EVENT-RELATED FUNCTIONAL MAGNETIC RESONANCE IMAGING OF REWARD-RELATED BRAIN CIRCUITRY IN CHILDREN AND ADOLESCENTS

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BACKGROUND: Functional disturbances in reward-related brain systems are thought to play a role in the development of mood, impulse, and substance abuse disorders. Studies in non-human primates have identified brain regions, including the dorsal / ventral striatum and orbital-frontal cortex (OFC), in which neural activity is modulated by reward. Recent studies in adults have concurred with these findings by observing reward-contingent blood oxygen level dependant (BOLD) responses in these regions during functional magnetic resonance imaging (FMRI) paradigms. However no previous studies indicate whether comparable modulations of neural activity exist in the brain reward systems of children and adolescents. METHODS: We used event-related FMRI and a behavioral paradigm modeled on previous work in adults to study brain responses to monetary gains and losses in non-psychiatric children and adolescents as part of a program examining the neural substrates of anxiety and depression in youth. RESULTS: Regions and time-courses of reward-related activity were similar to those observed in adults with condition-dependent BOLD changes in the ventral striatum, lateral and medial OFC; specifically, these regions showed larger responses to positive than to negative feedback. CONCLUSIONS: These results provide further evidence for the value of event-related FMRI in examining reward systems of the brain, demonstrate the feasibility of this approach in children and adolescents, and establish a baseline from which to understand the pathophysiology of reward-related psychiatric disorders in youth.

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1.0 INTRODUCTION

The application of modern cognitive neuroscience methods in studying clinical populations holds promise for identifying brain circuits that underlie specific pathologies, such as those related to mood, impulse, and substance abuse disorders. One circuit implicated in these affective and behavioral disturbances is the reward system. This system should be supportive in eliciting approach behaviors and associative learning mechanisms necessary to motivate action and pair behaviors with outcomes (White 1989; Young 1959). The reward system may also participate in the processing of emotionally salient information, such as positive or negative feedback. Dysfunctional developmental changes in this reward system could lead to (a) decreased motivation to seek rewards, such as diminished initiation of social interactions or to (b) excessive or maladaptive increases in certain kinds of reward-seeking behavior, such as pathological gambling (Hollander et al 2000) or substance abuse (Koob et al 1998). To understand these pathologies from the perspective of neurological changes in the reward system, we need to appraise their normal development in addition to the normal mature end-state of the system. While neurobiological research has become less invasive with the continued development of methods such as functional magnetic resonance imaging (FMRI), investigating the neural mechanisms of cognitive functions in younger age groups is far from routine. The primary goal of the present study was to demonstrate the feasibility of studying youth reward systems during event-related FMRI, as has been done in adult imaging studies. Achieving this goal was expected

to provide a basis from which future studies may explore the underlying neurobiological disturbances associated with the development of pathological conditions (e.g. anxiety and depression, compulsive behaviors, substance abuse) in children and adolescents at risk for or with established psychopathology.

Identification of specific elements of the reward system has become well established through electrophysiological studies in non-human primates, which have observed single-cell firing rates modulated by reward within the basal ganglia, ventral tegmental area, nucleus accumbens, amygdala, orbital-frontal and prefrontal cortex (Apicella et al 1991; Hikosaka and Watanabe 2000; Schultz et al 2000; Wise 2002). Neuroimaging studies in humans have corroborated the electrophysiology data in studies using a variety of methods and rewards. Brain responses in the afore mentioned regions have been elicited by primary rewards, such as tastes and smells (Berns et al 2001; O'Doherty et al 2002; Pagnoni et al 2002; Small et al 2001); monetary rewards (Breiter et al 2001; Delgado et al 2003; Delgado et al 2000; Elliott et al 2003; Knutson et al 2000; Thut et al 1997); abstract rewards such as video-game performance (Koepp et al 1998); simple feedback signals (Elliott et al 1997; Elliott et al 1998); and even faces (Aharon et al 2001). Many of these regions have also been linked to clinical pathologies related to gambling, depression, and substance abuse (Bechara et al 1994; Drevets 2000; Lafer et al 1997; Leshner and Koob 1999).

In the present study, a reward paradigm based on a previous event-related FMRI experiment by Delgado et al (2000) was implemented in children and adolescents. This design allowed for a per-condition evaluation of time-courses associated with reward-related brain activations, plus a simple behavioral task, a “guessing game”, was used so that performance would be minimally influenced by cognitive and/or developmental factors. Within the dorsal and

ventral striatum, Delgado et al (2000) found greater blood oxygen level dependant (BOLD) activity in response to positive feedback than to negative feedback. Therefore, we expected to replicate these results in children and adolescents by finding that within dorsal and ventral striatum, the BOLD activity elicited by rewarding trials is greater and more sustained than the response to losing trials. Additionally, we anticipated the possibility of revealing condition-specific patterns of activity in the orbital-frontal cortex, a region that has been found in other reward-related studies but for which a well-defined response pattern and functional role is still unclear.

