Spring 5-15-2015

How Gains and Losses Influence the Brain and Behavior: Relations to Age, Risk for Depression, and Individual Differences

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A dissertation presented to the
Graduate School of Arts & Sciences
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

May 2015
St. Louis, Missouri

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Acknowledgments

First, I would like to thank Dr. Deanna Barch, my thesis adviser. I can truly say that there is not another person, beyond my family, who has had such a profound and positive influence on my life. Over the past six years she has supported me, challenged me, and allowed me to find my own scientific voice. She is my teacher and my inspiration and I hope that one day I will be able to pay these gifts forward to students of my own.

I would also like to thank my thesis advisory committee for their time and advice, both of which have been invaluable. In particular Dr. Joan Luby has provided critical clinical and developmental perspectives that have greatly enhanced the studies presented in this dissertation.

Without Lori Ingram, Danielle Kelly, and Brooke Kinsaul, all of whom worked tirelessly to recruit participants and collect data, these studies would not have been possible. I would also like to thank Carol Cox for her friendship and expert guidance regarding the ever-important procedural details of conducing research. The CCP lab as a whole has provided invaluable advice and camaraderie, which have greatly shaped both this dissertation and my time at Washington University in St. Louis.

Finally, I would like to thank my family. Throughout my life my parents, Linda and Joe Luking, have provided unconditional support and have pushed me to realize my full potential. Together they have made innumerable sacrifices to provide me, and my sister, with the best education possible, for which I am deeply grateful. The importance of education is a value also shared by my extended family. I am incredibly lucky to be part of a long legacy of women who have not only chosen to pursue higher education, but have chosen to do so even when it was

difficult and uncommon. Without such shoulders to stand on, I would not be where I am today, and for that I am forever grateful.

This work was supported financially by an NSF IGERT program fellowship, NIH training grant (5T32GM081739) from the National Institute of General Medical Sciences, an NRSA F31 fellowship from NIMH, the Sidney R. Baer, Jr. Foundation, the Brain and Behavior Research Foundation, and by R01s MH090786 and MH64769.

Dedicated to my parents who have always encouraged me to ask ‘why’.

ABSTRACT OF THE DISSERTATION

How Gains And Losses Influence The Brain And Behavior:
Relations To Age, Risk For Depression, And Individual Differences

by
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Doctor of Philosophy in Biology and Biomedical Sciences
(Neurosciences)
Washington University in St. Louis, 2015
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Behavioral and neural response to rewards and punishments has been the subject of a growing literature with particular interest within developmental, psychopathology, and individual difference domains. There is now mounting evidence suggesting that adolescents show heightened response to reward relative to adults, and that adolescents with Major Depressive Disorder (MDD), elevated depressive symptoms, or at high-risk for depression show reduced response to reward. However, it is unclear whether similar relations between response to incentives and development/psychopathology are observed during childhood. Here we examine behavioral, neural (functional magnetic resonance imaging - fMRI), and self-reported responsiveness to gain and loss of rewards within healthy children and young adults. We relate observed neural/behavioral incentive responsiveness to 1) developmental stage, 2) risk for depression, and 3) self-reported incentive sensitivity. First, studies investigating developmental stage indicated that responsiveness to gain and loss of reward feedback show differing relations with age. Specifically, while children show elevated behavioral and neural (dorsal/posterior insula) response to loss of reward relative to adults, response to reward was similar across age groups. Second, we observed similar levels of both gain approach and loss avoidance behavior between healthy children at relatively high and low-risk for MDD, based on a positive/negative

maternal history of MDD respectively. Third, across several studies both elevated gain approach and elevated loss avoidance behavior related to elevated self-reported incentive sensitivity as assessed via different questionnaire types (i.e. hedonic capacity, Behavioral Inhibition System/Behavioral Activation System, and anhedonic depressive scales). Interestingly, gain approach and loss avoidance behavior predicted *unique* variance in self-reported incentive sensitivity (BAS drive) and relations between incentive sensitivity and behavior did not differ based on age or depression risk status. Together these results highlight the importance of responsiveness to feedback signaling the loss of reward from both developmental and incentive sensitivity perspectives. Future work is needed to examine how gain and loss responsiveness during childhood prospectively predicts changes in incentive responsiveness over development and incidence of depression/changes in depressive symptoms.

Chapter 1.

Incentive Processing – Age And Individual Differences

Rewards (i.e. stimuli/states that encourage approach or positive affective responses) and punishments (i.e. stimuli/states that encourage avoidance or negative affective responses) are among the most potent sources of information in the environment. Incentives (i.e. rewards, punishments, and/or their removal which encourage action) influence a wide range of core cognitive and affective processes including memory, learning, decision-making, motivation, mood, cognitive control, attention, and perception (Geier & Luna 2012, Henriques et al 1994a, Kahneman 1979, Linke et al 2010, Maunsell 2004). Because rewards/punishments play such a primal and ubiquitous role in cognitive/affective function they have been subjects of inquiry within variety of disciplines/theoretical backgrounds. Recently there has been particular interest regarding how incentive processing (i.e. how reward/punishment information is translated into action) and incentive sensitivity (i.e. basic affective, behavioral, neural reactivity to incentive cues/contingencies) relate to 1) typical development, 2) psychopathology/risk for psychopathology, and 3) differences we observe between individuals. However, few studies have investigated such responses during childhood or how these lines of research intersect.

As discussed in greater detail below, studies investigating typical development have largely focused on how neural/behavioral responses to reward evolve from *adolescence* to adulthood. Further, in separate work, researchers investigating psychopathology have linked reduced reward responsiveness to depression (and risk for depression) in *adolescence* and adulthood. Given the adolescent focus of both literatures, it is unclear how responses to gains and losses differ between children and adults, or differ between healthy children at relatively high- and low-risk for depression. There is a critical gap in the literature where, despite the limited cross between typical developmental and psychopathology related studies, models of depression etiology and risk often include developmental components and rely on the underlying

assumption that the increasing incidence of depression (and other types of psychopathology) observed over adolescence is related, at least in part, to developmental processes (see (Forbes & Dahl 2005) for commentary). Before researchers can fully explore this hypothesis it is first important to investigate typical and atypical incentive responsiveness during childhood, when there is relatively low incidence of major depressive disorder (MDD) and the changes in incentive responding associated with adolescence have not yet begun. As such, the studies presented in this dissertation aim to investigate how neural/behavioral responses to gain/loss feedback differ between 1) children and adults, and 2) children at relatively high and low risk for developing depression. Understanding how neural/behavioral responses to incentives in healthy children relate to those in healthy adults would provide an important normative baseline for future work investigating how developmental trajectories of gain and loss responsiveness relate to depressive symptomology or may diverge based on risk for depression. Further, characterizing incentive responsiveness in high-risk populations prior to adolescence will provide preliminary evidence, along with the extant literature, regarding whether populations at relatively high-risk for MDD show altered incentive responsiveness across many developmental time points, or whether such group differences are specifically observed during/after adolescence.

Only a handful of studies have investigated how reward responses relate to both individual differences and group differences in age or psychopathology. Studies that include individual difference analyses tend to do so within a given discipline. For example, age-differences in neural response to reward have been related to behaviors associated with typical adolescence (i.e. risk taking or decision-making) (Galvan et al 2007, Paulsen et al 2011a) while differences in neural response to reward between adolescents at high- and low-risk for depression have been related to current or future depressive symptomology (Bress et al 2012,

Olino et al 2014). While these studies have begun to link developmental or psychopathology-related changes in reward responding to behaviors of interest, few other studies have done so. Thus, while there is provocative evidence linking neural response to reward with both normative and abnormal behaviors during adolescence and adulthood, it is unclear whether similar relations between incentive-related behavior and self-reported symptomology/incentive sensitivity are observed across child and adult groups and across children at high and low-risk for depression. The studies presented in this dissertation investigate relations between self-reported incentive sensitivity/depressive symptomology and gain/loss behaviors and whether/how these relations may differ across age and depression-risk. Characterizing relations between incentive sensitivity/depressive symptomology in childhood and then investigating how such relations may differ based on depression risk first would provide a 'normative' developmental baseline for comparison with childhood pathology and secondly would potentially characterize new behavior/symptom correlates of risk in childhood.

To provide a context for asking these questions, the sections below briefly review the literatures investigating 1) neural responses to rewards/punishments in healthy adults, 2) differences between children and adults in behavioral and neural responses to rewards/punishments, 3) relations between neural/behavioral responses to rewards/punishments and a variety of incentive sensitivity self-report measures in adults/adolescents, and 4) relations between depression/depression risk and responses to rewards/punishments in adults and youths.

1.1 Neural Systems Involved In Incentive Processing

The translation of incentive information from the environment into emotional experience and motivated behaviors is a complex phenomenon involving a cascade of discrete component

processes. At the most basic level, incentive responding includes three components; 1) hedonic response (i.e. experience of pleasure) to incentive outcomes or incentive 'liking', 2) motivation to approach/avoid the incentive or 'wanting' (also termed incentive salience), and 3) learning processes by which actions/cues are related to incentive outcomes based on previous experiences (Berridge et al 2009). Importantly, while these components are dissociable in certain contexts, they are not by definition orthogonal processes. For example, pharmacologic stimulation of the nucleus accumbens and ventral pallidum (functions of these regions are discussed in greater detail below) that increases 'liking' of sweet taste also increases consummatory behavior (i.e. increased 'wanting') in animals (Smith & Berridge 2005). Further, motivational/physiologic states, such as hunger/satiation or salt deprivation, can alter indexes of 'liking' of specific substances both in humans and other animals (Kringelbach et al 2003, Tindell et al 2006). Finally, despite being separable, 'liking' and 'wanting' can both influence and in turn are affected by learning processes (Berridge 2012, Berridge et al 2009).

Understanding of these component processes and their relations has advanced with the emergence of studies regarding how brain regions individually and neural systems collectively respond to incentive information (see Figure 1.1 for summary of regions responsive to incentive information). A rich literature in animals and humans has established the role of the cortical-basal ganglia circuit and the extended limbic system in reward and punishment processing (for reviews see (Haber 2011, Haber & Knutson 2010)) with particular emphasis on dopaminergic, serotonergic, and opioid signaling. At the core of these systems is the basal ganglia/striatum comprised of the caudate, putamen, globus pallidus, and nucleus accumbens. Resent meta-analyses and functional connectivity studies have emphasized both dorsal/ventral and rostral/caudal functional distinctions within the striatum (Barnes et al 2010, Di Martino et al

2008, Draganski et al 2008, Greene et al 2014, Postuma & Dagher 2006).

The dorsal striatum/basal ganglia (DS), comprised of the caudate body, dorsal/rostral putamen, and the dorsal pallidum, receives significant dopaminergic innervation and shows reciprocal functional/structural connections with a number of regions, including the dorsal prefrontal cortex (DPFC), which is thought to be involved in cognitive control, the anterior cingulate cortex (ACC) involved in error processing, as well as with motor cortex (Barnes et al 2010, Di Martino et al 2008, Haber & Knutson 2010, Postuma & Dagher 2006). During simple gambling tasks the DS (particularly the caudate) shows differential responsivity to gain and loss outcomes, typically with greater activation following gain than loss outcomes (Delgado et al 2000). However, DS responses are sensitive to a number of factors beyond outcome valence, including outcome magnitude (Delgado et al 2003, Delgado et al 2000), action contingency (Tricomi et al 2004), number of response options (Tricomi & Fiez 2012), and probability of outcome (Tricomi & Lempert 2015). Given patterns of connectivity, dopaminergic innervation, and the functional patterns discussed above, the rostral DS has been strongly implicated in goal-directed action. Rostral components of the DS have also been implicated in actor/critic learning models where during instrumental conditioning the DS behaves as the theorized ‘actor’, relating actions to positive (i.e. rewarding) outcomes and thus increasing the selection of previously rewarded responses (O'Doherty et al 2004).

More caudal portions of the DS (particularly the dorsal caudal putamen) however are less sensitive to action-outcome contingencies and are involved in habitual responding when the outcome has been devalued (Tricomi et al 2009). This perseverative/’habitual’ responding, even when the outcome of an action is no longer ‘liked’ (i.e. has been devalued) is a good example of the dissociation between the ‘liking’ an outcome and the incentive salience or ‘wanting’ of a

conditioned/instrumental cue. Such task findings are consistent with connectivity studies where the caudal DS shows strong connectivity with sensory and motor regions while more rostral regions show stronger connectivity with associative and cognitive control regions (e.g. antierior cingulate cortex (ACC) and dorsal/medial prefrontal cortex (PFC)) (Barnes et al 2010, Di Martino et al 2008, Postuma & Dagher 2006).

The ventral striatum/basal ganglia (VS) is comprised of the caudate head, ventral components of the putamen/pallidum and nucleus accumbens. Although overly simplistic, opioid and GABAergic activity within the nucleus accumbens and ventral pallidum have been linked to 'liking' responses. In contrast, dopaminergic signaling, particularly within the nucleus accumbens, has been implicated in learning/prediction error signaling (Berridge et al 2009, Haber 2011, Haber & Knutson 2010, Smith et al 2011). The ventral striatum shows strong connectivity with oribitofrontal and ventral medial prefrontal corticies (OFC/vmPFC), the amygdala/hippocampus, and dopaminergic midbrain (Barnes et al 2010, Di Martino et al 2008, Postuma & Dagher 2006). Like the dorsal striatum, VS shows greater activation to reward feedback than loss/punishment feedback (Liu et al 2011). However, unlike the DS, the VS tends to show either deactivation to loss outcomes, particularly when that outcome is worse than expected, or no activation (Delgado et al 2000, Knutson et al 2001a). Further, the VS corresponds to the 'critic', evaluating observed outcomes relative to what was expected, in actor/critic models (O'Doherty et al 2004)

Other non-striatal limbic regions involved in incentive processing include the amygdala, hippocampus, and insular cortex. The amygdala's role in fear/punishment learning has been studied extensively, however, its role in stimulus-reward learning has been recognized relatively recently (Baxter & Murray 2002). The amygdala receives input from a wide variety of regions,

including the OFC and sensory regions, and efferent projections from the amygdala terminate in the VS (primarily nucleus accumbens), OFC, and vmPFC, among other regions, making it a key site in the incentive-processing network (Baxter & Murray 2002, Haber & Knutson 2010). Specifically, the amygdala is involved in several types of reward learning, signals affective/incentive salience ('wanting') of cues/stimuli in the environment, and shows activation to both aversive and appetitive stimuli (O'Doherty et al 2001b). However, the amygdala is not consistently highlighted in human incentive processing studies using fMRI, possibly due to habituation effects or task differences, for example the amygdala does not consistently show activation during simple guessing tasks without anticipation/learning components (Delgado et al 2003, Delgado et al 2000, Hommer et al 2003, Knutson et al 2001b, Smith et al 2009). Like the amygdala the hippocampus has efferent projections terminating specifically in the VS, however these projections are even more narrowly focused within the nucleus accumbens than those from the amygdala (Di Martino et al 2008, Friedman et al 2002, Haber & Knutson 2010). The hippocampus is most frequently discussed in the context of reward-related learning, however hippocampal activation is also reported in simple guessing tasks without learning components (Delgado et al 2000, May et al 2004).

Like the amygdala, the insula historically has been implicated in responding to aversive outcomes and physical states. However, there is increasing evidence that the insula has a much more complex set of functions and that anterior regions in particular respond to salient stimuli/events regardless of valence. Recent meta-analyses highlight that while the anterior insula (AI) is responsive to positive and negative outcomes during both anticipation and receipt (Liu et al 2011), the ventral and anterior/dorsal AI are also more broadly involved in cognitive functions such as focal attention and task-level control (Nelson et al 2010). The AI is richly

interconnected with a number of regions within frontal, rostral cingulate, and parietal cortices as well as with other limbic regions (Cauda et al 2012, Cauda et al 2011, Cloutman et al 2012). More dorsal and posterior portions of the insula show positive connectivity with sensory/motor regions, mid/posterior cingulate cortex, and amygdala (Cauda et al 2012, Cauda et al 2011, Cloutman et al 2012, Deen et al 2011, Roy et al 2013). From a functional stand point the posterior insula (PI) does seem to selectively respond during anticipation of negative outcomes (Liu et al 2011). Given this negative focus it is understandable that few reward-processing studies discuss more posterior components of the insula.

The ACC, particularly dorsal components, plays an important role in conflict monitoring and reward-related/affective decision-making (Bush et al 2002, Etkin et al 2011). Within incentive studies the dorsal ACC (dACC) has been implicated in responding during incentive anticipation, outcome, and evaluation and is most reliably activated during negative outcomes, when outcomes are lower than expected, or when shifts in behavior are required (Bush et al 2002, Liu et al 2011). The dACC has projections that terminate in both the dorsal and ventral striatum as well as functional connections with other cortical regions involved in cognitive control and error processing (Etkin et al 2011, Haber & Knutson 2010, Margulies et al 2007). The rostral anterior cingulate cortex (pregenual anterior cingulate cortex) shows greater activation to reward outcomes (Liu et al 2011) and shows stronger connectivity with limbic than cognitive control regions (Etkin et al 2011).

The orbitofrontal (OFC) and ventromedial prefrontal cortex (vmPFC) have both been implicated in value representation and are essential for evaluating and comparing items/actions of different values during decision-making (Hare et al 2009, Hare et al 2008, Padoa-Schioppa & Assad 2008, Rangel & Hare 2010). Responses within vmPFC and medial OFC have been linked

to incentive ‘liking’ as responses decrease following satiation and correlate with preference and pleasantness ratings (Kuhn & Gallinat 2012, McClure et al 2004, O'Doherty et al 2000). Morel lateral portions of the OFC have been implicated in decision-making and integrating incentive information (Bechara et al 1998, Kringelbach 2005, Rogers et al 1999). Both the OFC and vmPFC have efferent projections to the striatum terminating primarily in the VS (Haber & Knutson 2010), and are further reciprocally connected to sensory and affective systems (including the amygdala) (Kringelbach 2005). As such, the OFC and vmPFC are ideally suited to integrate information regarding different types of incentives from all sensory systems, which then allows for representations of subjective value (relative ‘liking’) that then inform more complex decision-making/learning processes.

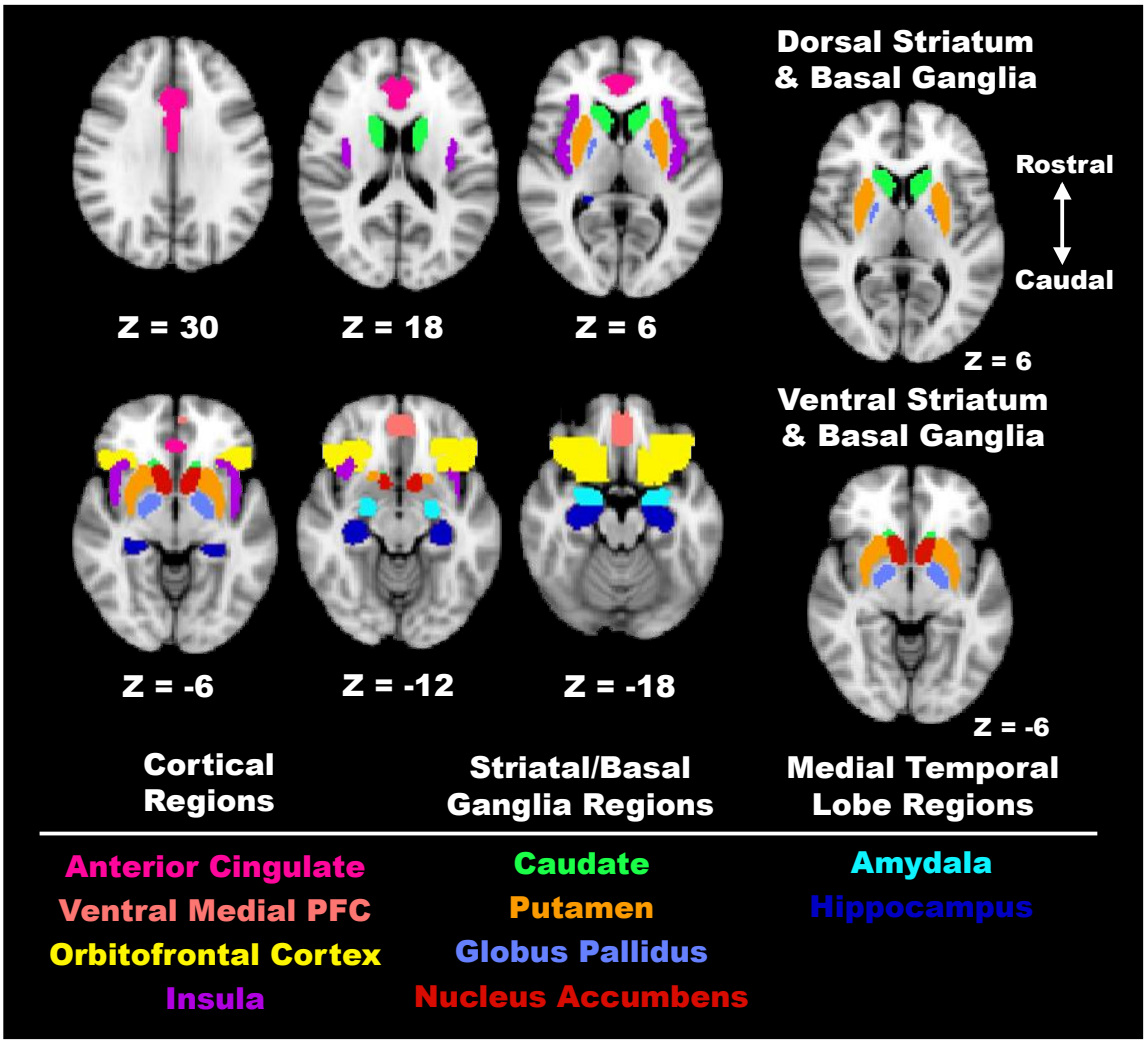


Figure 1.1: Reward/Punishment Processing Circuitry

1.2 Incentive Types And Processing Differences

Although the vast majority of incentive processing studies discussed above utilize secondary incentives (primarily money, although some developmental studies use points/token economies), a handful of adult fMRI studies have directly compared responses to secondary and primary incentives. Such studies, as well as a recent meta-analysis comparing primary and secondary fMRI studies, report responses to both types of incentives in largely overlapping regions including the ventral striatum, anterior insula, vmPFC, and ACC (Clithero et al 2011, Kim et al , Levy & Glimcher 2011, Sescousse et al 2013, Sescousse et al 2010, Simon et al 2014). However, there is also evidence of differential activity. Specifically when comparing response to erotic pictures (primary) versus monetary (secondary) feedback, more anterior components of the OFC respond maximally to secondary rewards while medial and more posterior OFC regions respond maximally to primary rewards (Sescousse et al 2010), a pattern highlighted in an earlier meta-analysis (Kringelbach & Rolls 2004). This study also found greater amygdala responses to primary than secondary rewards (Sescousse et al 2010). However, another factor to consider is that secondary rewards are not directly 'consumed' in the scanner, unlike erotic pictures that are immediately 'consumed'. Instead a lump sum of money is delivered post scan, thus differences in the timing of 'consumption' could explain the OFC/amygdala differences reported by Sescousse and colleagues.

Interestingly, a recent study has eliminated this confound by comparing anticipatory/receipt related responses during monetary and snack point trials (Simon et al 2014). In this study, lump sums of both incentives were received post scan and snack points could then be exchanged for 'primary' snack rewards. Again, responses were greater within more posterior portions of the OFC for primary (snack) rewards than monetary rewards. However, neither type

of reward elicited activation within the amygdala. Together these results suggest that differences in processing of primary and secondary rewards may in part relate to affective salience and immediacy of cues, particularly within the amygdala, but that anterior/posterior OFC differences relate to reward type independent of timing of reward 'consumption'. Primary rewards may be particularly advantageous for investigating developmental questions as they relieve concerns regarding how age may interact with the processing of abstract incentives and that in adults primary and monetary incentives seem to generally elicit similar responses, with the exception of anterior versus posterior OFC, and potentially amygdala.

1.3 Age And Reward/Gain Processing

While the studies discussed above in the neural systems section have been conducted within adult primate (both human and non-human) populations, developmental neuroimaging studies suggest that child populations recruit similar neurocircuitry during incentive processing. Given this similarity, age differences in incentive-related behaviors likely relate to age differences in the magnitude or pattern of responses within these regions to gain/loss feedback, rather than the recruitment of distinct neural systems (Galvan et al 2006, Helfinstein et al 2013, Kappel et al 2013, Padmanabhan et al 2011, Paulsen et al 2011a, van Leijenhorst et al 2006). Differences in responses, both behavioral and neural, during incentive processing tasks observed between child and adult groups are discussed in detail below.

Behavior

There are few behavioral studies specifically focusing on age differences in reward sensitivity; however, there are several studies focusing on reward related decision making and learning in children and adults. Specifically, the Iowa Gambling Task (IGT) and other gambling

task variants, where value and probability of receiving gain and loss feedback are manipulated, have been employed in a number of studies. These studies consistently highlight that children are less likely to repeat the same choice or 'stay' after receiving gain feedback (i.e. 'win-stay') than adults (Aite et al 2012, Cassotti et al 2011, Crone & van der Molen 2004, van den Bos et al 2009, van Duijvenvoorde et al 2008). Children are also more risk seeking than adults, even when 'safe' and 'risky' bets are of equal value (Paulsen et al 2011b). While most of these studies emphasize that risk aversion develops into adulthood or that optimal choice behavior (i.e. win-stay) emerges over development, it is also possible that age differences in impulsivity or exploration partly mediate age effects.

Looking at more global behavior on tasks like the IGT suggests that relative to adults, children have difficulty integrating incentive information over time to make adaptive choices (Cassotti et al 2011, Crone & van der Molen 2004). Further, these age effects are not related to working memory ability, intelligence, and inductive reasoning ability (Crone & van der Molen 2004). However, in IGT and other similar tasks it is difficult to dissociate the influences of feedback type as well as frequency and amount given that either a gain or loss occurs for every choice and decks that are 'disadvantageous' can also have higher frequency of small gains (see (Cassotti et al 2014) for developmental commentary). Given this confound of feedback type frequency and amount, it is unclear whether impaired IGT performance in children truly reflects a difficulty integrating feedback over time to inform future behavior or whether children and adults are differentially sensitive to feedback amount versus frequency.

fMRI

Although interest in reward processing from a developmental perspective has increased

dramatically in the past decade, the vast majority of developmental fMRI studies focus on adolescence, and only rarely are distinct child groups included for comparison. For example, a recent comprehensive overview of the developmental reward fMRI literature by Richards and colleagues (2013) showed that only seven of the 20 fMRI studies reviewed included a distinct 'child' group. Further, only one study had an upper age limit below 11 for the child group (i.e. most 'child' groups also included 11-13-year olds) and no studies including older children controlled for/investigated pubertal status. This literature is further limited as only two of the studies including a child group directly compared child and adult striatal BOLD responses to positive outcomes (Galvan et al 2006, Somerville et al 2011). The remaining studies either only tested for quadratic effects of age (i.e. only compared child and adolescent and then adult and adolescent responses), examined the difference between reward and punishment responses, or focused on cortical regions.

The few studies including explicit child groups tend to report similar ventral striatal responses to reward in child and adult groups (Galvan et al 2006, Somerville et al 2011). Other studies reporting quadratic effects of age with VS response peaking in adolescence also suggest similar striatal responses to monetary incentives in children and adults, but did not directly compare child and adult groups (Cohen et al 2010, Padmanabhan et al 2011, Van Leijenhorst et al 2010a). Studies investigating reward and negative feedback in more complex learning tasks report similar relations between dorsal striatal responses to reward versus negative feedback in children and adults (van den Bos et al 2009, van Duijvenvoorde et al 2008). Together these studies suggest that children and adults show similar striatal responses to feedback signaling monetary or point gain.

Interestingly, although no age differences have been observed within the striatum, studies

do report age effects within the dACC, lateral OFC, and DLPFC. Specifically, children tend to show enhanced responsiveness to reward within the dACC relative to adults (Padmanabhan et al 2011, van Duijvenvoorde et al 2008). Some studies also report greater child responsiveness to reward/positive feedback within the lateral OFC/inferior frontal gyrus (Galvan et al 2006, Somerville et al 2011), DLPFC, and superior parietal cortex (van Duijvenvoorde et al 2008). However, the few studies that investigate effects of both task/behavior and age on BOLD response report that age differences in activation reflect age differences in behavior (IFG (Somerville et al 2011)) or further interact with task effects (DLPFC/superior parietal cortex (van den Bos et al 2009)). Thus, while children and adults likely show different responses to incentive feedback within frontal/parietal regions, it is unclear whether these effects are driven by age differences in reward responsiveness or whether they reflect age differences in task difficulty or cognitive load/processing (see (Church et al 2010) for commentary on this issue).

1.4 Age And Loss/Punishment Processing

Behavior

Many of the behavioral studies discussed in the gain processing section above also utilize loss feedback. Like with gain, under typical task demands, children are more likely to choose a different response or 'shift' after receiving negative/loss feedback (i.e. 'lose-shift') (Aite et al 2012, Cassotti et al 2011, Crone & van der Molen 2004, van den Bos et al 2009), however with more complex behavioral responses some studies report reduced shifting post loss in children (van Duijvenvoorde et al 2008). Interestingly, recent work has highlighted a confound within the traditional IGT where 'advantageous' options that are optimal in the long run (i.e. lead to the best overall result due to small sized losses and larger gains), actually have more frequent, if smaller,

losses than ‘disadvantageous’ options characterized by infrequent, large losses (see (Cassotti et al 2014) for review and commentary). As discussed above, previous IGT studies concluded that children’s failure to increasingly select the advantageous options related to an immature ability to integrate incentive information over time and apply that knowledge during decision-making. However, when using new payout schemes where loss frequency and amount are dissociable, children show elevated sensitivity to the frequency of loss feedback relative to adults (Aite et al 2012, Cassotti et al 2014, Crone et al 2005). Thus, it seems that the ability to integrate loss frequency and amount improves with age. As such, children should show better performance than adults in avoiding frequent losses when the amount of that loss is not relevant for decision-making.

Interestingly, two recent studies investigating probabilistic and reversal learning indicate that children show faster learning rates for negative feedback than for gain/positive feedback, a pattern that reverses in adulthood (van den Bos et al 2012, van der Schaaf et al 2011). Behavior on both of these tasks has been shown in adults to be influenced by dopaminergic signaling, (Cools et al 2009, Frank & Hutchison 2009, Frank et al 2007, Robinson et al 2010) with elevated D2 receptor density/signaling specifically related to improved loss-avoidance behavior (Frank & Hutchison 2009). While there is relatively little primate work investigating changes in DA signaling from childhood to adulthood, the evidence does suggest that non-human primates show elevated DA receptor density during childhood relative to adulthood (for review see (Wahlstrom et al 2010)). There is also a large body of work conducted from the 1960s through the early 1980s investigating feedback driven discrimination learning in child populations. This literature also suggests that children show faster learning rates from loss/negative feedback than from gain/positive feedback alone (for meta analysis and review see (Getsie et al 1985)). Collectively

these findings suggest that children are more behaviorally reactive to loss than adults and show more advantageous behavior when simple lose-shift strategies are optimal.

fMRI

Several, but not all, of the incentive processing fMRI studies discussed above also included loss or negative feedback. The two studies investigating striatal response to negative feedback report similar patterns of activation within the caudate in children and adults (van den Bos et al 2009, van Duijvenvoorde et al 2008), but no studies, to our knowledge have focused on VS responses to loss/negative feedback in children and adults. The remaining fMRI studies employ other types of learning paradigms, mostly the IGT and other gambling task variants where feedback is complex, varying in amount and probability/risk. As such, it is not surprising that those studies exclusively focus on responses within the frontal and parietal cortices.

While several studies report age differences in response to loss/negative feedback within DLPFC, ACC, OFC, and/or superior parietal cortex, these findings are not consistent. For example, some studies report reduced response to negative feedback in children within the DLPFC and ACC (van den Bos et al 2009) and superior parietal cortex (van Duijvenvoorde et al 2008), while others find no general age differences in DLPFC/ACC (Crone et al 2008, van Duijvenvoorde et al 2008) or parietal (van den Bos et al 2009) responses. Similarly, some studies report elevated lateral OFC response to loss in children (van Leijenhorst et al 2006), but others report no global age differences to loss in the OFC (Crone et al 2008). These contradictions likely stem, at least in part, from differences in task structure/demands given that these studies collectively suggest children have difficulty responding differentially to loss/negative feedback of varying information value or signaling different courses of action. For example, while adults,

and to some extent adolescents, show different levels of DLPFC and ACC response to different types of loss/negative feedback, children fail to show such distinctions (Crone et al 2008, van den Bos et al 2009).

