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Insulin, Central Dopamine D2 Receptors, and Monetary Reward Discounting in Obesity

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INTRODUCTION

Human obesity has been associated with altered dopamine (DA) functioning (1), altered dopamine D2-like (D2, D3, D4) receptor binding in brain reward regions (2;3), as well as with altered reward-related behavior (4-6). The specific nature of these relations, however, remains unclear. Animal studies have demonstrated that the pancreatic hormone insulin binds to insulin receptors and thereby influences reward-related behavior. Because human obesity is often linked to insulin dysregulation (7;8), individual differences in insulin sensitivity or secretion, independent of obesity, may relate to D2 receptors and reward discounting in humans.

Animal studies have demonstrated that insulin binds directly to insulin receptors located on dopaminergic neurons in brain reward pathways (9), and regulates DA signaling, reward processing, and reward behavior by increasing dopamine transporter (DAT) density and function (10;11). A dopamine D2-like receptor-mediated mechanism may affect this process (12). Insulin increases brain reward thresholds (13), and reduces preference for food reward (14), operant responding for food reward (15), non-hedonic food intake (16), and hedonic food intake in sated animals (11).

Although the effects of insulin on reward processing and behavior have been demonstrated in animals, it is not known whether insulin affects DA-mediated reward-related behavior in humans. Ultimately, understanding the precise relations among dopaminergic dysfunction, altered reward-related behavior, and metabolic factors will be critical for identifying behavioral subtypes of obesity, and for specifying points of clinical intervention along the complex pathway linking neuroendocrine hormones and behavior.

The goal of the present study was to determine the specific relations among individual differences in insulin function, dopamine D2 receptors, and reward choice behavior in healthy obese and normal-weight adults. We hypothesized that impaired insulin function would relate to impaired reward discounting (specifically, greater preference for risky rewards, greater preference for immediate rewards) and lower D2R binding in reward regions of interest (ROIs).

MATERIALS AND METHODS

***Participants*.** Obese and normal-weight adults were studied as part of an ongoing, longitudinal investigation of dopaminergic function in obesity. After initial screening, individuals were assessed with a detailed history, including neurological and physical examinations, psychiatric interviews (Structured Clinical Interview for DSM-IV; American Psychiatric Association 1994), and routine blood tests (e.g., fasting plasma glucose, lipids, serum creatinine, hematocrit). Individuals were excluded for significant personal history of chronic illness (e.g., diabetes and other significant neurological, cerebrovascular, cardiovascular, or psychiatric diagnosis) (e.g., major depression, anxiety, eating disorder, and other DSM-IV Axis I disorders), head trauma, any dopaminergic drug (e.g., neuroleptics or metoclopramide), current heavy alcohol use (males >2 drinks per day, females >1 drink per day) or drug use (17), history of substance abuse or dependence, or IQ below 70 (as measured by the Wechsler Scale Adult Intelligence Scale (18)). The study was approved by the Washington University School of Medicine Human Research Protection Office and the Radioactive Drug Research Committee, and all participants gave informed consent prior to participation.

***Obesity and insulin measures*.** All participants underwent a dual-energy x-ray absorptiometry (DXA) total body scan to assess body composition (body mass index, BMI kg/m^2). Participants also had a 2-hour oral glucose tolerance test (OGTT), with arterialized hand vein sampling of insulin, C-peptides, and blood glucose levels at times –5, 0, 10, 20, 30, 60, and 120 minutes after drinking a standard 75g Glucola load. β-cell function was estimated using a minimal model derived from the OGTT to calculate a disposition index (DI; [insulin sensitivity × insuin secretion for the given amount of glucose]). Disposition index was selected as the primary measure of insulin function because it accounts for both how much insulin is secreted for a given amount of ingested glucose, and how effective insulin secretion is at clearing glucose (19); higher DI indicates better insulin function. The oral glucose minimal model produces insulin

sensitivity measures that compare well with insulin sensitivity estimated from an intravenous glucose tolerance test (20). Insulin sensitivity was estimated using the Matsuda insulin sensitivity index (Matsuda ISI; $(10{,}000/\sqrt{[(Glucose_{t0'}\ (mg/dL) \times Insulin_{t0'}\ (mU/L)) \times (Glucose_{mean} \times Insulin_{mean})]})$ (21), such that higher Matsuda ISI indicates greater insulin sensitivity. Insulin secretion was calculated using minimal model analysis (Phi Total), providing an index of insulin secretion in relation to plasma glucose that relies on plasma C-peptide as a function of glucose concentration (19), where higher Phi Total indicates greater pancreatic β-cell secretion of insulin in response to glucose load.