2.0 METHODS

2.1 PARTICIPANTS

Participants were 18 non-psychiatric children and adolescents ages 8-18 recruited through the Child and Adolescent Sleep & Neurobehavioral Laboratory at the Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania. All participants were medically and psychiatrically healthy and were assessed using the Schedule for Affective Disorders and Schizophrenia of School Age Children-Present and Lifetime version (K-SADS-PL) in order to confirm that they did not meet criteria for a mood or anxiety disorder and had no lifetime Axis I disorders (Kaufman et al 1997). Participants were consented according to the Institutional Review Board at the University of Pittsburgh Medical Center, which required written assent from the participant and written consent from a legal guardian. Data from 2 participants were excluded due to too few blocks being completed at the time of scan. An additional 4 participants were excluded from analyses due to excessive head movement within the scanner (inclusion criteria are discussed below), leaving the total number of participants included in the analysis at 12; their ages ranged from 9-16, mean 13.25, and their gender composition was 5 males, ages 10-16, mean 13.20 and 7 females, ages 9-16, mean 13.29. All but one subject was right handed.

To ensure participant comfort and maximize the likelihood of good data collection, special considerations were allowed for all participants. At the center of the procedures was an

MR simulator, which provided a similarly sized bore, sounds, head-coil, and apparatus just as that used in the actual MR magnet. All participants were exposed to the simulator to ensure their understanding of the environment and to gauge their comfort and likely success in the actual experiment. Although few participants made such a request, parents were permitted inside the control room and around the magnet after completing a standard safety screen. Time in the scanner that was spent acquiring structural data was occupied with movies projected on the stimulus presentation screen. Participant movement was further reduced through padded chinstraps that served as a reminder to participants not to move.

To be sure that each participant understood the task, the instructions were first presented verbally with paper printouts showing the various components of the task; then the participants performed the task on a computer outside the magnet such that they again saw each component of the task. Specifically, each type of feedback was accented to the participant.

2.2 PARADIGM

Participants were told they would be playing a game that consisted of guessing whether a hidden number behind a make-believe playing-card was greater or less than ‘5’. Participants were prompted to guess by a question mark ‘?’ appearing inside a playing-card shaped rectangle drawn in the middle of the screen. The range of possible numbers was ‘1’ through ‘9’, and the participants were informed of that as well. For every correct response, the participant would win $1.00 and lose $0.50 for every incorrect response. The ratio of 2:1 was selected based upon decision theory by Tversky and Kahneman (1981) as well as pilot testing by Delgado who found participants reported high level of discouragement when the win and loss amounts were equal.

Participants were told that the computer picked numbers randomly so there was no way to know what number was going to be revealed and specifically that the prompting question mark offered no clues. Additionally, participants were told that sometimes the computer would reveal the number '5', which the participant could not choose. In those cases, the participants would not win or lose any money and would receive a neutral feedback '--'. If a participant did not respond in time, they would see a pound sign '#' and would not win or lose any money. An illustration of possible choices and outcomes are presented in Figure 1. Participants responded to the task via an ergonomically designed button response system attached to the right hand.

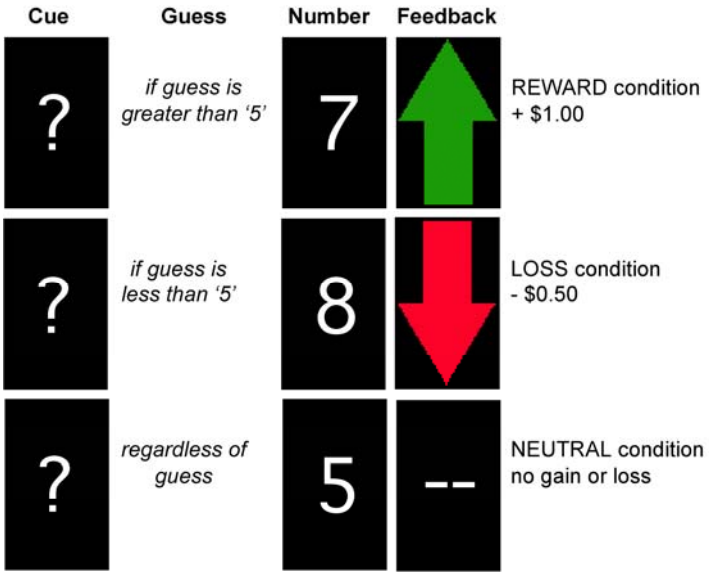

Figure 1. Components of the task

The order and timing of the task can be seen in Figure 2. At the beginning of each trial, a question mark '?' appeared in the center of the virtual card, prompting a response from the subject. The question mark remained on screen for 2500 msec, and participants had 2700 msec to make a response. A 500 msec blank card was presented after the question mark disappeared and

then the hidden number was exposed for 500 msec followed immediately by a feedback arrow, which also lasted 500 msec. The arrow pointed up and was printed in green if the participants' guess was correct. If the guess was wrong, participants saw a red arrow pointing down. All responses and visual stimuli were presented within the first 4 seconds of each trial. The stimuli plus an inter-trial interval of 12 seconds summed to a total trial length of 16 seconds and allowed for the hemodynamic response to return to baseline. The virtual card remained on-screen throughout the experiment, and subjects were instructed to focus on the center of the card during the ITI.

