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Quantifying familial influences on brain activation during the monetary incentive delay task: An adolescent monozygotic twin study

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Abstract

Although altered brain activation during reward tasks has been found in a number of heritable psychiatric disorders and health outcomes, the familial nature of reward-related brain activation remains unexplored. In this study, we investigated the degree to which the magnitude of mesocorticolimbic reward system signal intensities in anticipation of reward during the monetary incentive delay (MID) task was similar within forty-six pairs of adolescent, monozygotic twins. Significant within-pair correlations in brain activation during anticipation of gain were found in one third of the 18 reward-related regions investigated. These regions were the right nucleus accumbens, left and right posterior caudate, right anterior caudate, left insula, and anterior cingulate cortex. This serves as evidence for a shared familial contribution to individual differences in reward related brain activity in certain key reward processing regions.

Keywords

fMRI; Reward System; Individual Differences; Monetary Incentive Delay Task

Introduction

Research using fMRI has allowed for an expanded understanding of the neural correlates underlying a wide array of psychiatric disorders. For example, it is now possible to observe differences between psychiatric patients and non-patients based on altered patterns of brain activation seen during task-based functional magnetic resonance imaging (fMRI). This kind

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of information has added to our knowledge of the underlying neural processes impacting psychiatric outcomes. Still, little is known about whether such patterns of brain activation result from psychiatric disorders or serve as underlying liabilities. Recent years have seen the emergence of research using family and twin samples in fMRI to examine the heritability of task-related brain activation and functional connectivity patterns (Blokland et al., 2008; Blokland et al., 2011; Glahn et al., 2010; Matthews et al., 2007; Koten et al., 2009; Polk et al., 2007), giving us a better understanding of the etiology of certain types of brain activation. The present investigation extends this line of research by examining familial resemblance in monozygotic twin pairs for brain function related to reward processing.

Altered patterns of brain activation in the dorsal and ventral striatum and other reward processing brain regions have been identified for a number of psychiatric disorders. Atypical activation of these regions during the monetary incentive delay task (MID) has been observed in particular in a variety of psychiatric disorders associated with impulsivity, such as alcohol and drug abuse (Beck et al., 2009; Jia et al., 2011; Hommer et al., 2011), pathological gambling (Balodis et al., 2012), and attention difficulties and disorders (Scheres et al., 2007). Additionally, atypical brain activity during the MID task has been observed in poor health outcomes such as obesity (Balodis et al., 2013) and predicts impulsive-antisocial psychopathic traits and criminality (Buckholtz et al., 2010).

Differences in reward sensitivity, including blunted activation in the nucleus accumbens during reward anticipation, determined using the MID task, have also been found in healthy individuals with a family history of alcoholism (Andrews et al., 2011). Using a similar reward paradigm, Ivanov et al. (2012) found differences in ventral striatal activation between children with ADHD at high risk for substance abuse (with at least one biological parent with a history of substance abuse) compared with children with ADHD with no family history of substance abuse. Taken together, these findings indicate that individual differences in functioning during reward tasks may not only be indicative of specific diseases or impairments, but may also be partly familial in nature. To date, no studies have examined whether related individuals have similar patterns of brain activation during this, or any other, reward processing task.

Because of its design, the MID task has been useful for reliably (Wu et al., 2014) probing human incentive-motivational neurocircuitry (Knutson et al., 2001a). During each run of the task, subjects see a cue indicating a monetary amount that they could either win or lose, followed by a delay period, then a brief target to which subjects must respond, followed by a second delay period, and finally feedback about the amount of money gained or lost. Previous studies examining the anticipation of gain or loss have found activation in regions associated with reward processing, including the nucleus accumbens, the caudate, the insula, and the putamen (e.g., Samanez-Larkin et al., 2007; Bjork et al., 2004; Scheres et al., 2007).

The MID task has been helpful in expanding our understanding of reward related brain activation in adolescents. An accruing body of literature points to altered activation patterns in the ventral striatum during the anticipation stage of reward processing in the MID task as a potential neural marker of adolescent reward processing (Geier et al., 2010; Bjork et al., 2004; Bjork et al., 2010; Lamm et al., 2014). This stage of reward processing, which has

been likened to “wanting,” is thought to reflect incentive salience or desire for the reward (Spear, 2011). Knutson and Greer (2008) present findings indicating that there are greater affective changes during the anticipation stage of reward processing than during the receipt stage of reward processing, referring to this as ‘anticipatory affect.’ As a result, variation in brain activation during the anticipation phase of reward processing shows promise as a potential neural marker of adolescent reward processing, related to outcomes of interest, given its greater association with the affective features of reward processing (Wu et al., 2014).

