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Khadeeja Shabbir April 8, 2022

The Impact of Chronic Social Stress and Consumption of an Obesogenic Diet on the Trajectory of Insular Development in Infant and Juvenile Female Macaques

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Abstract

The Impact of Chronic Social Stress and Consumption of an Obesogenic Diet on the Trajectory of Insular Development in Infant and Juvenile Female Macaques
By Khadeeja Shabbir

Childhood obesity is a public health problem that continues to rise in the United States. Due to the long-term negative consequences in mental health, it is crucial to learn how children that are exposed to obesogenic, highly caloric diets (HCD) are impacted neurodevelopmentally. The consumption of obesogenic diets and the presence of chronic social stress are often comorbid, especially for children with a low socioeconomic status (SES). Both cause overlapping, potentially synergizing negative health effects. This longitudinal study investigates the effects of postnatal exposure to obesogenic diets and chronic psychosocial stress (social subordination stress) using a translational macaque model. The study followed 41 female macaques at Yerkes National Primate Research Center (YNPRC). There were 21 dominant animals from the top third of the hierarchy, and 20 subordinate animals from the bottom third of the hierarchy. Monkeys had access to either only low-calorie diet (LCD), or to both high-calorie diet (HCD) and LCD (Choice diet) from birth. Food intake (kilocalories (Kcal)) was recorded using radio-frequency identification (RFID) chips in subjects' wrists that opened automatic feeders according to the diet assigned at birth. Cumulative Kcal consumption was measured from birth to 6 months and from 6 months to 16 months. Body weights were measured at birth, 2 weeks, 6 months, and 16 months.

Brain structural MRI (sMRI) scans were collected at 2 weeks, 6 months, and 16 months of age. This study focuses particularly on the developmental effects of postnatal stress and diet on the insula (and each of its subregions, including the agranular insula (AI), dysgranular insular (DI), and insular proisocortex (IPro)) due to its implications in emotional/limbic, socio-cognitive,

and interoceptive functions. HCD exposure was associated with larger overall brain size (intracranial volume, or ICV) and insula and its subregions' volumes throughout development. Some effects emerged at 2 weeks, suggesting that maternal factors might mediate these neurodevelopmental impacts. These findings suggest that postnatal exposure to obesogenic diets is associated with increased whole-brain and insular growth in primates. Interestingly, social rank did not have significant effects for ICV nor insular development in this study, which contrasts previous literature.

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Introduction

The Effects of Obesogenic Diets and Chronic Stress

Pediatric obesity is a public health crisis, and its prevalence continues to rise (Anderson et al., 2019; Karnik & Kanekar, 2012). A review of the National Health and Nutrition Examination Survey, the official source for American obesity statistics, illustrated that the 5% pediatric obesity rate of 1978 had nearly quadrupled to 19.3% by 2018 (Anderson et al., 2019; Fryar et al., 2020). These numbers are concerning from a public health perspective because childhood obesity also increases the likelihood of obesity in adulthood five-fold (Simmonds et al., 2016) and has long-term, chronic health problems (Kelsey et al., 2014; Must et al., 1999; Visscher & Seidell, 2001).

Even for obese children who do not go on to become obese adults, there is still a higher risk of cardiac problems and higher mortality, for example (Kelsey et al., 2014). Furthermore, an increase in adipose tissue leads to increased pro-inflammatory adipokines, which can lead to chronic inflammation and obesity-related metabolic disorders; conversely, with calorie restriction, pro-inflammatory adipokines decrease and anti-inflammatory adipokines increase (Mancuso, 2016). Pediatric obesity increases the risk for various comorbidities in adulthood, including but not limited to hypertension, type 2 diabetes mellitus, coronary and cardiovascular disease, pulmonary disease, low self-esteem, anxiety, depression, and other psychiatric disorders (Morales Camacho et al., 2019; Perry et al., 2021; Rankin et al., 2016).

Overweight and obese children also had reduced cognitive performance according to neuropsychological tests (Bauer et al., 2015), and there is emerging, though scarce, evidence of overall brain gray matter loss and regional alterations (Taki et al., 2008). Several ways to tackle the obesity epidemic involve adopting an energy-balance approach emphasizing diet and

exercise (Hill, 2006). In a rodent model, diet and exercise reversed metabolic health effects of obese mice that were fed a high-fat diet (Palmer et al., 2012). A study of a school-based nutrition and exercise intervention for obesity in human children also improved metabolic health and scores on a self-reported mental status (Yu et al., 2020).

One important consideration to make regarding obesity is its relationship to chronic stress, including stress related to low socioeconomic status (SES). Low SES and poverty are major risk factors for both psychosocial stress and obesity, the latter aggravated by limited access to healthy foods in contrast to access to energy-dense "fast" foods and stress-induced emotional eating, which altogether results in higher consumption of cheaper, obesogenic, high-calorie diets (HCD) that are high in sugars and fat (Emerson et al., 2017; Larson et al., 2009; Morales Camacho et al., 2019; Quon & McGrath, 2014). Certain racial and ethnic groups are more at risk for low SES due to environmental and systemic factors, so they are more vulnerable to obesity (Newsome et al., 2021). Health disparities in underprivileged, underserved African-American populations are particularly striking, showing higher risk of obesity than other groups (Sutherland, 2021).

There may be specific, combined, or potentially synergistic effects of stress and obesity, and their underlying biological mechanisms and unfolding during brain development are not well understood. Chronic stress (including chronic psychosocial stress) can increase calorie consumption and thus play a role leading to obesity (Michopoulos, 2016)**,** in addition to other alterations in physical, mental, and brain health (McEwen, 2017; Quon & McGrath, 2014). Along with many other consequences, chronic stress from low SES has been shown to alter brain development and cause alterations in cortico-limbic areas (Lucassen et al., 2014; Radley et al., 2015; Tooley et al., 2021). In addition, chronic stress promotes over-eating in humans (Adam & Epel, 2007; Greeno & Wing, 1994) and animal models (Foster et al., 2006; Godfrey et al., 2018;

Hagan et al., 2003; Solomon et al., 2007), leading to increased risk for comorbid obesity (Evans et al., 2012). Particularly, chronic stress has been shown to influence obesity risk through emotional eating (Arce et al., 2010; Hill, 2006; Michopoulos, 2016). Females are also more vulnerable to emotional and stress-induced over-eating, obesity, and increased consumption of highly caloric (Western) diets (Arce et al., 2010; Suglia et al., 2012), which seem to result in brain structural alterations similar to those reported with chronic stress and ELS, including increased amygdala and decreased prefrontal cortex and insula volumes (Bruehl et al., 2011; Janowitz et al., 2015; Perlaki et al., 2018). For both humans and animal models, chronic stress shifts eating preferences to high-calorie foods (Hill et al., 2018). Furthermore, in the case of children, exposure to a high-fat diet in early life can affect dietary preferences as adults (Teegarden et al., 2009).

Chronic stress, particularly early in life (sometimes termed early-life stress -ELS- or early life adversity -ELA-) also has negative effects on the body, and it is especially problematic because of its effects on structural brain development (McEwen, 2017; Noble et al., 2012) that lead to long-term negative brain functional outcomes that underlie social, emotional, stress and reward/motivation alterations. Indeed, chronic stress and ELS result in neurodevelopmental alterations, including structural and functional alterations in cortico-limbic neural circuits such as the amygdala (Frodl et al., 2002; McEwen & Gianaros, 2010; Noble et al., 2012; Tottenham et al., 2010; Weniger et al., 2006), prefrontal cortex (Ansell et al., 2012; Arnsten, 2009), and insula (Ansell et al., 2012; Dannlowski et al., 2012). Alterations in these regions that are critical for the regulation of socioemotional, stress, and reward functions lead to psychopathology, including stress-related disorders such as anxiety, depression, drug addiction, and eating disorders (Boutelle et al., 2010; Carr et al., 2013; Dietz, 1998; Frodl et al., 2002; Goldstein & Volkow;

Sala et al., 2004; Tomasi & Volkow, 2013; VanTieghem & Tottenham, 2018; Weniger et al., 2006).

Obesity and chronic stress effects appear to be synergistic, as they are very often comorbid (Björntorp, 2001). Therefore, it would be useful to study the relationship between chronic stress and obesity as well as their development.

Current literature is scarce regarding the biological mechanisms underlying the impact of obesogenic diets and its potential synergism with stress. Performing these studies in humans is not possible because it would require randomized assignment to experimental group (stress, no-stress; highly caloric diet, low caloric diet) in longitudinal, prospective studies since birth.

In this study, I propose to examine the neurodevelopmental effects of both postnatal diet and psychosocial stress. I will focus on the insular cortex due not only to its sensitivity to stress and diet, but to its strong role in emotional representation, integration of interoceptive and metabolic information, sensory processing, reward and decision-making, and complex social functions. I will study different insular subregions to identify region-specific developmental effects of these postnatal factors on specific functions in a translational non-human primate (NHP) model.

The Macaque Social Subordination Stress Model

In studying the potentially synergistic neurodevelopmental effects of chronic psychosocial stress and consumption of obesogenic diets on brain regions that control emotional/limbic, socio-cognitive, and interoceptive functions, it is very helpful to use translational NHP models because they allow for strong experimental control of social status/rank, type of diet, and measures of kilocalories (Kcals) ingested from each diet, which is difficult to achieve with human subjects. In particular, social subordination in female rhesus macaque hierarchies has been validated as a translational model for chronic psychosocial stress (Michopoulos, Higgins, et al., 2012).

Automated feeders can be used to allow access of individuals to different diets while living in social groups and to measure the Kcals consumed of each diet, and these approaches have been validated by our group (Wilson et al., 2008).

Furthermore, the macaque model controls for several confounding variables. In humans, the stigma and stereotypes surrounding obesity across many societal realms cause weight-based discrimination and victimization, which in turn increase the adverse risk of both physiological and psychosocial health effects (Beck, 2016; Browne, 2021; Fruh et al., 2021). Using an NHP model controls not only for stigma, but also for other confounders, such as cognitive awareness, education, and drug and alcohol use, while allowing a better examination of social stress and obesity interactions and their effects. At the same time, NHPs such as rhesus macaques have very sophisticated social behaviors/interactions and a well-developed brain at birth that allows for better comparison to the human brain than many other mammals (like rodents) when analyzing brain structural MRI data across development. In addition, their longer development relative to less sentient mammals also allows for more translational results to the human developmental experience. Macaques also have similar cortical developmental trajectories to humans, which also makes them a good translational model (Kovacs-Balint et al., 2021).

Rhesus monkeys live in social groups with female, matrilineal-based social dominance hierarchies (Bernstein, 1976) and separate multi-male social dominance hierarchies. These social hierarchies are maintained through aggression, with socially subordinate animals receiving aggression and harassment from dominant animals (Abbott et al., 2003; Sapolsky, 2005; Silk, 2002). Though it may be surprising, the existence of the dominance hierarchy decreases fighting due to subordinates being more likely to submit (Bernstein & Gordon, 1974; Bernstein et al., 1974). The subordinates engage in submissive behaviors such as withdrawing, giving up their

food, or bearing physical aggression without retaliation. While the females stay in their natal group and have a relatively stable social status based on their mothers' status throughout their lifetime, males often migrate to different groups and can change their social rank (Wilson, 2016); for this reason, only females will be involved in this study.

Subordinates in the hierarchy experience frequent and unpredictable aggression, which is a significant stressor for them and causes overactivation of the hypothalamic-pituitary-adrenal (HPA) axis and other chronic stress phenotypes (Wilson, 2016). Over time, HPA axis overactivation also leads to impaired HPA axis negative feedback and stress-related neurobehavioral phenotypes (Michopoulos, Higgins, et al., 2012; Shively, 1998; Shively et al., 2005; Snyder-Mackler et al., 2016). A dysregulated HPA axis has huge impacts, from physiology to behavior to brain development. The resulting excessive cortisol causes an increase in adipose tissue in addition to chronic, low-grade inflammation, linking the process to obesity and negative health outcomes (Arce et al., 2010).

Importantly, this appears to start early in development. Although most of those reports are based on studies in adult females, we have emerging evidence that by the time subordinates are juveniles, they already show elevated cortisol secretion as well as structural brain alterations (Howell et al., 2014). This can be explained because infants always assume their mother's rank (Bernstein, 1976) and subordinates can begin receiving aggression as early as infancy in addition to observing harassment toward their relatives (Spencer-Booth, 1968). Although infants are rarely aggressed before weaning (Spencer-Booth, 1968) and there are maternal stress buffering effects, the adverse effects of subordinate status and obesogenic diets could still be transmitted to infants through maternal behavioral and biological signals in breast milk, such as glucocorticoids (GCs) and pro-inflammatory cytokines (Casabiell et al., 1997; Hart et al., 2004; Innis, 2007).

Furthermore, studies at the Yerkes NPRC have shown that adult subordinate female macaques show vulnerability to stress-induced overeating of highly caloric diets (Godfrey et al., 2018; Michopoulos, Higgins, et al., 2012).

