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Greater Impulsivity is Associated with Decreased Brain Activation in Obese Women during a Delay Discounting Task

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Abstract

Impulsivity and poor inhibitory control are associated with higher rates of delay discounting (DD) or a greater preference for smaller, more immediate rewards at the expense of larger, but delayed rewards. Of the many functional magnetic resonance imaging (fMRI) studies of DD, few have investigated the correlation between individual differences in DD rate and brain activation related to DD trial difficulty, with difficult DD trials expected to activate putative executive function brain areas involved in impulse control. In the current study, we correlated patterns of brain activation as measured by fMRI during difficult vs. easy trials of a DD task with DD rate (k) in obese women. Difficulty was defined by how much a reward choice deviated from an individual's 'indifference point', or the point where the subjective preference for an immediate and a delayed reward was approximately equivalent. We found that *greater* delay discounting was correlated with *less* modulation of activation in putative executive function brain areas, such as the middle and superior frontal gyri and inferior parietal lobule, in response to difficult compared to easy DD trials. These results support the suggestion that increased impulsivity is associated with deficient functioning of executive function areas of the brain.

Keywords

impulsivity; inhibitory control; executive function; delay discounting; intertemporal

Introduction

Cognitive control, including impulse control, is one of the key aspects of executive function. Maladaptive impulse control, or impulsivity, is a broad concept that includes poor inhibitory control over behavior, lack of planning, hypersensitivity to reward, insensitivity to negative consequences of behavior, and sensation/novelty seeking (Comings and Blum 2000; Dawe et al. 2004; Moeller et al. 2001; Patton et al. 1995; Zuckerman 1996). There are considerable individual differences in impulsivity (Congdon et al. 2012; Logan et al. 1997; Swann et al. 2002), and correlations have been reported between individual differences in impulsivity and differences in brain structure or function in areas thought to mediate executive function (Andrews-Hanna et al. 2011; Diekhof et al. 2011; Forstmann et al. 2008; Horn et al. 2003; Matsuo et al. 2009). In addition, studies have reported correlations between disorders such as addiction and obesity, behavioral measures of impulsivity (e.g., stop-signal, go/no-go, Stroop color-word, Simon, or delay discounting, DD, tasks), and neural measures of

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activation during such tasks (Jentsch and Taylor 1999; MacKillop et al. 2011; Nederkoorn et al. 2006; Norman et al. 2011; Reynolds 2006).

Delay discounting, which involves reward-based decision-making, is an approach for assessing impulsivity (Ainslie 1975; see Peters and Büchel 2011 for other processes associated with DD). Typically, choices are devalued ('discounted') as a function of time ('delay') (Ainslie 1975). DD is commonly assessed by asking individuals to make a series of choices between smaller, immediate rewards and larger, but delayed rewards. Each decision involves a tradeoff between value and time and is influenced by an individual's subjective preferences (Peters and Büchel 2011). Individual differences in choice preference are indexed by the parameter k , which represents the rate at which an individual will discount the subjective value of a reward as a function of temporal delay, with higher k indicating greater delay discounting (Kirby et al. 1999; Mazur 1987; Rachlin et al. 1991) and presumably greater impulsivity (Ainslie 1975).

A number of functional magnetic resonance imaging (fMRI) studies have examined how individual differences in impulsivity are related to patterns of brain activation during DD (Ballard and Knutson 2009; Bickel et al. 2009; Boettiger et al. 2007; Hoffman et al. 2008; Luo et al. 2012; Monterosso et al. 2007; Sripada et al. 2011). Particularly germane to the current study are the few reports looking at the association between impulsivity and brain activation related to DD trial difficulty, with more difficult trials defined as those with greater similarity of the subjective values of immediate and delayed choices; i.e., closer to the indifference point. Executive function would be expected to be more engaged by greater difficulty, and fMRI studies of DD have found that, in general, more difficult choices result in greater brain activation in regions putatively involved in higher level decision-making processes, cognitive control, and other executive functions (Marco-Pallarés et al. 2010; McClure et al. 2004; Meade et al. 2011; Monterosso et al. 2007; Pine et al. 2009). These regions include lateral prefrontal (inferior frontal gyrus, IFG; middle frontal gyrus, MFG; and superior frontal gyrus, SFG), medial prefrontal/anterior cingulate, and posterior parietal cortex. Previous fMRI studies have found correlations between impulsivity and activation related to trial difficulty in such regions. The relevance of relating impulsivity to activation on difficult DD trials is that one cognitive process invoked by more difficult DD trials may be inhibitory control. Selection of a delayed choice on such trials may require inhibitory control of the desire for immediate gratification, or less impulsivity. Reduced activation to difficult vs. easy DD trials might be indicative of executive function inefficiency or dysfunction related to inhibitory control. Previous studies have reported both negative and positive correlations between impulsivity (k) and activation related to trial difficulty in putative executive function regions. These discrepancies could be related to variations in the fMRI contrast, as also suggested by Bickel et al. (2009). In a combined analysis of results from methamphetamine-dependent and control participants, Monterosso and colleagues (2007) found a negative correlation, or that greater impulsivity (higher k) was associated with reduced activation in ventrolateral prefrontal cortex during difficult DD trials vs. no-choice control trials, with difficult DD trials operationally defined as those close to the individual's indifference point. Using a similar definition of difficulty, Hoffman et al. (2008), by contrast, found *positive* correlations in methamphetamine-dependent individuals and controls between k and activation on difficult DD trials vs. non-DD control trials in several areas, including the SFG. In normal participants, Bickel et al. (2009) also found *positive* correlations between k and activation on all DD trials vs. non-DD control trials in several regions, including the MFG.

