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Research Paper

Maternal high-fat diet results in cognitive impairment and hippocampal gene expression changes in rat offspring

Zachary A. Cordner[a], Seva G. Khambadkone[a,b], Gretha J. Boersma[a,1], Lin Song[a,2], Tyler N. Summers[a], Timothy H. Moran[a,b], Kellie L.K. Tamashiro[a,b,*]

[a] Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross 618, Baltimore, MD 21205, USA
[b] Cellular & Molecular Medicine Graduate Program, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross 618, Baltimore, MD 21205, USA

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ABSTRACT

Consumption of a high-fat diet has long been known to increase risk for obesity, diabetes, and the metabolic syndrome. Further evidence strongly suggests that these same metabolic disorders are associated with an increased risk of cognitive impairment later in life. Now faced with an expanding global burden of obesity and increasing prevalence of dementia due to an aging population, understanding the effects of high-fat diet consumption on cognition is of increasingly critical importance. Further, the developmental origins of many adult onset neuropsychiatric disorders have become increasingly clear, indicating a need to investigate effects of various risk factors, including diet, across the lifespan. Here, we use a rat model to assess the effects of maternal diet during pregnancy and lactation on cognition and hippocampal gene expression of offspring. Behaviorally, adult male offspring of high-fat fed dams had impaired object recognition memory and impaired spatial memory compared to offspring of chow-fed dams. In hippocampus, we found decreased expression of *Insr*, *Lepr*, and *Slc2a1* (GLUT1) among offspring of high-fat fed dams at postnatal day 21. The decreased expression of *Insr* and *Lepr* persisted at postnatal day 150. Together, these data provide additional evidence to suggest that maternal exposure to high-fat diet during pregnancy and lactation can have lasting effects on the brain, behavior, and cognition on adult offspring.

1. Introduction

Strong associations have long been observed between various high-fat (HF) or "Western" diets and metabolic disorders such as obesity, diabetes, and cardiovascular disease (reviewed in (Friedman, 2000, Cordain et al., 2005). A great deal of evidence also suggests that exposure to HF diets and the resulting metabolic dysfunction can profoundly impact behavior, cognition, and the brain. In human studies, HF diet, obesity, diabetes, and the metabolic syndrome have all been linked to Alzheimer's disease and other forms of cognitive impairment (Eskelinen et al., 2008; Pasinetti and Eberstein, 2008; Profenno et al., 2010).

In adult rodent studies, the association between HF diets, cognitive deficits, and brain changes have been robustly demonstrated across various species and strains, HF diet compositions, and behavioral assays of learning and memory, and this work has been previously reviewed (Kanoski and Davidson, 2011; Francis and Stevenson, 2013; Cordner and Tamashiro, 2015; Morin et al., 2017). There is tremendous diversity in the specific composition of "high fat" diets used across studies. This diversity includes not just differences in overall fat content, but also balance of different fatty acids, as well as other macro- and micro- nutrients. Perhaps the most common HF diets in use include lard- or shortening-supplemented compositions that mostly introduce additional saturated fats to the diet, high fat-high sugar and high fat-low sugar diets that are usually manufactured to alter fatty acid and carbohydrate content without altering protein or micronutrient content, and "cafeteria" diets that attempt to more closely mimic human food choice habits. While these different diets and dietary components may affect cognition in discernably different ways, similar cognitive deficits have been observed across essentially all commonly utilized "HF" diets.

Much work has also been done to understand potential mechanisms

* Corresponding author at: Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross 618, Baltimore, MD 21205, USA.
E-mail address: ktamashiro@jhmi.edu (K.L.K. Tamashiro).
[1] GGZ Drenthe Mental Health Institute, Department of Forensic Psychiatry, Assen, The Netherlands.
[2] Department of Physiology and Pathophysiology, Xi'an Jiaotong University School of Medicine, Xi'an, Shaanxi 710,061, PR China.

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underlying the cognitive effects of HF diet consumption in adulthood. Disrupted peripheral and central insulin, leptin, and glucose regulation have been widely reported and provide perhaps the most direct links between metabolic and cognitive dysfunction. With specific regard to insulin signaling, it is now well established that the insulin receptor is highly expressed in the hippocampus and cortex, that insulin signaling in these regions is critical for learning and memory, and that peripheral insulin insensitivity can have large effects on the brain (Abbott et al., 1999; Zhao et al., 1999; Zhao and Alkon, 2001; Woods et al., 2003; Grillo et al., 2009), reviewed in (Reagan, 2007; Fadel et al., 2013). In rodent studies, there are now several reports of impaired peripheral and central insulin signaling causally associated with HF diet-related cognitive impairment (Pintana et al., 2013; Pipatpiboon et al., 2013; Arnold et al., 2014).

In addition to insulin receptors, leptin receptors are also highly expressed in several brain regions including the hippocampus (Huang et al., 1996; Mercer et al., 1996), where leptin signaling may help regulate synaptic plasticity and trafficking of neurotransmitter receptors, reviewed in (Grillo et al., 2011; Fadel et al., 2013; McGregor et al., 2015). Further, leptin administration has been shown to improve cognitive performance in wild type mice (Farr et al., 2006), while rodent models of leptin deficiency have impaired spatial memory and long term potentiation (Li et al., 2002; Gerges et al., 2003). Specifically in response to HF diet, there is some evidence that HF exposure impairs leptin-mediated BDNF expression in the hippocampus (Yamada et al., 2011). While studies of central leptin signaling and cognition in the context of HF diet consumption are limited, there is clearly mounting evidence that disruption in hippocampal neuroendocrine signaling may be an important mechanism linking HF diet exposure to cognitive impairment (reviewed in (Kanoski et al., 2014)).