Subordinates must frequently give up their food to dominant animals, so even in an environment with an abundance of food and other resources, the subordinate macaques must be vigilant and wait to feed until dominant animals have finished, limiting their feeding bouts. Prior studies have shown that subordinate macaques also tend to "emotionally eat" (induced by stress) when given the chance, and that they prefer a higher caloric diet compared to dominant and intermediate individuals, which leads to increased fat mass and obesity (Arce et al., 2010; Wilson, 2016). When presented a Choice diet (with both LCD and HCD available), female subordinate macaques consumed more Kcals than female dominant macaques (Arce et al., 2010; Michopoulos, Higgins, et al., 2012). Female subordinate macaques specifically prefer to over-eat high-calorie foods when available (Michopoulos, 2016; Michopoulos, Toufexis, et al., 2012). Therefore, social subordination causes chronic stress that not only affects the brain, but also predisposes the animal to obesity-related issues.

Because a low social status, particularly when associated with adverse early experiences, and chronic and sustained stress, is a strong predictor for negative physical and mental health developmental outcomes in different species (Murthy & Gould, 2018; Quon & McGrath, 2014; Tooley et al., 2021), it is important to uncover the biological mechanisms underlying specific neurodevelopmental alterations in order to develop efficacious treatments and interventions. Activation of neuroendocrine stress systems such as the HPA axis and chronic low grade inflammation are likely biological mechanisms by which both chronic stress (Loucks et al., 2010; Lupien et al., 2000; Pollitt et al., 2008) and obesogenic diet consumption (Auvinen et al.,

2012; Ludgero-Correia et al., 2012) can induce structural changes in the brain, by way of altered dendritic arborization, synaptic density, and myelination (Arnsten, 2009; Datta & Arnsten, 2019; Fuchs et al., 2001; Howell & Sanchez, 2011; Kucharova et al., 2011; Lucassen et al., 2014; McEwen et al., 2016; Mottahedin et al., 2017; Teicher & Khan, 2019; VanTieghem & Tottenham, 2018).

Studying the developmental, potentially synergistic impact of social stress and high-calorie diet (HCD) on social and emotional networks in the brain via structural MRI (sMRI) is an interesting way to take a more in-depth, evidence-based approach in looking at what socio-cognitive and emotional effects may be taking place by affecting the structural development of the brain regions that control those functions. The insula is a brain region strongly involved in social, cognitive, and sensory-perceptual processes (Evrard, 2019; Nieuwenhuys; Rachidi et al., 2021), so analyzing its volume changes under different social and diet conditions would provide important insights. Currently, there is a paucity of literature on the effects of social subordination stress and HCD on the developmental trajectory of the insula and each of its subregions.

Functions of the insular cortex subregions and insular relations to stress and diet conditions

The human insular cortex is a complex, convoluted structure inside the Sylvian fissure that is divided by the central sulcus into anterior (three gyri) and posterior areas (two gyri) (Evrard, 2019; Nieuwenhuys, 2012). It occupies only two percent of cortical surface area, yet is connected to many sensory, limbic, and association areas in addition to its many intra-insular connections (Nieuwenhuys, 2012; Rachidi et al., 2021). The insula is involved in a myriad of functions, such as visceral sensing and motor activities, somatosensory integration, motor association, limbic integration, language, memory, autonomic functions, salience processing,

socio-emotional functions, cognition, and adaptive risk-taking in decision-making (Augustine, 1996; Lighthall et al., 2012; Singer et al., 2009; Uddin et al., 2017). The posterior insula is involved in interoceptive, visceral, physiological, and sensorimotor functions, while the anterior insula is more involved in socio-emotional functions and the introspection of feelings (Chiarello et al., 2013). A model of insular function proposes that information flows from the posterior to the anterior pole, with the posterior insula representing interoception, which is then integrated with emotion in the middle, and then the anterior insula is involved in self-awareness related to the sensation (Craig, 2009).

Along with the anterior cingulate cortex (with which it often shows correlated activity), alterations in the insula underlie psychiatric disorders such as depression, anxiety, obsessive-compulsive disorder (OCD), schizophrenia, PTSD, eating disorders, panic disorders, and bipolar disorder (Goodkind et al., 2015; Nagai et al., 2007). One study proposed that the insula contains a sensory-motor axis (the primary interoceptive cortex in the GI receives sensory inputs, and a part of the AI resembles the precentral gyrus in the frontal lobe), a spino-cranial axis (the dorsal fundus is organized topographically and represents spinal, trigeminal, and vagal inputs), and a cognition-emotion axis (dorsal AI corresponds to cognition, ventral AI to emotion) in the insula, illustrating the multitude of insular functions (Evrard, 2019).

Unlike the human insula, the macaque insula is smooth, which makes it difficult to compare to human insular regions based on macroscopic criteria alone, so using cytoarchitecture is a better way to establish homologies (Evrard, 2019). Some studies use “cortical type” to do so, which distinguishes regions based on laminar organization and cell features, which include isocortex, periallocortex, proisocortex, and koniocortex (Barbas & Pandya, 1989; Carmichael & Price, 1994). Isocortex and proisocortex are types of neocortices, and periallocortex is a

transitional type between these two. Proisocortex and periallocortex mostly have connections to limbic areas, whereas isocortex has more connections to sensory areas (Carmichael & Price, 1994). Another cytoarchitectural division categorization based on cell features, laminar distributions, and structural elements like the presence and type of Meynert's granule cell, resulted in divisions into agranular (anterior), dysgranular (middle), and granular (posterior) regions (Barbas & Pandya, 1989; Carmichael & Price, 1994; Evrard, 2019). In this study, I divided the insula into the agranular insula (AI), dysgranular insula (DI), granular insula (GI), and insular proisocortex (IPro) based on Paxinos and collaborators' neuroanatomical criteria for the macaque insula (Paxinos et al., 2000) adapted to MRI data. Medially and superiorly, the whole insula was defined by white matter (WM), and laterally and inferiorly, it was defined by the lateral sulcus.

The AI has many connections, receiving olfactory, thalamic, and limbic inputs (such as the locus coeruleus, the periaqueductal gray, and the amygdala) distributed over several areas (Carmichael & Price, 1994; Evrard, 2019; Evrard et al., 2014). Three AI areas anterior to the limen receive olfactory and/or thalamic inputs as well as the amygdala (Figure 2B). Other AI areas also have limbic inputs. The five AI areas anterior to the limen are similar to the areas described by Carmichael & Price (Carmichael & Price, 1994).

Studies using correlations between the Balanced Emotional Empathy Scale and fMRI percent blood oxygen level-dependent (BOLD) signal showed that the anterior insula is involved in self-awareness and complex social functions, such as empathy, social decision-making, and social structure learning (Fahrenfort et al., 2010; Harlé et al., 2012; Lau et al., 2020). It is also responsible for controlling motivational vigor through a circuit that connects insula with the brainstem (Deng et al., 2021), and it also computes risk predictions for decision-making

(Lighthall et al., 2012; Singer et al., 2009; Yang et al., 2022). One study investigated the anterior insula's role in binge-eating, which shares similarities with emotional eating) in rats, reporting that anterior insula activation suppressed binge intake, but not homeostatic food intake, or food intake for energy balance (Price et al., 2019).

The DI can be further divided into areas related to different functions (Carmichael & Price, 1994; Evrard, 2019; Evrard et al., 2014). The dorsal dysgranular areas are responsible for intrapersonal, agency behaviors, while the mound and ventral dysgranular areas are involved with interpersonal, social functions. The DI areas linked to interpersonal and social functions areas have inputs from the amygdala, pre-supplementary motor area, mirror neurons, and ventral striatum; in contrast, the DI area linked to intrapersonal and agency functions has inputs from the supplementary motor area, dorsal striatum, and posterior cingulate cortex (Evrard, 2019).

The GI also has separate areas related to different functions. The dorsal fundal areas are primarily involved in interoception and visceral representations (it is known as the primary interoceptive cortex), whereas the posterior granular areas are involved in vestibular and auditory functions (Evrard, 2019). The dorsal areas have inputs from the ventral medial thalamus through solitary tract nucleus and spinal lamina 1, coming ultimately from peripheral innervation. Interoceptive information may flow from the GI to the DI to the AI (Evrard, 2019).

The IPro that we delineated overlapped with the AI and DI from previous studies, and it has limbic connections (Carmichael & Price, 1994; Evrard, 2019; Paxinos et al., 2000).

The relationship between stress and the insula is complex. Post-traumatic stress disorder (PTSD) patients and individuals with ELS had significant insular volume reductions (Kunimatsu et al., 2020; Saleh et al., 2017). Cumulative adversity and stressful life events are also associated with right insular gray matter (GM) volume loss (Ansell et al., 2012). Furthermore, a meta-

analysis also showed that the insula has a similar relationship to the amygdala for PTSD, social anxiety disorder (SAD), and specific phobias, as all three lead to insular hyperactivation (Etkin & Wager, 2007). In fact, there is increased activation of the insula for many anxiety disorders (Shin & Liberzon, 2010). This indicates that the relationship between chronic stress and insular structural development is one that leads to both volume decreases and activity increases. A rodent study also showed that the insula has a direct role in anxiety (Méndez-Ruette et al., 2019). Furthermore, anterior insula functional network connectivity had a role in mediating the association between ELS (childhood maltreatment) and symptoms of depression (He et al., 2022), which relates to this study because it supports a role of the insula in both ELS and its neuropsychiatric outcomes.

There is also conflicting evidence regarding the relationship between diet and the insula. One study showed that the insular GM volume was inversely related to body fat change in the first six months of human life (Rasmussen et al., 2017). In a study with human adolescents, a larger insula volume was associated with being more likely to choose a lower caloric food (Hall et al., 2021). This study also suggested that studying the insular subregions in relationship to food choices would be important because the anterior insula is more involved in salience detection, whereas the posterior is more involved with responding to homeostatic changes (Hall et al., 2021). It is also interesting to note that anterior insula activity suppresses binge intake of high-fat foods in rodents (Price et al., 2019). Furthermore, a meta-analysis showed that obesity patients had decreased insular GM volumes (Herrmann et al., 2019). Conversely, a different study found that successful dieters had overall insular GM volumetric loss than unsuccessful dieters, and it showed that weight loss is linked to insular volume loss (Honea et al., 2016). Despite some inconsistencies in the literature (as some studies found that smaller insular

volumes are associated with increased body fat and choosing higher caloric foods, while another study found that insular volume loss is associated with weight loss after dieting), the insula seems to play a role in the effects of psychosocial stress and diet during development.

While the GI has a significant role in interoception, the other subregions are still relevant to diet, as obese subjects had more right anterior (AI, IPro) and middle insula (DI) activation than lean subjects to food (Scharmüller et al., 2012), and obese women had more AI activation in particular to HCDs than lean women (Stoeckel et al., 2008).

Aim and Hypotheses

The goal of this study was to examine the effects of postnatal exposure to social subordination stress and consumption of obesogenic diets on the structural development of the insula in female macaques, from infancy to the juvenile, prepubertal period. Female macaques of different social ranks (dominant, subordinate) were provided postnatal access to either a Choice diet (LCD, HCD) or to an LCD-only diet to examine whether postnatal diet interacted with social subordination stress to affect the developmental trajectory of specific insular subregion volumes. The AI is of interest due to its socio-limbic implications—many studies discuss the implications of the anterior insular cortex, which overlaps mostly with the AI, and some with the IPro. The DI is of interest here due to its involvement in both intrapersonal and interpersonal agency functions. The GI is of interest due to its interoceptive role, especially in relation to food consumption.

With respect to social status, we hypothesized that subordinates would have smaller whole insula and insular subregion volumes than dominants, and that these differences will increase over the course of development. This is supported by the literature reviewed above,

which indicates that chronic stress is linked to smaller insular volumes, though the insula is hyperactive. The limbic, emotional aspect of stress, fear, and avoidance is best represented in the anterior insula (AI, IPro) (Lin et al., 2015), and some in the intermediate (DI) region, while the posterior (GI) region mediates fear and threats (Rodríguez et al., 2020) without being involved in the self-awareness of these functions (Craig, 2009). Thus, all insular subregions are hypothesized to be smaller for subordinates relative to dominants.

In relation to diet effects, I hypothesized that animals in the Choice diet (particularly those who consumed more HCD kilocalories) would have smaller insular and subregion volumes than LCD-only animals and those who consumed fewer kilocalories. This is supported by literature above reporting that obese individuals and those who chose high-calorie foods had smaller insulas (Hall et al., 2021; Herrmann et al., 2019; Rasmussen et al., 2017). Accordingly, I hypothesized that all insular subregions would be smaller in Choice than LCD-only animals. Given that reviewed literature on the relationship between the insula and chronic stress indicated that increased insular activation is sometimes found in situations of decreased insular volumes, this could be the case for diet and food perception literature as well. The GI, involved in interoception and other sensory-related functions, is especially hypothesized to have a smaller size for Choice diet animals because viewing HCD foods increases cortical activation in regions associated with food perception (Ohla et al., 2012), and increased insular activity is sometimes reported in situations of decreased volumes. As for the other subregions, literature reviewed above showed that right anterior (AI, IPro) and middle insula (DI) were more activated in response to food in obese subjects than lean individuals (Scharmüller et al., 2012) and particularly more AI activation (Stoeckel et al., 2008), so this provides further support for the proposed effect on other regions.