A better approach may be to assess the difference in brain activation between difficult and easy DD trials (Kishinevsky et al. 2012; Marco-Pallarés et al. 2010; Monterosso et al. 2007), which may demonstrate more specific activation of putative executive function brain areas.

By subtracting out brain activation due to characteristics shared by all trials regardless of difficulty, the remaining brain regions will be those unique to difficult DD trials. Monterosso et al. (2007) found no significant correlations between k and activation to difficult vs. easy DD trials in a whole brain analysis in methamphetamine-dependent and control participants. We recently reported that difficult vs. easy DD trials, with difficult trials defined as those close in subjective value or near the individual's indifference point (for details, see Methods), resulted in fMRI activation in obese women in the IFG, MFG, medial SFG, and medial prefrontal cortex (Kishinevsky et al. 2012). However, we did not examine the correlation between individual differences in k and activation to difficult vs. easy DD trials in that study.

In summary, previous fMRI studies of DD have suggested that more difficult trials activate putative executive function brain regions and that the pattern of activation is modulated by individual differences in impulsivity, although it is unclear whether increased impulsivity is associated with increased or decreased brain activation in response to difficult trials. However, the only prior fMRI study to relate individual differences in impulsivity, as measured by k , to activation to difficult vs. easy DD trials, a comparison that would be expected to most specifically activate brain areas involved in executive function, found no significant correlations (Monterosso et al. 2007). In the present study, we analyzed fMRI data collected during performance of a DD task by a sample of obese women used in a longitudinal study to predict weight gain (see Kishinevsky et al. 2012). Obese women were the target of our prior fMRI study because of our previous behavioral findings that obese women had a greater delay discounting rate compared to non-obese women who did not differ in age, household income, or IQ (Weller et al. 2008; see also Fields et al. 2011; Rasmussen et al. 2010). However, in spite of the significant group differences we found in our behavioral DD study, results among the obese women were highly variable. Many exhibited discount rates similar to those of normal-weight women, while others had much higher rates (Weller et al. 2008, unpublished observations). This variability motivated us to investigate the neural correlates underlying individual differences in delay discounting rates within the obese sample studied in Kishinevsky et al. (2012). In the present analysis, we hypothesized that brain activation in regions involved in executive function in response to difficult vs. easy DD trials would be negatively correlated with k . Indeed, we found that higher k was associated with less activation in several executive function regions such as the MFG and SFG. Moreover, this relationship remained significant in most areas after statistically controlling for age, years of education, and estimated IQ.

METHODS

Participants

Otherwise healthy obese women ($n = 24$) were recruited from the University of Alabama at Birmingham (UAB) area (see Kishinevsky et al. 2012, for details). Eligible participants were female, obese ($BMI > 30 \text{ kg/m}^2$), right-handed, non-smokers and between the ages of 19 and 50. Participants meeting study criteria were scheduled for a laboratory session at which further exclusion criteria were assessed. Participants were excluded for presence of an eating disorder, participation in a weight-loss program or trying to lose weight, taking weight-loss drugs, history of a clinical diagnosis of ADHD, a chronic health condition such as hypertension or diabetes, past history of any serious neurological or more general medical condition, current or past substance abuse problem or other addictive disorder, use of psychoactive medication such as antidepressants, pregnancy, estimated full-scale IQ < 85 , or history of loss of consciousness > 5 min. The size of the magnet bore limited participation to those with an upper body width $< 22.5''$ and an upper body girth $< 58''$. All procedures were reviewed and approved by the UAB Institutional Review Board for Human Use.

Laboratory Session

In the laboratory, participants provided informed consent and completed several behavioral assessments that were used for additional screening or incorporated in data analyses (see Kishinevsky et al. 2012 for details). Participants completed self-report or paper-and-pencil measures of cognitive ability (Shipley Institute of Living Scale, which predicts WAIS full scale IQ scores; Weiss and Schell 1991; Zachary 1986; Zachary et al. 2000), handedness (Edinburgh Handedness Inventory; Oldfield 1971), and disordered eating (Eating Disorder Diagnostic Scale, EDDS; Stice et al. 2000, 2004). Because greater delay discounting has been shown to be correlated with age, lower income, less education, and lower IQ (de Wit et al. 2007; Green et al. 1996; Jaroni et al. 2004; Reimers et al. 2009; Samanez-Larkin et al. 2011; Shamosh et al. 2008), we collected these variables to use in correlational analyses assessing relationships among these factors and delay discounting.