Overall results from fMRI studies dovetail nicely with those from the behavioral literature. Both methodologies suggest that although children are quite sensitive and reactive to loss/negative feedback relative to adults, they are less sensitive to nuances in that feedback (i.e. showing strong lose-shift behavior even when this response style is detrimental or showing undifferentiated DLPFC response to negative feedback types with different information value). Unfortunately there are very few studies investigating child and adult response to loss overall, and no developmental studies focusing on the hedonic/affective in-the-moment response to loss and no studies where simple avoidance (i.e. lose-shift) strategies are optimal. As such, it is difficult to determine why children show such a strong, automatic, response to loss feedback. It may be that loss feedback itself is so salient and aversive to children that they are less able to subsequently use cognitive mechanisms to either inhibit the prepotent response or to engage an alternate, approach response. Elevated salience may also bias memory processes such that negative feedback (regardless of amount) is 'weighted' more heavily when integrating sequences of past outcomes. Loss/negative feedback is also more complex in many incentive processing tasks, for example in the IGT negative feedback does not always indicate the need to select from an alternative deck of cards. This ambiguity can make processing loss/negative feedback more difficult, thus age differences may simply reflect cognitive maturation.

The studies reviewed above have suggested that children and adults show similar striatal responsivity to loss (or gain) feedback, but there is also some evidence for age related differences in responses in cortical regions. Thus, it is possible that age differences in responding to

incentive feedback reflect cognitive maturation. Further, all of the studies discussed throughout gain and loss sections have exclusively employed secondary incentives such as money or points. It is likely that processing/valuation of secondary incentives differs from childhood to adulthood. As such, primary incentives like candy or appetitive/aversive liquids may better for investigating age differences in hedonic/affective components of incentive processing. Another limitation to the cognitive interpretation is that activation within several regions beyond the striatum, such as the insula and amygdala/hippocampus (Anderson et al 2003, Camara et al 2008, Elliott et al 2000, Phelps & LeDoux 2005, Small et al 2003), which have been strongly implicated in affective components of incentive learning/processing, was not investigated in any of these studies. Thus, future work employing simple tasks and primary incentives is needed to more thoroughly investigate hedonic/affective responding to loss (and gain) within limbic regions across childhood and adulthood.

In summary, the developmental literature suggests that children and adults recruit largely overlapping neurocircuitry during incentive processing and that striatal responses to reward are also similar. However, cortical responses to reward often differ dramatically between children and adults, particularly during more complex/cognitive incentive learning paradigms. There is little developmental neuroimaging work investigating response to loss in child and adult groups. The few studies that do investigate this question suggest that children are more responsive to negative than positive feedback, and that learning rates from negative feedback decrease from childhood to adulthood. However, children's ability to effectively use negative feedback to drive adaptive behavior seems to depend on task complexity, as child groups have difficulty discriminating between types of negative feedback and are more sensitive to loss frequency than overall amounts of loss. Together these results suggest that more basic components of incentive

processing show different developmental trajectories depending upon outcome valence, with elevated responsiveness to loss in childhood compared to adulthood, but similar responsiveness to gain in childhood and adulthood.

1.5 Major Depressive Disorder And Incentive Processing

Anhedonia, a lack of experienced pleasure, is a key component MDD (APA 2013) which has been linked to altered neural/behavioral responses to incentives in adults with MDD (discussed in detail below). Although there is growing evidence that adolescents with MDD and healthy adolescents at elevated risk for developing MDD show similarly altered behavioral/neural response to rewards, it is unclear whether similar MDD effects are observed for loss/punishment feedback or during childhood. Children as young as the preschool-age with depression show reduced joy and other features of melancholia/anhedonia (Luby et al 2004), however incidence of anhedonic symptoms in major depression increases from childhood to adolescence (Ryan et al 1987), coinciding with the adolescent typical increase in reward responding discussed above. As such, it is possible that while anhedonia (reduced pleasure) may be a feature of clinical major depression during childhood, *risk* for depression may not be strongly associated with reduced reward responding prior to adolescence. Given that no studies have investigated gain and loss-related behaviors in children at high and low-risk for MDD, it is unclear whether altered responding to incentives is in fact characteristic of MDD risk during this developmental stage. Relations between responsiveness to gain and loss/punishment and MDD/high-risk during adolescence and adulthood are discussed in detail below.

Reward Responding in MDD and High Risk Pediatric Groups

Adolescent and adults with major depression regularly report elevated

depressive/anhedonic symptoms and reduced hedonic capacity (i.e. experienced pleasure). Behaviorally, depressed individuals show reduced reward-related biases (Henriques et al 1994b, Pechtel et al 2013b, Pizzagalli et al 2008b), are less willing to expend effort to obtain reward (Treadway et al 2012), and show impaired reward learning/decision-making (Forbes et al 2007, Herzallah et al 2010, Maddox et al 2012). Depressed adults and adolescents also show decreased ERP measures of reward sensitivity (Bress et al 2013b, Foti et al 2014) and reduced BOLD response to reward within the striatum, the ACC, and the insula (Forbes et al 2006, Forbes et al 2009, Gradin et al 2011, Knutson et al 2008a, Kumar et al 2008, Pizzagalli et al 2009, Remijnse et al 2009, Robinson et al 2012, Smoski et al 2009, Zhang et al 2013). These results suggest that adolescents and adults with current MDD show similarly impaired reward responsiveness.

Interestingly, in never-depressed adolescents reductions in neural markers of reward responsiveness prospectively predict future onset of MDD/increases in MDD symptoms over time (Bress et al 2013a, Morgan et al 2012, Telzer et al 2014). Thus, it seems that reduced neural response to reward is evident in 'high-risk' adolescents (based on symptom/diagnostic outcomes) prior to disease onset. Other studies have used a family history of MDD to characterize high-risk, as ~40% of the offspring of depressed mothers go on to develop MDD, a much higher rate than for the offspring of non-depressed mothers (Goodman & Gotlib 1999, Hammen et al 2008a, Hammen et al 2008b). Studies investigating maternally defined high-risk groups have largely been conducted within adolescent (highly female) populations and generally report reduced striatal response to reward/positive stimuli (Gotlib et al 2010, McCabe et al 2012, Monk et al 2008, Olino et al 2014). However, it is unclear whether high-risk groups also show differences in reward-related behaviors and whether such differences are evident in childhood prior to the developmentally typical increase in reward responding associated with adolescence.

Punishment/Loss Responding in MDD and High Risk Pediatric Groups

The MDD literature is much less consistent regarding whether individuals with MDD exhibit elevated or reduced responsiveness to loss/punishment feedback. This inconsistency may be related to the fact that different theories of emotion reactivity in MDD actually predict opposing effects of MDD on responses to negative stimuli. Specifically, the negative potentiation hypothesis and emotion context insensitivity hypothesis (ECI) (Rottenberg 2005, Rottenberg 2007, Rottenberg et al 2005, Rottenberg et al 2002), predict *potentiated* and *blunted* reactivity to negative emotional stimuli respectively. As both hypotheses have behavioral and neuroimaging support it is not clear whether or under what circumstances MDD relates to potentiated response to negative feedback/loss (Bylsma et al 2008, Eshel & Roiser 2010, Knutson et al 2008b, McCabe et al 2009, Mueller et al 2015, Pagliaccio et al 2012, Santesso et al 2008b, Saxena et al Under Review, Steele et al 2007, Stoy et al 2012a).

Only one study, has investigated responses to monetary loss within an adolescent group at high-risk for MDD (Gotlib et al 2010), and no studies have done so within currently depressed adolescent populations. Thus, it is unclear whether such groups are characterized by altered responsiveness to loss. However, several studies investigating responding to aversive stimuli (i.e. unpleasant taste, negative emotional faces) suggest that both depressed and high-risk child/adolescent groups show elevated responsiveness, particularly within the amygdala and lateral OFC, while experiencing negative stimuli (McCabe et al 2012, Monk et al 2008, Pagliaccio et al 2012). Children and adolescents with MDD or at high-risk may also show enhanced responsiveness to feedback signaling the loss of something appetitive, however, it is also possible that group differences are more evident when actively consuming/viewing a negative stimulus than during more abstract loss feedback.

1.6 Individual Differences And Incentive Processing

There is also great variability in behavioral and neural response to incentives across individuals beyond effects of age and psychopathology. Within the adult literature variability in neural/behavior responses to incentives is often related to self-reported incentive sensitivity. Such relations are particularly interesting as they may provide information regarding the basic mechanisms of incentive processing/sensitivity and as they may elucidate mechanisms of psychopathology/risk. As such, how individual differences in self-reported incentive sensitivity relate both to behavior and activation within reward-related neural systems has received much attention in the literature.

Self-report measures of incentive sensitivity are typically designed to assess one of three related constructs, affective/hedonic response to incentives, motivation, or anhedonic/depressive symptoms. Pleasure scales, such as the Snaith-Hamilton Pleasure Scale (SHPS) (Snaith et al 1995), Fawcett-Clark Pleasure Scale (FCPS) (Fawcett et al 1983), Children's Pleasure Scale (CPS) (Kazdin 1989), and Chapman Physical/Social Anhedonia Scales (Chapman et al 1976), are designed to assess affective or hedonic responsivity to hypothetical positive events/stimuli. The Behavioral Inhibition System/Behavioral Activation System Scale (BIS/BAS) (Carver & White 1994) and Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia et al 2001) also assess affective response to reward, however, they have additional subscales that index affective response to punishment, and reward-related drive (motivation). Depressive symptom scales such as the Beck Depression Inventory (BDI – adults) and the Child Depression Inventory (CDI – child and parent about child versions) measure general depressive symptom severity, but can also be used to calculate melancholic/anhedonic depressive symptom subscales. Pleasure scales and depressive symptom scales (including anhedonic subscales) have

been used more frequently by studies investigating psychiatric or high-risk populations, however, these studies include healthy comparison groups and some studies also report relations between self-report and behavioral/fMRI data within each group separately. Conversely, the BIS/BAS scale has been widely used when investigating both typical incentive-related processes and differences between clinical and non-clinical populations.

Elevated self-reported hedonic capacity (via pleasure scales) has been linked to elevated behavioral and neural response to incentives. Healthy individuals with elevated hedonic capacity both rate affective responses to positive stimuli as being more positive and show elevated striatal response to those same stimuli (Dowd & Barch 2010). Importantly, individuals with elevated hedonic capacity not only report more positive affective responses to positive stimuli, they also report more *negative* affective responses to *negative* stimuli (Dowd & Barch 2010, Saxena et al Under Review). Studies investigating effects of hedonic capacity on behavior/learning rate similarly suggest blunted behavioral responsiveness to incentives (both gain and loss) with reduced hedonic capacity (Chase et al 2010, Steele et al 2007). Collectively, elevated hedonic capacity relates to enhanced behavioral and striatal responsivity to both positive and negative stimuli.

Within healthy populations individuals reporting elevated levels of reward responsiveness (BAS reward) and/or motivation (BAS drive) exhibit increased behavioral and neural responsiveness to incentive information. Specifically, individuals with elevated BAS report more positive affective responses to positive stimuli (Balconi et al 2009). Elevated BAS also relates to increased early attentional responses to appetitive pictures, assessed via EEG (N1 component and BAS reward) (Gable & Harmon-Jones 2013), and enhanced priming effects of reward on spatial attention (BAS drive) (Hickey et al 2010) . Further, elevated BAS relates to

increased ventral striatal responses to pictures of appetizing food and monetary gains (Beaver et al 2006, Simon et al 2010). In more complex economic decision-making tasks, individuals with elevated BAS drive/reward responsiveness seek to maximize the frequency of reward events (Scheres & Sanfey 2006) and show better performance on the IGT (Franken & Muris 2005). Interestingly there is also some evidence that individuals with elevated BAS drive also are more responsive to negative stimuli, specifically they show elevated response to disgusting pictures within the ventral striatum and OFC (Beaver et al 2006). Together this literature suggests that responsivity to incentives is generally elevated in individuals reporting elevated BAS (particularly BAS drive subscale) and this relation seems to span several different experimental modalities and components of incentive processing.

Elevated levels of general depressive and anhedonic depressive symptoms generally relate to reduced responding to incentive stimuli. Healthy individuals with elevated melancholic symptoms show less reward approach behavior in simple, implicit, probabilistic reward tasks (Huys et al 2013, Pizzagalli et al 2005) and healthy individuals with elevated depressive symptoms are less willing to expend effect to obtain reward (Treadway et al 2009). Further, elevated anhedonic/depressive symptoms have been related to reduced striatal response to monetary gains (Gradin et al 2011, Stoy et al 2012b, Wacker et al 2009) and medio-orbitofrontal cortex response to monetary gains (Wotruba et al 2014). Healthy adolescents with elevated self-reported depressive symptoms also show reduced striatal response to gains (Forbes et al 2010) and EEG markers of reward responsiveness (Bress et al 2012). Collectively the individual difference literature clearly suggests that a number of different self-report measures relate to reduced affective, behavioral, and striatal responses to rewards in healthy individuals. There is little evidence that individual self-report measures relate to specific components of reward

processing, but that they rather index more global reward responsiveness.

Critically, no studies, to our knowledge, have related behavior/neural response to incentives to child self-reported incentive sensitivity within school-aged child populations. A handful of studies have related depressive symptoms/positive affect and neural response to reward, these studies have been conduced in adolescent or combined child/adolescent groups (Bress et al 2012, Forbes et al 2010, Olino et al 2014). Further, while there are a handful of child studies linking reward-related behavior to maternal reports of child incentive sensitivity (Blair et al 2004) and child self-reported incentive sensitivity to depressive/externalizing symptomology (Kazdin 1989, Muris et al 2005), these studies either focus on pre-school aged children or do not assess behavioral responses. As such, it is unclear how self reported incentive sensitivity relates to gain/loss-related behaviors in late childhood or whether children and adults show similar relations between self-reported and behavioral indexes of incentive sensitivity.

1.7 Summary

The studies addressed here aim to investigate how neural/behavioral responses to gains/losses of child-friendly, candy incentives relate to differences in developmental stage, childhood risk for MDD, self-reported incentive sensitivity/depressive symptoms, and the interaction of these factors. Neuroimaging studies using primary incentives report largely similar patterns of activation as studies using monetary incentives, with differences noted within the amygdala and anterior versus posterior OFC. However, differences in timing of delivery of incentives may influence amygdala/OFC differences. Thus, chapter two investigates neural responses to candy gains/losses where net winnings are delivered post scan within a healthy young adult sample. There is little neuroimaging and behavioral work comparing adult and child

responsivity to both gain and loss feedback, and the few existing studies utilize complex/probabilistic tasks and monetary incentives. Collectively this literature suggests that children and adults show similar striatal and behavioral response to gain feedback, but that loss responsiveness may be enhanced in child populations. As such, chapter three uses a simple developmentally appropriate guessing game and candy incentives to investigate age differences in neural response to receipt of gain and loss feedback. Chapter four then investigates age differences in *behavioral* responses to gains and losses, using a probabilistic incentive learning task.

The adolescent MDD-risk literature suggests that healthy offspring of depressed mothers show reduced striatal responses to reward feedback, but it is unclear whether pre-pubertal high-risk groups also show reduced responsiveness to reward. Further, it is unclear whether high-risk groups would show enhanced responsiveness to loss feedback. To address these gaps in the literature, chapter five uses a probabilistic incentive task to investigate differences in gain approach/loss avoidance behavior between healthy children at high and low-risk for developing MDD. Chapter five also investigates whether relations between approach/avoidance behavior and individual differences in specific depressive symptom levels differ based on risk for MDD.

Adult studies investigating individual differences in behavioral responses to positive/negative feedback/stimuli suggests that individuals reporting elevated hedonic capacity, incentive sensitivity, and/or reduced depressive/anhedonic symptoms show enhanced responsiveness to gain and to some extent loss feedback. However, such relations have not been tested in healthy child groups and it is unclear whether adults and children will show similar relations between incentive-related behaviors and self-report measures. Chapters four, five, and six will examine these questions using a probabilistic incentive task to investigate age

differences in gain approach and loss avoidance behaviors and self-report questionnaires that assess different incentive-sensitivity constructs. Specifically, chapter four investigates whether relations between approach/avoidance behavior and self-reported incentive sensitivity (BIS and BAS – drive/motivation) are similar in children and adults, chapter five investigates relations between approach/avoidance behavior and specific depressive symptoms, and chapter six investigates relations between approach/avoidance behavior and hedonic capacity/approach motivation in children.

Chapter 2.

Candy And The Brain: Neural Response To Candy Gains And Losses

This chapter was published in the September 2013 issue of Cognitive Behavioral and Affective Neuroscience. My contributions to this paper included data collection, data analysis, and writing

Reference: Luking KR & Barch DM. Candy and the brain: neural response to candy gains and losses. Cognitive Behavioral and Affective Neuroscience (2013) vol. 13 (3) pp. 437-451.

Abstract

Incentive processing is a critical component of a host of cognitive processes, including attention, motivation, and learning. Neuroimaging studies have clarified the neural systems underlying processing of primary and secondary rewards in adults. However, current reward paradigms have hindered comparisons across these reward types as well as between age groups. To address methodological issues regarding the timing of incentive delivery (during scan vs. postscan) and the age-appropriateness of the incentive type, we utilized fMRI and a modified version of a card guessing game (CGG), in which candy pieces delivered postscan served as the reinforcer, to investigate neural responses to incentives. Healthy young adults 22–26 years of age won and lost large and small amounts of candy on the basis of their ability to guess the number on a mystery card. BOLD activity was compared following candy gain (large/small), loss (large/small), and neutral feedback. During candy gains, adults recruited regions typically involved in response to monetary and other rewards, such as the caudate, putamen, and orbitofrontal cortex. During losses, they displayed greater deactivation in the hippocampus than in response to neutral and gain feedback. Additionally, individual-difference analyses suggested a negative relation between reward sensitivity (assessed by the Behavioral Inhibition/Behavioral Activation Scales) and the difference between high-and low-magnitude losses in the caudate and lateral orbitofrontal cortex. Also within the striatum, greater punishment sensitivity was positively related to the difference in activity following high as compared to low gains. Overall, these results show strong overlap with those from previous monetary versions of the CGG and provide a baseline for future work with developmental populations.

2.1 Introduction

How we react to, seek out, avoid, or anticipate rewarding and aversive stimuli in our environment influences a host of cognitive and behavioral processes essential to everyday life. Understanding the basic functional mechanics of how gains and losses are processed in healthy adults is a critical first step before investigating how these processes change over the course of typical development, or how abnormalities in these processes manifest in child and adult onset psychopathology (Barch & Dowd 2010, Bjork et al 2008, Forbes et al 2006, Gotlib et al 2010, Knutson et al 2008b). A rich literature has established the neurocircuitry involved in reward and punishment processing in animals and humans (Haber & Knutson 2010). The animal literature has focused on primary rewards (i.e., food and liquids), but the human neuroimaging literature has more frequently focused on secondary rewards (i.e., money) that have value based on their ability to procure other rewards. However, monetary rewards may be less appropriate for examining the development of reward processing in young children, who may not yet understand the value of such abstract rewards and the exchange rate between specific amounts of money and desired goods. As such, the goal of the present study was to validate the modification of a gambling task using candy that is appropriate for use across a wide age range, including very young children.

Decades of work in animals and humans have established the roles of the striatum, orbitofrontal cortex (OFC), prefrontal cortex (PFC), and other regions of the limbic system in incentive processing (Haber & Knutson 2010). The majority of human studies investigating gain/loss processing have utilized secondary monetary rewards and have reported consistent patterns of activity during receipt of monetary gains versus loss or no-gain events (Delgado et al 2003, Elliott et al 2003, Galvan et al 2005, Knutson et al 2001b, O'Doherty et al 2001a).

Specifically, regions of the dorsal and ventral striatum, along with medial portions of OFC, display greater functional responses to reward events than to loss and/or baseline, as well as greater responses to larger versus smaller rewards (Elliott et al 2003, Galvan et al 2005, Knutson et al 2001b, Knutson et al 2003, Knutson et al 2000, Santesso et al 2008a, Simon et al 2010). Moreover, patients with neuropsychiatric illnesses characterized in part by a lack of experienced pleasure, such as depression and schizophrenia, display reduced striatal activation during reward processing (Dowd & Barch 2012, Forbes et al 2006, Knutson et al 2008b). This relation between hedonic capacity and striatal reward response also extends to healthy populations in which, again, individuals with greater reward responsivity (measured by Behavioral Activation Scale [BAS] total score), reduced behavioral inhibition (Behavioral Inhibition Scale [BIS] total score), and fewer anhedonic symptoms (Chapman Anhedonia Scales) display greater striatal activity during reward events (Dowd & Barch 2012, Simon et al 2010).

There is less consensus regarding regions that respond maximally to receipt of punishment/loss. Some studies have reported increased response to punishment/loss in regions such as the hippocampus, amygdala, and insula (Anderson et al 2003, Camara et al 2008, Elliott et al 2000, Phelps & LeDoux 2005, Small et al 2003). However, other studies have found increased responses in these regions to both punishment/loss and reward as compared to neutral events, possibly indicating encoding of salience rather than valence alone (Elliott et al 2000, Elliott et al 2003). The evidence is also mixed as to which regions of OFC and PFC respond maximally to losses; some studies have reported a lateral/medial punishment/reward distinction within the OFC, in which lateral regions showed increased response to punishment/loss events (Kringelbach et al 2004, O'Doherty et al 2001a, O'Doherty et al 2001b), while others have

reported greater response to reward in both lateral and medial PFC (Bjork et al 2004, Elliott et al 2003, Kim et al 2006, O'Doherty et al 2001a, Sescousse et al 2010, Simon et al 2010).

Monetary rewards are advantageous in many ways: They lend themselves to manipulation of amount without overwhelming concerns of satiation, are simple to deliver in a scanner via visual cue, and allow the participant to obtain any number of other goods that he or she desires with the money earned during the task. However, significant and systematic differences may exist in how monetary incentives are processed/valued across development. Specifically, monetary rewards may be less salient and may be more difficult to value for children, who have less life experience with money and less developed abstract reasoning/mathematical skills than do adults. Thus, the subjective value of a given amount of money likely changes from childhood through adolescence and into adulthood. Some innovative investigators have utilized token economies (systems in which points/tokens earned during the task are later exchanged for prizes) to reduce such developmental confounds (Geier & Luna 2012). While this approach is clearly effective for adolescent populations, preschool and school-aged children may have difficulty with such an abstract system of exchange. Token economies require the participant to understand the exchange rate between points and prizes (e.g., 15 points = 1 prize) and to associate a given trial's outcome with the subjective value of a prize. Moreover, enough points to obtain another whole prize are not typically won/lost on each individual trial, meaning that a given trial's derived value is equivalent only to a portion of a prize. This requires the child to maintain a representation of accumulated earnings across trials and to evaluate the current trial's outcome in the context of a total sum. Given the complexity of such secondary paradigms and developmental differences in abstract reasoning ability, children's

attention/motivational drive may be better captured when more immediate/tangible rewards (i.e., candy) are employed that can be directly represented on screen during the scan.

Primary rewards offer an opportunity to investigate incentive processing without as many concerns regarding how age may interact with the processing of abstract incentives. Primary-reward paradigms have utilized a host of incentives, including liquids (sweet, bitter, and/or salty solutions delivered in scanner), candy (delivered postscan), food odors (pleasant and unpleasant, delivered in scanner), and even erotic pictures (displayed in scanner), among others (Clithero et al 2011, Kim et al 2011, Kringelbach et al 2003, Levy & Glimcher 2011, O'Doherty et al 2001b, Sescousse et al 2010). Such studies in adults have yielded patterns of activation largely similar to those reported in monetary paradigms. Specifically, greater responses to the delivery of rewarding (e.g., juice, chocolate milk), as compared to neutral, solutions are found in regions such as the caudal OFC, medial OFC, basal ganglia, and anterior insula, where activity is related to the subjective pleasantness of the consumed liquid (Frank et al 2008, Kobayashi et al 2004, Kringelbach et al 2004, Kringelbach et al 2003, O'Doherty et al 2001b, O'Doherty et al 2002). Responses to "punishing" solutions such as saline and quinine also echo responses to monetary loss. Regions of lateral OFC, anterior cingulate cortex (ACC), hippocampus, amygdala (AMY), and insula (INS) display increased response to the delivery of punishing solutions. Again, results are also mixed regarding the medial/lateral OFC distinction for reward and punishment response when using primary rewards (Frank et al 2008, O'Doherty et al 2001b, O'Doherty et al 2002, Sescousse et al 2010, Zald et al 1998).

Also, a handful of studies have directly compared responses to primary and secondary rewards that help to generalize from the literature on monetary reward processing in adults to suggest the potential utility of using more primary rewards in young child populations (Chib et al

2009, Clithero et al 2011, Levy & Glimcher 2011, Sescousse et al 2010). Once again, similar patterns of responses are found in striatal and insular regions when primary and secondary rewards are employed. Of note is a potential dissociation within the OFC in terms of responses to these two types of rewards. A meta-analysis conducted by Kringelbach and Rolls (Kringelbach & Rolls 2004), including both primary-and secondary-reward studies, suggested a posterior/anterior distinction in OFC response to primary versus more abstract rewards, respectively. This posterior/anterior distinction has been further supported by work directly comparing primary (erotic pictures) and secondary (money) rewards (Sescousse et al 2010). However, some evidence has also supported the opposite pattern (Kim et al 2011).

Although the literature reviewed above suggests that primary and secondary rewards modulate many of the same neural systems, a number of challenges are encountered when adapting primary-reward paradigms for use in developmental populations in ways that would allow for clear conceptual and/or empirical comparisons to the existing monetary reward literature. First, the logistical characteristics of the paradigms historically used to deliver the two incentive types have often differed. In secondary paradigms, a trial's outcome is signaled via a visual cue indicating the size and valence (gain/loss) of the outcome—a lump sum of money to be delivered postscan. In primary paradigms, participants traditionally directly experience/consume the incentive in-scanner—that is, tasting a sweet liquid/smelling a pleasant odor. Second, the intrinsic properties of primary/secondary rewards often make comparisons problematic. This difference is most apparent in the punishment/loss domain, where directly consuming or experiencing something aversive (e.g., quinine/saline solution or unpleasant odor) may elicit different psychological and neural responses than does losing something appetitive (e.g., money or tokens). Other hindrances include difficulty in manipulating the magnitude of

primary rewards (e.g., delivery of larger liquid rewards can be uncomfortable and potentially dangerous, especially in children) and satiation/habituation, in which the value of an incentive can decrease throughout the experiment.

To address these challenges, we developed a modified version of the card guessing game (CGG), a task in which monetary gains/losses have traditionally been employed, and used fMRI to investigate how healthy adults respond to gains and losses of candy as a means of validating this paradigm before moving to its use in a developmental population (Delgado et al 2000). We felt that a paradigm in which primary rewards did not have to be consumed in-scanner would be most comparable to current secondary paradigms, would allow us to investigate responses to primary rewards without concerns regarding delivery timing, increased head motion, and choking hazards, and would be the simplest to implement from a logistical standpoint. Moreover, candy readily lends itself to developmental questions, children would not need to consume liquids in the scanner (a choking hazard associated with increased motion), and very young children might find it easier to comprehend differing amounts candy displayed on screen, as compared to differing amounts of money or points aggregated across trials and then later exchanged for prizes. As such, we believe that results from this paradigm will provide a baseline describing functional responses to candy rewards and losses in healthy young adults that can be used to inform future studies investigating these processes in developmental and other special populations, as well as directly comparing the responses to different reward types.

As our modification of the CGG uses a primary reward (candy) but delivers the reward out of the scanner, we hypothesized that our results would provide a bridge between the responses reported in studies using primary and secondary rewards. We expected to see reward- and loss-related modulation of BOLD activity in regions of the striatum, amygdala, and OFC, as

reported in previous studies using the CGG and other secondary-reward paradigms (Cox et al 2008, Delgado et al 2003, Delgado et al 2000, Delgado et al 2004, Forbes et al 2010, May et al 2004, Tricomi et al 2006, Tricomi et al 2004). What was less clear was whether, within the OFC, we would see a more anterior or posterior pattern of activity, which the literature suggests might in part relate to the type of reward used (primary vs. abstract). Additionally, we expected that individuals with greater reward responsivity and hedonic tone would display greater striatal activity during reward feedback, replicating findings in the extant literature (Dowd & Barch 2012, Simon et al 2010).

2.2 Method

Participants

A total of 21 young adults participated in this study. One participant was excluded from the analysis on the basis of a history of major depressive disorder (assessed via self-report on the Adult Behavior Check List; (Achenbach 2003)). The remaining 20 participants included ranged in age from 22 to 26 years (mean age = 23.95, SD = 1.353; eight males, 12 females). The participants were healthy and free of any major medical disorder, did not report a history of any mental disorder, had not taken psychotropic medications within the past two weeks, and were nonsmokers. They were recruited via posted advertisements at Washington University and were not given any instructions/restrictions regarding food or beverage consumption. All of the participants gave informed consent, and the Washington University in St. Louis Institutional Review Board approved the study.

Procedure

The experiment was conducted over the course of two separate in-person sessions: a behavioral session, followed by a neuroimaging session. In the behavioral session, participants

completed several individual-difference questionnaires (see below) and a demographic form. Additionally, participants completed a behavioral probabilistic reward task based on those of Pizzagalli (Pizzagalli et al 2005) and Tripp and Alsop (Tripp & Alsop 1999) that is not addressed in these analyses. The participants then returned on a different day (within three weeks of the behavioral session) to complete the neuroimaging session. During this fMRI session, they completed the Beck Depression Inventory (BDI; (Beck et al 1996)), out-of-scanner practice for the neuroimaging task, and an in-scanner CGG based on Delgado et al. (Delgado et al 2000), followed by a post-scan questionnaire.

Individual-Difference Measures

Participants were administered the following individual-difference measures during the behavioral session: (1) the Behavioral Inhibition Scale and Behavioral Activation Scale (BIS/BAS; (Carver & White 1994)), (2) the Chapman Anhedonia Scales (CS; (Chapman et al 1976)), and (3) the Snaith– Hamilton Pleasure Scale (SHPS; (Snaith et al 1995)). As the Chapman scales (both the physical and social components) were strongly correlated with the SHPS, a composite variable, hedonics (HED), was created by reverse-coding the physical and social components of the CS, computing z scores for the two reverse-coded CS scales and the SHPS, and then summing the three z scores, such that a higher HED value indicated that an individual was more hedonic. A subset of the participants also completed the Positive Affect and Negative Affect Scales (PANAS; (Watson et al 1988)), but these measures were not included in further analyses. Descriptive statistics and pairwise correlations between the individual-difference measures can be found in Supplemental Tables S2.1–S2.2.

Card Guessing Game

Participants were told that they would play a CGG in which they were to guess the number on a mystery card (represented by a "?") to potentially win or lose candy, on the basis of whether or not that guess was correct. The type of candy incentive, M&Ms or Skittles, was determined by the participant's preference, indicated during study enrollment (the visual feedback did not differ by candy types). The participants were told that potential card numbers ranged from 1 to 9 and that they should indicate whether they thought that the mystery card number was more or less than 5 by pressing one of two buttons with either the left or the right thumb. Participants were required to make their guess while the mystery card "?" was displayed onscreen (2,000 ms). If no response was made, the "?" was replaced by a fixation cross for the remaining duration of that missed trial. If a guess was made, feedback was displayed for 2,000 ms immediately following the button press. Feedback included the actual number on the card, a message of "Great Job!" and a green up arrow for gain trails, a message of "Sorry" and a red down arrow for loss trials, and a picture of the number of candy pieces gained or lost (see Figure 2.1).

Participants could gain or lose both large and small amounts of candy on the basis of their guess and the number on the card. Participants received a high gain (four candies) if their guess was "above 5" and the number was 8 or 9, or if their guess was "below 5" and the number was 1 or 2. They received a low gain (two candies) if their guess was "above 5" and the number was 6 or 7, or if their guess was "below 5" and the number was 3 or 4. Conversely, participants received a high loss (two candies) if their guess was "above 5" and the number was 1 or 2, or if their guess was "below 5" and the number was 8 or 9. They received a low loss (one candy) if their guess was "above 5" and the number was 3 or 4, or if their guess was "below 5" and the number was 6 or 7. Finally, if the number 5 was displayed, no candy was gained or lost, and the

feedback on these neutral trials included the card number, “Next Trial” and two dash marks (see Figure 2.1). The computer program was designed so that if the trial was meant to be—for example—a high-gain trial, the program adapted the card number to the participant’s choice, to ensure the appropriate outcome for that trial type. On the basis of previous research, a 2:1 ratio of gain to loss amounts was used, such that participants added four and two pieces of candy to their total on high-and low-gain trials, respectively, and lost one and two pieces from their total on low-and high-loss trials, respectively. This ratio was used to prevent frustration with the task and to maintain engagement, as well as to ensure that the participants received candy at the end of the task (Tversky & Kahneman 1981). The participants 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.