Methods

Subjects, Housing and Experimental Design

This study used 41 female rhesus monkeys (*Macaca mulatta*), born and raised at the Yerkes National Primate Research Center (YNPRC) Field Station (Lawrenceville, Georgia). They lived with their mothers and families in complex social groups housed in outdoor enclosures with attached climate-controlled indoor areas. Social groups had 2-3 adult males, 30-60 adult females, and their offspring. Behavioral, brain, body weight and food intake data were collected longitudinally between birth and menarche (see Figure 1 for overall experimental design, measures, and timeline) as part of a bigger study funded by an NIH/NICHD R01 grant (Stress and Obesity effects on Development -SOD-). Emory University's Institutional Animal Care and Use Committee (IACUC) approved the procedures, which complied with both the United States Department of Health and Human Services' "Guide for the Care and Use of Laboratory Animals" and the Animal Welfare Act. The YNPRC is fully accredited by AAALAC, International.

Multiparous dams were chosen according to their relative social status/rank, which was determined by group dominance matrices based on observations of dyadic agonistic interactions. In rhesus macaque social groups, there is a social dominance hierarchy in which lower-ranking animals show submissive behaviors (e.g. withdraw) towards higher-ranking animals (Bernstein et al., 1974). Based on behavioral observations using a standard ethogram (Wilson et al., 2013) that determined social ranks, animals in the extremes of the social hierarchy were selected: dominant dams from families in the top third of the hierarchy (DOM), or subordinate dams from families in the bottom third of the hierarchy (SUB). We excluded from the study dams with a history of infant neglect or physical abuse and infants with birth weight <450g to avoid the

confounding effect of adverse caregiving and the known detrimental effects of low birth weights on brain and behavioral development (Aarnoudse-Moens et al., 2009).

In order to control for potential heritable, biological and prenatal factors related to maternal social rank, including prenatal stress exposure or genetic/epigenetic transmission of traits (Phelan et al., 2011; Schneider et al., 2001), a cross-fostering design was used to randomly assign infants at birth to the same or to a different social rank group to that of their biological mother. This was meant to disentangle the effects of postnatal exposure to social status (e.g., social subordination stress) from prenatal/heritable rank effects. Because rhesus infants assume their mothers' rank (Bernstein, 1976), when an infant is raised by a foster mother of a different social status, they assume the foster mother's social rank in the hierarchy. Table 1 shows the breakdown of groups based on social rank, diet, and cross-fostering. Twenty-one infants were selected randomly to be cross-fostered within 48 hours of birth according to established procedures (Howell et al., 2017); the other 20 infants were raised by their biological mothers to also examine the potential effects of the cross-fostering manipulation. There were a total of 21 DOM and 20 SUB mother-infant pairs followed longitudinally throughout this study. Although female macaque social ranks are stable, they were reassessed monthly in case of rare changes. In addition to the categorical social rank group assignment (DOM, SUB), the relative rank of each subject was also calculated as the ratio of the postnatal dam's social status divided by the number of animals in the group that were older than three years, except for adult males, who establish their own social rank among themselves (Wilson, 2016). For example, a dam with a rank of 40 out of 100 animals would have a relative rank of 0.40, and her infant would also assume this rank (Bernstein, 1976).

Diet Conditions

Because a focus of the NIH/NICHD-funded Stress and Obesogenic Diet project was to study the effect of postnatal exposure to a high-calorie diet (HCD) in comparison to a healthy, low sugar/fat calorie diet on the development of brain structure, dams consumed a low-calorie diet (LCD) throughout pregnancy to control for prenatal diet effects on brain structure and behavior (Janthakhin et al., 2017; Sullivan et al., 2010).

Table 1 shows the experimental groups breakdown by social rank (DOM, SUB), postnatal diet (LCD-only, Choice -LCD, HCD-), and cross-fostering (cross-fostered: LCD -6 DOM, 4 SUB-, Choice: -6 DOM, 5 SUB-; non-cross-fostered: LCD -5 DOM, 6 SUB-, Choice: -4 DOM, 5 SUB-). Postnatal diet access of mothers and infants was experimentally controlled using automated feeders that subjects and their mothers could activate with radio-frequency identification (RFID) chips subcutaneously implanted in their wrists (Wilson et al., 2008). Automated feeders delivered either LCD or HCD pellets. Animals in the LCD diet had access to only the LCD feeders, whereas those in the Choice condition had access to both the LCD and HCD automated feeders, which models the Western human diet environment and allows for emotional eating in animal models (Michopoulos, Toufexis, et al., 2012; Wilson et al., 2008). The Choice condition also promotes increased consumption of HCD than providing access to only the HCD (Michopoulos, Toufexis, et al., 2012; Moore et al., 2013). LCD was sourced from LabDiet Monkey Diet 503A, which is a pelleted version of the standard, low-calorie feed, LabDiet Monkey Diet 5038 (Purina Mills International, St. Louis, MO). The LCD was 3.45 kilocalories(Kcals)/gram, broken down into 12% fat, 65.9% starch, 4.14% sugar, and 18% protein (Table 2). The HCD pellets (from D14051502B, Research Diets, Inc.) had more

Kcals/gram (4.25), broken down into 30% fat, 20.2% starch, 29.8% sugar, and 20% protein (Table 2). Vitamin and mineral content for LCD and HCD pellets were comparable.

Both food and water were available “ad libitum”. Dams had RFID chips implanted at the beginning of the study, whereas infants had them implanted at 6 weeks of age, which is before weaning but slightly after the typical first introduction of solid food (Maestripieri & Hoffman, 2012). Depending on the diet assignment, the RFID chip could operate either only LCD or both LCD and HCD feeders. Feeders dispensed one pellet for every RFID chip scan, which allowed for the quantification of caloric intake (Wilson et al., 2008). This feeding system was validated previously, showing that monkeys consume food as desired while systematically controlling access to the two experimental diets and giving accurate recordings of the Kcals consumed from each diet (Wilson et al., 2008). Furthermore, validation of the model has demonstrated that subjects almost always consume a pellet of food after taking it from the automated feeder (Wilson et al., 2008). LCD and HCD Kcal intakes were recorded continuously from birth to 16 months to determine how diet condition and social rank affected Kcal consumption, measured as Kcals per day. Diet intake data were then summed into total cumulative Kcal consumption of HCD and/or LCD consumption from the start of solid food consumption to 6 months, and from 6 to 16 months of age. Body weight (kg) data were also collected at birth, 2 weeks, 6 months, and 16 months. Developmental changes in Kcal intake of each diet as well as in body weight were analyzed using linear mixed models (LMM) by a previous undergraduate student in the lab and findings are currently being submitted to the journal *Biological Psychiatry* (Kyle et al., in preparation); a summary of those findings are presented in the Results section below with the proper citation, because they are also relevant for this thesis.

Structural Magnetic Resonance Imaging (sMRI)

Acquisition of MRI Images

The sMRI scans were obtained at 2 weeks, 6 months, and 16 months of age. On the day before the scan acquisition, 2 week- and 6-month-old infants were transported from the YNPRC Field Station with their mothers to the YNPRC Imaging Center; the 16-month-old juveniles were transported to the Imaging Center alone. A 3T Siemens Magnetom TRIO system (from Siemens Medical Solutions, Malvern, PA, USA) was used with an 8-channel phase array coil to collect T1- and T2-weighted sMRI scans in a single session. To collect T1-weighted scans, a 3D magnetization-prepared rapid acquisition with gradient echo (3D-MPRAGE) parallel imaging sequence was used (TR/TE = 2600/3.46msec; voxel size: 0.5mm^3, isotropic; 8 repetitions; GRAPPA, R=2). T2-weighted scans were acquired in the same direction (TR/TE = 3200/373msec; voxel size: 0.5mm^3 isotropic; 3 repetitions; GRAPPA, R=2), and combined with the T1 data to improve white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) border contrast, which helps delineate regions of interest -ROIs- (Knickmeyer et al., 2010).

Subjects were scanned under anesthesia (1% isoflurane, to effect) following induction by an intramuscular injection of telazol (2-4mg/kg body weight), and intratracheal intubation. During the scan, animals' vital signs were monitored with an electrocardiograph, oximeter, blood pressure monitor, and a rectal thermometer. A dextrose and 0.45% NaCl solution was administered with an intravenous catheter to maintain hydration, and a heating pad was used to maintain body temperature. A head holder with a mouthpiece and ear bars was used to immobilize the head and help scan it in the same position for all subjects while supine, and a vitamin E capsule taped to the right temple identified the right side of the head.

Infants were returned to their mothers upon recovering from anesthesia, and all animals were transported back to their enclosure at the Field Station the next day. For the 2-week age group, scans for three subjects are missing because either the mother or the infant was ill, but because they had data at the other ages, they were not dropped from the study. For the 16-month group, two subjects were dropped from the study and are missing their scans.

sMRI Data Processing

All sMRI data were processed using one or both of two open-source, in-house, atlas-based pipelines that were developed by the Neuro Image Research and Analysis Laboratories - NIRAL; University of North Carolina- (Styner et al., 2007; Wang et al., 2014). All structural data were processed using the AutoSeg 3.3.2 package, except for some processing steps for the 2-week data, where AutoSeg was used in combination with NeoSeg 1.0.7 to deal with neonatal challenges, such as GM/WM contrast inversion. The pipelines include semi-automatic processing tools that segment the brain images into probabilistic tissue maps of WM, GM, and CSF, and generate cortical lobar and/or ROI parcellations and subcortical ROIs. We have previously published these approaches and tools in studies of infant/juvenile macaque brain structural development (Kovacs-Balint et al, 2021).

T1- and T2-weighted images of each animal were averaged respectively. Then, the first step of the AutoSeg pipeline was the bias field correction. In this step, inhomogeneities in the signal intensity of the brain image—usually caused by issues with the radiofrequency coils—were corrected using N4-ITK bias field correction (Tustison et al., 2010; Wang et al., 2014) to improve tissue segmentation.

The next step was reference space alignment, in which AutoSeg registered the subject's T1- or T2-weighted image to the reference brain T1- or T2-weighted atlas with BRAINSFit, a tool in Slicer software for rigid body registration (Fedorov et al., 2012; Shi et al., 2016; Styner et al., 2007; Wang et al., 2014). There were different atlases for each age because of structural differences such as myelination/tissue (GM, WM, CSF) contrast, cortical gyrification, and region-specific differences in shape (Knickmeyer et al., 2008; Kovacs-Balint et al., 2021; Li et al., 2014); infant atlases were generated by our group (Shi et al., 2017): see Figure 2A).

Next, automatic atlas-based classification (ABC) tissue segmentation occurred. In this step, tissue was segmented into GM, WM, and CSF to distinguish brain from non-brain tissue by using Advanced Normalization Tools (ANTS) with the T1- and T2-weighted images (Liu et al., 2015; Styner et al., 2007; Wang et al., 2014). This automatic brain skull-stripping step generated a brain mask that was manually corrected using the ITK-Snap program for more accurate elimination of all non-brain tissue from the image. Following this, Slicer was used to smooth the resulting brain masks. Researchers involved in manual skull-stripping were blind to the subject's group assignment.

After the manual brain skull-stripping step, ABC was run a second time with the skull-stripped brain images for more accurate atlas registration, tissue segmentation into GM, WM, and CSF, and parcellation of ROIs (Wang et al., 2014). The second ABC round registered skull-stripped brain images to the skull-stripped atlas and generated warp fields for ROI parcellations. ROI parcellations and tissue segmentations were combined, allowing for the computation of GM volume in the insular subregions.

ROIs in the older brain atlas were manually edited and then backpropagated to earlier ages atlases, to be manually edited in the younger atlases according to published

neuroanatomical/functional macaque criteria (Paxinos et al., 2000; Paxinos et al., 1999; Saleem & Logothetis, 2006; Stephani et al., 2011). Figure 2 displays the specific macaque insula subdivisions we studied in our MRI images (agranular insula -AI-, dysgranular insula -DI-, granular insula -GI-, and insular proisocortex -IPro-) in a sagittal and coronal 12-month macaque atlas T1-MRI image following previous neurohistological, cytoarchitectonic and connectivity/functional criteria (Barbas & Pandya, 1989; Carmichael & Price, 1994; Evrard, 2019) as well as macaque brain stereotaxic/MRI atlases (Paxinos et al., 1999; Saleem & Logothetis, 2006) and modifications of available MRI ROI sets (Paxinos ROIs in the scalable rhesus brain atlas, based on Paxinos et al, 2000 definitions**,** https://scalablebrainatlas.incf.org/macaque/PHT00_on_F99 (Bakker et al., 2015; Paxinos et al., 2000)). AutoSeg generated GM, WM, and CSF tissue segmentations and ROI parcellations. Intracranial volume (ICV) was calculated as the sum of GM, WM, and CSF, and it was not calculated by hemisphere. Left and right whole insular, as well as AI, DI, GI, and IPro ROI volumes were calculated separately.

Statistical Analysis

IBM SPSS Statistics (version 28.0.1.0) was used to perform all statistical analyses. To summarize variables and visualize trends, we used mean±standard error of the mean (SEM). Data were first checked for normal distributions. Data that were not normally distributed according to the Shapiro-Wilk test were log10-transformed ($p \leq 0.05$) and checked again for normality. Repeated measures analysis of variance (RM ANOVA) was then used to evaluate the developmental effects of social subordination stress and obesogenic diet consumption on

structural MRI measures of intracranial volume (ICV) and insular total and subregions volumes. Effect sizes were calculated as η^2.