***Image acquisition, preprocessing, and analyses*.** Participants underwent magnetic resonance (MR) and PET scans. Structural MR T1-weighted anatomical images were acquired on a Siemens Magnetom Tim Trio 3T scanner using a 3-D MPRAGE sequence (sagittal orientation, TR=2400 ms, TE=3.16 ms, FA=8 degrees, slab thickness 176mm, FOV=256x256mm; voxel resolution= 1x1x1 mm). PET images were acquired on a Siemens/CTI ECAT EXACT HR+ scanner using [^{11}C]NMB, a high-affinity radioligand that is highly selective for the dopaminergic D2 receptor over the D3 receptor subtype of the D2 receptor family, and importantly, is not displaced by endogenous dopamine (22;23). [^{11}C]NMB was administered intravenously to each subject with a specific activity exceeding 2000 Ci/mmol, and an injected mass $\leq$ 7.3 μg of NMB. Regions of interest (ROIs) were selected *a priori* and identified using FreeSurfer (24), and included the caudate, putamen, and nucleus accumbens. Each region, except for the nucleus accumbens (due to its small size), was eroded by approximately 2 mm from the surface by combining a Gaussian smoothing filter with thresholding to reduce partial volume effects. For each participant, the dynamic PET images were co-registered to each other and to the participant's MPRAGE image as described previously (25). ROIs and the cerebellar cortex reference region were resampled in the same atlas space (26), and decay-corrected tissue activity curves were extracted for each ROI from the dynamic PET data. Dopamine D2R binding potentials (BP_{ND}) were determined for each ROI using the Logan graphical

method with the whole cerebellum as the reference region (27). Binding potentials were computed for each hemisphere and averaged across left and right caudate, putamen, and nucleus accumbens, in order to minimize the number of comparisons, and because no evidence suggested that these findings would be asymmetric.

***Behavioral paradigms and analyses*.** All participants underwent behavioral testing. Reward discounting was assessed using two reliable computerized neuropsychological tasks, a probability reward discounting task (PRD) and delay reward discounting task (DRD). Both tasks are thought to be mediated by dopamine (28-32), have been associated with distinct neural mechanisms in animals (33;34) and decision processes (35;36), and have been used in previous studies of obesity (6;37;38).

The PRD task was used to assess preference for smaller, certain rewards over larger, riskier rewards. Participants were asked to make a series of choices between two hypothetical monetary rewards: a smaller, certain reward (to be received "for sure"), and a larger reward to be received with some probability (10%, 25%, 50%, 75%, and 90%). The DRD task was used to assess preference for smaller, immediate rewards over larger future rewards. Participants were again asked to make a series of choices between two hypothetical monetary rewards: a smaller, immediate reward (to be received "now"), and a larger reward to be received in the future (1 week, 1 month, 6 month, 1 year, and 2 years from now). For both the PRD and DRD tasks, a series of "indifference points" was computed and plotted, representing the points at which the two rewards (e.g., the larger reward and the smaller reward) were of equal subjective value for an individual at each probability and at each delay interval. The degree of probability and delay reward discounting was determined by calculating the area under the curve (AUC) (39), an atheoretical measure that reflects the degree to which a reward decreases in subjective value as a function of probability ("odds against;" PRD_{AUC}) or delay (DRD_{AUC}) (40). Higher AUC values indicate less discounting as a function of probability or delay.