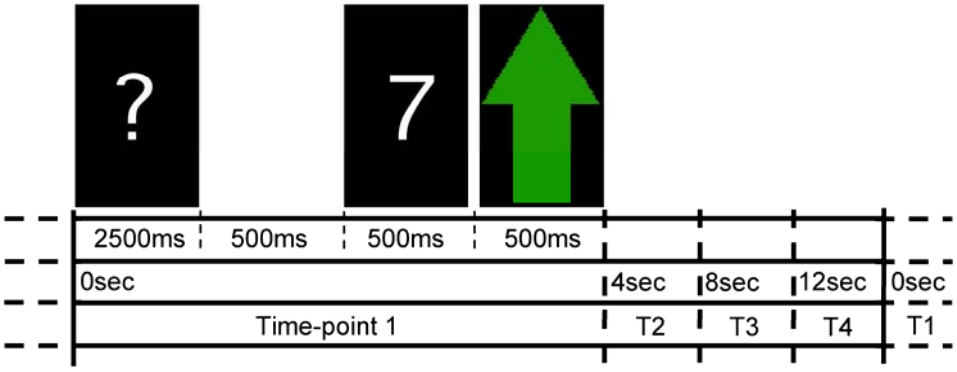

Figure 2. Timing of the task

The trials were presented in a fixed order such that the outcome of each trial was predetermined as being either a reward, loss, or neutral trial. The stimulus program, PsyScope, generated the hidden numbers based on the participants' response and in accordance with the predetermined trial type, controlling numbers of trial types (Cohen et al 1993). Trial order was determined with attention to prevent large runs of a single trial type (no more that 3 trials of one type allowed in a row) and sensitivity to participants' general affective state early in the task. The order generally had more 'wins' at the beginning to prevent participant discouragement,

slightly more ‘losses’ in the middle to even out the numbers of trials and ending with very evenly matched blocks between ‘wins’ and ‘losses’. This order is not to be confused with a block design, as the trial type is not reliable enough across any portion of the experiment to be analyzed in a blocked fashion. A total of 9 blocks were run, with each consisting of 15 trials. Of the total 135 trials, 40% (54) were reward, 40%, were loss, and 20% (27) were neutral. The total time spent in the scanner was roughly an hour and a half.

Participants were paid $30 per hour for time in the scanner and were given exactly the amount won while performing the task. Therefore, unless a participant asked to leave the experiment early, all subjects were paid a total of $72 ($45 for 1.5 hours in the scanner, plus $27 in ‘winnings’). While no formal post-questionnaire was administered, participants generally reported being engaged in the task, believed that they had performed well, did not formulate a strategy, and did not attempt to keep track of their performance beyond the first few trials of each block.

2.3 FMRI DATA ACQUISITION AND PREPROCESSING

Images were obtained using a 1.5 Tesla GE Signa 5x whole-body magnet and a standard RF headcoil. Thirty-six contiguous T1-weighted double-oblique axial slices (3.75 x 3.75 x 3.8 mm voxels) parallel to the Anterior / Posterior Commisure plane were collected to serve as structural images for cross registration of participants’ anatomy. A subset of twenty-six T2*-weighted slices ranging from +66.5mm above the AC/PC plane to -32.3 mm below made up the functional volume. Using a 2-interleave spiral sequence with TR = 2000msec [TE = 34 msec, FOV = 24 cm, Flip Angle = 70degress], one full volume time-point (scan) was acquired every 4 seconds

(Noll et al 1995). A total of 60 time-points were collected in each block and 540 over the course of the entire scanning session.

Images were reconstructed from K-Space using NeuroImaging Software (NIS, http://kraepelin.wpic.pitt.edu/nis/) and corrected for motion with Automated Image Registration (AIR) (Woods et al 1992). Any trial that contained a scan that AIR detected to be greater than one voxel (3.8 mm) away from the first image of each participants' entire scan or one half voxel (1.9 mm) away from the previous scan were discarded. Similarly, trials which involved a rotation greater than 3 degrees from the orientation of the first time-point or a 1 degree rotation from the preceding time-point were also removed. Trials in which the participant did not respond were also removed – the average number of no-response trials was only 1.6% of total trials (minimum = 0.0%, maximum 8.9%). After these steps, participants whose remaining data composed less than 20 trials per condition were removed entirely.

For each participant, a between-run baseline correction plus a within-run linear detrend was applied to remove between-run baseline differences and artifacts due to scanner drift, respectively. Per-voxel time-points that exceeded 3 standard deviations from the mean of each voxel were considered outliers and were corrected to the cutoff point of 3 standard deviations. The NIS package was used for the above stated preprocessing of functional imaging data. Brains were cross-registered using a 60 parameter warp function to a reference brain and those parameters were applied to align the functional data of each participant (Woods et al 1993). The reference brain for this study was the standard brain from the Montreal Neurological Institute (MNI) (ftp://ftp.mrc-cbu.cam.ac.uk/pub/imaging/Colin), re-sampled to match the voxel resolution of the T1-weighted structural images. To account for small anatomical differences not

addressed through the cross-registration, the data were smoothed using a three-dimensional Gaussian filter (6 mm Full Width Half Maximum).

