Hyporesponsive Reward Anticipation in the Basal Ganglia following Severe Institutional Deprivation Early in Life

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Abstract

■ Severe deprivation in the first few years of life is associated with multiple difficulties in cognition and behavior. However, the brain basis for these difficulties is poorly understood. Structural and functional neuroimaging studies have implicated limbic system structures as dysfunctional, and one functional imaging study in a heterogeneous group of maltreated individuals has confirmed the presence of abnormalities in the basal ganglia. Based on these studies and known dopaminergic abnormalities from studies in experimental animals using social isolation, we used a task of monetary reward anticipation to examine the functional integrity of brain regions previously shown to be implicated in reward processing. Our sample included a group of adolescents (n = 12) who had experienced global deprivation early in their lives in Romania prior to adoption into UK families. In contrast to a nonadopted comparison group (n = 11), the adoptees did not recruit the striatum during reward anticipation despite comparable performance accuracy and latency. These results show, for the first time, an association between early institutional deprivation and brain reward systems in humans and highlight potential neural vulnerabilities resulting from such exposures. ■

INTRODUCTION

The response to reward-predicting cues in the environment is a key mechanism by which organisms can adapt their behavior (Schultz, 2006; O'Doherty, 2004). Experimental and observational studies in animals, although not directly comparable with humans, have demonstrated the role of brain systems mediating such responses in motivational function (Wise, 2004; Wise & Bozarth, 1982). A critical brain region in this system is the nucleus accumbens in the ventral portion of the striatum (Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). The role of this region in motivational function is further highlighted by connections from and to midbrain dopaminergic neurons as well as its place in fronto-striatal circuitry with thalamic, anterior cingulate, and orbito-medial frontal cortical regions (Haber, Fudge, & McFarland, 2000; Haber & McFarland, 1999; Alexander, Delong, & Strick, 1986). Electrophysiological and lesion studies in experimental animals clearly show the sensitivity of dopaminergic pathways to early adverse experiences (Powell et al., 2003; Hall et al., 1998; Jones, Hernandez, Kendall, Marsden, & Robbins, 1992; Jones, Marsden, & Robbins, 1990; Sahakian, Robbins, Morgan, & Iversen, 1975). For instance, in rodents, repeated social isolation causes altered behavioral responses consonant with abnormal mesolimbic dopamine function, including hyperlocomotion in novel environments (Del Arco, Zhu, Terasmaa, Mohammed, & Fuxe, 2004), altered dopamine levels in the nucleus accumbens and prefrontal cortex (Fulford & Marsden, 1998b; Jones et al., 1992), altered responses to amphetamine and dopamine agonists (Phillips, Howes, Whitelaw, Robbins, & Everitt, 1994; Phillips, Howes, Whitelaw, Wilkinson, et al., 1994; Jones et al., 1990; Sahakian et al., 1975), and changes in behavioral sensitization to repeated amphetamine exposure (Weiss, Domeney, Heidbreder, Moreau, & Feldon, 2001; Ahmed, Stinus, Le Moal, & Cador, 1995). In marmoset monkeys, early life stress in the form of deprived parental care leads to increased peripheral dopamine markers and impaired behavioral inhibition and reversal learning, both functions thought to be mediated by dopamine and other monoamines (Pryce, Dettling, Spengler, Spaete, & Feldon, 2004). In rhesus monkeys, early adversity (peer-reared) resulted in enhanced reward responding in terms of consummation of sweetened water, although it was not clear if this reflected altered anticipation (wanting), or liking of reward (Nelson et al., 2009).

In humans, the effects of early negative experience on the development of the brain's motivational systems are suggested by two studies. First, children removed from their homes because of abuse and/or neglect are unable to adapt their reaction times to altered risk in a decision-making paradigm, suggesting altered reward processing (Guyer et al., 2006). Second, in a group of 13 adults reporting various forms of abuse before 14 years of age, reduced

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activity in the pallidum was evident during a reward anticipation paradigm (Dillon et al., 2009). The English and Romanian Adoptees (ERA) study cohort represent a group of people that experienced poor to appalling conditions in their early years living in the extremely deprived circumstances of state institutions of the Ceauşescu regime in Romania at the end of the 1980s. Typically, they remained in cots all day, had few if any toys or playthings, and were fed gruel through bottles with large teats; there was no personalized caregiving and very little talk or interaction with caregivers (see Castle et al., 1999; Rutter et al., 2009 for further details). Subsequently, these children were adopted into families living in the UK. Despite showing significant physical and cognitive catch up (Rutter, 1998) at the first longitudinal assessments (at ages 4 and 6), a substantial number of adoptees continue to show difficulties into mid-adolescence in a number of areas, specifically, quasi-autism (Rutter, Kreppner, et al., 2007), disinhibited attachment (Rutter, Colvert, et al., 2007), impaired cognition, and hyperactivity (Rutter, Kreppner, & O'Connor, 2001). The association between defined, early deprivation (and its consequences) and motivational dysfunction has not been reported.