Although 41 subjects were studied longitudinally, there were 3 animals with missing sMRI data at 2 weeks, and 2 other animals with missing sMRI data at 16 months. As a result, RM ANOVA analyses was run on a total of 36 subjects. RM ANOVA was conducted with age (2 weeks, 6 months, 16 months) as the repeated measures factor, and social rank (DOM, SUB) and diet (LCD-only, Choice) as the fixed factors to examine the main effects of these factors and their interactions. For analyses of insula ROIs, hemisphere was included in the model as an additional repeated measures factor (left, right). Although it would be important to examine the effects of biological mother's rank by repeating the RM ANOVA entering biological mother's rank as a covariate, I did not have time to include these analyses in the thesis. When data did not pass Mauchly's test of sphericity, Greenhouse-Geisser values were reported.

Since significant effects of diet and age were detected on total brain size (ICV; see Results), RM ANOVA was re-run for each ROI for ICV-corrected values to account for group differences in ICV when assessing effects on insula or insula subregions. Since the AutoSeg pipeline does not calculate ICV per hemisphere, left and right insular ROI volumes were first added together and then divided by the ICV, yielding ICV-corrected ROI values that indicate the percent of the brain that is occupied by the insula regions. Therefore, hemisphere was not a variable when analyzing ICV-corrected values. Analyses of ICV-corrected insular ROIs growth accounts for differences in overall brain size and is a method we and others have used before (Kovacs-Balint et al., 2021).

Post hoc pairwise comparisons using paired-sample *t*-tests were performed with Bonferroni multiple comparisons corrections when significant diet, rank and/or age interaction

effects were detected in the RM ANOVA models. The threshold for significant effects was set at a level of $p \leq 0.05$.

Results

Structural MRI data (RM ANOVA)

Intracranial volumes (ICV)

ICV data were normally distributed according to the Shapiro-Wilk test. It also passed Mauchly's test of sphericity as well as Levene's test of homogeneity of error variances. Upon running RM ANOVA, a main effect of age was found ($F_{(2,64)} = 1474.337$, $p=2.96*10^{-54}$, $\eta_p^2 =0.979$), with ICV increasing with age (Figure 3). A main effect of diet was detected as well ($F_{(1,32)} = 6.581$, $p=0.015$, $\eta_p^2 =0.171$), with Choice diet animals having a larger ICV than LCD-only animals (Figure 3). No other main or interaction effects were detected.

Whole Insula Volumes

Prior to ICV corrections, all whole insula volume data were normally distributed according to the Shapiro-Wilk test, except for the left insula at 6 months. Log10 transformation normalized the data. Mauchly's test of sphericity passed for age but not for age by hemisphere; therefore, Greenhouse-Geisser values were reported. All variables passed Levene's test of homogeneity of variances.

A main effect of age was found for uncorrected whole insula volumes ($F_{(2,64)}= 2104.039$, $p= 4.1429*10^{-59}$, $\eta_p^2 =0.985$), which increased with age (Figure 4). Main effects of diet were also found ($F_{(1,32)}=11.376$, $p=0.002$, $\eta_p^2 =0.262$), with animals in the Choice diet having a larger

whole insula volume than LCD-only animals (Figure 4). There was also an age by hemisphere interaction effect ($F_{(1.502, 48.054)}$= 12.171, p= 0.001423, η_p^2 = 0.276). No other significant main or interaction effects were detected.

ICV-corrected data were not normally distributed according to the Shapiro-Wilk test, but log10 transformation resolved this. Age did not pass Mauchly's test of sphericity, so Greenhouse-Geisser values are reported below. All variables passed Levene's test of homogeneity of error variances. ICV-corrected values retained the main effects of age ($F_{(2,64)}$ =171.435, p= 1.9731*10^{-26}, η_p^2=0.843) and diet ($F_{(1,32)}$ =6.730, p=0.014, η_p^2= 0.174) reported above. Thus, ICV-corrected global insula volume increased with age and was larger in animals in the Choice diet than LCD-animals (Figure 4). Because the ICV-corrected values were calculated by adding hemispheres and dividing by ICV, hemisphere was not included in the statistical model. No other main or interaction effects were detected.

Agranular Insula (AI) Volumes

Both uncorrected and ICV-corrected AI variables passed the Shapiro-Wilk test of normality, Mauchly's test of sphericity, and Levene's test of homogeneity of error variances.

A main effect of age was found on AI uncorrected volumes (F(2,64) = 656.122, p = 2.2882*10^{-43}, η_p^2 = 0.953), with increasing volumes with age (Figure 5). There was also a hemisphere effect ($F_{(1,32)}$ = 31.387, p= 0.000003, η_p^2 = 0.495), with a larger left than right hemisphere. In addition, there was a main diet effect ($F_{(1,32)}$ = 16.551, p= 0.000289, η_p^2 = 0.341), with Choice diet animals having a larger AI volume than LCD-only animals (Figure 5). There was also an age by hemisphere interaction effect ($F_{(2,64)}$ = 19.359, p= 2.6617*10^{-7}, η_p^2 = 0.377). No other main or interaction effects were found.

After ICV corrections, the main age ($F_{(2,64)} = 91.145$, $p = 1.8684*10^{-19}$, $\eta_p^2 = 0.740$) and diet effects remained ($F_{(1,32)} = 7.791$, $p = 0.009$, $\eta_p^2 = 0.196$), with Choice animals still showing larger AI volumes than those on the LCD-only diet (Figure 5). No other main or interaction effects were detected.

Dysgranular Insula (DI) Volumes

Uncorrected DI values passed the Shapiro-Wilk test of normality and Levene's test of homogeneity of error variances. Age passed Mauchly's test of sphericity, but age by hemisphere did not pass, so Greenhouse-Geisser values were reported.

For the uncorrected data, a main effect of age was found on DI volumes ($F_{(2,64)} = 611.234$, $p= 1.9815*10^{-42}$, $\eta_p^2 = 0.950$), with volumes increasing with age (Figure 6). There was also a main effect of diet ($F_{(1,32)} = 12.491$, $p= 0.001269$, $\eta_p^2 =0.281$), with animals in the Choice diet showing higher DI volumes than those in the LCD-only condition (Figure 6). An interaction effect of age by diet was also found ($F_{(2,64)} = 4.559$, $p=0.014$, $\eta_p^2 =0.125$). *Post hoc* pairwise comparisons of the means showed significant differences in DI volumes between the diet groups at each age studied (at 2 weeks: p=0.004, at 6 months: p=0.003, and at 16 months: p=0.00046, based on a Bonferroni-adjusted threshold of p=0.0055 for multiple comparisons -*p-value*/9 comparisons-; see asterisks in Figure 6). An age by hemisphere interaction effect was also detected ($F_{(1.642,52.545)} = 4.778$, p= 0.017, $\eta_p^2 =0.130$).No other main or interaction effects were found.

ICV-corrected DI values passed the Shapiro-Wilk test of normality upon log10 transformation, Mauchly's test of sphericity, and Levene's test of homogeneity of error variances for all ages except for 2 weeks. Only the main effect of age ($F_{(2,64)} = 101.324$, $p = 1.4714*10^{-20}$,

$\eta_p^2 = 0.760$) and the main effect of diet ($F_{(1,32)} = 7.791$, $p = 0.009$, $\eta_p^2 = 0.196$) remained following ICV-correction. No other main or interaction effects were detected.

Granular Insula (GI) Volumes

For uncorrected values, GI did not pass the Shapiro-Wilk normality test at 6 months for both hemispheres, but log10 transformation resolved this. Age passed Mauchly's test of sphericity, but age by hemisphere did not pass, so Greenhouse-Geisser values were reported. Levene's test of homogeneity of error variances was passed.

There was a main effect of age on GI volume ($F_{(1.661,53.144)} = 1259.707$, $p = 1.0722*10^{-43}$, $\eta_p^2 = 0.975$) with volume increasing with age; based on the graph, it seems that volumes grow much more from 2 weeks to 6 months than 6 months to 16 months (Figure 7). A main effect of hemisphere was also detected ($F_{(1,32)} = 26.867$, $p = 0.000012$ $\eta_p^2 = 0.456$), with a larger right than left hemisphere. In addition, a main effect of diet was found ($F_{(1,32)} = 6.584$ $p = 0.015$, $\eta_p^2 = 0.171$), with Choice animals having higher GI volumes than LCD-only animals. No other main or interaction effects were found.

For ICV-corrected values, even after log10-tranforming the data, the 6 months and 16 months data did not pass the Shapiro-Wilk test of normality. Age did not pass Mauchly's test of sphericity, so Greenhouse-Geisser values were reported. ICV-corrected GI data passed Levene's test of homogeneity of error variances. After ICV correction, the diet effect disappeared, and only a main age effect ($F_{(1.690, 54.064)} = 106.501$, $p = 3.5058*10^{-18}$, $\eta_p^2 = 0.769$) remained (Figure 7). No other main or interaction effects were detected.

Insular Proisocortex (IPro) Volumes

Uncorrected IPro data passed the Shapiro-Wilk normality test and Levene's test of homogeneity of error variances. Age and age by hemisphere did not pass Mauchly's test of sphericity, so Greenhouse-Geisser values were reported.

There was a main effect of age on IPro volume ($F_{(1.614,51.658)} = 475.191$, $p = 4.7107*10^{-32}$, $\eta_p^2 = 0.937$) with volumes increasing with age (Figure 8). In addition, there was a main effect of diet ($F_{(1,32)} = 7.934$, $p = 0.008$, $\eta_p^2 = 0.199$) with larger IPro volumes in Choice than LCD-only animals. An age by hemisphere interaction effect was also detected ($F_{(1.540,49.267)} = 5.597$, $p = 0.011$, $\eta_p^2 = 0.149$). No other main or interaction effects were found.

ICV-corrected IPro volume data also passed the Shapiro-Wilk normality test and Levene's test of homogeneity of error variances. Age did not pass Mauchly's test of sphericity, so Greenhouse-Geisser values were reported. After ICV corrections, the age effect ($F_{(1.456,46.590)} = 104.867$, $p = 7.1579*10^{-16}$, $\eta_p^2 = 0.766$) and diet effect ($F_{(1,32)} = 4.168$, $p = 0.050$, $\eta_p^2 = 0.115$) remained, though notably, the diet effect was borderline significant (Figure 8). No other main or interaction effects were detected.

Body Weight and Kilocalories consumed of the LCD and HCD Diets (LMM)

The analyses of effects of social rank, diet and biological mother on body weight and Kcals consumed of each diet were performed by a previous undergraduate student in the lab and reported elsewhere (Kyle et al, in preparation). I am summarizing the main findings here, as they are of relevance for this project. The studies found that body weight increased with age with no significant main or interaction effects of social rank or diet (Figure 9). Older animals consumed more Kcals, Choice animals consumed more Kcals than LCD-only animals, and dominant

animals consumed more Kcals than subordinates (Figure 10); consumption of HCD Kcals also increased with age in Choice subjects.

Discussion

Summary

This study examined the effects of postnatal exposure to a highly caloric diet and social subordination stress on the structural development of the total insular cortex and its subregions due to their role in emotional, socio-cognitive, and interoceptive functions. Brain structural MRI, body weight, and feeding data were collected longitudinally (from birth to 16 months of age) in female macaques from different social ranks (DOM, SUB) and diet conditions (LCD-only, Choice -access to both LCD, HCD-). The findings show that animals exposed postnatally to an obesogenic diet had larger overall brain volumes (ICV) and larger volumes of the insula and its subregions, except for the GI, even after controlling for the ICV differences. SUB and DOM animals had no significant differences between their insular volumes. Interestingly, several of the obesogenic diet effects were already detectable at 2 weeks of age, suggesting potential transmission through maternal biological signals (such as milk) since the infants did not have access to the automated feeders until 6 weeks of age. Altogether, our findings suggest that postnatal exposure to an obesogenic diet have significant, insult-specific effects on structural brain development, which emerge during infancy and remain present through the juvenile period. For the DI, the obesogenic diet effect at 2 weeks became exacerbated throughout the juvenile period. Our findings further suggest that cumulative HCD Kcals consumed are an important underlying biological mechanism of region-specific structural effects, excepting the GI.

Kilocalorie Consumption and Body Weight

A previous study in the lab (Kyle el al, in preparation) showed that animals in the Choice diet condition consumed more Kcals of HCD than those in the LCD-only group, although contrary to predictions, it was the DOM and not SUB animals that showed hypercaloric consumption of HCD pellets, resulting in total higher HCD + LCD Kcals consumption from 0-6 months and 6-16 months in DOM than SUB animals. From a life-history theory (Laskowski et al., 2021) and ontogenetic perspective, DOM animals could be consuming more HCD Kcals to increase their adipose tissue and accelerate menarche (Terasawa et al., 2012), which would allow them to start reproducing earlier. Indeed, DOM macaques tend to have an earlier menarche (Wilson et al., 2013).