***Primary statistical analyses*.** Planned data analyses were conducted using SPSS v. 20.0. To test the hypothesis that impaired insulin sensitivity and secretion (low DI) is related to impaired DA functioning (low D2R binding potential) in primary reward regions (caudate, putamen, nucleus accumbens), Pearson's partial correlation coefficients were calculated between DI and D2R BP_{ND} in each ROI, controlling for age, gender, BMI, and education, using a Bonferroni-corrected threshold ($p<.02$) for significance testing; covariates were selected because they have been shown to correlate with dependent variables of interest in previous studies (6;37). To test the hypothesis that impaired insulin function (lower DI) relates to altered reward choice (greater preference for risky or immediate rewards), Pearson's partial correlation coefficients were calculated between DI and reward choice variables (PRD_{AUC}; DRD_{AUC}), controlling for age, gender, BMI, and education. We explored the effects of DI on variables of interest by examining relations with Matsuda ISI and Phi Total separately, but only in cases when the correlation with DI was significant, in order to minimize the problem of multiple comparisons. Bonferroni-corrected thresholds ($p<.025$) were used for significance testing. Cohen's effect size calculations for each Pearson's correlation (Cohen's *d*; (41)) and for each hierarchical linear regression (Cohen's f^2) were completed using StatCalc (42). All analyses were first completed in the total sample (obese and normal-weight groups combined). Analyses were then conducted within each group separately in order to characterize more precisely any potential relations due to the fact that group membership was determined by BMI.

RESULTS

Participants. 14 obese adults (2 male), and 14 normal-weight adults (4 male) were studied. One participant in the normal-weight group had a BMI greater than 25 kg/m^2 (27.7 kg/m^2), however, this participant was included in the normal-weight group because other weight parameters (e.g., percent body fat) fell into the normal-weight category. PET data for two obese participants were lost due to participant attrition, and DRD and PRD data from one obese and one normal-weight subject were lost due to computer failure; these four participants were excluded from pair-wise analyses. Descriptive statistics are summarized in **Table 1**.

General Results. Obese and normal-weight participants did not differ in age, education, D2R BP_{ND} in caudate, putamen, nucleus accumbens, or reward choice (PRD_{AUC}; DRD_{AUC}) after applying Bonferroni correction (p <.02 for all comparisons). As expected, obese and normal participants did differ significantly in body mass index (p<.001) and insulin measures, Disposition Index (p<.002) and Matsuda ISI (p<.001); the group difference in Phi Total was not significant (p=.04) after Bonferroni correction. Analyses were based on the hierarchical linear regression model using appropriate covariates (e.g., in step two, regressing out BMI when isolating the effects of insulin function, and regressing out insulin function when isolating the effects of BMI, after including age, gender, and education in step one). Levene's test for equality of variances revealed that equal variances could be assumed for each variable, except for BMI (F=6.17; p=.02), Disposition Index (F=8.37; p<.008), and Matsuda ISI (F= 4.38; p=.05). One-sample Kolmogorov-Smirnov tests showed no evidence of non-normality in the distributions of BMI within the obese (z=.88; p=.43) and normal-weight (z=.47; p=.98) groups, the Disposition Index within the obese (z=.95, p=.33) or normal-weight (z=.91, p=.38) groups, and the Matsuda ISI Index within the obese (z=.85, p=.46) or normal-weight (z=.56, p=.91) groups.

Relation of D2R BP_{ND} to Reward Choice. In the total sample, obese group, and normal-weight group, D2R BP_{ND} in caudate, putamen, or nucleus accumbens did not correlate with either reward choice measure (PRD_{AUC}; DRD_{AUC}), controlling for age, gender, education, BMI, and DI (**Table 2**).

Relation of D2R BP_{ND} to Insulin Function. D2R BP_{ND} in caudate, putamen, nucleus accumbens did not correlate with DI, controlling for age, gender, BMI, and education (**Table 3**).

Relation of Insulin Function to Reward Choice. In the combined obese and normal-weight group, DI correlated with DRD_{AUC} (r=.495; p=.019; Cohen's f^2=.32), controlling for age, gender, BMI, and education; better insulin function related to greater preference for larger, delayed rewards (**Figure 1**). This effect was driven not primarily by either insulin sensitivity (r=.28; p=.21; Cohen's f^2=.10) or beta cell response (r=–.06; p=.80; Cohen's f^2=.003), controlling for age, gender, BMI, and education. Within the normal-weight group alone, DI showed a trend-level correlation with DRD_{AUC} (r=.62; p=.08; Cohen's f^2=.65), controlling for age, gender, BMI, and education. Better insulin function may relate to greater preference for larger, delayed rewards; but this was only a trend-level correlation (any p<.10). There were no significant results within the obese group alone (r=.44; p=.23; Cohen's f^2=.25).