2.4 DATA ANALYSIS

A repeated measures, 2-way analysis of variance (ANOVA), which used condition (3 levels: reward, loss, neutral) and scan (4 levels: time-points 1-4) as a within subjects factors, was performed on the imaging data. Subject was a random factor. The analyses were (a) the main effect of scan that identified regions that respond to general task demands common to all conditions (e.g. visual information, motor responding) and (b) the interaction of condition and scan that identified regions that show a differential BOLD response between conditions. The main effect of scan reveals regions showing statistically significant BOLD changes across time-points within a trial, irrespective of trial type; the interaction of condition and scan reveals regions for which the modulation of BOLD activity is dependent on the trial type. To avoid Type 1 errors, regions of interest (ROIs) were restricted to include at least 7 contiguous voxels, each with a false positive probability of $p < .005$ (Forman et al 1995). A grey-matter only mask was also used and prevented excessive computation of extra-cerebral space sampled by the scanner, white matter tracks, and ventricles. These analyses were implemented through the NIS package that computes a map, per analysis, of statistical F values for each voxel to which critical F and voxel contiguity thresholds may be applied conjunctively to isolate ROIs. An important point is that these ROIs are not based on a priori voxel coordinates – they are the outcome of an exploratory analysis. Once ROIs were identified, MNI coordinates were transformed (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) to standard Talairach coordinates

(1988) and inspected using AFNI (Analysis of Functional NeuroImages) software (Cox 1996). Event-related time-series data were computed to observe the hemodynamic response in each ROI; the time-series data were transformed to a percent change from the baseline activity at the first time-point of each trial (T1). ROIs revealed by the 2-way ANOVA to show an interaction of condition and scan were subjected to post-hoc t-tests on the time-series data. The purpose of these tests was to identify and exclude ROIs for which there was no significant difference ($p < .05$) between reward and loss conditions for any time-point. This criterion allowed us to avoid making inferences about regions that showed responses only attributable to the neutral condition, for which we had no a priori hypotheses.

3.0 RESULTS

3.1 MAIN EFFECT OF SCAN

The main effect of scan revealed regions associated with (a) sensory processing, such as bilateral fusiform gyrus, (b) motor processing, such as supplementary motor area and (c) reward processing, such as dorsal and ventral striatum. Table 1 lists all of the ROIs found in the main effect of scan analysis. Sensory and motor areas did not show responses that differentiated on the basis of the rewarding feedback and are therefore interpreted to reflect processing that is present across all conditions. Figure 3 shows the activation pattern observed in the left fusiform gyrus as having a hemodynamic shape but not different between conditions. We interpret the dorsal and ventral striatum activation in this main effect analysis as being involved in the processing of reward information on the basis of previous reward literature and our results from the interaction analysis. Responses to the feedback that differ between conditions are discernable through the interaction of condition and scan analysis. Overall, these results confirm that the guessing game paradigm engaged areas associated with sensory and motor demands that would be expected in any cognitive task that required responses from a participant. Additionally, the main effect of scan analysis detected areas responsible for reward-related processing.

Table 1. Main effect of scan

			Talairach Coordinates		
Regions of Activation	**Brodmann Areas**	**Laterality**	**x**	**y**	**z**
Anterior Cingulate / SMA	8, 24, 32	L	0	26	33
Posterior Cingulate	23, 31	L	-2	-25	38
Frontal Operculum		L	-39	18	-2
		R	47	18	-3
Medial OFC	10, 11	L	-1	41	-10
Pre-Central Gyrus	4, 6	L	-41	4	30
		R	48	9	29
Post-Central Gyrus	1, 3	L	-50	-21	37
Superior Parietal	7	L	-32	-49	49
		R	29	-68	49
Inferior Parietal	40	R	49	-52	46
Superior Temporal	42	R	50	-16	11
Middle Temporal	39	R	56	-56	15
Medial Temporal	27, 28	L	-22	-24	-4
		R	26	-27	-2
Parahippocampus	30	R	13	-45	6
Hippocampus	28	R	21	-23	-9
Dorsal Striatum / Caudate		L	-10	7	9
		R	12	11	9
Ventral Striatum		L	-16	14	-4

		R	15	12	-3
Thalamus		L	-8	-14	13
		R	9	-17	13
Pulvinar		L	-14	-30	7
		R	9	-29	2
Fusiform Cortex	19, 37	L	-36	-59	-8
		R	39	-57	-2
Lingual Gyrus	18, 19	L	-17	-56	0
		R	22	-54	-1
Precuneus	7	R	1	-74	47
Occipital Cortex	18, 19	L	-26	-89	5
		R	35	-89	4