Other relatively well studied potential mechanisms of HF diet-related cognitive deficits include decreased expression of brain-derived neurotrophic factor (BDNF) in the hippocampus and cortex, dysfunction of blood-brain barrier permeability and transport, and increased burden of oxidative stress and inflammation due to direct effects of fatty acids and indirect effects of increased adiposity, reviewed in (Cordner and Tamashiro, 2015).

Data regarding the effects of maternal diet on the offspring's brain and long-term cognitive function, however, and more limited and mixed. One study in rats showed that maternal consumption of HF diets can impair performance of young adult offspring in the Morris water maze (Page et al., 2014). Another study in mice found deficits in the hippocampus-dependent Barnes maze among adolescent, but not adult offspring of HF-fed dams (Tozuka et al., 2010). Conversely, a study in rats found improved performance in the Morris water maze among adult offspring born to dams fed diets high in either saturated or trans fats (Bilbo and Tsang, 2010).

In this study, we use a rat model to further clarify the effects of maternal diet during pregnancy and lactation on offspring cognition and begin to investigate potential underlying mechanisms. We demonstrate that adult offspring of HF-fed dams have impaired cognitive performance. In the brain, offspring of HF-fed dams have decreased hippocampal expression of both the insulin receptor (*Insr*) and leptin receptor (*Lepr*), which persists well into adulthood.

2. Methods

2.1. Animals

Pregnant female Sprague-Dawley rats (Charles River, Kingston, New York) were received on gestation day (G) 2. All dams were individually housed in tub cages and maintained on a 12-h light / 12-h dark cycle with lights on at 0600. A total of 40 dams were divided into two weight-matched groups ($n = 20$ per group). Beginning on G2, dams were given ad libitum access to water and either standard chow diet (CHOW; LabDiet 5001, 13.5% kcal from fat, 28.5% kcal from protein, 58% kcal from carbohydrates) or HF diet (Research Diets D12492, 60% kcal from fat, 20% kcal from protein, 20% kcal from carbohydrates). Dams remained on their respective diets from G2 throughout the remainder of the experiment.

The day each dam gave birth was defined as postnatal day (P) 0 for the respective litter of pups. On P1, pups were weighed and litters were culled to 10 pups each (5 male and 5 female). Animals were weighed weekly thereafter. On P21, one male pup per litter was killed by rapid decapitation. The brain was extracted, flash frozen on powdered dry ice, and stored at −80 °C for further analysis as described below. All pups were weaned onto standard chow (LabDiet 5001) at P21. Starting on P95, one male per litter was used for behavioral testing. At P150, a behaviorally naïve male littermate was killed by rapid decapitation. The brain was extracted, flash frozen on powdered dry ice, and stored at −80 °C for further analysis as described below.

All animal procedures were approved by the Animal Care and Use Committee of the Johns Hopkins University School of Medicine.

2.2. Behavioral testing

Behavioral testing began approximately at P95 and was completed in the following order: locomotor activity test, novel object recognition test, Barnes maze. Behavioral tests were separated by at least 2 days.

2.2.1. Locomotor activity

The activity monitor consists of a 40 cm^2 square testing arena and an automated tracking system (Omnitech Electronics Inc., Columbus, Ohio). Beginning in the middle of the light phase (and corresponding with the start time of all other behavioral tests) each rat was placed individually into the center of a testing arena in room that was novel to all animals. Rats were allowed to freely explore for 30 min. Distance traveled was automatically recorded via infrared beam breaks and was accumulated in 5-min bins.

2.2.2. Novel object recognition test

Two objects of different color, shape and size (Duplo-Lego blocks, Lego, USA) were placed in opposite corners of a 60 cm^2 square testing arena. On the first day of the test, each rat was placed in the center of the arena and allowed to explore for 5 min. Twenty-four hours later, one 'familiar' object was replaced with a 'novel' object. Each rat was again placed in the center of the arena and allowed to explore for 5 min. Time spent exploring each object was recorded.

2.2.3. Barnes maze

The Barnes maze consists of a dark grey PVC circular platform (122 cm diameter, elevated 70 cm above the floor), with 18 holes (9.5 cm diameter) equally spaced around the perimeter. A hidden escape box was placed under one of the holes. Three visual cues and a bright light were fixed around the perimeter of the maze. Rats were allowed to explore the maze during two trials a day for five consecutive days. If a rat failed to find the escape box within 180 s it was gently guided to the escape where it was allowed to remain for 10 s. One week after the final acquisition trial, each rat was given a single probe trial with the escape box present. Latency to entering the escape box was measured for each trial.

2.3. Hippocampal gene expression

Brain tissue was used to measure gene expression by real-time PCR (P21 and P150). The dentate gyrus and dorsal hippocampus (HPC) were isolated together from 400uM thick frozen coronal sections using a blunted 16-guage needle (inner diameter 1.65 mm) based on published coordinates (Paxinos and Watson, 2004). Dentate gyrus coordinates relative to bregma: (anterior-posterior −2.8 mm, medial-lateral ± 0.4 mm, dorsal-ventral −4.4 mm). CA3 of the dorsal hippocampus coordinates relative to bregma: (anterior-posterior −2.8 mm, medial-

lateral ± 1.4 mm, dorsal-ventral −3.0 mm).