In addition, within the obese group alone, DI correlated with PRD_{AUC} (r=–.84; p=.005; Cohen's f^2=2.40; **Figure 2A**), controlling for age, gender, BMI, and education, such that better insulin function related to greater preference for the smaller, more certain reward. Follow-up analyses showed that Matsuda ISI correlated with PRD_{AUC} (r=–.67; p=.049; Cohen's f^2=.81; **Figure 2B**), but not Phi Total (r=.07; p=.85; Cohen's f^2=.03; **Figure 2C**), controlling for age, gender, BMI, and education, suggesting that better insulin sensitivity related to greater preference for the smaller, more certain reward. There were no significant

correlations within the combined (r=–.04; p=.87; Cohen's f^2=.001) or normal-weight groups (r=.37; p=.34; Cohen's f^2=.15).

Relation of BMI to Reward Choice. To determine whether any relation between BMI and PRD_{AUC} existed, independent of insulin function, we correlated BMI with PRD_{AUC}, controlling for age, gender, education, and DI. Within the obese group alone, BMI correlated with PRD_{AUC} (r=–.78; p=.01; Cohen's f^2=1.57), such that higher BMI related to greater preference for smaller, certain rewards (**Figure 3**). There were no significant correlations within the combined (r=–.10; p=.67; Cohen's f^2=.009) or normal-weight (r=–.05; p=.90; Cohen's f^2=.002) groups. Finally, to determine whether any relation between BMI and DRD_{AUC} existed independent of insulin function, we correlated BMI with DRD_{AUC}, controlling for age, gender, education, and DI. There were no significant correlations within the combined (r=.42; p=.054; Cohen's f^2=.21), obese (r=–.18; p=.64; Cohen's f^2=.04), or normal-weight groups (r=–.59; p=.10; Cohen's f^2=.53).

DISCUSSION

This study demonstrated a relation between insulin function and reward discounting in normal-weight and obese adults. The results suggest that insulin function, and insulin sensitivity in particular, relates to reward discounting in obese and normal-weight humans, independent of the degree of obesity (BMI).

We examined relations within the obese and normal-weight groups, both combined and separately, and tested for between-group differences. First, our results showed that in obese and normal-weight participants, better overall insulin function, measured by disposition index (DI) (i.e., a composite measure based on the product of insulin sensitivity and β-cell function), related to preference for the larger, delayed reward (more patience). To function effectively in many situations, individuals must forgo immediate gratification and persist in goal-directed behaviors to achieve some future desired outcome. Our results suggest that individuals with good overall insulin function may be better able to abstain from immediate, smaller rewards, so as to obtain larger, more delayed rewards; for example, choosing a larger lottery payout to be received "later" rather than choosing a reduced lottery payout "now" (or, choosing better health "later," rather than choosing a second ice cream cone "now"). In humans, the directionality of this relation remains unknown. That is, does better insulin function reduce the degree of delay reward discounting, or does lower discounting lead to better insulin function? Animal studies have shown that, for example, intraventricular insulin reduces non-hedonic food intake in sated animals (16), suggesting that insulin levels in healthy non-human animals directly influence reward behavior. In humans, this is poorly characterized.

Second, within the obese group, better overall insulin function related to greater preference for smaller, certain rewards (more risk aversion). To function effectively in the world, individuals must appropriately weigh the risks associated with uncertain rewards. Our results suggest that among obese individuals,

those with better overall insulin function may be more likely to select a smaller, certain reward rather than a larger, less certain reward. Subsequent analyses showed that the relation between insulin function and risk-based reward choice was driven by insulin sensitivity (Matsuda ISI) and not pancreatic beta cell response (Phi Total). The observed pattern may be due to the fact that in the prodrome to type 2 diabetes, insulin sensitivity decreases before pancreatic beta cell response diminishes (43), suggesting that insulin sensitivity in neurons diminishes before pancreatic function fails overall. This could be the case in our pre-diabetic obese participants who showed poor insulin sensitivity and some degree of beta-cell response. Future studies of obese individuals with type 2 diabetes would provide more clarity with respect to these findings. For example, in obese individuals with type 2 diabetes, one might expect to see that both insulin sensitivity and pancreatic beta-cell response both contribute to the relation between overall insulin function (DI) and reward discounting.

