fMRI Reactivity to Trial Difficulty on a Delay Discounting Task Predicts Weight Gain in Obese Women

by

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Obesity is a serious public health issue. Obesity may be accompanied by abnormalities in executive function circuitry related to impulsivity. A useful task for studying impulsivity is the delay discounting (DD) of money task, in which an individual chooses in a series of trials between an immediate and a delayed, but greater, amount of money. On the DD task, individuals with various addictions make more immediate than delayed choices, compared to controls. Similar results have been observed in obese compared to healthy-weight women. Functional neuroimaging studies in addicted individuals have found that lower activation in executive function/inhibitory control areas during a cognitive task can serve as a predictor of drug relapse or treatment outcome. In the present study, we used functional neuroimaging during a decision-making task to predict weight gain in obese women. Participants completed a modified version of the DD task while a Siemens Allegra 3 Tesla magnet was used to acquire BOLD-based functional magnetic resonance imaging (fMRI) data. Each participant’s body weight was measured at the fMRI session and in a subsequent lab session 1.3-2.9 years later. fMRI data were analyzed with SPM5 software for executive function regions of interest (ROI) activated in previous fMRI studies of DD (inferior, middle and superior frontal gyri; anterior cingulate cortex; inferior and superior parietal lobules); a whole brain analysis was also done.
Confirming the results of previous fMRI studies, we found that more Hard vs. Easy trials on the DD task produced greater activation in executive function areas of the brain, and that more impulsive individuals had less activation on difficult trials than less impulsive individuals. Most significantly, decreased neural activation in executive function areas (inferior, middle, and superior frontal gyri; inferior parietal lobule) on Hard vs. Easy trials predicted a greater percent of weight gain/year. Our results suggest that impulsivity, a possible risk factor for obesity, may stem from hypoactivation of brain regions mediating executive function. Further research on differences in executive system activation as predictors of weight gain could improve cognitive/behavioral therapies by focusing on approaches that target potentially dysfunctional inhibitory control brain areas.

Keywords: impulsivity, inhibitory control, delay discounting, intertemporal, obesity, BMI
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>vi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>7</td>
</tr>
<tr>
<td>MATERIALS AND METHODS</td>
<td></td>
</tr>
<tr>
<td>- Participants</td>
<td>13</td>
</tr>
<tr>
<td>- Lab Session 1</td>
<td>14</td>
</tr>
<tr>
<td>- Computation of Individual Lab k</td>
<td>15</td>
</tr>
<tr>
<td>- Magnet Session</td>
<td>16</td>
</tr>
<tr>
<td>- Lab Session 2</td>
<td>18</td>
</tr>
<tr>
<td>- MRI Data Acquisition</td>
<td>19</td>
</tr>
<tr>
<td>- fMRI Data Analysis</td>
<td>20</td>
</tr>
<tr>
<td>RESULTS</td>
<td></td>
</tr>
<tr>
<td>- Demographic Characteristics</td>
<td>27</td>
</tr>
<tr>
<td>- Behavioral Data Analysis</td>
<td>27</td>
</tr>
<tr>
<td>- fMRI Results</td>
<td>28</td>
</tr>
<tr>
<td>- fMRI activation related to trial difficulty on a DD task</td>
<td>28</td>
</tr>
<tr>
<td>- Relationship between fMRI activation on Hard &gt; Easy trials and ln(k)</td>
<td>29</td>
</tr>
<tr>
<td>- Relationship between fMRI activation on Hard &gt; Easy trials and Rate of Weight Gain</td>
<td>29</td>
</tr>
<tr>
<td>- Multiple regression analysis of activation on Hard &gt; Easy trials with rate of weight gain and demographic variables</td>
<td>29</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td></td>
</tr>
<tr>
<td>- Behavioral performance related to trial difficulty on a DD task</td>
<td>40</td>
</tr>
<tr>
<td>- fMRI activation related to trial difficulty on a DD task</td>
<td>40</td>
</tr>
<tr>
<td>- Impulsivity, measured by ln(k), as a predictor of fMRI activation in executive function areas on more difficult trials</td>
<td>41</td>
</tr>
</tbody>
</table>
fMRI activation on Hard > Easy trials as a predictor of %Gain/year................42
Impulsivity, executive dysfunction, and obesity...........................................43
Caveats........................................................................................................45

CONCLUSIONS ..........................................................................................47

LIST OF REFERENCES ..............................................................................49

APPENDICES

A  IRB Approval..........................................................................................58
<table>
<thead>
<tr>
<th>Tables</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Demographic characteristics and assessments of female participants</td>
<td>24</td>
</tr>
<tr>
<td>(n=21)</td>
<td></td>
</tr>
<tr>
<td>2  Correlations between ln(k) and participant demographic characteristics and assessments (n=21)</td>
<td>31</td>
</tr>
<tr>
<td>3  BOLD activation on Hard &gt; Easy trials in executive function areas</td>
<td>32</td>
</tr>
<tr>
<td>(n=21)</td>
<td></td>
</tr>
<tr>
<td>4  Significant negative correlations between Hard &gt; Easy activation and ln(k) (n=21)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5  Significant negative correlations between Hard &gt; Easy activation and rate of weight gain, between first and second weighings</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Illustration of DD task paradigm</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Trial Difficulty on a DD task as a function of implied-k</td>
<td>26</td>
</tr>
<tr>
<td>3A</td>
<td>Reaction time as a function of implied k (n=21)</td>
<td>35</td>
</tr>
<tr>
<td>3B</td>
<td>%Now choices as a function of implied k (n=21)</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>Greater activation on Hard &gt; Easy trials in the IFG and MFG</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>Less impulsive participants showed greater activation on Hard &gt; Easy trials in IPL, MFG, and ACC</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>Greater activation on Hard &gt; Easy trials in MFG, IFG, and IPL correlated negatively with %Gain/year in obese women</td>
<td>39</td>
</tr>
</tbody>
</table>
INTRODUCTION

The increasing prevalence of obesity and the fact that it is a major contributing risk factor for a variety of illnesses has pushed the issue of obesity to the forefront of healthcare concerns, with the CDC ranking obesity as the number one health threat facing America (Mokdad, 2004). Obesity currently ranks as the second leading cause of preventable death in the United States, killing 400,000 individuals annually at a cost of $122.9 billion (Mokdad, 2004; NIH, 2008). There have been a few longitudinal studies of weight trajectory in obese individuals, with mixed findings (Savage et al., 2009; Berset et al., 2011). Given that obesity has a complex and multifaceted etiology, research into potential risk factors and predictors of continued weight gain in obesity would be beneficial.

Recently, Volkow and others have made useful parallels between obesity and addiction (Wang et al., 2004; Volkow & Wise, 2005; Volkow et al., 2008). Current models suggest that addiction is accompanied by deficits in executive function (e.g., Volkow et al., 2004) and abnormalities in brain circuits involving executive function, specifically in brain areas mediating decision-making or in the control of impulsive behavior, such as the prefrontal cortex (PFC), anterior cingulate cortex (ACC), superior parietal lobule (SPL), and inferior parietal lobule (IPL) (Passingham, 1993; Gazzaniga et al., 2002; Volkow et al., 2004; Seeley et al., 2007). In the addicted state, the salience of the substance of abuse (alcohol, tobacco, or illicit substance) overcomes the normal inhibitory response. Without this inhibitory control of the drive to seek drugs, a positive feedback system is established, where consumption of the addictive substance leads to
increased saliency, increased activation of the reward pathway, and the need to continuously use the addictive substance (Volkow et al., 2004).