While in the laboratory, participants completed a modified version of a DD of money task (Kishinevsky et al. 2012; after Kirby et al. 1999) that was implemented in Eprime (version 1.2, Psychology Software Tools, Pittsburgh, PA) and was run on a PC. The Kirby et al. (1999) DD task has been used in many studies of DD, including fMRI studies of DD (e.g., Marco-Pallarés et al. 2010; Monterosso et al. 2007). On the DD task, each trial was 11 s long, beginning with a fixation cross (+) presented for 2, 4, or 6 s, and followed by the two choices, Now and Later, pseudo-randomly presented on the left and right sides of the monitor (see Figure 1 of Kishinevsky et al. 2012). On the 96 DD task trials (e.g., \$20 now vs. \$54 in 94 days) and 12 control trials (\$0 now vs. \$0 now), participants indicated their choices with a button press of the right or left index finger. Control trials were meant to serve as possible sensorimotor controls during the scanning session and were included in the laboratory session to familiarize the participants with the entire task.

At the end of the lab session, participants were compensated \$10 for their participation. In addition, after completing the DD task, each participant randomly selected one of the DD task trials and subsequently received a check for half of her choice on that trial after the specified interval. Immediate payments were made in cash.

Computation of Individual Lab k

Each trial on the lab task consisted of a Now value, a 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

$$Now = Later \div [1 + (imp-k)(Delay)]$$

There were eight imp-k values, ranging from 0.0004 to 0.25. For all trials at a given imp-k value (i.e., the ‘indifference point’), the Now and Later choices would have equal subjective values for an individual whose discount rate, k, matched the trial imp-k value, and would, therefore, be equally likely to be chosen. On trials with a lower imp-k, the Now reward would have greater subjective value and would be more likely to be chosen, whereas on trials with a higher imp-k, the Later reward would have greater subjective value and would be more likely to be chosen. Using non-linear (i.e., exponential) regression, we determined the imp-k value or ‘indifference point’ that estimated 50% Now and 50% Later choices for each participant; that point defined her discount rate (k). Determining the subject-specific k allowed us to administer “tailored” versions of the DD task in the magnet session. Because distributions of k values are severely skewed, data analyses relating discount rate to other participant variables were performed using the natural log transformation, $\ln(k)$ (e.g., Hoffman et al. 2008; Monterosso et al. 2007).

A participant was excluded from the magnet portion of the study if it became evident she did not understand the task, was not paying attention, was using a rule as opposed to assessing each trial independently (e.g., always selecting the Now choice if the delay was larger than 14 days); or if her k from the lab session placed her beyond the limits of the $\text{imp-}k$ values that characterized our magnet tasks.

Magnet Session

Because some studies have found that menstrual cycle phase can modulate reward or executive function (e.g., Dreher et al. 2007; Jacobs and D'Esposito 2011), all women were scanned in the follicular phase of the menstrual cycle (i.e., within 10 days of the onset of menses). Each participant received one of eleven modified versions of the DD task in the scanning session, with $k3$ values (see below) ranging from .0018 to .17. Each version consisted of 160 trials, divided into four 7:24 minute runs of 40 trials each, of which 30 were task trials and 10 were sensorimotor control trials. The task trials comprised five $\text{imp-}k$ values, labeled as $k1$ through $k5$. Each participant was assigned a version of the task such that $k3$ closely matched her lab k and $k1 - k5$ spanned a range from well below to well above $k3$. The lowest and highest $\text{imp-}k$ categories for that task, $k1$ and $k5$, respectively, represented trials intended to be easy for that participant (large differences in subjective value between the Now and Later choices, similar to Marco-Pallarés et al. 2010). Trials with intermediate $\text{imp-}k$ values, $k2 - k4$, were more difficult (similar subjective values of the Now and Later choices). Based on the individualized selection of the range of $\text{imp-}k$'s, participants were predicted to make almost all Now choices for $k1$, an approximately equal number of Now and Later choices for $k3$, and almost all Later choices for $k5$.

Obtaining useful data from a subject was dependent on her performance on the magnet DD task being consistent with her previous performance on the laboratory DD task. If a participant noticeably changed her rate of discounting between the two sessions, the task was switched after the first scanning run to a version of the task with a $k3$ value one or two steps higher or lower.

For the entire task, if a participant's choices showed %Now to be a monotonically decreasing function of $\text{imp-}k$, then her responses were considered to be 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 excluded. Each participant's magnet k was calculated using non-linear regression with %Now regressed against $\text{imp-}k$, as was done for the laboratory session calculations.