Tissue punches were placed in Qiazol immediately after isolation. Total RNA was then extracted using the RNeasy Lipid Tissue Mini Kit (Qiagen, Valencia, CA). cDNA was generated using the QuantiTect Reverse Transcription Kit (Qiagen, Valencia, CA).

Candidate genes previously implicated in both metabolism and cognition were selected. Expression levels of the insulin receptor (*Insr*) (Reagan, 2007; Fadel et al., 2013), leptin receptor (*Lepr*) (Grillo et al., 2011; Fadel et al., 2013; McGregor et al., 2015), glucose transporter 1 (*Slc2a1*) (Jais et al., 2016), brain-derived neurotrophic factor (*Bdnf*) (Park et al., 2010; Molteni et al., 2004), glucocorticoid receptor (*Nr3c1*) (Sasaki et al., 2014), acid sphingomyelinase (*Smpd1*) (Park et al., 2018), FK506 binding protein 5 (*Fkbp5*) (Balsevich et al., 2014; Kalyan-Masih et al., 2016), and gastrin releasing peptide receptor (*Grpr*) (Kauer-Sant'Anna et al., 2007; Roesler et al., 2006; Yang et al., 2017) were assessed relative to beta-actin (*Actb*). Quantitative real-time PCR reactions were carried out in triplicate using 1xTaqMan master mix (Applied Biosystems, Foster City, CA), 1xTaqMan probes for each gene, and 2 µg of cDNA in a total of 20 µL. Real-time PCR reactions were performed on an Applied Biosystems 7900HT Fast Real-Time PCR system under standard conditions for 40 cycles. Data were analyzed using the -ΔΔCt method.

2.4. Statistical analysis

Statistical analysis was completed using Statistica 7 (StatSoft, Inc., Tulsa, OK). Data are expressed as averages ± standard error of the mean (SEM). Differences between groups were assessed by *t*-test or repeated measures ANOVA with 'diet' as the between subject factor followed by Tukey post hoc analysis. For all statistical tests, $P < 0.05$ was considered significant.

3. Results

3.1. Adult male offspring of HF dams have increased body weight across the lifespan

Body weight of the offspring was monitored throughout the experiment. Repeated measures analysis of variance revealed a main effect of time ($P < 0.05$) and maternal diet ($P < 0.05$) such that all rats gained weight over time and offspring of HF dams were consistently heavier than those of CHOW dams. Post hoc analysis revealed a difference between groups beginning at P7 and this persisted into adulthood (Fig. 1).

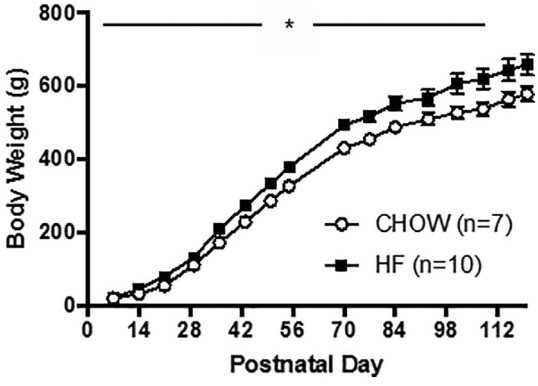

Fig. 1. Offspring of HF dams have increased body weight across the lifespan. Male offspring of HF dams were consistently heavier than those of Chow dams beginning at P7 and persisting into adulthood. Data represent average ± SEM. *$P < 0.05$.

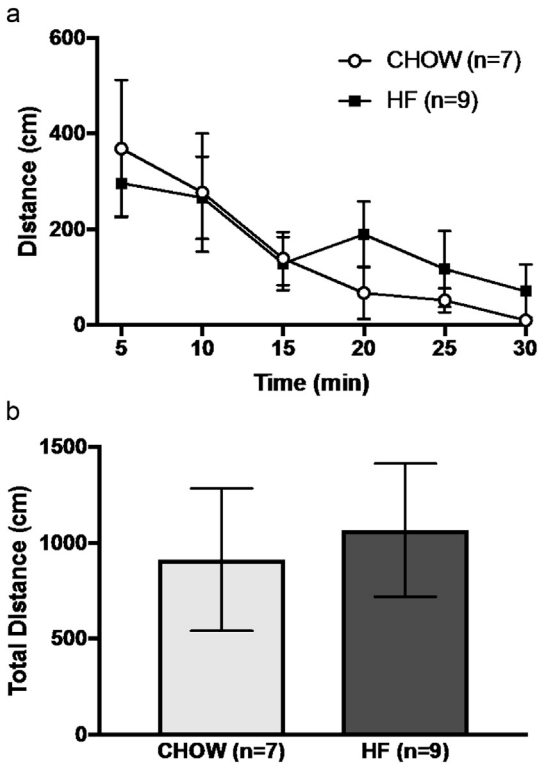

Fig. 2. Locomotor activity in a novel environment. During adulthood, locomotor activity was assessed in a 30-min open field test that took place in the middle of the light phase and in a novel environment. We found no difference between CHOW and HF dams (a, b). Data represent average ± SEM.

3.2. Adult male offspring of HF dams have impaired cognitive performance

Locomotor activity during the middle of the light phase (at the time when all other behavioral experiments were conducted) was assessed in a single 30-min open field test. We found no difference between CHOW and HF offspring (Fig. 2a,b).