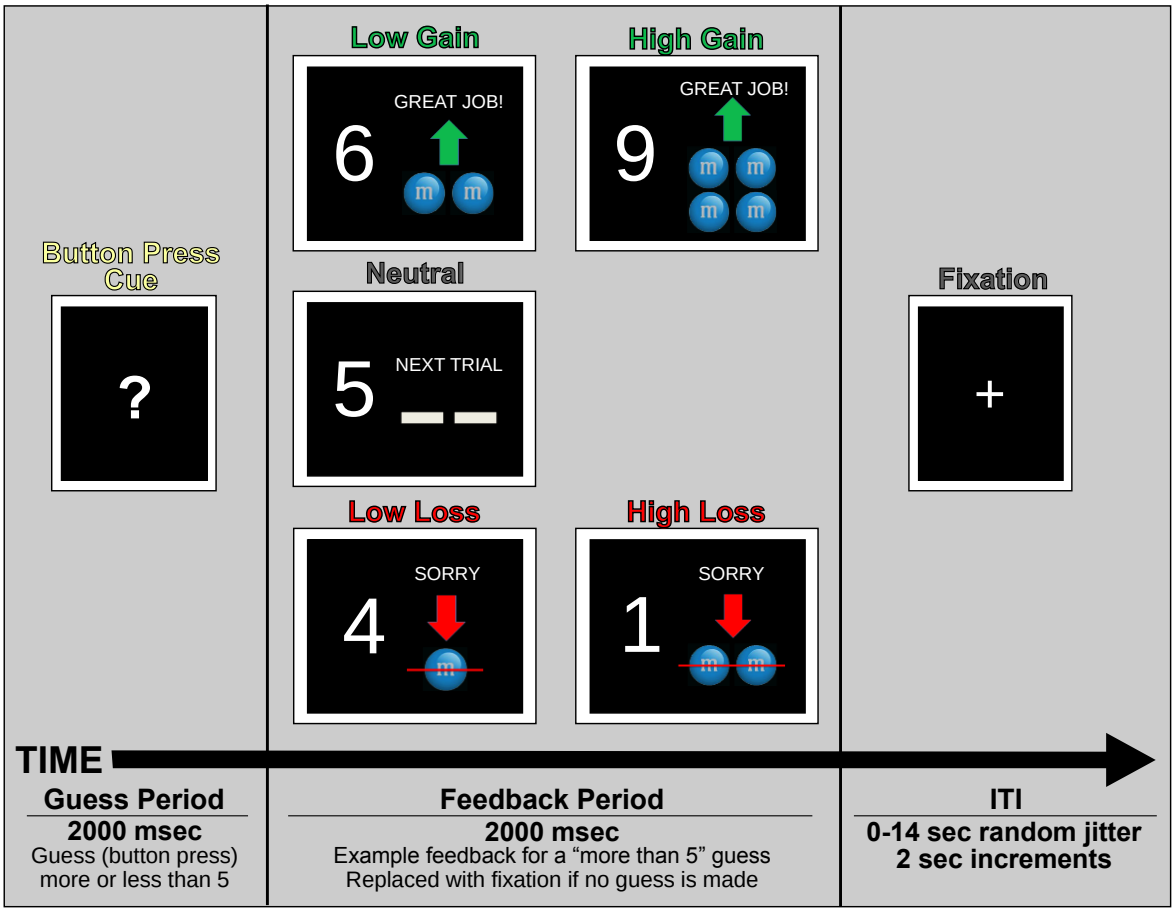


Figure 2.1: Timing Of The Card Guessing Game

Example of possible feedback types following a "more than 5" guess. Each trial lasted 4 s in total. The cue to make a guess (?) was displayed for up to 2 s. Feedback (including the number on the mystery card, an arrow denoting gain/loss or dashes for no gain/loss, and the amount of candy exchanged) was 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. The inter-trial intervals (ITIs) lasted from 0 to 14 s, with a 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 the feedback.

To ensure that all participants understood the task, written instructions were presented on a computer using PsyScope software, followed by actual task practice, prior to entering the fMRI scanner (Cohen 1993). All trial types were experienced during the practice task, and participants were told that any candy earned during the practice would be added to their candy total. This served as a candy endowment to offset any initial losses during the in-scanner task.

In-scanner trials were presented in a fixed order with a rapid event-related design, using PsyScope software on a Macintosh computer for both stimulus presentation and data collection. The computer selected a card number on each trial following the participant's guess, depending on the predetermined trial type. Determining the card number shown after the participant's button press ensured that the guess, predetermined trial type (gain, loss, or neutral), and card numbers were always congruent and that there were no "correct/incorrect" guesses. This is the standard procedure with the CGG and ensures that all participants experience roughly the same events in the 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 eight potential instances (if the participant made a guess for all trials) of the five trial types—high/low gain/loss and neutral— delivered in a fixed pseudorandom order, such that each participant experienced the same order of events. On average, participants failed to make a response on four trials over the course of the entire scanning session. Each trial lasted 4,000 ms (see Figure 2.1), followed by an inter-trial interval (ITI) of 0–14,000 ms that was randomly jittered in 2,000-ms increments. All participants completed the six scan blocks, and no data were excluded due to excessive head movement (excessive motion was defined by a mean voxel-wise standard deviation, mode 1,000 normalized, of greater than 15 for a given blood oxygenation level dependent [BOLD] run).

Participants were given $50 as compensation for their time along with 150 M&Ms/Skittles at the end of the scanning session, regardless of performance.

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 = 2,400 ms, FOV = 256 mm, flip angle = 8°, one acquisition, 176 slices, 1x1x1 mm voxels) image and functional images collected with a 12-channel head coil using a standard gradient-echo EPI sequence sensitive to BOLD contrast (T2*) (TR = 2,000 ms, TE = 27 ms, FOV = 384 mm, flip = 77°). During each functional run, 150 whole-brain volumes were acquired, consisting of 36 contiguous axial images with isotropic voxels (4 mm3) acquired parallel to the anterior–posterior commissure plane. Two functional runs of 160 TRs (~11 min total) were acquired while participants rested with eyes closed.

The fMRI data were preprocessed using in-house Washington University software. Prior to preprocessing, the first four 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 the whole-brain signal intensity to a fixed value and removing the linear slope on a voxel-by-voxel basis to counteract any effects of drift (Bandettini et al 1993); (2) corrected for head motion using rigid-body rotation and translation correction algorithms (Friston 1994, Snyder 1996, Woods et al 1992); (3) registered to Talairach (Talairach & Tournoux 1988) space using a 12-parameter linear (affine) transformation; and (4) smoothed with an 8-mm full-width-at-half-maximum 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), also incorporating regressors for linear trend and baseline shift to estimate the hemodynamic response function for each trial

type. The task analyses used a GLM approach that did not assume a specific hemodynamic response shape. While it is possible that developmental effects could mostly be explained by differences in magnitudes of activation, it is also likely that development would interact with BOLD response over time. Thus, we felt that using an unassumed (FIR type) approach would provide the most information without imposing assumptions regarding the shape of the hemodynamic response that might bias future investigations. For each trial type, neural responses at ten time points (20 seconds) were estimated relative to baseline fixation, in order to provide adequate temporal resolution of the hemodynamic response. We felt that this approach provided the best balance between the cost of power and the benefit of a more complete picture of the hemodynamic response. The task was designed to focus on trial outcomes and did not allow for the dissociation of anticipation and receipt of feedback. Although time courses were estimated beginning with trial onset, participants were quick to make a response (the mean reaction time was 521.8 ms, standard deviation 91.4 ms), and thus feedback onset occurred well within the first time point on average for each participant. These estimates were then entered into group-level analyses treating subjects as a random factor. We also computed an assumed response shape GLM for each participant for use in the individual-difference analyses, since this type of GLM provided us with a single beta estimate for each condition. This GLM included the same five trial types (and regressors for linear trends and baseline shifts across runs) and used the Boynton function (Boynton et al 1996).

fMRI Data Analysis

To examine the influence of the valence (gain vs. loss) and magnitude (low vs. high) of feedback, we performed a voxelwise repeated measures analysis of variance (ANOVA) with three within-subjects factors: Outcome Valence (two levels: gain, loss), Outcome Magnitude

(two levels: high, low), and Time Point within trial (the ten frame estimates for each trial type, beginning at trial onset). We then followed up this analysis with an additional repeated measures ANOVA to identify regions where activation was related to salience (i.e., responses to gain/loss were similar and different from neutral) rather than the valence and/or magnitude of feedback. Because there was only one level of neutral feedback, neutral trials were not included in the first ANOVA. The second ANOVA included Time Point and Condition (gain [both high-and low-gain trials], neutral, and loss [both high-and low-loss trials]) as within-subjects factors.

In the analyses described above, we focused on regions showing interactions with time point within trials, given our use of unassumed (FIR type) GLMs. When appropriate, post hoc ANOVAs were performed within all significant regions identified by the ANOVAs described above. For these post hoc analyses, the mean percent signal change across each region was extracted for each of the ten estimated time points. This was done for each applicable condition, and then post hoc ANOVAs were run comparing two trial types (e.g., gain vs. neutral) over the ten time points.

To focus our results, these two voxel-wise ANOVAs were conducted within an anatomically defined a priori mask developed by S. M. Beck and colleagues (Beck et al 2010). This mask (see Supplemental Figure S2.1) covered an a priori network of regions implicated in reward processing that were hand-drawn in Talairach space on the basis of anatomical landmarks and previously published functional coordinates, including the dorsal and ventral striatum, ventral tegmental area, substantia nigra, amygdala (AMY), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (VMPFC), and insula (INS). ANOVA results within the a priori mask were corrected for multiple comparisons using a combined p-value/cluster-size threshold ($p < .005$ and 21 voxels) determined using AlphaSim simulations (smoothing = 2 voxels, 1,000

iterations, voxels in mask = 5,332) to provide a false-positive rate of $p < .05$ for the whole mask (Forman et al 1995, McAvoy et al 2001).

To reduce redundancy across the two ANOVA results, all significant regions identified in the first ANOVA were converted to a binary mask. This mask was then applied to the second ANOVA prior to thresholding. The remaining voxels were subjected to the same multiple-comparison correction criteria ($p < .005$ and 21 voxels). Regions identified in each of the two ANOVAs were then partitioned such that peaks of activity were considered separate regions if they were more than 10 mm apart, as measured by a peak-splitting algorithm (Kerr et al 2004, Michelon et al 2003).

We also conducted exploratory voxel-wise whole-brain analyses, which were corrected for multiple corrections using a p-value/cluster-size threshold ($p < .0013$ and 17 voxels) determined by Monte Carlo simulations, in order to provide a whole-brain false-positive rate of $p < .05$, and partitioned such that peaks of activity were considered separate regions if they were more than 12 mm apart according to the same peak-splitting algorithm (Kerr et al 2004, Michelon et al 2003). Whole-brain results are reported and discussed in the Supplemental materials. We felt that the combination of threshold and cluster size provided a good balance between detecting small regions showing strong effects and larger regions with subtler task-related activity differences.

Individual-Difference Data Analysis

To identify regions where task activation was related to reward/punishment sensitivity and hedonic tone, individual-difference measures of reward sensitivity (BAS total score), loss sensitivity (BIS total score), and hedonics (HED) were each correlated separately with magnitude estimates from the assumed GLMs. Magnitude estimates used in the correlation

analyses included differences between each of the four individual trial types and neutral (e.g., HG–NU). Additionally, differences between the high and low trial types for both loss and gain (HL–LL and HG–LG) were included on an exploratory basis. Functional regions identified by the correlations within the mask were thresholded using a p-value/cluster-size threshold ($p < .005$ and 26 voxels) in order to provide a false positive rate of $p < .01$. To identify potential multivariate outliers, Mahalanobis D2 scores were computed for each resultant region using the individual-difference measure and imaging contrast of interest as independent variables. No participant passed the $p < .001$ threshold required for multivariate outliers for any region. To further test the robustness of the reported effects, correlations were computed again within the regions identified in the voxel-wise correlations without participants whose multivariate outlier score was less than $p < .05$. All discussed correlations remained significant ($p < .05$) when these participants were removed from the analyses.

2.3 Results

We started the analysis using an ANOVA with Valence (gain, loss), Magnitude (high, low), and Time Point (ten time points within-trial estimate; Time Point 1 corresponding to the onset of the button press cue) as within-subjects factors.

Effects Of Valence

Regions identified as displaying a Valence x Time Point interaction within the reward mask included areas of the insula, lateral OFC, caudate, putamen, amygdala, and hippocampus (Table 2.1 and Figures 2.2-2.3). All of these regions other than the hippocampus showed greater activation during gain than loss trials. The hippocampus showed less deactivation for gain than for loss trials. Planned within-region post-hoc ANOVAs involving all trial types, including neutral trials that were not included in the original ANOVA, indicated that activity was greater in

gain than in neutral trials in the lateral OFC region, but that neutral trials did not differ significantly from loss trials. In addition, neutral trials elicited greater activity than did loss trials in dorsal putamen regions and the insula. However, neutral-trial activity did not differ significantly from gain or loss in the remaining regions (including ventral putamen, caudate, thalamus, amygdala, and hippocampus), as is shown in Table 2.1, Figure 2.3, and Supplemental Figures S2.2 and S2.3. This result was surprising, as graphs depicting time courses particularly for the caudate/putamen regions seemed to indicate a difference between neutral and either gain or loss peak activation in several of these regions.

Table 2.1: Valence X Time Point Interaction Regions

Region of Activation	Laterality	Talairach Coordinates x	y	z	Pattern
Activation					
Lateral Orbitofrontal Cortex BA 47	R	42	26	-9	G>N=L
Insula BA 13	R	35	-5	16	G=N>L
Dorsal Putamen	R	27	-13	10	G=N>L
Dorsal Putamen	R	24	5	9	G=N>L
Dorsal Putamen	L	-26	-13	10	G=N>L
Dorsal Putamen	L	-23	3	11	G=N>L
Putamen/Caudate	L	-17	9	4	G>L
Putamen/Caudate	R	15	9	5	G>L
Ventral Putamen	L	-23	-2	-3	G>L
Ventral Putamen	R	22	-1	-7	G>L
Ventral Putamen	R	30	-13	-4	G>L
Thalamus	L	-8	-8	18	G>L
Amygdala	L	-18	-5	-13	G>L
Caudate Body	L	-15	7	17	G>L
Caudate Body	R	15	12	15	G>L
Caudate Body	L	-6	3	6	G>L
Deactivation					
Hippocampus	L	-26	-17	-11	L>G

Note: These regions displayed a Valence x Time Point interaction within the a priori reward mask. Post hoc analyses detailed in the Methods section were performed on each region. Regions in which activation during neutral trials did not significantly differ from activity during either gain or loss trials are noted as showing either G > L or L > G patterns of activity. BA = Brodmann area; L = left; R = right; G = gain; N = neutral; L = loss

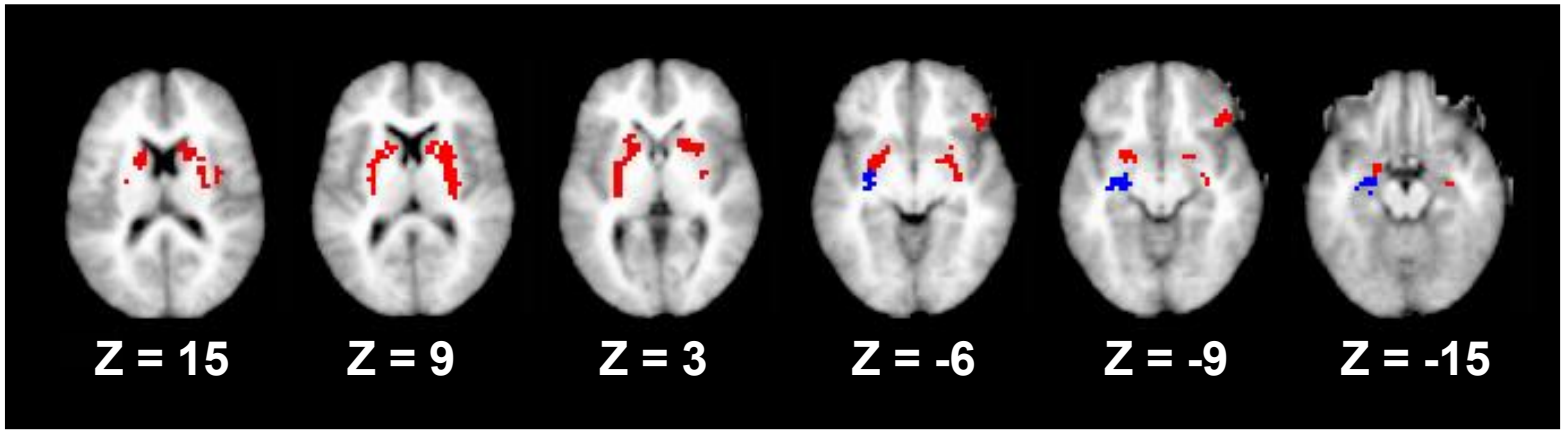


Figure 2.2: Valence By Time Point Interaction Rois – *A priori* Reward Mask

ROIs identified as showing a significant valence by timepoint interaction within the *a priori* reward mask.
Red = ROIs with greater activation during gain trials compared to loss trials
Blue = ROI with greater deactivation during loss trials compared to gain trials

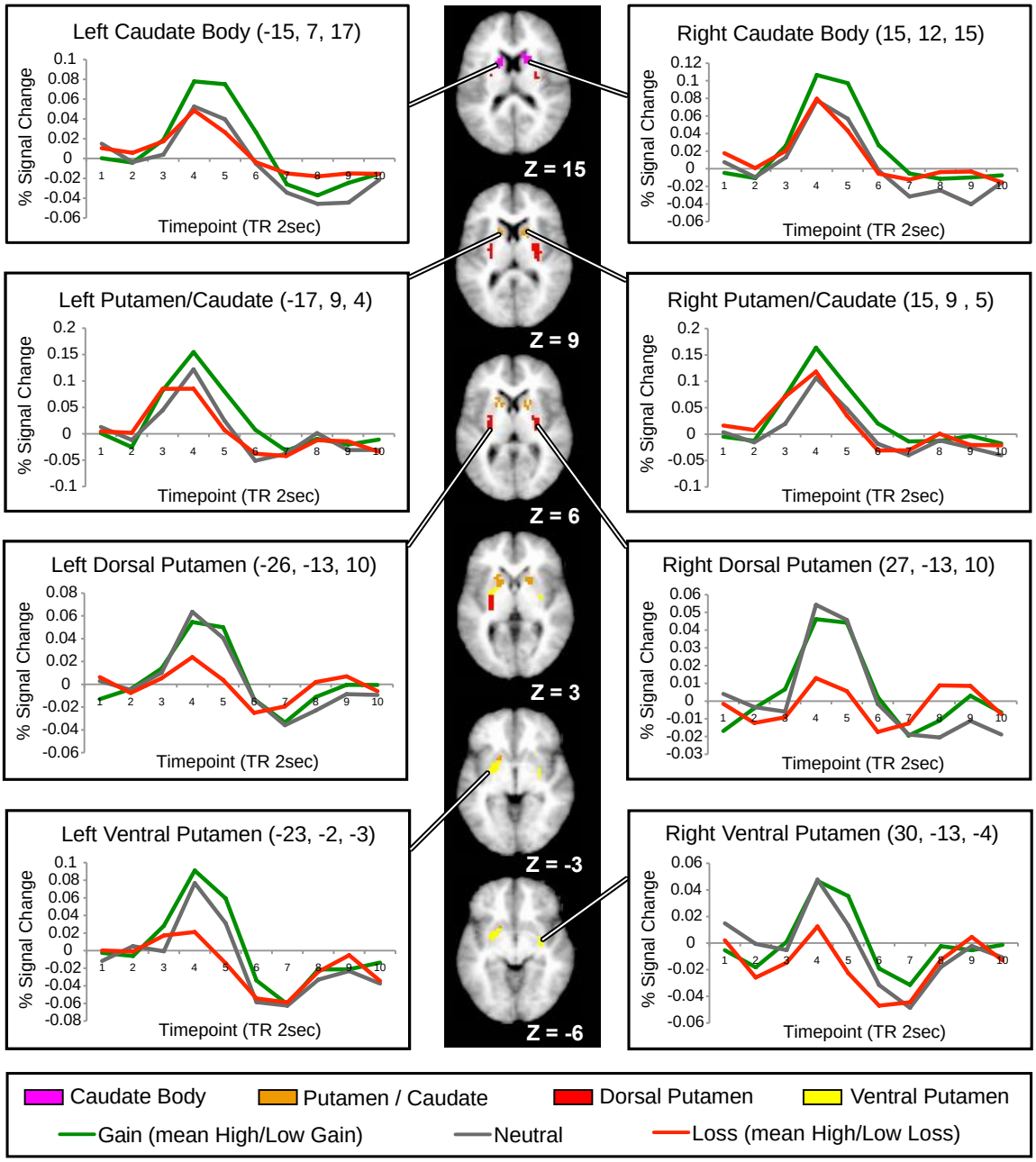


Figure 2.3: Valence X Time Point Interaction Timecourses

Representative time courses of greater activation following gain feedback as compared to neutral and loss striatal regions displaying a rostral/caudal distinction in response to neutral feedback. Dorsal and ventral putamen regions display greater activation feedback. Caudate regions, as well as rostral putamen/caudate regions, show following gain and neutral feedback as compared to loss feedback.

To further investigate the relation between neutral and gain/loss activation within the striatum, we performed exploratory post hoc paired t tests designed to specifically test for differences in peak activation between the neutral condition and the gain and loss conditions. Percentages of signal change for individual trial types (neutral, gain, loss) were averaged for Time Points 4 and 5 (the time points corresponding to the peak response across all regions included in these analyses) within each caudate and putamen region identified in the analyses described above (Valence x Magnitude ANOVA). Because of the exploratory nature of these post hoc tests, uncorrected p values are reported. Interestingly, the relation between neutral and gain/loss activation differed along the rostral–caudal axis of the striatum. Specifically, within the caudate and more rostral putamen/caudate regions, neutral-trial activity did not differ from loss activation, but did differ from gain. Within the caudal putamen regions, neutral-trial activity significantly differed from loss-trial activity, while it did not differ from gain-trial activity (*p* values are reported in Supplemental Table 2.3).

Effects Of Magnitude And The Interaction Of Valence And Magnitude

No regions displayed a significant two-way interaction between magnitude and time point or a three-way interaction between valence, magnitude, and time point within the a priori anatomical mask.

Effects Of Salience

The ANOVA above identified regions where activity differed depending on the valence of the trial outcome. However it is possible that some regions encode salience rather than the valence of feedback. In these regions, we would expect to see similar patterns of activity to feedback of different valences (gain/loss) that would differ significantly from the response to neutral feedback. To identify such regions, we conducted an additional voxel-wise ANOVA

within our a priori mask that included the neutral condition. Thus, this ANOVA used condition (gain, loss, or neutral) and time point as within-subjects factors. However, no significant regions unique to the Condition x Time Point interaction were found within the a priori reward mask.

Individual-Difference Results

To evaluate whether individual differences in task-related activity were related to individual differences in reward/punishment sensitivity or hedonic tone, magnitude estimates for the difference between the trial types and neutral (e.g., HL–NU) and the difference between high and low trials within gain/loss (e.g., HG–LG) were correlated with BAS, BIS, and HED within the a priori reward mask. Only contrasts with significant correlations ($p < .01$, corrected for multiple comparisons using a combination of p value and cluster size [$p < .005$, $n = 26$]) are reported.

Behavioral Activation System (BAS) Correlations

Interestingly, reward sensitivity (BAS total score) was most strongly correlated with loss-related activity, and not with gain-related activity as hypothesized (Table 2.2B-D, Supplemental Figures S2.4–S2.6). Specifically, low-loss trial activity showed a positive correlation with BAS in a region of inferior frontal gyrus (49, 19, –1). A positive correlation was also found between BAS and the difference between low-loss and neutral-trial activity (LL–NU) within the right caudate and a portion of the right lateral OFC. The same lateral OFC and caudate regions displayed a negative correlation between BAS and the difference between high-and low-loss trial activity (HL– LL; Supplemental Figures S2.4–S2.6). Specifically, as BAS increased, so did the difference in activity between low-loss and neutral trials, and the difference in activity between high and low loss decreased with increasing BAS scores in these lateral OFC and caudate regions.

Table 2.2: BIS/BAS Correlation ROIs

Region of Activation	Laterality	Talairach Coordinates x	y	z
A) HG-LG Positive Correlation with BIS				
Putamen	R	23	2	8
Claustrum	R	38	-8	8
Putamen	L	-19	1	12
Caudate Body	L	-12	7	8
Insula BA 13	R	39	-4	-3
Insula BA 13	L	-36	9	6
B) LL-NU Positive Correlation with BAS				
Inferior Frontal Gyrus BA 47	R	46	19	-1
Caudate Body	R	11	7	13
C) HL-LL Negative Correlation with BAS				
Putamen	L	-22	-3	9
Caudate Body	R	11	10	11
Inferior Frontal Gyrus BA 47	R	50	18	-1
Putamen	L	-29	1	-2
Caudate Body	L	-14	3	17
Putamen	R	28	-12	9
Claustrum	R	35	-11	0
Putamen	L	-33	-17	0
Putamen	R	24	1	6
Superior Temporal Gyrus BA38	R	37	2	-9
Insula BA13	L	-34	-23	16
Insula BA13	R	41	-3	7
Lateral Globus Pallidus	L	-13	3	4
Claustrum	L	-33	10	3
Putamen	R	21	1	-8
Caudate Body	L	-18	11	12
Claustrum	R	33	8	8
Inferior Frontal Gyrus BA 47	R	50	33	-2
Putamen	R	24	15	-5
D) Overlap between HG-LG with BIS and HL-LL with BAS				
Insula**	R	38	-7	2
Putamen	L	-21	0	10
Putamen	R	23	0	7
Caudate Body	L	-13	5	10

Note: (A) Regions displaying a significant correlation between BAS and the difference between low-loss and neutral trial activity (LL–NU). (B) Regions displaying a significant correlation between BAS and the difference between high-loss and low-loss trial activity (HL–LL). (C) Regions displaying a significant correlation between BIS and the difference between high-gain and low-gain trial activity (HG–LG). (D) Regions showing a positive correlation between HG–LG and BIS, along with a negative correlation between HL–LL and BAS.

L = left; R = right; BA = Brodmann area; HG = high gain; LG = low gain; NU = neutral; HL = high loss; LL = low loss; BAS = BAS total score; BIS = BIS total score.
** The correlation between HG–LG and BIS was non-significant when a within-region-of-interest correlation was conducted excluding the participant with the lowest BIS score.

Behavioral Inhibition System (BIS) Correlations

Mirroring the BAS correlation results, punishment sensitivity (BIS) was most strongly associated with gain-trial activity, and no significant correlations were found with loss related activity (Supplemental Figures S2.4 and S2.6, Table 2.2A and D). Portions of the insula, caudate, and putamen displayed a positive correlation between BIS and the difference between high-and low-gain trial activity (HG–LG), indicating that individuals with increased punishment sensitivity show greater neural responses to high-gain than to low-gain trials, while those with between BAS and HL–LL and a positive correlation be-lower punishment sensitivity showed the opposite relation.

Several regions, including the left caudate and bilateral putamen, showed both a significant negative correlation between BIS and HG–LG. The BIS correlation did not remain significant within the insula region when a potential outlier was excluded (Supplemental Figure S2.6).

Hedonics correlations

No regions showing a significant correlation between the hedonics composite variable (HED) and any task conditions were found within the a priori reward mask.

2.4 Discussion

The goals of this study were to develop a paradigm using primary rewards congruent with current secondary-reward paradigms, and then to establish baseline responses in healthy young adults for use in future investigations of gain/loss processing in developmental populations. To do this, we modified a version of the CGG, which previously had utilized monetary incentives, to employ small candy pieces (consumed out of scanner) as reinforcers. This modification allowed

us to modulate both incentive valence (gain, loss, neutral) and magnitude (high, low) similarly to previous monetary studies.

Valence Effects

Consistent with the secondary-reward literature, we observed strong valence (gain vs. loss) effects in regions of the dorsal (caudate body/putamen) and ventral (ventral putamen) striatum, lateral OFC, insula, thalamus, hippocampus, and amygdala (Cox et al 2008, Delgado et al 2003, Delgado et al 2000, Delgado et al 2004, Elliott et al 2003, Estle et al 2007, Kim et al 2011, Knutson et al 2001b, O'Doherty et al 2001b, Tricomi et al 2006, Tricomi et al 2004, Valentin & O'Doherty 2009, Zald et al 1998). All regions except the hippocampus displayed greater activation during gain feedback than during loss feedback, with bilateral putamen displaying the most extensive effects. Dorsal striatal activation, particularly the caudate, is the most consistently reported valence effect observed in studies using the CGG. Feedback-modulated responses in this region are expected, given that the CGG requires a timely button-press that the participant believes will impact the type of feedback that he or she receives (gain vs. loss) and the dorsal striatum's involvement in the goal-directed action component of reward-processing/decision-making (O'Doherty et al 2004, Tricomi et al 2004).

We also observed an interesting dissociation between responses to neutral feedback in the caudate body/rostral putamen and more caudal portions of the putamen. In caudate and rostral putamen regions, activation was similar to neutral and loss feedback, and less than activation to gain responses, while in more caudal putamen regions, neutral and gain responses were similar and greater than loss responses. This pattern of activity may indicate a reduced response during loss trails in the caudal putamen, as opposed to an increased response to gain/neutral feedback, and vice versa in more rostral regions. It is important to note that our analyses investigating these

effects were exploratory; however, this pattern of activation was remarkably consistent, both between hemispheres and within the given structures. Studies investigating functional dissociations within the striatum have traditionally focused on comparisons between the dorsal and ventral striatum, with less evidence for a rostral/caudal distinction in function (Joel et al 2002, O'Doherty et al 2004). However, functional connectivity studies have reported distinct patterns of connectivity for the caudate and more caudal putamen, with the caudate displaying positive functional relations with frontal control regions (e.g., DLPFC and ACC), while the putamen displayed positive functional connections with cortical regions involved in movement (Barnes et al 2010, Di Martino et al 2008). How these patterns of connectivity relate to our findings is unclear, and future work will be needed to determine whether this result is replicable and how it relates to dissociations in function across basal ganglia subregions.

We also observed valence effects in the ventral putamen, as have been seen in previous CGG studies using monetary incentives (Delgado et al 2003, Delgado et al 2000, Delgado et al 2004). We did not, however, observe valence effects in the nucleus accumbens. Other CGG studies have also shown ventral striatal activity in the ventral putamen/pallidum but not in the accumbens (Cox et al 2008, Delgado et al 2003, Delgado et al 2000, Delgado et al 2004, Forbes et al 2010, May et al 2004, Tricomi et al 2004). While the ventral striatum, including the ventral putamen, is involved in representation of incentive value, the nucleus accumbens may be maximally sensitive to anticipation/prediction of rewards or to when reward information can be used to alter behavior (Delgado et al 2005, Knutson et al 2001b, O'Doherty et al 2004, Tricomi et al 2004). Additionally, this is a very small region, and possibly there could have been significant between-subjects variability in accumbens morphology within our sample. Another explanation

of the absence of nucleus accumbens activity could be the pseudorandom structure of the CGG, which is ideal for isolating responses to task feedback independent of learning effects.

In addition to finding no valence effects in the accumbens, most adult studies using the CGG have not reported valence effects in the OFC, although a recent article with a larger sample (n = 28) reported valence effects in regions of medial OFC (Cox et al 2008, Delgado et al 2003, Delgado et al 2000, Delgado et al 2004, Forbes et al 2010, May et al 2004, Tricomi et al 2004, Wilbertz et al 2012). It is surprising that few adult CGG studies have reported OFC activation, considering the role of the OFC in incentive processing and given that studies with younger participants have reported both medial and lateral OFC valence effects (Forbes et al 2010, May et al 2004). Unlike other adult CGG studies, we found a significant effect of valence in the lateral OFC, such that activity to high-gain trials was greater than activity to either neutral or loss trials. May and colleagues also reported increased response to reward in lateral OFC, using a monetary version of the CGG in children and adolescents (May et al 2004). Reward-processing studies frequently report a lateral/medial OFC distinction in activity patterns, with greater response to punishment in lateral regions and greater response to reward in medial regions (Kringelbach 2005, Kringelbach & Rolls 2004). However, some studies have suggested that this lateral/medial relation may rely at least in part on whether the gain/loss feedback leads to behavioral change (Breiter et al 2001, Elliott et al 2003, Kringelbach 2005, Kringelbach & Rolls 2004). As our task was specifically designed such that behavior could not be used to influence task feedback, it is not entirely clear why we (and May et al., 2004) found gain-related responses in lateral OFC, although this may reflect some more general property of value processing in response to gain (Elliott et al 2003, Kringelbach 2005, Kringelbach & Rolls 2004, O'Doherty et al 2001a).