A particularly useful paradigm for studying the ventral striatum in the context of motivated behavior is the monetary incentive delay (MID) task (Knutson, Adams, Fong, & Hommer, 2001). This event-related task allows investigation of the brain response to reward-predicting cues prior to making a simple response to a target stimulus, is appropriate for use in adolescent populations (Bjork et al., 2004), and has recently been validated using reward-related [^{11}C]raclopride PET imaging as an index of dopamine release (Schott et al., 2008). Impairments in ventral striatal activity during reward anticipation have been demonstrated in patients with schizophrenia (Juckel et al., 2006), attention-deficit/hyperactivity disorder (Strohle et al., 2008; Scheres, Milham, Knutson, & Castellanos, 2007), detoxified alcoholics (Wrase et al., 2007), and adults previously maltreated as children or adolescents (Dillon et al., 2009); the same task is sensitive to amphetamine (Knutson et al., 2004) and antipsychotic medication (Abler, Erk, & Walter, 2007).

Taking together all these elements provides a rationale for exploring the role of motivational systems in mediating the relationship between early deprivation and cognitive and behavioral outcomes in the ERA sample. The current study represents the first step in this process by comparing the recruitment of reward circuitry in a subsample of adolescents from this group to healthy controls using the MID task. This was one of three tasks included in the pilot imaging battery, the other two were a stop signal task measuring inhibition (Rubia, Smith, Brammer, Toone, & Taylor, 2005) and a task exploring social inference (Schultz et al., 2003). Based on the current literature, we predicted reduced activation to reward-predicting stimuli in the ventral striatum, which would interact with the level of reward.

METHODS

Participants

Fourteen Romanian adoptees were recruited from the 165 children in the ERA Romanian sample. Initial contact was made with 25 adoptees, who lived within relative geographical proximity to London, and agreement to participate was obtained from 17. These were identified on the basis of their levels of impairment. Approximately half scored in the top 15% of the full sample upon assessment in at least one out of four areas of difficulty (quasi-autism, hyperactivity, cognitive impairment, and disinhibited attachment, i.e., indiscriminate social approach and undifferentiated intimacy). This sampling approach allowed a broad range of impairment levels to be included in the study. Three potential participants were not included because they failed to meet selection criteria for MRI scanning or were unavailable for scanning on the available dates. Two further participants were excluded from the data analysis, with one being unable to perform the cognitive task and errors in data processing leading to exclusion of the other. All 12 remaining Romanian adoptees had experienced more than 6 months in institutions in Romania (9–41 months) before being adopted to UK families. Entry into the institutions occurred within the first few months of life and, therefore, age at adoption also approximates time spent in institutions. Five had deprivation-related impairments (as defined above). These five adoptees did not differ from the other adoptees in terms of time spent in institutions, sex, or age. The healthy comparison group comprised 11 UK-born, nonadopted age- and sex-matched adolescents from local schools ($p = .68$ and $p = .82$, respectively). Details of the Romanian and comparison groups are given in Table 1.

The study was approved by The Institute of Psychiatry and South London & Maudsley NHS Trust (Bethlem & Maudsley Hospitals) Research Ethical Committee. All participants and one parent for each participant provided written informed consent.

Image Acquisition

A 1.5-T GE Signa HDx Scanner (General Electric Medical Systems, Milwaukee, WI) was used to acquire gradient-echo, echo-planar images with TR = 2000 msec, TE = 40 msec, FOV = 24 cm, in-plane resolution = 3.75 mm^2, and matrix size = 64^2. A total of 21 axial slices aligned parallel to the AC–PC line was obtained with a thickness 5 mm (0.5 mm gap). For each of 2 runs of the MID task, 300 T2*-weighted image volumes were acquired over 10 min. A T2*-weighted high-resolution MR image was also acquired using single-shot EPI with TR = 3000 msec, TE = 40 msec, FOV = 24 cm, 3 mm slice thickness with 0.3 mm gap, matrix = 128^2, and 43 slices for estimation of normalization parameters to a standard space. Stimuli were presented using a computer running Windows XP Professional and projected onto a screen using

Table 1. Participant Information for the Romanian Adoptees and the Healthy Comparison Group

	Healthy Comparison Group	*Romanian Adoptees*	*Statistical Comparison*
n	11	12	–
Age (years)	16.0 (0.85)	16.1 (0.77)	*ns*
Sex (# males)	6	6	*ns*
Handedness (# right)	8	11	*ns*
Verbal IQ	107 (16)	96 (17)	*ns*
Performance IQ	101 (15)	80 (17)	$p = .005$
Full-scale IQ	105 (15)	86 (13)	$p = .003$
Time spent in institutions (months)	N/A	23.1 (8.0)	N/A

Values in brackets are standard deviations for the corresponding means.

an LCD projector. Participants viewed the projector through a mirror and made responses using a button box.