Similarly, cognitive impairments have been found in obese as compared to normal-weight adults, specifically with regard to executive function and decision-making processes (Elias et al., 2003; Cournot et al., 2006; Kuo et al., 2006; Li et al., 2008; Cserjési et al., 2009). Obese individuals or those with a higher body mass index (BMI) show more deficits than those with a lower BMI while performing the Iowa Gambling Task, a task that simulates the decision-making process in the weighing of rewards and risks (Davis et al., 2004; Pignatti et al., 2006). Obese women have deficits on a measure of inhibitory control, the Stop-Signal Task, and obese children tend to behave more impulsively than their normal-weight counterparts on a behavioral measure of impulsivity (Sigal & Adler, 1976; Nederkoorn et al., 2006; Braet et al., 2007). Overweight and obese individuals show higher levels of urgency and lack of perseverance, two aspects of impulsivity (Mobbs et al., 2010).

Delay-discounting (DD), a particularly useful task for tapping into the impulsivity aspect of executive function, is the extent to which an individual will discount the value of a future reward as a function of the delay to it. The more distant a future reward is, the more its subjective value decreases in comparison to a smaller, yet immediate, reward. Everyone would choose a large amount of money over a small amount of money. However, if a delay to the larger amount of money is introduced and increased, at some point, some individuals will prefer the smaller reward. The individual’s subjective value of the larger amount of money has decreased with the introduction of a delay (Mazur, 1987; Bickel et al., 1999; Kirby et al., 1999). The variable $k$ describes an individual’s
discount rate. A higher k indicates a higher rate of discounting. An individual with a higher k discounts the future more steeply than one with a lower k and can be thought of as being more impulsive; thus, k can also be considered as an impulsiveness parameter (Madden et al., 2003).

There are established links between higher rates of DD and high alcohol consumption, smoking, opiate dependence, various other substance use disorders, gambling, and ADHD (Madden et al., 1997; Vuchinich & Simpson, 1998; Bickel et al., 1999; Kirby et al., 1999; Mitchell, 1999; Barkley et al., 2001; Bickel & Marsh, 2001; Monterosso et al., 2001; Steinberg et al., 2009). For example, Kirby et al. (1999) found that heroin addicts discounted more steeply than control patients and their discount rates were positively correlated with impulsivity. Vuchinich and Simpson (1998) used a DD task with hypothetical rewards to show a relationship between the severity of alcohol abuse and impulsiveness; college students who were identified as heavy drinkers had significantly higher discount rates, meaning that they were more impulsive, than light drinkers. Reynolds et al. (2004) found that adult smokers discounted more and were more impulsive than non-smokers. Studies building on previously established parallels between addiction and obesity (e.g., Volkow et al., 2004) found that obese women displayed higher rates of impulsivity on a DD task than non-obese women who did not differ in age, household income, or IQ (Weller et al., 2008), and that higher percent body fat was related to more impulsive performance on a DD task (Rasmussen et al., 2010). Impulsivity on a DD task was found to be a moderating factor between the relative reinforcing value of food and food intake in non-obese and obese women (Rollins et al., 2010; Applehans et al., 2011).
Several papers have used neuroimaging to suggest associations between obesity and deficits in brain regions mediating executive function. Hypoactivation of the right PFC in obese individuals has been proposed as an explanation for overall poorer cognitive control of food intake (Alonso-Alonso & Pascual-Leone, 2007). Individuals with a higher BMI are more likely to have smaller brain volumes and structural brain abnormalities in executive function areas such as the middle frontal gyrus (MFG) (Pannacciulli et al., 2006; Gunstad et al., 2008; Taki et al., 2008). As BMI increases in otherwise healthy adults, a negative correlation between PFC and cingulate gyrus glucose metabolism emerges (Volkow et al., 2009).

Previous findings have established the validity of using fMRI to examine the neural pathways that are involved in delay discounting and decision-making (e.g., Monterosso et al., 2007; Bickel et al., 2009; Pine et al., 2009; Marco-Pallarés et al., 2010; Sripada et al., 2010). More difficult choices on the DD task produced greater brain activation than easier choices in executive function areas such as the prefrontal and parietal cortex than easier choices (McClure et al., 2004; Pine et al., 2009; Marco-Pallarés et al., 2010). Compared to normal individuals, methamphetamine-dependent individuals were more impulsive and showed decreased activation in areas previously reported as executive function areas during difficult DD trials (Monterosso et al., 2007; Hoffman et al., 2008). Sober alcoholics showed reduced lateral orbitofrontal cortex (OFC, which overlaps with part of the IFG) activation on later trials compared to non-alcoholics (Boettiger et al., 2007). There have been no fMRI studies of DD in obese individuals.
Another use of fMRI studies of decision-making has been to use activation during a cognitive task to predict treatment response or future abstinence in addicts, but such studies have been relatively limited. Activation in the posterior cingulate, temporal cortex, and right insular cortex during a decision-making task predicted relapse in methamphetamine-dependent individuals (Paulus et. al, 2005). For cocaine-dependent individuals performing a Stroop task, a task involving inhibitory control of a prepotent response, pretreatment brain activation in the ventromedial prefrontal cortex (VMPFC), posterior cingulate, and putamen was positively correlated with duration of subsequent abstinence (Brewer et al., 2008).

There have been no fMRI studies in obese individuals examining how the neural bases of decision-making or inhibitory control might relate to weight change. There is considerable variability among adults in weight change over time, with the average (non-obese) adult female gaining about 1.3 lbs per year (Mozaffarian et al., 2011). In addition, most overweight individuals who lose weight tend to regain it (Kramer et al., 1989; Wadden et al., 1989; Jeffery et al., 2000). Certain behavioral and demographic characteristics have been found to be correlated with subsequent weight gain. For example, stress, initial BMI, smoking, ethnicity, diet quality, disinhibition, cognitive restraint, and physical activity are associated with weight change (Williamson et al., 1993; Sherwood et al., 2000; Savage et al., 2009; Berset et al., 2010; Kimokoti et al., 2010). In the present study, we used longitudinal weight measurements to examine whether neural activation during Hard vs. Easy trials of a DD task could predict weight gain. In addition, we used a multiple regression analysis to determine whether prediction of weight gain by brain activation was independent of possible confounding variables.
Thus, previous studies have shown that greater impulsivity is associated with obesity and is predictive of weight gain. Also, individual differences in impulsivity are related to differences in activation of executive function areas during DD tasks. However, no previous studies have explored the relationships among brain activation during such tasks, impulsivity, and weight gain. In the present study, fMRI data were collected during performance of a DD task by a sample of obese women, who were weighted on the day of the scan and at a subsequent time. We hypothesized (1) that greater impulsivity, as indexed by k, would predict greater subsequent weight gain; (2) that obese women with higher impulsivity, as indexed by the DD parameter k, would show less neural activation in executive function regions during Hard vs. Easy DD trials than those with less impulsivity, similar to results found in those with drug or alcohol addictions; and (3) greater activation in executive function areas on Hard > Easy trials would be negatively correlated with subsequent weight gain, independent of any of the assessed demographic characteristics.
MATERIALS AND METHODS

