Developmental Cognitive Neuroscience 9 (2014) 82–92

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

Kids, candy, brain and behavior: Age differences in responses to candy gains and losses

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ARTICLE INFO

Article history:
Received 22 August 2013
Received in revised form 13 January 2014
Accepted 17 January 2014

Keywords:
Reward
Development
Gain
Loss
fMRI
Child

ABSTRACT

The development of reward-related neural systems, from adolescence through adulthood, has received much recent attention in the developmental neuroimaging literature. However, few studies have investigated behavioral and neural responses to both gains and losses in pre-pubertal child populations. To address this gap in the literature, in the present study healthy children aged 7–11 years and young-adults completed an fMRI card-guessing game using candy pieces delivered post-scan as an incentive. Age differences in behavioral and neural responses to candy gains/losses were investigated. Adults and children displayed similar responses to gains, but robust age differences were observed following candy losses within the caudate, thalamus, insula, and hippocampus. Interestingly, when task behavior was included as a factor in *post hoc* mediation analyses, activation following loss within the caudate/thalamus related to task behavior and relationships with age were no longer significant. Conversely, relationships between response to loss and age within the hippocampus and insula remained significant even when controlling for behavior, with children showing heightened loss responses within the dorsal/posterior insula. These results suggest that both age and task behavior influence responses within the extended reward circuitry, and that children seem to be more sensitive than adults to loss feedback particularly within the dorsal/posterior insula.

1. Introduction

The transition from childhood to adolescence marks the beginning of a developmental period characterized by age-typical increases in risk taking behavior (Steinberg, 2008). Much recent work has focused on the typical development of neural systems involved in reward processing and how enhanced neural response to reward relates to increased risk taking in situations in which the risk may involve potential rewards (Galvan et al., 2006, 2007). While this literature has largely focused on comparing adolescent and adult responses to monetary incentives (see (Galvan, 2010; Geier and Luna, 2009; Richards et al., 2013) for recent reviews), risk-taking behaviors may be influenced by responses to both reward and negative outcomes and

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1878-9293
http://dx.doi.org/10.1016/j.dcn.2014.01.005

how potential gains and losses relate to risk taking may vary across age (Galvan et al., 2007; Massar et al., 2012). Further, the relative contributions of age-related differences in responses to positive versus negative outcomes to variation in risk-taking behavior may differ for transitions from childhood to adolescence and adolescence to adulthood (Steinberg, 2008). Thus, it is important to investigate neural responses to both gains and losses within school-aged children prior to the onset of puberty, to serve as a relative baseline for future studies investigating the neural correlates of developmental and individual differences in risk taking.

To date only a handful of incentive processing studies have included distinct pre/early pubertal child groups and directly compared child and adult functional responses to incentive receipt (Galvan et al., 2006; Padmanabhan et al., 2011; van den Bos et al., 2009; van Leijenhorst et al., 2010). Further, few studies have investigated responses to receipt of incentives *and* loss of incentives, utilized non-monetary rewards, or employed specialized methods to address analytical and data quality issues that inherently accompany studies with multiple age groups (see (Church et al., 2010) for commentary on age group comparison methods). As such, how responses to gains *and* incentive losses differ between pre-pubertal child and adult populations is the focus of the current study.

Children and adults engage largely overlapping neural systems when responding to the receipt of incentives, however, the magnitude or pattern of responses in these regions to positive/reward feedback often differs between age groups (Galvan et al., 2006; Padmanabhan et al., 2011; Paulsen et al., 2011; van Leijenhorst et al., 2006). Specifically, both groups show similar striatal responses to gains/correct feedback, with age differences reported mostly in dorsal prefrontal (DLPFC), anterior cingulate (ACC), and orbitofrontal regions (OFC) (Crone et al., 2008; Galvan et al., 2006; Paulsen et al., 2011; van den Bos et al., 2009; van Duijvenvoorde et al., 2008; van Leijenhorst et al., 2010). Studies comparing adult and child responses to negative incentives/incorrect feedback suggest that children show heightened responses to such feedback. In simple paradigms, older children show increased lateral OFC responses to loss (van Leijenhorst et al., 2006), are slower to learn win-stay rules than lose-shift rules (Berman et al., 1970), and show greater learning rates for negative versus positive feedback (van den Bos et al., 2012). In more complex tasks children are less able to discriminate between different types of negative feedback (Crone et al., 2008), are less able to use negative feedback to optimize behavior (Crone et al., 2008; van Duijvenvoorde et al., 2008), and are particularly sensitive to loss frequency during decision-making (Crone et al., 2005).

Together these findings have contributed to the general interpretation that while more basic hedonic responses are similar in children and adults, regulation of those responses/learning signals by regions involved in higher-order cognitive processes, such as the DLPFC and ACC, is inefficient or reduced in children compared to adults (Somerville and Casey, 2010; Somerville et al., 2010). Although cognitive control and regulation improve from childhood to adulthood, several task design/analysis factors may be contributing to the relative cortical/cognitive versus subcortical/hedonic focus in the child versus adult literature. Firstly, the complex nature of these tasks may make them particularly sensitive to age differences in cognitive components of feedback processing, but less sensitive to age differences in emotional/hedonic components of feedback processing. Secondly, developmental incentive studies have primarily utilized secondary rewards, such as money or token economies, (see (Galvan and McGlennen, 2013) for liquid incentives in adolescents and adults). While such rewards have many advantages, they may bias findings particularly with younger school-age/preschool children. Primary rewards, such as candy or sweet liquids, may be more motivating and better capture the attention of younger children with fewer cognitive demands. Thirdly, the relationship between age differences in basic task behavior and age differences in incentive-related activation has been relatively underexplored in the developmental reward literature. This is important given that study examining the relationship between age differences in activation and behavior report different patterns of 'age differences' in activation when behavior is and is not accounted for analytically (Brown et al., 2005; Casey et al., 1997; Church et al., 2010; Schlaggar et al., 2002).