Despite this difference, there were no effects of rank on HCD kilocalories consumed, or on body weight between social rank or diet groups (Kyle et al., in preparation). Thus, postnatal access to obesogenic diets increases Kcal consumption without detectable body weight increases; however, it is possible that body weight differences emerge later on, during puberty, when female macaques go through a growth spurt (Tanner et al., 1990). Although these findings contrast with previous evidence of higher HCD and HCD+LCD Kcals consumed in SUB than DOM animals from adult female macaques studies in small social groups, the different findings in our study could be due to our developmental focus on infants and juveniles in large social groups (Arce et al., 2010; Michopoulos, Toufexis, et al., 2012; Moore et al., 2013). Another potential explanation could be that in the large social groups SUB animals had limited access to the feeders due to higher competition and/or group dynamics. There were also some LCD-only DOM animals that stole HCD pellets by holding the feeder gate open, but this was not a generalized phenomenon that explained the differences.

Diet Effects

In addition to the expected ICV increase with age, the main findings of this study were that postnatal consumption of HCD in the Choice diet resulted in larger brain and overall insula size than in the LCD-only group (Choice>LCD-only) across development. The bigger ICV volumes in animals exposed to obesogenic diets contrasts with human literature where obesity in adults was associated with smaller whole brain GM volumes (Debette et al., 2010; Hamer & Batty, 2019; Han et al., 2021). However, the larger insula volumes in Choice animals are consistent with human studies showing that weight loss during dieting is linked to insular GM volume loss (Honea et al., 2016). A potential explanation for the difference between the human adult obesity studies, the Honea and collaborators, and ours is that chronic obesity could lead to neuronal damage through sustained stress hormones and inflammation mechanisms reviewed above; another difference is that our subjects were developing and not adults, and they were assessed at an age where the extensive pruning of cortical connections seen during adolescence had not yet occurred (Khundrakpam et al., 2016; Zhang et al., 2021). Also, the chronicity of obesity in the adult literature could have caused differences in insular development with an initial overgrowth (as reported here), followed by cortical over-pruning during puberty, and therefore later volume reductions. However, a study in children and adolescents also showed that obesity was associated with smaller frontal and limbic gray matter (Alosco et al., 2014).

An interesting observation is that the effects of the Choice diet on ICV and insula volumes were present at 2 weeks already, before the introduction of solid food. This diet effect could potentially be transmitted through the subject's mother's milk, since all dams consumed LCD until birth (therefore, the diet effects are not due to prenatal programming), and the access of Choice mothers to HCD feeders was activated postpartum. In mouse and rat studies, maternal

high-fat diets lead to obesity and behavioral alterations in pups (Sasaki et al., 2013; Sun et al., 2012), supporting the possibility that maternal diets could have impacted the fast ICV neonatal development. Furthermore, since there were no significant body weight differences, it is unlikely that Choice diet effects were mediated by obese phenotypes. An interesting alternative explanation is that early insular volume increases could have driven the HCD consumption rather than the other way around. However, although two weeks is a very rapid time frame for insular volume changes to take place based on maternal diet, it is possible that even small structural changes at that early developmental stage could program the insula to grow faster and increase preference for the HCD later on, driving further insula volume increases. In other words, HCD consumption could be programmed by early exposure through the mother's milk. Further studies are required to clearly discern whether this is the case.

Contrary to our hypothesis, animals in the Choice diet showed larger, rather than smaller, total insula volumes than those in LCD-only condition, even after data was ICV-corrected. Although this finding is not consistent with a study with human adolescents, where a larger insula volume was associated with choosing lower caloric foods (Hall et al., 2021) the larger insula volumes found in Choice animals are supported by other human studies showing that weight loss during dieting is linked to insular GM volume loss (Honea et al., 2016). As discussed above, a potential difference between obesity studies and ours is that obesity could lead to chronic neuronal damage through sustained elevations in inflammation and cortisol. Another difference is the developmental nature of our studies. Our results indicate that the consumption of HCD, which contains higher fat and sugar, is associated with insular volume growth. This could potentially be explained by increases in neuronal complexity and pruning dysfunctions caused by HCD consumption, as Sholl analysis in rats showed that a Western-style diet increased

neuronal complexity in the entorhinal cortex, which may be caused by decreased pruning (Sarfert et al., 2019). The insula is integral to both feeding and stress responses because of its interoceptive, emotion processing, and reward functions (Liberzon et al., 2007; Reynolds & Zahm, 2005). Overeating in adolescent girls has also been linked to increased insular activation (Carnell et al., 2012), and it could be a manifestation of an outcome of early diet-induced alterations in insular structure.

For the AI, Choice animals showed larger volumes than LCD-only animals. The main diet effects were preserved after ICV correction, which suggests that there is more AI-regional growth for Choice animals than can be accounted by the diet-induced increase in overall brain size. This contrasts with previous literature showing that anterior insula activation (which mostly overlaps with AI) suppresses binge-eating (Price et al., 2019), which may lead one to posit that increased AI volume might also be associated with a decrease in emotional eating, and therefore a smaller HCD consumption. However, regional activations and volumes do not necessarily correlate with each other, as has been demonstrated for the amygdala in PTSD (Ousdal et al., 2020). The right insula was also found to have a role in routine restraint from high-calorie food (Wood et al., 2016). Since AI has a role in restraint from food consumption, it would be helpful to carry out an fMRI study in order to gain insight of AI activity in the Choice animals in response to high-calorie foods. A larger AI volume for the Choice diet could point to the fact that interoceptive information flows from the GI to the DI to the AI, and because the interoceptive cortex activates more in response to seeing an HCD due to its involvement in taste pleasantness (Evrard, 2019; Ohla et al., 2012). So, the AI could be associated with consumption of Choice diet due to its role in the flow of interoceptive information.

For the DI, diet effects were preserved after ICV correction, suggesting that there is more DI-regional growth for Choice animals than can be accounted by the diet-induced increase in overall brain size. The intrapersonal/agency area of the DI helps integrate interoceptive information with input from other regions that relate to motion, and the rest of it has social function. The interoceptive inputs are most relevant part of the DI to feeding and therefore diet, so it is possible that this relates to the effects observed; in fact, insular cortex is activated more in response to viewing high-calorie diets than low-calorie diets due to its role in perceiving taste pleasantness (Ohla et al., 2012), and interoceptive information flows from the GI to the DI (Evrard, 2019). In relation to this macaque model, we could propose that eating an HCD pellet would activate the DI due to the flow of interoceptive information. The difference of DI volumes between the diets over time amplifies with age, indicating the important impact of different diet conditions on brain development.

Surprisingly for the GI, diet effects disappeared after controlling for ICV. The right insula is involved in evaluating interoception about taste awareness of especially of high-calorie foods (Ohla et al., 2012). The GI is involved in interoception, so it is interesting that the part of the insula most involved in eating-related sensation/behavior does not have significant diet effects after correcting for ICV, which suggests that the diet effects are not specific to the GI but driven by global effects of diet on overall brain size. However, the interoceptive information about taste pleasantness is transmitted to the other three subregions where the diet effect was retained, and where there is a strong integration between the interoceptive information, emotion, and awareness (Craig, 2009; Simmons et al., 2013). The reason why the GI does not have a region-specific diet effect, whereas the other subregions do, remains to be elucidated.

For the IPro, the main effects of diet were preserved by the ICV correction, suggesting more IPro-regional growth for Choice animals than can be accounted by the diet-induced increase in overall brain size. Given that the interoceptive cortex (in GI) activates more in response to seeing an HCD as it is involved in taste pleasantness, this effect could extend to the other parts of the insula where interoceptive information flows (Evrard, 2019; Ohla et al., 2012). Since the IPro is at the most caudal part of the insula, interoceptive information that travels to it is abstract (Simmons et al., 2013). In addition, olfactory inputs could play a role in this taste perception since at the caudal insula there are olfactory and limbic connections (Evrard, 2019).

Brain Growth Mechanisms Relevant to Diet

Higher Kcal consumption of the HCD could initially lead to more dendritic arborization in GM and myelination (some of it taking place even in WM within the GM), which ultimately results in larger brain volumes. The reported brain shrinkage effects in obesity might not occur until the emergence of obese phenotypes, including increased adiposity, excess cortisol production, and inflammation (Baudrand & Vaidya, 2015; Ellulu et al., 2017; Pasquali et al., 2002).

Evidence from studies in adolescent rodents support the HCD consumption cellular effects on neuronal complexity, which could be also caused by pruning impairments induced by diet (Sarfert et al., 2019). However, this explanation is unlikely in our study, given that most GM pruning takes place during puberty and our study was completed before puberty.

Studies in rat models have also shown other potential cellular mechanisms that explain HCD-related increase in brain GM volume, including elevated microglia and astrocytes in the hippocampus (Graham et al., 2016; Kang et al., 2016). As animals ingesting higher HCD Kcals may have more inflammation due to an overactivated HPA axis, this inflammation could over-

activate microglia and also impact synaptic pruning, myelination, and brain structure, which influence brain volume (Kucharova et al., 2011; Mottahedin et al., 2017). More work is needed to uncover the details of the mechanisms behind the effect of a Choice diet on ICV and insular volumes.

Absence of Rank Effect

Contrary to the robust effects of diet on brain development and to our original hypotheses, no rank effects were found on ICV or on any insular ROI, which contrasts with a previous study by another undergraduate in the lab where SUB animals had larger whole insulas than DOM animals according to LMM analyses (Kyle et al., in preparation). One possible explanation of the differences with my study was that RM ANOVA omitted five subjects due to missing data at certain ages. Another potential difference between findings reported here and previous studies about how social subordination affects insular volumes is that most previous studies were done on adults (Ansell et al., 2012; Etkin & Wager, 2007; Kunimatsu et al., 2020). In this study, even though subjects were still exposed to the social hierarchy, the fact that they were still developing could have led to differences on neuronal structural effects. Notably, since the animals in this study did not go through puberty, the typical cortical GM pruning related to puberty has not taken place (Knickmeyer et al., 2010) and has not yet been impacted by social rank.

Relevance of the Amygdala

Another relevant structure as we discuss chronic stress and diet is the amygdala, a component in the limbic system which helps process strong emotions such as fear and modulates fear-related behavior. The amygdala, like the insula, is also sensitive to stress and it is hyperactivated in anxiety disorders such as PTSD, social anxiety disorder (SAD), and specific phobias, illustrating

that both brain regions may be involved in chronic stress and emotions associated with it (Etkin & Wager, 2007). In relation to diet, increased amygdala volumes are linked to a bigger waist circumference and obesity (Janowitz et al., 2015; Perlaki et al., 2018). A maternal diet high in fat is also linked to amygdala dendritic remodeling (Janthakhin et al., 2017). Notably, Kyle and collaborators found that subordination and the Choice condition in the same animals used here resulted in larger amygdala volumes, which could represent overactivity from both chronic psychosocial stress and HCD consumption.

Interestingly, amygdala-prefrontal cortex wiring regulates food reward (Baxter & Murray, 2002). The amygdala helps regulate food intake and it plays a role in reward through its connections with the anterior cingulate cortex and striatum, and some of its neuropeptides also control food intake (Zhang et al., 2011). GABA and serotonin receptor 2a (5HT2a) in the central nucleus of the amygdala, in particular, modulate food consumption with a positive valence; rewarding factors such as taste can influence consumption, and some studies found that positive valence increases food intake by increasing its rewarding properties, as 5HT2a was involved in conditioning flavor preferences (Douglass et al., 2017).

Limitations and Future Studies

This study has several limitations. Due to time constraints, I used RM ANOVA instead of LMM, which is not ideal because it cannot deal with missing longitudinal data; therefore, a more flexible statistical model, such as linear mixed models (LMM) should be used for the preparation of the manuscript. Using RM ANOVA caused some subjects with missing data to be omitted entirely from the study, resulting in a final sample size of 36 (from the initial 41), with 8-11 animals for our smallest cells (social rank by diet interaction effects), which limits the power to detect complex factors interactions. Future studies should use LMM for longitudinal statistical

analyses to account for any missing values. Also, in future statistical analyses, the effects of biological mother and cross-fostering should be included in the model as covariates, and multiple regression models run to address whether kilocalories, inflammatory markers, and/or cortisol are significant predictors of specific structural effects of diet and social rank.

Another limitation was that only females were used in the study due to the female-bias composition of rhesus social groups, composed by matrilineal social hierarchies; that is, we do not have enough adult breeder males per social group (sometimes only 1) to do social rank studies in males. Previous studies have found that in male macaques, although adult SUB had higher cortisol than DOM, a significant difference in cortisol is not detected between different ranks of adolescents (Feng et al., 2016). It would be important to examine all the developmental questions in this study with male macaques.

In terms of the automatic feeders used in this design, it allowed for some LCD-only dominants to steal HCD pellets by holding the feeder open; although this occurred in relatively few instances, an ideal design would avoid such occurrences.