Monetary Incentive Delay Task

This task was adapted from the design described by Knutson et al. (2001) and can be considered as a cued reaction time test for which the cues signal the possibility of winning different levels of reward. The MID task was originally designed to minimize performance effects of varying incentive levels, which can confound the interpretation of task-related brain activations, by (i) emphasizing the need for response speed on all trials and (ii) employing a tracking procedure whereby the response window was adjusted to obtain a set proportion of correct and incorrect trials (Knutson et al., 2001). The task used in the current study had these two elements.

For each trial, one of four cues was used to signify no reward, low (20 pence), middle (£1.00), or high (£2.00) reward followed by a delay of 2000–2900 msec (average 2500 msec). After the delay, or anticipatory period, a white square (target) appeared on the center of the screen. A button box response was required while the white square was present in order for the cued reward amount to be "won." The time the target was present for (the response window) varied from trial to trial in 25-msec steps (150–350 msec) in order to obtain an average of approximately 66% target hits across all four cue conditions. Following the response, feedback was given (1650 msec) indicating a win or no win by showing the amount of money won and the total winnings. The screen went blank after the feedback for a variable delay to take each trial to 10 sec in length.

Data Analysis

Neuroimaging data were preprocessed and analyzed in SPM5 (www.fil.ion.ucl.ac.uk/spm) running in MATLAB 7.0.1 on a Windows XP computer. Images were initially realigned to the first scan (and then the mean image) from the time series. Parameters for normalization into standard space defined by the EPI template in SPM were determined from the high-resolution EPI image and applied to the coregistered time series of functional images. Data were spatially normalized using an 8-mm FWHM Gaussian kernel.

The data were analyzed using the general linear model (Friston et al., 1995). For individual sessions, regressors were defined for correct and incorrect trials for each of the four cues (and the subsequent anticipatory period), the target white square, and the feedback (and subsequent delay before the next trial). In addition, movement parameters from the realignment procedure were included in the individual models. Appropriately weighted linear contrasts were used to test the effect of reward on the cue-related anticipation period and feedback for each individual. For example, the contrast for all reward anticipation versus neutral was weighted as -3 for the neutral trials and $+1$ for each of the three reward trials. A high-pass filter of 128 sec was applied to the data and first-order temporal autocorrelation was modeled.

The contrast images from the first-level analysis were analyzed at the second level. One-sample t tests were used to define the activated networks in the Romanian and comparison groups separately and an independent-samples t test was used to compare the groups at the whole-brain level. All analyses were thresholded at $p = .001$ at the voxel level with clusters of activated voxels considered statistically significant at $p < .05$, corrected for multiple comparisons across the whole brain. In addition to the whole-brain analysis, region-of-interest (ROI) analysis was also performed. Predefined ROIs were derived from a previous analysis of the networks activated in adolescents performing the MID task (Bjork et al., 2004). These regions were the ventral striatum, caudate nucleus, amygdala, dorsal midbrain, thalamus, and right anterior insular cortex. Regional boundaries were taken from the WFU Pickatlas (Tzourio-Mazoyer et al., 2002), with the exception

of the ventral striatum which was based on the definition of Martinez et al. (2003), and anterior insular cortex which was defined as a sphere of 10-mm radius around the peak coordinate described in the prior study of healthy adolescents (Bjork et al., 2004). Data for the three contrasts of rewarded (low, middle, and high) and nonrewarded trials for these regions were extracted using the MarsBar toolbox [http://marsbar.sourceforge.net] (Brett, Anton, Valabregue, & Poline, 2002) and analyzed in SPSS version 15, which was also used for the analysis of accuracy and reaction time data from the task.