Finally, BMI also was associated with greater preference for smaller, more certain rewards, independent of insulin function, but only within obese individuals, suggesting that BMI may contribute independently to a lower degree of probability reward choice in obesity. In other words, these data suggest that higher BMI contributed to less risk-taking behavior (more risk aversion). Higher-BMI obese individuals made less risky choices than did lower-BMI obese individuals. Surprisingly, BMI did *not* relate to greater delay discounting (preference for smaller, more immediate rewards), independent of insulin function. These results stand in contrast to previous work. Rasmussen et al. (2010) reported that higher percent body fat (PBF), but not BMI, related to greater discounting of probabilistic monetary rewards (44). Weller et al. (2008) showed greater delayed reward discounting in obese as compared to leaner women on a hypothetical monetary discounting task (37). However, the results of these studies are difficult to interpret because studies have found an effect of percent body fat, but not BMI (44), or only in women, and not in men (37). These studies also failed to exclude psychiatric and medical conditions (e.g., type 2

diabetes) that could confound the interpretation of results. Because of these inconsistent results, we believe that our study, which is based on a rigorously screened sample, may be better able to detect specific relations among obesity, insulin function, and reward discounting behavior.

Our study suggests that dopamine D2-specific receptor status is not related to BMI, reward discounting behavior, or insulin function (as measured by the disposition index; DI), in well-screened adults. This result contrasts with previous human studies that have suggested that reduced D2/D3 receptor availability in reward regions is related to obesity and pathological reward-driven behavioral phenotypes (e.g., drug addiction, cigarette smoking) (45). Our results are also in contrast to animal work showing that the effect of insulin on reward may be mediated, in part, through a dopamine D2-like receptor mediated mechanism (12). For example, one animal study showed that probability discounting correlated with striatal D2/D3 receptor availability, such that high wager sensitivity related to low striatal D2/D3 receptor density (46). The unique receptor-binding properties of the D2-specific ligand, [^{11}C]NMB, may provide evidence toward understanding these discrepant findings (22;23).

These previous studies in humans and animals, however, used the radioligands [^{11}C]raclopride or [^{18}F]fallypride, which are known to be displaceable by endogenous dopamine or are non-selective for D2R versus D3R, confounding potential between-group differences in binding potential differences in D2R versus D3R specific binding sites, differences in endogenous dopamine tone or release, or some combination of both. This is particularly important when considering the different human brain distributions of D2R and D3R (47), and the likely different functional roles of D2R and D3R in reward discounting and reward-related behaviors.

In addition, it may be the case that BMI, reward discounting behavior, and insulin function more closely relate to the dopamine D3 receptor or some other aspect of the midbrain dopamine signaling system (e.g., the dopamine transporter) than D2R. Future human studies that examine such specific aspects of the midbrain dopamine system are needed to unravel the complex relations among different components of the dopamine reward signaling pathway, BMI, reward discounting, and insulin function.

The study has some limitations. First, although our sample size was moderate, it is larger than most of the existing human obesity studies of DA receptors and behavior (referenced above). However, based on effect sizes from studies of the effects of insulin on cognition (with significant effects ranging from Cohen's *d* =–.42– to +1.73) (48), this study was sufficiently powered to detect moderate relations between insulin and behavior. Nonetheless, larger and more heterogeneous samples will be needed to confirm and extend our findings. Second, these results are correlational. It is possible that insulin dysregulation influenced behavior, or it is possible that individuals with altered reward behavior are more likely to have poor eating habits leading to insulin dysregulation. Longitudinal investigation of changes in insulin function or weight will be important in understanding the directionality of these relations. However, experiments in nonhuman animals show that insulin can affect reward sensitivity, and *our data provide the first evidence in humans that insulin function and reward behaviors are related*. Third, this study did not measure other aspects of DA functioning (e.g., DA tone, presynaptic DA release, pre- versus post-synaptic D2R density, D3R BP, DAT membrane density or function) with respect to insulin function and behavior. Additional studies will be integral to understanding the complex relations among obesity, insulin, midbrain and extrastriatal dopamine signaling systems, other monoamine and neuroendocrine signaling systems, functional networks, and reward discounting behavior.