Cognitive testing began on P100 and took place during the middle of the light period. Rats were first tested in the novel object recognition task, which is likely dependent on several brain regions including the hippocampus as well as perirhinal, entorhinal, prefrontal, inferior temporal, and orbitofrontal cortices though there remains much controversy in the field (Wan et al., 1999; Oliveira et al., 2010; Suarez et al., 2018; Cordner and Tamashiro, 2015). During the acquisition phase of the task (day 1), the amount of time spent exploring objects did not differ between groups (data not shown). However, during the recall phase (day 2), offspring of HF dams spent significantly less time exploring a novel object ($P < 0.05$; Fig. 3a).

Rats were next tested in the Barnes maze, which is largely hippocampal dependent, reviewed in (Cordner and Tamashiro, 2015). During the acquisition phase of the task, repeated measures analysis of variance revealed a time by diet interaction ($P < 0.05$). Post hoc analysis revealed that offspring of HF dams had increased escape latency on trials 2–5, 7, and 8 ($P < 0.05$, Fig. 3b). One week after the acquisition phase was completed, all rats were tested in a single probe trial. All rats completed the task, but offspring of HF dams had significantly longer escape latency ($P < 0.05$, Fig. 3c).

3.3. Male offspring of HF dams have altered gene expression in the hippocampus

Given the behavioral findings, expression of candidate genes was assessed in the HPC on P21 and P150. At P21, offspring of HF dams had significantly lower expression of insulin receptor (*Insr*), leptin receptor

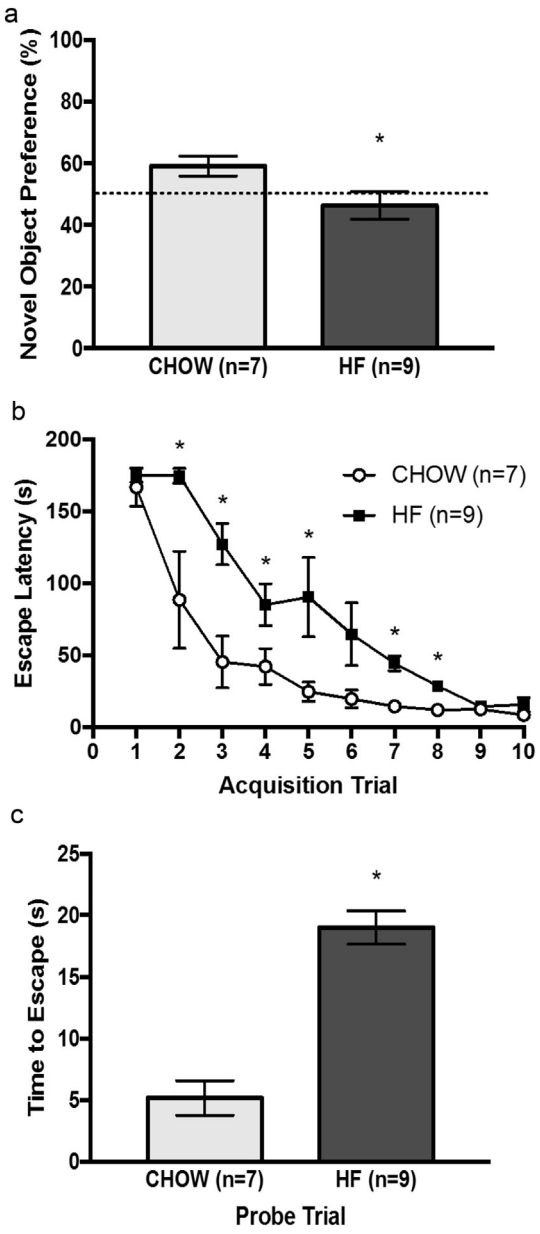

Fig. 3. Offspring of HF dams have impaired cognitive performance. During adulthood, learning and memory was assessed in the novel object recognition test and Barnes maze. Adult male offspring of HF dams were found to have decreased novel object recognition (a), as well as slower learning (b) and impaired delayed recall (c) in the Barnes maze. Data represent average ± SEM. *$P < 0.05$.

(*Lepr*), and glucose transporter 1 (*Slc2a1*) in the HPC ($P < 0.05$; Fig. 4a). At P150, offspring of HF dams continued to have lower expression of *Insr* and *Lepr* in the HPC ($P < 0.05$) but there was no longer a difference in expression of *Slc2a1* (Fig. 4b). There were no significant differences observed in the expression of *Bdnf*, *Nr3c1*, *Smpd1*, *Fkbp5*, or *Grpr* at either time point (Fig. 4a, b).

4. Discussion

The adverse health effects of various high fat and "Western" diets are now well known and include obesity, diabetes, cardiovascular disease, and cancer. Additionally, these diets have been strongly associated with neuropsychiatric disorders like major depression, anxiety, Alzheimer's disease, and perhaps addiction. The pathways leading to these outcomes are, of course, numerous. However, there appears to be convergence on a smaller set of pathogenic mechanisms such as direct toxic effects of fatty acids, increased burden of oxidative stress and inflammation, disruption of insulin, leptin, and glucose signaling, cell cycle imbalance, and alterations in the microbiome.

