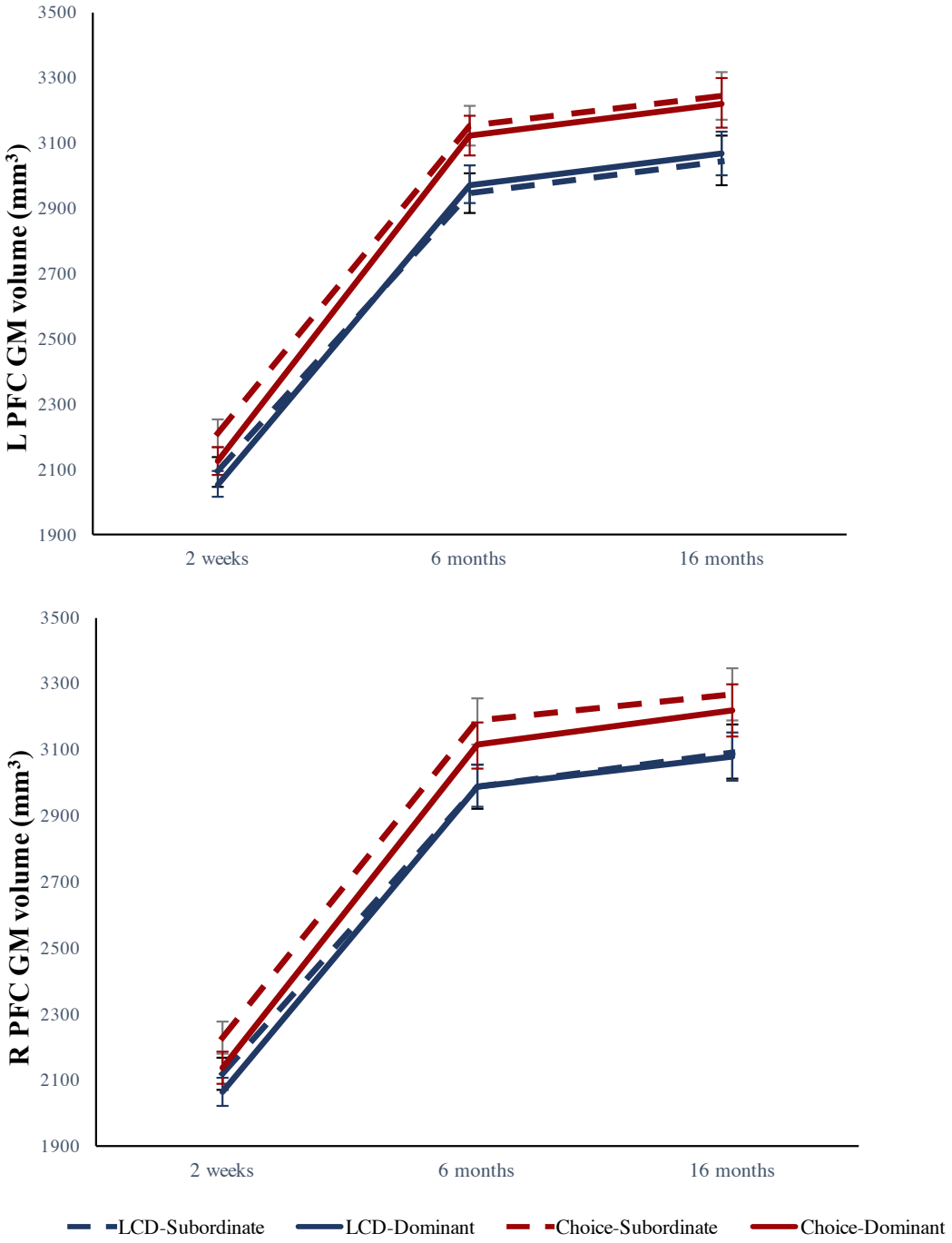


Figure 7. Effects of diet on PFC GM development. Mean (± SEM) PFC GM volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. There was a main effect of Age ($F(2, 127)=861.93$, $p<.001$; increasing). After controlling for the effects of ICV, there was a main effect of Diet ($F(1, 38)=5.45$, $p=.025$; HCD>LCD).