Participants

Otherwise healthy obese women (n = 26; mean age ± SD: 32.4 ± 9.8) were recruited using fliers posted around the University of Alabama at Birmingham (UAB) campus and advertisements in the university newspaper. Participants were screened for eligibility by telephone before being sent a consent form. Eligible participants were female, obese (Body Mass Index or BMI > 30 kg/m$^2$), right-handed (Edinburgh Handedness Inventory; Oldfield, 1971), non-smokers, and between the ages of 19-50. Exclusion criteria included: a substance abuse problem or other addictive disorder, use of psychoactive medication such as antidepressants, having been clinically diagnosed as having ADHD, pregnancy, a chronic health condition such as diabetes or past history of a serious medical condition, a history of loss of consciousness greater than 5 min, meeting the full criteria for an eating disorder (Eating Disorder Diagnostic Scale, EDDS; Stice et al., 2000, 2004), a Shipley score < 85 (Zachary, 1986), and evidence of Axis I psychopathology or history of psychosis or active depression. Participants had normal vision or vision correctable with contacts or by plastic eyeglass lenses available at the magnet (± 6 diopters). Safety requirements for scanning in the magnet were that participants have no ferromagnetic material in their body and not be claustrophobic. Finally, participants had to have an upper body width < 22.5” and an upper body girth <
57-58”", the latter two parameters being the limits of the magnet bore used. All procedures were reviewed and approved by the UAB Institutional Review Board for Human Use.

Lab Session 1

After providing informed consent, participants came to the lab where they completed several behavioral assessments that were used for additional screening and later analyses related to the DD task (Table 1). Participants had their height and weight measured to compute their Body Mass Index (BMI), a proxy measure of obesity, and completed questionnaires assessing cognitive ability (estimated using the Shipley Institute of Living Scale, found to predict WAIS full scale IQ scores; Zachary et al., 1986; Zachary, 2000; Weiss & Schell, 1991), handedness (Edinburgh Handedness Inventory; Oldfield, 1971), number of years of education, parental household income (Weller et al., 2008), and the presence of an eating disorder (EDDS; Stice, Telch, & Rizvi, 2000). Participants also completed the Barratt Impulsivity Scale (BIS-11; Patton, Stanford, & Barratt, 1995). The BIS-11 is a widely used self-report scale with three subscales associated with different facets of impulsivity: attention, a deficit in the ability to maintain attention on a stimulus; motor, performing actions without forethought; and non-planning, an emphasis on the present over the future. Because greater impulsivity on the DD task has been shown to be correlated with higher BIS scores (e.g., Crean et al., 2000), younger age, lower income, less education, and lower IQ (Green et al., 1996; Kirby & Maraković, 1996; Reynolds et al., 2006; de Wit et al., 2007; Reimers et al., 2009), we collected these variables to use in a correlation analysis assessing the relationship between these factors and performance on the delay discounting task.
While in the lab, participants completed a modified version of the DD of money task (Kirby et al., 1999) on a PC, consisting of 96 real trials (e.g., $20 now vs. $54 in 94 days) and 12 control trials (e.g., $0 now vs. $0 now). Control trials were included to serve as possible sensorimotor controls during the scanning session and were included in the lab session to familiarize the participants with the task. Each trial was 11 s long, beginning with a fixation cross (+) presented for 2, 4, or 6 s, followed by the two choices, Now and Later, pseudo-randomly presented on the left and right sides of the monitor (Fig. 1). After the participant made a decision, a gray box located under the corresponding choice turned green, indicating the choice had registered.

At the end of the lab session, participants were compensated a predetermined, nominal amount for their participation; in addition, after completing the DD task, each participant randomly selected one of the DD trials and subsequently received half of her choice on that trial after the specified interval. Immediate payments were made in cash; for future payments, participants completed a W-9 form and received a check in the mail.

Computation of Individual Lab \( k \)

Each trial on the lab task consisted of a Now value, Later value, a delay (in days), and an implied \( k \) (imp-\( k \)) value. These values were related to each other using a hyperbolic discounting function (Mazur, 1987), here represented as

\[
\text{Now} = \frac{\text{Later}}{1 + (\text{imp-}k)(\text{Delay})}
\]

There were 8 imp-\( k \) values, ranging from 0.0004 to 0.25. For all trials at a given imp-\( k \) value, the Now and Later choices have equal subjective values for an individual whose
individual k matches the trial imp-k value. On trials with a lower imp-k, those individuals would be more likely to choose the now reward; as the imp-k increases, the individual would be more likely to choose the delayed reward on that trial.

For each participant, we performed a non-linear (i.e., exponential) regression on her percent of now choices (%Now) for each imp-k value regressed on imp-k. Discount rate (k) was defined as the value on the x-axis corresponding to a predicted value of 50% for %Now. Determining the subject specific k allowed us to administer tailored versions of the DD task in the magnet session. Because k values are not normally distributed, data analyses were performed using the natural log transformation, ln(k) (Hoffman et al., 2008; Monterosso et al., 2007; Epstein et al., 2010).

Participants were excluded from being used in the magnet portion of the study if it became evident they did not understand the task, were not paying attention, resorted to using a rule as opposed to assessing each trial independently; e.g., always choosing the Now choice if the delay was larger than 14 days, or if their k was too low (< 0.0017) or too high (> .18) for us to select one of the available magnet versions of the task.

Magnet Session

Since some studies have found that menstrual cycle phase can modulate reward or executive function (e.g., Dreher et al., 2006; Jacobs & D’Esposito, 2011), all women were scanned while in the follicular phase of their menstrual cycle. At the magnet session, the participants completed a magnet safety questionnaire, reviewed the directions for the task, and had their weight recorded.
Each participant received one of ten modified versions of the DD task in the scanning session. Each version of the DD task consisted of 160 trials, divided into four 7:24 minute runs of 40 trials each, of which 120 trials were real (e.g., $20 now vs. $54 in 94 days) and 40 were sensorimotor controls (e.g., $0 now vs. $0 now). Across all of the available DD tasks, monetary amounts ranged from $0.37 - $78 for Now choices and from $29 - $86 for Later choices. Delays ranged from 1 - 116 days. The 120 real trials comprised five imp-k values. The lowest and highest imp-k categories, k1 & k5, respectively, represented trials intended to be easy for that person (large differences in subjective value between the Now and Later choices); e.g., $35 now vs. $37 in 58 days (k1); or $20 now vs. $50 in 1 day (k5) (Figure 2). Trials with intermediate imp-k values, k2-k4, were more difficult (similar subjective values of the Now and Later choices); e.g., $25 now vs. $47 in 17 days (k3). For each participant, the imp-k values spanned a range from well below to well above that person’s lab k. If k3, or the target k, of a task closely matched an individual’s k, the individual would be predicted to make an approximately equal number of Now and Later choices. For the magnet session, each participant was assigned a version of the task such that the target k closely matched the individual’s lab k.

Obtaining useful data from a subject was dependent on her performance on the magnet DD task being consistent with her performance on the lab version of the DD task. Each participant’s ratio of Now to Later choices during the first run of the DD task was calculated. If a participant appeared to have changed her level of impulsivity such that the individualized DD task was inappropriate for her (i.e., substantially different numbers of Now vs. Later choices), we switched to a different DD task with a target k just slightly
higher or lower; e.g., if a participant was making significantly more Now than Later choices, then after the first block of trials, we shifted to the task with the next highest target k to encourage her to make more Later choices. In the reverse situation, we would shift to a task with a lower target k, on which the participant would be expected to make more immediate choices. This was to ensure that the administered task accurately reflected the subject’s k. Each participant’s magnet k was calculated using non-linear regression on her percent of Now choices (%Now) regressed on the corresponding imp-k, as was done for the lab session calculations.