In the current study, we investigated within-pair similarity for task-related brain activation during the MID task using a community sample of 46 pairs of adolescent, MZ twins. Our fMRI analyses focused on the anticipation stage of the gain compared to no-incentive contrast. We explored twin similarity in regions of interest (ROIs) based on regions activated in previous studies examining the anticipation of gain (Knutson et al., 2001a; Knutson et al., 2001b; Bjork et al., 2004). We also examined twin similarity during the anticipation of loss compared to no-incentive based on regions activated in previous studies looking at loss (Knutson et al., 2001a; Bjork et al., 2004; Bjork et al., 2010). Additionally, we looked at twin similarity in the difference in activation between large and small gains and large and small losses in the regions identified for gain and loss respectively. The ROIs for gain and loss included the caudate, putamen, insula, nucleus accumbens, amygdala, thalamus, posterior cingulate, medial prefrontal cortex, precentral gyrus, anterior cingulate, supplementary motor area, middle occipital gyrus, left cuneus and medial frontal gyrus.

Given the sizable literature finding altered patterns of brain activation during the anticipation stage of the MID task in both psychiatric patients and in adolescents, we sought to understand adolescent MZ twin similarity during the anticipation stage of gain and loss processing during the MID task. We extended the few prior studies (Andrews et al., 2011; Ivanov et al., 2012) suggesting that family history of psychopathology may be associated with deviant brain activation by investigating the degree to which MZ twins resembled each other in terms of their reward system activation during the MID task. The value of using MZ twins in such a design to evaluate familial patterns of activation has been used to advantage in prior research with an MZ twin community sample to evaluate twin similarity in various measures (Iacono & Lykken, 1979; Bell et al., 1994). We hypothesized that MZ twins would be correlated in their task-related brain activation during the gain compared to no-incentive contrast of the monetary incentive delay task. This study also adds to the existing literature on twin similarity in task-related brain activation by focusing on brain function during a relatively circumscribed period in mid-adolescence, a developmental period characterized by profound change in neuroanatomy and connectivity (Spear, 2011).

Methods

Participants

Forty-eight pairs of MZ twins, mean age $16.46 \pm .91$ S.D. (range 15–17 years) enrolled in the study. They included 24 female and 24 male twin pairs. Twin pairs were recruited from the Minnesota Center for Twin and Family Research (MCTFR) register of twin families ascertained from Minnesota birth records with twins born between the years of 1991 and

1994. Zygosity was determined using three separate estimates: 1) Parents completed a zygosity questionnaire, 2) trained staff evaluated the twins' physical similarities, and 3) trained staff utilized an algorithm of physical measurement. A serological analysis using a panel of DNA markers was performed when these estimates did not agree and there was any remaining ambiguity. Previous analyses with other similarly recruited twin samples have shown this method to perfectly predict the blood-based classifications in a sample of 50 twin pairs (Billig et al., 1996). Exclusion criteria for participation included a history of maternal substance abuse, current orthodontic treatment such as dental braces or permanent retainers, or any other MRI ineligibility such as claustrophobia or ferromagnetic materials in the body.

Participants were scanned on the same day as their co-twins and the scanning sessions lasted 90 minutes per twin. Participants received \$150 for their time, which included a mock scan, the actual scan session, interviews, and behavioral measures, which were conducted at the Department of Psychology and at the Center for Magnetic Resonance Imaging at the University of Minnesota. This data collection was part of a longitudinal study, in which subjects received \$150 for their prior participation, one year earlier, as well as a \$200 completion bonus after finishing both years' sessions. The University of Minnesota Institutional Review Board approved the study. All participants gave assent and a parent gave consent for every participant. 47 twin pairs completed structural and functional scans, after one pair of male twins dropped out, declining to participate in the scanning session.

Participants were introduced to the scanning environment with the use of a simulator scanner located in the Department of Psychology at the University of Minnesota during a pre-scan visit. The simulator mimicked the bore diameter, head coil, bed motion, scanner noise, and stimulus presentation equipment used in the scanner.

Stimuli, Materials & Procedure

Monetary Incentive Delay (MID) Task: During the task, gains and losses varied in magnitude. Four gain cues and four loss cues, as well as a neutral cue, were included. Each cue was displayed for 250 msec. Reward cues were designated with a circle: a large gain (\$5.00; 6 trials/run) was indicated by a circle with three horizontal lines; a medium gain (\$1.00; 6 trials/run) was indicated by a circle with two horizontal lines; and a small gain (\$0.25; 6 trials/run) was indicated by a circle with one line. A circle with no lines was also included, which indicated a gain trial of unknown magnitude (\$5.00, \$1.00, or \$0.25; 6 trials/run). Losses were designated by a square with the same characteristics: a large loss (\$5.00; 6 trials/run) was indicated by a square with three horizontal lines; a medium loss (\$1.00; 6 trials/run) by a square with two lines; and a small loss (\$0.25; 6 trials/run) by a square with one line. A square with no lines was included to cue a potential loss of unknown magnitude (\$5.00, \$1.00, \$0.25; 6 trials/run). Additionally, there was a neutral cue for the no-incentive condition, designated by a triangle, which indicated no gain or loss (12 trials/run). After each cue, participants saw a crosshair fixation, which lasted a randomly determined, variable length of time (ranging from 2000–2500 ms). Following this delay, a solid white target square was presented for a pre-determined, fixed length of time (ranging from 180–280 ms), which prompted a response in the form of a button press. The duration of the target was individually titrated for each participant based on his or her reaction time