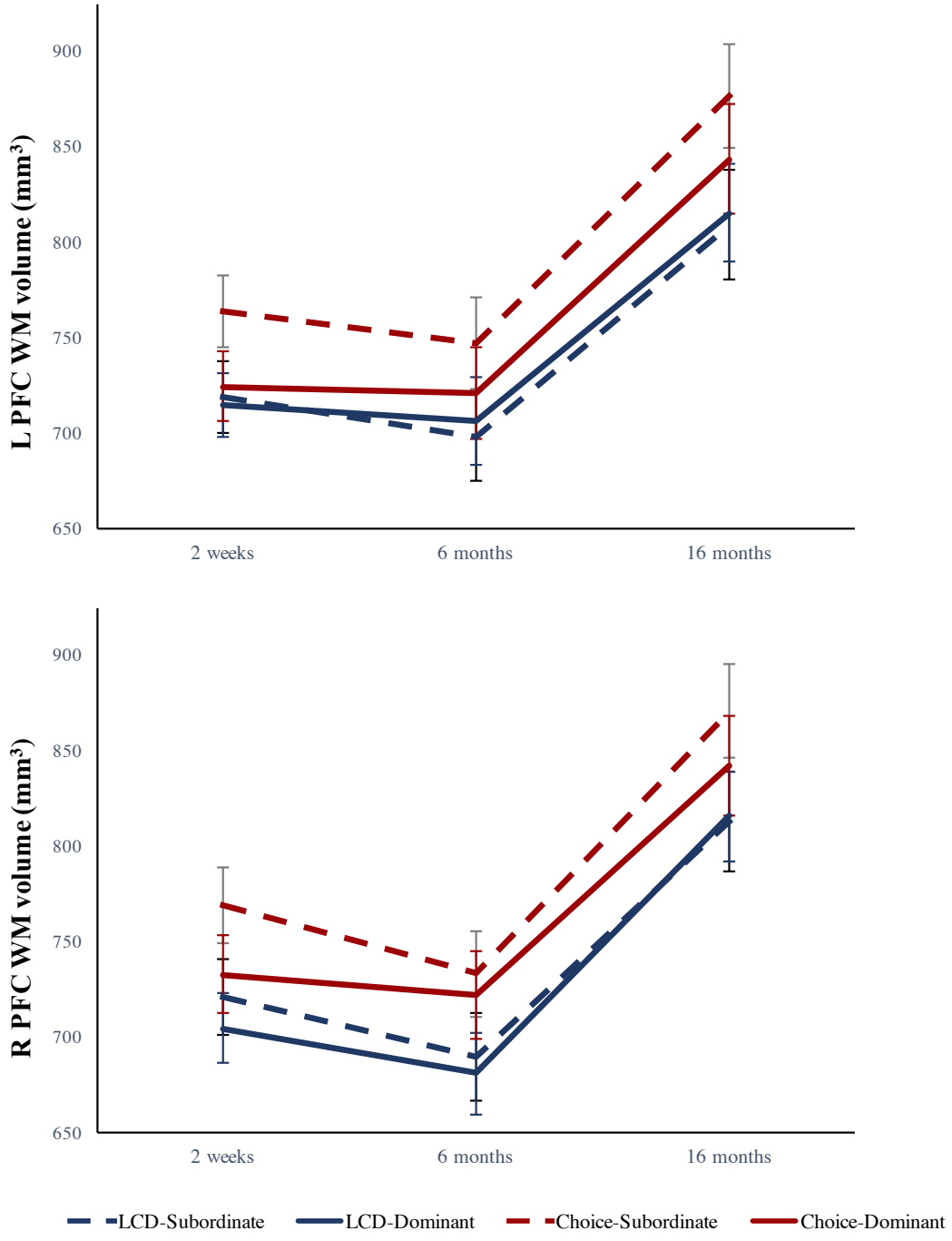


Figure 8. Effects of diet on PFC WM development. Mean (± SEM) PFC WM volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. There was a main effect of Age ($F(2, 128)=56.89$, $p<.001$; increasing overall). After controlling for the effects of ICV, there was a main effect of Diet ($F(1, 38)=4.43$, $p=.042$; HCD>LCD).