Furthermore, despite manually editing the insular subregions in each age brain atlas (template) using published neuroanatomical criteria for macaques (Paxinos et al., 2000; Paxinos et al., 1999; Saleem & Logothetis, 2006), and the high resolution (0.5mm3, isotropic) of our T1- and T2-weighted MRI , there are still limits in our the ability to identify cytoarchitectonic divisions. Future studies using higher strength magnets and better coils could improve anatomical resolution to evaluate the structural development of the smaller regions within the insular subregions studied here. In particular, given that the mound, ventral, and posterior ventral fundal regions of the DI have social functions, whereas the dorsal region has agency functions, it would be interesting to compare the development between these different DI areas. Also, in

future studies WM insular volumes should be included, and fMRI techniques can be used to examine the functional correlates of the structural effects reported here.

We are currently collecting structural MRI data on these animals now that they are adults. These adults are all eating LCD diets, but evaluating their sMRI data will provide insight into the long-term effects of exposure to a particular diet (Choice or LCD-only) during development and cumulative effects of psychosocial subordination stress throughout their lives.

Significance

This study is significant despite its limitations because it demonstrates the effects of postnatal exposure to highly caloric, obesogenic diets and social subordination on the structural development of the insula and its subregions in comparison to whole brain growth. A strength of the study was its ability to disentangle confounding variables often found in humans through use of a NHP model, as well as its ability to disentangle rank and diet from each other by assigning subjects from each rank to each diet condition. No effects of social ranks were detected in this study on ICV and insular cortex volumes, which is interesting given the literature about the topic. Some aspects of this study may contribute to this discrepancy; for example, subjects were still developing, and they were reared in large social groups, which could lead to different effects of social/stress experiences on their brain structural development at the same time that group dynamics may differ from those in small social groups in prior publications. HCD exposure was shown to increase insular volumes, even after controlling for overall brain size effects (except for GI). It also showed that HCD-related volumetric changes were not due to an obese phenotype. Diet effects appeared in infancy, indicating that there may be transmission of effects via maternal factors such as milk. Diet effects on the insula remained when subjects were juveniles, showing the lasting nature of diet conditions during development. Given that the insula is associated with

neuropsychiatric disorders, the presence of these conditions could be affected during infancy and sustained throughout development. The data presented in this study suggest that an obesogenic diet changes the development of the ICV, insula, and its subregions. This has major implications for people who consume obesogenic diets, such as those with a low SES.

Tables and Figures

Table 1. Experimental Groups. Experimental groups showing the infant's social rank (SUB, DOM) and Diet condition (LCD-only, Choice), broken down by cross-fostered vs. non-cross-fostered animals.

Cross-fostered Subjects					Non-Cross-fostered Subjects			Total (diet)
Mother's rank	**SUB**	**DOM**	**DOM**	**SUB**	**Mother's rank**	**DOM**	**SUB**	
Infant's rank	**DOM**	**SUB**	**DOM**	**SUB**	**Infant rank**	**DOM**	**SUB**	
LCD-only	4	1	2	3	**LCD-only**	5	6	**21**
Choice	4	2	2	3	**Choice**	4	5	**20**
Total (status)	**8**	**3**	**4**	**6**	**Total (status)**	**9**	**11**	**41**

Table 2. Percent composition of nutrients in LCD and HCD pellets.

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

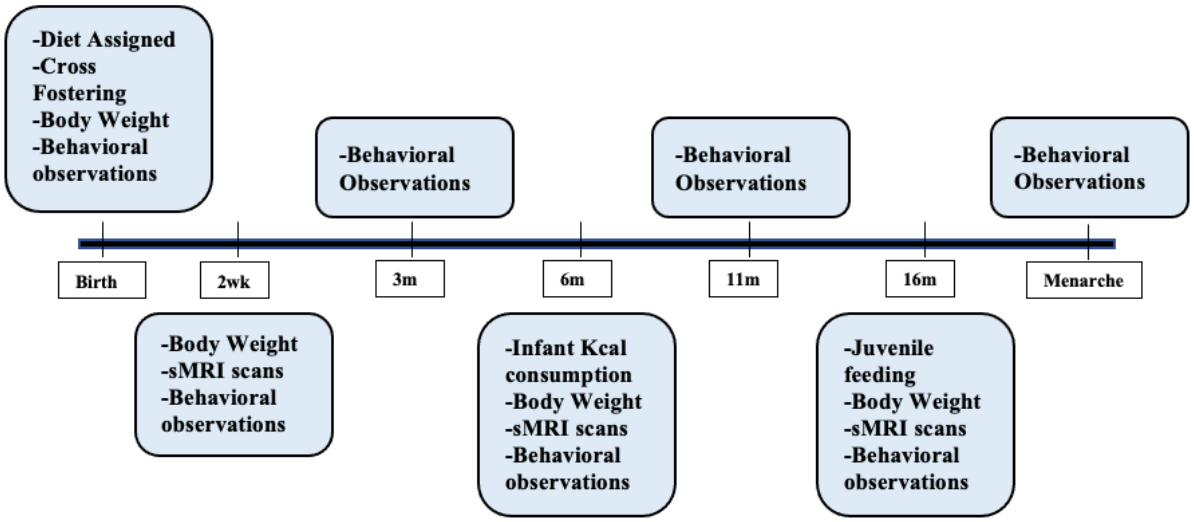

Figure 1. Experimental Design. At birth, infants were assigned to a diet condition and cross-fostered, if applicable. Body weight was measured at birth, 2 weeks, 6 months, and 16 months. Behavioral observations occurred at every age listed. Cumulative kilocalorie (Kcal) consumption was calculated from birth to 6 months, and from 6 to 16 months. Structural MRI (sMRI) scans were acquired at 2 weeks, 6 months, and 16 months.

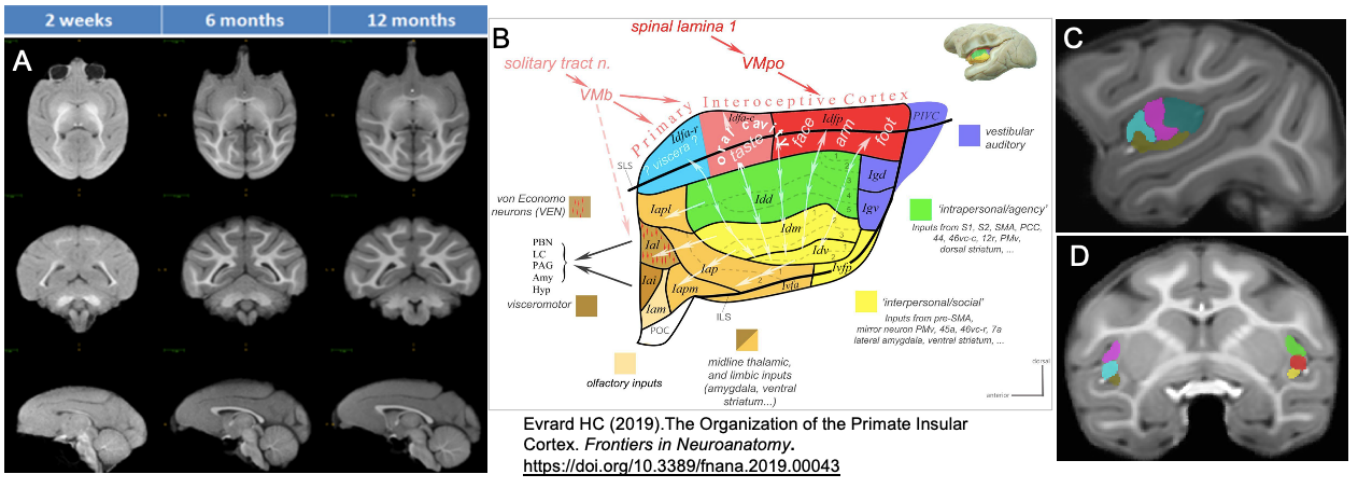

Figure 2. Atlases and Insular Subregions. (A) Infant-juvenile rhesus macaque atlases for the three different ages. (B) primate insular organization, and (C -sagittal view-, D -coronal view-) insular subregions in atlas space for AutoSeg. (C) sagittal slice of left 12-month insular subregion atlas: turquoise: AI; pink: DI; teal: GI; mustard: IPro. (D) coronal slice of 12-month insular subregion atlas: left hemisphere: red: AI; green: DI; yellow: IPro. Right hemisphere: turquoise: AI; pink: DI; mustard: IPro (GI not visible in this coronal slice).

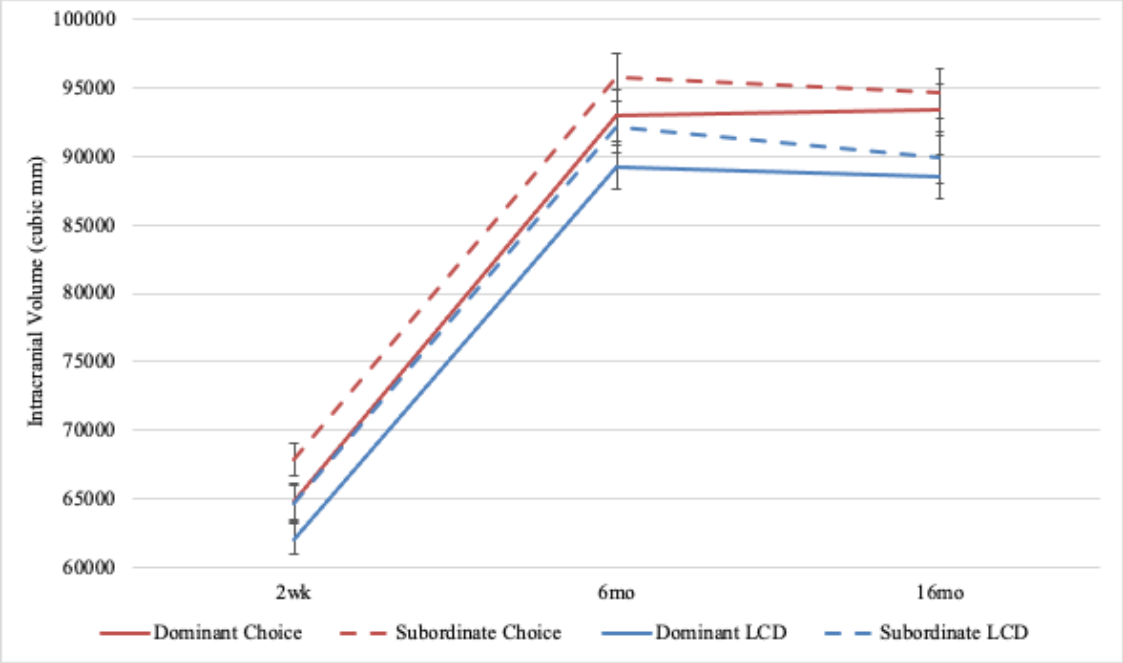

Figure 3. Effects of social rank, diet, and age on intracranial volume (ICV) development. Mean± SEM of ICV by experimental group are displayed at 2 weeks, 6 months, and 16 months of age. ICV increased with age ($F_{(2,64)} = 1474.337$, $p=2.96*10^{-54}$, $\eta_p^2 =0.979$). Animals in the Choice diet had a larger ICV than LCD-only animals ($F_{(1,32)} = 6.581$, $p=0.015$, $\eta_p^2 =0.171$).

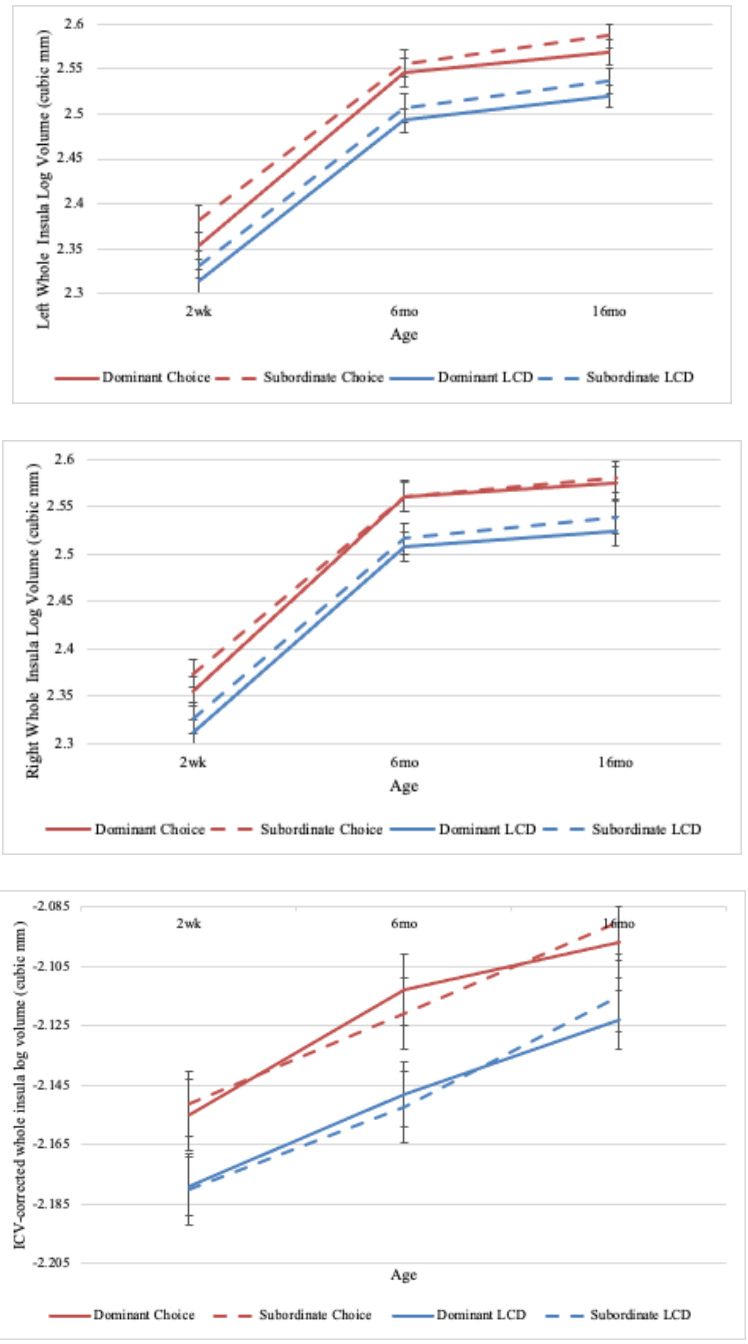

Figure 4. Effects of social rank, diet, and age on whole insula volume development. Mean± SEM of whole insular volumes by experimental group are depicted at ages 2 weeks, 6 months, and 16 months. Whole insula volumes increased with age ($F_{(2,64)}$= 2104.039, p= 4.1429*10^{-59}, η_p^2 =0.985). Choice diet animals had larger whole insula volumes than LCD-only animals ($F_{(1,32)}$=11.376, p=0.002, η_p^2 =0.262). There was also an age by hemisphere interaction effect ($F_{(1.502,\ 48.054)}$= 12.171, p= 0.001423, η_p^2 = 0.276). The main effects of age ($F_{(2,64)}$ =171.435, p= 1.9731*10^{-26}, η_p^2=0.843) and diet ($F_{(1,32)}$ =6.730, p=0.014, η_p^2= 0.174) are also displayed in the ICV-corrected graph.