during the previous run, so that individuals with shorter reaction times would also have a shorter duration for pressing the target. During the first run, the duration of the target time was determined by subjects' reaction times during a practice run of the task, completed during the structural scan, in which they did 20 trials of target detection without gain or loss cues. The target duration determined for each participant was designed to allow accurate responding approximately 70% of the time. Following the button press, a second fixation cross appeared, which lasted between 1720–2320 ms, depending on the length of the first fixation period as well as the participant's reaction time for that trial. Participants then received feedback about any money gained or lost during the trial, and their cumulative earnings to that point in the task run. The feedback display was presented for 1650 ms. Between each trial, a blank screen was presented for 100 ms, serving as an interstimulus interval. Additionally, before the start and at the conclusion of each run of the task, there were two fixation periods which, when combined, lasted a total of 12000 ms. Figure 1 depicts one representative trial of the task displaying a medium gain cue. The gain, loss, and no-incentive trial types were presented pseudo-randomly, and trial order varied from subject to subject and across runs. Each participant performed three runs of the task consisting of 60 6-second trials. This resulted in 180 task trials, overall.

fMRI acquisition: Imaging was performed using a 3T Siemens Trio MRI Scanner at the Center for Magnetic Resonance Research at the University of Minnesota. Images were collected with a 12-channel head coil and vacuum pillow in order to reduce head motion. High-resolution anatomical scans were collected for morphometric analyses and localization of function. The images were acquired using the following sequence: MPRAGE, TE = 3.65 ms, TR = 2530 ms, flip angle = 7°, FOV = 256 mm, matrix = 256 × 256, slice thickness = 1 mm, 240 sagittal slices. During the structural scan, participants completed a practice run of the MID task, described above. This was used to determine the duration of target stimulus in the first run of the task.

A mirror on the head coil enabled subjects to view the behavioral task projected onto a rear-projection screen at the head of the scanner bore. Functional scans were collected using a T2*-sensitive echo planar sequence (EPI, TE = 28 ms, TR = 2.0 sec, flip angle = 90°, FOV = 200 mm, matrix = 64 × 64, slice thickness = 4.0 mm with no gap, in-plane resolution = 3.125 × 3.125 mm², 34 axial slices with interleaved slice acquisition). Whole brain imaging allowed us to examine ROIs, which we defined based on previous studies using the MID task. These regions, for the gain compared to no-incentive contrast, included: anterior cingulate cortex, amygdala, caudate, insula, nucleus accumbens, putamen, thalamus, mPFC, and posterior cingulate (Knutson et al., 2001a; Knutson et al., 2001b; Bjork et al., 2004). For the loss compared to no incentive contrast, these regions included: left cuneus, putamen, caudate, right insula, thalamus, right middle occipital gyrus, right precentral gyrus, right medial frontal gyrus, mesial cerebellum and supplementary motor area (Knutson et al., 2001a; Bjork et al., 2004; Bjork et al., 2010). Some regions from the gain compared to no-incentive and loss compared to no-incentive contrasts overlap, due to shared circuitry during these two types of reward processing (Liu et al., 2011). Two disabled acquisitions were included at the start of each run to allow for signal stabilization. Overall, a total of 558

volumes (186 repetitions $\times$ 3 runs) were collected across all three runs of the task, not including the disabled acquisitions.

fMRI analyses: Our analyses focused on changes in blood oxygen level-dependent (BOLD) signal contrast (activation) during the anticipatory delay period, after subjects saw a cue and before they had a chance to respond. We specifically focused on the contrasts between gain trials and no-incentive trials, large gain trials and small gain trials, loss trials and no-incentive trials, and large loss trials and small loss trials. Analyses were conducted using FMRIB's Software Library (FSL; www.fmrib.ox.ac.uk/fsl/).

Each functional data set was registered to the relevant anatomical dataset using a rigid-body linear transformation, and each participant's anatomical data were registered to a standard coordinate space (Montreal Neurological Institute's MNI 152 2mm volume) using a full affine transformation to allow cross subject comparisons in a common space.