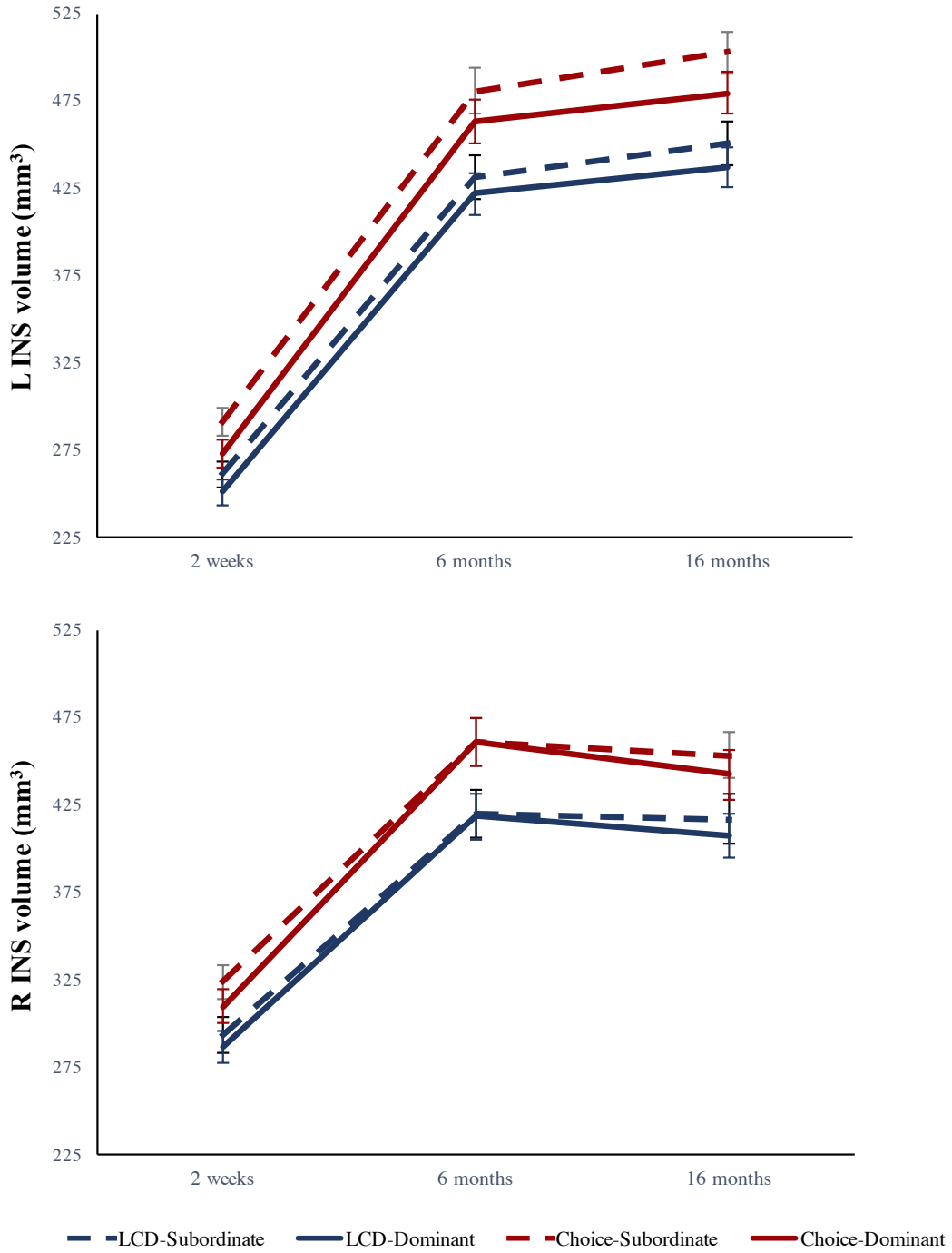


Figure 9. Effects of diet and social status on total INS development. Mean (± SEM) INS volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. There was a main effect of Age ($F(2, 138)=648.98$, $p<.001$; increasing). After controlling for the effects of ICV, there was a main effect of Diet ($F(1, 38)=12.27$, $p=.001$; HCD>LCD), and an Age x Diet interaction ($F(2, 45)=4.83$, $p=.013$).