Participants were compensated \$20 for their participation. In addition, after completing the DD task, each participant randomly selected one of the task trials and subsequently received her choice on that trial, as described previously.

MRI Data Acquisition

Structural and functional data were collected from each participant using a Siemens Allegra 3-Tesla head-only magnet with a single-channel transmit-receive (T-R) head coil. Each imaging session consisted of fMRI scans of activation while the participant performed the DD task and a high-resolution anatomical scan to ensure that the participant's brain was anatomically normal. Functional MR images were acquired using single-shot T2*-weighted echo-planar imaging (EPI) with blood oxygen level-dependent (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 with a 1 mm gap at a scan resolution of 64×64 , reconstructed to 128×128 , and $240 \times 240 \times 149$ mm FOV. The high-resolution structural scan was acquired using

a sagittal T1-weighted image with magnetization-prepared rapid gradient echo (for details, see Kishinevsky et al. 2012).

Stimuli were presented via a PC running E-prime software 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 presses were recorded using MRI-compatible button pads.

fMRI Data Analysis

Event-related fMRI data were preprocessed and analyzed using the SPM5 software package (Wellcome Dept. Imaging Neuroscience, London, UK), run within Matlab (7.3; Mathworks, Inc.; see Kishinevsky et al. 2012 for details). Preprocessing followed conventional procedures: 1) slice time-correction, 2) spatial realignment using INRIAlign (Freire et al. 2002), 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 $2 \times 2 \times 2 \text{ mm}^3$ voxels, and 5) high-pass temporal filtering with a cut-off of 128 s as well as temporal smoothing using an autoregressive (AR(1)) model. Functional data from a participant were not used if within-run movement before correction exceeded 2 mm in translational movement or 2° in rotational movement.

Statistical analyses were performed at the individual and group levels using the General Linear Model (GLM) and Gaussian random field theory. 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 as a stick function with its onset at 500 ms before the button push. At the first level, activation was computed for each individual subject on difficult > easy trials by convolving the time course of activation with the canonical hemodynamic response function (HRF). Trial difficulty was defined based on the imp-k for each trial as described above; that is, k1 and k5 trials were easy trials and k2, k3, and k4 were difficult trials. To account for motion artifacts, the realignment parameters were entered as regressors of no interest in these analyses.

Second level (group) analysis was performed on the contrast estimates 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 group analysis examined activation in response to difficult > easy trials with $\ln(k)$ as a regressor in order to investigate whether activation was related to the degree of delay discounting.

fMRI data were analyzed using both Regions of Interest (ROI) analysis and whole-brain analyses. The ROI analysis addressed our *a priori* hypotheses regarding executive function areas with improved statistical power. Executive ROI's selected were cognitive control structures that were expected to be more activated by difficult choices; that is, subdivisions of lateral prefrontal cortex: IFG, MFG, and SFG; inferior parietal lobule (IPL); superior parietal lobule (SPL); and subdivisions of medial prefrontal cortex (Boettiger et al. 2007; Hoffman et al. 2008; Kishinevsky et al. 2012; Marco-Pallarés et al. 2010; Monterosso et al. 2007; Pine et al. 2009; Sripada et al. 2011). For medial prefrontal cortex, we used ROI's for the anterior cingulate cortex and, above it, the SFG, because the latter's medial aspect included parts of medial prefrontal cortex of interest. The ROI's were defined structurally by applying the AAL or Talairach Daemon atlases, using templates from the WFU Pickatlas toolbox in SPM5 (Lancaster et al. 2000; Maldjian et al. 2003, 2004; see Kishinevsky et al. 2012 for details).

Statistical parametric maps were derived from the resulting t values 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). For whole-brain analyses, cluster size threshold was determined within SPM5 on the basis of Gaussian random field theory to maintain the family-wise error rate (FWE) at 0.05 across the entire brain. For each analysis of each ROI, small volume correction was used to set a cluster threshold maintaining FWE = .05 within that ROI. From SPM5, we obtained parameter estimates for the peak voxel in each significant cluster.

Finally, for each of the significant correlations obtained in the above regression analysis, we also sought to assess the relationship between $\ln(k)$ and brain activation independent of potential confounding effects of IQ, years of education, and age because higher k has been reported to be associated with lower IQ, less education, and (sometimes) younger age (Green et al. 1996; Jaroni et al. 2004; Samanez-Larkin et al. 2011; Shamosh et al. 2008).