Functional data runs were preprocessed using the following steps: motion correction using the first volume in the functional series as the reference volume; slice timing correction; skull stripping; field-map based unwarping; spatial smoothing using a 6 mm FWHM Gaussian filter (based on recommendations provided in Saatchi & Knutson, 2013); grand-mean scaling; and high-pass temporal filtering with a 25 sec cutoff. The three linear and three rotational motion estimates produced by the motion correction step were collapsed into a single root mean square (rms) metric. After preprocessing, each run was evaluated for excessive motion. Volumes showing absolute displacement (relative to the reference volume) greater than 3 mm rms or relative displacement (from one volume to the next) greater than 1.5 mm rms were marked as having motion. Additionally, for any volume that exceeded the relative displacement criterion, the preceding and following volumes were also marked for motion. One participant who had two runs with greater than 25% of volumes showing motion was excluded from further analysis, along with his twin. The final functional data set submitted to further analysis consisted of 46 twin pairs.

Preprocessed data from each run were next submitted to a first-level general linear model (GLM) using the following predictors of interest for the anticipatory delay period within each trial: small loss, small gain, medium loss, medium gain, large loss, large gain, unknown loss, unknown gain, and no-incentive. These task predictors were convolved with a prototypical gamma-function approximation of the hemodynamic response. The temporal derivative for each task predictor was also added to the model. Predictors of no interest included three linear translation and three rotation motion predictors, as well as a nuisance predictor for volumes that exceeded the motion criteria. Task predictors were time-locked to the onset of the anticipatory delay portion of each trial and extended for the duration of the anticipatory delay period. All task predictors were coded in milliseconds. Contrasts of interest compared 1) all gain predictors (i.e., small, medium, large, and unknown gain) against the no-incentive predictor, 2) the large gain predictor against the small gain predictor, 3) all loss predictors (i.e., small, medium, large, and unknown loss) against the no-incentive predictor, 4) and the large loss predictor against the small loss predictor. Output from the first-level analyses was combined within-subject using a GLM to produce a single

statistical map for each contrast of interest for each participant that encompassed all three runs of the task.

Though our main interest in the functional data concerned the strength of MZ twin correlations in BOLD activation, we were also interested in whether the paradigm activated the same regions in our adolescent sample as it had in previous studies using the task. To examine this, the within-subject output was passed to two separate group-level GLM's, one comprised of first-born twins and one comprised of second-born twins. These analyses produced mean statistical maps of the any-gain versus no-incentive contrast and any-loss versus no-incentive contrast, for each group. To verify that the activation in our sample was comparable to that found in previous studies, ROIs were created based on regions activated in a selection of prior MID studies in which gain was contrasted with no-incentive for the anticipatory delay period (Knutson et al., 2001a; Knutson et al., 2001b; Bjork et al., 2004) or loss was contrasted with no-incentive for the anticipatory delay period (Knutson et al., 2001a; Bjork et al., 2004; Bjork et al., 2010), including papers that had focused on MID task activation in adolescents. Talairach coordinates were converted into the MNI152 coordinate space. A spherical mask with a radius of 5 mm was created for each point coordinate. We confirmed that these ROIs were significantly activated in our sample using small volume corrections in the gain compared to no-incentive and loss compared to no-incentive contrasts in both the first born and second born twin group-level GLMs.

To ensure that there were no group differences in magnitude of activation during the gain compared to no-incentive and loss compared to no-incentive contrasts we extracted each participants' mean signal value from each ROI (which were different for the gain and loss contrasts) using the unthresholded statistical maps from the within-subject GLM. We then calculated an average value of activation in each ROI for the first born and second born twin groups. Next, we used IBM SPSS Statistics Version 20 software to determine if there were differences in overall task activation between twin groups in these regions. We ran paired t-tests to examine whether there might be differences associated with activation in each of the ROIs for each birth order group. Although the birth order groups are not independent, comparing them nevertheless provides an opportunity to determine if effects seen in one are reproduced in the other.

Next, we ran analyses at the level of twin pairs. First, in order to ensure that the effects of age and sex were not driving twin similarity, we regressed the extracted signal magnitude in all of the ROIs against each subject's age and sex. Using the residuals of BOLD activation for the four contrasts of interest from the MID task, we conducted within-twin pair intraclass correlations in Mplus version 6 (Muthén & Muthén, 2010). We re-ran all correlations without outlying values to determine whether outliers were driving significance. To ensure that the significant correlations obtained for brain activation were specific to the MZ twins, and would not be found in unrelated individuals, each subject was randomly paired with another, unrelated subject, to create 46 unrelated pairings for all four contrasts. We then computed intraclass correlations for these pairs.

We performed bootstrap analyses in Mplus to obtain empirical 95% and 99% confidence intervals on twin correlations for task-related brain activation. The bootstrap is a non-

parametric method for estimating the sampling distribution of a statistic. It relies on random sampling with replacement from the original sample and is useful in situations where asymptotic assumptions may not be warranted (for example, owing to a modest sample size).

Behavioral Analyses: We examined accuracy collapsed across all runs for all trial types, weighting the no-incentive trials twice, and calculated mean accuracy for both twin groups on the task. We conducted a paired t-test between first-born and second born twins on overall accuracy. Next, within each twin group we conducted paired t-tests between large and small gains and large and small losses. We also conducted repeated-measures ANOVA within each twin group comparing accuracy across the gain, no incentive, and loss conditions.