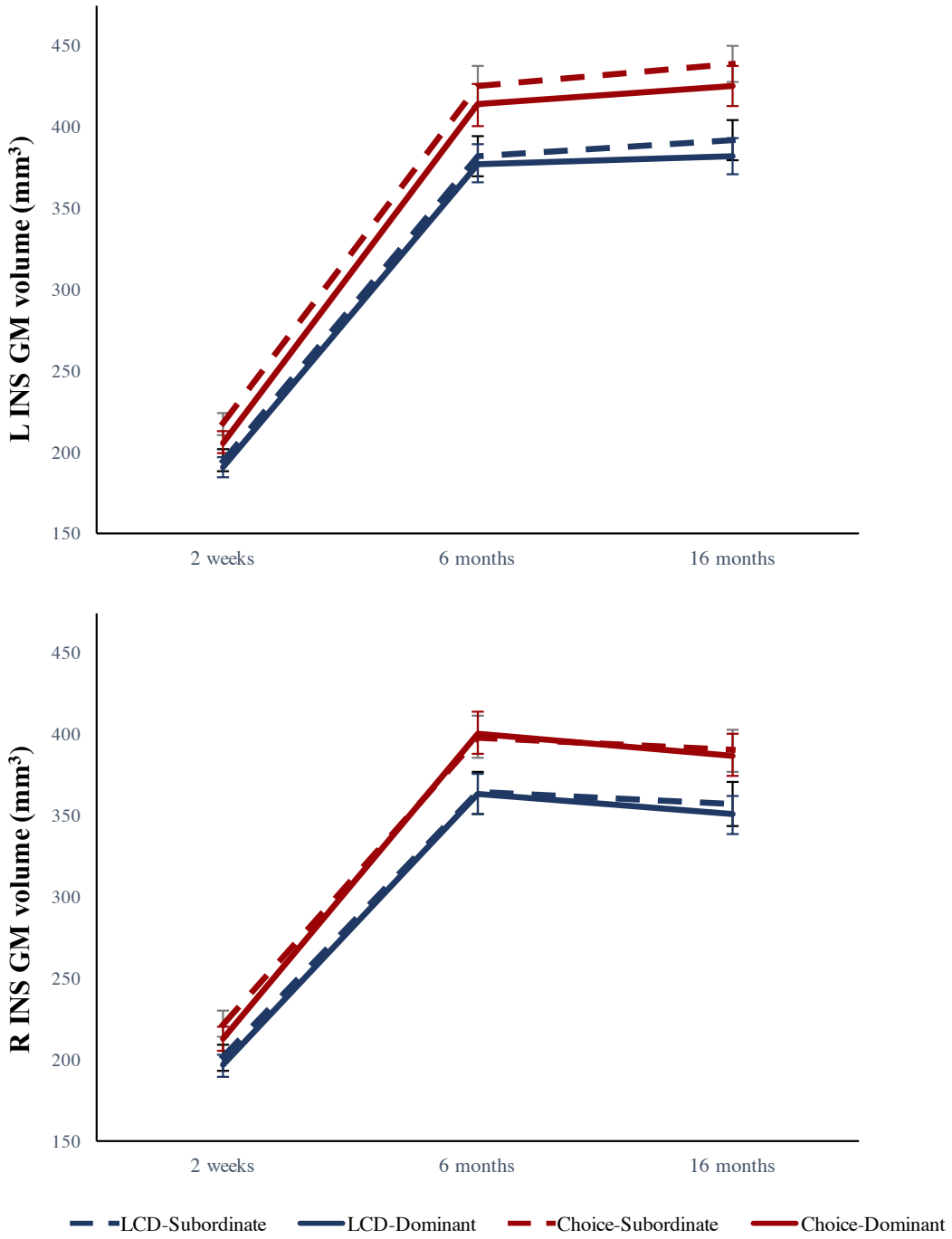


Figure 10. Effects of diet on INS GM development. Mean (± SEM) INS GM volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. There were main effects of Age ($F(2, 142)=1076.61$, $p<.001$; increasing) and Hemisphere $F(1, 186)=14.20$, $p<.001$; L>R). After controlling for the effects of ICV, there was a significant main effect of Diet ($F(1, 38)=9.81$, $p=.003$; HCD>LCD), and an Age x Diet interaction ($F(2, 48)=8.41$, $p=.001$).