RESULTS

Demographic Characteristics

Of the 24 women scanned, useful fMRI data were obtained for $n = 19$. These 19 fMRI participants and the five excluded were the same as those in the fMRI analysis of activation to difficult DD > easy DD trials of Kishinevsky et al. (2012). Data from five participants were not used either because of data artifacts or because the participant provided inconsistent responses on the DD trials, appeared to use a mental shortcut or rule, or had too much head movement. The 19 participants had a mean age of 33.4 yrs ($SD = 9.8$; range 19 – 49), mean Shipley estimated IQ of 108.1 ($SD = 8.3$; range 89 – 119), mean education of 15.8 years ($SD = 7.8$; range = 12 – 22), mean BMI of 34.3 kg/m^2 ($SD = 3.6$; range 30.8 – 42.9), and about half were Caucasian and half African American (see Table 1 of Kishinevsky et al. 2012 for more detailed demographic information). Fourteen of the women were scanned on days 2–10 of the follicular phase of their menstrual cycle. The remaining five were postmenopausal or were not cycling for other reasons.

Behavioral Data Analysis

The correlation between $\ln(k)$ obtained in the laboratory session and in the magnet session was $r = .68$ ($p = .0013$), confirming the results of previous studies that found k to be a reasonably stable trait measure (Beck and Triplett 2009; Odum 2011; Ohmura et al. 2006). Because of the robust positive correlation between the two measurements of $\ln(k)$, only the magnet value was used for subsequent correlational analyses. There were significant negative correlations between $\ln(k)$ and education ($r = -.60$) and age ($r = -.585$; p 's $< .010$) and a marginally significant negative correlation with annual income ($r = -.41$; $p = .08$). There was no significant relationship between $\ln(k)$ and estimated IQ, BMI, or ethnicity (all p 's $> .17$).

For every data set included in the fMRI analysis, %Now decreased monotonically with imp- k and the decrease in %Now from k_1 to k_5 ranged from 79.2–100% (cf Johnson and Bickel 2008).

fMRI Results

Relationship between and $\ln(k)$ and fMRI activation on difficult > easy trials—

ROI analyses revealed significant negative correlations between $\ln(k)$ and activation on difficult vs. easy DD trials in several putative executive function areas (Table 1). These were in the executive function ROI's, MFG (bilaterally) and IPL (right side), with activation in the IFG (left) marginally significant (Figure 1A, B, D). Whole-brain analysis showed

additional significant clusters with peak voxels in another putative executive function area, SFG (bilaterally; Figure 1D), as well as such areas as the precuneus, superior temporal gyrus, and posterior-to-middle cingulate cortex (Table 1). Neither the ROI nor whole brain analyses revealed significant *positive* correlations between $\ln(k)$ and activation to difficult vs. easy trials.

As additional analyses performed outside of SPM (SYSTAT 11, SYSTAT Software), correlations were computed between individual subjects' parameter estimates for the peak voxel in each significant cluster and education, age, and IQ. Because correlations with $\ln(k)$ were significant for age and education, these variables were included in regression models to statistically remove their contribution to the relationship between $\ln(k)$ and brain activation. Statistically controlling for education and/or age left the relationship between $\ln(k)$ and activation significant for all regions except the right SFG, left IFG, and right posterior cingulate. For these latter regions, activation was significantly correlated with both of these demographic variables. Although correlations were not significant in our data between IQ and $\ln(k)$ or the parameter estimate values, given the positive correlation between IQ and executive function found in many studies (e.g., de Wit et al. 2007), we also statistically controlled for IQ. There was no change in results after controlling for IQ. As reported previously (Kishinevsky et al. 2012), there was also no relationship between activation and BMI. As indicated in the scatterplots (Figure 1, *bottom row*), these and, in fact, all significant correlations, reflect continuous functions relating activation and $\ln(k)$. In cases in which outliers were identified (using SYSTAT 11), the correlations were not substantially affected by their removal and remained significant.

DISCUSSION

Overview

On a monetary DD task, *more* impulsive participants had *less* modulation of activation in putative executive function brain areas, as well as some additional regions, on difficult vs. easy trials. These findings will be discussed in relation to previous fMRI studies of DD and impulsivity, other fMRI studies of impulsivity, and in relation to the known functions of the activated brain areas.

Impulsivity as a Predictor of Brain Activation in Executive Function Areas on More Difficult DD Trials

As hypothesized, *greater* impulsivity in participants, as behaviorally defined by the discount parameter k obtained from performance of the DD task during scanning, was associated in fMRI ROI analysis with *less* modulation of activation in areas putatively involved in executive function (i.e., MFG and IPL) during difficult vs. easy DD trials. The whole-brain analysis additionally identified another executive function area, SFG, as well as other areas, such as the posterior to middle cingulate, precuneus, and STG, with negative correlations between $\ln(k)$ and activation.

For most executive function regions (MFG bilaterally, left SFG, and right IPL) and most of the additional areas, the results indicate a relationship between $\ln(k)$ and activation independent of education or age. With these variables included in the model, however, the relationship between $\ln(k)$ and brain activation was no longer significant for right SFG, left IFG, and right posterior cingulate. These outcomes leave open the possibility that, in these specific regions, the observed relationship between discounting and activation was actually a reflection of inter-participant variability in education and/or age. Accounting for estimated IQ score in the model had no effect, suggesting that none of the correlations between higher k and lower activation were confounded by IQ.