There has also long been appreciation for the ways in which the early life environment and parental factors can have profound and lasting effects on offspring. In studies of dietary effects, this concept of early life "priming" was perhaps first well-articulated by the "Barker Hypothesis" to explain how early life malnutrition and low birth weight increases risk for the metabolic syndrome and coronary heart disease when offspring are later exposed to a nutrient rich environment (Hales and Barker, 1992; Barker, 1995). In the years since it was first introduced, the concept of the Barker Hypothesis has been applied more broadly to study not just the effects of in utero exposure to undernutrition, but also other determinants of health and disease such as overnutrition, unbalanced nutrition, stress, and environmental deprivation, reviewed in (Gillman, 2005; Gluckman et al., 2009).

Interestingly, like the maternal undernutrition described in the original Barker Hypothesis, both maternal overnutrition and prenatal stress have also been found to increase risk for metabolic dysfunction later in life (Tamashiro et al., 2009; Purcell et al., 2011; Sun et al., 2012; Teegarden and Bale, 2008; Pankevich et al., 2009), reviewed in (Tamashiro and Moran, 2010; Sullivan et al., 2011; Grissom and Reyes, 2013; Morris et al., 2015; Speakman et al., 2015; Sullivan et al., 2015), and, as previously noted, these metabolic problems as well as direct effects of HF diets have also been closely associated with cognitive deficits, reviewed in (Kanoski and Davidson, 2011; Francis and Stevenson, 2013; Cordner and Tamashiro, 2015; Morin et al., 2017).

In this study, we turned our attention to the effects of maternal HF diet exposure on offspring cognition. When rat dams were given access to HF diet only during pregnancy and lactation, we found that adult male offspring were impaired in two widely utilized tests of learning and memory despite the fact that offspring had been weaned onto a standard chow diet. Others have undertaken similar studies with sometimes conflicting results. For example, one study in rats suggested that maternal consumption of HF diets can impair performance of young adult offspring in the Morris water maze (Page et al., 2014). Another study in mice used the Barnes maze to demonstrate deficits among adolescent but not adult offspring of HF-fed dams (Tozuka et al., 2010). Two studies in rats found Morris water maze deficits only among offspring that were born to HF-fed dams and then continued on a HF diet into adulthood (White et al., 2009; Can et al., 2012) and one study in rats actually found improved performance in the Morris water maze among adult offspring born to dams fed diets high in either saturated or trans fats (Bilbo and Tsang, 2010). Together, these data suggest that while maternal HF diet exposure may contribute to cognitive impairments in offspring, far more work remains to be done to better define sensitive periods, which diet compositions are most deleterious, whether similar effects occur in humans, and what interventions may be effective. Additionally, as most work to date has involved male offspring, future studies of sex differences will be critically important, and others have demonstrated sex differences in metabolic phenotype and behavior in response to models of maternal HF diet exposure (Samuelsson et al., 2008; Sullivan et al., 2010; Sullivan et al., 2017). It should be noted that future studies should pay special attention to experimental design as there are demonstrated sex differences in baseline performance in commonly used assays of rodent cognition (D'Hooge and De Deyn, 2001), the estrous cycle can differentially influence behavior across multiple days of testing (Marcondes et al., 2001), and HF diet exposure is known to alter the estrous cycle (Akamine et al., 2010).

In investigating mechanisms that may be driving impaired offspring cognition, we focused on the hippocampus. First, the hippocampus is implicated as the common region involved in mediating task performance on both behavioral assays used in the current study, the novel object recognition test and the Barnes maze. Brain lesion and genetic