In exploring twin similarity in the task from behavioral standpoint, we were interested in twin similarity in reaction times. First, we conducted a paired t-test to determine whether there were statistically significant differences between the first-born and second-born twin groups in reaction times. Next we conducted intraclass correlations in Mplus, bootstrapping the confidence intervals, on reaction times. We ran correlations on overall reaction time (collapsed across all trial types and all runs), large gain trials, large loss trials, small gain trials, and small loss trials. Additionally, to determine the relationship between reaction time and BOLD activation in all of the ROIs, we ran correlations between BOLD activation in all of the ROIs and reaction time in both twin groups. Reaction time for these correlations with BOLD activation was defined as the difference between reaction time during the gain or loss trials compared to the no-incentive trials.

Results

The intraclass correlations, *p*-values, and bootstrapped confidence intervals for gain compared to no-incentive can be found in Table 1, and for the other contrasts in Supplemental Tables 1, 2, and 3. Our results show that in the right nucleus accumbens, left and right posterior caudate, right anterior caudate, left insula, and anterior cingulate cortex, twins are significantly, moderately correlated in their task-related brain activation during gain anticipation. Correlations between randomly paired individuals reveal no significant correlations, providing evidence for familial contribution to reward processing in these ROIs.

Birth Order Effects and Twin Similarity on MID Task Performance

Task accuracy was calculated for both birth order groups. First born twins had an average accuracy of 72.88% (*SD* = .074) and second born twins had average accuracy of 72.41% (*SD* = .061). There was no significant difference in accuracy between twin groups ($t = .387$, $p = .700$). In both groups there was a statistically significant impact of magnitude on accuracy, wherein both twin groups were more accurate on the large gain and loss conditions when compared to the small gain and loss conditions. There was no statistically significant difference between overall gain and overall loss in accuracy. There was no statistically significant difference in mean overall reaction times between twin groups.

In both twin groups, the difference between reaction time during all of the gain trials as compared to the no incentive trials was negatively correlated with increased activation in the ROIs (corrected for age and sex), except for activation in the right putamen in the second born twin group. Without correcting for multiple comparisons, activation in the left insula ($-.317, p = .032$), left thalamus ($-.329, p = .026$), and right amygdala ($-.327, p = .026$) were significantly correlated (at $p = .05$) with faster reaction time in the first-born twin group. In the second born twin group, activation in the anterior cingulate ($-.301, p = .042$), left putamen ($-.328, p = .026$), left thalamus ($-.306, p = .038$), right insula ($-.292, p = .049$), right nucleus accumbens ($-.302, p = .042$), and right thalamus ($-.304, p = .040$) were all significantly correlated with faster reaction time.

During the loss compared to no-incentive contrast, there were no significant correlations (at $p = .05$) between brain activation in any of the ROIs and reaction time during the loss trials compared to the no-incentive trials in the first born twin group. In the second born twin group, there was one significant correlation between activation in the right putamen ($.319, p = .031$) and reaction time, not correcting for multiple comparisons.

Twin similarity was evident in task performance. Significant intraclass correlations within twin pairs were observed for overall reaction time ($.568, p < .001$), large gain reaction time ($.564, p < .001$), small gain reaction time ($.304, p = .041$), large loss reaction time ($.433, p = .001$), and small loss reaction time ($.288, p = .025$).

Brain Activation During the MID Task

Task activation was determined for both twin groups using small volume corrections (SVCs) for the ROIs for the gain compared to no-incentive contrast and the loss compared to no-incentive contrast. For both first and second born twins, SVC revealed a significant increase in BOLD signal during the gain compared to the no-incentive contrast in all of the ROIs except for in the right putamen. We found significant activation in the anatomical right putamen (defined using the Harvard-Oxford Subcortical Atlas) in both twin groups. This indicates activation in a similar region, but not the narrowly defined ROI based on the identified regions found in previous studies. Figure 2 shows the main effect of gain compared to no-incentive for first born and second born twins, shown on axial, coronal, and sagittal slices in MNI space ($z=3.0, p < .001$).

For the loss compared to no-incentive contrast, using SVC, we found a significant increase in BOLD signal in the right putamen, left putamen, right insula, left thalamus, right precentral gyrus, supplemental motor area, mesial cerebellum, right caudate right anterior thalamus, and right medial caudate in both first born and second born twins. For the loss compared to no-incentive contrast, no significant activation was found in the right middle occipital gyrus, or the right medial frontal gyrus in the first born twin group, and no significant activation was found in the left or right tail of the caudate or the right medial frontal gyrus in the second born twin group.

Mean signal values were extracted for each individual in each group for each ROI. After regressing out the effects of sex and age, all of the individual scores were averaged within the groups. Using paired t-tests in SPSS, we determined that there were no significant

differences in task-related brain activation between the first-born and second-born twins in any of these regions in the gain compared to no-incentive contrast or the loss compared to no-incentive contrast.