RESULTS

Task Performance

Accuracy on the MID task did not differ between the Romanian adoptees (mean = 60%, *SD* = 11%) and the comparison group (mean = 65%, *SD* = 1.2%). The variance in accuracy was larger in the Romanian adoptees (Levene's test, $F = 9.13, p = .006$) due to two participants having a low accuracy (36% and 38%). The analysis of the neuroimaging data only included correct trials and differences observed were not due to either of these participants and so they were included in the analyses. Response times (see Figure 1) did not differ between the two groups [$F(1, 21) = 0.02, p = .89$], suggesting they were equally engaged by the task. In keeping with the original studies of the MID task that emphasize rapid responding on all trials, there was also no main effect of reward level [$F(1, 21) = 0.33, p = .57$] and no interaction between group and reward level [$F(1, 21) = 0.08, p = .78$]. The target response window also did not differ between the groups [comparison group = 257 msec, *SD* = 18; adoptees = 261 msec, *SD* = 27; $F(1, 21) = 0.24, p = .64$]. The amount of money won was equivalent between the groups [comparison group = £33.00, *SD* = 2.23; adoptees = £29.58, *SD* = 6.82; $F(1, 21) = 2.52, p = .13$]. These findings did not differ after exclusion of the two low-accuracy performers. On the advice of the ethical committee, participants were all told that they will receive a proportion of their winnings, but were each given a fixed amount of £10 at the end of the session.

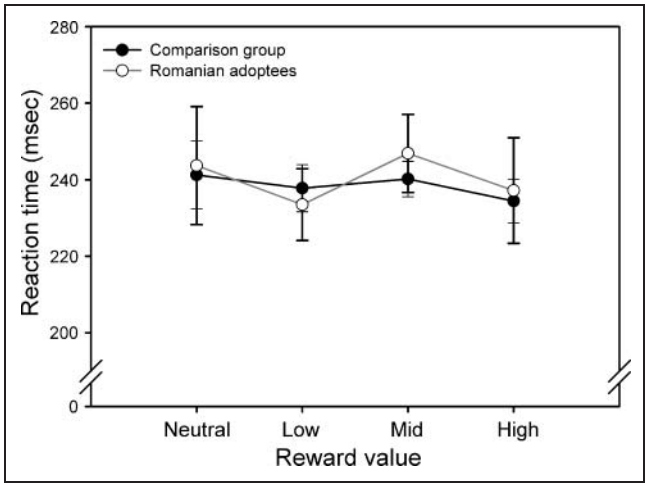

Figure 1. Reaction times on the different reward conditions of the MID task did not differ between the Romanian adoptees and the comparison group. Values plotted are means with standard errors of the means.

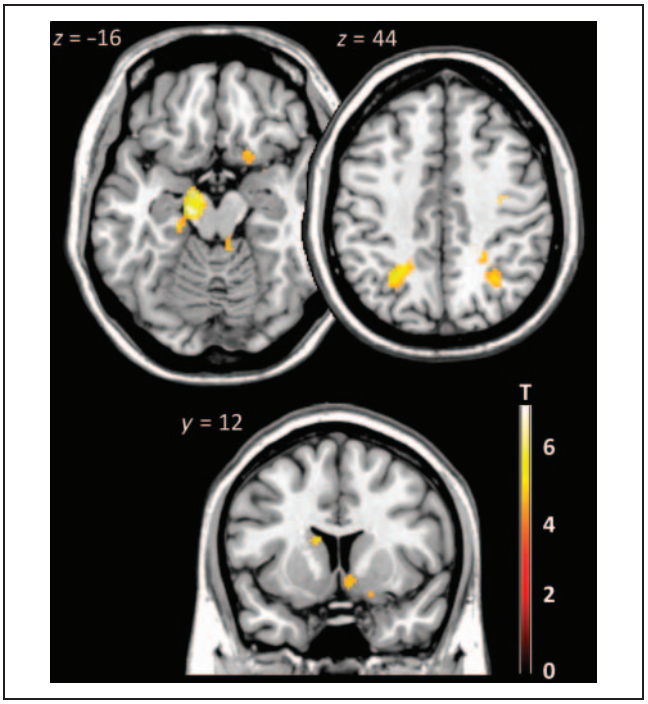

Figure 2. Brain sections overlaid with activations for the reward conditions contrasted against the neutral condition for the comparison group. The upper left transaxial section shows the midbrain activation (peak voxels at −14, −18, −16), the upper right section the posterior parietal lobe activations (−24, −54, 46 and 32, −58, 42), and the lower coronal section shows the ventral striatum (8, 12, −8). Activated voxels are shown at a threshold of $p = .001$, uncorrected for multiple comparisons. The midbrain and posterior parietal lobe clusters are significant clusters of activation at $p = .05$ (whole-brain corrected) and the ventral striatum cluster is significantly activated at $p = .05$, corrected for multiple comparisons for the predefined ventral striatal region. The caudate nucleus activation also visible on the coronal section did not survive correction for multiple comparisons across the striatal ROI.