Also of interest is the posterior position of our lateral OFC region. As noted above, there is evidence in the literature that more abstract rewards, such as money, elicit activation in more anterior portions of OFC, while primary rewards elicit activation in more posterior portions of OFC (Kringelbach & Rolls 2004, Sescousse et al 2010). However, we did not have clear hypotheses regarding whether we would observe valence effects in posterior versus anterior OFC, given of our combination of elements from secondary-and primary-reward tasks (timing of reward delivery and reward type, respectively). Interestingly, studies using monetary CGGs have reported valence effects in anterior portions of the OFC, while in our candy version, valence effects were observed more posteriorly (Forbes et al 2010, May et al 2004). Thus, our results are generally consistent with an anterior–posterior gradient of secondary (abstract) to primary rewards in OFC responses. However, the OFC is a difficult region of the brain to image, and the signal within our sample was much stronger in posterior than in more anterior portions of the OFC. Thus, these OFC results should be interpreted as a positive finding regarding valence effects in posterior OFC, but not as a strong null finding regarding anterior OFC response to primary-like rewards, as their absence could reflect reduced signal quality.

Other regions identified as showing significant valence effects in our candy version of the CGG, including regions of the amygdala, hippocampus, thalamus, and insula, have mixed support from other monetary CGG studies. Regions of thalamus are constantly identified in CGG studies, but support is mixed as to whether the thalamus shows general responsivity to the task (e.g., main effect of time) or to valence-specific effects (Delgado et al 2003, Delgado et al 2000, Delgado et al 2004, Forbes et al 2010, May et al 2004, Tricomi et al 2006). Studies that have reported thalamic valence effects have shown greater activity to reward than to loss feedback, in line with our results (Delgado et al 2003, Tricomi et al 2006). We also observed greater

activation to gain than to loss trials in the amygdala. This result is consistent with a hypothesized role for the amygdala in processing affectively salient stimuli. However, surprisingly, previous CGG studies have not reported modulation of amygdala activity as a function of valence (Elliott et al 2003; Forbes et al 2010; Knutson et al 2001; Sescousse et al 2010). We observed greater deactivation in the hippocampus to loss than to gain events, but again, previous CGG studies have not shown hippocampal modulation. Insula regions have been identified in several CGG studies (e.g., Delgado et al 2000; Delgado et al 2004), but only one study reported significant valence effects (Tricomi et al 2006). In this prior study, the insula region displayed greater activation to loss than to reward, the opposite pattern of activity we report. However, our insula region (35, –5, 16) was located anterior and medial to the region identified by Tricomi et al. (2006). The majority of CGG studies have focused on effects of valence within the striatum, whereas we chose to focus on regions within a much larger a priori mask. It is possible that previous CGG studies failed to find valence effects in regions such as the amygdala and hippocampus simply because the effects fell outside of a priori regions of interest, and thus were subjected to a higher statistical threshold.

Magnitude Effects

Other groups using the CGG have found interactions between valence and magnitude particularly within the caudate (Delgado et al 2003, Elliott et al 2000). Unlike these other studies, we did not find a significant interaction between feedback valence (gain, loss) and magnitude (high, low) within the dorsal striatum, although we did observe significant valence effects in the caudate. A possible explanation for this result could be that the difference between the high-and low-magnitude conditions was not large enough to elicit significantly different striatal responses between high and low trials, or that the effect size is small in this paradigm, and more trials

would be needed to detect such a relation. Importantly, particularly for future between-group developmental studies, it is possible that healthy young adults who receive monetary compensation for their time are not engaged sufficiently by winning or losing a few small candies to elicit parametric modulation of the BOLD response by outcome "value," though it is possible that such differences in amounts of candy would be more salient in younger children.

Individual-Difference Effects

We observed a relation between task-related activity in several striatal/insular regions and individual differences in reward and punishment sensitivity (BIS/BAS total scores) (Carver & White 1994), but failed to identify any regions showing task activity related to our hedonics composite score. Interestingly, BAS scores were related to loss rather than to gain responses. Specifically, bilateral regions of the caudate displayed a negative correlation between BAS and the difference in response to high-loss and low-loss feedback. This correlation was related to reduced response to low-loss feedback in individuals with lower BAS total scores. The right caudate region also displayed a positive correlation between BAS and the difference in responses to low-loss and neutral feedback. This correlation was related to both decreased response to low-loss and increased response to neutral feedback in individuals with lower BAS scores. Similar correlations with BAS and task activity were found within a region of right lateral OFC that also displayed greater response to high-gain feedback than to low-gain, neutral, and loss feedback in the main analyses. Again, individuals with increased reward sensitivity showed reduced differences between different levels of loss.

Our individual-difference results are a bit counterintuitive, given evidence that reward sensitivity (BAS) is traditionally thought to relate to processing of appetitive stimuli, and punishment sensitivity (BIS) to relate to aversive processing. However, some evidence has

linked BAS with negative affect following significant events (Carver 2004). Our results suggest that individuals who are more sensitive to reward show reduced responses to low losses within the striatum, potentially suggesting a heightened sensitivity to minor losses. In contrast, they also suggest that individuals more sensitive to punishment show increased response to the best gain option and less response to the worst gain option, potentially suggesting more sensitivity to the relative "bad" versus "good" options within available gains. Given that most of the previous studies examining individual differences in punishment and reward sensitivity have used monetary rewards, it will be important to directly compare these individual relations for monetary versus more primary rewards in future studies.

Also of note are our null findings involving the composite hedonics variable HED. Although other studies have reported negative relations between striatal activation during reward and anhedonia in control samples, it is possible that we simply did not have enough power and/or that our nonclinical population did not have enough variance in hedonic tone to detect this relation (Dowd & Barch 2010, Dowd & Barch 2012).

Limitations And Future Directions

Although we observed results that were largely consistent with those of other CGG studies, interpretation of results that differed from those of monetary studies would be strengthened by future within-subjects studies designed to directly compare responses to candy and monetary incentives. Because we were interested in designing a paradigm appropriate for use across a wide developmental spectrum, we chose to use small amounts of candy delivered postscan as an incentive. While we believe that this paradigm has promise for developmental applications, it is by no means the only option, and is not entirely free of potential developmental confounds. Studies utilizing and directly comparing responses to other incentive types (e.g., food

odors, liquid rewards, and even social rewards) and structures (e.g., token economies), while they are perhaps more difficult to implement for developmental questions, are certainly warranted to empirically evaluate which methods are best designed to address developmental incentive-processing questions.

We chose to focus our individual-difference analyses on self-report measures of reward/punishment sensitivity, but interesting individual differences within task behavior that we did not investigate may influence group-level task responses. For example, interesting individual differences are likely to exist in how the neutral condition is interpreted (positively, as successfully avoiding loss; negatively, as failing to obtain a gain; or maybe as a combination of the two, depending on what feedback has recently occurred). Also, although this task was explicitly designed to elicit responses to gain/loss that were independent of any ongoing learning, it is possible that some individuals did try to adjust their behavior in an organized attempt to obtain more gains. Studies with larger and more diverse samples would be better designed to investigate these questions.

Future studies will also be needed to determine the influence of the timing of reward delivery (in-scanner vs. postscan) on incentive processing. In-scanner ratings of hedonic and/or affective response to the different feedback types/amounts would also have strengthened our interpretations and ensured that participants were actively engaged in the task over the course of the entire experiment. Thus, our results are an important first step in establishing methods for delivering primary rewards in a manner congruent with traditional monetary studies, but validation in larger, more diverse samples will be needed for both our individual-difference and valence effects.

Conclusions

We aimed to create a modified version of the CGG that would both be appropriate for developmental populations and allow for more direct comparison with secondary-reward paradigms. As hypothesized, we observed differential activity to gain and loss feedback in the striatum, amygdala, and OFC. Unlike other monetary CGG studies, a posterior OFC region displayed valence-dependent activation in our task. This finding potentially supports an anterior/posterior distinction in OFC response to abstract/primary rewards, but poor anterior OFC signal quality could also explain these null results. Overall, our results show strong continuity with previous studies using both primary and secondary rewards, and provide an important baseline for use of this paradigm with child and other special populations.

2.5 Supplemental Information

To investigate effects of valence and magnitude at the whole brain level we ran the same three voxel-wise ANOVAs discussed in the methods section: 1) ANOVA with valence (gain, loss), magnitude (high, low) and timepoint (10 timepoints within trial estimate) as within subject factors; 2) ANOVA with condition (gain, neutral, loss) and timepoint as within subject factors; and 3) ANOVA with high-condition (high gain, neutral, high loss) and timepoint as within subject factors. We corrected for multiple comparisons using a combined p-value/cluster size threshold ($p<.0013$ and 17 voxels) determined by Monte Carlo simulations to provide a whole-brain false-positive rate of $p<.05$. The resulting activation maps were partitioned such that peaks of activity were considered separate ROIs if they were more than 12mm apart based on a peak-splitting algorithm (Kerr et al 2004, Michelon et al 2003). Post hoc ANOVAs were performed within all significant ROIs from the condition and high-condition ANOVAs to identify the conditions that significantly differed from one another.

Whole Brain Effects of Valence

Whole brain analysis (Supplemental Table S2.4 and Figure S2.9) again revealed regions in the striatum, including the caudate, putamen, globus pallidus, insula and hippocmpus that showed valence by timepoint interactions indicating differential activity between gain and loss trials. However, the whole brain analysis also identified regions in a number of additional areas in the brain showing these effects, including several ROIs in the frontal cortex and the parietal cortex, as well as the cerebellum. ROIs significant at the whole brain level (Supplemental Table 2.4) displayed two main patterns of activity. Regions with higher activation to gain than loss trials included regions previously identified as involved in reward and error processing, including the putamen, caudate, globus pallidus, posterior cingulate gyrus, superior frontal gyrus,

medial frontal gyrus and amygdala, as well as regions involved in visual and motor processing such as cuneus, fusiform gyrus, inferior occipital gyrus, lingual gyrus, declive, and post/precentral gyri. ROIs displaying greater deactivation to loss compared to gain trials include regions of superior frontal gyrus, medial frontal gyrus, middle frontal gyrus, precuneus, post/precentral gyri, superior temporal gyrus, hippocampus, cingulate gyrus, middle temporal gyrus, paracentral lobule, pulvinar and the inferior parietal lobule.

Whole Brain Effects of Magnitude

Regions in the superior frontal cortex, occipital cortex, precentral gyrus and parahippocampal gyrus all displayed significant interactions between magnitude and timepoint within trial (see Supplemental Table 2.5). A number of regions in primary and secondary visual cortex, including portions of the cuneus, and inferior and middle occipital gyri all showed greater activity to the high magnitude outcomes compared to the low magnitude outcomes, potentially reflecting the greater visual stimulation or attention associated with the high magnitude conditions (i.e., more "candies" on the screen). A similar pattern was present in the precentral gyrus. However, a region of the parahippocampal gyrus showed deactivation, with a greater decrease from trial onset in the high versus low magnitude conditions.

Whole Brain Interaction of Valence and Magnitude

Regions in occipital cortex, temporal cortex, the cingulate and the cerebellum all displayed showed magnitude X valence X timepoint interactions (see Supplemental Table 2.6). For the Middle Occipital Gyrus, activity was greatest for high gain trials, and lowest for high loss trials with similar activity levels for the remaining trial types. In the declive, activity levels were greatest during high gain and low loss trials whereas low gain and high loss trial related activity were similar and lower. A region of the middle temporal gyrus displayed deactivation during all

trial types with greater deactivation during high loss and low gain trials. In the middle temporal gyrus deactivation was greatest for both high loss and low gain trials.

Whole Brain Analyses Including Neutral Trials

Several regions showed patterns of activity where gain and loss trial activity was similar but differed from neutral. As shown in Supplemental Figure S2.8, regions in the middle temporal gyrus, lingual gyrus, precuneus, cuneus, supramarginal gyrus, superiror parietal lobule, postcentral gyrus, parahippocampal gyrus, cingulate gyrus, and inferior semi-lunar lobule all showed greater activation during neutral trials compared to gain and loss trials. Conversely, activity was greater during loss and gain trials compared to neutral trials in regions of the middle occipital gyrus, cingulate gyrus, precuneus, pyramus, culmen, middle occipital gyrys, fusiform gyrus, superior/inferior paretal lobules, declive, and superior/middle/inferior frontal gyri (Supplemental Table 2.7). Many of these regions are associated with visual processing and attentional control, and may reflect differences between the visual complexity of the gain/loss and neutral stimuli (Figure 2.1) as well as increased attention to gain and loss outcomes as compared to a neutral outcome.

Several regions also displayed task related deactivation. Regions in the superior and middle temporal gyri and superior frontal gyrus showed greater deactivation during neutral trials compared to gain and loss trails whereas regions of the insula, precentral gyrus, superior parietal lobule, paracentral lobule, transverse temporal gyrus and middle/superior/transverse temporal gyri showed the greatest deactivation during gain and loss trials compared to neutral.

Signal Quality

To determine the number of participants with quality signal within each voxel each participant's anatomical average was thresholded such that all voxels with signal above 500 (an

admittedly somewhat arbitrary value) were assigned a value of one. Of note, qualitatively similar results were found when we used a higher signal value threshold of 750. Thresholded anatomical averages from each participant (n=20) were summed resulting in a map (Supplemental Figure 2.10) depicting the number of participants with signal above 500 for each voxel. Signal was below 500 for half the sample in the medial and anterior OFC. It is not uncommon to experience signal dropout within the OFC. Thus, it is important to highlight that null findings in these regions cannot be attributed solely to a lack of task effects as poor signal quality could also explain the lack of task related findings.

Supplemental Table S2.1
Descriptive Statistics for individual difference measures, movement parameters, and behavior

	N	Minimum	Maximum	Mean	Std. Deviation
Behavioral Activation Scale - total score	20	29	47	40.95	4.42
Behavioral Inhibition Scale - total score	20	14	27	21.30	3.08
Beck's Depression Inventory - total score	19	0	12	2.26	2.94
Snaith Hamilton Pleasure Scale - total score	20	9	28	20.05	5.22
Chapman Social Anhedonia - total score	19	2	23	6.16	5.23
Chapman Physical Anhedonia - total score	19	3	20	8.08	4.45
Hedonics - composite score	19	-7.55	3.11	-0.33	2.85
Movement RMS per frame	20	0.04217	0.21657	0.09719	0.04133
Mean Voxelwise Standard Deviation	20	6.99827	12.67307	9.77789	1.58341
Button Press Reaction Time (msec) – mean across all trials	20	387.6	737.5	521.8	91.4

Supplemental Table S2.2

Pairwise Correlations Between Individual Difference Measures

		BIS	BDI	SHPS	PA	SA	HED
1) Behavioral Activation Scale Total Sore (BAS)	Pearson Correlation	-.15	-.12	.27	-.21	-.43	.36
	Sig. (2-tailed)	.53	.62	.25	.39	.07	.13
	N	20	19	20	19	19	19
2) Behavioral Inhibition Scale Total Score (BIS)	Pearson Correlation		.227	-.083	-.105	.445	-.166
	Sig. (2-tailed)		.350	.728	.670	.056	.496
	N		19	20	19	19	19
3) Beck Depression Inventory Total Score (BDI)	Pearson Correlation			-.062	-.088	.121	-.037
	Sig. (2-tailed)			.800	.729	.633	.884
	N			19	18	18	18
4) Snaith Hamilton Pleasure Scale Total Score (SHPS)	Pearson Correlation				-.504*	-.697**	.867**
	Sig. (2-tailed)				.028	.001	.000
	N				19	19	19
5) Chapman Physical Anhedonia Score (PA)	Pearson Correlation					.545*	-.802**
	Sig. (2-tailed)					.016	.000
	N					19	19
6) Chapman Social Anhedonia Score (SA)	Pearson Correlation						-.879**
	Sig. (2-tailed)						.000
	N						19
7) Hedonics - composite score (HED)							

**p<0.01 (2-tailed)

*p<0.05 (2-tailed)

Supplemental Table S2.3
Basal Ganglia ROI Post-Hoc Paired Tests

Region of Activation	Laterality	Talairach Coordinates x	y	z	Paired t-test p-values G - N	L - N	HG - N	HL - N
Regions where N=G>L								
Dorsal Putamen	R	27	-13	10	0.467	0.002	0.997	0.006
Dorsal Putamen	L	-26	-13	10	0.986	0.001	0.519	0.006
Ventral Putamen	R	30	-13	-4	0.405	0.007	0.33	0.011
Ventral Putamen	L	-23	-2	-3	0.4	0.011	0.076	0.016
Ventral Putamen	R	22	-1	-7	0.296	0.023	0.07	0.012
Dorsal Putamen	L	-23	3	11	0.572	0.049	0.208	0.037
Dorsal Putamen	R	24	5	9	0.922	0.001	0.055	0.013
Regions where N=L<G								
Putamen/Caudate	L	-17	9	4	0.042	0.305	0.017	0.317
Putamen/Caudate	R	15	9	5	0.02	0.987	0.002	0.749
Caudate Body	R	15	12	15	0.027	0.685	0.004	0.851
Caudate Body	L	-15	7	17	0.053	0.596	0.009	0.496
Caudate Body	L	-6	3	6	0.067	0.503	0.033	0.679

Note: Post Hoc paired t-tests were performed within all basal ganglia ROIs identified as displaying significant valence x timepoint interaction. The mean activation at timepoints 4 and 5 for gain, loss, neutral, high gain, and high loss trials were used in four t-tests (gain – neutral, loss – neutral, high gain – neutral, high loss – neutral) to determine the relation between neutral and other trial type activity.

In putamen regions neutral activity *did not* differ from gain but it did differ from loss. In caudate and caudate/putamen regions neutral activity *did* differ from gain but *did not* differ from loss.

Yellow indicates regions where $p<0.05$
Blue indicates regions where $p<0.10$
L = Left; R = Right (in 'Laterality' Column)
G = Gain; N = Neutral; L = Loss; HG = High Gain; HL = High Loss

Supplemental Table S2.4
Valence x Time Point Interaction ROIs – Whole Brain

Region of Activation	BA	Laterality	Talairach Coordinates x	y	z	Pattern
Activation						
Precentral Gyrus	4	L	-18	-26	71	G>N>L
Postcentral Gyrus	3	L	-32	-31	56	N>G>L
Precentral Gyrus	4	R	25	-25	53	N>G>L
Putamen		R	26	-20	10	G>N>L
Postcentral Gyrus	3	L	-42	-16	48	G=N>L
Putamen		L	-28	-19	9	G=N>L
Cuneus	19	R	11	-92	31	G=N>L
Putamen		R	29	-8	13	G=N>L
Medial Frontal Gyrus	6	L	-8	-10	47	G=N>L
Precentral Gyrus	6	R	41	-8	50	G=N>L
Parahippocampal Gyrus	30	R	22	-37	7	G=N>L
Cingulate Gyrus	24	L	-7	1	41	G=N>L
Caudate		R	20	14	18	G=N>L
Cuneus	18	L	-10	-101	0	G>L=N
Cuneus	18	R	14	-97	7	G>L=N
Inferior Occipital Gyrus	17	L	-12	-92	-8	G>L=N
Inferior Occipital Gyrus	17	R	18	-89	-5	G>L=N
Declive		L	-20	-83	-15	G>L=N
Lingual Gyrus	18	L	0	-89	-2	G>L=N
Fusiform Gyrus	19	R	26	-83	-13	G>L=N
Declive		L	-56	-60	-19	G>L=N
Declive		L	-50	-73	-21	G>L=N
Putamen		R	21	7	7	G>L
Putamen		L	-21	8	1	G>L
Lateral Globus Pallidus		L	-22	-4	-6	G>L
Precentral Gyrus	6	L	-44	-7	56	G>L
Postcentral Gyrus	3	R	41	-25	60	G>L
Amygdala		R	22	-5	-9	G>L
Precentral Gyrus	6	L	-56	-6	34	G>L
Putamen		L	-18	4	15	G>L
Postcentral Gyrus	3	R	48	-18	52	G>L
Cerebellar Tonsil		R	3	-55	-36	G>L
Cuneus	19	L	-9	-95	26	G>L
Posterior Cingulate	23	R	3	-34	20	G>L
Superior Frontal Gyrus	8	L	-39	16	54	G>L
Parahippocampal Gyrus	27	R	17	-30	-4	G>L
Parahippocampal Gyrus	27	L	-18	-35	0	G>L
Postcentral Gyrus	3	L	-54	-12	51	G>L

Deactivation						
Medial Frontal Gyrus	6	R	2	-21	51	L>N>G
Superior Frontal Gyrus	8	L	-22	33	49	L>G=N
Postcentral Gyrus	3	R	25	-32	65	L>N>G
Superior Frontal Gyrus	8	R	15	41	47	L>G=N
Superior Frontal Gyrus	8	L	-7	50	45	L>N>G
Posterior Cingulate	29	L	-4	-53	11	L>G=N
Postcentral Gyrus	3	L	-20	-32	60	L>N>G
Superior Frontal Gyrus	6	L	-5	34	53	L>G=N
Hippocampus		R	32	-21	-14	L>G=N
Pulvinar		L	-12	-32	16	L>G=N
Medial Frontal Gyrus	6	L	-2	-19	71	L=N>G
Superior Frontal Gyrus	6	L	-14	22	63	L=N>G
Paracentral Lobule	6	R	1	-31	72	L=N>G
Superior Temporal Gyrus	42	R	63	-24	12	L>G>N
Precuneus	7	L	-7	-43	52	L>G>N
Medial Frontal Gyrus	8	L	-3	37	39	N>L>G
Middle Frontal Gyrus	8	L	-26	19	45	L>G
Precuneus	31	L	-12	-50	27	L>G
Hippocampus		L	-28	-20	-12	L>G
Precuneus	31	R	2	-49	30	L>G
Middle Temporal Gyrus	21	L	-62	-5	-7	L>G
Cingulate Gyrus	31	L	-10	-31	37	L>G
Precuneus	7	L	-5	-62	35	L>G
Deactivation then Activation						
Inferior Parietal Lobule	40	R	55	-60	39	L>G=N
Precuneus	19	R	41	-78	41	L>G=N

Note: Regions displaying an interaction of valence x timepoint significant at the whole brain level Post Hoc analyses detailed in Methods section were performed on each region. Regions in which activation during neutral trials did not significantly differ from activity during either gain or loss trials are noted as showing either R>L or L>R patterns of activity.
BA = Broadmann Area
L = Left; R = Right (in 'Laterality' Column)
G = Gain; N = Neutral; L = Loss

Supplemental Table S2.5
Magnitude x Timepoint Interaction ROIs – Whole Brain

Region of Activation	BA	Laterality	Talairach Coordinates x	y	z	Pattern
Activation						
Inferior Occipital Gyrus	18	R	27	-85	-10	H>L
Inferior Occipital Gyrus	18	R	37	-91	-6	H>L
Middle Occipital Gyrus	18	R	24	-97	3	H>L
Inferior Occipital Gyrus	18	L	-25	-89	-10	H>L
Deactivation						
Precentral Gyrus	6	L	-62	-10	31	L>H
Parahippocampal Gyrus	19	L	-33	-45	-3	H>L

Note: Regions displaying an interaction of magnitude x timepoint significant at the whole brain level
BA = Broadmann Area
L = Left; R = Right (in 'Laterality' Column)
H = High; L = Low

Supplemental Table S2.6
Valence x Magnitude x Time Point Interaction ROIs – Whole Brain

Region of Activation	BA	Laterality	Talairach Coordinates x	y	z
Activation					
Middle Occipital Gyrus	19	L	-46	-60	-7
Declive		R	26	-63	-13
Deactivation					
Middle Temporal Gyrus	21	R	63	-5	-13

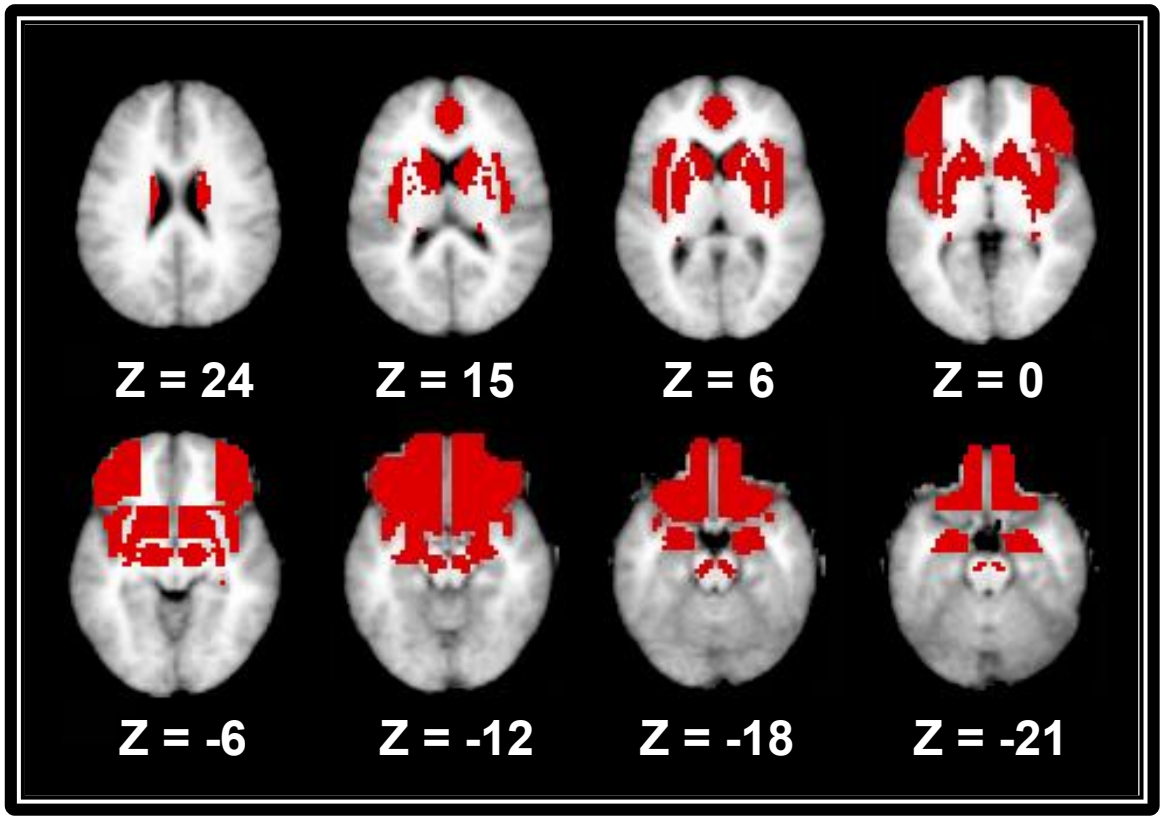
Note: Regions displaying an interaction of valence x magnitude x timepoint significant at the whole brain level
BA = Broadmann Area
L = Left; R = Right

Supplemental Table S2.7
Condition x Time Point Interaction ROIs – Whole Brain

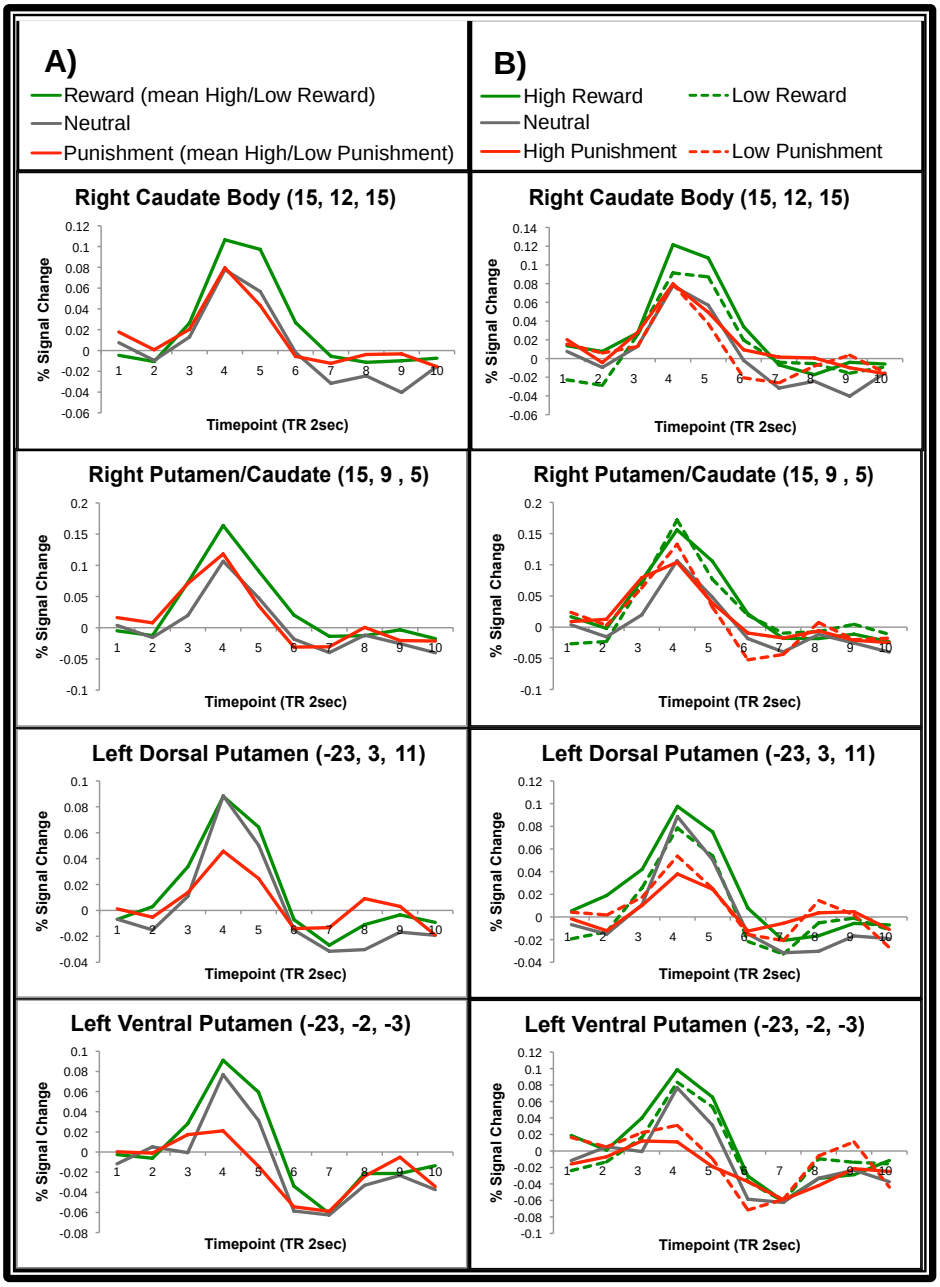
Region of Activation	BA	Laterality	Talairach Coordinates x	y	z	Pattern
Activation						
Lingual Gyrus	18	L	-10	-72	-7	N>G=L
Middle Temporal Gyrus	21	R	59	-54	-1	N>G=L
Cuneus	19	R	10	-87	27	N>G=L
Parahippocampal Gyrus	19	L	-23	-53	-4	N>G=L
Supramarginal Gyrus	40	R	52	-50	30	N>L=G
Superior Parietal Lobule	7	R	17	-63	60	N>G=L
Postcentral Gyrus	5	R	35	-43	57	N>G=L
Precuneus	7	R	9	-81	45	N>G=L
Precuneus	7	R	19	-71	45	N>G=L
Middle Temporal Gyrus	22	R	56	-42	4	N>G=L
Parahippocampal Gyrus	19	R	21	-44	-5	N>G=L
Cuneus	19	L	-9	-88	22	N>G=L
Lingual Gyrus	18	R	12	-68	-2	N>G=L
Inferior Semi-Lunar Lobule		L	-38	-70	-45	N>G=L
Cuneus	18	R	1	-97	12	N>G=L
Inferior Semi-Lunar Lobule		L	-11	-76	-42	N>L=G
Middle Temporal Gyrus	39	R	51	-56	12	N>L=G
Precuneus	7	L	-17	-73	47	N>G=L
Cuneus	19	L	-6	-87	36	N>G=L
Fusiform Gyrus	19	L	-35	-77	-11	L=G>N
Middle Occipital Gyrus	18	L	-30	-89	-3	L=G>N
Inferior Parietal Lobule	40	R	40	-50	46	L=G>N
Culmen		L	-32	-52	-16	L=G>N
Fusiform Gyrus	19	R	33	-68	-10	L=G>N
Fusiform Gyrus	18	L	-23	-88	-18	L=G>N
Inferior Parietal Lobule	40	R	48	-40	46	L=G>N
Superior Parietal Lobule	7	R	36	-64	51	L=G>N
Declive		R	32	-55	-13	L=G>N
Middle Occipital Gyrus	18	L	-28	-95	11	L=G>N
Inferior Parietal Lobule	40	L	-51	-54	41	L=G>N
Middle Frontal Gyrus	8	R	35	31	39	G=L>N
Cingulate Gyrus	23	R	2	-29	27	L=G>N
Inferior Parietal Lobule	40	L	-35	-48	38	L=G>N
Superior Frontal Gyrus	8	R	38	17	51	L=G>N
Inferior Frontal Gyrus	45	R	55	17	6	G=L>N
Declive		L	-26	-76	-22	L=G>N
Middle Frontal Gyrus	6	R	30	7	47	G=L>N
Cingulate Gyrus	31	R	11	-29	45	L=G>N
Middle Frontal Gyrus	6	R	28	-1	58	G=L>N
Pyramis		L	-37	-80	-34	G=L>N

Right Cerebellum		R	1	-88	-27	G=L>N
Deactivation						
Superior Temporal Gyrus	39	L	-58	-59	24	N>L=G
Superior Frontal Gyrus	6	R	19	19	61	N>G=L
Middle Temporal Gyrus	39	L	-58	-68	11	N>L=G
Superior Frontal Gyrus	6	R	6	33	60	N>L=G
Superior Parietal Lobule	7	L	-25	-46	59	L=G>N
Paracentral Lobule	5	R	4	-41	52	L=G>N
Superior Temporal Gyrus	39	R	55	-63	27	L=G>N
Insula	13	R	43	-9	1	L=G>N
Middle Temporal Gyrus	39	R	44	-74	23	G=L>N
Superior Temporal Gyrus	21	R	59	-10	-4	L=G>N
Paracentral Lobule	31	R	1	-10	45	L=G>N
Superior Frontal Gyrus	6	R	7	-5	66	L=G>N
Medial Frontal Gyrus	4	R	18	-31	58	L=G>N
Transverse Temporal Gyrus	41	R	48	-17	10	L=G>N
Superior Frontal Gyrus	8	R	18	42	41	G=N>L

Note: Regions displaying an interaction of condition and timepoint significant at the whole brain level
BA = Broadmann Area
L = Left; R = Right (in 'Laterality' Column)
G = Gain; N = Neutral; L = Loss



Supplemental Figure S2.1
A Priori Reward Mask
A priori mask covering reward related regions including the striatum, regions of the medial temporal lobe (ie. amygdala, hippocampus), insula, orbital frontal cortex and dopaminergic midbrain.