If a participant’s choices when graphed showed %Now to be a monotonically decreasing function of imp-k, then her responses were considered as being consistent and usable for data analysis. If a participant was inconsistent in her responses, did not complete all runs of the task, was later determined to have used a rule to answer all of the trials, or was apparently not paying attention, then her data were not used for analysis.

Participants were compensated a predetermined, nominal amount for their participation; in addition, after completing the DD task, each participant randomly selected one of the DD trials and subsequently received her choice on that trial. Immediate payments were made in cash, whereas future payments were made as described previously.

Lab Session 2

Because obtaining a second weight measurement was not an original goal of the fMRI study, participants were re-consented before returning for a final lab session where their body weights were recorded. Rate of weight gain per year (%Gain/year) was
computed for each participant. This post-hoc design feature resulted in a variable interval between the first and second weight assessments, ranging from 15.6 – 34.8 mos. Participants were paid an additional small amount for this last visit.

MRI Data Acquisition

Structural and functional data were collected from each participant using a Siemens Allegra 3-Tesla head-only magnet with an 8-channel T-R head coil, housed in UAB’s Civitan International Research Center. Each imaging session consisted of the following scans: a) scout (3-plane localizer scan); b) fMRI scans of blood oxygen level-dependent (BOLD) activation while the participant performed the DD task, and a c) 3-D high-resolution anatomical scan. The latter was used to ensure that each participant’s brain was neurologically normal. Head motion was restricted using memory foam inserts placed inside the head coil. Functional MR images were acquired using single-shot T2*-weighted echo-planar imaging (EPI) with BOLD contrast [echo time (TE) = 30 ms; repetition time (TR) = 2.2 s; flip angle = 70°]. We acquired 30 axial-oblique slices 4 mm thick (interleaved) with a 1 mm gap, at a scan resolution of 64 x 64, reconstructed to 128 x 128, and 240 x 240 x 149 mm FOV. The high-resolution structural scan was acquired using a sagittal T1-weighted image with magnetization-prepared rapid gradient echo (MP-RAGE) [160 slices; 1 mm thick; T1 = 1.1 s; TR = 2.3 s, TE = 3.93 ms, flip angle = 12°, and 256 x 256 x 160 mm FOV].

The stimuli were presented via a computer running E-prime software (Psychology Software Tools, Pittsburgh, PA) interfaced with an IFIS-SA (Integrated Functional Imaging System) visual display to project the visual stimuli to the participant via a rear-
projecting mirror mounted on the head coil. Button pushes were recorded using MRI-compatible button pads.

fMRI Data Analysis

The fMRI data were preprocessed and analyzed using the SPM5 software package (Wellcome Dept. Imaging Neuroscience, London, UK), run within Matlab (7.3; Mathworks, Inc.). The functional DICOM images were converted into Analyze format (.img, .hdr files). Preprocessing followed conventional procedures: 1) slice time-correction to the onset of the 15th slice (middle slice); and 2) spatial realignment using INRIAlign, a motion correction algorithm unbiased by local signal changes (Freire et al., 2002). This realignment produced a mean functional image for each of the four runs and matched it to the EPI template provided in SPM5. Additional steps consisted of: 3) spatial normalization to standard Montreal Neurologic Institute (MNI) brain space; 4) spatial smoothing using a three-dimensional Gaussian kernel of 6 mm full-width at half-maximum (FWHM), resulting in a resampled in-plane resolution of $2 \times 2 \times 2$ mm$^3$ voxels; and 5) high-pass filtering with a cut-off of 128 s to remove low-frequency artifacts or drifts in signal, as well as temporal filtering using an autoregressive (AR(1)) model. Functional data from a participant were not used if they failed to meet the movement inclusionary criteria, which were that within-run movement before correction did not exceed 2 mm in translational movement and 2° in rotational movement.

Statistical analyses were performed at the individual and group levels using General Linear Model (GLM) and Gaussian random field theory, as implemented in SPM5. Single-subject contrast maps were generated within the context of the GLM on a
voxel by voxel basis, modeling the time course of brain activation with the onset for each trial set at 500 ms before the button push.

At the first level, activation was computed for each individual subject on Hard > Easy trials by convolving the time course of activation, using a boxcar function, with the canonical hemodynamic response function (HRF). For the Hard > Easy trial contrast, trial difficulty was defined based on the imp-k for that trial; e.g., k1 and k5 trials were easy and k2 - k4 were difficult trials. This would test if the DD task were tapping into executive function by identifying regions activated more by difficult trials.

In order to further validate our DD analysis using imp-k as a measure of trial difficulty, we also calculated the percent of now choices (%Now) and reaction time (RT) for Hard and Easy trials. Greater trial difficulty should correspond to %Now choices close to 50%. Reaction time was defined as the period from presentation of the two choices to the button push, with larger RT’s expected to indicate more difficult trials.

Second level (group) analyses were performed using a random-effects model of the beta images from the single-subject contrast maps. The contrast maps were smoothed prior to analysis with a three-dimensional Gaussian kernel of 6 mm FWHM, achieving a smoothing of 6.83 mm FWHM at the second level. Our first group analysis examined activation in response to Hard > Easy trials. The next analysis used the basic Hard > Easy contrast, adding ln(k) as a regressor in order to investigate whether activity in executive function areas was related to impulsivity in our sample. In order to see whether patterns of activation were related to weight gain, we performed another group level fMRI analysis of Hard > Easy with rate of weight change (% Gain/year) as a regressor, and the duration between the fMRI session and the later recording of weight added to the model.
as a second regressor. This latter variable was included because of our observation of an association between rate of weight gain and interval duration.

Statistical parametric maps were derived from the resulting t value associated with each voxel and superimposed on SPM’s normalized T1-weighted images. Using cluster-level inference, cluster size was defined as the number of contiguous voxels with $p < .01$ (uncorrected). The cluster size threshold was defined within SPM5 on the basis of Gaussian random field theory to maintain the family wise error rate (FWE) = 0.05.

fMRI data were analyzed using a region of interest (ROI) analysis and whole-brain analysis. Performing an ROI analysis allowed us to address our *a priori* hypothesis and improve statistical power; the executive ROI’s selected were executive system structures that were expected to be more activated by difficult choices; i.e., anterior cingulate cortex (ACC), inferior parietal lobule (IPL), superior parietal lobule (SPL), inferior frontal gyrus (IFG), middle frontal gyrus (MFG), and superior frontal gyrus (SFG) (Boettiger et al., 2007; Monterosso et al., 2007; Hoffman et al., 2008; Pine et al., 2009; Marco-Pallares et al., 2010; Sripada et al., 2010). The ROI’s were defined structurally by applying either the AAL or Talairach Daemon atlases using templates from the WFU Pickatlas toolbox within SPM5 (Lancaster et al., 2000; Maidjian et al., 2004); the IFG, MFG, and SFG ROI’s excluded the motor cortex (Brodmann areas 4 and 6).