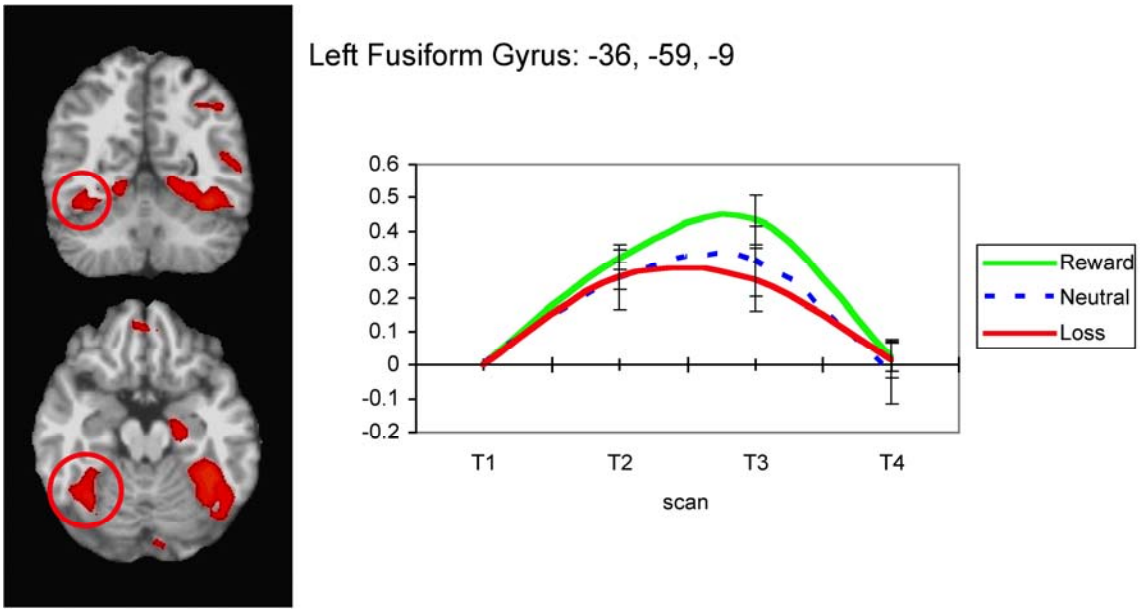

Figure 3. FMRI activation for main effect of scan

3.2 INTERACTION OF CONDITIONS AND SCAN

The interaction of condition and scan identified regions previously found in other reward-related imaging paradigms; these ROIS included the ventral striatum, lateral and medial OFC that were predicted by our hypotheses. Table 2 lists all of the ROIs found by the interaction analysis that also satisfied the criterion that post-hoc T-tests reveal a significant modulation of hemodynamic response between reward and loss conditions. Only one ROI, a rostral cingulate cluster, did not satisfy the above post-hoc T-test and appeared to be driven by a large decrease in BOLD to neutral feedback. ROIs and time-courses for the ventral striatum, lateral and medial OFC are presented in Figure 4. The left ventral striatum showed a response peaking around T2 the reward condition that was sustained across T3 before returning to baseline; whereas the time-course for the loss condition showed a similar peak at T2 but a more immediate return to baseline at T3. The left lateral OFC showed a later and more transient signal peaking at T3 for the reward condition; whereas the loss condition showed very little modulation of activity across the trial. The response to the reward condition in the medial OFC response showed a T3 response similar to lateral OFC but maintained activation through T4; again, the response to the loss condition was did not change greatly over the trial. The superior frontal gyrus showed a pattern of activation very similar to the left lateral OFC with a transient peak at T3 for only the reward condition. Both cingulate ROIs showed increasing hemodynamic responses for all conditions with a slightly larger and later peak at T3 for the reward condition; the peak for the loss condition occurred at T2. The middle temporal gyrus showed a sustained time-course for the reward condition and an overall decrease of activation for the loss condition that returned to baseline only at the end of T4. Overall, these results indicate that children and adolescents exhibit modulations of reward-related activity similar to that found previously in adults. In

addition to identifying regions associated with reward processing, the temporal dynamics suggest that these regions are specifically sensitive to positive feedback.

Table 2. Interaction of condition and scan

Regions of Activation	Brodmann Areas	Laterality	Talairach Coordinates			*n* Voxels	*F*
			x	y	z		
Superior Frontal Gyrus	9	L	-8	49	41	10	6.052
Inferior Parietal Cortex	40	R	50	-58	49	9	3.844
Anterior Cingulate Gyrus	24, 32	R	1	30	21	27	6.435
Cingulate Gyrus	23, 24, 31	R	2	-6	38	19	12.309
Lateral OFC	10	L	-43	45	-7	7	6.323
Medial OFC	10, 11	L	-3	51	-8	8	6.556
Ventral Striatum		L	-10	6	-5	21	4.739
Middle Temporal Gyrus	21, 22	L	-52	-20	-7	26	7.609