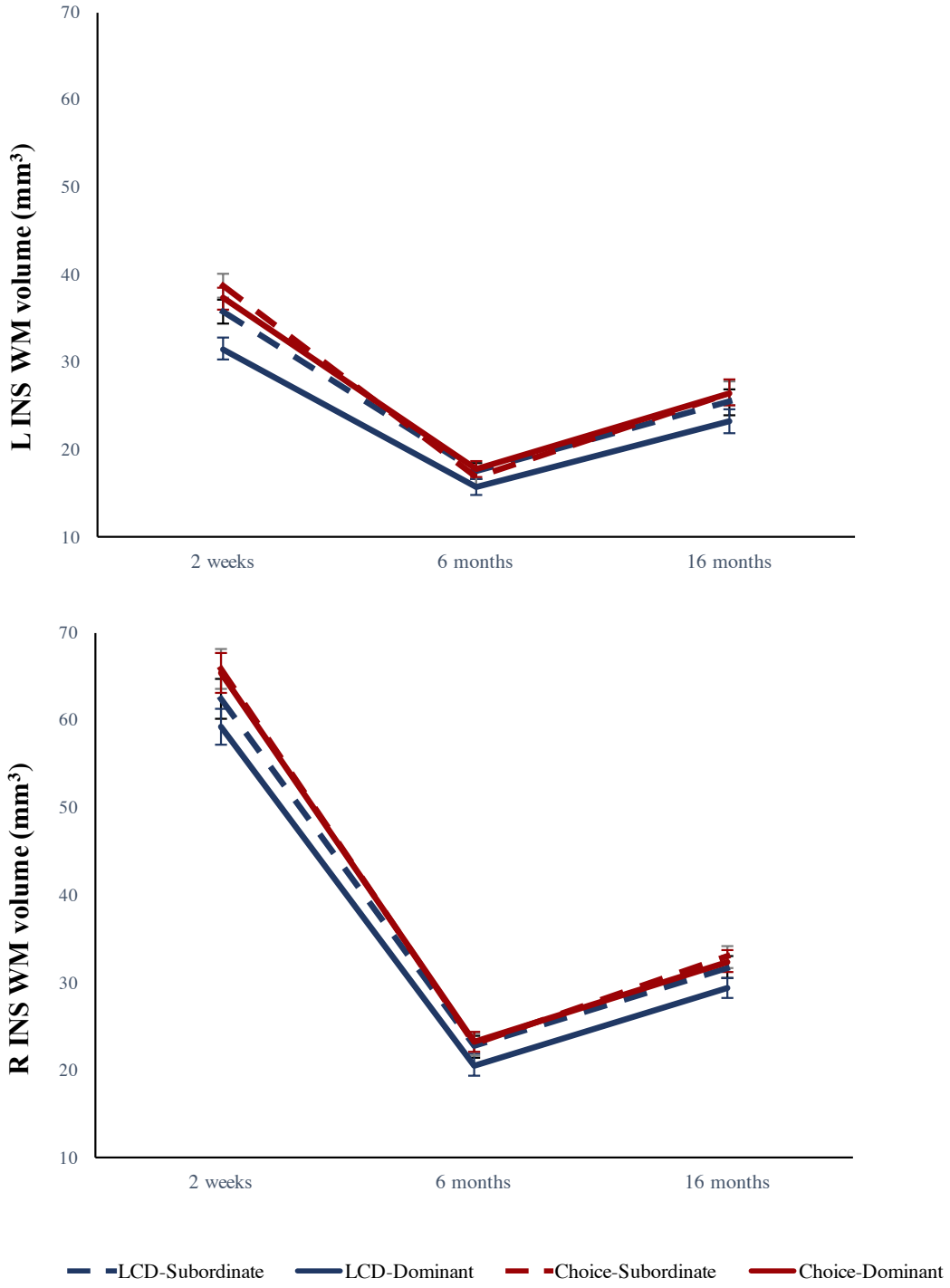
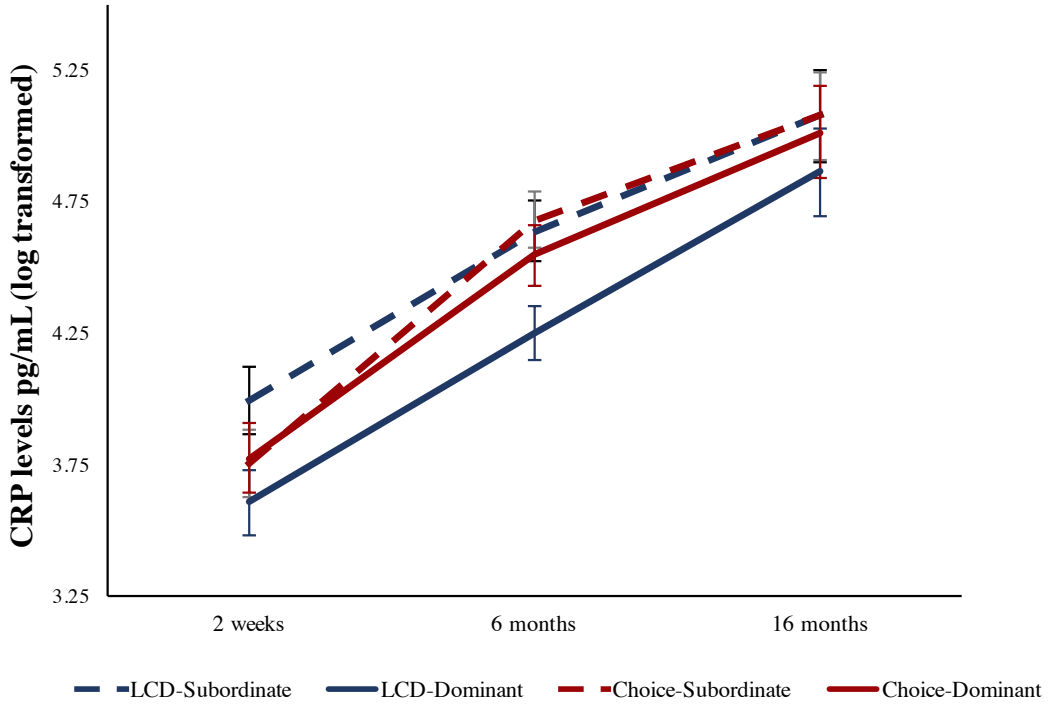


Figure 11. Effects of diet and social status on INS WM development. Mean (± SEM) INS WM volumes by experimental group are shown at 2 weeks, 6 months, and 16 months of age. There were main effects of Age ($F(2, 143)=803.30$, $p<.001$; decreasing then increasing) and Hemisphere ($F(1, 149)=479.93$, $p<.001$; R>L). After controlling for the effects of ICV, there was a main effect of Diet ($F(1, 53)=6.57$, $p=.013$; HCD>LCD).