Our results demonstrate that, as in animals, the pancreatic hormone insulin is related to reward behavior in humans. In particular, better insulin function related to less problematic risk- and delay-based reward discounting. In addition, we show that within obese individuals, BMI related to greater preference for smaller, more certain rewards, independent of insulin function. We found no significant relations between insulin D2R BP_{ND} and insulin function, or D2R BP_{ND} and reward discounting, in obese or normal-weight individuals. Our results suggest that the relations among BMI, metabolic dysfunction, and reward discounting may not be primarily mediated by D2 BP_{ND}, but may instead relate to other aspects of the DA signaling system (e.g., D3R, DAT), likely in concert with other monoaminergic and brain regulatory systems. Improving insulin function may provide a novel behavioral treatment target for future, more clinically relevant, studies of obesity and weight reduction.

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TABLES

Table Captions.

Table 1 – Table showing descriptive statistics for obese and normal-weight groups for BMI, demographic, and insulin-related measures. ** indicates $p<.02$. Cohen's effect sizes (Cohen's *d*) are shown for each variable.

Table 2 – Table showing relation between D2R BPND and reward discounting. PET data for two obese participants were lost due to no-shows on scan day, and DRD and PRD data from one obese and one normal-weight subject were lost due to electronic failure; these participants were excluded from relevant pair-wise analyses. Pearson's partial correlations are shown for the Combined, Obese, and Normal-weight participants, controlling for age, gender, education, BMI, and Disposition Index (DI).

Table 3 – Table showing relation between D2R BPND and insulin function. PET data for two obese participants were lost due to no-shows on scan day; these participants were excluded from relevant pair-wise analyses. Pearson's partial correlations are shown for the Combined, Obese, and Normal-weight participants, controlling for age, gender, education, and BMI.

Table 1 – Descriptive Statistics

		OBESE (N=14)			NORMAL (N=14)			Independent Samples t-test	
	Mean	**St. Dev.**	**Range**		**Mean**	**St. Dev.**	**Range**	**t**	**Cohen's effect size (*d*)**
BMI (kg/m^2)	39.84	4.13	33.7–46.7		22.58	2.31	18.9–27.7	13.65**	5.35
Age (years)	33.22	6.37	22.7–40.9		29.57	5.65	22.4–39.7	1.66	0.63
Education (years)	14.93	1.73	12.0–18.0		16.21	1.31	14.0–18.0	–2.22*	–0.86
Matsuda ISI	4.65	3.45	1.23–10.53		12.28	5.68	4.76–21.40	–4.30**	–1.69
Phi Total	39.85	20.43	18.30–95.42		27.12	7.14	15.95–41.24	2.20*	0.86
Disposition Index (DI)	141.56	72.78	61.33–280.66		329.08	179.76	156.08–758.42	–3.63**	–1.42

Table 2 – D2R BP_{ND} Does Not Relate to Reward Discounting

		PRD (AUC)	DRD (AUC)
COMBINED OBESE AND NORMAL (N=24)			
	PRD (AUC)		*r=0*.03; *p*=0.89
	DRD (AUC)	*r=0*.03; *p=0*.89	
	Putamen D2R BP_{ND}	*r*=–0.08; *p*=0.74	*r*=–0.29; *p*=0.22
	Caudate D2R BP_{ND}	*r*=0.18; *p*=0.45	*r*=–0.20; *p*=0.42
	Nucleus Accumbens D2R BP_{ND}	*r*=0.07; *p*=0.78	*r*=–0.17; *p*=0.49
OBESE (N=11)			
	PRD (AUC)		*r*=0.10; *p*=0.85
	DRD (AUC)	*r*=0.10; *p*=0.85	
	Putamen D2R BP_{ND}	*r*=0.03; *p*=0.95	*r*=–0.58; *p*=0.29
	Caudate D2R BP_{ND}	*r*=0.07; *p*=0.90	*r*=0.11; *p*=0.83
	Nucleus Accumbens D2R BP_{ND}	*r*=0.11; *p*=0.98	*r*=–0.66; *p*=0.16
NORMAL-WEIGHT (N=13)			
	PRD (AUC)		*r*=–0.28; *p*=0.50
	DRD (AUC)	*r*=–0.28; *p*=0.50	
	Putamen D2R BP_{ND}	*r*=0.19; *p*=0.66	*r*=0.05; *p*=0.91
	Caudate D2R BP_{ND}	*r*=0.61; *p*=0.11	*r*=–0.28; *p*=0.50
	Nucleus Accumbens D2R BP_{ND}	*r*=0.09; *p*=0.83	*r*=0.08; *p*=0.85