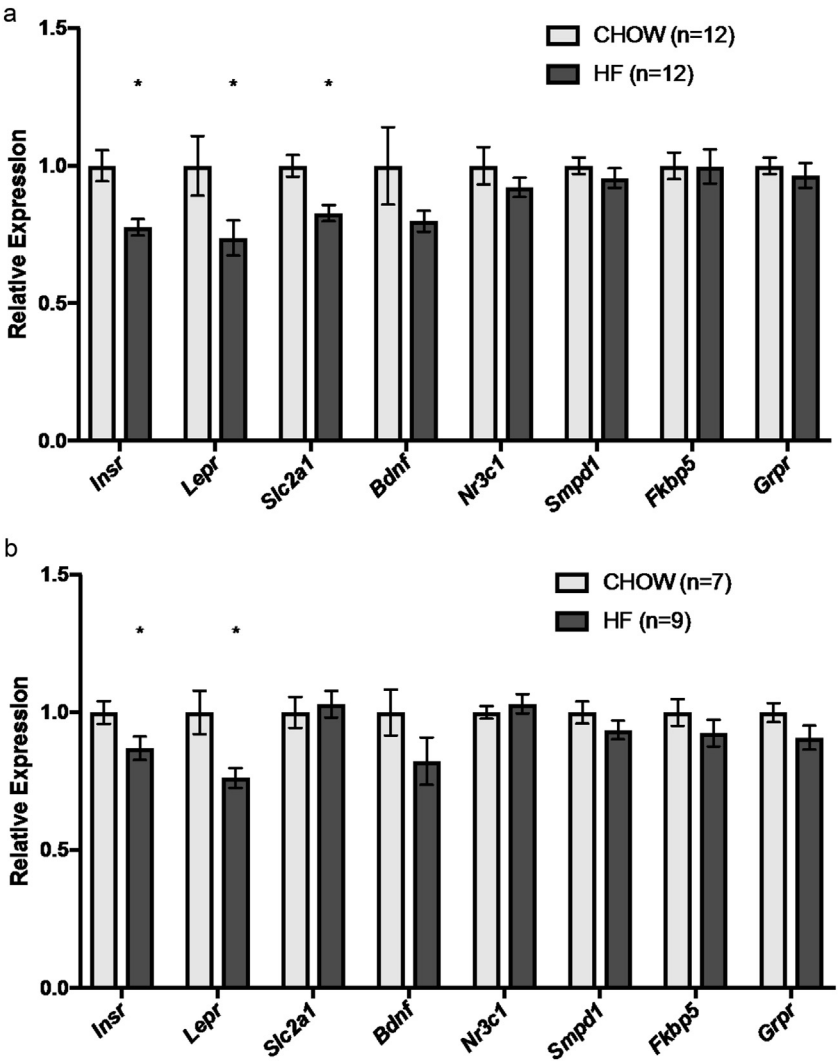

Fig. 4. Offspring of HF dams have altered gene expression in the hippocampus. At P21, offspring of HF dams had significantly lower hippocampal expression of insulin receptor (*Insr*), leptin receptor (*Lepr*), and glucose transporter 1 (*Slc2a1*) (a). At P150, adult offspring of HF dams continued to have lower expression of *Insr* and *Lepr* (b). Data represent average ± SEM. $^{*}P < 0.05$.

studies have historically established the hippocampal dependency of spatial learning and memory (O'Keefe and Black, 1977; Bach et al., 1995), reviewed in (Shapiro, 2001; Vorhees and Williams, 2014), and electrophysiological recording in rodents performing the Barnes maze consistently demonstrate learning-dependent hippocampal activity (Barnes, 1979; Bott et al., 2016). The role of the hippocampus in recognition memory, as assessed here by the novel object recognition test, is more controversial, with several brain regions including the perirhinal, entorhinal, prefrontal, inferior temporal, and orbitofrontal cortices suggested to be important for NOR task performance (Oliveira et al., 2010; Wan et al., 1999; Barker and Warburton, 2011; Cohen and Stackman Jr, 2015; Bird, 2017). Hippocampal involvement in novel object preference is postulated to be dependent on testing protocol, with hippocampal recruitment when the intertrial interval between the acquisition and recall phases is longer than 10 min, as was used in our study (Barker and Warburton, 2011; Bird, 2017; Cohen and Stackman Jr, 2015). While we focused on hippocampal function in this study, future directions include investigation of other regions potential implicated by our cognitive findings, especially the cortex.

A second rationale for our focus on the hippocampus is its particular vulnerability to insult. Hippocampal damage and alterations in function are well documented in many neurological and psychiatric diseases (Araujo and Lapchak, 1994; Frisoni et al., 2010; Small et al., 2011; Jardim et al., 2016). Beyond overt disease, the sensitivity of the hippocampus has been demonstrated across a range of insults, from physical injury to chronic stress to various other environmental exposures. The plasticity of the hippocampus – the capacity for neurogenesis and long term potentiation underlying its role in learning and memory – has been cited as a possible reason for this vulnerability (Williamson and Bilbo, 2013). This concept was perhaps first clearly articulated in the stress field by Bruce McEwen, who proposed adrenal steroids as the link between hippocampal plasticity and vulnerability, and the hippocampus as the link between stress-induced hypothalamic-pituitary-adrenal axis dysfunction and higher order cognition (McEwen, 1994). Others have suggested that hippocampal vulnerability may be in part due to the relatively high metabolic demands of hippocampal neurons leading to increased oxidative stress, reviewed in (Wang and Michaelis, 2010). The likely overlapping and interacting nature of these various environmental, neuroendocrine, neuroimmune, and metabolic modulators of hippocampal vulnerability has been previously reviewed (Michaelis, 2012; Williamson and Bilbo, 2013). One commonality between these potential mediators is their role in normal hippocampal development and function, a role gone awry in the presence of environmental stressors and the resulting allostatic overload (McEwen, 2001). Considering this commonality, the known role for metabolic hormones in normal hippocampal development and function, and the

growing evidence for a relationship between metabolic and cognitive dysfunction, metabolic hormones have emerged as an additional set of mediators, joining adrenal steroids and immune signaling molecules in linking environmental disruption and hippocampal malfunction. As recent example of the interplay between these various factors, a study of adult diet-induced obese mice demonstrated that intra-hippocampal insulin infusion improves spatial learning and memory and may act in part by reducing neuroinflammation (Gladding et al., 2018).

There is a growing body of evidence demonstrating overlap among metabolic, cognitive, and neuroimmune mediators that informed our choice of candidate genes. With particular regard to insulin and leptin, in addition to their well-characterized role in peripheral metabolic signaling, both are known to cross the blood brain barrier and act as key regulators of hippocampal plasticity and cognition [(Banks et al., 1996, Banks et al., 2012), reviewed in (Fadel et al., 2013, Reagan, 2007, Flak and Myers, 2016, Van Doorn et al., 2017, Ferrario and Reagan, 2018)]. In our study, we found lower expression of *Insr*, *Lepr*, and *Slc2a1* among P21 offspring exposed to HF diet. Interestingly, these differences in expression of *Insr* and *Lepr* persisted well into adulthood. While few others have investigated the effects of maternal diet on hippocampal *Insr* and *Lepr* in offspring, the relationships between HF diet exposure, disrupted *Insr* and *Lepr* signaling, and cognition are well established (Cordner and Tamashiro, 2015; Fadel et al., 2013; Reagan, 2007; Biessels and Reagan, 2015). Yet, several important questions remain. First, it is not clear whether the disrupted gene expression in maternal HF diet-exposed offspring is due directly to maternal programming of brain development, secondary to impaired peripheral metabolism within the offspring themselves, or a combination of both. As a related matter, the question of potentially narrower or more specific exposure windows that might lead to these outcomes should be explored in the future. In some ways, others have begun to investigate this question of critical periods as related to hippocampal insulin signaling, which plays a critical role in neurodevelopment, neurogenesis, and cognition across the lifespan in what as been described as a “neuroplasticity continuum,” (Ferrario and Reagan, 2018) showing that signaling disruption at any point along this continuum can have varying consequences for cognition, reviewed in (Ferrario and Reagan, 2018; Williamson and Bilbo, 2013).

