BJPO/2015/001586, Data supplement

Method

Participants

Additional exclusion criteria for both the TD and RAD groups were as follows: premature birth (gestation ≤ 36 weeks); any history of diagnosed bipolar, psychotic, obsessive-compulsive, or tic disorder; any history of substance abuse or recent substance use; head trauma with loss of consciousness or epilepsy; significant fetal exposure to alcohol or drugs; perinatal or neonatal complications; medical conditions that could adversely affect growth and development; and left-handedness according to the Edinburgh handedness inventory (1).

Experimental task

The monetary reward task procedure is shown in Fig. DS1. During each trial (3 s), participants were presented with three cards labeled “A,” “B,” and “C” and within 2 s. Immediately after the button press, the chosen card was highlighted, and the outcome was displayed for 1 s. Participants knew that the expected value of the 8 reward trials was 240 yen. The NMR condition or a fixation rest condition (24 s) was always inserted between the two reward conditions, so that the start and end of the reward manipulations could be clearly defined. All participants completed a practice task for 2 min before scanning. Each session consisted of four blocks of trials from each of the four conditions (HMR, LMR, NMR and fixation rest) and therefore lasted 6 min 24 s (4 blocks x 4 conditions x 24 s per block). All participants were encouraged to try to earn as much money as possible and were told that one session would be randomly chosen at the end of the experiment and that their earnings in that session would be given to them.

fMRI acquisition and analysis

The first 4 volumes of each fMRI session were discarded to allow for stabilization of the magnetization, and the remaining 128 volumes were used for analysis. Following realignment, all images were normalized to the SPM8 (EPI) image template. The anatomically normalized EPI data were spatially smoothed in three dimensions using an 8-mm full-width half-maximum Gaussian kernel.

For the statistical analyses, motion-related artifacts were modeled as regressors of no interest using the six parameters (three displacements and three rotations) obtained by the rigid-body realignment procedure. The data were high-pass filtered with a cut-off period of 128 s to remove low-frequency signal drifts. An autoregressive model was used for whitening the residuals to meet the general linear model assumptions (2). The resulting set of voxel values for each comparison constituted a statistical parametric map of t statistics.

Sensitive period analysis

This is a form of machine learning in which a large number of unpruned decision trees are generated and their results aggregated. Random forest regression has the advantage of high accuracy, no restrictions regarding the distribution and scaling properties of the data, high tolerance for multicolinearity, does not assume a linear relationship between degree of exposure and outcome, can detect and model interactive effects between predictor variables and provides a novel means of determining variable importance (3, 4). We used a variant of Breiman's approach with conditional trees as the base learners to avoid a potential problem with biased estimates that can emerge when variables differ in range or number of categories. Conditional forest regression indicates importance by assessing the decrease in accuracy, as noted by the increase in mean square error (MSE), of the forest's fit following permutation of a given predictor variable. Permutation of important predictor variables produces a large increase in MSE, whereas permutation of unimportant predictors produces little or no increase in MSE.

While random forest regression is well suited for identifying ages when exposure severity has the most important predictive effect on an outcome (5), we also sought to determine whether the magnitude of importance at peak periods could have occurred by chance. Hence, we used a re-randomization test in which we calculated the maximal increase in MSE with severity of exposure at any age in the original data set, and then tested for this degree of increase in MSE in 10,000 alternative random forests regressions in which the association between regional volume and exposure histories was randomly reshuffled.

In another analysis, random forest regression was used to determine the comparative importance of exposure to neglect versus physical, psychological, or sexual abuse plus the comparative importance of abuse by mother, father, or grandmother. Number of types of maltreatment and number of perpetrators were included as additional predictors as multiplicity of exposure or polyvictimization may be more important determinants than specific type of exposure. For these analyses, we used contrast estimates of HMR condition (HMR minus NMR) for left and right striatum. Regional response was centered and scaled to provide an arbitrary mean of 100 and SD of 10, to facilitate comparisons between hemispheres in importance of exposure at each age using the increase in MSE criteria. Each forest consisted of 200 trees with four variables randomly selected for evaluation at each node.

Results

Behavioral results

Reaction times for the different reward conditions between the TD and RAD groups are shown in Fig. DS2.