Relation to Previous Findings

We previously reported that, for the same participants, difficult compared to easy DD trials produced activation in putative executive function areas - IFG, MFG, and middle cingulate/medial prefrontal cortex (Kishinevsky et al. 2012). These results are similar to those of some comparable fMRI studies of DD (e.g., Hoffman et al. 2008; McClure et al. 2004; Pine et al. 2009), except that we found fewer areas activated. This difference was probably because we compared difficult to easy DD trials, which may improve the specificity for isolating executive function/cognitive control brain areas involved in difficult DD choices.

Although numerous fMRI studies have examined relationships between impulsivity and brain activation during DD (Ballard and Knutson 2009; Bickel et al. 2009; Boettiger et al. 2007; Claus et al. 2011; Hoffman et al. 2008; Monterosso et al. 2007; Sripada et al. 2011), most did not use the difficult > easy trial contrast used in this study. Monterosso et al. (2007) found, for controls and methamphetamine abusers combined in a whole brain analysis, that those with greater impulsivity, as measured by *k*, had less activation in ventrolateral prefrontal cortex on blocks of difficult DD trials compared to no-choice trials. However, no relationship was found between *k* and activation on blocks of difficult > easy choices, and no positive correlations with delay discounting were reported. On the other hand, two studies reported *positive* correlations between discounting and activation to DD trials vs. comparison trials of various sorts. In methamphetamine-dependent individuals and controls, Hoffman et al. (2008) found a positive correlation between *k* and activation on difficult DD trials vs. magnitude estimation control trials in the amygdala, posterior parietal cortex, and SFG. In healthy controls, Bickel et al. (2009) found a positive correlation between *k* and activation on all DD trials vs. non-DD control trials in MFG, medial frontal gyrus, cuneus, and cerebellum. Bickel et al. (2009) suggested that these differences across studies could be related to variations in the control task used. Notably, only one of the three previous studies that related *k* to difficult DD trials used the contrast used in the present study, activation to difficult > easy DD trials, and that study (Monterosso et al., 2007) had methodological (i.e., whole brain analysis, block design) and participant characteristic (i.e., methamphetamine abusers) differences from the present study.

Although few fMRI studies have examined the relationship between impulsivity and brain activation related to DD trial difficulty, other tasks have been used to explore the relationship between impulsivity and brain activation. For example, Horn and colleagues (Horn et al. 2003) used the go/no-go task and correlated fMRI activation with scores from two trait measures of impulsivity, the Barratt Impulsiveness scale (BIS) and Eysenk's Impulsivity, Venturesomeness, and Empathy scale (IVE-I). In their sample of normal adult males, they found negative correlations between BIS and IVE-I impulsivity scores and activation to no-go trials in anterior medial SFG, IPL, and the middle temporal gyrus, as well as positive correlations with the right IFG and insula. The negative correlation suggests that more impulsive individuals had less activation in putative inhibitory control-related brain areas, with activity assumed to relate to the engagement of inhibition. In a study comparing brain activation in adolescents and adults to the Stroop task, Andrews-Hanna et al. (2011) found that the degree of dorsolateral prefrontal cortex activation in adolescents was positively correlated with a self-report measure of impulse control. Our results are similar to those of both studies, in that we found negative correlations between impulsivity and brain activation in frontal cortex in response to a task assumed to engage inhibition. Although some studies have reported *positive* correlations between impulsivity and activation in putative executive function brain areas in response to inhibitory control tasks (e.g., Brown et al. 2006), such differences may be due to differences in the assessment of impulsivity, BIS vs. DD $\ln(k)$, the fMRI task used, go/no-go vs. DD, or participant demographic variables.

Functions of Areas Activated in the Present Study

DD has been characterized as an inhibitory or self control task (e.g., Appelhans et al. 2011), as one must inhibit the desire to select the immediate reward. That is, at least some of the areas activated by difficult vs. easy DD trials (Kishinevsky et al. 2012) may be activated because such decisions require greater inhibitory control to *not* select the almost-as-desirable other choice. Inhibitory control is thought to involve a network of areas: lateral prefrontal cortex, medial prefrontal cortex including the anterior cingulate gyrus and cortex dorsal to it including the pre-SMA (within our medial SFG), and IPL (Chambers et al. 2007; Chen et al. 2009; Coutlee and Huettel 2011; Rubia et al. 2001; Tabu et al. 2011; Zheng et al. 2008). However, some of these areas could be activated by DD for reasons other than inhibitory control. In addition, inhibitory control may not be the sole explanation for why all areas were activated in the present study, as not all areas (i.e., posterior cingulate) have been implicated in inhibition.