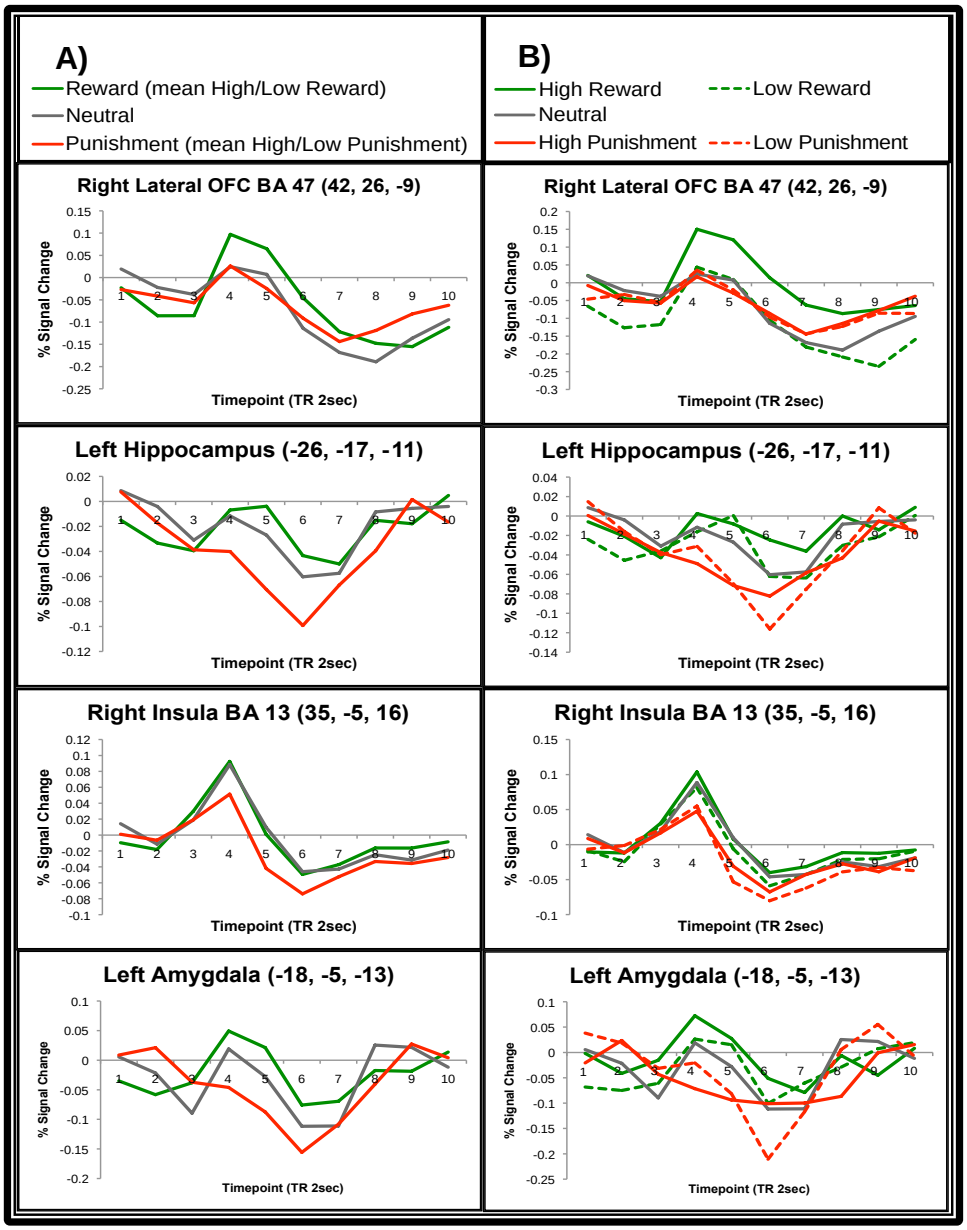


Supplemental Figure S2.2

Timecourses for Striatal Regions displaying Valence x Time Point Interaction

Timecourses within representative striatal regions with a significant valence by timepoint interaction for A) for gain (average of high and low gain), neutral, and loss (average of high and low loss) trials and B) high gain, low gain, neutral, low loss, and high loss trials.

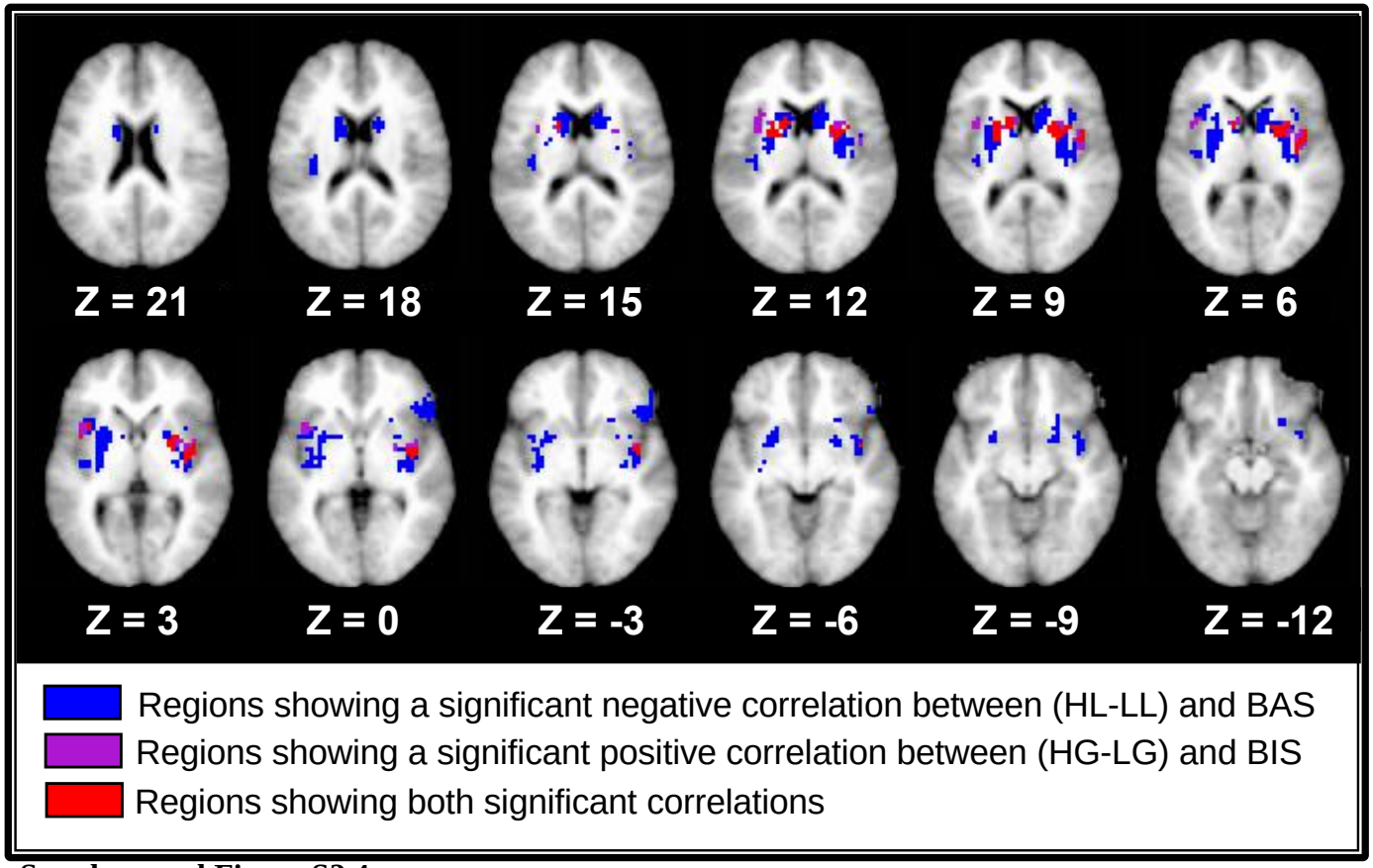
In Doral Putamen regions activation to gain and neutral conditions does not differ and is greater than activation to loss conditions. In all other regions neutral does not significantly differ from either gain or loss.



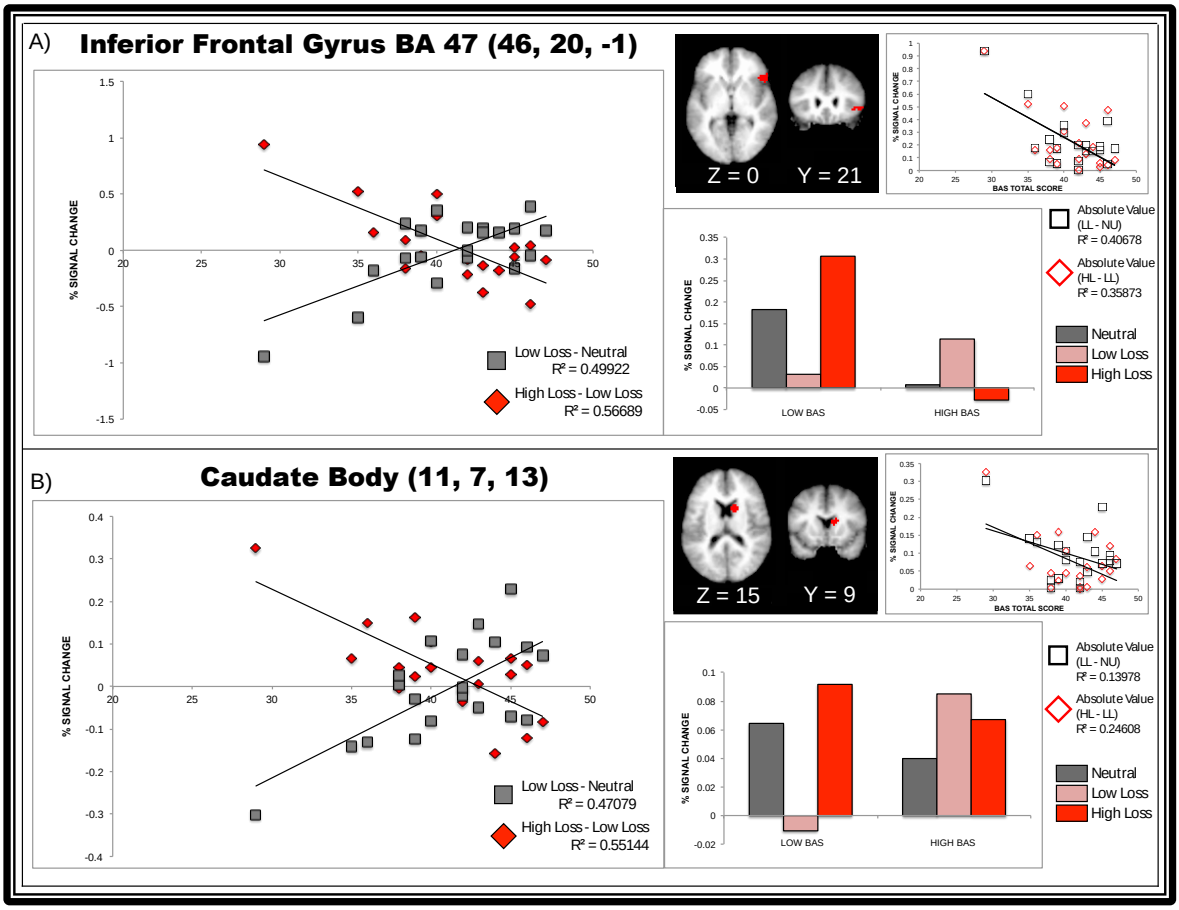
Supplemental Figure S2.3

Timecourses for Non-Striatal Regions displaying Valence x Time Point Interaction

Timecourses within non-striatal regions with a significant valence by timepoint interaction for A) for gain (average of high and low gain), neutral, and loss (average of high and low loss) trials and B) high gain, low gain, neutral, low loss, and high loss trials.



Supplemental Figure S2.4
BIS and BAS Correlation Map
HL = High Loss, LL = Low Loss, LG = Low Gain, HG = High Gain
BAS = BAS total score, measure of reward sensitivity from BIS/BAS Scale (behavioral activation/inhibition scale)
BIS = BIS total score, measure of punishment sensitivity from BIS/BAS Scale (behavioral activation/inhibition scale)

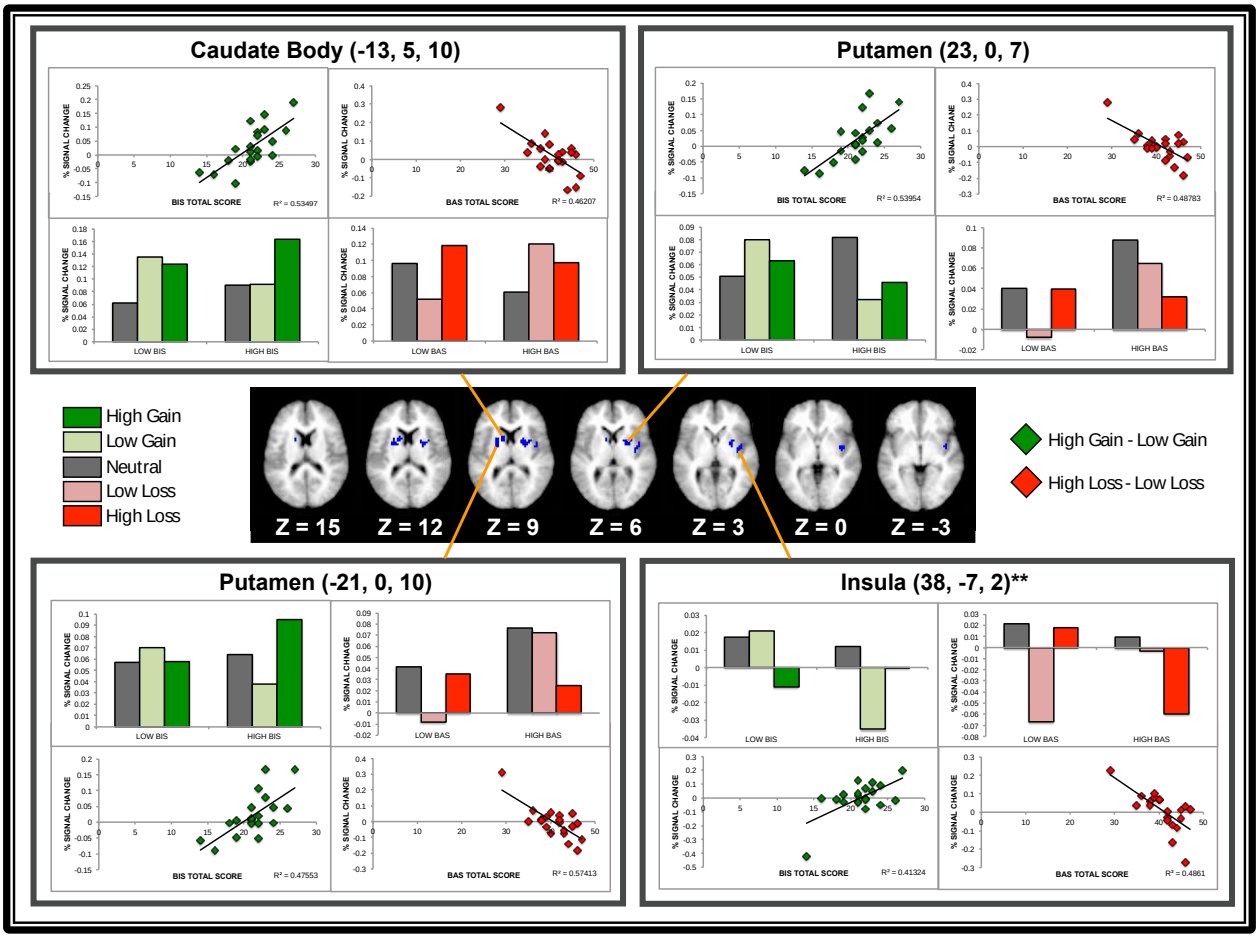


Supplemental Figure S2.5

BAS Correlations with Lateral OFC and Caudate

Regions identified as displaying significant correlations between BAS and both the difference in low loss (LL) and neutral (NU) trial activity, and the difference in high loss (HL) and low loss (LL) trial activity. A) Scatter plot depicting positive relation between BAS and LL-NU trial activity and negative relation between BAS and HL-LL trial activity in the right lateral OFC (46, 20, -1); B) scatter plot depicting the positive relation between individual differences in BAS and and LL-NU trial activity and negative relation between BAS and HL-LL trial activity in the bilateral caudate (mean of left (-12, 5,13) and right (11, 7, 13) caudate activation).

BAS = BAS total score, measure of reward sensitivity from BIS/BAS Scale - high/Low BAS determined by median split



Supplemental Figure S2.6

BAS and BIS Correlation Overlap Regions

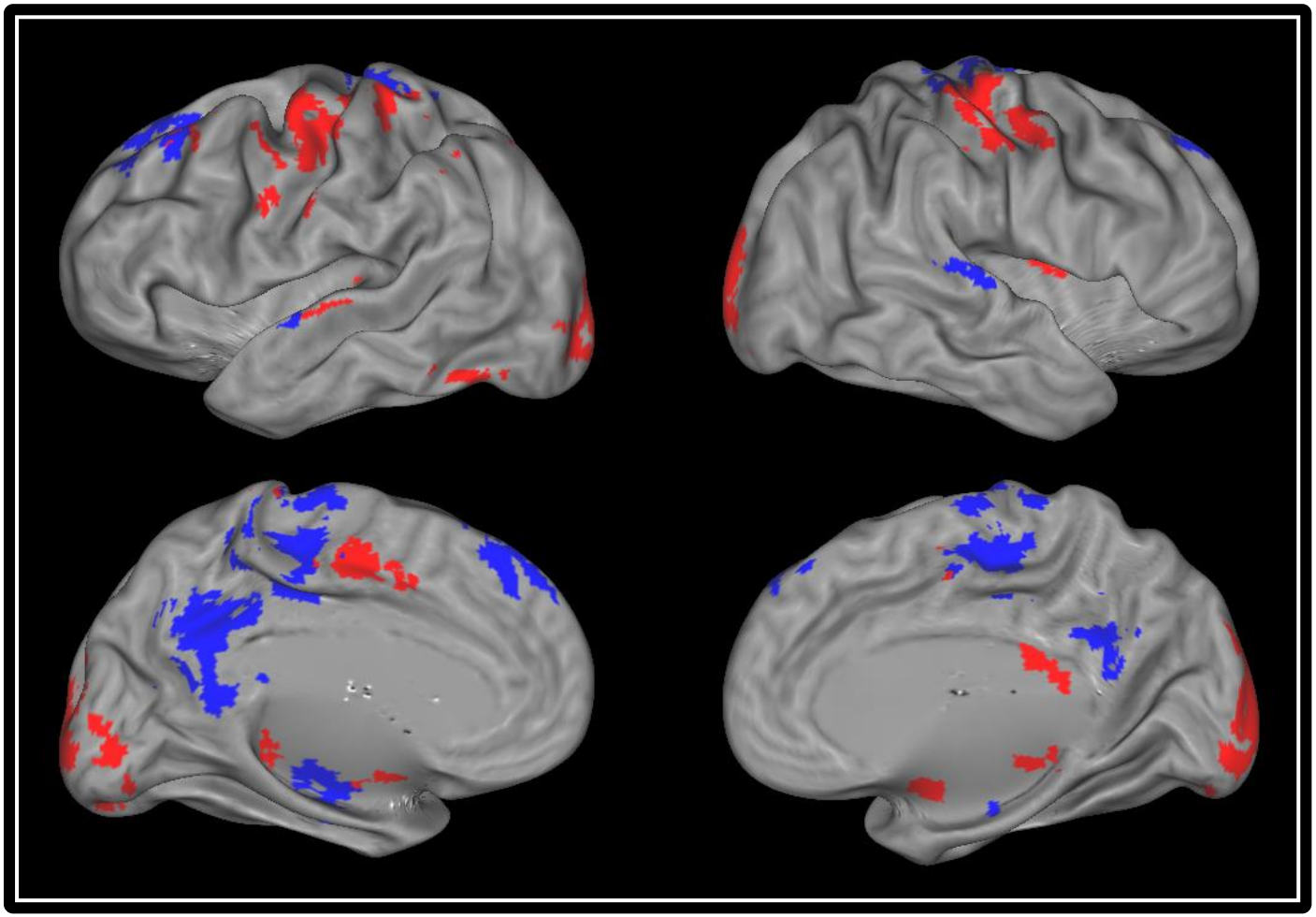
All regions displayed significant correlations between both BAS and the difference in high loss (HL) and LL trial activity, and BIS and the difference in high gain (Zeff et al) and low gain (LG) trial activity. Scatter plots depict a negative relation between BAS and HL-LL trial activity and a positive relation between BIS and HG-LG trail activity.

BAS = BAS total score, measure of reward sensitivity from BIS/BAS Scale (behavioral activation/inhibition scale)

BIS = BIS total score, measure of punishment sensitivity from BIS/BAS Scale (behavioral activation/inhibition scale)

High/Low BIS/BAS determined by median split

**Correlation between High Gain – Low Gain and BIS is non-significant when a within ROI correlation is conducted excluding the participant with the lowest BIS score.



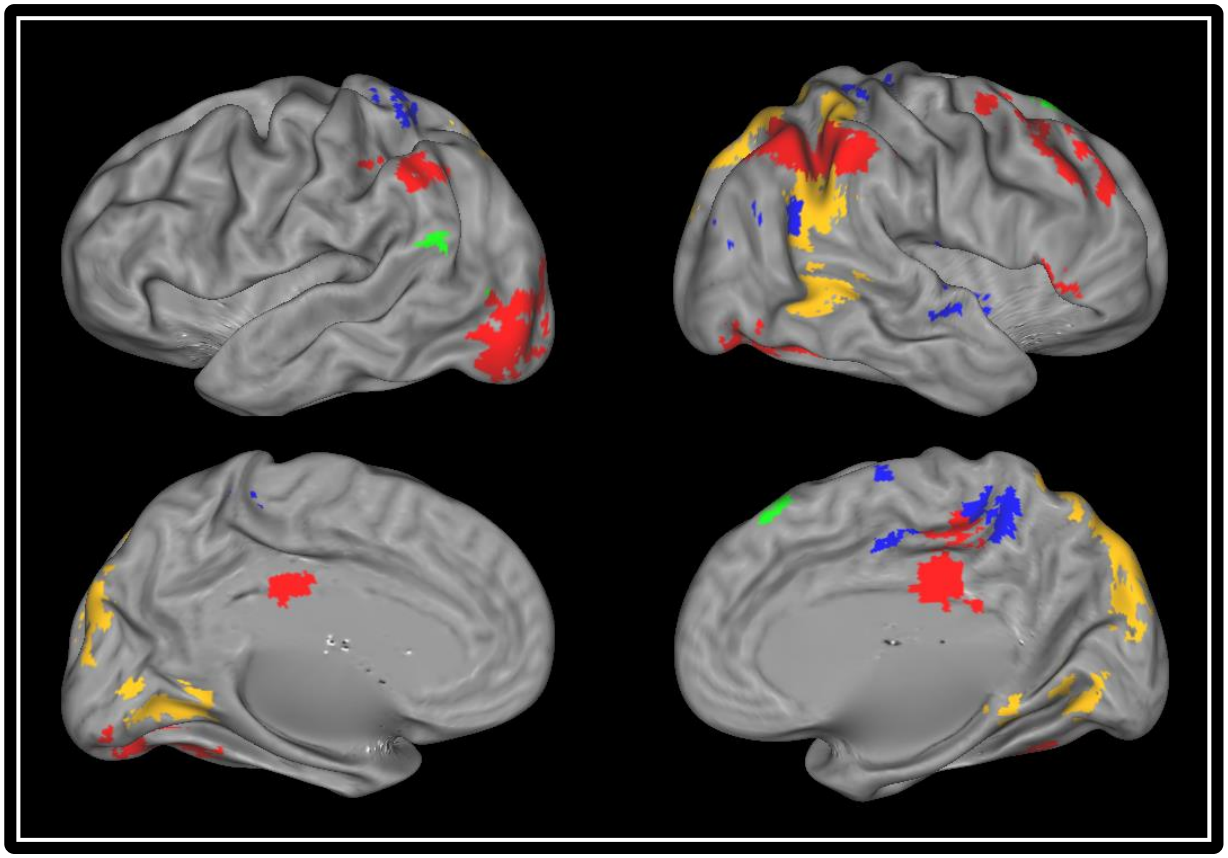
Supplemental Figure S2.7

Valence X Time Point Interaction ROIs – Whole Brain Map

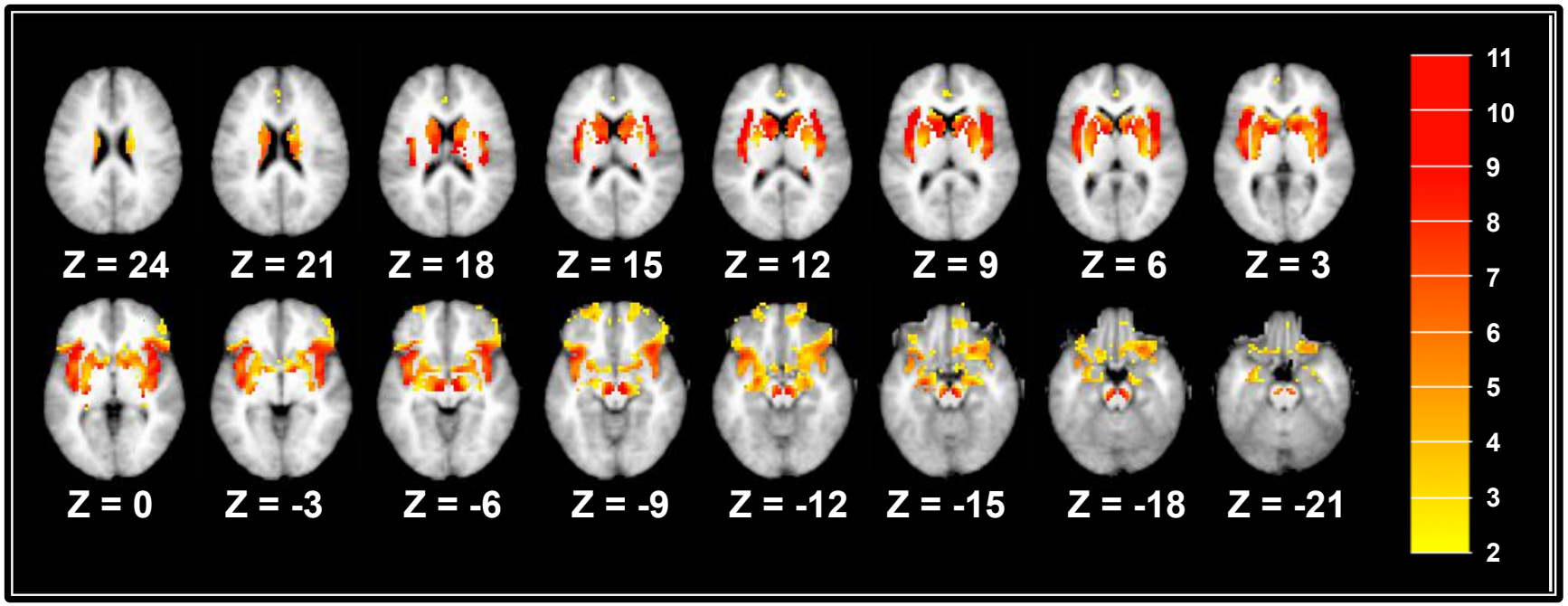
ROIs identified as showing a significant valence by timepoint interaction corrected for multiple comparisons at the whole brain level.

Red = ROIs with greater activation during gain trials compared to loss trials

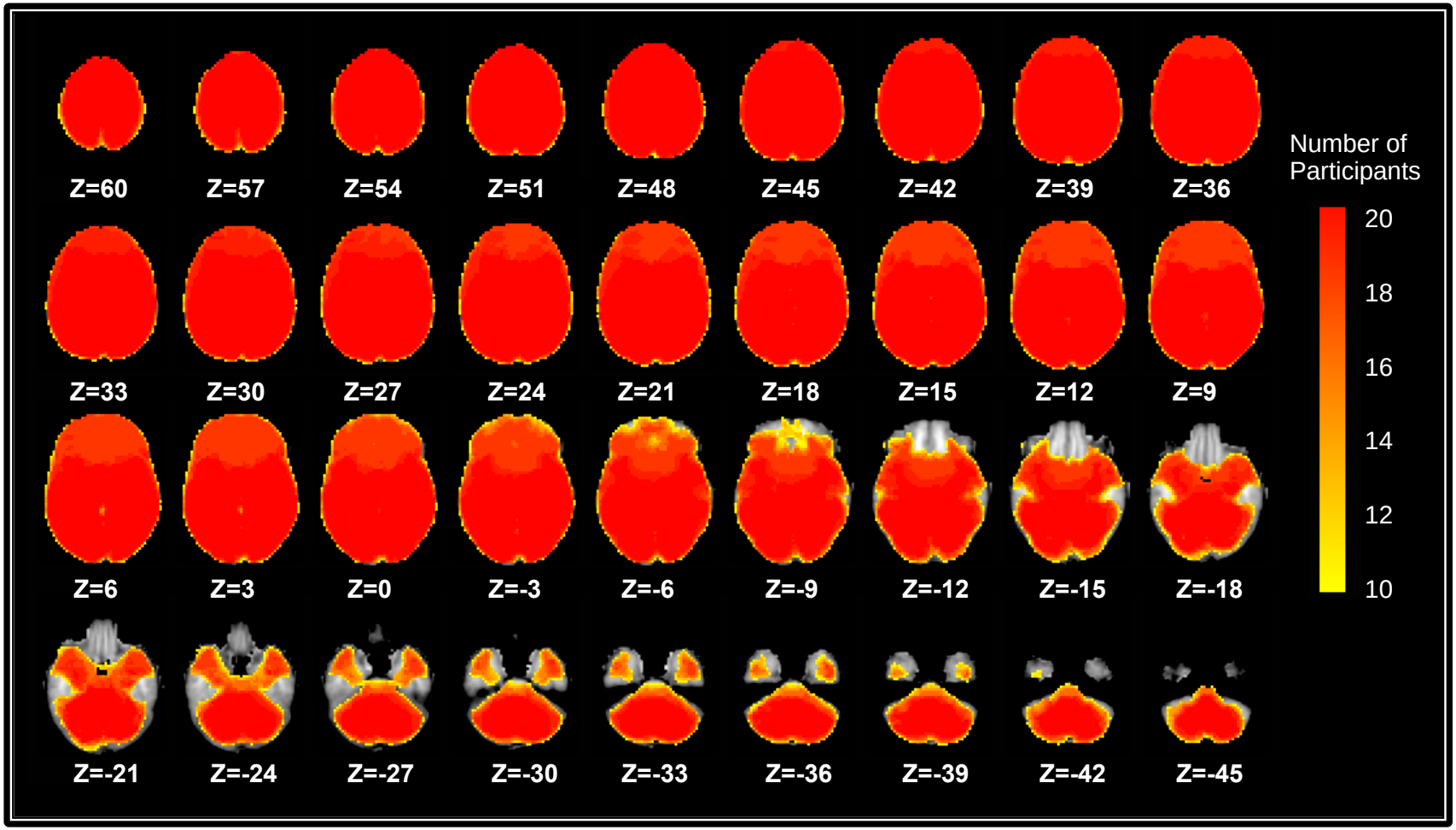
Blue = ROIs with greater deactivation during loss trials compared to gain trials



Supplemental Figure S2.8
Condition X Time Point Interaction – Whole Brain Map
ROIs identified as showing a significant condition by timepoint interaction at the whole brain level.
Red = ROIs with greater activation during gain and loss trials compared to neutral trials.
Yellow = ROIs with greater activation during neutral trials compared to gain and loss trials.
Blue = ROIs with greater deactivation during gain and loss trials compared to neutral trials.
Green = ROIs with greater deactivation during neutral trials compared to gain and loss trials.



