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Higher insulin and higher body fat via leptin are associated with disadvantageous decisions in the Iowa gambling task

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HIGHLIGHTS

- Decision-making tested with the Iowa Gambling Task (IGT) after meal
- Measured body fat by DXA and insulin and leptin during oral glucose tolerance test
- Participants with lower insulin (30 min post-load) and body fat did better on IGT
- Lower leptin (30 min), rather than body fat, determined better IGT performance
- Leptin interacted with insulin and blunted effect of insulin at high leptin levels

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ABSTRACT

Elevated body mass index and post-prandial state are associated with disadvantageous choices on the Iowa Gambling Task (IGT). Whether physiological factors including percent body fat, and peripheral glucose, insulin, and leptin concentrations, are associated with IGT performance is unknown. In196 healthy adults without diabetes, we measured body fat by DXA scan, glucose, insulin and leptin ($n = 138$) concentrations during an oral glucose tolerance test and IGT performance after a standardized meal. Glucose was not associated with IGT performance. Disadvantageous IGT performance was associated with higher percent body fat ($r = -0.16$, $p = 0.03$), 30-min insulin concentrations ($insulin_{30}$, $r = -0.27$, $p < 0.001$), and 30-min leptin concentrations ($leptin_{30}$, $r = -0.23$, $p = 0.008$). Mediation analysis demonstrated that $leptin_{30}$ was almost completely responsible for the percent body fat effect on IGT performance. Even adjusted for age, sex, race, and education, $insulin_{30}$ ($b = -46.5$, $p = 0.03$) and $leptin_{30}$ ($b = -50.9$, $p = 0.03$) concentrations remained independently associated with IGT performance and interacted together such that higher $leptin_{30}$ blunted effects of higher $insulin_{30}$ ($b = 23.8$, $p = 0.048$). These findings may indicate an internal metabolic signature of energy availability (higher body fat, insulin, and leptin levels) associated with disadvantageous IGT performance.

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1. Introduction

The capacity to adjust behavioral decisions to acquire external rewards such as food is necessary for survival. Hunger motivates individuals to acquire and consume food; conversely, the fed state diminishes these food-related behaviors. Individuals who are not hungry rate food less positively [1] and purchase less high-calorie foods than those who are hungry [2]. Though the acquisition of food and money may seem like unrelated behaviors, there is evidence that different satiety states may influence decisions about food and non-food objects including money [3,4]. Sated participants were less likely to acquire nonfood objects compared with hungry participants, without influencing how much these items were liked [4]. The Iowa Gambling Task (IGT), a neuropsychological tool which uses cards and monetary rewards to simulate real life decision-making about short-term and long-term rewards under uncertainty, can be used to study decision making related to non-food objects; compared with fasted subjects of similar body mass index (BMI), fed subjects made less advantageous choices on the IGT [3]. While the transition from a fasted to the fed state reflects an acute change, individuals who had higher body mass index (BMI) were associated with worse performance on the IGT [5–7] indicating that longer-term changes in energy balance might directly or indirectly affect performance on the IGT. Since higher BMI and the postprandial state are indicative of greater energy availability and were associated with worse performance on the IGT, it is possible that internal neuroendocrine factors linked to BMI and the postprandial state influence IGT score.

Insulin and leptin are potential candidates for such neuroendocrine factors influencing IGT performance since they a) are elevated in the

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postprandial and obese states, respectively [8] and b) are known from animal models [9] to influence neural systems previously shown to be involved in IGT performance in human studies [10–12]. Like insulin, blood glucose also rises after food or glucose intake. Glucose, delivered through the bloodstream, serves as the main source of fuel for the brain and is necessary for normal cognitive function, most evident during severe acute hypoglycemia when cognition is clearly impaired. On the other hand, higher glucose levels are also negatively associated with a variety of cognitive function tests among those with and without diabetes [13,14].

Whether glucose, insulin, and leptin levels or percent body fat are associated with IGT performance is not known. Although BMI, a surrogate index of body fat, has been shown by others to be associated with decision-making on the IGT [5], it does not provide as accurate a measure of body composition and can misclassify those who are physically fit [15]. Compared with BMI, percent body fat has been shown to be more closely associated with some biological changes linked to non-cognitive but obesity-related outcomes [16,17].