Finally, we examined twin intraclass correlations in the residuals of task-related activation in the ROIs from the contrasts of gain compared to no-incentive, loss compared to no-incentive, large gain compared to small gain, and large loss compared to small loss. Within-twin pair correlations for task-related brain activation during the gain compared to no incentive contrast, p -values, and the bootstrapped confidence intervals for these effects during the gain compared to no-incentive contrast are shown in Table 1. All correlations considered to be significant had both 95% and 99% confidence intervals that did not contain zero. Additionally, Bonferroni correction of $p = .05$ for 18 comparisons during the gain compared to no-incentive and large gain compared to small gain contrasts yielded a corrected criterion of $p = .003$. Significant correlations in the gain compared to no-incentive contrast were found in one third of the ROIs. These ROIs included the anterior cingulate, left posterior caudate, right nucleus accumbens, left insula, right posterior caudate, and right anterior caudate. Scatterplots for significant correlations for the contrast of gain compared to no-incentive are displayed in Figure 3.

There were no significant correlations in the large gain compared to small gain contrast. After using a Bonferroni correction of $p = .05$ for 15 comparisons during the loss compared to no-incentive and large loss compared to small loss contrasts yielded a corrected criterion of $p = .003$. No significant ICCs were found in the loss compared to no-incentive contrast. After removing one twin pair from the loss compared to no-incentive contrast, in which both twins had extreme outlying values in multiple ROIs (greater than 3 standard deviations from the mean), we found significant correlations in the right medial caudate and supplementary motor area. For the large loss compared to small loss contrast there were significant correlations in the right caudate, left cuneus, right precentral gyrus, and supplementary motor area. The tables with the correlations for the large gain compared to small gain, loss compared to no-incentive, and large loss compared to small loss contrasts are available in Supplemental Tables 1, 2, and 3.

Results from the random pairing of first and second born twins for the gain compared to no-incentive contrast revealed no significant correlations in residuals of task-related brain activation in any of the brain regions analyzed. Similarly, there were no significant correlations in the random pairings for the loss compared to no-incentive contrast, the large gain compared to small gain contrast, and the large loss compared to small loss contrast.

Discussion

The current study is the first to investigate the extent to which individual variation in brain activation associated with a reward paradigm (the MID task) is correlated within pairs of MZ twins. Using an MZ twin design, this study showed that reward-related brain activation during the anticipation of gain is familial, and thus may be an important marker for disorders associated with altered reward processing. Brain regions including the nucleus accumbens, caudate, insula, and anterior cingulate cortex showed significant within twin correlations in

task related brain activation during the anticipation of reward, indicating a shared familial contribution to activation in key areas associated with reward. These findings are particularly noteworthy given the fact that the participants are all mid-adolescents, a developmental period defined by substantial neurodevelopmental changes (Spear, 2011).

When twin pairs were split into two groups based on birth order, there were no significant differences between twin groups in brain activation in any of the ROIs. Both groups showed statistically significant activation during the gain compared to no-incentive contrast in all of the ROIs identified from previous studies using the task, except for the right putamen. This indicates that, by and large, the task was activating the same anatomical regions in both of our sub-samples, regardless of birth order, as it had in previous studies during the gain compared to no-incentive contrast. In the group analyses from the loss compared to no-incentive contrast, neither twin group had above threshold activation for the right medial frontal gyrus. The first born twin group also did not have significant activation in the right occipital gyrus and the second born twin group did not have significant activation in the left or right tail of the caudate, regions which had been activated in previous studies using the task. The more variable findings during the loss contrast are in line with previous studies that seem to indicate that anticipation of gain more consistently activates a specific brain circuit, as compared to anticipation of loss (Knutson et al., 2008).

For the group analyses for this study, we created two statistical maps, one for each twin group based on birth order. This allowed us to conduct group analyses of neuroimaging data without including twin pairs in the same analysis, which would have violated the assumption of independence of observations. Additionally, this method allowed us to confirm that there were no birth order effects on task-related brain activation during the MID task, as well as enabling us to verify that the ROIs found in the gain and loss contrasts in previous studies were, by and large, activated in our sample. We also found evidence for the task effects “replicating” in our study, with both twin groups activating the same ROIs during the gain contrast and, for the most part, during the loss contrast of the MID task. This provided a type of within-study replication that, although not based on independent samples, nevertheless provided support for the activation observed in our sample.

MZ twins showed moderate correlations in one third of those regions examined during the gain compared to no-incentive contrast during the anticipation stage of reward processing. The moderate correlations seen during this gain contrast are supported by the moderate and significant intraclass correlations seen within twin pairs in the behavioral measure of reaction time. The highest twin correlations for reaction time were found in the overall reaction time and in the large gain condition, followed by the large loss condition, and with lower (though still highly significant) correlations for small gain and small loss conditions. Similarly, we found higher correlations between BOLD activity and reaction time during the gain compared to no-incentive contrast as compared to the loss compared to no-incentive contrast.