Finally, a modified version of the previous multiple regression analysis was performed to investigate whether a correlation existed between the rate of weight gain (with interval duration accounted for in the model) and fMRI activation on Hard > Easy trials (using the eigenvalues for the peak voxel within each significant cluster)
independent of impulsivity and other participant variables such as ethnicity, age, BMI, IQ, income, education, and BIS subscale scores. Thus, each analysis incorporated rate of weight gain interval and one of these subject variables.
Table 1

*Demographic characteristics and assessments of female participants (n = 21)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian; African American</td>
<td>11 (52%); 10 (48%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.4 ± 9.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.8 ± 2.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IQ</td>
<td>107.8 ± 8.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Initial Weight (lbs)</td>
<td>211.0 ± 26.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Initial BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>32.7 ± 3.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parental Annual Income ($)</td>
<td>34,610&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>k</td>
<td>0.004; 0.007; 0.020&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>BIS - Attention</td>
<td>16.0 ± 4.3&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>BIS - Motor Impulsivity</td>
<td>21.0 ± 5.7&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>BIS - Lack of Planning</td>
<td>23.0 ± 3.9&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean ± Standard Deviation  
<sup>b</sup> Median  
<sup>c</sup> 25<sup>th</sup> Percentile; Median; 75<sup>th</sup> Percentile  
<sup>d</sup> Mean ± Standard Deviation; n = 20  
<sup>e</sup> Mean ± Standard Deviation; n = 19
Figure 1. Illustration of DD task paradigm.

Illustration of DD task paradigm used in the present study. Each 11 s trial began with a fixation cross presented for 2, 4, or 6 s. The participant’s choice, made by left or right hand button push, caused the gray box under each choice to turn green.
Figure 2. Trial difficulty on a DD task as a function of implied-$k$.

<table>
<thead>
<tr>
<th>Easy (~100% Now)</th>
<th>Difficult (~50% Now, ~50% Later)</th>
<th>Easy (~100% Later)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k1</td>
<td>k2</td>
<td>k3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>k4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>k5</td>
</tr>
</tbody>
</table>
RESULTS

Demographic Characteristics

Of the 26 participants run in the magnet, useful data were obtained for n = 21 (Table 1). Data from five other participants were not used either because the participant provided inconsistent responses on the DD trials, appeared to use a mental shortcut or rule, had too much head movement, or because of data artifacts. Three of the 21 usable participants failed to appear for the final lab session to have their weight recorded and were excluded from the final analyses involving rate of weight change. Participant weight change ranged from a loss of 28.4 lbs to a gain of 26.9 lbs. Rate of weight gain was converted to percent gain per year (%Gain/year).

Behavioral Data Analysis

Pearson correlational analyses between the participant’s magnet ln(k) and demographic variables and assessments revealed that ln(k) was negatively correlated with age and education (Table 2). Magnet ln(k) was positively correlated with the lab-derived ln(k), BIS – Attention, and BIS – Motor Impulsivity. The lab-derived ln(k) (but not magnet-derived ln(k)) had a negative correlation with the Total Shipley IQ score, as well as its two subscales. Neither the lab nor magnet derived ln(k)’s correlated significantly with weight change, BMI, income, ethnicity, or BIS – Non-Planning (Table 2). Weight
gain did not significantly correlate with any of the other variables for which data were collected.

Our first goal was to validate our use of imp-k in the DD task behaviorally by demonstrating that trial difficulty could be accurately defined based on the percent of Now choices (%Now) or by reaction time (RT); e.g., harder trials corresponded to longer RT’s and a %Now closer to 50%. We found that RT and %Now did provide convergent measures of task difficulty. The mean RT for the hard trials, k2-k4 (2.54 s), was significantly longer than the mean RT for easy trials, k1 (2.19 s; \( t[20] = 5.50, p < .0005 \)) and k5 (2.1 s; \( t[20] = 5.60, p < .0005 \)) (Figure 3A). The %Now choices for hard trials, k2 - k4 (40.8%), was significantly different than the %Now choices for the easier k1 (86.6%; \( t[20] = 6.52, p < .0005 \)) and k5 trials (6.39%; \( t[20] = 8.29, p < .0005 \)), consistent with what was expected (Figure 3B).

fMRI Results

*fMRI activation related to trial difficulty on a DD task*

Results of the first fMRI analysis validated our DD task as tapping into areas of the brain previously shown to be involved in executive function. Choices that were more difficult produced greater activation than easy choices in the executive function ROI’s, as had been found previously (McClure et al., 2004; Pine et al., 2009; Marco-Pallares et al., 2010). ROI analysis showed greater activation on Hard > Easy trials in the IFG and MFG; the whole-brain analysis found additional activation in the dorsal cingulate gyrus, extending into medial prefrontal cortex (PFC) (Table 3, Figure 4).
**Relationship between fMRI activation on Hard > Easy trials and ln(k)**

A multiple regression analysis showed that level of impulsivity was associated with neural activation, revealing a negative correlation between ln(k) and activation in executive function areas (Table 4). Brain areas that showed significantly less activation on Hard vs. Easy trials in more impulsive participants; i.e., those with a smaller negative value of ln(k), were the ROI’s IFG, MFG, and IPL (Figure 5). Activation in the ACC was significant using a voxel-level FDR corrected p. Whole-brain analysis showed activation in additional areas: the precuneus, superior temporal gyrus, precentral gyrus, and posterior cingulate cortex.

**Relationship between fMRI activation on Hard > Easy trials and Rate of Weight Gain**

Patterns of neural activation during Hard > Easy trials were found to negatively correlate with rate of weight gain in a multiple regression model in which activation was predicted by %Gain/year and interval duration. As shown in Table 5, ROI analysis revealed a negative correlation between %Gain/year and activation within the IFG (Figure 6). Additional whole brain analysis revealed negative correlations between rate of weight change and activation in MFG, SFG, and IPL (Figure 6). That is, individuals displaying less activation on Hard trials gained more weight than those displaying greater activation.
Multiple regression analysis of activation on Hard > Easy trials with rate of weight gain and demographic variables

The correlations between rate of weight gain and activation in executive function areas were still significant when individual participant variables such as IQ, ethnicity, income, age, and education were added to the multiple regression model described in the previous section. Thus, for every one of these ROI’s, there was a relationship between rate of weight gain and Hard > Easy activation independent of any of the participant variables (Table 5).
Table 2

*Correlations between ln(k) and participant demographic characteristics and assessments (n = 21)*

<table>
<thead>
<tr>
<th></th>
<th>Magnet ln(k)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab ln(k)</td>
<td>0.704</td>
</tr>
<tr>
<td>Age</td>
<td>-0.604 (p = 0.008)*</td>
</tr>
<tr>
<td>IQ</td>
<td>-0.258*b</td>
</tr>
<tr>
<td>Education</td>
<td>-0.561 (p = 0.008)*</td>
</tr>
<tr>
<td>Parental Income</td>
<td>-0.209</td>
</tr>
<tr>
<td>BIS – Attention</td>
<td>0.581 (p = 0.007)*</td>
</tr>
<tr>
<td>BIS – Motor Impulsivity</td>
<td>0.574 (p = 0.008)*</td>
</tr>
<tr>
<td>BIS – Non-planning</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI</td>
<td>0.021</td>
</tr>
<tr>
<td>%Weight Gain/year</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*a r_{crit}(19) = 0.43