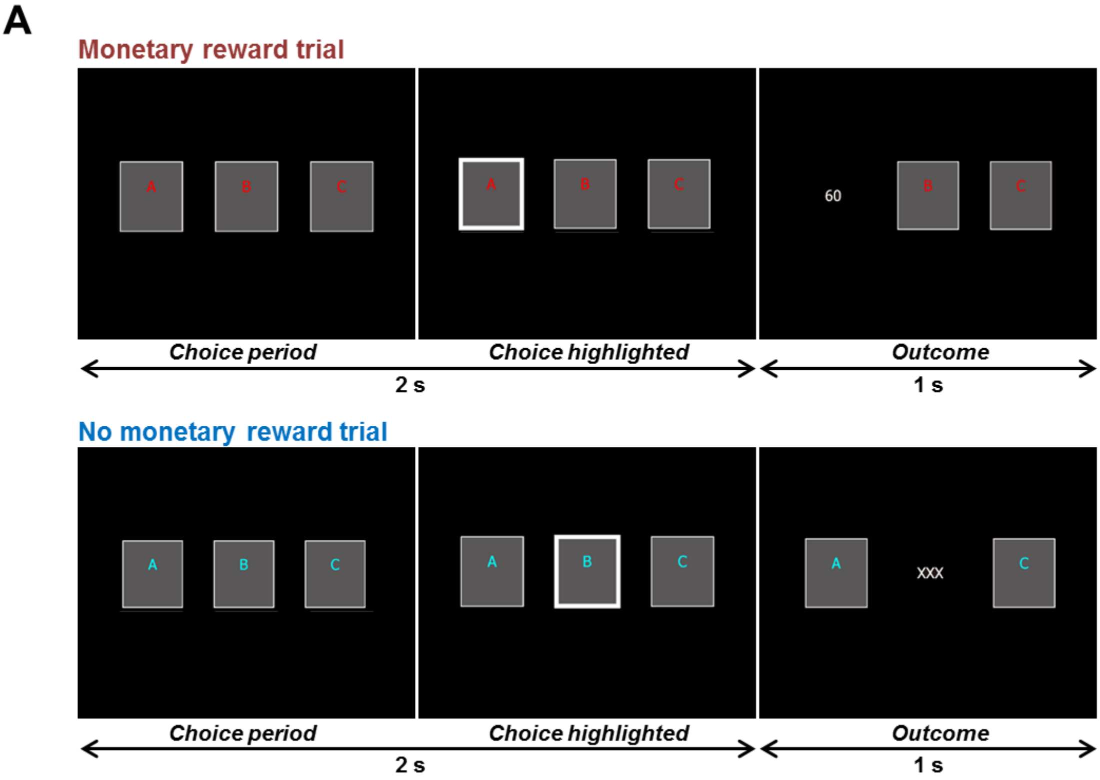
Imaging results

Activity in brain regions associated with the HMR and LMR conditions (HMR or LMR *minus* NMR) in the TD and RAD groups is shown in Table DS1.

Sensitive period analysis: Age of exposure

Degree of right striatal activation could be also predicted with reasonable accuracy based on type of maltreatment and identify of the perpetrator(s) ($r = 0.560$, $p < 0.003$) (Fig. DS3A). Neglect emerged as the most important specific type of maltreatment, but was dwarfed in importance by total number of types of maltreatment experienced. Father emerged as the most important perpetrator in this sample but was also eclipsed by the importance of number of different perpetrators. Altogether, multiplicity of exposure was the most important single predictor ($p = 0.0009$). Number of perpetrators was the second most important predictor, and the likelihood of obtaining two measures with this degree of importance was low ($p = 0.0005$).

Left striatal activation was also predicted with significant accuracy from information on type of maltreatment and identify of the perpetrator(s) ($r = 0.453$, $p < 0.018$) (Fig. DS3B). The pattern was similar to that for right striatum with neglect as the most important type of exposure and father as the most important perpetrator. However, number of perpetrators was the most important single predictor ($p = 0.0134$) and maltreatment by father the second most important predictor. Number of types of maltreatment was the third most important predictor.



B

	Monetary Reward Level		
	High Monetary Reward (HMR) block	Low Monetary Reward (LMR) block	No Monetary Reward (NMR) block
Average amount of money obtained	330 yen (270-390 yen)	150 yen (90–210 yen)	None

Fig. DS1. Time course of trials with monetary reward and no monetary reward conditions. (A) Each block consisted of eight trials with monetary reward or no monetary reward conditions (24 s). (Top) In each monetary reward trial, participants were asked to choose one card within 2 s, and the outcome of the chosen card (0, 30, or 60 yen) was shown for 1 s. (Bottom) In each no monetary reward trial, participants were similarly asked to choose one card, but the outcome was always “XXX”, indicating no monetary reward. For half the participants, the colors (red and blue) used for the letters on the cards in the monetary reward and NMR conditions were switched to control for differences in activity related to visual processing of colours.

(B) Study design of the monetary reward experiment. The amount of money each subject could earn in each block was predetermined in order to manipulate the monetary reward level.