Supplemental Figure S2.9
Main Effect of Time within a priori Reward Mask
Z-score map of the main effect of Time ANOVA results for all trial types within the *a priori* reward mask. Scale = Z of 2-11



Supplemental Figure S2.10

Adult Whole Brain Signal Quality Map

Whole brain map depicting the number of participants with signal>500 within each voxel. Of note, medial and anterior aspects of the OFC were particularly impacted by poor signal quality across the sample.

Chapter 3.

Kids, Candy, Brain And Behavior: Age Differences In Responses To Candy Gains And Losses

This chapter was published in the July 2014 issue of Developmental Cognitive Neuroscience. My contributions to this paper included data collection, data analysis, and writing

Reference: Luking KR, Luby JL, and Barch DM. Kids, candy, brain and behavior: Age differences in responses to candy gains and losses. Developmental Cognitive Neuroscience (2014) vol. 9C pp. 82-92.

Abstract

The development of reward-related neural systems, from adolescence through adulthood, has received much recent attention in the developmental neuroimaging literature. How- ever, 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 relations with age were no longer significant. Conversely, relations 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.

3.1 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 2007, Galvan et al 2006). While this literature has largely focused on comparing adolescent and adult responses to monetary incentives (see (Galvan 2010, Geier & Luna 2009, Richards et al 2013) for recent reviews), risk-taking behaviors may be influenced by responses to both reward and negative outcomes and 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 adult-hood (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 2010b). 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 2011a, 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 2011a, van den Bos et al 2009, van Duijvenvoorde et al 2008, Van Leijenhorst et al 2010b). 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 1970), and show greater learning rates for negative versus positive feedback (van den Bos et al 2012). In more com-plex 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 com-pared to adults (Somerville & 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 & 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 relation 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 relation 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 relations 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 relations to be located within regions involved in goal-directed action, such as the striatum.

3.2 Methods

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 pro-vided 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 & 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 the18 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 gen-der/ethnicity and are included in these analyses (Luking & 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.

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 Supplemental Figure S3.1). 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 Material).

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 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 Figure 3.1).

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 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 Figure 3.1) followed by an inter-trial interval (ITI) of 0–14000 ms that was randomly jittered in2000 ms increments.

Participants gained and lost both large and small amounts of candy. On high gain 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 numbers6/7 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 5card 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 & Kahneman 1981). Adult participants received $50, child participants received $30, and parents received $40 as compensation. Children and adults received 150 M&Ms/Skittles at the end of scanning regardless of task performance.

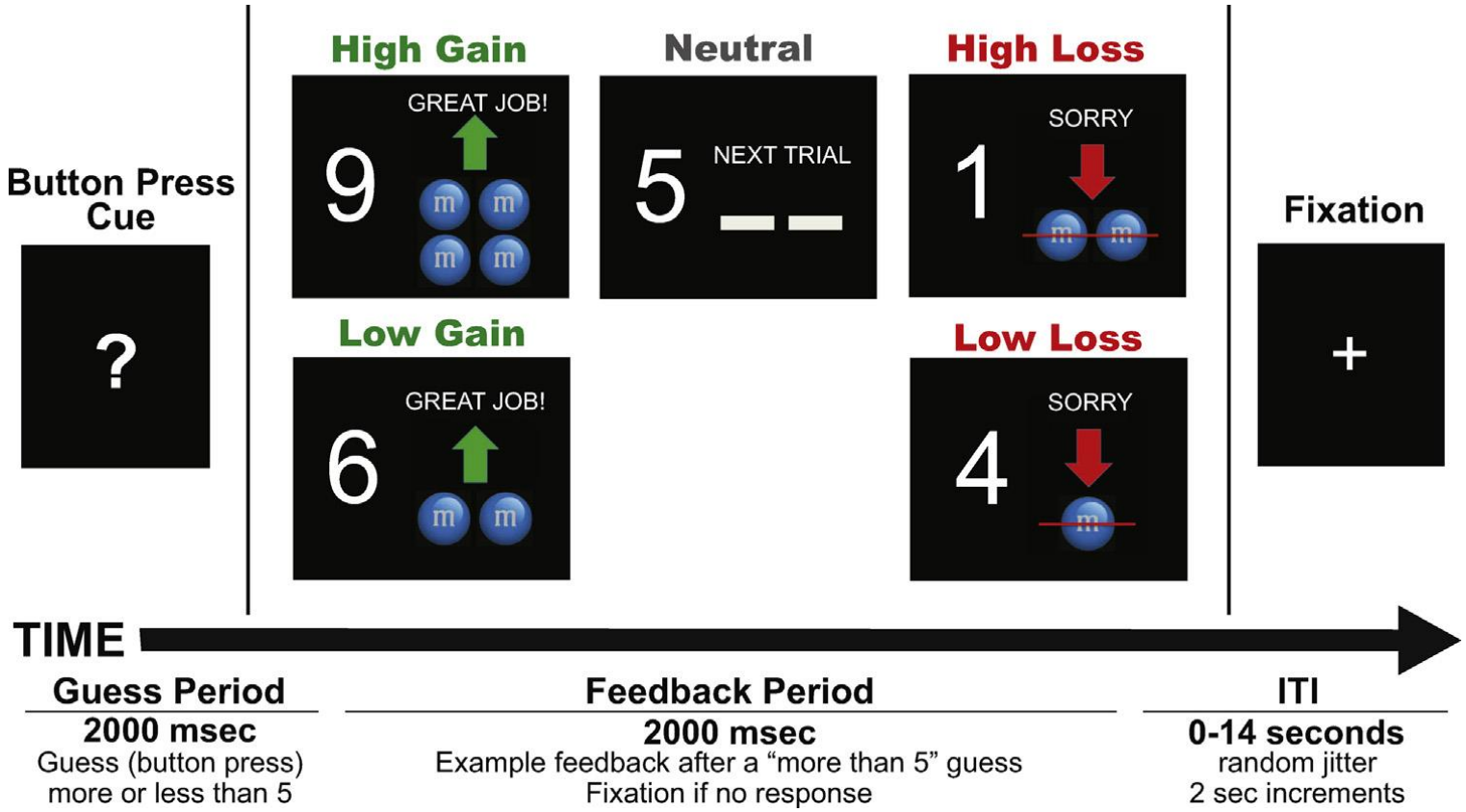


Figure 3.1: Timing Of Card Guessing Game

Example of feedback for 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.

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 a12-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 mm3) acquired parallel to the anterior–posterior commissure plane.

The fMRI data were preprocessed using in-house Washington University software. Prior to preprocessing, the first4 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 1994, Woods et al 1992); (3) registered to a Talairach (Talairach & 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 base-line 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 randomfactor.

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 Supplemental Table S3.1). 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, Power et al 2012). A repeated measures ANOVA (two factors: Age Group [children, adults] and remaining trials [HG, LG, NU, LL, HL]) indicated that the number of trialsr emaining 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 Material

and Supplemental Figure S3.2 for assessment of signal dropout in OFC and methods for dealing with this problem.

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 feed-back type. Within each age group there was a wide range of 'stay' choices following different trial types (Supplemental Figure S3.3A).

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 Feed-back 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.

fMRI data analysis

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 con-ducted 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 timepoints corresponding to the peak response (mean of TRs 4and 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).

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 relation 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 relations 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 & 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 relations 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 out-comes. 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 & Robbins 1983, Paulus et al 2001).

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. This mask (Supplemental Figure S3.4) 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.

3.3 Results

Results from behavioral ANOVAs

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;$p < 0.001$) (Supplemental Figure S3.3B). Across feedback types, adults were more likely to repeat the same choice compared to children (Age Group; $F_{1,34}$= 12.75; $p = 0.001$) (Supplemental Figure S3.3C). Feedback Condition and Age Group did not significantly interact ($p > 0.69$).

Reaction time ANOVA

Reaction time (see Supplemental Table S3.2) 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 3.2). 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 ($p > 0.20$).

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 ($p > 0.72$).

fMRI effects of age

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 3.1 and Figure 3.2). 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.

Table 3.1: Regions Showing A Time Point × Age Group Interaction

	Talairach 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 x 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 x Age Group ROI	35	18	7	26	R	Anterior Insula	13	A	A	A > C	--

Note: 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).

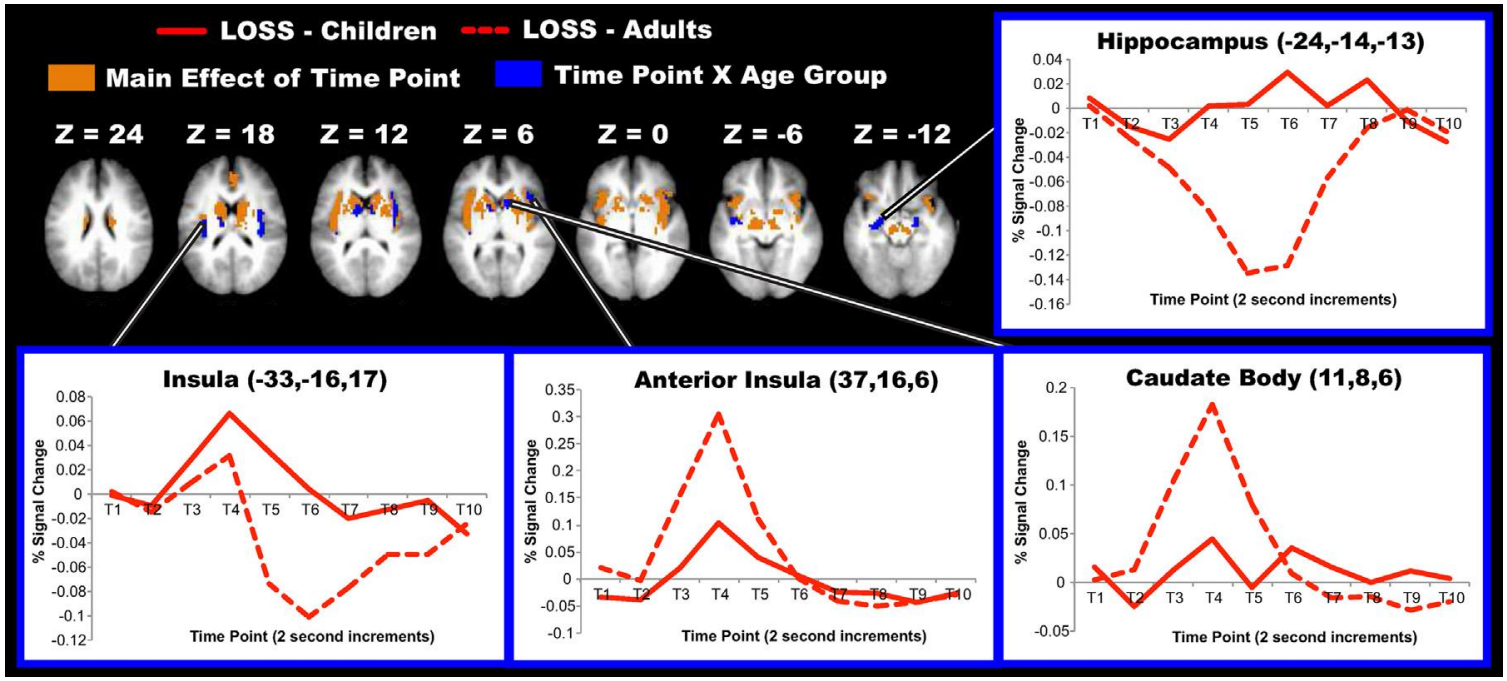


Figure 3.2: Regions Identified In The Time Point × Age Group ANOVA – Loss Trials

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.

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 (Supplemental Table S3.4 and Figure 3.3). 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 feed back and again adults showed greater activation than children (Table 3.1).

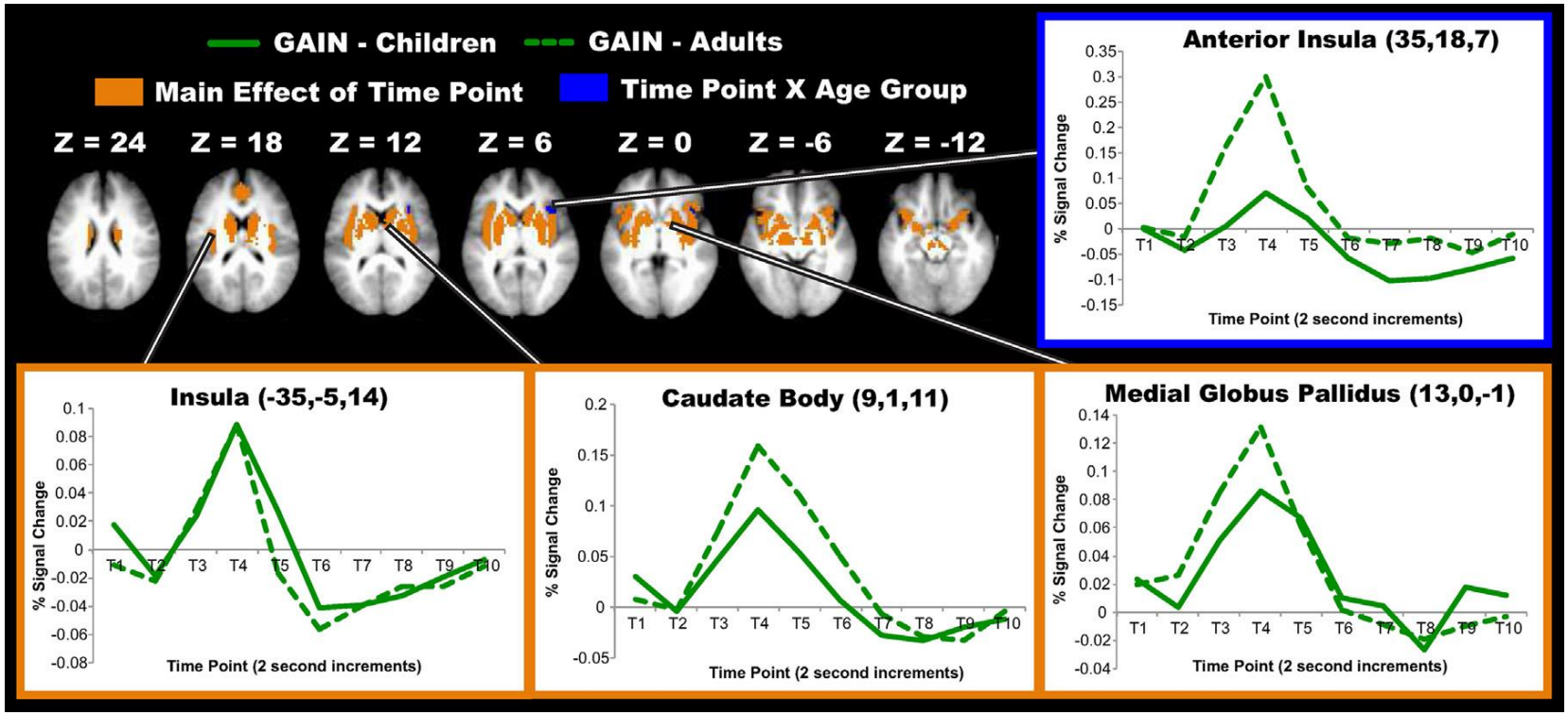


Figure 3.3: Regions Identified In The Time Point × Age Group ANOVA – Gain Trials

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.

fMRI effects of behavior

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 relation with activation in any ROI (see Supplemental Table S3.5). However, Strategy did show a direct effect on activation within the caudate/thalamus and the relation 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 Figure 3.6A). 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 Figure 3.6B) and lack of loss-related deactivation within the hippocampus even when controlling for behavior.

3.4 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 relations 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.

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 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 & 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 1970, Cassotti et al 2011, Crone et al 2005, van den Bos et al 2012) (relations 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 & Pike 2009, Hua et al 2011). Further, although it seems that the hemodynamic response shape, including the BOLD under-shoot, 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 relation 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 & 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,

Delgado et al 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 inactivation patterns is not well understood.

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 & 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.

Relations 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 relation 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.

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 pat-terns 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 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 relations 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.

3.5 Supplemental Material

Individual Difference Measures

Adults and children were administered a variety of individual difference questionnaires that are not the focus of the current report. To assess depressive symptoms at time of scan, adults completed the Beck Depression Inventory, while child participants and parents completed the Child Depression Inventory (child and parent versions respectively) (Beck et al 1996, Kovacs 1985). Children and adults were administered the child/adult versions of the Behavioral Inhibition/Behavioral Activation Scale (Carver & White 1994) and Positive Affect Negative Affect Scales (Watson et al 1988). Adults also completed the Chapman Anhedonia Scales (Chapman et al 1976); the Snaith Hamilton Pleasure Scale (Snaith et al 1995); and the Adult Behavior Checklist (Achenbach 1997). Parents completed the Adult Behavior Checklist, the Child Behavior Checklist, and the Tanner Pubertal Scale Questionnaire (Achenbach 1991, Achenbach 1997, Carskadon & Acebo 1993, Petersen et al 1988). Children also completed the Short Mood and Feelings Questionnaire (Angold et al 1995).

Signal Quality Checks

The Orbital Frontal Cortex (OFC) is notorious for signal dropout problems. Because signal quality issues may differ between the two age groups, we examined signal quality in each group independently and then used that information to constrain our analyses. Each participant's anatomical average was thresholded such that all voxels with signal above 500 were assigned a value of one. Thresholded anatomical averages from each participant in the child (n=18) and adult (n=18) groups were summed resulting in two maps depicting the number of adult participants (Supplemental Figure S3.2A) and child participants (Supplemental Figure S3.2B) with signal above 500 for each voxel. Signal was particularly poor in the OFC within the child

group compared to the adult group (Supplemental Figure S3.2C). Thus, although the OFC is a critical component of reward processing circuitry, we felt that the asymmetry in data quality between the age groups would bias our analyses and masked all voxel-wise ANOVA analyses to only include voxels where at least 12 of the 18 participants in both the child and adult groups had sufficient signal quality (Supplemental Figures S3.2/S3.4). To further evaluate signal quality, we inspected timecourses for each individual within each ROI and any individual for whom % signal change at TR 1 was beyond 0.2% above/below zero was flagged as having poor signal quality. The repeated measures ANOVA that identified that region was then recalculated within that ROI excluding participants meeting the poor signal quality criterion. We only report regions where the interaction originally identifying that region remained significant ($p<0.01$) following exclusion for poor signal quality. This process ensured that outliers showing poor signal quality did not drive the interaction identifying a given ROI.

AlphaSim Parameters

AlphaSim simulations were conducted with smoothing of 2 voxels and 1,000 iterations. A false-positive rate of $p < 0.01$ was investigated. The *a priori* reward mask, where 2/3 of children and 2/3 of adults had sufficient signal quality, consists of 2844 voxels.

Mediation Analyses

To evaluate the extent to which the Time Point X Age Group interaction reported in the ANOVAs above was mediated by behavior, we conducted post-hoc mediation analyses within regions showing a significant interaction between Age Group and Time Point (Time Point X Age Group ANOVAs using gain/loss trials). Specifically, we employed the "indirect" SPSS macro by Preacher and Hayes using activation (% signal change for gain trials [Gain ANOVA ROIs] or loss trials [Loss ANOVA ROIs]) at peak response (mean of time points 4/5) and return to

baseline (mean of time points 7/8) as dependent variables in two sets of simple mediation analyses (Preacher & Hayes 2008). For both analyses Age Group (dummy variable coded as adults=0, children=1) served as the independent variable. The difference in staying post HG and post HL feedback (referred to as "Strategy") was included as a mediator. The proportion of "stay" choices across all feedback types/trials (referred to as "Stay") and mean reaction time (msec) across all feedback types/trials (referred to as "Mean RT") were included as covariates (see Supplemental Figure S3.5 for path diagram). This analysis structure allowed for quantification of Age Group's effect on activation both directly (path c) as well as indirectly through the mediators (path c`). Further, the indirect effect can be broken down into the direct effect of Age Group on the mediator and the direct effect of the mediator on activation partialing out the effect of Age Group. For all regions 95% bias corrected confidence intervals (CIs) were investigated utilizing 5000 bootstrap samples.

Supplemental Table S3.1
Number of Child-Adult Pairs with 3, 4, 5 or 6 Usable BOLD Runs

	3 BOLD Runs	4 BOLD Runs	5 BOLD Runs	6 BOLD Runs
Child Adult Pairs with Given number of BOLD Runs	2	4	1	11
Age Range of Child(ren)	8-9	7-10	8	7-11
Mean Age (Standard Deviation) of Child(ren)	8.5 (.707)	8.33(1.53)	8	9.18(1.17)

Supplemental Table S3.2
Reaction Times for Age Groups

	Total N	Reaction Time (msec) post Gain Feedback mean (st dev)	Reaction Time (msec) post Neutral Feedback mean (st dev)	Reaction Time (msec) post Loss Feedback mean (st dev)
All Participants	36	640 (164)	621 (158)	631 (157)
Child Age Group	18	741 (154)	715 (154)	738 (136)
Adult Age Group	18	539 (101)	526 (92)	523 (87)

Supplemental Table S3.3
Post Scan Questionnaire Ratings

	N	Minimum	Maximum	Mean	Standard Deviation
How did you feel when you lost candy?					
ADULTS	14	-2	0	-1.00	0.56
CHILDREN	14	-2	1	-0.64	0.93
How did you feel when you won candy?					
ADULTS	14	1	2	1.50	0.52
CHILDREN	14	0	2	1.71	0.61

Supplemental Table S3.4

Regions Showing a Main Effect of Time Point - From Gain/Loss Time Point X Age Group ANOVAs

	Talairach Coordinates			Cluster Size	Laterality	Region Name	BA	Activation Type
	X	Y	Z					
LOSS - Main Effect of Time Point ROIs	1	37	19	42	R	Anterior Cingulate	32	A
	-16	-19	21	12	L	Caudate Body		A
	-11	5	9	66	L	Caudate Body		A
	-10	-8	18	33	L	Caudate Body		A
	8	8	11	78	R	Caudate Body		A
	-34	13	7	92	L	Claustrum		A
	-32	-3	-5	31	L	Claustrum		A
	29	15	14	15	R	Claustrum		A
	35	11	5	42	R	Claustrum		A
	38	-9	-3	45	R	Claustrum		A
	-35	16	-7	58	L	Inferior Frontal Gyrus	47	A
	45	17	-2	31	R	Inferior Frontal Gyrus	47	A
	-43	-2	1	41	L	Insula	13	A
	-36	-20	8	48	L	Insula	13	A
	-34	-7	14	56	L	Insula	13	A
	31	20	3	42	R	Insula		A
	38	-7	12	42	R	Insula	13	A
	42	5	0	35	R	Insula		A
	-18	-6	11	24	L	Lateral Globus Pallidus		A
	-16	-1	-7	16	L	Lateral Globus Pallidus		A
	15	0	2	42	R	Lateral Globus Pallidus		A
	-13	-12	-6	27	L	Midbrain/Brainstem		A
	-6	-24	-14	41	L	Midbrain/Brainstem		A
	8	-12	-6	17	R	Midbrain/Brainstem		A
	9	-24	-12	39	R	Midbrain/Brainstem		A
	-22	8	10	59	L	Putamen		A
	-18	14	1	32	L	Putamen		A
	21	-12	8	23	R	Putamen		A
	22	10	4	90	R	Putamen		A
	29	-23	-2	12	R	Putamen		A
	39	2	-12	44	R	Superior Temporal Gyrus	38	A
	11	-9	17	49	R	Thalamus		A
	14	-20	19	21	R	Thalamus LPN		A
	37	-20	5	25	R	Claustrum		D
GAIN - Main Effect of Time Point ROIs	-21	-2	-9	79	L	Amygdala		A
	3	38	19	66	R	Anterior Cingulate	32	A
	9	1	11	87	R	Caudate Body		A

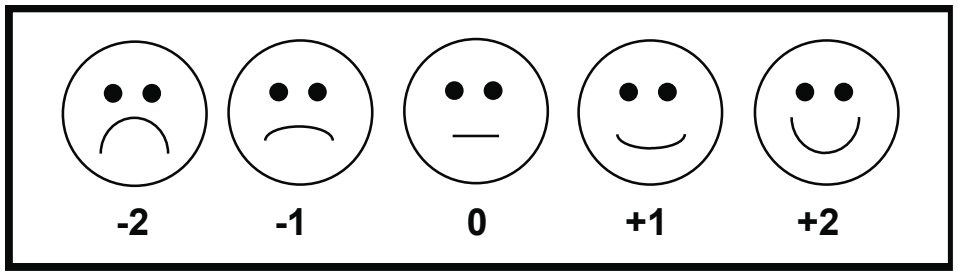
	13	-15	19	56	R	Caudate Body		A
	14	15	12	75	R	Caudate Body		A
	-14	-19	20	18	R	Caudate Tail		A
	29	21	5	20	R	Claustrum		A
	36	-2	13	89	R	Claustrum	13	A
	-6	-3	-12	18	L	Hypothalamus		A
	-41	17	-4	43	L	Inferior Frontal Gyrus	47	A
	-31	13	-11	58	L	Inferior Frontal Gyrus	13	A
	33	16	-15	59	R	Inferior Frontal Gyrus	47	A
	42	22	-1	32	R	Inferior Frontal Gyrus	47	A
	-43	-7	3	54	L	Insula	13	A
	-42	5	-4	39	L	Insula	13	A
	-35	-25	14	44	R	Insula	13	A
	-35	-5	14	58	R	Insula	13	A
	-31	12	11	73	L	Insula	13	A
	27	14	13	22	L	Insula		A
	35	-25	18	25	L	Insula	13	A
	39	9	5	81	R	Insula	13	A
	13	0	-1	28	R	Medial Globus Pallidus		A
	-5	-24	-13	40	L	Midbrain/Brainstem		A
	8	-23	-12	52	L	Midbrain/Brainstem		A
	-14	-10	-9	30	L	Parahippocampal Gyrus	28	A
	15	-8	-9	13	R	Parahippocampal Gyrus	28	A
	-30	-23	-2	36	L	Putamen		A
	-28	-13	-3	57	L	Putamen		A
	-26	-2	10	50	L	Putamen		A
	-22	-10	6	47	L	Putamen		A
	-19	8	7	169	L	Putamen		A
	20	1	-8	61	R	Putamen		A
	21	-3	8	76	R	Putamen		A
	24	10	2	68	L	Putamen		A
	29	-21	5	56	R	Putamen		A
	32	-12	-3	98	R	Putamen		A
	-33	3	-10	22	L	Superior Temporal Gyrus	38	A
	-11	-7	15	85	R	Thalamus		A

BA = Brodmann Area A = Activation
Cluster Size is in voxels D = Deactivation

Supplemental Table S3.5

Mediation Analyses within Time Point X Age Group ROIs

	Talairach Coordinates				Y = % change at Peak Response (mean TRs 4 and 5)									
					Direct Effect of Strategy (path b)		Direct Effect of Age Group (path c`)		Indirect Effect of Age Group on Activation through Strategy (pathc) - Bootstrap Statistics					
	X	Y	Z	Region Name	Coefficient	P-value	Coefficient	P-value	Data	Boot	Bias	SE	95 % CI Lower Limit	95 % CI Upper Limit
LOSS - Time Point x Age Group ROIs	-38	-13	-5	Insula	-0.06	0.223	0.05	0.129	-0.01	-0.01	0.00	0.01	-0.05	0.00
	-33	-16	17	Insula	-0.06	0.229	0.06	0.077	-0.01	-0.01	0.00	0.01	-0.06	0.01
	36	2	13	Insula	-0.04	0.477	0.10	0.006	-0.01	-0.01	0.00	0.01	-0.05	0.01
	35	-23	17	Posterior Insula	-0.06	0.222	0.05	0.106	-0.01	-0.01	0.00	0.01	-0.05	0.01
	-34	-27	13	Posterior Insula	-0.05	0.271	0.05	0.108	-0.01	-0.01	0.00	0.01	-0.06	0.01
	37	16	6	Anterior Insula	0.02	0.884	-0.12	0.245	0.00	0.01	0.01	0.04	-0.06	0.14
	11	8	6	Caudate Body	-0.13	0.041	-0.08	0.074	-0.02	-0.02	0.00	0.02	-0.08	0.01
	-11	-5	13	Thalamus VAN	-0.23	0.000	-0.07	0.074	-0.03	-0.04	0.00	0.03	-0.11	0.01
	-24	-14	-13	Hippocampus	0.01	0.944	0.13	0.017	0.00	0.00	0.00	0.02	-0.03	0.05
	20	-15	-14	Parahippocampal Gyrus	-0.04	0.592	0.08	0.097	-0.01	-0.01	0.00	0.02	-0.07	0.01
GAIN - Time Point x Age Group ROI	35	18	7	Anterior Insula	-0.07	0.672	-0.14	0.263	-0.01	0.00	0.01	0.05	-0.14	0.06
	Talairach Coordinates				Y = % change at Peak Response (mean TRs 7 and 8)									
					Direct Effect of Strategy (path b)		Direct Effect of Age Group (path c`)		Indirect Effect of Age Group on Activation through Strategy (pathc) - Bootstrap Statistics					
	X	Y	Z	Region Name	Coefficient	P-value	Coefficient	P-value	Data	Boot	Bias	SE	95 % CI Lower Limit	95 % CI Upper Limit
LOSS - Time Point x Age Group ROIs	-38	-13	-5	Insula	0.03	0.513	0.05	0.079	0.00	0.00	0.00	0.01	0.00	0.04
	-33	-16	17	Insula	-0.02	0.656	0.04	0.145	0.00	0.00	0.00	0.01	-0.03	0.01
	36	2	13	Insula	0.02	0.621	0.06	0.018	0.00	0.00	0.00	0.01	-0.01	0.04
	35	-23	17	Posterior Insula	0.00	0.908	0.05	0.062	0.00	0.00	0.00	0.01	-0.02	0.01
	-34	-27	13	Posterior Insula	-0.02	0.704	0.03	0.279	0.00	0.00	0.00	0.01	-0.03	0.01
	37	16	6	Anterior Insula	0.15	0.076	0.00	0.954	0.02	0.03	0.00	0.03	-0.01	0.14
	11	8	6	Caudate Body	0.11	0.082	-0.02	0.671	0.02	0.02	0.00	0.02	-0.01	0.11
	-11	-5	13	Thalamus VAN	0.15	0.027	-0.02	0.619	0.02	0.03	0.00	0.03	-0.01	0.11
	-24	-14	-13	Hippocampus	0.03	0.591	0.05	0.188	0.00	0.00	0.00	0.01	-0.01	0.04
	20	-15	-14	Parahippocampal Gyrus	0.06	0.308	0.07	0.109	0.01	0.01	0.00	0.01	-0.01	0.06
GAIN - Time Point x Age Group ROI	35	18	7	Anterior Insula	0.10	0.505	-0.10	0.326	0.01	0.02	0.00	0.04	-0.02	0.21



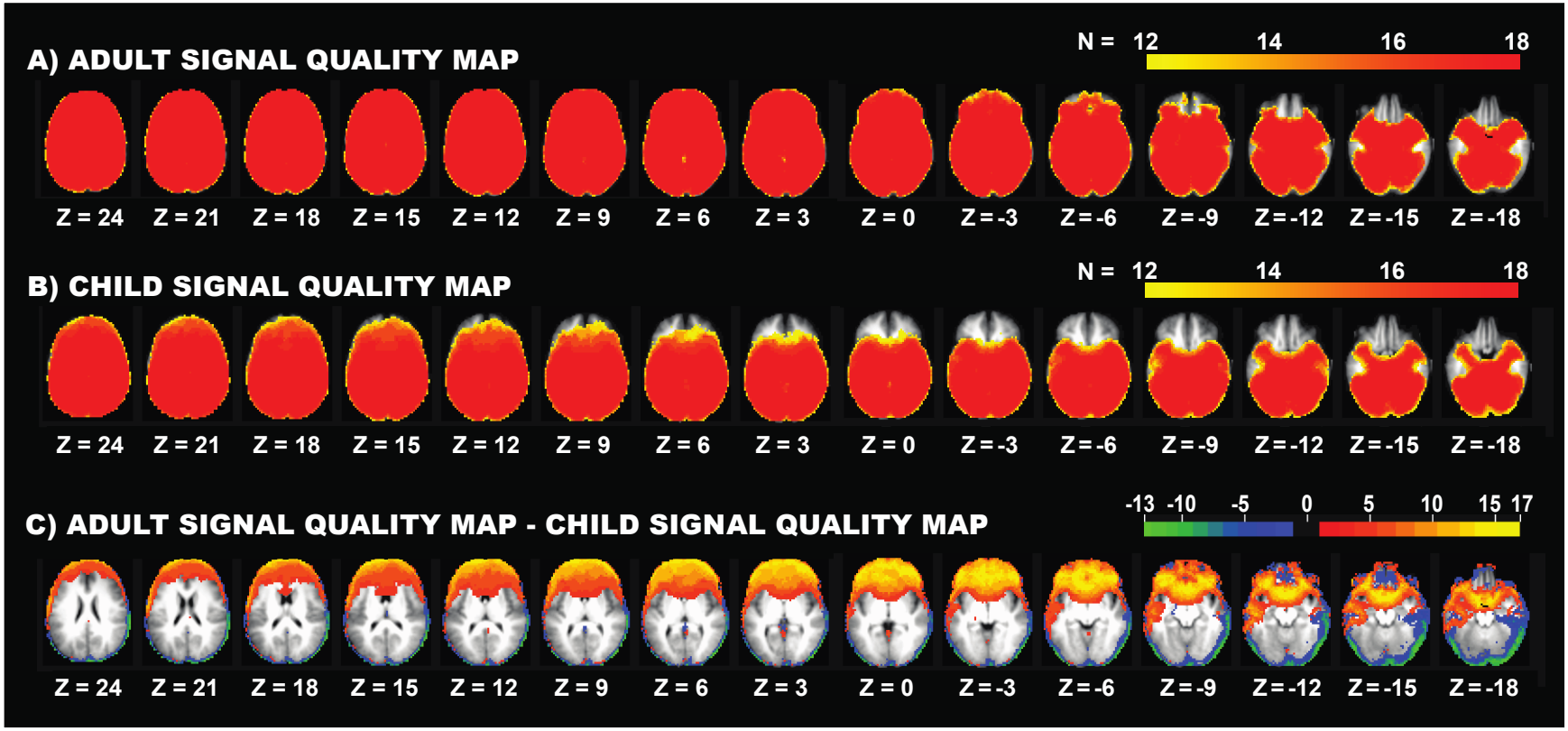
Supplemental Figure S3.1

Post-Scan Questionnaire Response Options

Participants were instructed to "Circle the face that applies for each question"

1) "How did you feel when you won candy?"
2) "How did you feel when you lost candy?"