The regions with moderate and significant within pair correlations during the reward processing include the left caudate, right caudate, right nucleus accumbens, anterior cingulate and left insula. Though all of the regions examined have been implicated in

previous studies using the MID task, the specific regions that have shown within twin pair correlations, in particular the caudate, the nucleus accumbens, and the anterior cingulate, play an important role in the decision-making, contingency learning, and motivational features of reward processing (O'Doherty et al., 2004; Balleine, Delgado, Hikosaka, 2007). Additionally, there is evidence that certain regions are more reliably activated by the MID task (Wu et al., 2014) over time, including activation of the right and left nucleus accumbens during the gain compared to no-incentive contrast, providing one potential explanation for higher correlations within twin pairs in certain of the ROIs, such as the right nucleus accumbens. This study by Wu and colleagues only examined test-retest reliability in three ROIs, namely the mPFC, the insula, and the nucleus accumbens. As a result, future studies are necessary to determine whether task reliability in certain ROIs may be part of the explanation as to why there are higher correlations within twin pairs in brain activity in certain regions, given that test-retest reliability represents the upper limit for familial correlations. The within twin pair correlations in task-related brain activation in these regions indicate that individual variation in the specific reward-related functions of these regions is influenced by familial factors. This finding is supported by the low correlations, with a median of close to zero, computed between random pairings of study subjects. This suggests that twins are considerably more similar within pairs, for certain features of task related brain activation, than randomly paired individuals are.

The moderate twin correlations in a number of ROIs during the reward processing add to the study by Andrews et al. (2011) which found higher rates of altered reward processing during the MID task in family members of alcoholics. This study provides further evidence for the potential strength of this neural pattern to serve as an endophenotype for certain psychiatric outcomes and impulsive behaviors, which have shown correlations with altered patterns of reward processing. One other study (Lessov-Schlagger et al., 2013) also examined reward processing in MZ twins, but focused on twins who were discordant for smoking behavior, and thus was studying twin differences, not similarities, in reward processing. Thus, this study is the first to show twin similarity in reward related brain activation, regardless of psychopathology.

We have reason to believe that these findings may reflect genetic effects. Prior imaging studies have shown that certain polymorphisms in genes associated with the dopaminergic system may moderate the reward responses in the ventral striatum specifically during the anticipation phase of reward processing during fMRI studies (Yacubian et al., 2007; Dreher et al., 2009). Studies such as these indicate that activation in the reward system during the anticipation stage, assessed using fMRI during the MID or similar tasks is likely influenced by the heritable variation in dopamine neurotransmission. These studies find that, in regions such as the ventral striatum, specific genetic polymorphisms moderate task related brain activation during reward processing. This line of research provides preliminary evidence for differences in the heritable dopaminergic system moderating brain activation. Though not the full story, these prior studies can help offer one possible explanation for the moderately sized task-related brain activation correlations we see in MZ twin pairs in this study in only some, but not all, of the ROIs. Further research, integrating twins, fMRI, and genotyping, could help bring greater clarity to our understanding of the heritability and genetics of reward processing.

Due to the lack of DZ twin pairs, we are limited in our ability to interpret the effects as due to genetic influence. Previous studies using fMRI in twins have not found evidence for shared environmental influences on twin similarity in brain activation but have found evidence for a genetic influence on twin similarity in brain activation. As a result, we have reason to believe that the moderate correlations in task-related brain-activation in certain ROIs, which we see in MZ twins, contrasted with the very low correlations in random pairings of subjects, are potentially due to genetic similarity. In the largest study of twin similarity to date, Blokland et al. (2011) found no role of shared environment in explaining twin similarity in brain activation during the n-back task of working memory. Based on the moderate, significant correlations within MZ twin pairs in task related brain activation during the MID task found in the current study, future studies are justified using both MZ twins and DZ twins to extend these findings.

It is important to note that within FSL and other comparable fMRI software there is currently no facility for fitting biometrical models to twin data. This means that it is challenging to perform voxel-by-voxel comparisons between activation in two twin groups due to the enormous number of voxels in a whole brain analysis and, therefore, the resulting number of accompanying comparisons. Additionally, there is no way to correct for the non-independent data when all twins are included within one group analysis, such as clustering twin data within families, in current neuroimaging software. As a result, these types of analyses are most often done, as we have done in this paper, by extracting mean values for ROIs and analyzing the data in external statistical programs, such as Mplus. A negative outcome of this method is that a single data point represents an entire structural location and the internal spatial variation provided by the multiple voxels within the ROI is lost. With the growth of neuroimaging genetics as a field, there is a need for imaging software that can directly fit biometrical models to twin and family data.