Lateral Prefrontal Cortex—We found a negative correlation between $\ln(k)$ and activation to difficult > easy DD trials in parts of lateral prefrontal cortex (MFG, SFG), unconfounded by age, education, or IQ. Lateral prefrontal cortex (LPFC) is commonly implicated in various executive function processes involving inhibition, as well as complex decision-making, integrative planning, and behavioral goal selection (e.g., Tanji and Hoshi 2008; for review see Coutlee and Huettel 2011). A causal role for LPFC in modulating delay discounting was demonstrated by Figner et al. (2010), who used transcranial magnetic stimulation (TMS) to temporarily disrupt the functioning of LPFC during a DD task. This increased the likelihood that participants chose the immediate reward, especially during difficult trials (Figner et al., 2010). One interpretation of this finding is that lateral prefrontal cortex is involved in the inhibition of prepotent responses to immediate rewards, or “resistance to temptation” (Figner et al. 2010). Also in support of the contribution of lateral prefrontal cortex to cognitive control, Hare et al. (2009) found that when “self-controllers” resisted tasty but unhealthful foods, they showed greater activation in dorsolateral prefrontal cortex during successful self-control trials. These results are consistent with our finding of decreased activation in the MFG and SFG during difficult vs. easy trials being associated with increased impulsiveness.

Inferior Parietal Cortex—More difficult DD choices were previously found to produce activation in parietal cortex (McClure et al. 2004; Monterosso et al. 2007). In the present study, we found less activation in the IPL to difficult vs. easy DD trials in those with greater impulsivity. The IPL has been implicated in executive function and inhibitory control (e.g., Hedden and Gabrieli, 2010), so decreased activation in our study could reflect deficiencies in these functions. IPL is also part of the attention network (for review see Ptak 2011), so decreased activation by more difficult trials could reflect lesser recruitment of attentional resources.

Posterior Cingulate Cortex—One region activated in our study not related to inhibitory cortex is posterior cingulate cortex (PCC). We found that posterior cingulate cortex was less activated to the difficult > easy trial contrast in those with greater impulsivity. In other fMRI studies of DD, activation in PCC has been found for more difficult DD trials, choices involving immediate money, delays, or the subjective values of rewards (Bickel et al. 2009; Kable and Glimcher 2007; McClure et al. 2004; Peters and Bickel 2009; Spirada et al. 2011). More broadly, the posterior cingulate has been implicated in a variety of functions, such as the assignment of resources to cognitive processes and decision salience or uncertainty, as in picking an unusual option (for review, see Heilbrunner et al. 2011). The PCC is also part of the brain’s default network (Raichle et al. 2001). It has been suggested that thinking about delays in the DD task might activate default network areas such as PCC

because of the prospective thinking involved (Luhmann et al. 2008; Weber and Huettel 2008). Thus, less activation of PPC in more impulsive individuals could indicate less prospective thinking.

Relationship to Obesity?

Although we have previously demonstrated relationships between DD trial difficulty-elicited brain activation and subsequent weight gain in already obese women (Kishinevsky et al. 2012), these effects appear to be independent of the relationships reported in the current paper. The activations related to weight gain in Kishinevsky et al. (2012) did not correlate with $\ln(k)$. Likewise, the activations in the current study do not correlate with weight gain nor BMI (results not shown). Thus, the effects in these two studies are functionally distinct, perhaps relating to different aspects of executive function. One explanation for this possibility is that the DD task itself requires multiple aspects of decision-making, as suggested previously (Kishinevsky et al. 2012; Reynolds et al. 2006).

Caveats

It is important to note some of the limitations of this study. Because our sample consisted only of obese women, it remains an open question whether our results would generalize to men and/or to the non-obese. Other studies have reported gender differences in fMRI activation in response to cognitive tasks (Bell et al. 2006; Butler et al. 2007) and, in particular, to inhibitory control tasks (Li et al. 2006; Liu et al. 2012; Wang et al. 2009). Differences in executive function including inhibitory control have also been reported for obese vs. non-obese samples, or related to body mass index (BMI; e.g., Batterink et al. 2010; Hendrick et al. 2011). However, the generality of the negative correlation we found in the present study, between impulsivity and activation in brain areas associated with putative executive function, is supported by the findings of other correlational studies of impulsivity and brain activation in non-obese and/or male or mixed gender samples (Andrews-Hanna et al. 2011; Horn et al. 2003; but see Brown et al. 2006). Moreover, although no correlational investigation can establish a causal link between the studied variables, when considered in the context of previous correlational and experimental investigations of DD, impulsivity, and the brain regions studied, the present findings are highly consistent with a biobehavioral model that attributes impulsivity to low functioning in putative executive function areas of the brain.

Another limitation is that although we excluded participants for using antidepressant medication, which would have excluded some individuals with depression, we did not assess for the presence of depression or depressive symptoms, which have a high comorbidity with obesity (Zhao et al. 2011) and may relate to greater delay discounting (Takahashi et al. 2008; but see Lempert & Pizzagalli, 2010). Thus, the relationship we found between k and executive dysfunction could be confounded by the presence of depression or depressive symptoms in the obese women of our study.