As less work has focused on potential differences between adults and children in more basic components of incentive processing and associated limbic/subcortical activation patterns, the goal of the current study was to investigate differences between pre-pubertal children and adults within these systems during both gain and loss of incentives. We chose to employ fMRI and a simple card guessing game (CGG) based on Delgado et al. (2000, 2004) where small candy pieces served as the incentive to address the concerns regarding cognitive/complex tasks and secondary incentives discussed above. In addition to traditional group analyses designed to investigate age differences in activation, we employ analyses to evaluate relationships between age differences in activation and age differences in task behavior.

Given that the prior literature suggests adults and children show similar striatal responses to receipt of adult-centric secondary incentives, we expect to observe either similar or enhanced striatal responses to child-centric candy gains in children compared to adults. Although no prior neuroimaging studies comparing pre-pubertal children and adults have investigated responses to loss of incentives, based on the behavioral literature we predict that children will show enhanced neural responses to losses. As behavior has not been investigated in fMRI studies using the CGG, we do not have specific *a priori* hypotheses regarding how behavior may relate to activation, although if observed, we would expect such relationships to be located within regions involved in goal-directed action, such as the striatum.

2. Methods

2.1. Participants

Twenty-eight children enrolled in this study. One was excluded prior to neuroimaging due to diagnosis of a

neurological disorder. The remaining 27 children participated in the neuroimaging component of the study, 22 of which completed the scanning protocol. Eighteen of the children who completed the scanning protocol provided a sufficient amount of quality fMRI data (defined below) and are included in these analyses. Child participants were aged 7–11 years (mean age = 8.89, SD = 1.28; 8 males and 10 females). To assess pubertal status parents (either mother or father) completed a Pubertal Staging Questionnaire (Carskadon and Acebo, 1993; Petersen et al., 1988) twice, once as part of the phone screen and once on paper during the in-person assessment. Occasionally one parent completed the phone screen and another completed the paper version. All children were pre-pubertal (Tanner Stage 1) based upon the phone screen. However, 3 of the 18 children included in these analyses were classified as Tanner Stage 2 based on parents' written responses to the Pubertal Staging Questionnaire. Thus, we characterize our sample as pre/early pubertal.

Eighteen healthy young adults from a previous study, aged 22–26 years (mean age = 23.95, SD = 1.35), were matched to the child participants based on gender/ethnicity and are included in these analyses (Luking and Barch, 2013). All adult and child participants were healthy and free of any major medical disorder and had not taken psychotropic medications within two weeks of the assessment/scan (parental or self-report). Parents of child participants did not report a history of any mental disorder either for the child or for anyone in the immediate family. Adult fMRI participants also did not report a history of any mental disorder.

Participants were recruited through posted advertisements at Washington University. All adult participants gave written informed consent and all child participants gave written informed assent. The Washington University in St. Louis Institutional Review Board approved all study procedures.

2.2. Procedure

All participants completed two experimental sessions (behavioral and neuroimaging) and results of the neuroimaging task will be discussed in this article. To prepare for the neuroimaging session, child participants completed a practice MR scan during the behavioral session. On the day of scan both adult and child participants completed the same out-of-scanner practice for the neuroimaging task and an in-scanner card guessing game based on Delgado et al. (2000, 2004) followed by a Post-Scan Questionnaire where participants rated how they felt when candy was won/lost (no rating was obtained for neutral feedback). This rating used 5 faces that ranged from a large frown to a large smile (see Fig. S1). For analysis, the faces were assigned values of −2 to 2 from the most negative through most positive, respectively. Data on this questionnaire were acquired from 14 children and 14 adults, as 4 adults and 4 children had already completed the study before this measure was added to the protocol. Adults and children were also administered individual difference questionnaires that are not the focus of the current report (see *Supplemental Materials*).

2.3. Card guessing game

Participants were told they would play a card guessing game where they were to guess the number on a mystery card (represented by a "?") and potentially win or lose candy based upon whether or not that guess was correct. Participants indicated whether they preferred to play for Skittles or M&Ms and were told that they would receive a lump sum of candy at the conclusion of the experiment reflecting the net amount of candy earned during the task. To ensure that all participants understood the task, written instructions were presented on a computer using PsyScope software (the instructions were also read aloud to all child participants) followed by actual task practice prior to entering the fMRI scanner (Cohen et al., 1993). During practice, participants were told that potential mystery card numbers ranged from 1 to 9 and to indicate if they thought the mystery card number was more or less than 5 via one of two button presses (either the left or right thumb). Participants were required to make an above/below five guess while the mystery card "?" was displayed on screen (2000 ms). If no guess was made after 2000 ms, the "?" was replaced by a fixation cross for the remaining 2000 ms of that trial. Feedback was displayed for 2000 ms immediately following a button press guess. Feedback included the selected card number, written feedback ('Great Job!', 'Sorry', or 'Next Trial'), and a picture of the number of candy pieces gained or lost (see Fig. 1).