Neuroimaging Analysis

Comparison Group

For the one-sample *t* test conducted in the comparison group of 11 participants, there were five significant clusters of activated voxels for the contrast of reward anticipation conditions versus anticipation following the neutral cue (see Figure 2). In accordance with our a priori hypothesis, a significant cluster of activated voxels was present in the ventral portion of the striatum [peak $x, y, z = 8, 12, -8$, $p(\text{corr}) < .05$]. The remaining clusters were located within the precentral gyrus, the dorsal midbrain (extending to the amygdala), and the posterior parietal lobe (bilateral) as shown in Table 2. The cluster present in the caudate nucleus

Table 2. Regions Activated during the Reward Anticipation Period of the MID Task in the Comparison Group

Region	*x*	*y*	*z*	*k*	*t*	*p(corr)*
R Precentral gyrus	34	−12	40	172	10.77	.045
L Dorsal midbrain	−14	−18	−16	357	7.08	.001
	−14	*−8*	*−18*	–	*6.97*	
	−12	*−34*	*−12*	–	*6.79*	
L Superior parietal lobule	−24	−54	46	231	6.05	.013
R Angular gyrus	24	−42	38	235	6.01	.012
	32	*−58*	*42*	–	*4.99*	
R Ventral striatum	8	12	−8	50	5.12	.038*

*Corrected *p* value after small-volume correction for the ventral portion of the striatum.

[−12, 12, 16] did not survive correction for multiple comparisons, but was included in the predefined ROI analysis. The contrast of rewarded and nonrewarded outcomes (feedback) did not show significant differences within this sample and, therefore, further analysis focused on the anticipation components of the task.

Romanian Adoptees

Whole-brain analysis of the Romanian adoptees did not reveal any significant clusters of activation.

Comparison between Groups

The ROI analysis showed a loss of the effect of reward anticipation in the Romanian group across the network of regions selected on the basis of previous research in adolescents (Bjork et al., 2004). These effects, defined as an interaction between reward level and group, were clearest and reached statistical significance in the ventral striatum and tended toward significance in the caudate nucleus (Table 3 and Figure 3). For these regions, there was a significant increase in activation dependent on the reward level for the comparison group, which was absent in the Romanian group. Post hoc analysis of simple effects confirmed that, for both these regions, activation differed across the groups for the middle and high reward conditions (all $p < .05$), but was similar for the low reward condition. The thalamus showed a similar response pattern although the interaction effect did not reach statistical significance. The differences observed were not modulated by the degree of deprivation-related problems ($n = 5$ with problems, $n = 7$ without problems). Exploratory whole-brain analysis did not reveal any additional differences between the Romanian and comparison groups.

Correlational Analyses

The possible interrelationships between changes in brain response to different levels of reward, reaction times, time spent in institutions, and hyperactivity scores (Goodman, 1997) were tested using Pearson's product–moment correlation coefficient. No correlations were statistically significant. The relationships between IQ and brain activation did not meet the assumptions for ANCOVA and, therefore, the influence of IQ upon the brain activations and performance was tested within each group only to ascertain if IQ influenced striatal activation. Those in the Romanian group with higher performance IQ tended to have a larger BOLD response to high reward in the thalamus (r = .58,

Table 3. Mean Activation (±*SD*) in the Predefined ROIs for the Two Groups during the Low, Middle (Mid), and High Reward Conditions Contrasted against the No-reward Condition

Region of Interest	*Group*	*Low*	*Mid*	*High*	*Group Effect (F, p)*	*Interaction Effect (F, p)*
Ventral striatum	Romanian	0.11 ± 0.17	0.14 ± 0.18	0.07 ± 0.19	**4.92, .038**	**5.11, .035**
	Comparison	0.04 ± 0.18	0.65 ± 0.18	0.80 ± 0.20		
Caudate nucleus	Romanian	0.12 ± 0.17	−0.23 ± 0.17	0.14 ± 0.18	**4.89, .038**	*2.80, .07*
	Comparison	0.01 ± 0.18	0.61 ± 0.18	0.67 ± 0.19		
Amygdala	Romanian	0.43 ± 0.28	−0.15 ± 0.19	0.14 ± 0.18	1.21, .28	1.76, .20
	Comparison	0.03 ± 0.29	0.52 ± 0.20	0.41 ± 0.18		
Midbrain	Romanian	0.35 ± 0.19	−0.03 ± 0.19	0.33 ± 0.18	1.83, .19	1.63, .21
	Comparison	0.21 ± 0.20	0.60 ± 0.20	0.60 ± 0.18		
Thalamus	Romanian	0.33 ± 0.22	−0.04 ± 0.23	0.30 ± 0.23	*3.94, .060*	2.23, .15
	Comparison	0.33 ± 0.24	0.85 ± 0.24	0.89 ± 0.24		
R Insula	Romanian	−0.01 ± 0.18	−0.18 ± 0.22	−0.10 ± 0.27	0.44, .52	1.78, .20
	Comparison	−0.19 ± 0.20	0.06 ± 0.24	0.32 ± 0.29		

The interaction effects if for Group × Reward level. Significant effects are highlighted in **bold**, with trends highlighted in *italics*.