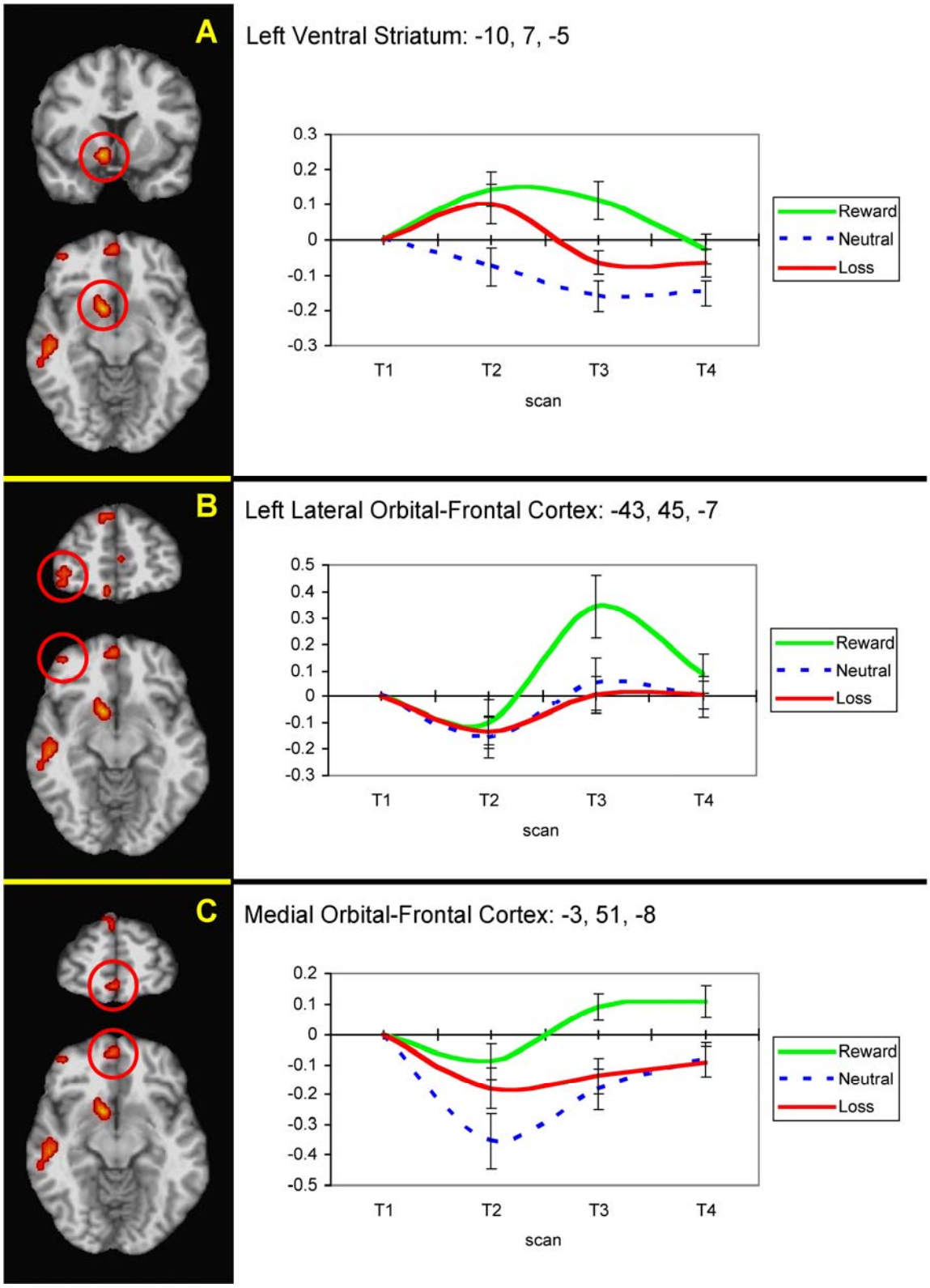

Figure 4. FMRI activation for the interaction of condition and scan

3.3 GENDER AND AGE ANALYSIS

To evaluate possible confounds stemming from age and gender effects, 2 additional analyses were run on the time-series data from the ROIs identified in the primary analysis of the interaction of condition and scan. An ANOVA performed using gender (see composition under Methods and Materials, Participants) as a between subjects factor and using condition and time as within subjects factors revealed no significant differences for any of the ROIs. To establish the effects of age we performed linear regression at each time-point for each ROI on the difference of percent change between win and loss conditions. The analysis was not significant at any time-point suggesting that age did not account for a significant amount of the variability between win and loss conditions.

3.4 BEHAVIORAL ANALYSIS

We conducted behavioral analyses to determine whether there were any biases in responding that were related to age. We examined: (a) the influence of age on reaction time (RT), (b) age effects on choice (greater than ‘5’ / less than ‘5’), and (c) age effect on possible strategies of responding relative to feedback. Using linear regression, age did not account for a significant amount of the variability in RT ($r = .508$, $p = .092$) or percentage of a specific choice ($r = .071$, $p = .827$). We tested a strategy where participants may be more likely to make the same choice as one previously rewarded (Win-Stay) or may be more likely to select the opposite choice in the case of a previous loss (Lose-Switch). Again using linear regression, age did not account for a significant amount of the variability in the percentage of trials in which subjects followed a

strategy of Win-Stay ($r = .140$, $p = .664$) or Lose-Switch ($r = .092$, $p = .776$). Together these results indicate that age did not influence any patterns of behavior which may have in turn affected our imaging analysis.