Existing literature lends support to both maternal programming and offspring metabolic impairment in contributing to our cognitive findings. In rats, the majority of hippocampal development occurs during the prenatal and early postnatal periods, coinciding with the maternal HF diet exposure period in our model (Bayer and Altman, 1974; Martin and Berthoz, 2002; Wills et al., 2010; Ferrario and Reagan, 2018; Williamson and Bilbo, 2013). With regard to insulin signaling, hippocampal expression of *Insr* is highest during this early developmental period, where it is postulated to play a critical role in neurogenesis, neuronal maturation, and synaptogenesis, reviewed in (Chiu and Cline, 2010). Perinatal environment contributes to the establishment of this signaling. For example, during gestation, maternal obesity has been shown to increase placental transport of both metabolic hormones and nutrients to the developing fetus, reviewed in (Sullivan et al., 2014; Rivera et al., 2015; Howell and Powell, 2017). While maternal insulin does not appear to cross the placental barrier, maternal glucose does, and when transported in high amounts as in the case of maternal metabolic impairment has been shown to increase production of insulin by the fetal pancreas, thereby exposing the developing fetal brain to a hyperinsulinemic environment (Oken and Gillman, 2003). Maternal leptin, on the other hand, does cross the placental barrier to directly act on the developing fetal brain (Luo et al., 2013; Djiane and Attig, 2008). Both insulin and leptin action during this period have been shown to alter the development of hypothalamic circuitry (Djiane and Attig, 2008; Bouret, 2010; Bouret et al., 2008; Simerly, 2008). In line with these proposed mechanisms, we have shown previously that within this model, maternal HF diet during gestation leads to metabolic dysregulation in dams including impaired glucose tolerance and hyperglycemia, increased fat mass, and hyperleptinemia, and that prenatal HF-exposed placenta have altered structure as well as changes in nutrient transporter expression (Song et al., 2017; Sun et al., 2012; Tamashiro et al., 2009).

Beyond the fetal period, maternal programming continues during the early postnatal period, when offspring are exposed to the effects of both milk composition and maternal rearing behavior. We and others have shown that maternal HF diet and obesity can alter milk composition (Rolls et al., 1986; Del Prado et al., 1997; Gorski et al., 2006; Schroeder et al., 2009; Gomes et al., 2018; Franco et al., 2012; Purcell et al., 2011). We have further demonstrated that this compositional change towards higher fat, more energy-dense milk is accompanied by both increased maternal nursing behavior and increased independent milk ingestion by pups, meaning that offspring in our model are not only exposed to fattier, more calorically-dense milk, but perhaps more of it (Purcell et al., 2011). In the context of insulin and leptin, both have been shown to pass through milk to exert direct effects on offspring (Grosvenor et al., 1993). While in prior studies we have not found changes in milk insulin or leptin content at P21, we have previously demonstrated glucose intolerance, hyperinsulinemia, and hyperleptinemia within pups at this same timepoint, suggesting that differential milk composition and nursing behavior may in part contribute to the P21 hippocampal *Insr* and *Lepr* changes demonstrated here by altering early postnatal metabolic regulation in offspring (Sun et al., 2012). It is also important to note that other groups have shown hormonal changes to milk composition in response to maternal obesity or HF diet exposure (Franco et al., 2012; Gomes et al., 2018; Gorski et al., 2006), and that it is possible that there are unmeasured differences in milk insulin, leptin, or other hormones within our offspring prior to the P21 timepoint that may be playing a role in developmental programming. Considered together, the perinatal span of hippocampal development, the sensitivity of the developing hippocampus to insulin- and leptin-mediated neurotrophic function, and evidence for changes in both prenatal and early postnatal dam-to-pup communication, it appears likely that maternal programming of insulin- and leptin-mediated hippocampal development plays some role in mediating the cognitive phenotype demonstrated here.

The peripheral metabolic changes exhibited by maternal HF diet-exposed offspring additionally calls to question the relationship between offspring metabolic impairment and offspring cognitive impairment. Many studies have now shown that maternal diets have significant effects on metabolic function of offspring well into adulthood, reviewed in (Sullivan et al., 2014). This long-lasting metabolic effect is reflected in the current study by an observation that offspring of HF fed dams remained heavier well into adulthood despite being fed a low-fat chow diet. We previously reported that maternal consumption of HF diet during gestation and lactation alters placental morphology and expression of nutrient transporters (Song et al., 2017) while also resulting in offspring leptin resistance, impaired glucose tolerance (Sun et al., 2012), and altered ingestive behavior (Purcell et al., 2011; Treesukosol et al., 2014), all of which could contribute to the greater risk for HF diet-induced obesity among HF offspring (Tamashiro et al., 2009).