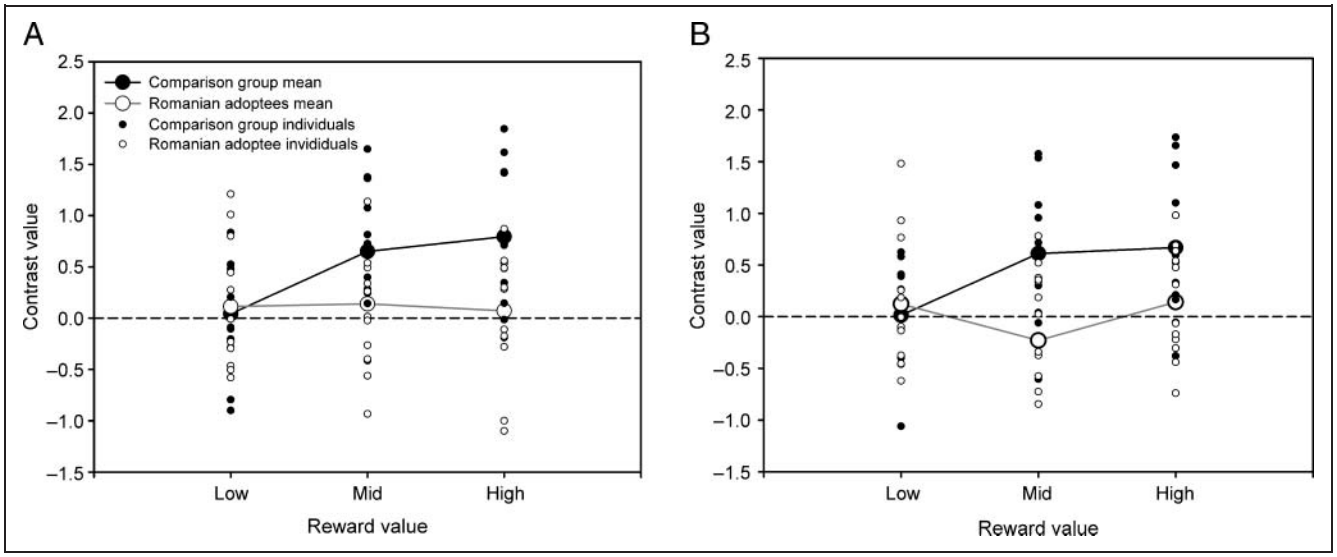

Figure 3. The activation in the (A) ventral striatum and (B) caudate nucleus for the anticipation of different reward magnitudes in the Romanian adoptees and comparison groups. Large circles are means for each group at each reward level and small circles are the values for each individual. Closed circles = comparison group; open circles = adoptees. The two groups differ for the middle and high reward levels.

$p = .048$). For the reaction times, those in the Romanian group with higher verbal IQ tended to respond faster to targets that followed the middle ($r = -.6, p = .037$) and higher ($r = -.53, p = .079$) reward cues.

DISCUSSION

The anticipation of reward is thought to be a critical element of motivational processing in the brain. We have shown that, compared with a healthy comparison group, adolescents who experienced severe global deprivation early in life have reduced recruitment of reward anticipation circuitry. Reduced ventral striatum activation on the MID task has previously been shown after an acute administration of amphetamine, antipsychotic medication, in patients with schizophrenia, detoxified alcoholics, and patients with ADHD (Strohle et al., 2008; Abler et al., 2007; Scheres et al., 2007; Wrase et al., 2007; Juckel et al., 2006; Bjork et al., 2004; Knutson et al., 2004). However, the Romanian adoptees evidenced an *absence* of ventral striatal activity across all reward levels.