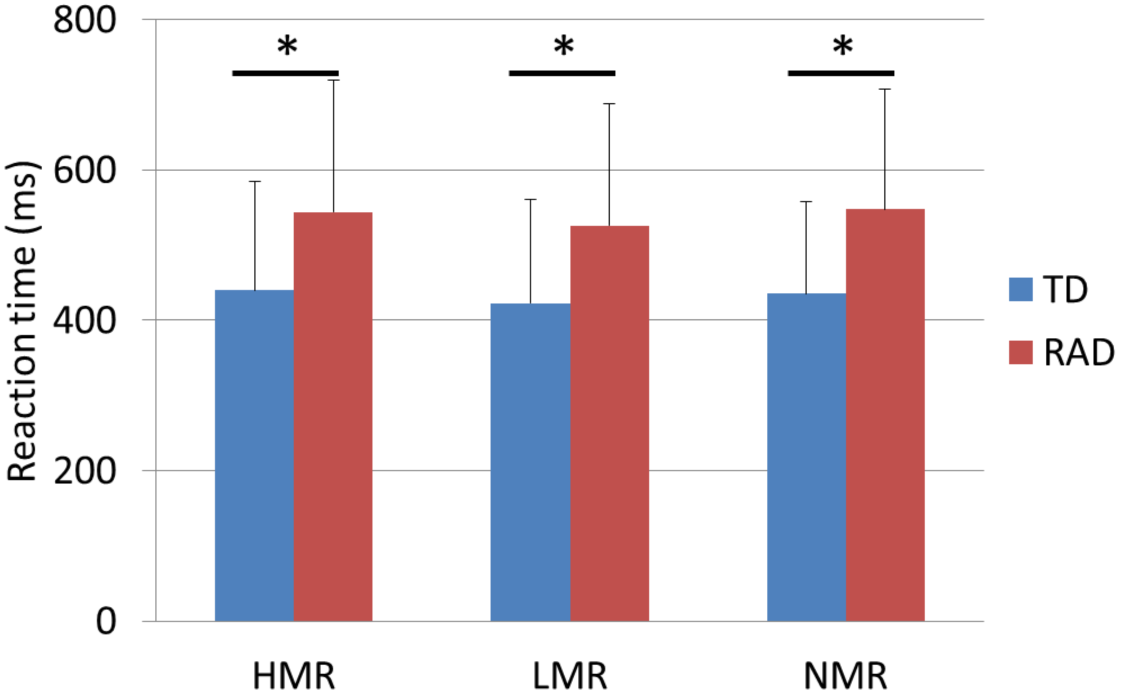


Fig. DS2. Reaction times for the different reward conditions between the TD and RAD groups. The plotted values are means with standard errors of the mean. *$p < 0.05$ compared with the TD group (two-way ANOVA).