*b Significant correlation, p < 0.05

*b Correlation significant with lab-derived ln(k) r = -0.66, p = 0.001
Table 3

**BOLD activation on Hard > Easy trials in executive function areas (n = 21)**

<table>
<thead>
<tr>
<th>Executive ROI Analysis</th>
<th>BA</th>
<th>Hem</th>
<th>Cluster</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>p, FWE corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>9</td>
<td>L</td>
<td>124</td>
<td>-50</td>
<td>6</td>
<td>34</td>
<td>3.83</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-42</td>
<td>0</td>
<td>36</td>
<td>3.75</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-36</td>
<td>4</td>
<td>30</td>
<td>3.67</td>
<td>0.014</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>R</td>
<td></td>
<td>184</td>
<td>48</td>
<td>32</td>
<td>26</td>
<td>4.19</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>34</td>
<td>32</td>
<td>3.92</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>32</td>
<td>24</td>
<td>3.82</td>
<td>0.003</td>
</tr>
<tr>
<td>Whole Brain Analysis</td>
<td>BA</td>
<td>Hem</td>
<td>Cluster</td>
<td>x</td>
<td>y</td>
<td>z</td>
<td>t</td>
<td>p, FWE corrected</td>
</tr>
<tr>
<td>Cingulate Gyrus</td>
<td>L</td>
<td></td>
<td>733</td>
<td>-12</td>
<td>12</td>
<td>46</td>
<td>5.49</td>
<td>4.8 x 10^{-5}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-8</td>
<td>4</td>
<td>-18</td>
<td>5.15</td>
<td>4.8 x 10^{-8}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-12</td>
<td>18</td>
<td>32</td>
<td>4.41</td>
<td>4.8 x 10^{-8}</td>
</tr>
</tbody>
</table>


a Brodmann Area  
b Hemisphere: R, right, L, left  
c Cluster size; number of contiguous voxels with p < 0.01  
d x, y, and z coordinates in MNI space  
e Family-wise error corrected at the cluster level  

If an area was found to be activated in both the whole-brain and ROI analysis, it was reported only in the ROI analysis portion of the table.
Table 4

*Significant negative correlations between Hard > Easy activation and ln(k) (n = 21)*

<table>
<thead>
<tr>
<th>Executive ROI Analysis</th>
<th>BA</th>
<th>Hem</th>
<th>Cluster</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>p, FWE corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior Frontal Gyrus</td>
<td></td>
<td>L</td>
<td>140</td>
<td>-48</td>
<td>44</td>
<td>6</td>
<td>4.58</td>
<td>0.008</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>9</td>
<td>R</td>
<td>261</td>
<td>32</td>
<td>24</td>
<td>40</td>
<td>5.65</td>
<td>0.000028</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>L</td>
<td>581</td>
<td>-46</td>
<td>24</td>
<td>44</td>
<td>5.60</td>
<td>0.0000001</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>R</td>
<td>247</td>
<td>40</td>
<td>-52</td>
<td>50</td>
<td>5.49</td>
<td>0.00017</td>
</tr>
<tr>
<td>Anterior Cingulate Cortex</td>
<td></td>
<td>R</td>
<td>53</td>
<td>8</td>
<td>26</td>
<td>20</td>
<td>5.14</td>
<td>0.093a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Whole Brain Analysis</th>
<th>BA</th>
<th>Hem</th>
<th>Cluster</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>p, FWE corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precuneus</td>
<td></td>
<td>L</td>
<td>446</td>
<td>0</td>
<td>-60</td>
<td>46</td>
<td>5.95</td>
<td>0.000025</td>
</tr>
<tr>
<td>Posterior Cingulate Cortex</td>
<td>31</td>
<td>L</td>
<td>211</td>
<td>-6</td>
<td>-30</td>
<td>40</td>
<td>4.51</td>
<td>0.014</td>
</tr>
<tr>
<td>Superior Temporal Gyrus</td>
<td></td>
<td>R</td>
<td>565</td>
<td>44</td>
<td>-54</td>
<td>18</td>
<td>5.15</td>
<td>0.0000016</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
<td></td>
<td>R</td>
<td>227</td>
<td>18</td>
<td>-24</td>
<td>65</td>
<td>4.67</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*a voxel-level FDR corrected, p = 0.031
Other conventions as in Table 3*
Table 5

**Significant negative correlations between Hard > Easy activation and rate of weight gain, between first and second weighings**

<table>
<thead>
<tr>
<th>Executive ROI Analysis</th>
<th>BA</th>
<th>Hem</th>
<th>Cluster</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>p, FWE corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior Frontal Gyrus</td>
<td></td>
<td>R</td>
<td>101</td>
<td>48</td>
<td>34</td>
<td>10</td>
<td>3.96</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42</td>
<td>24</td>
<td>12</td>
<td>3.55</td>
<td>0.025</td>
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<td></td>
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<td>46</td>
<td>26</td>
<td>2</td>
<td>2.96</td>
<td>0.025</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td></td>
<td>R</td>
<td>98&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8</td>
<td>18</td>
<td>54</td>
<td>4.33</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>98&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-10</td>
<td>13</td>
<td>54</td>
<td>3.45</td>
<td>0.039</td>
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</table>

<table>
<thead>
<tr>
<th>Whole Brain Analysis</th>
<th>BA</th>
<th>Hem</th>
<th>Cluster</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>p, FWE corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle Frontal Gyrus</td>
<td></td>
<td>R</td>
<td>204</td>
<td>50</td>
<td>38</td>
<td>26</td>
<td>5.89</td>
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<td></td>
<td>R</td>
<td>209</td>
<td>42</td>
<td>18</td>
<td>52</td>
<td>4.61</td>
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<td>24</td>
<td>42</td>
<td>4.38</td>
<td>0.009</td>
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<td></td>
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<td></td>
<td>32</td>
<td>18</td>
<td>54</td>
<td>3.92</td>
<td>0.009</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td></td>
<td>L</td>
<td>178</td>
<td>-24</td>
<td>60</td>
<td>12</td>
<td>4.06</td>
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<td></td>
<td>666</td>
<td>-30</td>
<td>-66</td>
<td>4.69</td>
<td>5.5 x 10^-8</td>
</tr>
</tbody>
</table>

<sup>a</sup>The multiple regression incorporated rate of weight change and interval between weighings as regressors.

<sup>b</sup> Regions of activation encompassed within the same cluster

Other conventions as in Table 3
Figure 3A. Reaction time as a function of implied k (n = 21).

* p < .05 vs k2 - k4
Figure 3B. %Now choices as a function of implied k (n = 21).

* p < .05 vs k2 - k4
Figure 4. Greater activation on Hard > Easy trials in the IFG and MFG.

Greater activation on Hard > Easy trials in obese women (n = 21) in (A) left inferior frontal gyrus (IFG; coronal view) and (B) right middle frontal gyrus (MFG; sagittal view). Both A and B were identified from ROI analysis. Activation is overlaid on the SPM5 single subject T1 template. The color bar indicates t values.
Figure 5. Less impulsive participants showed greater activation on Hard > Easy trials in IPL, MFG, and ACC.

Greater activation on Hard > Easy trials in less impulsive obese women (n = 21), impulsivity defined by ln(k), in (A) right inferior parietal lobule (IPL; coronal view), (B) bilateral middle frontal gyrus (MFG; coronal view) and (C) right anterior cingulate cortex (ACC; sagittal view). A, B, and C were identified from ROI analysis. Other conventions as in Fig. 4.
Figure 6. Greater activation on Hard > Easy trials in MFG, IFG, and IPL correlated negatively with %Gain/year in obese women.