We therefore sought to evaluate the association of IGT performance with percent body fat and peripheral glucose, insulin and leptin levels. In 196 healthy non-elderly adults, we measured percent body fat by DXA scan, glucose and insulin levels during an oral glucose tolerance test (OGTT) and IGT performance after a standardized meal. Leptin was further measured in 138 of the 196 subjects on OGTT samples that were available.

2. Methods

2.1. Human subjects

Subjects ($n = 196$) were recruited from metropolitan Phoenix, Arizona, USA and participated in one of six inpatient studies (Clinical Trial Identifiers: NCT00856609, NCT00739362, NCT00342732, NCT01224704, NCT01237093, NCT00523627) in the Clinical Research Unit of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in Phoenix, AZ, USA. For each of the inpatient studies, the first four days were identical, allowing merging of data across these studies; subjects were admitted, placed on a weight-maintaining diet, and had a DXA scan on day 2, performed the Iowa Gambling Task on day 3, and had an OGTT on day 4. There were no interventions performed and subjects were not manipulated in any other way during these four days. All subjects were between 18 and 55 years of age and provided written informed consent prior to starting the study. Based on history and physical examination and basic laboratory testing performed on the admission day, subjects were healthy, without prior diagnosis of diabetes or other serious medical problems (e.g. mental health, autoimmune, cardiovascular, or cerebrovascular diseases) and were not taking medications. Subjects also underwent urine testing for pregnancy (females only; CLIAwaived, San Diego, CA, USA), nicotine (CLIAwaived, San Diego, CA, USA), and drugs of abuse (Innovacon, San Diego, CA, USA), and were non-pregnant, non-smokers, and without current substance abuse. All protocols were approved by the Institutional Review Board of NIDDK.

2.2. Body composition

On admission to the Clinical Research Unit, volunteers were placed on a standard weight-maintaining diet (20% protein, 30% fat, and 50% carbohydrate) for 3 days, calculated based on weight maintaining energy needs as previously described [18]. The caloric content of breakfast and lunch was approximately one-quarter of weight maintaining energy needs and designed to resemble a typical American breakfast (e.g. sausage, egg, biscuit, fruit juice, butter) or lunch (e.g. bean burrito, carrot, fruit, orange juice). On day 2, body composition was assessed by using dual energy X-ray absorptiometry (DXA; Lunar Corp, Madison, WI, USA) and percent body fat was calculated as previously described [19].

2.3. Iowa gambling task

On day 3, anytime within one-hour after finishing breakfast or lunch, a computer-version of the IGT (Psychological Assessment Resources, Lutz, FL, USA) was used to measure simulated real-life decision making in the setting of uncertain rewards and penalties [20]. In the IGT, participants are instructed to win as much money as possible. Subjects are presented with four card decks (A, B, C, and D) from which to choose cards, one at a time. After choosing a card, subjects are immediately given information on whether there is a gain or loss of money. Decks A and B are considered disadvantageous, giving large rewards in addition to large intermittent penalties which result in long-term net loss. Decks C and D are considered advantageous, giving small rewards but also small intermittent penalties which result in long-term net gain. The task ends after 100 cards are selected with participants blinded to the card at which the game ends. Subjects are scored based on how many advantageous decks are chosen minus the number of disadvantageous decks. Compared with lower scores, relatively higher scores indicate overall more advantageous decision-making.

2.4. Metabolic factors in oral glucose tolerance test

On day 4 after admission, a 75 g oral glucose tolerance test (OGTT) was performed with glucose and insulin concentrations measured at −15, 0, 30, 60, 120 and 180 min. Glucose concentrations were measured using the glucose oxidase method (Beckman Glucose Analyzer 2, Beckman Instruments, Fullerton, CA, USA, or Analox GM9 Glucose Analyzer, Analox Instruments, Lunenburg, MA, USA). Glucose tolerance was classified according to American Diabetes Association criteria [21]. Plasma insulin concentrations were measured by AT AIA Pack IRI on TOSOH analyzer (Tosoh Bioscience, King of Prussia, PA, USA). Total and incremental area under the curve (AUC and iAUC, respectively) for insulin and glucose were calculated using the trapezoidal method. Plasma was available from 138 of the 196 subjects (70%) for leptin measurements at −15, 0, 30, 60, 120, and 180 min from the OGTT. Plasma leptin was measured in duplicate using ELISA kits (EMD-Millipore, Billerica, MA, USA). The intra-assay and inter-assay coefficients of variation (CV) for leptin was 5.3% and 9.2%, respectively.