A)



B)

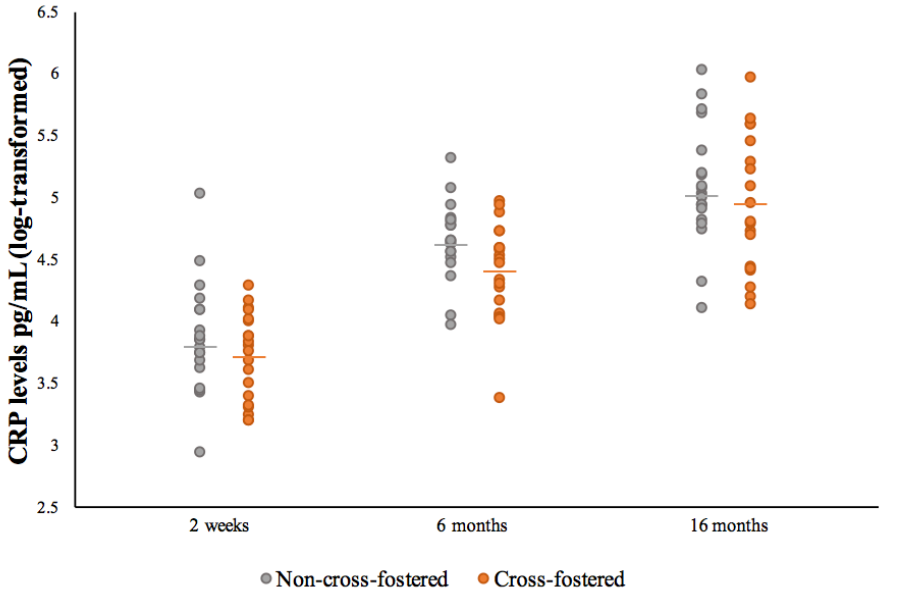
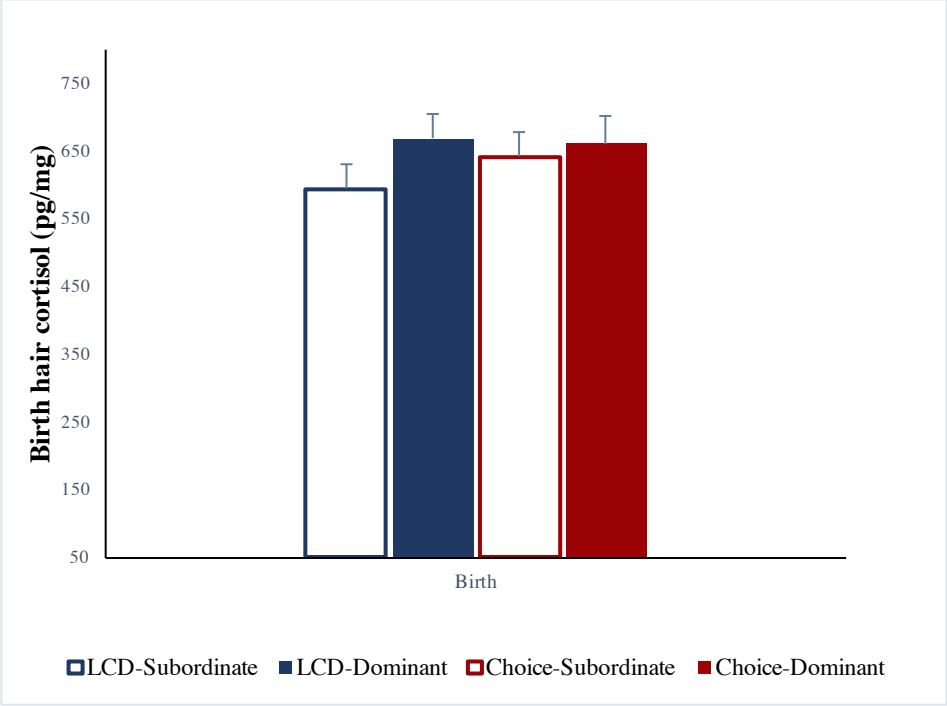


Figure 12. CRP levels. A) Mean (± SEM) CRP levels by experimental group are shown at 2 weeks, 6 months, and 16 months of age. CRP levels increased with age ($F(2, 58)=75.95$, $p<.001$), and there was a main effect of Social Status ($F(1, 87)=5.06$, $p=.027$; SUB>DOM); B) Mean and subject distribution of CRP levels by cross-fostering status at 2 weeks, 6 months, and 16 months of age. Cross-fostering had a significant effect on CRP levels ($F(1, 90)=6.61$, $p=.012$; Non-cross-fostered>Cross-fostered).