Greater activation on Hard > Easy trials in MFG, IFG (A, sagittal), and IPL (B, axial) correlated negatively with %Gain/year in obese women (n = 18). A was identified from whole brain analysis and B from ROI analysis. Other conventions as in Fig. 4.
DISCUSSION

Behavioral performance related to trial difficulty on a DD task

The present study investigated BOLD fMRI activation on Hard > Easy trials on a modified DD task, with difficulty defined as a function of trial implied k (imp-k). Behavioral measures of task difficulty, RT and %Now choices, provided convergent measures of trial difficulty on the DD task, validating our definition of trial difficulty based on trial imp-k. Greater impulsivity on the DD task, as defined by ln(k), was negatively correlated with younger age, lower parental income, less education, and lower intelligence, and positively correlated with higher BIS scores, consistent with the results of previous studies (e.g., Crean et al., 2000; Shamosh et al., 2008; Reimers et al., 2009). We found no correlation in our obese sample between impulsivity on the DD task and BMI, as previously reported (e.g., Reimers et al., 2009).

fMRI activation related to trial difficulty on a DD task

Executive function involves many processes, including planning, monitoring and correcting errors, multitasking, switching strategies, and inhibition (Gazzaniga et al., 2002, Roth & Saykin, 2004). Areas of the brain involved in executive function include subdivisions of PFC (IFG, MFG, and SFG), parietal cortex (IPL, SPL) and ACC (Passingham, 1993; Gazzaniga et al., 2002; Volkow et al., 2004; Seeley et al., 2007). Our version of the DD task resulted in greater activation in executive function areas of the
brain such as the IFG and MFG during hard trials, compared to easier trials, mirroring the results of comparable studies in normal or addicted individuals (e.g., McClure et al., 2004; Boettiger et al., 2007; Hoffman et al., 2008; Pine et al., 2009; Marco-Pallares et al., 2010). For example, Hoffman et al. (2008) observed less activation during difficult trials of a DD task in the dorsolateral prefrontal cortex (which would include the MFG), intraparietal sulcus, and anterior cingulate cortex (ACC) in methamphetamine-dependent individuals compared to controls.

Impulsivity, measured by ln(k), as a predictor of fMRI activation in executive function areas on more difficult trials

As hypothesized, greater impulsivity in obese women, as assessed by the discount parameter ln(k), was associated with less activation in the IFG, MFG, IPL, and ACC during Hard vs. Easy trials. Monterosso et al. (2007) found in methamphetamine-dependent individuals that activation in IFG on more difficult trials negatively correlated with impulsivity on a DD task; i.e., more impulsive individuals had decreased IFG activation compared to less impulsive individuals. Decreased activation in ACC, IFG, and MFG was associated with greater impulsivity in methamphetamine-dependent participants and controls on more difficult choices on a DD task (Hoffman et al., 2008). Sober alcoholics with greater impulsivity on a DD task also displayed decreased lateral orbitofrontal cortex (IFG) activation on later choices, compared to controls (Boettiger et al., 2007). Our observed activation in the precuneus and posterior cingulate on Hard > Easy trials as a function of impulsivity also parallels previous findings that impulsivity on
the DD task correlates negatively with activation in these areas in methamphetamine users and controls (Hoffman et al., 2008).

fMRI activation on Hard > Easy trials as a predictor of %Gain/year

The present study found that decreased BOLD activation in IFG, MFG, SFG, and SPL on Hard vs. Easy trials of the DD task predicted a greater rate of weight gain. Functional neuroimaging studies of drug treatment adherence or relapse have found that activation in executive function/inhibitory control areas can serve as predictors of relapse in methamphetamine-dependent individuals (Paulus et al., 2005) and cocaine-dependent individuals (Brewer et al., 2008).

Similar results have been found related to body weight. When presented with images of high-calorie foods, successful dieters, compared to non-dieters, had greater fMRI activation in prefrontal regions implicated in other studies in inhibitory control than currently obese individuals and never-obese healthy controls (McCaffery et al., 2009).

Extrapolating this finding over time would predict more weight gain in such individuals. These results suggest that a sufficiently robust pattern of executive system activation, enhances inhibitory control over the processing of reward value and can predict subsequent weight gain.

Deficits in executive function could be due to poor working memory, which is responsible for maintaining active information and inhibiting interference from competing or irrelevant stimuli. However, Shamosh et al. (2008) found that while intelligence, measured by IQ, and working memory both predicted impulsivity on a DD task, working memory alone did not account for any additional variance in delay
discounting after incorporating IQ in the model. In our study, decreased activation, in areas previously implicated in executive function, for the contrast of Hard vs. Easy DD trials was found to predict rate of weight gain independent of individual differences in subject variables such as IQ, parental income, age, education, and ethnicity; adding these factors to the regression model did not eliminate the statistical relationship between Hard > Easy activation and rate of weight gain.

Impulsivity, executive dysfunction, and obesity

In this longitudinal, prospective study using functional neuroimaging of a cognitive task, we found that lower activation in executive function areas to Hard vs. Easy trials of a DD task predicted greater rate of weight gain in obese women. In addition, we found that more impulsive obese women showed less activation in areas that have been associated with executive function during Hard vs. Easy trials of the DD task.

One interpretation of impulsivity is that inhibition utilizes executive function neural circuitry to a greater extent than does “giving in”. Inhibition is crucial in human behavioral control, since it allows us to suppress automatic, impulsive, or routine behavior, and therefore avoid errors. Our results are consistent with current neural models of addiction and over-eating that suggest that response inhibition by the executive-function areas moderates hedonic reward processing (e.g., Volkow et al., 2008, Applehans et al., 2011). Cues associated with stimuli, such as food, trigger a “wanting” desire in the reward system which is (under some circumstances) ideally overridden by inhibitory control processes in executive function areas. When functioning properly, response inhibition by executive function areas modulates reward-driven behavior,
allowing for healthy weight maintenance (Applehans et al., 2009). Overeating or addiction may result when the reward value of cues overwhelms normal response inhibition (Rollins et al., 2010; Applehans et al., 2011). This is exactly the result found in a recent fMRI study by Hare and colleagues (2009), who studied dieters or “self-controllers” vs. “non-self-controllers.” When the self-controllers had to decide whether to choose for later consumption tasty but unhealthful foods, they had greater activation in dorsolateral prefrontal cortex and, in particular, the left inferior frontal gyrus, during successful than failed self-control trials when they decided to not choose the tasty but unhealthful food. Overweight adolescents displayed reduced activation on a response inhibition task in the SFG, MFG, medial prefrontal cortex, ventrolateral prefrontal cortex, and orbitofrontal cortex compared to non-obese adolescents (Batterink et al., 2010).

The IFG has been implicated in inhibitory control and is especially activated under conditions of increased response competition (Roth & Saykin, 2004). Although some studies have suggested that it is mainly involved in inhibition of motor responses, others have shown that the IFG is also involved in non-motor inhibition and serves in general-purpose inhibition (e.g., Chambers et al., 2007; Swick et al., 2008). Individuals with lesions in the IFG display more impulsive behavior and have difficulty inhibiting attention to extraneous information on working memory tasks (Miller & Cummings, 1999). This is consistent with our finding of decreased activation in the right IFG during difficult vs. easy trials being correlated with increased impulsiveness and greater rate of weight gain.

Another area associated with executive function is the anterior cingulate cortex (ACC). Amongst its many suggested roles, the anterior cingulate has been suggested to
function in inhibitory control over motivation, allocation of attention, mediation of goal-directed behaviors, monitoring conflict between choices, and helping an individual recognize an error committed and reduce future errors (e.g., Allman, Hakeem, & Watson, 2002; Roth & Saykin, 2004; Pochon et al., 2008; Yeung & Nieuwenhuis 2009).

Methamphetamine-dependent individuals showed lower activation in the ACC compared to non-dependent controls on harder trials of a DD task (Monterosso et al., 2007; Hoffman et al., 2008).