2.5. Statistical analysis

Non-normally distributed data were $\log_{10}$ transformed and summarized with the geometric mean. Pearson correlation coefficients were determined for normally distributed variables to evaluate bivariate associations between continuous data, while Spearman correlation coefficients were used for data which remained skewed despite $\log_{10}$ transformation. Differences in mean between groups were compared using the Student's *t*-test.

To evaluate further the association between independent variables and total raw IGT score across all 100 cards (dependent variable), multivariable models were fit with the SAS procedure, PROC GLM (general linear model). Variables found to be related to IGT score on bivariate analysis and other variables previously reported to be associated with decision-making ability were entered in the multivariable models including age [22], sex [23], race/ethnicity [24], and education [25]. Interactions between variables related to IGT score were also assessed in these models.

Mediation analysis based on hierarchical multivariable regression models [26] was used to evaluate whether the effect of percent body fat on IGT performance was exerted through the influence of percent body fat on peripheral leptin levels. More specifically, the total effect of percent body fat on IGT performance was partitioned into two components according to the causal model shown in Fig. 3: the indirect

effect through leptin and the direct effect independent of leptin. The Sobel test [27] was used to test whether the indirect effect was significantly greater than zero, namely that the effects of percent body fat on IGT performance are mediated by leptin.

To examine the impact of independent variables on IGT during the task progression, the 100 sequential card selections were divided into five sequential blocks of 20 card selections, and scored within each card block. To account for performance on sequential card blocks from the same subject as a repeated measure, performance on each block was examined using mixed-model ANOVA with the SAS procedure PROC MIXED [28]. These mixed models evaluated percent body fat, insulin, and leptin divided into high and low levels based on median split, and accounted for repeated measures using a first-order autoregressive covariance structure.

All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA) except for mediation analysis [29] which was performed in SPSS (version 21, IBM Corp., Armonk, NY, USA) using the PROCESS macro. Alpha was set at 0.05 for analyses.

3. Results

3.1. Subject characteristics

Subject characteristics are shown in Table 1. Participants for the full cohort ranged in age from 18 to 55 years (35 ± 10, mean ± SD). Most were men (65% male, 35% female) and self-identified as Native American (34%) or white (31%). About half (46%) had some education above high school. Body mass index ranged from 17.4 kg/m^2 to 57.8 kg/m^2 (32 ± 8). By World Health Organization BMI classification [30], 107 (55%) were with obesity (BMI ≥ 30.0 kg/m^2), 55 (28%) were overweight (BMI 25.0–29.9 kg/m^2), 32 (16%) were normal weight (BMI 18.5–24.9 kg/m^2), and 2 (1%) were underweight (BMI < 18.5 kg/m^2). Participants had mean 36% body fat (±12).

Mean fasting and 120-min glucose levels after the OGTT were 96 mg/dl (±7, range 80–123 mg/dl) and 128 mg/dl (±30, range 55–199 mg/dl), respectively. Most (111, 57%) had normal glucose regulation (normal fasting and 120-minute glucose levels) and 85 (43%) had impaired glucose regulation (either impaired fasting glucose, impaired glucose tolerance, or both).

3.2. Associations with Iowa gambling task

Age, sex, race, education and glucose during the OGTT were not associated with total IGT score (Table 2). Although BMI was not significantly correlated with IGT score ($r = -0.11$, $p = 0.13$), higher percent body fat was negatively correlated with IGT score ($r = -0.16$, $p = 0.03$), indicative of poorer performance (Table 2, Fig. 1a). Lower IGT scores were also associated with higher fasting insulin ($r = -0.20$, $p = 0.006$), 30-minute insulin ($insulin_{30}$, $r = -0.27$, $p < 0.001$), 60-minute insulin ($r = -0.16$, $p = 0.03$), insulin AUC ($r = -0.22$, $p = 0.002$) and insulin iAUC ($r = -0.21$, $p = 0.003$) and with (Table 2). Lower IGT scores were also associated with higher leptin levels at all of the time points during the OGTT: fasting ($r = -0.22$, $p = 0.008$), 30-min ($leptin_{30}$, $r = -0.23$, $p = 0.008$), 60-min ($r = -0.21$, $p = 0.012$), 120-min ($r = -0.21$, $p = 0.014$), and 180-min ($r = -0.22$, $p = 0.010$). Among the OGTT timepoints, insulin and leptin at 30-min were most strongly correlated with IGT score (Table 2, Fig. 1b and c).

Table 1
Characteristics of study participants.