In-scanner trials were presented in a fixed pseudo-random order with a rapid event-related design using PsyScope software on a Macintosh computer for stimulus presentation and data collection (Cohen et al., 1993). The computer selected a card number on each trial following the participant's guess depending on the predetermined trial type. This is the standard procedure with the card guessing game and ensures that all participants experience roughly the same events in scanner (i.e., no one by chance gets a disproportionate amount of high gain trials). The task was divided into six blocks each lasting 5 min and containing 8 instances of each of the five trial types described below (if the participant made a response on all trials). Each trial lasted for 4000 ms (see Fig. 1) followed by an inter-trial interval (ITI) of 0–14000 ms that was randomly jittered in 2000 ms increments.

Participants gained and lost both large and small amounts of candy. On high gain (HG) trials 4 candy pieces were earned and card numbers 8/9 or 1/2 were displayed following above or below 5 guesses, respectively. On low gain (LG) trials 2 candies were earned and card numbers 6/7 or 3/4 were displayed following above/below 5 guesses. Conversely, on high loss (HL) trials 2 candies were lost and card numbers 1/2 or 8/9 were displayed following above/below 5 guesses, respectively. On low loss (LL) trials 1 candy was lost and card numbers 3/4 or 6/7 were displayed following above/below 5 guesses. Neutral trials with no candy gain or loss occurred when the number 5 card was displayed independent of the guess. We selected a 2:1 ratio of gain to loss amounts to prevent frustration with the task, to maintain engagement, and to ensure a net positive outcome (Tversky and Kahneman, 1981). Adult participants received $50, child participants received $30,

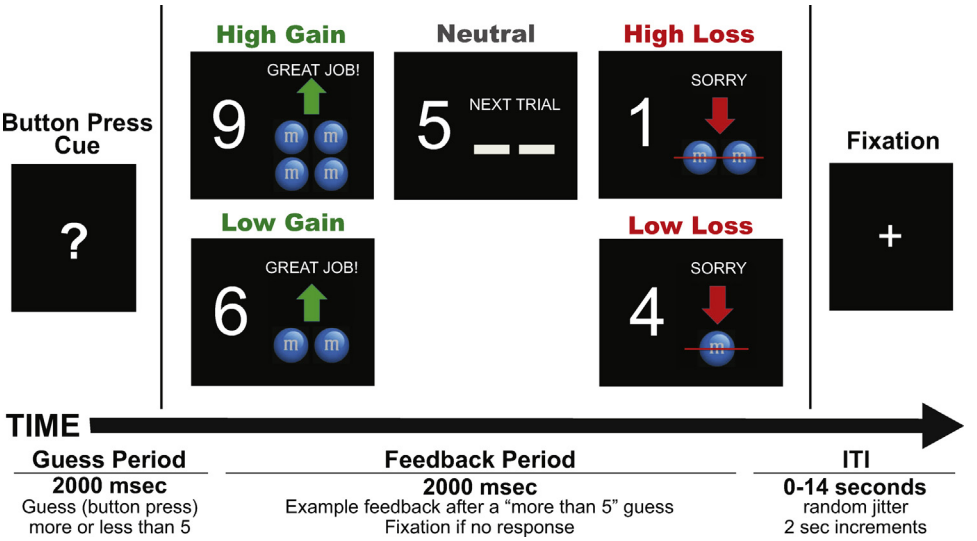

Fig. 1. Timing of card guessing game – example feedback types following a "more than 5 guess". Each trial lasted 4-s in total with the cue to make guess (?) displayed for up to 2-s and feedback (including the number on the mystery card, arrow denoting win/loss or dashes for no win/loss, and amount of candy exchanged) presented as soon as a guess was made and lasted for 2-s. A fixation cross was presented for any remaining portion of the 4-s. Inter-trial intervals (ITIs) lasted 0–14 s with random jitter in 2-s increments. If a guess was not made during the 2-s cue to make a guess, a fixation cross was presented for 2-s in place of feedback.

and parents received $40 as compensation. Children and adults received 150 M&Ms/Skittles at the end of scanning regardless of task performance.

2.4. fMRI data acquisition and processing

Imaging data were collected using a 3 T TIM TRIO Siemens whole body system and included a T1 [sagittal acquisition, TE = 3.16 ms, TR = 2400 ms, FOV = 256 mm, flip angle = 8°, 1 acquisition, 176 slices, 1 mm × 1 mm × 1 mm voxels] image and functional images collected with a 12-channel head coil using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast (T2*) (TR = 2000 ms, TE = 27 ms, FOV = 384 mm, flip angle = 77°). During each functional run 150 whole-brain volumes were acquired consisting of 36 contiguous axial images with isotropic voxels (4 mm^3) acquired parallel to the anterior–posterior commissure plane.

The fMRI data were preprocessed using in-house Washington University software. Prior to preprocessing, the first 4 frames of each run were discarded to allow for signal stabilization. The data were then: (1) reconstructed into images and normalized across runs by scaling whole-brain signal intensity to a fixed value and removing the linear slope on a voxel-by-voxel basis to counteract effects of drift (Bandettini et al., 1993); (2) corrected for head motion using rigid-body rotation and translation correction algorithms (Friston et al., 1994; Snyder, 1996; Woods et al., 1992); (3) registered to a Talairach (Talairach and Tournoux, 1988) space template atlas optimized for the children and adults in this study using a 12 parameter linear (affine) transformation; and (4) smoothed with a 8 mm FWHM Gaussian filter.

Estimates of functional activation during each of the five trial types (high/low gain/loss and neutral) were obtained by using a general linear model (GLM) incorporating regressors for linear trend and baseline shift. The GLM did not assume a specific hemodynamic response shape because of concerns regarding potential age differences in the shape or timing of this response. Instead, a finite impulse response (FIR) approach was used where the neural response at 10 time points/TRs (20 s total with TR = 2000 ms) were modeled for each trial relative to baseline fixation with time point 1 corresponding to the onset of the guessing cue "?". These estimates were then entered into group levels analyses treating subjects as a random factor.