Conclusion

This study represents the first effort to study familial influences on brain activation during reward processing, as measured by the MID task. We believe that the moderate and significant correlations that we found in a number of ROIs in this reasonably large sample of MZ twins in task-related brain activation during the anticipation of gain compared to no-incentive now justifies further research with the MID task using bigger data sets including both MZ and DZ twins. Future research in this area could contribute to a better understanding of the relative genetic and environmental contributions to reward-related brain activation, and may strengthen the utility of using altered brain activation during the MID task as an endophenotype. A better grasp of the genetic contributions to reward processing could open doors to research on a number of psychiatric conditions, personality traits, and externalizing behaviors, all theorized to result in part from altered reward processing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Brain activation was correlated in MZ twins in key brain regions during a reward task.
- MZ twins showed similar magnitude of brain activation during anticipation of gain.
- MZ twin correlations in magnitude of task activation suggest that it is familial.
- Nucleus accumbens, caudate, insula and ACC activations were correlated in twin pairs.

Figure 1.

Structure of task for a medium gain trial. (a) Cue lasting 250 ms (b) Delay period lasting 2000–2500 ms, randomly determined and variable from trial to trial (c) Target screen, requiring button press, lasting for a fixed duration between 180–280 ms, titrated for each subject, based on their reaction time during the previous run (d) Second delay period lasting between 1720–2320 ms, depending on the length of the previous periods (e) Feedback on task performance, including money lost or gained during that trial and cumulative earnings across the run, lasting 1650 ms (f) Interstimulus interval (not depicted in figure), lasting 100 ms between each trial.

Figure 2.

Mean activation in first-born and second born twins. Group activation at the $z > 3$ ($p < .001$) level for the first-born twins and the second-born twins from the gain compared to no-incentive contrast is shown in MNI space. The task reliably activates the mesocorticolimbic system in nearly all of the regions of interest identified from regions from previous studies using the task in this contrast, in both twin groups.

Figure 3.

Twin similarity in brain activation during the anticipation stage of the task, during the gain compared to no-incentive contrast. These scatterplots depict all regions during the gain compared to no-incentive contrast that had significant twin correlations in the residuals of task-related brain activation after correcting for age and sex.

Table 1

Intraclass Correlation Coefficient for Within-Twin Pair Brain Activation (Corrected for Age and sex) for Gain Compared to No-Incentive¹

Brain ROI	ICC	99% Bootstrap CI	95% Bootstrap CI	P-value	X,Y,Z Talairach
Left Thalamus	.25	-.09, .63	-.02, .53	.074	-5, -6, 10 ²
Right Thalamus	.43	.06, .96	.14, .80	.010	3, -6, 9 2,3,4
Left Putamen	-.24	-.93, .14	-.74, .11	.279	-18, 10, -8 ^{2,4}
Right Putamen	.39	.06, .68	.11, .56	.005	20, 4, 6 ⁴
Left Anterior Caudate	.14	-.26, .52	-.15, .43	.347	-7, 1, 9 ⁴
Left Posterior Caudate	.41	.10, .80	.15, .68	.003	-7, 10, 3^{2,3,4}
Right Anterior Caudate	.53	.14, 1.00	.23, .93	.003	8, 3, 10⁴
Right Posterior Caudate	.51	.19, .87	.25, .78	<.001	10, 10, 2^{2,3}
Left Amygdala	-.03	-.44, .34	-.33, .25	.865	-16, 0, -11 ⁴
Right Amygdala	-.10	-.75, .32	-.57, .23	.635	20, 0, -14 ^{2,3}
Left Nucleus Accumbens	.33	.00, .76	.06, .68	.040	-8, 12, 0 ³
Right Nucleus Accumbens	.38	.03, .71	.13, .63	.003	11, 15, -2^{2,3,4}
Left Insula	.42	.11, .75	.18, .68	.001	-28, 14, -4^{3,5}
Right Insula	.04	-.32, .34	-.23, .29	.760	35, 17, -3 ³
Anterior Cingulate	.35	.03, .67	.13, .60	.003	1, 19, 30⁴
Posterior Cingulate	-.15	-.49, .13	-.40, .09	.209	0, -28, 30 ⁴
Anterior mPFC	.15	-.17, .49	-.11, .43	.297	3, 28, 33 ⁴
Posterior mPFC	.32	.03, .66	.09, .56	.007	3, 14, 41 ⁴

¹ Bold text indicates significant correlations (Bonferroni corrected for multiple comparisons at .05/18, $p = .003$) for within-twin brain activation and their associated p -values. The ROIs represented are the residuals of BOLD activation, after regressing out age and sex related differences.

² Bjork et al., 2004.

³ Knutson et al., 2001b.

⁴ Knutson et al., 2001a.

⁵ Previous studies hypothesized bilateral activation in the insula (see Knutson et al., 2001b), but did not find left insula activation. Our study showed clear bilateral activation, therefore we included a left insula region based on the region hypothesized by Knutson et al., 2001b; Breiter et al., 1997).