Characteristic	Full cohort $n = 196$	Leptin subcohort $n = 138$
Age (years), mean (SD)	35 (10)	36 (11)
Sex, n (%)		
Male	128 (65)	94 (68)
Female	68 (35)	44 (32)
Race/ethnicity, n (%)		
Native American	67 (34)	45 (33)
Black	31 (16)	23 (17)
White	61 (31)	44 (32)
Other/Hispanic	37 (19)	26 (19)
Education > high school, n (%)	90 (46)	61 (44)
Body mass index (kg/m^2), mean (SD)	32 (8)	31 (8)
Waist circumference (cm), mean (SD)	42 (9)	41 (9)
Body fat (%), mean (SD)	36 (12)	34 (12)
Glucose regulation		
Normal, n (%)	111 (57)	85 (62)
Impaired, n (%)	85 (43)	53 (38)
Glucose, fasting (mg/dl), mean (SD)	96 (7)	95 (7)
Glucose, 30-min (mg/dl), mean (SD)	153 (25)	154 (24)
Glucose, 60-min (mg/dl), mean (SD)	164 (39)[a]	161 (37)
Glucose, 120-min (mg/dl), mean (SD)	128 (30)	125 (31)
Glucose, 180-min (mg/dl), mean (SD)	86 (22)	85 (23)
Glucose AUC (mg/dl), mean (SD)	23,701 (3847)[a]	23,387 (3791)
Glucose iAUC (mg/dl), mean (SD)	6464 (3342)[a]	6260 (3407)
Insulin, fasting (uU/ml), mean (95% CI)	11 (10−12)	10 (8–11)
Insulin, 30-min (uU/ml), mean (95% CI)	101 (92–112)	96 (85–108)
Insulin, 60-min (uU/ml), mean (95% CI)	117 (106–129)[a]	107 (97–120)
Insulin, 120-min (uU/ml), mean (95% CI)	74 (64–84)[a]	64 (55–75)[c]
Insulin, 180-min (uU/ml), mean (95% CI)	19 (17–23)[a]	17 (14–20)[c]
Insulin, AUC (uU/ml), mean (95% CI)	14,848 (13,535–16,289)[b]	13,503 (12,169–14,983)[d]
Insulin, iAUC (uU/ml), mean (95% CI)	12,537 (11,305–13,903)[b]	11,317 (10,030–12,769)[d]
Leptin, fasting (ng/ml), mean (95% CI)	–	9.9 (8.0–12.2)
Leptin, 30-min (ng/ml), mean (95% CI)	–	8.7 (7.1–10.8)
Leptin, 60-min (ng/ml), mean (95% CI)	–	8.8 (7.2–10.7)
Leptin, 120-min (ng/ml), mean (95% CI)	–	8.3 (6.8–10.1)[c]
Leptin, 180-min (ng/ml), mean (95% CI)	–	8.7 (7.1–10.6)[c]
Iowa Gambling Task (total score)	2.8 (25)	3.2 (25)

Geometric mean reported for leptin and insulin. AUC, total area under the curve; iAUC, incremental area under the curve. For full cohort n = 196 except: [a] n = 195; [b] n = 193. For subcohort n = 138 except [c] n = 137; [d] n = 136.

Table 2
Associations with Iowa Gambling Task total score.

Characteristic	r	p-Value
Age (years)	0.06	0.37
Male Sex	–	0.31
Race/Ethnicity	–	0.08
Education > high school	–	0.30
Body mass index (kg/m^2)	−0.11	0.13
Waist circumference (cm)	−0.13	0.07
Body fat (%)	−0.16	0.03
Impaired glucose regulation (vs. NGR)	–	0.63
Glucose, fasting (mg/dl)	0.01	0.88
Glucose, 30-min (mg/dl)	−0.08	0.27
Glucose, 60-min (mg/dl)[a]	0.07	0.31
Glucose, 120-min (mg/dl)	−0.002	0.98
Glucose, 180-min (mg/dl)	−0.04	0.61
Glucose AUC (mg/dl)[a]	0.01	0.88
Glucose iAUC (mg/dl)[a]	0.007	0.92
Insulin, fasting (uU/ml)	−0.20	0.006
Insulin, 30-min (uU/ml)	−0.27	<0.001
Insulin, 60-min (uU/ml)[a]	−0.16	0.03
Insulin, 120-min (uU/ml)[a]	−0.13	0.07
Insulin, 180-min (uU/ml)[a]	−0.12	0.10
Insulin, AUC (uU/ml)[b]	−0.22	0.002
Insulin, iAUC (uU/ml)[b]	−0.21	0.003
Leptin, fasting (ng/ml)[c]	−0.22	0.008
Leptin, 30-min (ng/ml)[c]	−0.23	0.008
Leptin, 60-min (ng/ml)[c]	−0.21	0.012
Leptin, 120-min (ng/ml)[d]	−0.21	0.014
Leptin, 180-min (ng/ml)[d]	−0.22	0.010