2.5. Motion assessment and scrubbing, age group matching, and signal quality

All six BOLD runs could not be included for several children due to excessive motion. We excluded runs with a mean voxel-wise standard deviation greater than 15. Four of the 22 children who completed the full scanning protocol had less than 3 BOLD runs that passed this signal quality criterion and are not included in these analyses. All BOLD runs from adult participants passed this signal quality check. To address the difference in amount of useable data between age groups, we matched adult participants to child participants in the following ways. First, adults were each matched to individual children based upon gender and ethnicity. Next, for each adult, only the BOLD runs corresponding to those deemed usable from the paired child were used to create that adult's GLM (see Table S1). This process ensured that between age group comparisons were not biased by different amounts of data.

We also applied previously validated head motion corrections, termed "motion scrubbing", adapted for task fMRI (Power et al., 2012). Any frame whose displacement

relative to the previous frame was greater than 0.5 mm (sum across both rotational [pitch, roll, and yaw] and linear [*x*,*y*,*z*] aspects) was not included in the participant's GLM (Pagliaccio et al., 2013). A repeated measures ANOVA (two factors: Age Group [children, adults] and remaining trials [HG, LG, NU, LL, HL]) indicated that the number of trials remaining post motion scrubbing did not differ between age groups (main effect of Age Group; $F_{1,34} = 2.09$; $p = 0.16$) for any of the trial types (interaction; $F_{4,34} = 0.69$; $p = 0.60$). See *Supplemental Materials* and Fig. S2 for assessment of signal dropout in OFC and Section 2 for dealing with this problem.

2.6. Behavioral data analysis

While the fixed pseudo-random structure of the CGG is designed to elicit incentive-related responses independent of overt behavioral strategy or learning, it is possible that some individuals behaved as if their choice behavior and task feedback were linked across trials and that this may have differed as a function of age. To explore this possibility, we quantified each individual's choice behavior as a function of previous trial feedback. We then calculated the proportion of "stay" choices following each feedback type by dividing the number of times a participant repeated the same button press after a given feedback type (as compared to the prior trial) by the total number of trials of that feedback type. Within each age group there was a wide range of 'stay' choices following different trial types (Fig. S3A).

To determine whether: (1) stay/shift behavior, (2) reaction time, or (3) ratings of emotional experience during the CGG differed across groups, three ANOVAs were conducted, each with Age Group (child, adult) as the between-subjects factor. The first two ANOVAs also included Feedback Condition as a within-subject factor (gain [mean of high/low magnitudes], neutral, loss [mean of high/low magnitudes]), with either the proportion of "stay" choices or the mean reaction time in milliseconds following that trial type as the dependent measure. The third ANOVA included Feedback Type (loss or gain) as a within-subject factor, with self-rated feeling as the dependent measure (feeling ratings were not obtained for neutral trials). *Post hoc t*-tests and one-way ANOVAs were conducted to determine the nature of interactions where appropriate.

2.7. fMRI data analysis

2.7.1. Effects of age on activation following gain/loss

To identify regions where responses to feedback of a specific valence differed across time and with age, we conducted two voxelwise repeated measures ANOVAs (one using gain trials and one using loss trials) with one within-subject factor, Time Point within trial (the 10 frame estimates for each trial type), and one between-subjects factor, Age Group (children, adults). For brevity and to increase power, high and low magnitude trials of a given feedback type were combined in all analyses, as including magnitude as an additional factor yielded qualitatively similar results and no interactions of magnitude with Time Point were observed. Given our use of an FIR approach, a significant main effect of Time Point indicates differences in activity across time points within trial. As is standard when using an FIR approach, we focused on interactions with Time Point (e.g., Time Point × Age Group), as these indicate a significant difference in the hemodynamic response (a difference in peak amplitude or in shape/timing of response).

To determine the source of any interactions with Time Point, we conducted *post hoc t*-tests within regions identified by voxel-wise analyses. For each region and condition, the mean percent signal change was extracted for the time points corresponding to the peak response (mean of TRs 4 and 5) and return to baseline (mean of TRs 7 and 8) and *t*-tests were conducted to characterize differences between groups at TRs 4/5 and 7/8. As these *post hoc* tests are primarily meant to be descriptive and are conducted within regions that were defined using a threshold that corrects for multiple comparisons, tests where $p < 0.05$ are considered meaningful and reported (see below for details of multiple comparison corrections).

2.7.2. Effects of behavior and age on activation following gain/loss

Patterns of group effects on activation can vary greatly depending on whether behavior is included as a part of group analyses (Brown et al., 2005; Casey et al., 1997; Church et al., 2010; Schlaggar et al., 2002). Common methods for investigating the comparative effects of behavior and (age) group on activation include: (1) evaluating the relationship between activation and behavior (controlling for age) within regions identified in initial age group contrasts (Casey et al., 1997) and (2) conducting a second set of between-group analyses using a subset of adults and children that are matched based on behavior as a follow-up to typical age-group analyses (Brown et al., 2005; Schlaggar et al., 2002). Although not without limitations, these approaches allow investigators to identify age differences in activation related to differences in more basic behavior (e.g., accuracy or reaction time) and those related to processing differences within the domain putatively manipulated by the task at hand (e.g., working memory or cognitive control). This is a critical distinction as not all group differences in activation observed, for example, during task switching or working memory tasks may reflect differences in how child and adult brains engage in task switching/working memory specifically, but rather they also might reflect maturation in general response speed/accuracy or propensity to engage in different cognitive strategies such as proactive or reactive cognitive control.