Table 3 – D2R BP_{ND} Does Not Relate to Insulin Function

		Disposition Index (DI)
COMBINED OBESE AND NORMAL-WEIGHT (N=26)		
	Putamen D2R BP_{ND}	*r*=–0.20; *p*=0.37
	Caudate D2R BP_{ND}	*r*=0.01; *p*=0.97
	Nucleus Accumbens D2R BP_{ND}	*r*=–0.21; *p*=0.34
OBESE (N=12)		
	Putamen D2R BP_{ND}	*r*=0.37; *p*=0.37
	Caudate D2R BP_{ND}	*r*=0.48; *p*=0.23
	Nucleus Accumbens D2R BP_{ND}	*r*=–0.18; *p*=0.67
NORMAL-WEIGHT (N=14)		
	Putamen D2R BP_{ND}	*r*=–0.39; *p*=0.26
	Caudate D2R BP_{ND}	*r*=–0.13; *p*=0.73
	Nucleus Accumbens D2R B BP_{ND}	*r*=–0.30; *p*=0.39

Figures

Figure 1 – Scatterplot of scaled score residuals (after regressing age, gender, BMI, and education). Greater insulin function related to increased preference for larger, delayed rewards in both normal-weight (solid circles) and obese (open circles) individuals (p<0.025).

Figure 2 – Scatterplot of scaled score residuals (after regressing age, gender, BMI, and education). Greater insulin function related to lower preference for risky rewards in obese participants. Greater insulin function overall (higher DI; Matsuda ISI × Phi Total) related to increased preference for smaller, certain rewards in obese individuals (Figure 2A; Cohen's f^2 = 2.40). Greater insulin sensitivity (higher Matsuda ISI) related to increased preference for smaller, certain rewards in obese individuals (Figure 2B; Cohen's f^2=.81). Beta-cell function (Phi Total) was unrelated to probability discounting (Figure 2C; Cohen's f^2=.65).

Figure 3 – Scatterplot of scaled score residuals (after regressing age, gender, education, and insulin function (DI)). Body mass index (BMI) related to increased preference for larger, riskier rewards in obese individuals (Cohen's f^2=1.57).

Figure 1 – Insulin Function Relates to Delay Reward Discounting in Normal-weight and Obese Participants