Insulin and leptin concentrations were non-normally distributed and $\log_{10}$-transformed. Pearson correlation coefficient and Student's t-test used for continuous and group variables, respectively. NGR, normal glucose regulation; AUC, total area under the curve; iAUC, incremental area under the curve. n = 196 except: [a] n = 195; [b] n = 193; [c] n = 138; [d] n = 137.

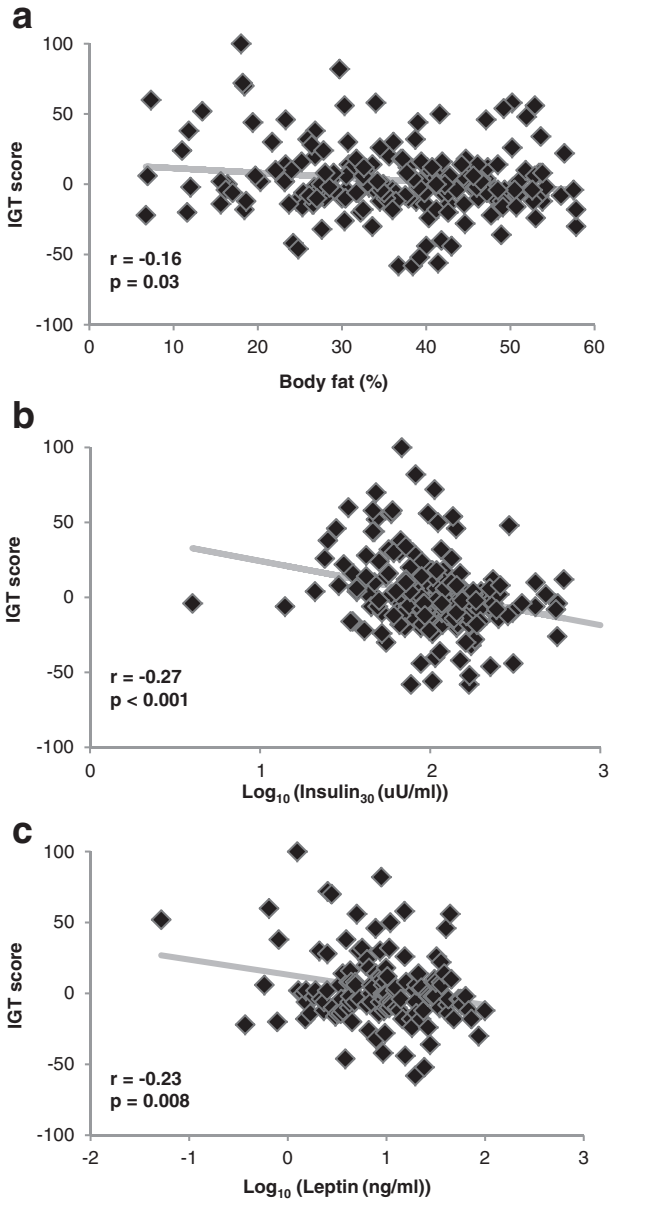

Fig. 1. Associations between Iowa Gambling Task score. (a) percent body fat, (b) 30-minute insulin, and (c) 30-minute leptin. Unadjusted Pearson correlation coefficients are shown.

3.3. Analysis of Iowa gambling task by card block

When analyzed with repeated measures analysis to account for each sequential IGT blocks of 20 cards the main effect for groups divided by percent body fat above and below the median remained significant ($p = 0.034$), indicating that those with lower percent body fat had higher IGT scores over the entire IGT task as compared to those with higher percent body fat (Fig. 2a). Similarly, in separate repeated measures analysis, the main effects for insulin$_{30}$ ($p = 0.004$) and leptin$_{30}$ ($p = 0.005$) above and below the median for each variable were statistically significant, indicating that those with lower insulin$_{30}$ and lower leptin$_{30}$ had higher IGT scores over the entire IGT task compared with those with higher insulin$_{30}$ and higher leptin$_{30}$ (Fig. 2b, c) .