In comparison to the neutral, or no reward conditions, the Romanian group did not activate the ventral striatum, or caudate nucleus, both of which showed a parametric response to reward magnitude in the comparison group. This effect suggests a lack of sensitivity to reward, or differences in reward value, which could potentially have a number of causes and consequences in the adoptees. First, it could be that the Romanian group did not engage with the task as well as the comparison group. This seems unlikely because (i) they were able to successfully complete the training on the task and could articulate the meaning of the different reward cues and (ii) their reaction times were not different from the comparison group. Similar to the original version of the MID task given to healthy adults (Knutson et al., 2001) and adolescents (Bjork et al., 2004), there was also virtually no difference in reaction time between the incentive conditions for both groups. The groups were also matched in terms of the average target window time and total monetary gain, which is important because it is known that performance differences can confound interpretation of functional brain imaging data (Callicott et al., 2003). However, we cannot rule out the possibility that differences in brain activation were also present during the training period and so it would be important to test general learning ability in this group, although it is notable that striatal activation during reward anticipation was not significantly related to IQ in either group. Given that the Romanian adoptees were engaged by the task, the hyporesponsiveness of ventral and dorsal striatal regions to reward anticipation could lead to effects in opposite directions. On the one hand, anhedonic or apathetic behavior may result, or on the other hand, compensatory reward seeking. Thus, the Romanian adoptees may be at heightened risk of substance abuse, other risk-taking behaviors associated with poor decision-making (Ernst & Fudge, 2009), or mood disorders (Martin-Soelch, 2009; Salamone, Correa, Farrar, & Mingote, 2007; Nestler & Carlezon, 2006). It remains to be seen how the neurobiological effects relate to the heterogeneous patterns of impairment and disorder found among a subgroup of children who had experienced severe deprivation in the ERA study.

The ventral striatum does not, of course, act alone, with prefrontal cortical, amygdala, and hippocampal influences on its function (Kalivas & Volkow, 2005; Haber et al., 2000). The amygdala has previously been implicated in the pathophysiological outcome of severe early deprivation (Mehta et al., 2009; Eluvathingal et al., 2006). Taken together with recent evidence linking amygdala and hippocampal white

matter connectivity to the ventral striatum with novelty seeking behavior (Cohen, Schoene-Bake, Elger, & Weber, 2009), this indicates an additional mechanism by which ventral striatal hyporesponsiveness may alter reward-related behavior, suggesting systems-level impairments in functionality following early deprivation. Detailed mapping of white matter pathways and brain connectivity patterns in the ERA sample, measured with both structural and functional imaging, are now required to fully elucidate the precise relationships between the abnormalities revealed, to date, and their impact upon daily life.

It is also possible that differences in ventral striatum activity reflect effects of valence or salience. It is difficult to disentangle these outcomes within this study, although previous work (Cooper & Knutson, 2008) manipulating certainty has suggested that both valence and salience are important factors contributing to ventral striatum activation in the MID task. It is thought that motivation is translated to action through activation of the caudate nucleus, which is also dysfunctional in the adoptees (Lauwereyns, Watanabe, Coe, & Hikosaka, 2002; Salamone & Correa, 2002), and various cortical areas (Gold, 2003; Kobayashi, Lauwereyns, Koizumi, Sakagami, & Hikosaka, 2002), including premotor cortex representing response preparation elements of motivation and orbito-frontal regions representing reward value (Hampton, Adolphs, Tyszka, & O'Doherty, 2007; Roesch & Olson, 2007). Tasks that enable the precise delineation of the component processes will be an important advance in determining the cortical contributions to reduced activation to reward-predicting stimuli in the basal ganglia. The reduced activation associated with expectation may lead to the prediction that the cortical response to reward outcome may also be dysfunctional as seen in ADHD (Strohle et al., 2008).

Based on the regions of reduced activation to reward-predicting stimuli, we would hypothesize that the dopaminergic system is a prime candidate for further research in the full ERA cohort. It seems likely that the striatal hyporesponsiveness is related to a *reduction* in dopamine function (Knutson & Gibbs, 2007), although it is important to note that changes in BOLD signal are not a direct measure of such an effect, thus whether the changes definitively result from a hyper- or hyporesponsiveness of dopamine neurons is unclear. Social isolation in rats can result in heightened dopamine release (Fulford & Marsden, 1998a) in the nucleus accumbens and the effect of amphetamine in healthy human volunteers, which causes increases in extracellular dopamine, is to reduce ventral striatal responsiveness on the MID task (Knutson et al., 2004). However, the differential influence on tonic and phasic firing of midbrain dopamine neurons of isolation rearing in either rodents or humans is not known. The pattern of results would also be expected if the neutral cue for no reward was as "salient" as the reward-related cue, reducing the differential involvement of striatal structures in *reward* anticipation. This would suggest impaired behavior guided by relevant cues and lead to abnormalities in attribution of appropriate responses to different environmental cues that have different associations with rewarding outcomes. Despite these limitations in interpretation, the recent proposal that BOLD signal increases in the ventral striatum may occur via increases in dopamine D1 receptor stimulation (Knutson & Gibbs, 2007), theoretically implies that pharmacological treatments that increase dopamine D1 receptor stimulation such as methylphenidate have the potential to improve activation of the reward systems in the ERA cohort. However, at this stage, the influences this may have on the domains of deprivation-related problems of quasi-autism, disinhibited attachment, cognitive impairment, and hyperactivity remain to be tested. In summary, the ventral striatal hyporesponsiveness may represent a mechanistic underpinning of a vulnerability to future reward-related difficulties in behavioral adaptation on exposure to environmental risk as can be conceived in the move to independent living. This will become more apparent as the ERA cohort enters adulthood, with possible negative outcomes including substance abuse and mood disorders.