To investigate relationships between age, behavior, and activation we conducted *post hoc* mediation analyses within ROIs showing an interaction of Time Point and Age Group using Hayes' "indirect" SPSS macro version 4.2 (Preacher and Hayes, 2008). We were specifically interested in controlling for basic behavior such as reaction time and global proportion of stay choices, as these factors showed effects of age (discussed in Section 3). However, we were also were interested in potential relationships between activation, age, and more complex behavioral patterns such as strategy that may relate to how different groups interact with/perceive the CGG. As such, mediation analyses test whether differences in 'strategy' (proportion

of stay choices post High Gain feedback – proportion of stay choices post High Loss feedback) mediate age differences in peak/return to baseline activation while controlling for reaction time and global proportion of stay choices (see *Supplemental Materials* for details). We chose to focus on behavior following high gain/loss feedback in mediation analyses, as they were the best and worst possible outcomes. Further, this difference serves as a gross metric of win-stay/lose-shift behavior, a well-studied strategy commonly observed during decision-making under uncertainty (Evenden and Robbins, 1983; Paulus et al., 2001).

2.7.3. Masking and corrections for multiple comparisons

To focus our results, all voxel-wise analyses were masked to only include voxels within a set of *a priori* regions of interest (ROIs). This mask (Fig. S4) was developed by Beck et al. (2010) based on a network of regions implicated in reward processing including the dorsal and ventral striatum, amygdala, ventromedial prefrontal cortex (VMPFC), and insula. Regions were hand-drawn in Talairach space on the basis of anatomical landmarks and previously published coordinates. Voxel-wise analyses were corrected for multiple comparisons using a combined *p*-value/cluster size threshold ($p < 0.006$ and 25 voxels) determined using *AlphaSim* simulations to provide a false positive rate of $p < 0.01$ for the entire *a priori* mask (Forman et al., 1995; McAvoy et al., 2001). After thresholding, maps were then partitioned such that peaks of activity were considered separate ROIs if they were more than 10 mm apart based on a peak-splitting algorithm (Kerr et al., 2004; Michelon et al., 2003) and contained at least 10 voxels post splitting.

To reduce redundancy, an additional hierarchical masking process was used to ensure that a given ROI was discussed only in the context of one effect, rather than multiple effects. Specifically, we masked maps of lower order effects (e.g., main effect of Time Point) by maps from higher order effects (e.g., Time Point × Age Group) prior to thresholding, so that a given region was only presented in the highest order interaction for which it was significant. This process resulted in non-overlapping maps for effects within a given ANOVA.

3. Results

3.1. Results from behavioral ANOVAs

3.1.1. Stay/shift behavior ANOVA

The proportion of "stay" choices significantly differed depending on the feedback type of the previous trial such that participants were more likely to repeat the same choice, or "stay", following gain and neutral feedback than following loss feedback (Feedback Condition; $F_{2,68} = 8{,}98$; $p < 0.001$) (Fig. S3B). Across feedback types, adults were more likely to repeat the same choice compared to children (Age Group; $F_{1,34} = 12.75$; $p = 0.001$) (Fig. S3C). Feedback Condition and Age Group did not significantly interact ($p > 0.69$).

3.1.2. Reaction time ANOVA

Reaction time (see Table S2) significantly differed depending on the previous trial's feedback type (Feedback Condition; $F_{1,68} = 3.99$; $p = 0.02$) with slower RTs following gain than neutral feedback ($t(35) = 3.12$; $p = 0.004$) (see Supplemental Table 2). Overall children were slower than adults (Age Group; $F_{1,34} = 24.82$; $p < 0.001$). Feedback Condition and Age Group did not significantly interact ($p > 0.20$).

3.1.3. Post-Scan Questionnaire ANOVA

Data from the Post-Scan Questionnaire are shown in Table S3. Participants felt differently after winning than losing candy (Feedback; $F_{1,26} = 149.53$; $p < 0.001$). There was a trend toward children feeling more positively overall (Age Group; $F_{1,26} = 3.23$; $p = 0.08$). Feedback and Age Group did not significantly interact ($p > 0.72$).

3.2. fMRI effects of age

3.2.1. Time Point × Age Group ANOVAs

Loss Trials: The ANOVA using loss trials identified several regions where Time Point interacted with Age Group. A portion of the right anterior insula showed greater responses in adults than children (Table 1 and Fig. 2). Interestingly, several more dorsal/posterior insula regions also showed a Time Point × Age Group interaction. However, within these regions, children showed enhanced loss responses compared to adults without a strong post-stimulus undershoot. Within the caudate body and thalamus adults showed strong peak activation to loss feedback compared to children whose responses were much weaker. Finally, adults showed loss feedback related deactivation in the hippocampus/parahippocampal gyrus while children showed little activation in these regions.

Gain Trials: Children and adults showed similar levels of activation following gain feedback within the vast majority of the striatum/thalamus, insula, amygdala/hippocampus, and anterior cingulate (Table S4 and Fig. 3). Interestingly only one region, a portion of the right anterior insula similar to the one discussed above in the loss ANOVA, showed a Time Point × Age Group interaction during response to gain feedback and again adults showed greater activation than children (Table 1).