3.4. Mediation analysis for percent body fat, leptin and Iowa gambling task

Leptin$_{30}$ was correlated with both BMI ($r = 0.68$, $p < 0.001$) and percent body fat ($r = 0.92$, $p < 0.001$). To evaluate the relationship between percent body fat and leptin$_{30}$ with IGT score, a mediation analysis was performed to quantify the effect of percent body fat on IGT via leptin$_{30}$ (Fig. 3). All the conditions for running a mediation analysis, using leptin as the mediator variable, were fulfilled (i.e. percent body fat and leptin ($b = 0.04$, $p < 0.001$) were strongly correlated and the significant association between leptin$_{30}$ and IGT score persisted after adjustment for percent body fat ($b = -19.85$, $p = 0.046$)) (Fig. 3). There was a significant effect for leptin$_{30}$ mediating the association between percent body fat and IGT score (indirect effect $= -0.80$, $p = 0.045$ by Sobel test). After accounting for leptin$_{30}$, the association between percent body fat and IGT score was almost completely suppressed and became non-significant (direct effect $= 0.44$, $p = 0.31$); the sign of the path coefficient for percent body fat's effect on IGT score flipped from negative to positive when accounting for the effects of leptin$_{30}$ mediation, indicating that leptin$_{30}$ suppressed the effect of percent body fat's association with IGT score.

3.5. Multivariable analysis

Even after adjusting for age, sex, race, and education, both percent body fat ($b = -3.2$, $p < 0.001$) and insulin$_{30}$ ($b = -74.9$, $p < 0.001$) remained independently associated with IGT score with an interaction between percent body fat and insulin$_{30}$ ($b = 1.5$, $p = 0.001$) such that higher percent body fat blunted the effect of higher insulin$_{30}$. Since the mediation analysis described above indicated that leptin$_{30}$, rather than percent body fat, independently determined IGT performance (Fig. 3), we constructed a separate model with insulin$_{30}$ and leptin$_{30}$. Even with adjustment for age, sex, race, and education, both insulin$_{30}$ ($b = -46.5$, $p = 0.03$) and leptin$_{30}$ ($b = -50.9$, $p = 0.03$) remained independently associated with IGT with an interaction between insulin$_{30}$ and leptin ($b = 23.8$, $p = 0.048$). The interaction pattern between insulin$_{30}$ and leptin$_{30}$ was similar to the interaction between insulin$_{30}$