As previously noted, there is a large body of work showing that adult animals exposed to a HF diet exhibit robust significant changes to spatial and recognition memory accompanied by peripheral and central insulin resistance and leptin resistance. Human studies have also shown an association between metabolic syndrome and cognitive decline, with relative risk for dementia being 73% higher in individuals with type 2 diabetes mellitus compared to non-diabetic individuals (Biessels et al., 2014). While the correlation is apparent, the relationship between peripheral and central metabolic impairment is complex and difficult to dissociate in studies of dietary exposure, reviewed in (Biessels and Reagan, 2015). More recently, some light has been shed on the role of central versus peripheral metabolic impairment on hippocampal dysfunction, learning, and memory. For example, one study demonstrated

that virally mediated insulin receptor knockdown in the rat hippocampus is sufficient to cause cognitive impairment and decreased hippocampal synaptic plasticity in the absence of peripheral metabolic change (Grillo et al., 2015). Conversely, intrahippocampal administration of insulin appears to improve cognitive performance without changing peripheral metabolism (Gladding et al., 2018). Another study using short hairpin-mediated leptin receptor knockdown showed that leptin signaling directly mediates hippocampal spine formation (Dhar et al., 2014). Together, these results suggest that insulin- and leptin-mediated cognitive impairment is not entirely dependent on peripheral metabolic derangement and that peripheral and central contributions can be experimentally dissociated.

While our results begin to elucidate potential brain changes underlying the association between maternal HF diet and cognitive impairment in offspring, work remains in defining clear causative mechanisms. Environmental manipulations such as those used in our study are on one hand more translationally relevant, but they are also broad in action, with behavioral phenotypes likely dependent on changes to several interacting systems and pathways. First, as in other studies of maternal HF diet, it is difficult to dissociate the effects of exposure to HF diet itself and the resulting metabolic impairment in the dam, reviewed in (Cordner and Tamashiro, 2015). Second, while they formed a focus of this study, insulin and leptin signaling are far from the only cognition-mediating pathways affected by obesity and overnutrition, with other known mediators including HPA axis dysregulation, mitochondrial dysfunction, and neuroinflammation, reviewed in (Biessels and Reagan, 2015; Cordner and Tamashiro, 2015). Interestingly, some of these systems have actually been shown to act upstream of hippocampal insulin and leptin resistance, and in turn may be further perpetuated by a resistant state (Biessels and Reagan, 2015). Third, even apart from interactions with other systems, insulin- and leptin-mediated promotion of hippocampal plasticity is complex and entangled, with activation of either receptor initiating multiple overlapping signaling cascades that themselves exhibit significant cross-talk, reviewed in (Fadel and Reagan, 2016). It is necessary to note that as they stand, our results focus solely on identifying persistently downregulated receptor expression. Follow up studies on various downstream consequences in the insulin and leptin signaling cascades, as well as the relative contribution of each, will be important. Moreover, given the several different functions that insulin and leptin signaling play in hippocampal plasticity across the lifespan, including but not limited to promotion of neurogenesis, neuronal maturation, synaptogenesis, and long term potentiation (Ferrario and Reagan, 2018), connecting such results to specific structural or functional plasticity changes, especially in the context of development, will be an important direction for future studies.

Finally, while the complexity involved in disentangling these interactions is daunting, doing so may open the door for novel and targeted interventions. As one example that has already shown some promise, intranasal insulin treatment appears to improve cognitive performance in both clinical and translational studies, acting by several overlapping mechanisms including improved hippocampal functional connectivity, reduced neuroinflammation, and increased synaptic plasticity (Chen et al., 2014; Zhang et al., 2015), reviewed in (Chapman et al., 2018). While to date most of these studies have focused on cognitive impairment in the context of type 2 diabetes mellitus and Alzheimer's disease, examining the ability of intranasal insulin treatment to ameliorate maternal HF diet-induced cognitive impairment would be an interesting future direction. In addition to pharmacotherapies, behavior intervention is another and perhaps more widely employable approach. In many studies, exercise or environmental enrichments have been shown to improve cognitive performance and markers of hippocampal function in adult animals including hippocampal insulin resistance (Redila and Christie, 2006; Kang and Cho, 2014; Ryan and Kelly, 2016; Cordner and Tamashiro, 2016). Additionally, maternal exercise exposure during gestation has been shown to improve cognitive performance even in offspring whose mothers consumed a low-fat diet (Robinson and Bucci, 2012; Parnpiansil et al., 2003). However, very few studies have focused on the potential for exercise to mediate the impact of maternal HF diet on offspring cognition and metabolic function. As maternal obesity rates continue to rise understanding the complex mechanistic interplay underlying cognitive consequences to offspring and using this understanding to develop clinically translatable interventions will be crucial.

Though much work remains to be done, the data presented here, consistent with a number of other studies, re-emphasizes how the maternal environment can have long-lasting consequences for offspring. Specifically, our work suggests that maternal exposure to HF diet can alter the hippocampal expression of genes that are involved in both metabolism and cognition and predispose offspring to cognitive impairment in adulthood. Going forward, it will be critically important to carefully define sensitive periods for HF diet exposure that contribute to the observed phenotype, further explore causal mechanisms, and investigate potential interventions such as exercise, diet, or pharmacological treatment that might mitigate the long-term effect of maternal diet on offspring.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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