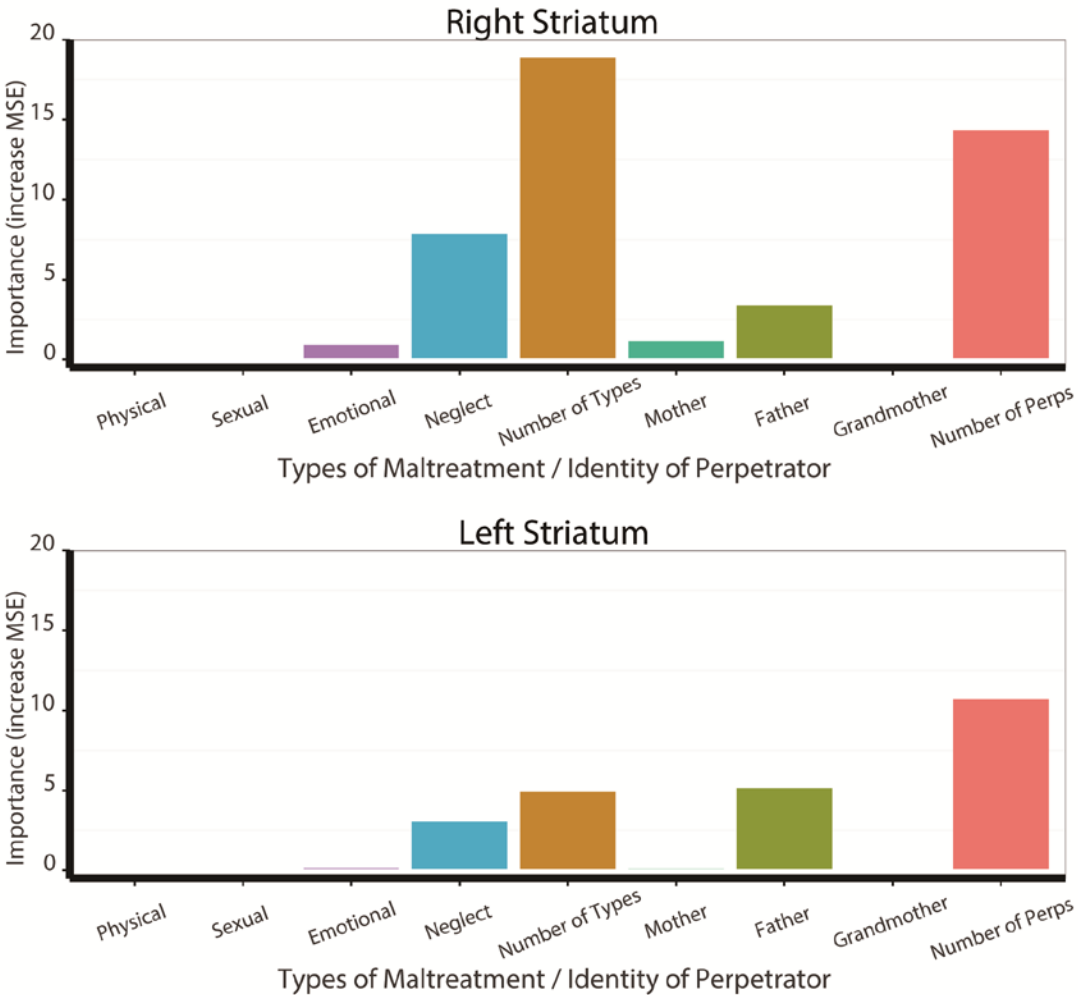


Fig. DS3. Maximal sensitivity by type of maltreatment and identity of the perpetrator(s) (maximal importance of type of maltreatment and identity of the perpetrator(s), regardless of age) in RAD. Results of random forest regression with conditional trees indicating importance of exposure to early maltreatment from birth to 15 years of age on contrast estimates of HMR condition (HMR minus NMR) for the right and left striatum. Importance is indicated by degradation in fit, as indicated by the increase in mean square error (MSE), following effective elimination of each age from the model by permutation.

Table DS1. Activity in brain regions associated with the high monetary reward (HMR) and low monetary reward (LMR) conditions in the TD and RAD groups.

Brain region	Cluster (mm^3)		Side	MNI coordinate			
	Size	*p* value		X	Y	Z	*T*-value
TD groups							
HMR *minus* NMR							
Caudate / NAc	51056	< 0.001	R	8	14	-4	9.16
			L	-10	10	-4	7.88
Cerebellum	25744	< 0.001	L	-44	-72	-34	5.72
			R	2	-64	-44	5.44
Anterior cingulate cortex	11184	< 0.001	R	6	34	30	6.26
			L	-10	30	26	5.00
Middle frontal gyrus	5544	0.002	R	48	24	34	5.07
Middle frontal gyrus	4720	0.004	R	34	8	58	6.05
Inferior occipital gyrus	2816	0.034	R	30	-96	-8	4.83
LMR *minus* NMR							
Caudate / NAc	41336	< 0.001	R	14	12	-4	8.12
			L	-10	8	-4	6.26
Cerebellum	18744	< 0.001	L	-30	-70	-26	6.19
Medial prefrontal cortex	16464	< 0.001	R	2	28	42	6.59
			L	-4	20	46	6.40
Middle frontal gyrus	15416	< 0.001	R	36	6	56	7.97
Inferior parietal lobule	7768	< 0.001	R	34	-50	44	4.85
Precuneus	5680	0.001	L	-12	-66	42	5.84
Cerebellum	4360	0.004	R	6	-66	-46	5.40
RAD groups							
HMR *minus* NMR							
Cerebellum	8544	< 0.001	L	-6	-84	-22	6.48
LMR *minus* NMR							
Brainstem	12888	< 0.001	R	4	-16	-16	6.16
			L	-4	-14	-14	6.08
Insula	3544	0.012	R	32	26	0	5.27
Inferior parietal lobule	3112	0.020	R	48	-58	44	4.55

NAc, Nucleus accumbens; NMR, No monetary reward; L, left; R, right; MNI, Montréal Neurological Institute. The statistical threshold was set at $p < 0.001$ at the voxel level and $p < 0.05$ with an FWE correction for multiple comparisons at the whole-brain cluster level.

Supplementary references

1. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;**9**:97-113.
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5. Choi J, Jeong B, Polcari A, Rohan ML, Teicher MH. Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. *Neuroimage* 2012;**59**:1071-9.