3.3. fMRI effects of behavior

3.3.1. Mediation analyses

'Strategy' did not significantly mediate the effect of Age Group on activation in any region and neither covariate (mean reaction time and general propensity to repeat the same choice) showed a significant relationship with activation in any ROI (see Table S5). However, Strategy did show a direct effect on activation within the caudate/thalamus and the relationship between age group and activation was no longer significant in these regions after controlling for covariates and strategy. Within the caudate/thalamus staying more after high gain than high loss was associated both with lower peak activation and greater activation during the return to baseline (Supplemental Fig. 6A). Conversely, the direct effect of age group remained significant within the dorsal insula and hippocampus even when controlling for behavior with children showing enhanced responses to loss within the insula (Supplemental Fig. 6B) and lack

Table 1
Regions showing a Time Point × Age Group interaction – from gain/loss Time Point × Age Group ANOVAs.

Taliarach coordinates			Cluster size	Laterality	Region name	BA	Activation type		Activity pattern at TR 4/5	Activity pattern at TR 7/8
X	*Y*	*Z*					Adults	Children		
LOSS – Time Point × Age Group ROIs										
−38	−13	−5	26	L	Insula	13	A	A	C > A	C > A
−33	−16	17	14	L	Insula	13	A	A	C > A	C > A
36	2	13	36	R	Insula	13	A	A	C > A	C > A
35	−23	17	25	R	Posterior insula	13	A	A	C > A	C > A
−34	−27	13	12	L	Posterior insula	13	A	A	C > A	C > A
37	16	6	29	R	Anterior insula	13	A	A	A > C	–
11	8	6	34	R	Caudate body		A	A	A > C	–
−11	−5	13	37	L	Thalamus VAN		A	A	A > C	–
−24	−14	−13	32	L	Hippocampus		D	–	A > C	A > C
20	−15	−14	30	R	Parahippocampal gyrus	28	D	A	A > C	C > A
GAIN – Time Point × Age Group ROI										
35	18	7	26	R	Anterior insula	13	A	A	A > C	–

BA, Brodmann area; A, adults; C, children.
Cluster size is in voxels.
In activation type column: A, activation; D, deactivation; –, neither activation nor deactivation (activation type column); –, no significant differences in post hoc tests (activity pattern columns).

of loss-related deactivation within the hippocampus even when controlling for behavior.

4. Discussion

This study's goal was to directly compare pre/early pubertal children's and young adult's behavioral and neural responses to gain and loss of incentive feedback as a baseline for future developmental and individual difference studies. While children and adults recruited largely overlapping circuits when processing gain feedback, there were extensive age differences in the magnitude and shape of BOLD responses to loss within the insula, caudate/thalamus, and hippocampus/parahippocampal gyrus. However, when relationships between age, behavioral, and BOLD responses were investigated concurrently, insular responses varied with age while striatal responses showed effects of behavior. This finding of increased insular responses to loss in children along with previous work suggesting that in children risk-taking relates to anticipated negative outcomes, while in adults it relates to anticipated positive outcomes (Galvan et al., 2007) suggests that future studies investigating risk taking in children should take care to include loss conditions in addition to gain.

4.1. Age differences in response to candy losses

As reviewed in the introduction, differences in cortical activation patterns and behavior reported in previous studies suggest that children may be more sensitive to

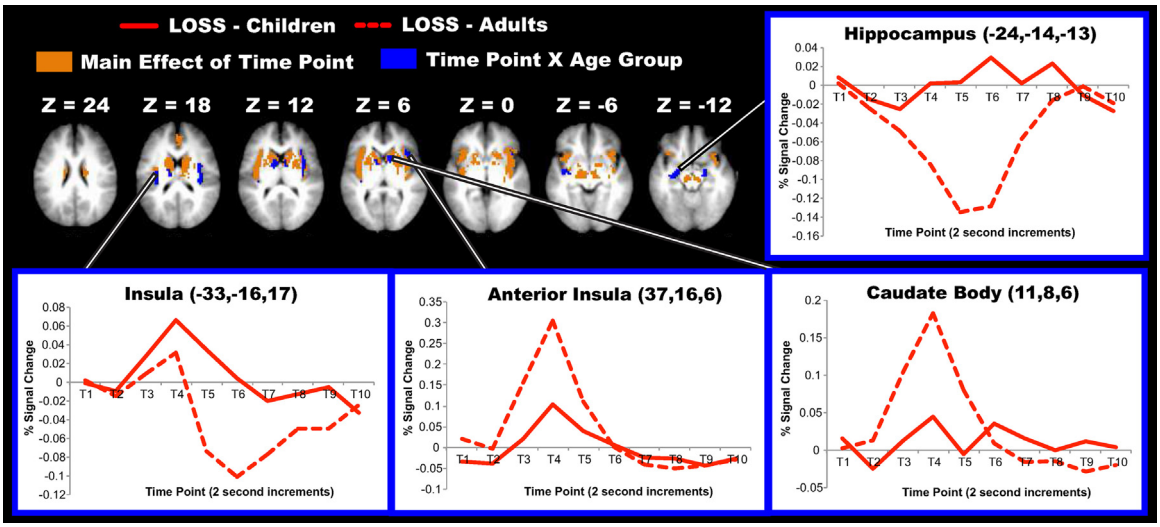

Fig. 2. Regions identified in the Time Point × Age Group ANOVA using gain trials. Age group differences in the response to loss of reward feedback were observed within the insula, striatum, and hippocampus/parahippocampal gyrus. Children showed greater loss-related responses within the dorsal/posterior insula compared to adults. Within the anterior insula, striatum, and hippocampus/parahippocampal gyrus children showed little if any loss-related activation, unlike adults. Blue regions showed a Time Point × Age Group interaction. Orange regions showed a main effect of Time Point that did not interact with Age Group. Dashed lines represent adult responses to loss feedback. Solid lines represent child responses to loss feedback. (For interpretation of the references to color in text, the reader is referred to the web version of this article.)