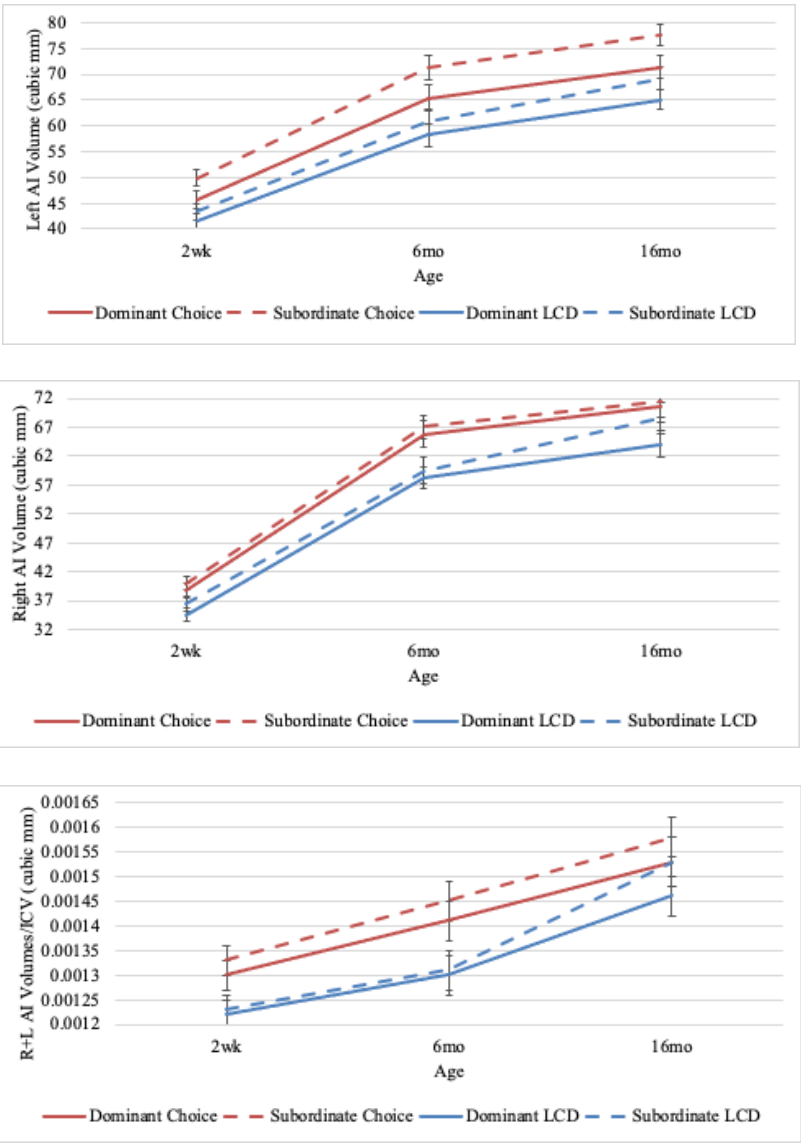

Figure 5. Effects of social rank, diet, and age on agranular insula (AI) volume development. Mean± SEM of AI volumes by experimental group are depicted at ages 2 weeks, 6 months, and 16 months. AI volumes increased with age ($F(2,64) = 656.122$, $p = 2.2882*10^{-43}$, $\eta_p^2 = 0.953$). Choice diet animals had larger AI volumes than LCD-only animals ($F_{(1,32)} = 16.551$, $p= 0.000289$, $\eta_p^2 = 0.341$). There was also a main hemisphere effect ($F_{(1,32)} = 31.387$, $p= 0.000003$, $\eta_p^2 = 0.495$), with a larger left AI hemisphere than right, and an interaction effect of age by hemisphere ($F_{(2,64)} = 19.359$, $p= 2.6617*10^{-7}$, $\eta_p^2 = 0.377$). The ICV-corrected graph also shows AI volumes increasing with age ($F_{(2,64)} = 91.145$, $p = 1.8684*10^{-19}$, $\eta_p^2 = 0.740$) and larger AI volumes for Choice animals ($F_{(1,32)} = 7.791$, $p =0.009$, $\eta_p^2 = 0.196$).

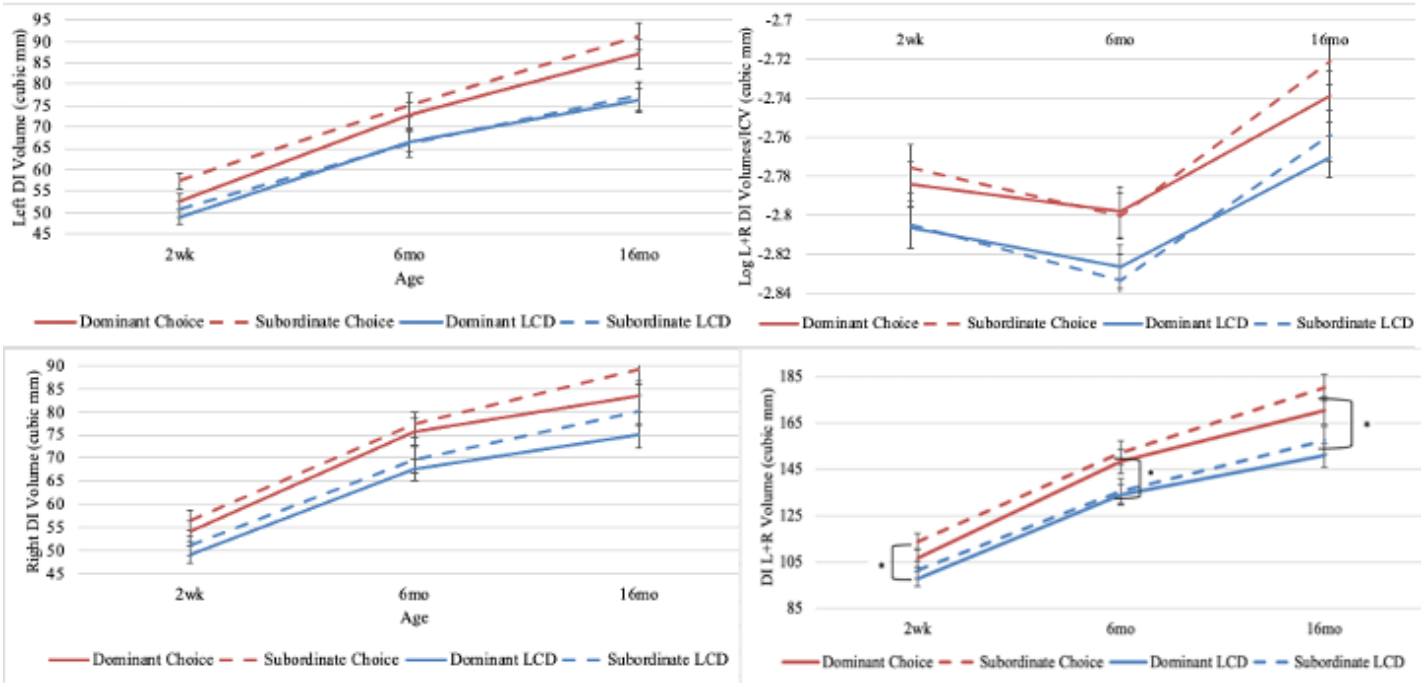

Figure 6. Effects of social rank, diet, and age on dysgranular insula (DI) volume development. Mean± SEM of DI volumes by experimental group are depicted at ages 2 weeks, 6 months, and 16 months. DI volumes increased with age ($F_{(2,64)} = 611.234$, p= $1.9815*10^{-42}$, $\eta_p^2 = 0.950$). Choice diet monkeys had larger DI volumes than LCD-only animals ($F_{(1,32)} = 12.491$, p= 0.001269, $\eta_p^2 = 0.281$). There was also age by diet interaction effect ($F_{(2,64)} = 4.559$, p=0.014, $\eta_p^2 = 0.125$; *: p<0.0055 show *post hoc* significant differences between Choice and LCD-only groups at different ages), and an age by hemisphere interaction effect ($F_{(1.642,52.545)} = 4.778$, p= 0.017, $\eta_p^2 = 0.130$). The ICV-correct graph also shows DI volumes increasing with age ($F_{(2,64)} = 101.324$, p = $1.4714*10^{-20}$, $\eta_p^2 = 0.760$) and larger volumes in Choice than LCD-only animals ($F_{(1,32)} = 7.791$, p =0.009 , $\eta_p^2 = 0.196$).

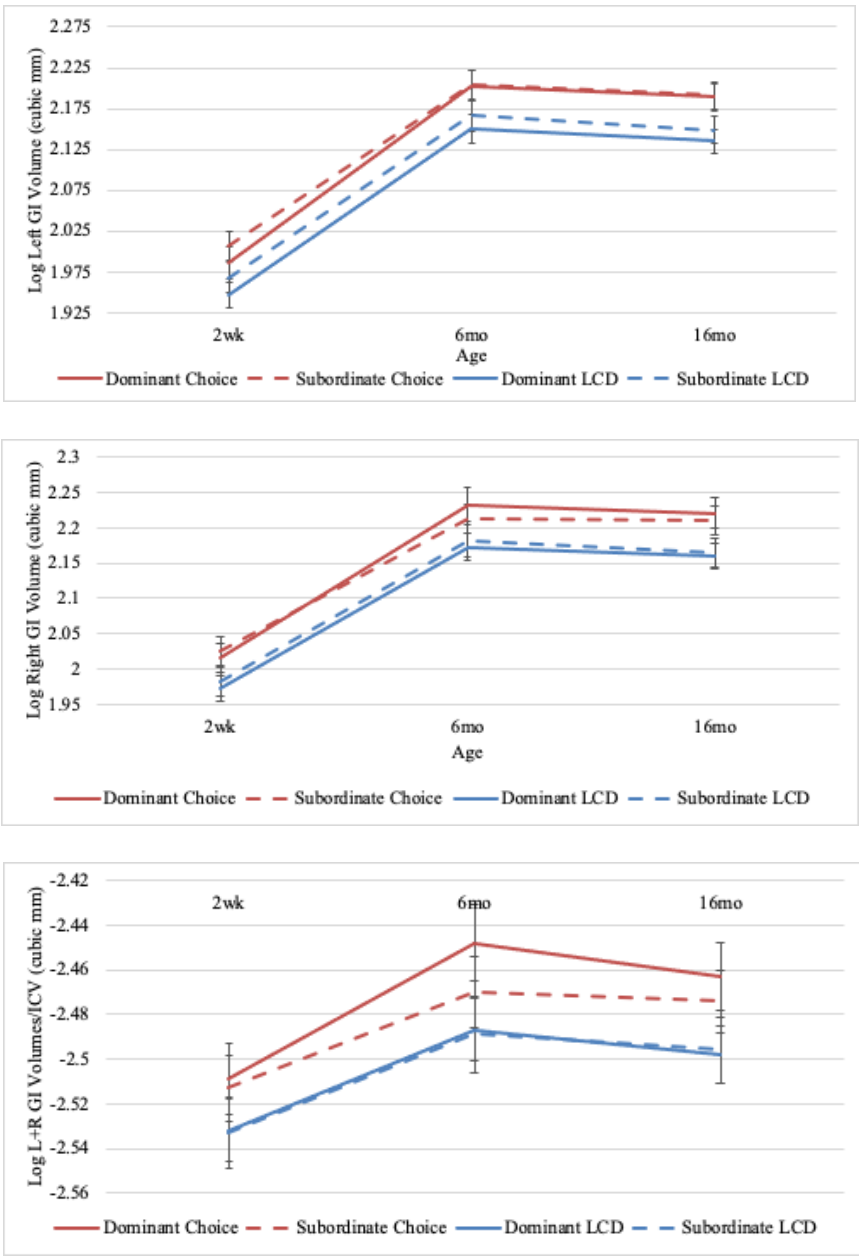

Figure 7. Effects of social rank, diet, and age on granular insula (GI) volume development. Mean± SEM of GI volumes by experimental group are depicted at ages 2 weeks, 6 months, and 16 months. GI volumes increased with age ($F_{(1.661,53.144)} = 1259.707$, $p= 1.0722*10^{-43}$, $\eta_p^2 =0.975$). Choice diet animals had larger GI volumes than LCD-only animals ($F_{(1,32)} = 6.584$ $p= 0.015$, $\eta_p^2 =0.171$). A main effect of hemisphere was detected as well ($F_{(1,32)} = 26.867$, $p= 0.000012$ $\eta_p^2 =0.456$). The ICV-correct graph also depicts that GI volumes increase with age ($F_{(2,64)} = 101.324$, $p = 1.4714*10^{-20}$, $\eta_p^2 = 0.760$).