4.0 DISCUSSION

The present study identified brain regions in children and adolescents that are modulated by rewarding feedback. Activation of the ventral striatum, lateral and medial orbital-frontal cortex replicates previous reward-related imaging studies, and the time-course information from our event-related design further characterizes the hemodynamic responses in these regions. Beyond being activated by general reward processing alone (i.e. feedback signal processing), these regions showed different BOLD responses that were contingent upon the valence of the feedback. As such they may also be involved in the processing of affective information.

The sustained activation over the course of a rewarding trial compared to a losing trial in the ventral striatum concurs with the results of Delgado et al (2000), which showed the same hemodynamic pattern in this region. Reward-related activation of the ventral striatum has been observed in other imaging studies examining specific affective feedback or stimulus processing (Becerra et al 2001; Breiter et al 2001; Delgado et al 2003; Elliott et al 2000b; Elliott et al 2003; Erk et al 2002; Hamann and Mao 2002; Knutson et al 2001b) as well as during anticipation or prediction of rewarding outcomes (Berns et al 2001; Cools et al 2002; Knutson et al 2001a; McClure et al 2003; O'Doherty et al 2002; Pagnoni et al 2002). Single-cell animal studies also show a role for the ventral striatum in both reward detection and reward prediction (Apicella et al 1991; Schultz et al 1992). Neuromodulatory mechanisms such as enhanced dopamine release in the ventral striatum have been found with respect to rewarding events (Koepp et al 1998) and

may serve to alter associative learning signals within the basal ganglia (Robbins et al 1989). The ventral striatum also has connections to cortical and limbic regions; thus, sustained processing in this region may reflect integration of reward-related information from areas such as the amygdala and OFC (Groenewegen et al 1999; Nakano et al 2000; Ongur and Price 2000). Taken together, the results from these studies suggest that the striatum has a multifaceted role in reward processing; however, the lack of informed response selection in our guessing game task leads us to interpret the current study's result in the ventral striatum as reflecting reward feedback processing rather than future reward prediction.

Activation within medial and lateral OFC replicates previous findings in human imaging studies of reward-related processing. Studies by Rolls and colleagues have found that the OFC is responsive to multiple modalities of reward stimuli, including primary (unlearned) rewards, such as taste and touch; these studies have also found that the OFC plays a role in establishing reward-related learning associations from both visual and olfactory input (see Rolls 2000 for review). Activation to variable kinds of stimuli is not surprising when considering the OFC's general diversity of connections with prefrontal, premotor, sensory and limbic areas (Cavada et al 2000). However, there is evidence for a functional distinction between the medial and lateral regions (Elliott et al 2000a; Ongur and Price 2000). For instance, in a reversal learning FMRI study by O'Doherty et al (2001), medial OFC was found to be more responsive to monetary rewards and showed a positive correlation between size of reward and magnitude of signal; in contrast, the lateral OFC was more highly activated for losses and also showed a positive correlation between the size of the loss and the magnitude of signal. Evidence from Elliott et al (2000a) suggests that the medial OFC codes the reward value of stimuli as a basis for selection, whereas the lateral OFC serves more to suppress previously associated reward-responses as would be required for

reversal learning or changing strategies. Although our present study did show that separable regions of the OFC were active, there was not a clear functional distinction that reflected affective specialization, as might be suggested by O'Doherty et al (2001) and Elliott et al (2000a). The 'guessing' format of our task, lack of graded reward and loss values, and lack of need to suppress a specific response does not allow us to test for these separate processes. However, it is apparent from our results that the OFC is generally active in children and adolescents during reward processing and in the case of a simple feedback signal differentiates between rewards and losses.

These results concur with much of the previous research findings on the reward system, however there are a few potentially interesting differences between our study and the previous study in adults. In contrast with the first Delgado et al (2000) study, as well as a similar follow-up study examining magnitude of reward effects (Delgado et al 2003), we did not find dorsal striatum activation in the analysis of the interaction of condition and scan at our criterion threshold. Delgado et al (2000) found BOLD responses in this region bilaterally with a time-course that showed sustained activation for reward over loss trials, very similar to the left ventral striatum in both studies. To investigate this surprising and potentially negative result, we lowered the statistical threshold for the interaction analysis which revealed a left dorsal striatum ROI that did show sustained activation for the reward condition. This evidence precludes us from asserting that the dorsal striatum is not differentially active to reward in children and adolescents, however, it is unclear whether this statistical discrepancy is meaningful or if the level to which the dorsal striatum is engaged has any functional implications. For example, there is evidence to suggest that dorsal striatum is more highly engaged when a sense of agency exists and provides a connection between action taken by the organism and the outcome (Schultz et al 2000). FMRI

studies that use tasks in which outcome is not contingent on action have found ventral but not dorsal striatal activation (Berns et al 2001; Breiter et al 2001). Therefore, it is possible that the differences observed between adults and children in the dorsal striatum reflect a developmental difference in the processing of action-reward relationships. Although, the discrepancy of dorsal striatum activation in the present study is provocative, an experimental paradigm which directly compares children and adults while controlling for all other variables is required to determine any real quantitative differences.