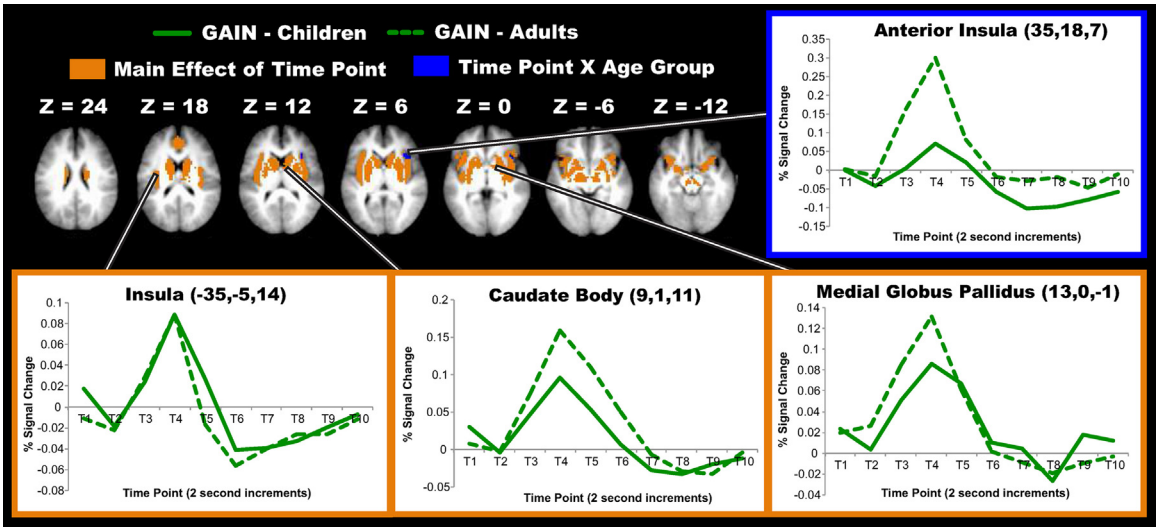

Fig. 3. Regions identified in the Time Point × Age Group ANOVA using loss trials. Children and adults showed similar responses to gain feedback within the vast majority of the insula, anterior cingulate, and striatum. Only a small portion of the right anterior insula showed an effect of age with children showing reduced response to gain feedback. Blue regions showed a Time Point × Age Group interaction. Orange regions showed a main effect of Time Point that did not interact with Age Group. Dashed lines represent adult responses to gain feedback. Solid lines represent child responses to gain feedback. (For interpretation of the references to color in text, the reader is referred to the web version of this article.)

incorrect/loss feedback during simple tasks, and that during more complex tasks they are less able to effectively use/ignore such feedback to optimize behavior (Crone et al., 2008; van den Bos et al., 2012; van Duijvenvoorde et al., 2008; van Leijenhorst et al., 2006). All observed age differences in activation, with the exception of the anterior insula, were related to responses following loss of reward rather than receipt of reward. Within the dorsal/posterior insula children displayed greater peak responses to loss that did not subsequently dip below baseline. Relatively little is known about the function of the dorsal/posterior insula. However this region has strong connections with the more dorsal/posterior cingulate and motor cortex (Cauda et al., 2011; Menon and Uddin, 2010). As such, heightened child responses to loss within the mid/posterior insula could be related to age differences in general behavior (i.e., reaction time or global switching) or in the propensity for loss/negative feedback to influence learning/choice behavior (Berman et al., 1970; Cassotti et al., 2011; Crone et al., 2005; van den Bos et al., 2012) (relationships between loss responses and behavior are discussed further below). As discussed below, our analyses did not reveal an influence of behavior on insula responses in the current study. However, it is possible that the use of more complex learning tasks would reveal such effects.

Also, much of the difference between age groups within regions showing age differences in response to loss related to the post-stimulus BOLD undershoot. Relatively few studies, developmental or otherwise, have investigated the vascular or cognitive factors thought to influence this portion of the hemodynamic response (Chen and Pike, 2009; Hua et al., 2011). Further, although it seems that the hemodynamic response shape, including the BOLD undershoot, undergoes changes between infancy and adulthood (Hua et al., 2011), the full profile and the underlying cardiovascular mechanisms of these developmental changes is unknown (Harris et al., 2011). Understanding these changes is particularly important given the statistical assumption inherent in all age group analyses utilizing an assumed response shape, that the general shape of the hemodynamic response and its relationship to neural activity is similar across ages.

Within the right anterior insula adults showed greater activation following loss compared to children. A recent study by Galvan and McGlennen using aversive liquids found a similar age difference within the anterior insula where adolescents' responses to loss were reduced compared to adults' (Galvan and McGlennen, 2013). While Galvan and McGlennen interpreted this result to indicate that aversive outcomes are more affectively salient for adults than *adolescents*, we interpret our results as indicating a difference in general salience of cue/feedback between adults and *children*, as we observed similar age differences (i.e., reduced child responses) within this region following both gain and loss, as discussed in more detail below.

Age differences in loss responses were also observed within the caudate/thalamus and hippocampus/parahippocampal gyrus with children showing very little response to loss relative to baseline in these regions. This pattern within the dorsal striatum and thalamus is somewhat surprising given how reliably the region is recruited during the CGG across age groups in previous studies, though these studies have focused on older populations (Delgado et al., 2000, 2004; Forbes et al., 2010; May et al., 2004). How responses in the caudate/thalamus related to behavior is discussed below. Within the hippocampus/parahippocampal gyrus adults showed strong loss-related deactivation while children showed little if any activation. Although the hippocampus has not received much focus in the developmental incentive literature, studies investigating stimulus-response learning

do report similar age effects, which are not further related to complex behavior (Casey et al., 2002; Thomas et al., 2004). It is also important to note that the hippocampus undergoes complex structural maturation patterns across childhood/adolescence (Gogtay et al., 2006) and how such structural changes may relate to age-differences in activation patterns is not well understood.