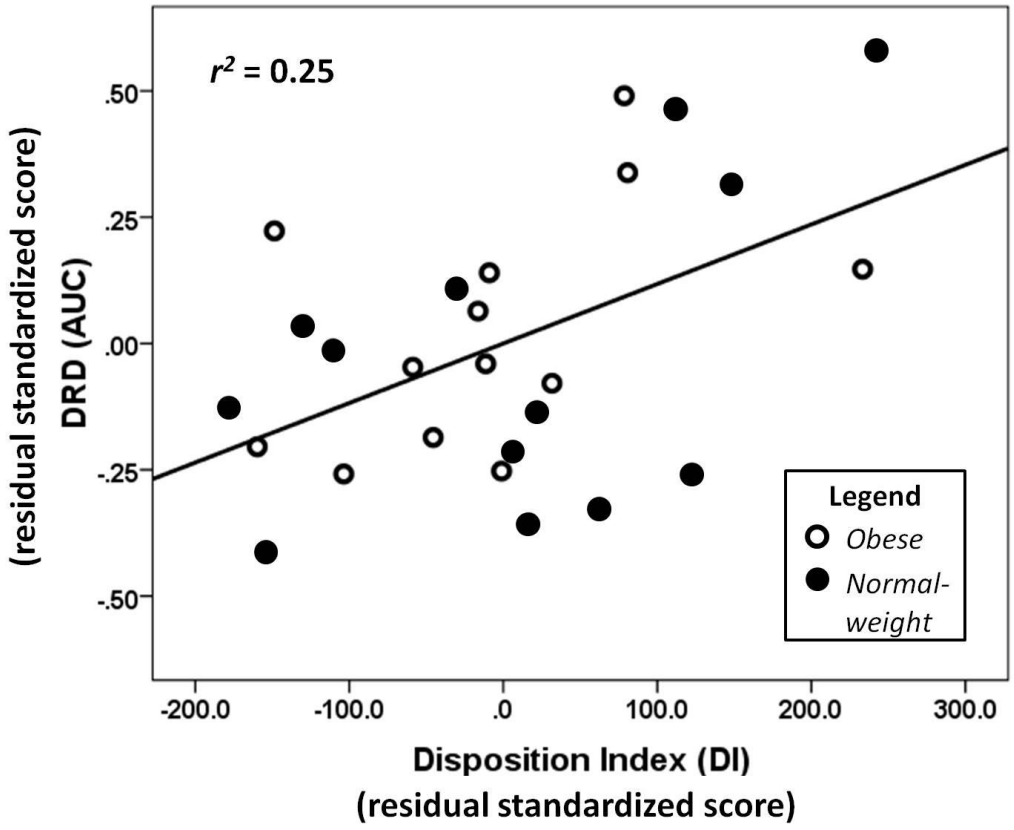
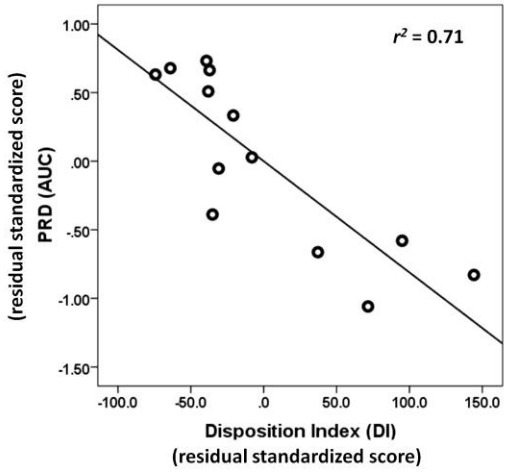
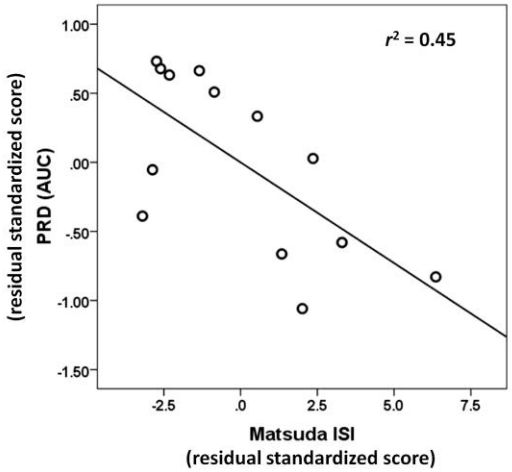


Figure 2 – Insulin Function Relates to Probability Reward Discounting in Obese Participants

A.



B.



C.

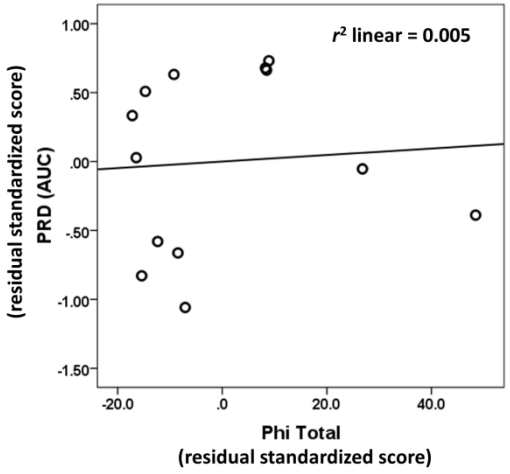


Figure 3 – BMI Relates to Probability Reward Discounting in Obese Participants