The present study revealed activation of the medial and lateral OFC that was not observed in the previous study by Delgado et al (2000). One explanation is that our study used a more advanced cross-registration algorithm to align the imaging data from each participant to the reference brain; we used a 60 parameter warp function whereas Delgado et al (2000) used a 15 parameter linear function (Woods et al 1993). The enhanced alignment should have allowed of a greater degree of anatomical overlap between brains, therefore providing a greater overlap of signal. The ventral surface of the prefrontal cortex is known to be difficult region to study due to the close proximity of nasal and ocular cavities that lead to a rapid drop off of signal (i.e. susceptibility artifacts). Although the enhanced alignment would not have offered any direct protection against susceptibility artifacts, the greater overlap in existing signal from within the OFC may have provided the present study more power to detect changes of the BOLD signal.

In addition to overlapping with regions previously associated with reward processing, the ventral striatum, medial and lateral OFC have also been implicated in mood, impulse, and substance abuse disorders. Abnormalities in cerebral blood flow and metabolism have been found in the basal ganglia and OFC of patients with major depression (see Drevets 2000 for review; Elliott et al 1998; Lafer et al 1997). Bechara et al (2000; 1998) have performed a number

of gambling studies which have found poorer performance for participants with medial OFC lesions; these patients tend to make choices that lead to sporadic large rewards but overall lead to heavy losses. In a group of healthy participants, Rogers et al (1999) found that the OFC was engaged when participants were deliberating a task that juxtaposed magnitudes of reward and probabilities of wins and losses. In studies of drug abuse, the dopaminergic (DA) projections from the ventral striatum / nucleus accumbens (regions which have enhanced DA release to drugs of abuse) influence the OFC to create hypoactivity in the absence drug use and hyperactivity in the presence drug use (Di Chiara 1998; Leshner and Koob 1999; Volkow and Fowler 2000). Evidence for reward systems being central to the interactions between these pathologies is apparent in the comorbidity of major depression and nicotine addiction documented by Cardenas et al (2002) as well as a general dysfunction of dopaminergic action found in a variety of mental diseases (Schmidt et al 2001). Recent work by Ernst et al (2003) found similar deficits in decision-making between adolescents with behavioral disorders and adult substance abusers, suggesting that behavioral disorders and propensity for drug abuse may share underlying mechanisms.

A left-lateralized pattern of activation is also apparent in the interaction of condition and scan analysis. Delgado et al (Delgado et al 2000) also found a similar pattern of lateralization in adults, with stronger effects present in the left hemisphere of bilateral ROIs. Other imaging studies that use money as the rewarding stimuli show this pattern as well (Koepp et al 1998; Thut et al 1997). While we do not have a clear interpretation for this pattern, some research suggests that positive emotions are processed to a higher degree in the left rather than right hemisphere (Davidson and Irwin 1999) and reduced metabolic levels have been observed in the left

hemisphere in participants with mood disorders (Drevets et al 1998). Therefore this may be an important distinction to maintain as further clinical research develops.

The results of this study confirm the potential value of using event-related FMRI for investigating the brain reward systems of children and adolescents. By using tailored techniques for participant handling and appropriate task selection we were able to engage our young subjects for an extended period of time in the MR environment. The event-related design provided data on the temporal dynamics of the ROIs specific to condition rather than only a general region detection (Buckner 1998). In this study, the interaction indicated regions specifically modulated by the valence of feedback and presents a clearer picture of contingent neural processing than that allowed for by a block-design FMRI paradigm. Of particular relevance to our participant sample, event-related FMRI is less invasive (in terms discomfort from an IV line as well as radiation exposure) than PET and allows for a greater repertoire of cognitive designs.

In addition to determining the feasibility of using FMRI to study the brain reward systems of children and adolescents, this study (a) corroborates previously observed reward-related regions such as the ventral striatum, medial and lateral OFC, (b) characterizes the hemodynamic responses in those regions, and (c) adds to the growing body of literature describing the brain reward system. Although this study has generally corroborated the findings of other reward-related imaging studies in adults, we do not discount the possibility of developmental changes in brain reward systems. In fact our prediction for future research would be that we will be able to detect differences, and that those differences will be important factors in understanding how these systems function both normally and pathologically. While current event-related FMRI designs allow a non-invasive in vivo look at functional activity of the brain,

new fast event-related designs will allow even shorter examination times and increased power from greater numbers of trials (Dale and Buckner 1997). Parallel to the progression of work achieved in adult populations, next on the horizon for our program will be studies examining motivated decision-making and the anticipation or prediction of rewards, thereby parsing the various components of brain reward systems. Using the present study as a basis, this future line of research is expected to increase our understanding of the development and functional role of the brain reward systems and to identify the neural substrates potentially involved in the pathophysiology of mood, impulse, and substance abuse disorders.

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