4.2. Age differences in response to candy gains

Studies with well-delineated child comparison groups investigating responses to gains/correct feedback have reported similar striatal responses in children and adults (Galvan et al., 2006; van den Bos et al., 2009; van Duijvenvoorde et al., 2008). However, these studies used secondary incentives, which may be less engaging for children than adults, and thus might have masked evidence for increased responses to gains in children. If this is the case, given our use of child-friendly candy incentives, we would expect to observe enhanced child responses to gain within the striatum compared to adults. However, children and adults showed similar responses to candy gain feedback within the dorsal and ventral striatum as well as the vast majority of the insula and anterior cingulate suggesting that children do not show greater striatal response to gain compared to adults when secondary incentives are employed.

Interestingly, the only region showing a significant effect of age group was a portion of the right anterior insula nearly identical to the anterior insula region identified in the loss ANOVA. Again this region showed *reduced* child responses to candy feedback. The anterior insula is involved in attention and task control and, in adults, is strongly functionally connected with the salience network (Cauda et al., 2011; Menon and Uddin, 2010; Nelson et al., 2010). There is also evidence supporting a decrease in sustained activation and an increase in transient activation from childhood through adulthood within the anterior insula/inferior frontal gyrus, particularly during tasks with low demand (Brahmbhatt et al., 2010; Burgund et al., 2006). As such, reduced insula activation in children could relate to age differences in transient attentional capture by the choice cue/winning, differences in general cognitive/neural properties supporting sustained versus transient activation patterns, or other general factors such as group normalization or movement, although we have taken care to minimize such group differences. However, in sum our results in regards to gain responses contribute to the growing literature suggesting that for the most part children and adults show similar sub-cortical responses to gain, even when child-centric candy incentives are employed.

4.3. Relationships between task behavior and neural response to feedback

Although instructions for the CGG indicated a link between the response on a given trial and that trial's outcome, neither the instructions nor the fixed feedback order allowed for a link between responses and outcomes *across* trials. Despite those two factors, participants generally behaved as if outcomes and choices were in-fact linked across trials with choices varying based on the previous trial's outcome. To investigate how behavior related to activation and whether differences in behavior mediated any of the abovementioned age differences in activation, mediation analyses were conducted within ROIs showing a Time Point × Age Group interaction. Although strategy (proportion of 'stay' choices post high gain versus high loss) did not mediate age differences observed within the caudate/thalamus, a significant direct effect of strategy on activation was observed. This relationship held even with controlling for the general propensity to 'stay' and mean reaction time, and further, the effect of age group on activation was no longer significant. Within the mid/posterior insula, no effects of behavior on activation were observed, and the effect of age group remained significant, with children showing enhanced responses to loss relative to adults within the mid/posterior insula. These results suggest an effect of strategy on feedback-related responses within the caudate/thalamus, but also suggest that the age effects within the caudate/thalamus did not entirely reflect age variation in strategy.

4.4. Limitations, conclusions, and future directions

One issue with the use of candy incentives might be that adults did not find them particularly salient. However, adults displayed strong activation following both gains and losses within the reward circuitry and all striatal age differences were in the direction of *increased* adult responses to candy feedback. Future studies directly comparing responses to different incentive types across broader age ranges are needed to establish whether patterns of age differences in activation vary depending on incentive type. A second issue is that we were unable to investigate activation within the OFC and some of the ventral striatum, regions that have shown interesting developmental effects in previous studies, due to age differences in signal quality within these regions. As such, future studies are needed to investigate the source of these age differences in OFC and ventral striatal signal quality, as well as to examine age effects on responses to gains/losses within these regions using methods that provide better signal quality. A third issue is that many of our age differences were found in the magnitude of the BOLD return to baseline or undershoot, and we have relatively little understanding of what these might reflect at either the cognitive or neurobiological level. As such, further research is needed on factors that might influence these components of the BOLD results, such as the choice of baseline (Galvan, 2010) and/or how such differences may influence analyses using assumed response shapes. Fourthly, our definition of "strategy", the global difference in staying after high gain and high loss feedback for the entire task, was very broad. While this difference describes gross win-stay/lose-shift-like behavior, a well-studied type of strategy, it is not the only type of behavioral "strategy" in which participants may have engaged. Further, we do not yet understand the factors that drive individual differences in the use of such strategies or why they may differ with age. In addition, our strategy definition focused on the average response to high gain/loss trials across the entire task. However it

is likely that how a given participant interacted with the task changed over time and future studies that examine the evolution within a session, and how this interacts with age, will be useful. Finally, future studies are warranted focusing specifically on potential relationships between response to losses, in addition to gains, and risk taking behavior both at the individual difference level and across development.

In conclusion, children seem to be more sensitive than adults to loss feedback. Specifically, extensive age differences following loss feedback were observed within the insula, even when controlling for behavior, while striatal activation was related to both age and behavior. Together these results highlight the importance of evaluating neural responses not only to gains but also to losses in child populations as differences between age groups varied following gain and loss feedback. Additionally, these results highlight the importance of controlling for behavior and age differences in task approach/experience even when the task is not designed to elicit overt behaviors.

Conflict of interest

None declared.

Acknowledgements

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2014.01.005.

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