Summary and Conclusions

In summary, we found that more impulsive obese women had decreased activation in response to difficult vs. easy DD trials in brain areas implicated in executive function, especially inhibitory control, as well as attention and prospective thinking. Our study has an advantage over previous studies of DD that it used a strong control for difficult DD trials, that is, easy DD trials, rather than a less specific control, in the fMRI contrast and included an ROI analysis, to increase power. Our negative correlations between brain activation and impulsivity agree with those of some other correlational fMRI studies of other inhibitory control tasks (e.g., go/no-go) and self-report measures of impulsivity. Our study has the added strength of also including a behavioral measure of impulsivity, obtained during

scanning, rather than a self-report measure alone (e.g., Andrews-Hanna et al. 2011; Horn et al. 2003; Liu et al. 2012). Previous research has found that impulsivity is a multi-dimensional construct assessed by self-report measures, which capture an individual's perception of their behavior, and behavioral measures, which are objective measures of impulsivity (e.g., Meda et al. 2009). Interestingly, in the current study, we found that the behavioral data ($\ln(k)$), but not the self-report data (BIS), correlated with putative executive function brain activity. In addition, only putative executive function brain activity, not behavioral or self-report measures of impulsivity, predicted subsequent weight gain (see Kishinevsky et al. 2012).

More impulsive individuals may be at greater risk of problems such as some forms of obesity, addiction, ADHD, or other impulse control disorders (e.g., Reynolds 2006; van den Berg et al. 2011; Winstanley et al. 2006). Short term improvements in delay discounting have been reported with changes in cognitive strategy (Bickel et al. 2011; Cheng et al. 2012; Peters and Büchel 2010; Radu et al. 2011). Remediation might also include the brain as a target. It has been shown that smokers can effectively use emotion regulation strategies to modulate brain areas involved in executive function and that enhanced control was associated with decreased cravings (Kober et al. 2010). In a promising new line of research, we have shown that real time fMRI neurofeedback, in conjunction with emotion regulation strategies, can be used to help cigarette smokers learn to modulate their own brain activation in regions involved in executive function (Stoeckel et al. 2011). This procedure leads to reduced cigarette cravings and, in some cases, a decrease in smoking behavior (Stoeckel et al. 2010, 2011). It remains to be seen if such approaches can influence delay discounting over a longer time frame and in real life.

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Figure 1.

Top row, brain areas showing significant activation on difficult > easy DD trials negatively correlated (r) with $\ln(k)$ in the (A) left IFG (sagittal view), (B) bilateral MFG (axial view), (C) bilateral SFG (coronal view), and (D) right inferior parietal lobule (IPL; coronal view). A, B and D were identified from ROI analysis and C from whole brain analysis (Table 1). Activation is overlaid on the SPM5 single subject T1 template. Bars indicate t values.

Bottom row, scatterplots of brain activation (PE, parameter estimate) with regression lines of activation from the brain regions above vs. $\ln(k)$. For illustrative purposes, A, $r = -0.746$; B, $r = -0.783$; C, $r = -0.681$; D, $r = -0.794$. In all cases the relationship between activation and $\ln(k)$ remained significant when any outliers (e.g., A; data point with PE = -9.5), as diagnosed by SYSTAT 11, were removed.

Table 1

Significant negative correlations between difficult > easy activation and ln(k) (n = 19)

Executive ROI Analysis	BA ^a	Hem ^b	Clust ^c	p, FWE corrected ^d	x ^e	y ^e	z ^e	t
Middle Frontal Gyrus	9	R	142	0.009	32	24	40	5.74
	8	L	441	0.0000013	-46	24	44	5.05
	6	R	109	0.001	38	12	54	4.08
					28	0	48	3.55
Inferior Frontal Gyrus		L	83	0.058 ^f	-46	42	8	4.60
Inferior Parietal Lobule	40	R	122	0.001	38	-52	50	5.41
Whole Brain Analysis	BA	Hem	Clust	p, FWE corrected	x	y	z	t
Superior Frontal Gyrus		L	240	0.004	-20	18	64	3.73
		R			4	22	66	3.73
Precuneus		L	544	0.0000012	0	-60	46	5.98
	7	R			14	-62	50	4.72
Post/Mid Cingulate Cortex	31	L	165	0.043	-6	-30	42	4.32
		R			10	-20	38	3.60
Superior Temporal Gyrus		L	336	0.00023	-44	-54	18	4.68
Angular Gyrus		L			-42	-58	36	3.69
Cerebellum, Culmen		L	179	0.027	-22	-64	-34	4.61
Cerebellum, Declive					-34	-60	-30	4.16

^aBrodman Area

^bHemisphere: R, right; L, left

^cClus, cluster size; number of contiguous voxels with p < 0.01

^dFamily-wise error corrected at the cluster level

^ex, y, and z coordinates in MNI space

^fMarginally significant

Other abbreviations: mid, middle; post, posterior. 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.