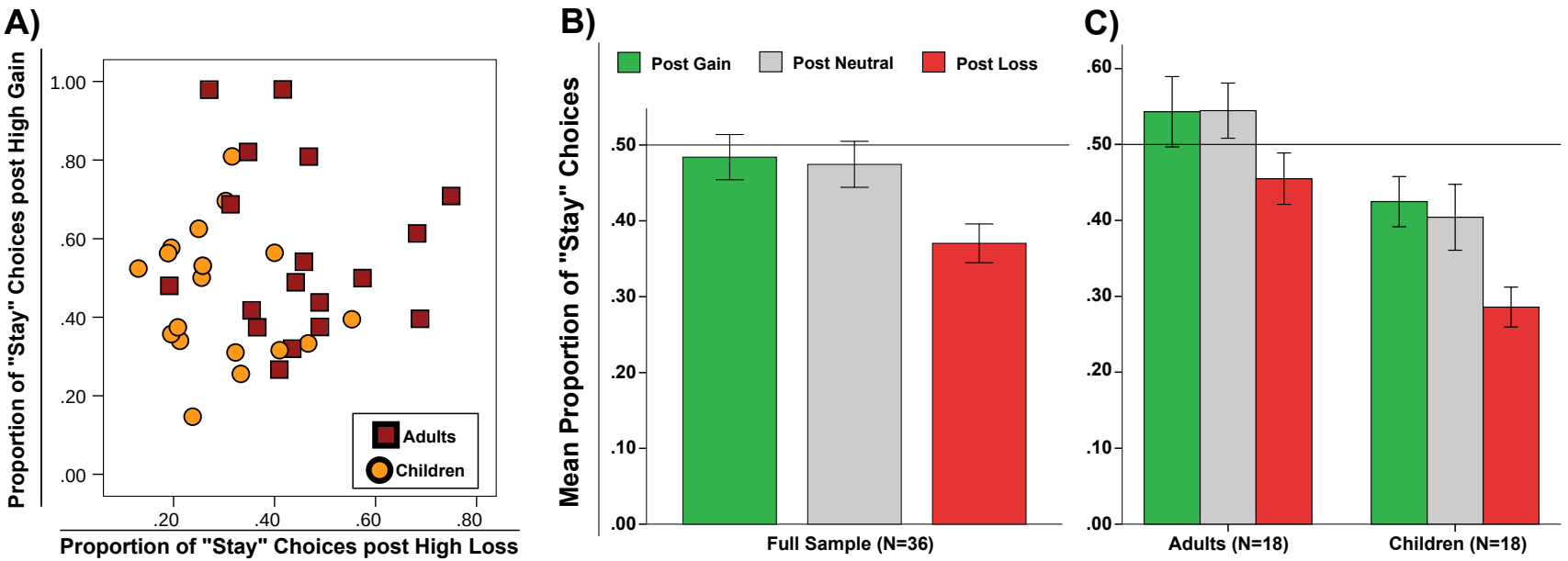
For analysis face responses were coded as having values from -2 to 2 for the most negative to most positive respectively. Participants were not asked to rate feelings following neutral feedback.



Supplemental Figure S3.2

Signal quality in adult and child age groups

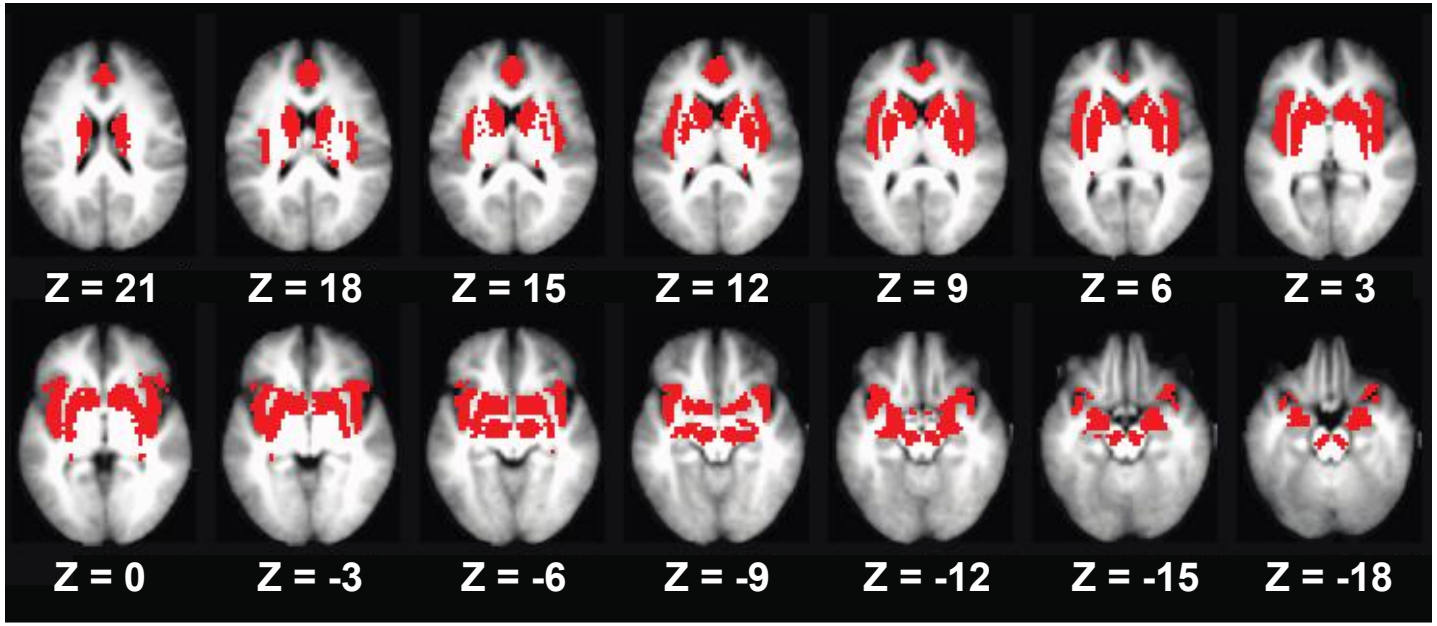
Maps represent the number of (A) adults and (B) children with sufficient signal quality (anatomical average > 500) for each voxel. (C) represents the difference between the adult signal quality map (A) and child signal quality map (B) such that positive values indicate greater signal quality in the adult age group and negative values indicate greater signal quality in the child age group. Children systematically showed reduced signal quality compared to adults within the orbitofrontal and ventral prefrontal cortices as well as in the ventral striatum. Interestingly, children had better signal quality than adults within the most posterior/ventral aspects of the occipital lobe and cerebellum.



Supplemental Figure S3.3

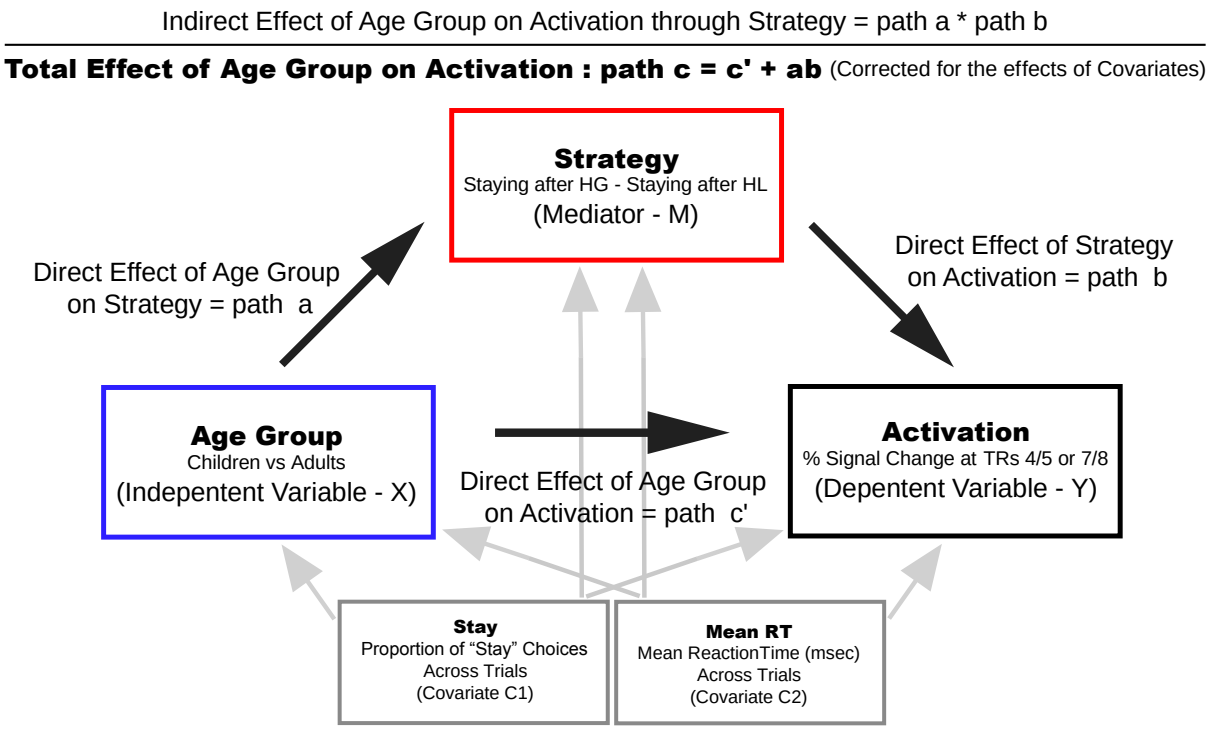
Stay/Shift Choice Behavior Following all Feedback Types

A) There was a wide range of guessing behavior within each age group. B) Stay versus shift behavioral choices differed based upon the type of feedback received on the previous trial. Overall participants were more likely to repeat the same behavioral choice following gain feedback compared to following loss feedback. C) Adults were more likely to repeat the same behavioral choice across all feedback types compared to children. Bars represent +/- one standard error of the mean.

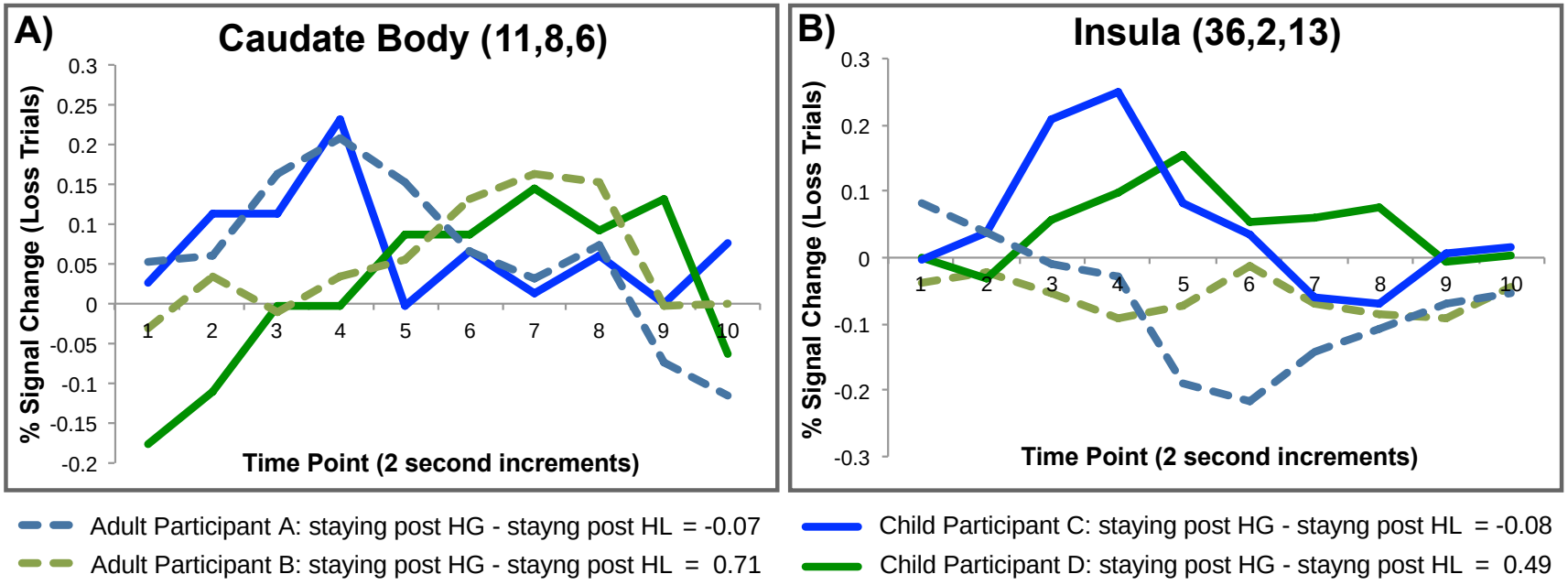


Supplemental Figure S3.4
A priori Reward Mask
A priori Reward Mask including reward regions from (Beck et al 2010) masked to only include voxels where at least 2/3 of children and at least 2/3 of adults had sufficient signal quality.

Mediation Analysis Model



Supplemental Figure S3.5
Mediation analysis model
Independent variable (X) = Age Group (children=1, adults=0)
Mediator = Strategy (proportion of stay choices post High Gain – proportion of stay choices post High Loss)
Covariate 1 (C1) = Stay (proportion of "stay" choices across all trials/feedback types)
Covariate 2 (C2) = Mean RT (mean reaction time in msec across all trials/feedback types)
Dependent Variable (Y) = % Signal Change at TRs 4/5 or 7/8
Path "a" represents the direct effect of Age Group on Strategy and path "b" represents the direct effect of Strategy on Activation. Path c` indicates the direct effect of Age Group on Activation. Together the product of path a and path b represents the indirect effect of Age Group on Activation through Strategy. The total effect of Age Group on Activation, path c, is comprised of the direct (path c`) and indirect (path a * path b) effects of the independent variable on the dependent variable.



Supplemental Figure S3.6

Representative Loss Time Courses from Individual Participants

Loss time courses from a representative adult (Participant A, dashed blue line) with little difference between the proportion of stay choices post High Gain (Zeff et al) and High Loss (HL), an adult (Participant B, dashed green line) with a large positive difference in staying post HG - HL, a child (Participant C, solid blue line) with little difference in staying post HG and HL, and a child (Participant D, solid green line) with a large positive difference in staying post HG - HL. Both the caudate and insula ROIs showed an interaction with Time Point (loss trials) and Age Group at the voxel-wise level. Mediation analyses showed a direct effect of 'strategy' on activation within the caudate with more WSLS-like participants (larger positive difference in staying post HG – post HL) showing reduced activation at TRs 4/5 (section A). Conversely, a direct effect of age group on activation within the insula was observed even when controlling for task behavior in mediation analyses. Specifically, children showed greater activation at TRs 4/5 than adults (section B).

Chapter 4.

Do Losses Loom Larger For Children Than Adults? Relations Between Age, Behavioral Activation/Inhibition, And Incentive-Related Behaviors

Abstract

The large impact of loss of reward on behavior has been well documented in adult populations. However, whether similarly elevated responsivity to loss relative to gain is observed in children and adults remains unclear. It is also unclear whether relations between incentive-related behavior and self-reported reward/punishment sensitivity are similar across different developmental stages. To investigate this, 7-10-year-old children (N=70) and young adults (N=70) completed the BIS/BAS Scale along with two probabilistic incentive tasks assessing gain approach and loss avoidance behavior. Gain approach behavior did not differ across age groups, however children exhibited significantly more loss avoidance than adults. Relations between self-report measures and behavior were similar across age groups. Participants reporting elevated motivation (BAS drive) showed both elevated gain approach and loss avoidance, where both types of behavior predicted unique variance in BAS drive. Results highlight the often-neglected role of loss responsivity in motivation, and during childhood.

4.1 Introduction

Losses and rewards are among the most potent sources of information guiding how we interact with our environment. Importantly, the pull of rewards and push of punishments differ both across people and across development. Yet, few studies have investigated how *both* gain and loss sensitivity relate to approach/avoidance behaviors and how this varies across the developmental spectrum. Understanding how incentive sensitivity and behavior relate within and across developmental stages has broad implications for public policy, parenting, education, and mental health, as evidence already links incentive sensitivity to a variety of domains including learning, risk for psychopathology, and risk taking within older age groups (Somerville & Casey 2010, Somerville et al 2010, Spear 2011).

The developmental behavioral/neuroimaging literature has focused primarily on response to reward feedback. This literature largely reports similar striatal responses to rewards in children and adults, with responses to reward feedback peaking in adolescence (Galvan et al 2006, Luking et al 2014, Richards et al 2013). However, the few studies investigating negative feedback suggest that responsivity to loss/punishment shows a different developmental trajectory. Specifically, adults show reduced neural response to loss/punishment feedback relative to both children (insula) and to adolescents (striatum and lateral orbitofrontal cortex) (Galvan & McGlennen 2013, Luking et al 2014, van Leijenhorst et al 2006). Further, children show faster learning rates from negative than positive feedback (a pattern which reverses in adulthood) (van den Bos et al 2012) and loss feedback may be better than reward for facilitating response inhibition in childhood (Barringer & Gholson 1979, Costantini & Hoving 1973, Geier & Luna 2012, Getsie et al 1985). Together these results suggest that childhood may be a time of heightened response to loss feedback relative to adulthood as well as relative to reward. However, to our knowledge, no studies have compared behavioral responsivity to both gain and loss of

reward in childhood and adulthood.

There are also important inter-individual differences in incentive responsivity that relate to mental health and functional outcomes. For example, individuals with elevated reward sensitivity are less likely to develop depression (Bress et al 2013a) and show better recovery if they do develop depression (McFarland et al 2006). However, elevated reward responsivity has also been linked to elevated substance use (Loxton & Dawe 2001), risk taking (Galvan et al 2007), manic symptoms (Meyer et al 2001), and reduced cooperation (Skatova & Ferguson 2011). Elevated responsivity to punishment/loss has been linked to anxiety and other mood disorders (Eshel & Roiser 2010, Johnson et al 2003, Muris et al 2005). However, elevated loss/punishment sensitivity can also be beneficial, relating to lower levels of risky behaviors and elevated group contributions during economic games (Galvan et al 2007, Skatova & Ferguson 2011). Investigations of how individual differences in incentive sensitivity relate to behavior across developmental stages may be useful for informing risk trajectories given the importance of incentive sensitivity in risk for/protection from psychopathology, and emerging evidence of developmental differences in the relative importance of these motivations and responses.

Carver and White's1994 Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) Scale has been useful for assessing individual differences in reward and punishment sensitivity. BIS/BAS subscales indexing punishment sensitivity (BIS), reward responsiveness (BAS reward), drive to obtain reward (BAS drive), and fun/sensation-seeking (BAS fun seeking) have been linked to a variety of psychiatric symptoms in children, adolescents, and adults (Colder & O'Connor 2004, Johnson et al 2003, Loxton & Dawe 2001). However, only recently has measurement invariance of the BIS/BAS from childhood through adulthood been tested and established (i.e. the same construct is being measured across ages) by removing specific

items/subscales from Carver and White's original measure that show weak or inconsistent factor loadings/structure across developmental stages (Pagliaccio et al Under Review). Thus, modified BIS/BAS subscales can be calculated from the standardly administered BIS/BAS and are appropriate for studies including multiple developmental stages.

To investigate relations between self-reported BIS/BAS and approach/avoidance behaviors across children and adults, participants completed the BIS/BAS and developmentally-appropriate versions of the probabilistic reward task utilized extensively in adult populations by Diego Pizzagalli and others. Children and adults with elevated anhedonic depressive symptoms (Luking et al Under Review, Pizzagalli et al 2005) show reduced effects of reward on choice behavior during this task. A modified version of this task where punishment (loss of reward) feedback is received in conjunction with the standard reward paradigm, allows for separate investigation of loss avoidance and gain approach behaviors.

Given the extant behavioral and neuroimaging literature reviewed above, we expected that children and adults would display similar levels of gain approach behavior, while children would display enhanced loss avoidance. Further, we expected that elevated self-reported behavioral activation (BAS) would relate to elevated gain approach behavior similarly across development but it was unclear whether or how BAS would relate to loss avoidance. Finally, we predicted that BIS would relate to loss avoidance rather than gain approach behavior.

4.2 Method

Participants

Child (N=70) and young adult (N=70) pairs, matched on sex and ethnicity, were formed from four separate studies investigating gain and loss processing; no matched pairs were excluded. Sample sizes for each of the four studies were determined a priori based on estimates

of power and practicality concerns and in no case were sample sizes/stopping rules based on observed effects. Participants were predominately female (N=41 in each age group) and Caucasian (N=44 in each age group) and were recruited from the St. Louis metropolitan area. Children were 7-10 years old (M=8.5; SD=1.1) and pre-/early-pubertal based on parent report (Petersen et al 1988). Young adults were 18-29 years old (M=20.1; SD=2.1). Young adults and parents provided written consent and children provided written assent in accordance with the Washington University in St. Louis Institutional Review Board.

Procedure and Probabilistic Incentive Learning Tasks (PILT)

Participants completed two modified versions of the probabilistic reward task based on (Heerey et al 2008, Pizzagalli et al 2005), here termed PILT-Positive (PILT-P) and PILT-Negative (PILT-N), to assess gain and loss responsivity respectively (Figure 4.1). Tasks were administered using E-prime (Schneider et al 2012).

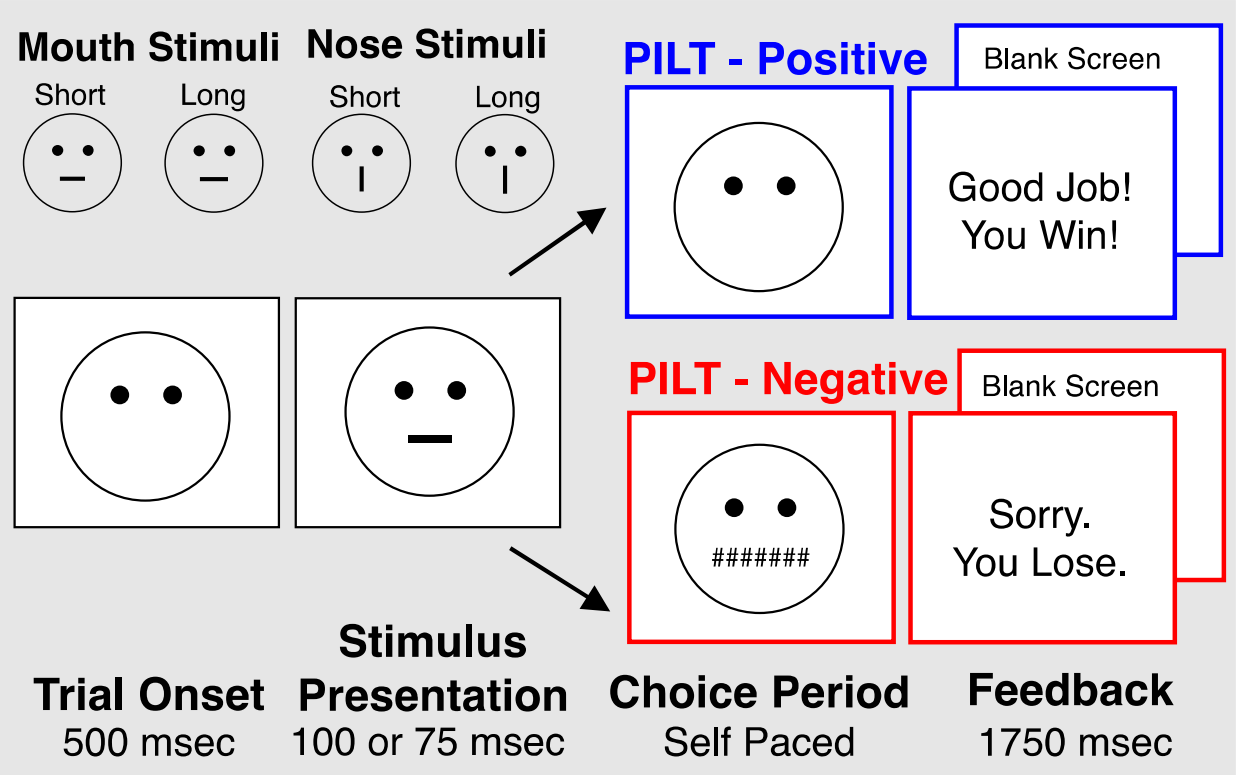


Figure 4.1: Schematic Diagram Of The Progressive Incentive Learning Task (PILT)

The PILT-Positive version where candy/money could be gained is depicted in blue. The PILT-Negative version where candy/money could be lost is depicted in red. Stimuli were presented for 75 msec for adults and 100 msec for children; other task parameters were the same for both age groups.

On each trial, participants performed a perceptual discrimination and indicated whether a long or short stimulus was briefly presented. For the PILT-P, a portion of correct responses received gain feedback while, for the PILT-N, a portion of incorrect responses received loss feedback. Critically, for both tasks, one of the two responses (termed the RICH response) was scheduled to receive three times the amount of feedback as the alternative (LEAN) response. This asymmetry leads healthy, hedonic adults or children to preferentially select the RICH response across PILT-P task blocks (positive response bias) (Luking et al 2015, Luking et al Under Review, Pizzagalli et al 2008a, Pizzagalli et al 2005) and to preferentially avoid the RICH response across PILT-N task blocks (negative response bias) (Luking et al 2015, Luking et al Under Review).

To make the task more developmentally appropriate, children received candy (M&Ms or Skittles) as incentive feedback while adults received monetary incentives. Children earned one candy piece for gain feedback in the PILT-P and lost one candy piece from a 70-piece endowment for loss feedback in the PILT-N. Adults won 5 cents for gain feedback in the PILT-P and lost 5 cents from a $7.00 endowment for loss feedback in the PILT-N. Children completed three blocks of 40 trials (120 total), while adults completed three 60-trial blocks; however, for adults, only the first 120 trials were included in the present analyses to match the children. Not all trials received incentive feedback; specifically, 36 correct/incorrect 'RICH' responses and 12 correct/incorrect 'LEAN' responses were scheduled to receive gain/loss feedback for the PILT-P/PILT-N, respectively. To increase difficulty and thus the number of incorrect responses in the PILT-N, a perceptual mask (row/column of pound signs; see Figure 4.1) was displayed following the nose/mouth stimulus and stimulus presentation time was decreased from 100 to 75 milliseconds for adults. Despite this manipulation, accuracy was relatively high, meaning that the

full number of scheduled incorrect feedback instances did not occur for all participants. Thus, number of feedback instances for both the PILT-P and PILT-N were included as continuous predictors in all analyses.

Nose and mouth stimuli (Figure 4.1) were counterbalanced across tasks for a given participant to minimize learning effects across tasks. The stimulus set used were also counterbalanced across subjects for three studies (one adult and two child) and fixed across subjects for the remaining adult study. Task order was also fixed for the two larger studies (one adult, one child). As such, the majority of participants (85%) completed the PILT-P first and nose stimuli were used during the PILT-P for a majority of adults (84%). The proportion of participants that completed the PILT-P first did not differ across age groups ($X^2(1, N = 140) = 0.50, p = 0.478$); however, the proportion of participants where nose stimuli were used in the PILT-P did differ across age groups ($X^2(1, N = 140) = 0.16.04, p < 0.001$) . Mean discriminability and response bias (formulas below) for the PILT-P/N did not differ significantly based on PILT-P stimulus type or task order (effect of task order on PILT-N discriminability $p = 0.145$, effect of stimulus type on response bias $p = 0.215$ for the PILT-N, remaining $p > 0.250$).

Individual Difference Measures

Children and young adults completed the child and adult version of the Behavioral Inhibition/Behavioral Activation Scale (BIS/BAS) respectively (Carver & White 1994, Muris et al 2005). Mean scores were calculated for the revised, age-invariant subscales (BAS drive, BAS reward, and BIS) (Pagliaccio et al Under Review). It is important to note that while the factor structure, item loadings, thresholds, and unique/residual variances of the revised BIS/BAS showed age invariance, mean differences in all BIS/BAS subscales were still observed across development by Pagliaccio et al., (2015). Possible subscale scores ranged from one to four with a

four indicating the greatest level for the given construct (see Supplemental Table S4.1 for subscale means/items).

Data Processing

As in previous studies (Luking et al 2015, Luking et al Under Review, Pizzagalli et al 2005), individual trials with reaction time (RT) either beyond 150-2500 msec or beyond +/- 3 standard deviations from the participant's mean RT were excluded, after which discriminability and response bias were calculated for each of the three blocks of 40 trials. Greater discriminability (log d) indicates improved ability to distinguish long from short stimuli. Response bias (log b) assesses behavioral responsivity to feedback. Positive values are typically observed during the PILT-P and indicate a greater propensity to select the more frequently rewarded (RICH) stimulus. Negative values are typically observed during the PILT-N and indicate a greater propensity to select the LEAN stimulus, i.e. to avoid the more frequently punished response.

$$Discriminability\ (\log d) = \frac{1}{2}\log\left(\frac{RICHcorrect * LEANcorrect}{RICHincorrect * LEANincorrect}\right)$$

$$Response\ Bias\ (\log b) = \frac{1}{2}\log\left(\frac{RICHcorrect * LEANincorrect}{RICHincorrect * LEANcorrect}\right)$$

Data Analysis

All analyses were conduced using SPSS 20.0.0. Analyses investigating response bias focused on mean or change in bias across the initial (block 1) and final (block 3) task blocks; analyses did not examine block 2 as is typical for studies using the PILT (Luking et al 2015, Luking et al Under Review, Pizzagalli et al 2005).