Studies of social isolation in experimental animals are consistent with the regional changes observed in this study as they may relate to abnormal dopamine responses in the striatum (Busche, Polascheck, Lesting, Neddens, & Teuchert-Noodt, 2004; Howes, Dalley, Morrison, Robbins, & Everitt, 2000; Fulford & Marsden, 1998b; Hall et al., 1998; Phillips, Howes, Whitelaw, Robbins, & Everitt, 1995) or ventral tegmental area (Peters & O'Donnell, 2005). Both of these regions showed a clear response to reward anticipation in the control group, and although the cluster of activation for the midbrain overlapped more convincingly with the substantia nigra (and dopamine neurons here also respond to reward-predicting cues; Morris, Nevet, Arkadir, Vaadia, & Bergman, 2006), these small areas are notoriously difficult to image accurately with fMRI and may benefit from selective scanning at the expense of imaging the rest of the brain (D'Ardenne, McClure, Nystrom, & Cohen, 2008). However, the attenuation of the response of the midbrain region in the Romanian group was not statistically significant although the BOLD responses were summarized from the midbrain area as a whole, to accommodate difficulties in precise localization of the effects. Thus, an increase in power and spatial localization may indeed be beneficial to detection of possible effects of early deprivation in this small region.

Limitations

There are a number of limitations to this study. The first set of limitations relates to the groups under investigation. Although the results are in keeping with expectations from research in experimental animals, nonhuman primates, and adult humans, the number of adoptees was too small to reliably examine relationships between the degree of current problems and striatal abnormalities. Thus, we do not have the statistical power to disentangle the effects of deprivation from current psychopathology, although,

within our sample, there was no indication that those with greater deprivation-related problems differed in brain activation from those without such problems. However, it is encouraging that a recent study in a heterogeneous group of 13 adults with previous physical, sexual, or emotional abuse also showed reduced basal ganglia activation (limited to the pallidum) during a similar monetary incentive task (Dillon et al., 2009). Taken together, these studies provide a compelling argument to extend these findings into the larger ERA cohort. Such an extension of this work should also incorporate the nondeprived, but adopted, controls closely matched on demographic and cognitive variables. The comparison group used in this study, although matched in age and sex, had a higher IQ than the adoptees. Importantly, IQ did not correlate with striatal brain activation in either group, although the ability to analyze subgroups matched on IQ would clearly be beneficial. Due to the nature of the early adversity in the Romanian adoptees, details on pre- and perinatal adversity, and thus, their influence on the development of brain motivation networks are not known. The larger ERA study has utilized birthweight as a proxy measure for prenatal adversity and the contribution of this factor in the outcome measures is limited (Sonuga-Barke et al., 2008).

The second set of limitations relates to the paradigm. Although the analyses conducted show reduced activation to reward-predicting stimuli, further contrasts that allowed examination of potential abnormalities during the neutral (nonrewarded) condition were not possible using the existing task design, which would require an additional baseline condition. However, it was the middle and high reward conditions, and not the low reward condition, that showed difference between the groups. Thus, the adoptees may also present with altered activation during the neutral cue condition, likely reflecting attentional or visuomotor difficulties in addition to the findings in the striatum that were dependent on the reward level. The similarity in reaction times between the groups does, however, suggest that any difficulties with attentional or visuomotor processes were minimal. Importantly, this means that the neuroimaging differences are unlikely to simply reflect variations in performance between the groups.

In conclusion, we have confirmed our hypothesis of abnormal ventral striatal responsivity following severe early deprivation in a group of Romanian adoptees. Other determinants of ventral striatal function are just beginning to be understood. For example, functional genetic variants of the dopamine transporter can alter responsivity of the brain reward system (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009), with those homozygous for the 10-repeat allele (10/10) showing a reduced response in the ventral striatum and caudate nucleus during reward anticipation compared to carriers of the 9-repeat allele. Recent findings indicate that within the larger ERA cohort, the 10/10 carriers are more vulnerable to the effects of institutional deprivation in terms of ADHD symptoms (Stevens, Sonuga-Barke, Asherson, Kreppner, & Rutter, 2006). In this respect, it is noteworthy that the same task as used in this study is sensitive to ADHD (Strohle et al., 2008; Scheres et al., 2007), leading to the hypothesis that institutional deprivation, genetic variability, and symptomatic outcome all contribute to striatal function during motivated behavior.

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