A)



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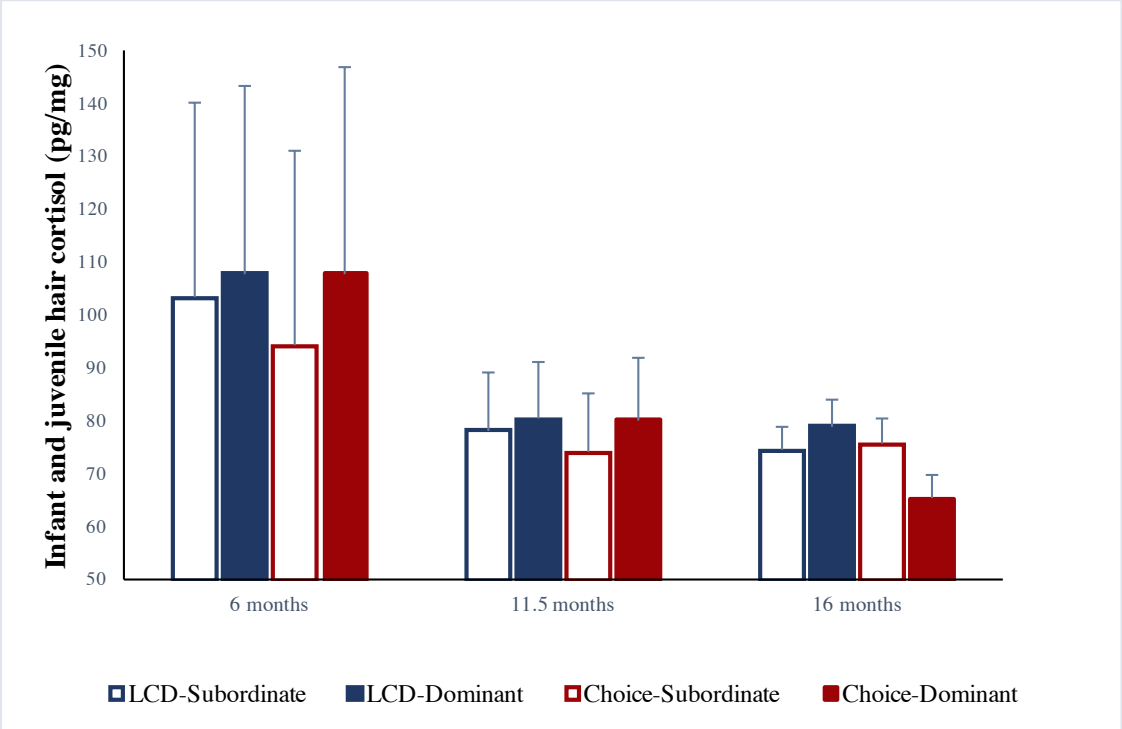

Figure 13. Hair cortisol levels. A) Mean (+ SEM) hair cortisol levels by experimental group at birth; B) Mean (+ SEM) hair cortisol levels by experimental group at 6 months, 11.5 months, and 16 months of age.