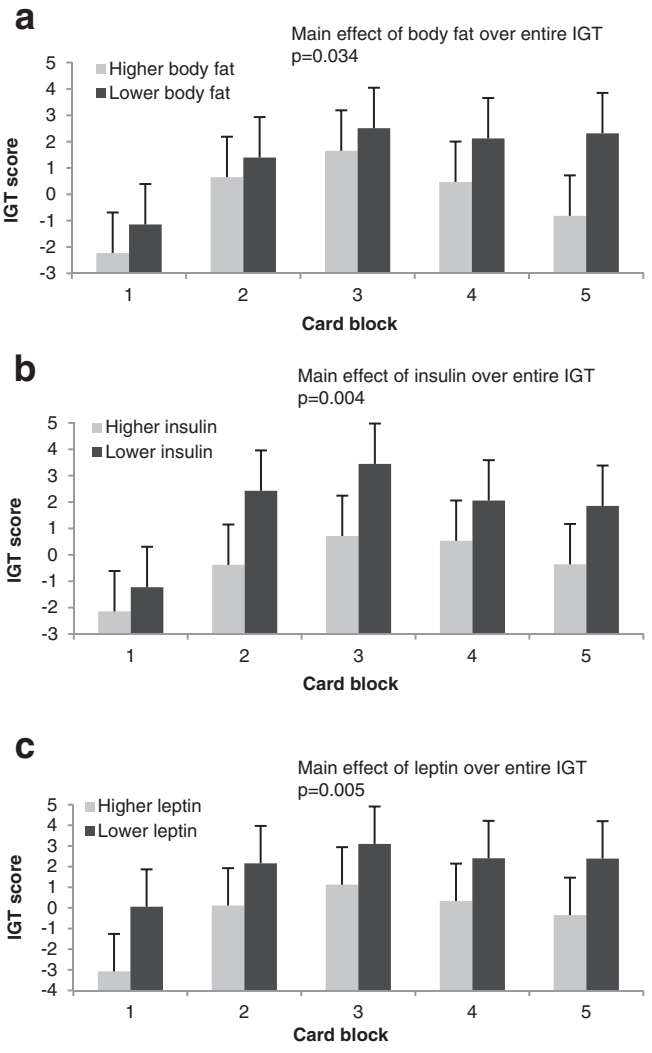

Fig. 2. Performance during progression of Iowa Gambling Task (IGT). Results of repeated measure analysis accounting for IGT block as repeated measure for (a) percent body fat, (b) 30-minute insulin, and (c) 30-minute leptin. Higher and lower groups based on median split. Each card block represents 20 cards and are sequential (card block 1 = cards 1 to 20).

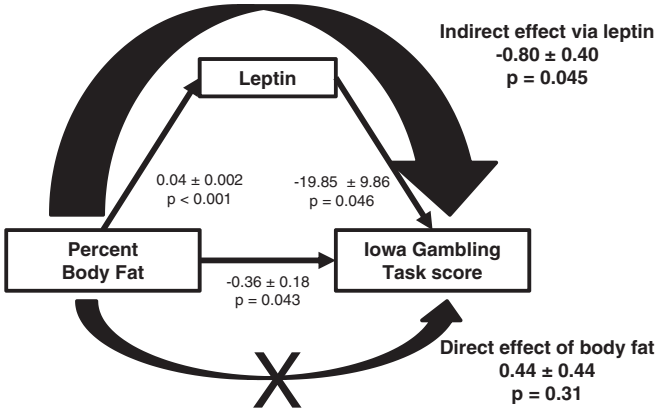

Fig. 3. Mediation analysis. Percent body fat (independent variable), 30-minute leptin (mediator) and Iowa Gambling Task score (IGT, dependent variable). Path coefficients are reported along with standard error and significance. The indirect effect via leptin was calculated as product of the path coefficient between percent body fat and leptin times the path coefficient between leptin and IGT, and it was tested for significance by the Sobel test.

and percent body fat, such that at higher $leptin_{30}$ levels, $insulin_{30}$ had a lesser effect on IGT scores compared with the $insulin_{30}$ effect at lower $leptin_{30}$ levels. In the multivariable analysis, $insulin_{30}$ and $leptin_{30}$ were analyzed as continuous variables but, for illustrative purposes in Fig. 4, $insulin_{30}$ and $leptin_{30}$ were divided using median split to illustrate the main effects of $insulin_{30}$ and $leptin_{30}$ and the interaction between $insulin_{30}$ and leptin.

4. Discussion

We evaluated the relationship between postprandial performance on the IGT and metabolic factors including percent body fat, insulin, glucose and leptin measured during an OGTT in a population of healthy non-elderly adults without diabetes. Individuals with relatively lower percent body fat, leptin and insulin did better on the IGT. In mediation analysis, we found that leptin rather than percent body fat independently influenced IGT performance. Moreover, we found that insulin and leptin not only acted independently, but also interacted together to influence IGT score.

Unlike others [5–7], we did not find a significant correlation between BMI and IGT score. However, we did find a correlation between percent body fat and IGT score and that this association was almost completely driven by leptin levels. If body composition effects are important, the lack of association between BMI and IGT score can be explained by the fact that leptin is more closely associated with percent body fat rather than BMI, which is a less accurate method to estimate body fat than DXA scan [31].

It has been proposed by others that the emotional/limbic system may be strongly involved during the IGT in early card selection at a time when participants are trying to decipher which card decks are advantageous and which are disadvantageous [32]. This emotional/limbic system may allow one to label an environment (e.g. card decks in the human IGT), as "good" or "bad" and feeds information to the cognitive control system which becomes more involved in late card selection to guide behavior and optimize long-term decisions [32]. Our participants with relatively higher insulin and higher leptin levels performed worse on the IGT compared with those with lower insulin and lower leptin. Insulin and leptin, serving as a satiety signals for food by decreasing