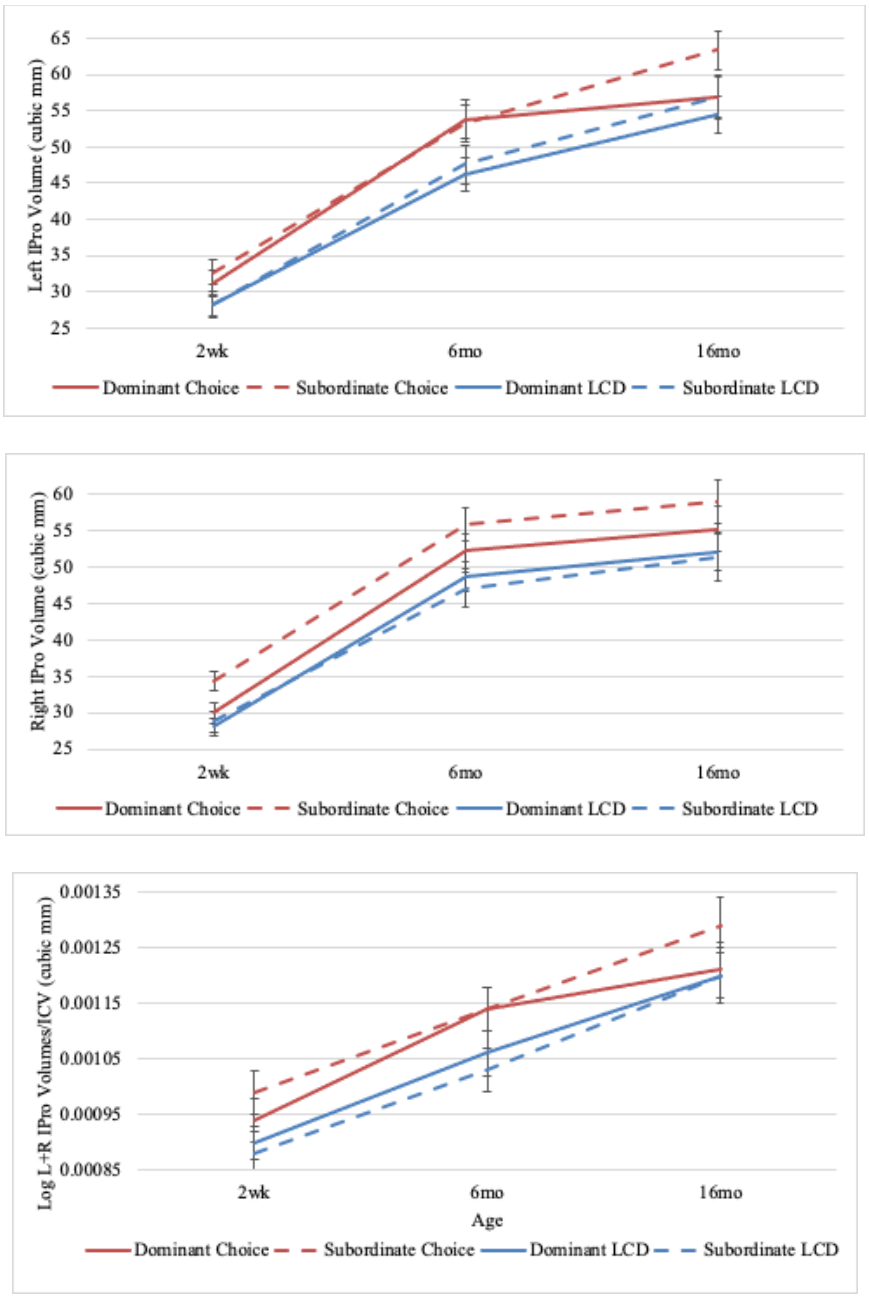

Figure 8. Effects of social rank, diet, and age on insular proisocortex (IPro) volume development. Mean± SEM of IPro volumes by experimental group are depicted at ages 2 weeks, 6 months, and 16 months. IPro volumes increased with age ($F_{(1.614,51.658)} = 475.191$, $p = 4.7107*10^{-32}$, $\eta_p^2 = 0.937$). Choice diet animals had larger IPro volumes than LCD-only animals ($F_{(1,32)} = 7.934$, $p = 0.008$, $\eta_p^2 = 0.199$). A main effect of hemisphere was detected as well ($F_{(1.540,49.267)} = 5.597$, $p = 0.011$, $\eta_p^2 = 0.149$). The ICV-correct graph also depicts IPro volumes increase with age ($F_{(1.456,46.590)} = 104.867$, $p = 7.1579*10^{-16}$, $\eta_p^2 = 0.766$) and larger IPro volumes in Choice than LCD-only animals ($F_{(1,32)} = 4.168$, $p = 0.050$, $\eta_p^2 = 0.115$).

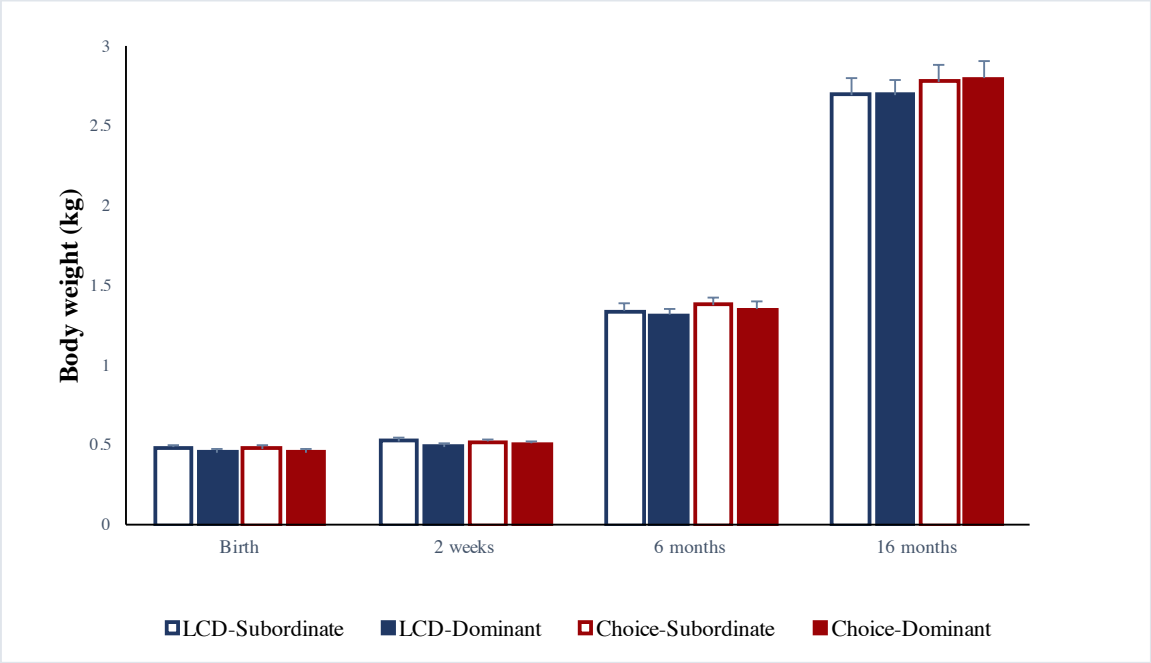

Figure 9. Effects of social rank, diet, and age on body weight. Mean±SEM body weight are plotted by experimental group at birth, 2 weeks, 6 months, and 16 months of age. As expected, body weight increased with age ($F(3, 47)=1181.10$, $p<.001$). No other main diet or social rank or interaction effects were detected. *Courtesy of Margaret Kyle (Kyle et al, in preparation).*

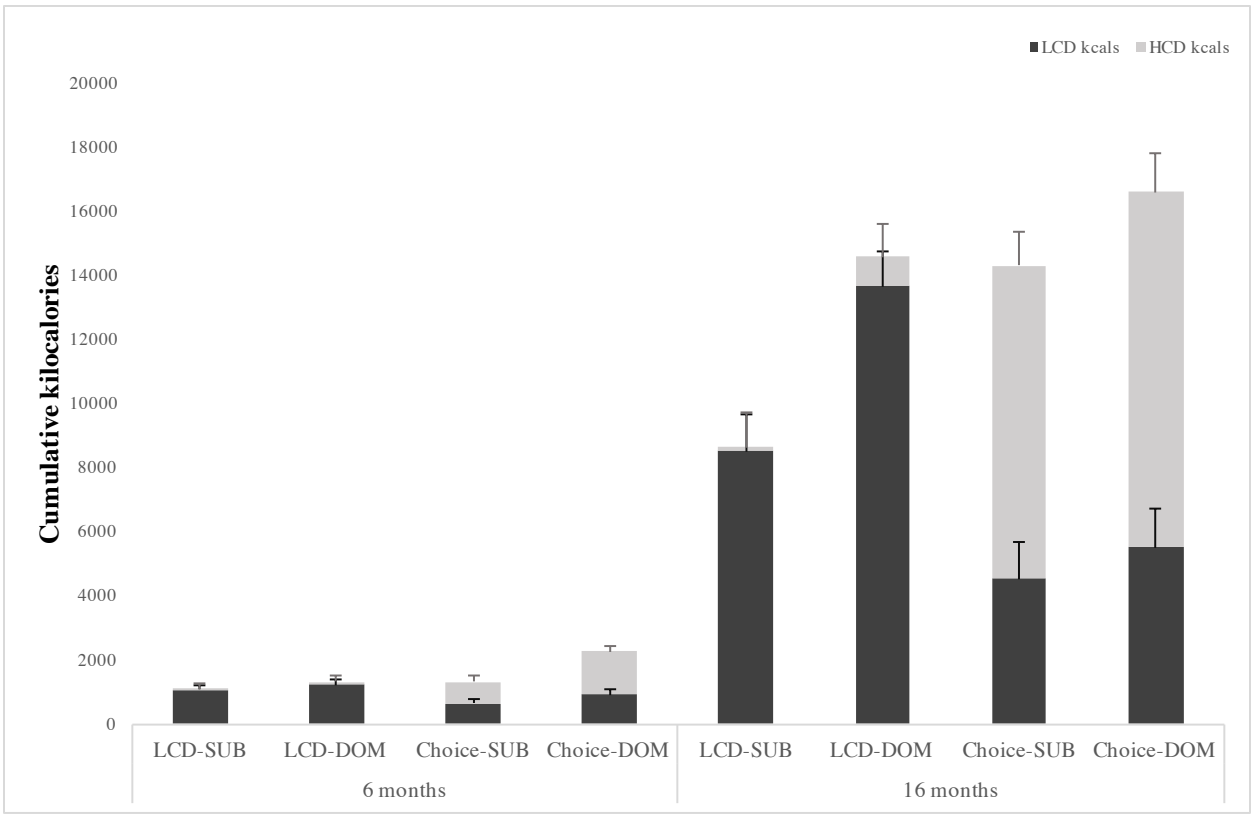

Figure 10. Effects of social rank, diet, and age on kilocalorie consumption of each diet. Mean±SEM cumulative LCD Kcals (in dark grey) and HCD Kcals (in light grey) are shown by experimental group at 6 and 16 months of age (cumulative Kcals consumed from RFID implanted at 6 wks-6months, and from 6-16 months, respectively). Total Kcal consumption increased with age ($F_{(1, 37)}$=304.56, p<.001). There were also main effects of diet ($F_{(1, 37)}$=11.74, p=.002; HCD>LCD), and rank ($F_{(1, 37)}$=12.53, p=.001; DOM>SUB), as well as age by diet ($F_{(1, 37)}$=6.43, p=.016) and age by rank ($F_{(1, 37)}$=7.38, p=.010) interaction effects on total Kcals consumed. In Choice subjects, HCD Kcal consumption also increased with age ($F_{(1, 37)}$=80.52, p<.001). *Courtesy of Margaret Kyle (Kyle et al, in preparation).*

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