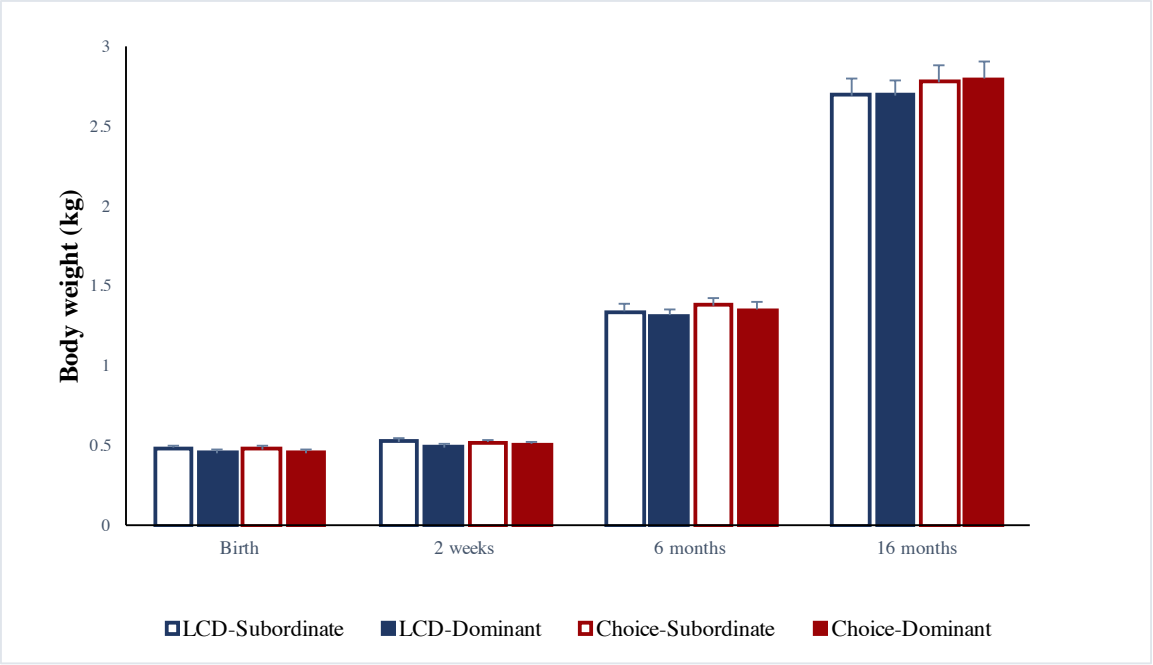

Figure 14. Body weight. Mean (+ SEM) body weight by experimental group at birth, 2 weeks, 6 months, and 16 months of age.

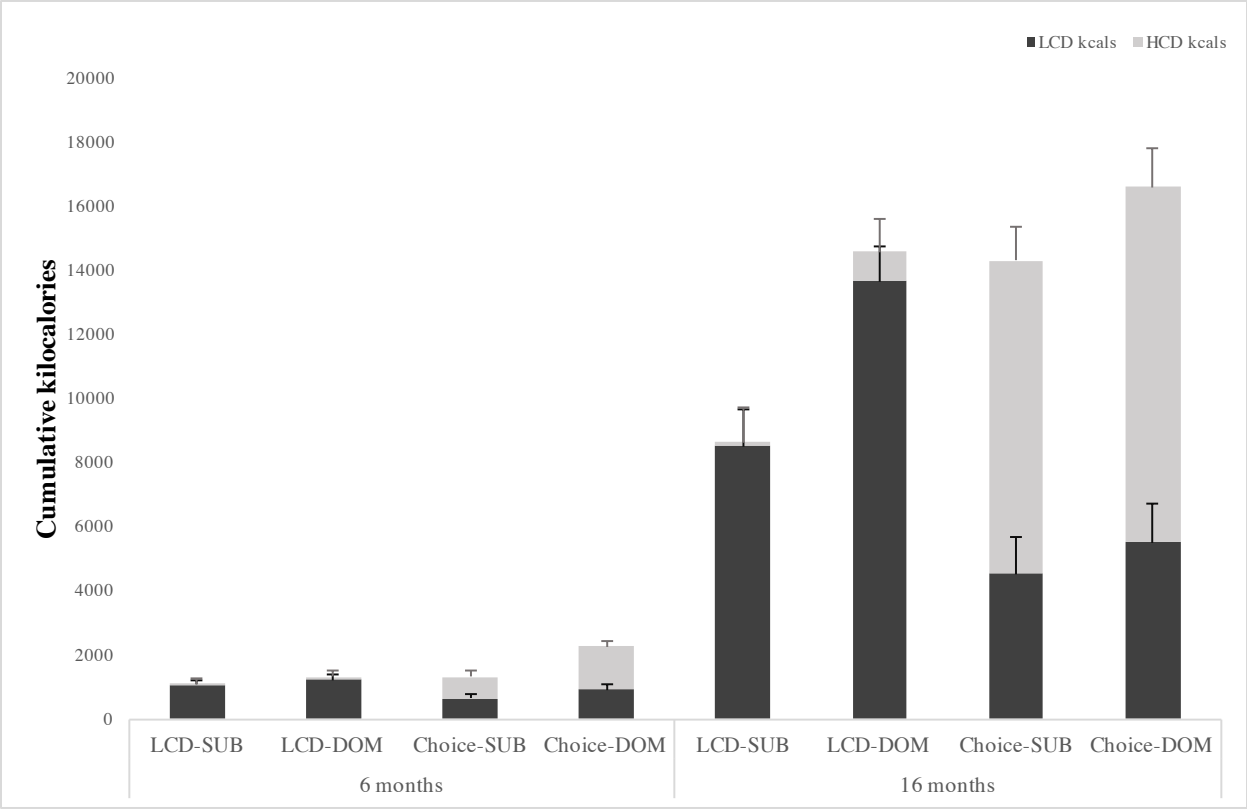

Figure 15. Effects of diet and social status on Kcal consumption. Mean (+ SEM) LCD Kcals (in dark grey) and HCD Kcals (in light grey) are shown by experimental group at 6 and 16 months of age. Total Kcal consumption increased with age ($F(1, 37)=304.56$, $p<.001$), and there were main effects of Diet ($F(1, 37)=11.74$, $p=.002$; HCD>LCD), and Social Status ($F(1, 37)=12.53$, $p=.001$; DOM>SUB). There were Age x Diet ($F(1, 37)=6.43$, $p=.016$) and Age x Social Status ($F(1, 37)=7.38$, $p=.010$) interactions on total Kcals consumed. In Choice subjects, HCD Kcal consumption increased with age ($F(1, 37)=80.52$, $p<.001$).

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