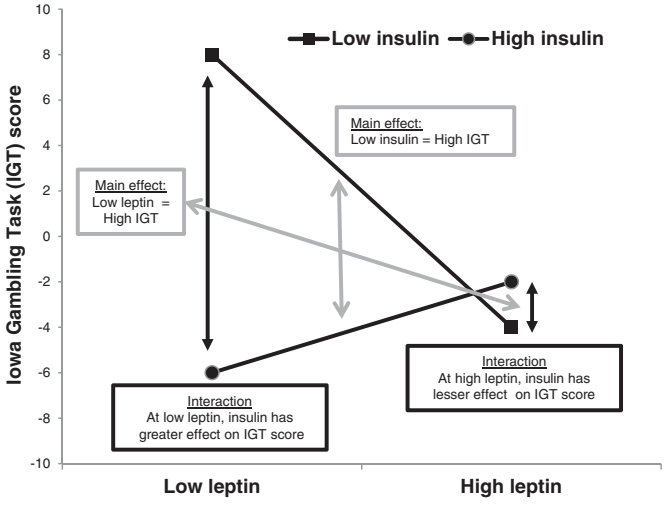

Fig. 4. Illustration of main effects of insulin and leptin and interaction between insulin and leptin. Higher and lower 30-minute insulin and leptin levels are based on median split for illustrative purposes. Relatively lower insulin and leptin levels were independently associated with higher (better) Iowa Gambling Task scores. The interaction was such that, at relatively lower leptin, insulin had a greater effect on IGT score; at higher leptin, insulin had a relatively lesser effect on IGT score.

salience of cues for food, may also be decreasing the salience of cues for money during the IGT.

In addition to independent effects of insulin and leptin, we found an interaction between leptin and insulin such that higher leptin levels appeared to blunt modulation by higher insulin concentrations. In one prior study, centrally co-administered insulin and leptin was shown to interact sub-additively to reduce food intake in rats such that the presence of one blunted the effect of the other [33], similar to the interaction pattern that we found during the IGT. The interaction between insulin and leptin may reflect modulation of overlapping neural circuitry or molecular crosstalk in pathways downstream from their receptors [9].

Our study has several limitations. The OGTT, from which the insulin and glucose measurements were obtained, was performed on a separate day as the IGT performance. Since we did not conduct the OGTT at the same exact time the subject was performing the IGT, we could not definitively exclude differences in metabolic state. However, we want to note that potential differences are minimized by conducting the OGTT and DXA within 2 days of the IGT and by the fact that participants eat standardized meals with consistent macronutrient composition. There may also be differences between insulin and glucose levels after a mixed meal compared with levels after a glucose load. However, insulin and glucose responses between oral glucose tolerance test and mixed meal are correlated [34]. We also did not measure cerebrospinal fluid (CSF) levels of these metabolic factors but it should be noted that blood levels of glucose, insulin and leptin are associated with CSF levels [35–37]. Insulin and leptin are secreted in the periphery by pancreatic beta cells and adipocytes, respectively, and cross the blood-brain barrier (BBB) by independent transport systems [38,39] so peripheral levels may have an effect on brain signaling. Lastly, our findings are based on an association study and causation cannot be established.

Despite these limitations, the current study has several strengths. We studied a multi-ethnic group with a wide range of ages and adiposity, determined by a gold-standard for measuring percent body fat. Similar to the percent of adults in the United States with overweight including obesity (71%), most of our participants were also with overweight including obesity [40]. Since it has been previously shown that IGT performance differed by whether individuals are in the fasted or fed states [3], we controlled for this by studying subjects only in the postprandial state on our metabolic ward. It should be noted that although participants underwent the IGT within one-hour after the meal, differences in time of day (breakfast versus lunch) or in fine timing (e.g. starting immediately after the meal versus undergoing the IGT later in the time period) might also influence IGT performance. Future studies should evaluate how these endocrine factors influence IGT performance in the fasting state and in relation to the length of time after specific meals. Our participants also received screening by comprehensive history and physical examination, routine blood work, and urine testing to control for conditions which may influence cognitive decision making such as mental or physical illness and substance abuse. Since this study included only healthy participants and excluded those with possible co-morbid conditions that may secondarily influence cognition, the findings indicate that cognitive changes associated with obesity may be occurring prior to the development of these conditions.

5. Conclusions

In summary, we found a relationship between peripheral signals of energy balance and IGT performance in the postprandial state in a group of healthy non-elderly adults without diabetes. We showed that percent body fat was associated with IGT performance, but that leptin, rather than body fat, independently accounted for IGT performance. In addition, we also found insulin and leptin, independently and interacting together, were associated with IGT performance. The interaction between insulin and leptin was such that at relatively higher leptin levels, the effect of insulin was reduced. These findings indicate an internal metabolic signature of energy availability (higher body fat percentage and higher insulin and leptin concentrations) that may influence behavioral decisions.

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