Studies have also reported structural brain differences as a function of adiposity. Obese adults had smaller IFG and MFG volumes compared to non-obese individuals (Pannacciulli et al., 2006). Obese adolescents had lower OFC volumes than non-obese adolescents (Maayan et al., 2011). A longitudinal increase in BMI in otherwise healthy women was associated with reduced gray matter volume (Soreca et al., 2010). It is unclear how reduced brain volume found in these areas is related to reduced neural activation, as found in the present study.

Caveats

It is important to note some of the limitations of this study. Because our participants consisted only of obese women, it remains an open question whether our results would be generalizable to the non-obese or to men. Although rate of weight gain was not correlated with any of the demographic variables collected such as IQ, age, or income, it is possible that weight gain was related to variables that we did not examine; e.g., lifestyle factors such as diet and exercise (Van Wye et al., 2007) or genetics (Boettiger et al., 2007). Another limitation of our study is that rate of weight gain might
be related to psychopathology such as depression or ADHD, both of which have a reported comorbidity with obesity (Altfas, 2002; Pagoto et al., 2009, Carpiniello et al., 2009; de Wit et al., 2010) and neither of which was formally assessed in our study. ADHD, in particular, also involves executive dysfunction (Roth & Saykin, 2004) and is related to increased impulsivity on the DD task (Malloy-Diniz et al., 2007). Although we did not formally test for ADHD, during the screening process, participants were asked if they had ever been clinically diagnosed as having ADHD and all participants answered negatively. In addition, a paper comparing adults with ADHD to controls found significantly higher individual BIS subscale (18-21) and total scores (mean = 77) in those with ADHD compared to controls (mean = 59) (Malloy-Diniz et al., 2007), the latter being similar to the BIS total scores of our 18 participants (mean = 60). This suggests that our participants did not have ADHD.
CONCLUSIONS

In summary, this is the first longitudinal, prospective study to use functional neuroimaging during a cognitive task to predict weight gain. The fact that it was done with obese participants will need to be followed up. This study provides supportive evidence for behavioral (Epstein et al., 2010; Applehans et al., 2011) and neurobiological models (Alonso-Alonso & Pascal-Leone, 2007) of cognitive inhibition modulating reward processing.

Weight management or weight loss can be seen as the result of the dominance of inhibitory control over over-eating. Less efficient use of executive system regions may lead to an inability of the executive system to override the hedonic-driven reward system, resulting in relatively more impulsive choices, and, in this study, was a predictor of rate of weight gain. Within the context of obesity, if executive function areas are functioning less efficiently, this could have a significant impact on diet and lifestyle choices, thereby increasing the risk of weight gain and obesity. Further research on cues that trigger reward system activation and differences in executive system activation as predictors of weight gain could improve cognitive/behavioral therapies by enhancing and focusing on approaches that target potentially dysfunctional brain areas involved in inhibition.

As a final comment, it is possible that the observed differences in patterns of neural activation in more impulsive vs. less impulsive individuals on the DD task represent neuroadaptations as a result of weight change, rather than pre-existing risk
factors for obesity, as recent studies have reported changes in brain activity after diet-induced obesity (Val-Laillet et al., 2011) or bariatric weight-loss surgery (Gunstad et al., 2010).
LIST OF REFERENCES


APPENDIX A

IRB Approval
Project Revision/Amendment Form

Form version: October 28, 2019

- Federal regulations require IRB approval before implementing proposed changes. See Section 14 of the IRB Guidebook for investigators for additional information.
- Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator's Brochure, questionnaires, surveys, advertisements, etc.). See item 4 for more examples.

1. Today's Date
   April 15, 2011

2. Principal Investigator (PI)
   Name (with degree): Rosalyn Weller, Ph.D.
   Department: Psychology
   Office Address: 415 Campbell Hall (CH)
   E-mail: reweller@uab.edu
   Blazer ID: rewell
   Division (if applicable): CAS
   Office Phone: 934-8563
   Fax Number: 975-6110
   Contact person who should receive copies of IRB correspondence (Optional):
   Name:
   Phone:
   Office Address (if different from PI):

3. UAB IRB Protocol Identification
   3.1. Protocol Number: F070629010
   3.2. Protocol Title: Functional Brain Imaging Studies of Decision-Making in Obese Women
   3.3. Current Status of Protocol—Check ONE box at left: provide numbers and dates where applicable:
   - Study has not yet begun: No participants, data, or specimens have been entered.
   - In progress, open to accrual: Number of participants, data, or specimens entered: 74
   - Enrollment temporarily suspended by sponsor
   - Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.): Date closed:
   - Number of participants receiving interventions:
   - Number of participants in long-term follow-up only:
   - x Closed to accrual, and only data analysis continues: Date closed: Dec. 31, 2009
   - Total number of participants entered: 74

4. Types of Change
   Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.
   - Protocol revision (change in the IRB-approved protocol)
   - Protocol amendment (addition to the IRB-approved protocol)
   - Add or remove personnel: Address whether new personnel have any conflict of interest. See "Change in Principal Investigator" in the IRB Guidebook if the principal investigator is being changed.
   - Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication: Include applicable name(s) and address whether new personnel have any conflict of interest.
   - Change in source of funding; this change may require a new IRB application.
   - Add or remove performance sites: Include the site and location, and describe the research procedures performed there. Also include copy of subcontract, if applicable. If this protocol includes acting as the Coordinating Center for a study, attach IRB approval from any non-UAB site added.

FOR 224

Page 1 of 3
5. Description and Rationale
In Item 5.a. and 5.b, check Yes or No and see instructions for Yes responses.
In Item 5.c. and 5.d, describe—and explain the reason for—the change(s) noted in Item 4.

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.a. Are any of the participants enrolled as normal, healthy controls?</td>
<td></td>
</tr>
</tbody>
</table>

Yes x No
5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?
If yes, describe in detail in Item 5.c. how this change will affect those participants.

Yes x No
5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol.

Felix Kshirovsky was previously added to my HSP as an undergraduate research assistant Aug. 3, 2007. Felix is now a graduate student working on a master’s thesis in biology and I am his graduate mentor. He will perform secondary data analyses of fMRI data already collected as part of my (current) HSP. The tentative title of his thesis is, “fMRI reactivity to trial difficulty on a delay discounting task in obese women”. He will see whether greater impulsivity on especially more difficult choices on the delay discounting task (difficulty as defined a new way) is correlated with less brain activation in decision-making parts of the brain.

5.d. Consent and Recruitment Changes: In the space below,
(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).

Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
* a copy of the currently approved document (showing the IRB approval stamp, if applicable)
* a revised copy highlighting all proposed changes with “tracked” changes
* a revised copy for the IRB approval stamp.

Signature of Principal Investigator: [Signature]
Date: [Date]
FOR IRB USE ONLY

☐ Received & Noted ☑ Approved Expedited* ☐ To Convened IRB

Signature (Chair, Vice-Chair, Designee) [Signature]

DOLA [Date]

Change to Expedited Category Y / N / NA

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 50.111
Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federal Wide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on September 29, 2013. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: WELLER, ROSALYN E
Co-Investigator(s):
Protocol Number: F070629010
Protocol Title: Functional Brain Imaging Studies of Decision-Making in Obese Women

The IRB reviewed and approved the above named project on 4/6/2011. The review was conducted in accordance with UAB’s Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 4/6/2011

Date IRB Approval Issued: 04-12-11
Identification Number: IRB00000196

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

Ferdinand Wirthaler, M.D.
Chairman of the Institutional Review Board for Human Use (IRB)