Relations among individual difference measures and differences by age group

Correlations between BIS, BASd, and BASr were conducted within each age group

(Supplemental Table S4.1). Independent samples t-tests were conducted to test for differences in BIS/BAS levels across age groups. As there was no strong evidence for differential/specific relations between BASd versus BASr and approach/avoidance behavior and given the strong intercorrelation (collinearity) between these subscales, subsequent analyses were conducted in parallel using either BASd or BASr. As qualitatively similar results were observed for the two sets of analyses, results with the BASd are presented in the main text and BASr analyses are displayed in Supplemental Materials available online.

Effects of age group and individual differences on response bias

Repeated measures ANOVAs were conducted to investigate how response bias differed across tasks, blocks, groups, BIS, and behavioral activation (one ANOVA included the BAS drive subscale [main text] and one included the BAS reward sensitivity subscale [supplement]). Task (PILT-P, PILT-N) and Block (first block – block 1, last block – block 3) served as the within-subject repeated measures; main effects of Task Type and Task Type by Block interactions were investigated. Age Group (children=0; adults=1) and PILT-P stimulus type (nose=0; mouth=1) served as between-subjects factors. BAS (drive or reward), BIS, number of PILT-P and PILT-N feedback events were included as continuous predictors. Given our hypotheses regarding age and behavioral inhibition/activation, we focus on main effects and interactions of these factors with Task Type and Task Type by Block.

Post-hoc regressions (for the whole sample and split by age) were preformed to determine sources/directions of significant effects in the repeated measures ANOVA. In post-hoc regression analyses, mean response bias (block 1, block 3) for each task was used as a dependent measure to parse main effects and interactions with Task Type while response bias change (block 3 – block 1) for each task was used to parse interactions of Task Type and Block. Age Group,

PILT-P stimulus type, BIS, BAS, and the number of feedback instances were included as predictors.

Effects of age group on speed and accuracy following feedback

Post-feedback slowing and decreases in accuracy are commonly observed where the degree of slowing tends to be largest following incorrect feedback and in some studies is proportional to an individual's processing/sensitivity to that feedback (Notebaert et al 2009). To further test whether losses loom larger for children than adults on other metrics beyond response bias, we conducted two repeated measures ANOVAs to examine group differences in 1) reaction time and 2) accuracy based on previous trial feedback (versus no feedback) and Task Type. Task (PILT-P, PILT-N) and Feedback (feedback, no feedback) served as within-subject repeated measures. For the PILT-P, the factor 'Feedback' included speed/accuracy averaged across trials following *correct* responses that received either gain feedback or no feedback while for the PILT-N the factor 'Feedback' included speed/accuracy averaged across trials following an *incorrect* response. Age Group and PILT-P Stimulus Type served as between-subjects factors. Post-hoc independent samples t-tests were conducted to determine the source and direction of significant interactions. A Bonferronni correction for multiple comparisons (0.05/4=0.0125) was used to determine significance for effects/interactions from the 4 main ANOVAs.

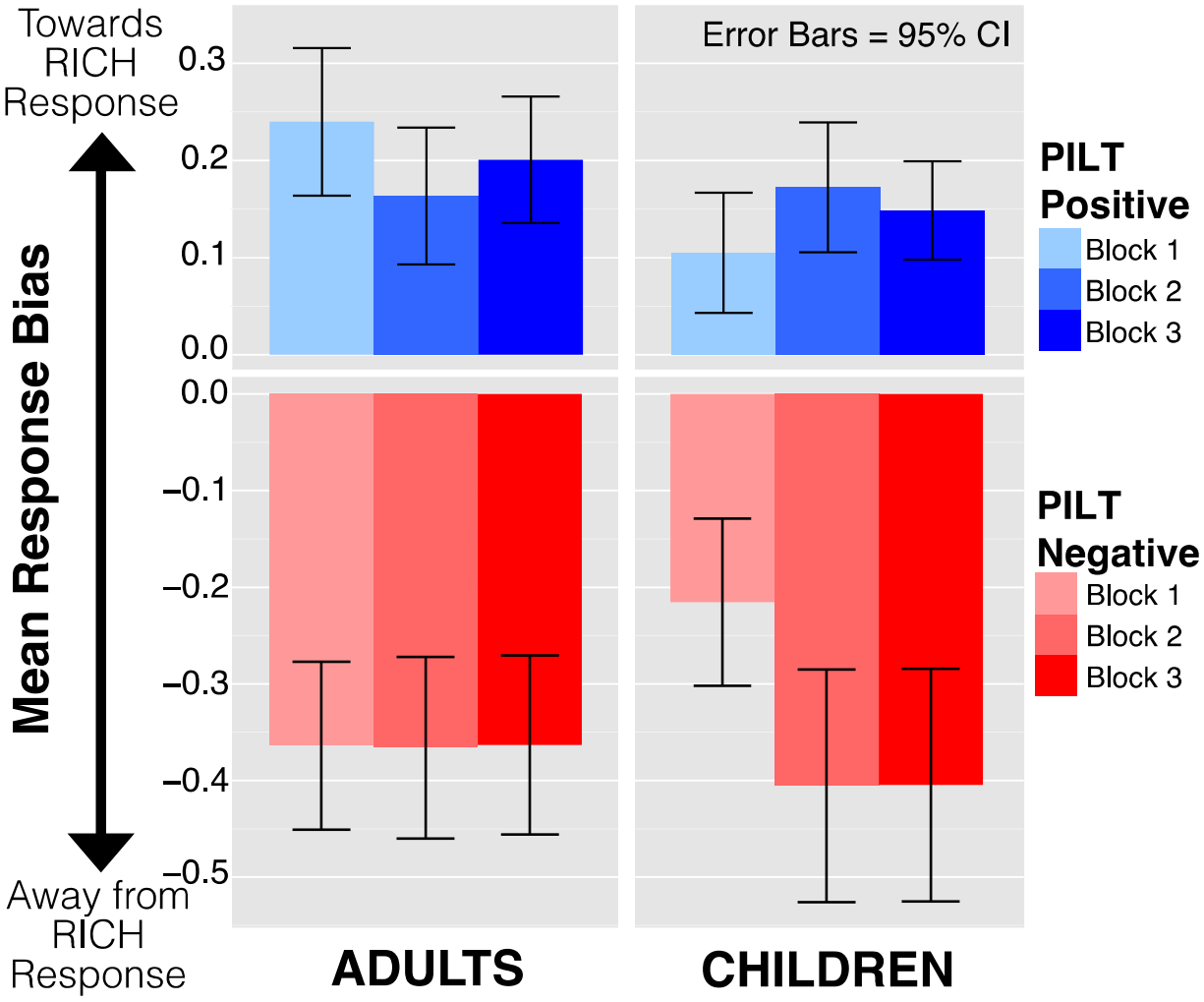


Figure 4.2: PILT-Positive And PILT-Negative Response Bias
Response bias (log b) within each block of 40 trials during the PILT-Positive (blue) and PILT-Negative (red) for adults and children.

4.3 Results

Do Children and Adults Show Similar Levels of/Relations Between Behavioral Inhibition and Behavioral Activation?

Both children and adults showed strong positive relations between BASd and BASr (all $p \leq 0.001$), neither of which significantly related to BIS (all $p > 0.250$). Further, adults reported significantly higher scores on all subscales relative to children (BIS and BASr $p < 0.001$; BASd $p = 0.042$). See Supplemental Table S4.1 for intercorrelations and BIS/BAS descriptive statistics by group.

Do Losses Loom Larger For Children Than Adults?

Results from the repeated measures ANOVA investigating relations between response bias and Age Group are shown in Table 4.1 and Supplemental Table S4.2, post hoc regressions are shown in Table 4.2 and Supplemental Table S4.3. Children and adults both developed response biases that significantly differed from zero, such that both groups learned to preferentially select the more frequently rewarded RICH response during the PILT-P and to avoid the more frequently punished RICH response during the PILT-N (Figure 4.2). However, both mean response bias and response bias change (difference between the last and first block) differed by Age Group (main effect of Age Group and interaction of Task Type, Block, and Age Group in Table 4.1 and Figure 4.3A). Specifically, relative to adults, children showed both elevated mean levels of loss avoidance (more negative response bias) as well as a greater shift in loss avoidance (more negative change in response bias from the first to last block) across the PILT-N (Table 4.2, Supplemental Table S4.3). However, no significant effects of age were observed for PILT-P mean bias or bias change (Table 4.2, Supplemental Table S4.3). Further, in the child group, PILT-N mean response bias was over twice that of the PILT-P (estimated

marginal means [standard error]; PILT-N = -0.43 [0.04], PILT-P = 0.19 [0.02]) while PILT-N and PILT-P mean response bias were of similar size for adults (estimated marginal means [standard error]; PILT-N = -0.30 [0.05], PILT-P = 0.23 [0.03]). Together these results suggest that children and adults show similar levels of gain approach behavior, but that children show enhanced loss avoidance relative to adults, i.e. losses loom larger for children than adults.

Table 4.1: Repeated Measures ANOVA Investigating Effects Of Age, Task Type, Block, BIS, And BAS On Response Bias

Interaction Type and Factor/Predictor	F-Statistic	Partial η^2	p-value
Main Effects			
Task Type	0.27	0.002	0.608
Age Group	13.32**	0.091	<0.001
BAS Drive	6.24	0.045	0.014
BIS	0.08	0.001	0.782
Two-Way Interactions with Task Type			
Block	7.21*	0.051	0.008
Age Group	2.26	0.017	0.135
BAS Drive	2.90	0.021	0.091
BIS	<0.01	<0.001	0.986
Three-Way Interactions with Task Type and Block			
Age Group	6.86*	0.049	0.010
BAS Drive	8.82*	0.062	0.004
BIS	1.18	0.009	0.280

Note: BAS = Behavioral Activation Scale, BIS = Behavioral Inhibition Scale. See Table S2 in the Supplemental Material available online for full ANOVA results. *$p<0.0125$ **$p\leq0.001$

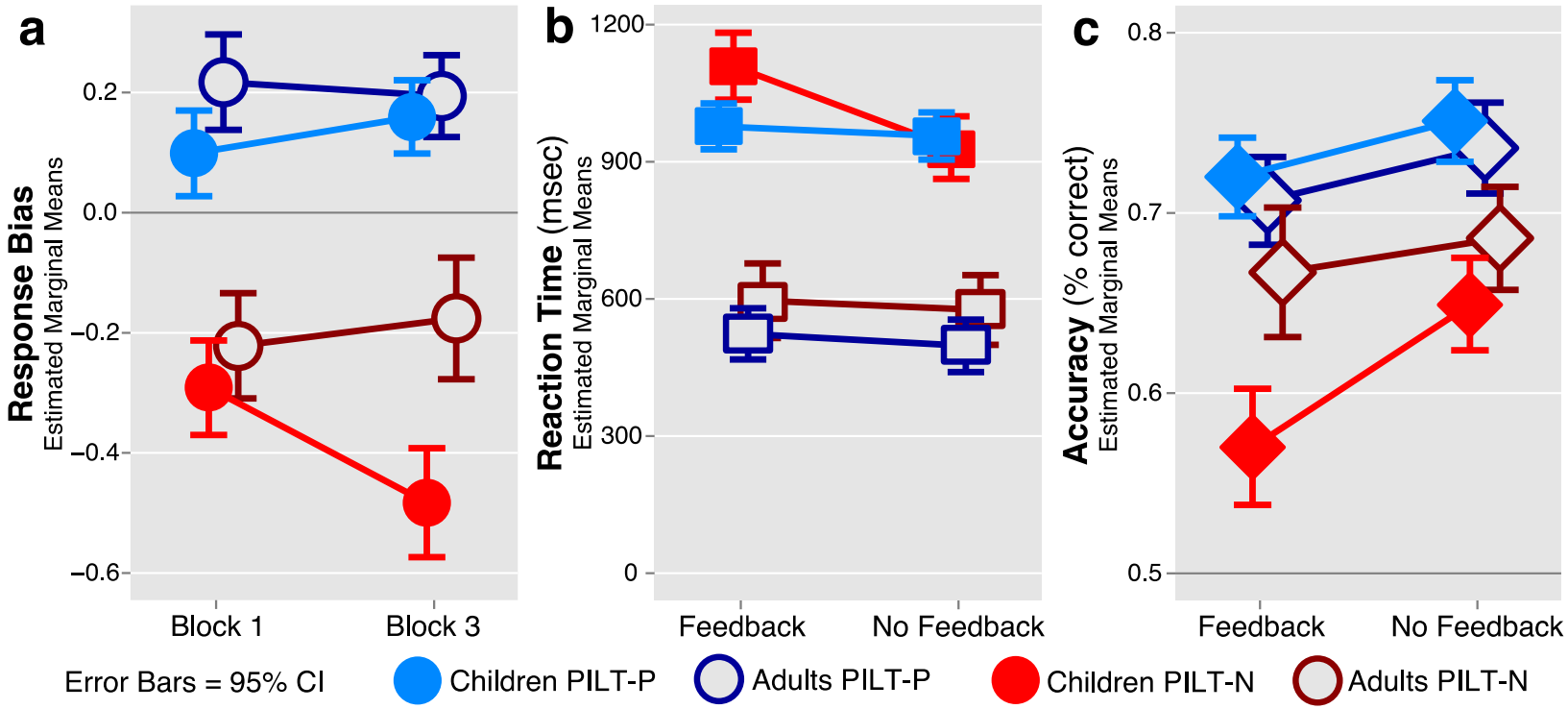


Figure 4.3: Relations Between Age Group And Behavior

Estimated marginal means from repeated measures ANOVAs investigating a) response bias, b) mean reaction time, and c) mean accuracy during the PILT-Positive (PILT-P) in blue and PILT-Negative (PILT-N) in red. Values are controlled for Stimulus Type and Feedback Amount are presented in all panels; panel A values are also controlled for BIS and BASd. Darker colors and open markers represent values for the adult group, brighter colors and solid markers represent child group values.

Table 4.2: Post Hoc Regressions Predicting Mean Response Bias And Response Bias Change For The PILT-Positive (PILT-P) And PILT-Negative (PILT-N)

Dependent Variable and Predictors	b	β	t-statistic	p-value
PILT-P Mean Response Bias				
Age Group	0.07	0.17	1.65	0.102
BIS	-0.01	-0.02	-0.18	0.860
BAS Drive	-0.02	-0.06	-0.73	0.466
PILT-P Response Bias Change				
Age Group	-0.03	-0.05	-0.46	0.644
BIS	-0.06	-0.13	-1.27	0.206
BAS Drive	0.12	0.26	3.10*	0.002
PILT-N Mean Response Bias				
Age Group	0.23	0.31	3.40*	0.001
BIS	-0.02	-0.03	-0.41	0.686
BAS Drive	-0.10	-0.20	-2.87*	0.005
PILT-N Response Bias Change				
Age Group	0.28	0.37	3.37*	0.001
BIS	-0.01	-0.02	-0.19	0.849
BAS Drive	-0.08	-0.15	-1.82	0.071

Note: PILT = Probabilistic Incentive Learning Task, Age Group = 0-Children vs. 1-Adults, BIS = Behavioral Inhibition Scale, BAS = Behavioral Activation Scale, b = unstandardized beta, β = standardized beta. Step 2 of Regression Models Reported in Supplemental Table S4.3 *$p<0.0125$ **$p\leq0.001$

Results from the repeated measures ANOVA investigating relations between RT or accuracy and Age Group are shown in Table 4.3 and Supplemental Table S4.4 and post hoc regressions are shown in Supplemental Table S4.5. Relative to adults, children were slower overall (main effect of age group) and age differences in RT further differed based on feedback (two-way interaction of Age Group with Feedback) (Figure 4.3B). The post-hoc regression showed that children were significantly slower to respond than adults post-feedback versus post-no feedback ($\beta = -0.27$, $t = -2.81$, $p = 0.006$; Supplemental Table S4.5). The interaction of Age Group and Feedback also differed across Task Types (three-way interaction of Age Group, Feedback, and Task Type). Post-hoc regressions indicated that children showed exaggerated post-feedback slowing relative to adults following loss feedback ($\beta = -0.31$, $t = -3.30$, $p = 0.001$; Supplemental Table S4.5) but not following gain feedback ($\beta = -0.03$, $t = -0.36$, $p = 0.720$; Supplemental Table S4.5).

Table 4.3: Repeated Measures Anovas Investigating Effects Of Age, Task Type, And Previous Trial Feedback On Reaction Time And Accuracy

Interaction Type and Factor/Predictor	Reaction Time ANOVA			Accuracy ANOVA		
	F-Statistic	Partial η^2	p-value	F-Statistic	Partial η^2	p-value
Main Effects						
Task Type	0.04	<0.001	0.852	11.25*	0.076	0.001
Previous Trial Feedback	2.20	0.017	0.140	1.60	0.011	0.208
Age Group	141.90**	0.458	<0.001	4.71	0.024	0.032
Two-Way Interactions with Task Type						
Previous Trial Feedback	1.34	0.010	0.249	0.02	<0.001	0.889
Age Group	0.23	0.003	0.630	15.99**	0.073	<0.001
Two-Way Interaction with Previous Trial Feedback						
Age Group	7.92*	0.036	0.006	2.77	0.025	0.098
Three-Way Interaction with Task Type and Previous Trial Feedback						
Age Group	7.96*	0.041	0.005	2.91	0.023	0.091

Note: See Supplemental Table S4.4 for full ANOVA results. *$p<0.0125$ **$p\leq0.001$

As intended by the post-stimulus perceptual mask, participants were generally less accurate during the PILT-N than the PILT-P (main effect of task Table 4.3 and Supplemental Table S4.4, Figure 34.C), allowing a necessary increase in incorrect responses that could receive loss feedback (see methods). Task Type also significantly interacted with Age Group; while children were significantly less accurate during the PILT-N than adults ($t(138) = -6.82$, $p < 0.001$, Cohen's $d = -1.15$, $r = -0.50$), accuracy did not significantly differ for children and adults during the PILT-P ($t(138) = -1.39$, $p = 0.166$, Cohen's $d = -0.24$, $r = -0.12$).

Relative to adults during the PILT-N, children showed 1) both more negative response bias and more negative change in response bias, 2) greater slowing post loss feedback than no feedback, 4) greater decreases in general accuracy (Figure 4.3A-C). No significant age differences were observed during the PILT-P for 1) mean response bias or change in response bias, 2) differences in RT following feedback versus no feedback, or 3) differences in accuracy.

Do Individual Differences in Behavioral Inhibition/Activation Predict Incentive-Related Behaviors Across Age?

We used repeated measures ANOVA (Table 4.1, Supplemental Tables S4.2 and S4.6) and post-hoc regressions (Table 4.2, Supplemental Tables S4.3 and S4.7) to test whether individual differences in BIS and BASd predicted behavioral responsivity to incentive feedback and whether this was similar across age groups. A significant main effect of BASd and a significant three-way interaction of BASd with Task Type and Block were observed across the full sample (Table 4.1, Supplemental Table S4.2) as well as within each age group individually (adults $p = 0.017$, children $p = 0.076$; Supplemental Tables S4.6-4.7). In planned follow-up regression analyses, BAS drive was both a significant positive predictor of change in PILT-P response bias ($\beta = 0.26$, $t = 3.10$, $p = 0.002$) and a significant negative predictor of mean PILT-N

response bias (β = -0.20, t = -2.87, p = 0.005) indicating that individuals with elevated BASd show *both* greater increases in gain approach across the PILT-P *and* greater loss avoidance during the PILT-N (Table 4.2 and Supplemental Table S4.3, see Supplemental Table S4.7 for regressions within each age group; Figure 4.4). Importantly, the interaction of Age Group and BASd did not significantly predict response bias for either task (PILT-P change β = 0.46, t = 1.21, p = 0.230; PILT-N mean bias β = -0.04, t = -0.14, p = 0.892; Supplemental Table S4.3). Further, the main effect and interactions with BIS were not significant (all p > 0.250; Tables 4.1-4.2, Supplemental Table S4.3).

Are Gain Approach and Loss Avoidance Behaviors Independent Predictors of BAS Drive?

Given that both PILT-P bias change and PILT-N mean bias significantly related to BASd, we conducted an additional post-hoc regression to investigate whether bias during each task predicted independent or common variance in BASd. Specifically, age group, PILT-P bias change, and PILT-N mean bias were used to predict BASd. Residualized bias scores (controlling for stimulus type and feedback amount) were used as predictors of BASd given that stimulus type/feedback amount were significant predictors of bias in the previous analyses and that our post-hoc question focused on relations between bias and BASd. Regressions without age group were also conducted within each age group.

Interestingly, both PILT-N mean bias (β = -0.25, t = -3.09, p = 0.002, Supplemental Table S4.8) and PILT-P bias change (β = 0.24, t = 3.09, p = 0.003) were significant *unique* predictors of BASd when also controlling for Age Group (Supplemental Table S4.8). Moreover, similar results were observed within each age group separately (Supplemental Table S4.8) suggesting that relations between BASd and PILT-P and PILT-N do not reflect the same underlying process but instead reflect *unique* variance in BASd in both children and adults.

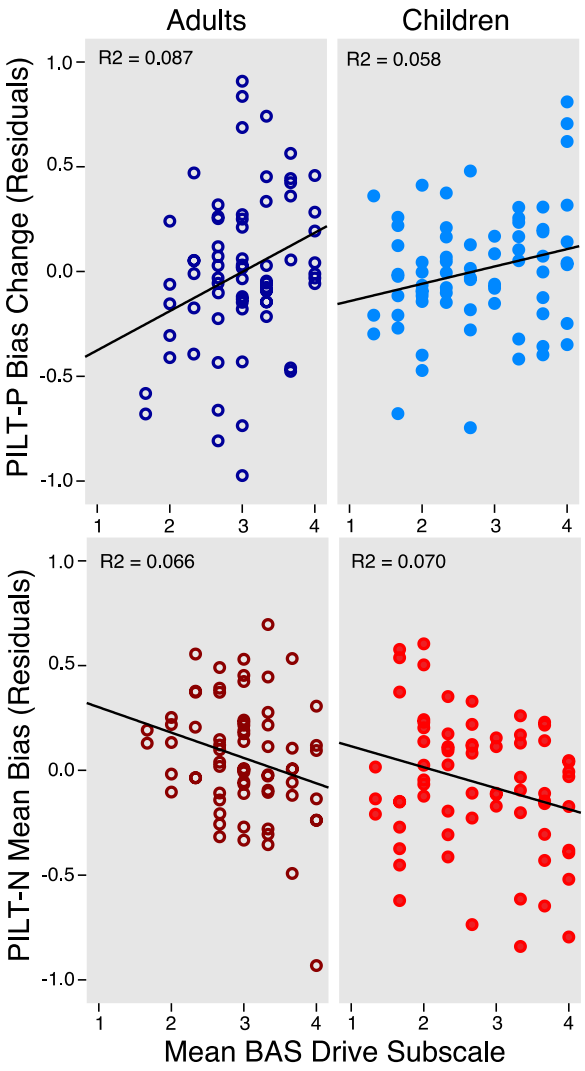


Figure 4.4: Relations Between BAS Drive And Response Bias

Relations between self-reported BAS drive and response bias during the PILT-Positive (PILT-P – blue) and PILT-Negative (PILT-N – red) within each age group. Individual adult values are indicated by darker colors and open markers, individual child values are indicated by brighter colors and closed markers. PILT bias values represent standardized regression residuals controlling for Age Group, Stimulus Type, and Feedback Amount.

4.4 Discussion

Despite a burgeoning literature regarding differences in reward-related behavior from adolescence to adulthood, little is known regarding how loss avoidance differs from childhood to adulthood. We report significantly elevated loss avoidance in children relative to adults, but no significant difference in gain approach between age groups. Across age groups, individuals reporting elevated levels of BASd showed enhanced behavioral responsivity to gain *and* loss feedback. Further, gain approach and loss avoidance predicted *unique* variance in BASd across age groups.

In the past several decades, there has been a shift in parenting and education policy to focus on the benefits of positive feedback while punishment has been discouraged due to damaging effects on self-esteem and the parent-child relationship (Gershoff 2002). However, loss (of reward) as a consequence for unwanted behaviors (or failing to complete wanted behaviors) can be powerful for shaping child behavior without the damaging effects of more active forms of punishment. The current findings suggest that children are quite sensitive to loss feedback and make larger changes in behavior based on this feedback than adults, a pattern mirrored by studies investigating learning rates from positive and negative feedback (Barringer & Gholson 1979, Getsie et al 1985, van den Bos et al 2012). In fact, despite receiving less feedback during the PILT-N than the PILT-P, response bias driven by loss was approximately twice the size of response bias driven by gain in the child group. This suggests that losing something appetitive may be particularly motivating for school-aged children. Importantly, loss feedback appears to be effective in eliciting changes in specific behaviors, but not effective in improving speed and/or overall accuracy, as children showed reduced accuracy during the loss task *and* slower reaction times following loss feedback versus no feedback relative to adults.

These findings could have important implications for informing educational incentives for school-aged children.

Across age groups, participants reporting elevated BASd showed *both* greater gain approach behavior *and* greater loss avoidance and, importantly, each behavior predicted *unique* variance in BASd. The current findings along with the handful of studies linking elevated anhedonia (i.e. reduced experienced pleasure) and blunted responsivity to both positive and negative feedback/stimuli (Chase et al 2010, Dowd & Barch 2010, Luking et al 2015, Steele et al 2007), suggest that reduced drive/hedonic capacity may be better conceptualized as a general deficit in responding to incentive feedback rather than a hypo-responsivity specific to reward. At first glance, this reconceptualization may seem counterintuitive given that questionnaires assessing motivation/hedonic capacity (including Carver & White's BAS) and associated theories tend to focus on response to reward/positive events. However, in the current task elevated gain approach and loss avoidance both lead to similar outcomes, greater net winnings, and thus may both tap into approach motivation constructs.

This reconceptualization has important implications not only theoretically, but also clinically. Motivational/hedonic deficits are experienced across a wide variety of psychiatric disorders and are highlighted in the NIMH's RDoC initiative (Insel et al 2010). Given that gain approach and loss avoidance both predict unique variance in BASd, an interesting future direction will be to investigate whether altered gain approach and/or loss avoidance inform novel distinctions in domains of psychopathology associated with altered motivation/hedonic capacity. It is also interesting that loss avoidance in this task related significantly to motivation but not punishment sensitivity (BIS). It is possible that BIS would more strongly relate to PILT-N behavior if punishments, such as aversive tastes or mild shocks, were delivered instead of loss of

reward, as BIS questions assess responsivity to punishment/negative social outcomes. Future studies investigating *punishment* avoidance along with gain/loss approach/avoidance are needed to evaluate whether BASd specifically predicts behavioral shifts towards appetitive outcomes (irrespective of the valence of feedback driving that behavior) or predicts responsiveness to all outcomes, including punishment.

Relations between self-reported BASd and approach/avoidance behavior are of further interest given that similar patterns were observed in both age groups, suggesting that mechanisms underlying such relations are likely conserved across age. Longitudinal studies are needed to explicitly test this hypothesis. It is also interesting that age differences in BIS/BAS did not explain the observed age differences in behavior. Specifically, *elevated* BASd was related to *elevated* loss avoidance in both children and adults. However while adults displayed *greater* BASd relative to children, they also displayed *reduced* loss avoidance relative to children, thus it is unclear what factor(s) may mediate the observed age difference in loss avoidance. There is some evidence that developmental differences in striatal-prefrontal functional connectivity predicts differences in the relative influence of reward and negative feedback on learning from childhood to adulthood (van den Bos et al 2012). However, future behavioral/neuroimaging studies investigating loss avoidance and gain approach are needed to explore the mechanisms explaining the current age difference, given that responses to negative feedback and loss of reward are not necessarily equivalent.

Limitations

In the current study, incentive feedback was tied to performance on a given trial, which allowed the number of feedback instances to differ, particularly with varying accuracy during the PILT-N. Children were generally less accurate than adults during the PILT-N and received more

loss feedback, which could have influenced age effects. However, as *more* loss feedback related to *reduced* loss avoidance within each group, and that age effects remained when controlling for feedback amounts, it is unlikely that children's *elevated* loss avoidance is explained by larger loss feedback amounts. Another potential limitation is that children and adults received different incentives. Although we feel that this is a stronger approach than offering fixed monetary rewards, which is susceptible to age differences in incentive valuation, future studies using similar incentives are needed to replicate current findings. A final potential limitation is our use of self-reported BIS/BAS as self-report accuracy may differ across age. Importantly, measurement invariance from childhood through adulthood, i.e. whether the same construct is being measured across groups, has been tested and verified for the current BIS/BAS subscales. Further, similar relations between behavior and BIS/BAS self-report were observed in each age group. Thus, it is unlikely that issues with self-report in the child group substantially impacted the current results.

Conclusions

In sum, the current study highlights the often-neglected role of loss feedback from both a developmental and individual differences standpoint. Behavioral responsivity to loss feedback is elevated in children and in individuals with elevated BAS across developmental epochs. Thus, loss feedback may be a particularly useful motivator during childhood and may be an effective and potentially less damaging alternative to other punishments. Further, individuals reporting greater motivation (BAS drive) showed elevated loss avoidance *and* elevated gain approach behavior across age groups. This finding suggests a re-conceptualization of drive as comprised of behavioral/motivational sensitivity to both reward and loss feedback, rather than focusing only on positive feedback/outcomes. Future studies are needed to investigate the neural underpinnings

of both developmental differences in loss avoidance as well as the unique relations between gain and loss responsivity and drive. Additional investigation of this area is warranted to inform applications to parenting, education, and child development policy.

Supplemental Table S4.1
BIS/BAS Intercorrelations and Descriptive Statistics by Age Group

Scale	Pearson's r						Mean (St Dev)		
	ADULTS			CHILDREN			ADULTS	CHILDREN	T-statistic
1) Behavioral Inhibition System Subscale	1	2	3	1	2	3	3.23 (0.51)	2.35 (0.72)	8.35**
2) Behavioral Activation System - Drive Subscale	0.05			0.09			3.00 (0.59)	2.74 (0.84)	2.06†
3) Behavioral Activation System - Reward Responsiveness Subscale	0.03	0.41**		0.14	0.52**		3.77 (0.30)	3.55 (0.45)	3.4**

Note: Item response options range from 1-Not True to 4-Very True. Responses were averaged within a subscale such that a score of 4 indicates the maximum level of that construct. T-statistics indicate the results of a group t-test comparing mean scores for adults vs. children. **$p \leq 0.001$ †$p < 0.05$
Behavioral Inhibition Scale Questions: I worry about making mistakes, Criticism or scolding hurts me quite a bit, I feel pretty worried or upset when I think or know somebody is angry at me, I feel worried when I think I have done poorly at something important
Behavioral Activation - Drive Subscale Questions: When I want something I usually go all-out to get it, I go out of my way to get things I want, If I see a chance to get something I want I move on it right away
Behavioral Activation - Reward Sensitivity Subscale Questions: When I get something I want, I feel excited and energized, When I'm doing well at something I love to keep at it, It would excite me to win a contest

Supplemental Table S4.2

Repeated Measures ANOVA Investigating Effects of Age, Task Type, Block, BIS, and BAS on Response Bias

Interaction Type and Factor/Predictor	BAS Drive			BAS Reward Responsiveness		
	F-Statistic	Partial η^2	p-value	F-Statistic	Partial η^2	p-value
Main Effects						
Task Type	0.27	0.002	0.608	0.32	0.002	0.578
Age Group	13.32**	0.091	<0.001	13.87**	0.094	<0.001
BAS	6.24	0.045	0.014	4.53	0.033	0.035
BIS	0.08	0.001	0.782	0.04	<0.001	0.848
PILT-P Stimulus Type	7.07	0.050	0.090	7.83*	0.056	0.006
Gain Feedback Amount	8.92*	0.063	0.003	11.60**	0.080	0.001
Loss Feedback Amount	45.76**	0.256	<0.001	47.62**	0.264	<0.001
Two-Way Interactions with Task Type						
Age Group	2.26	0.027	0.135	2.43	0.018	0.122
BAS	2.90	0.021	0.091	1.88	0.014	0.172
BIS	<0.01	<0.001	0.986	<0.01	<0.001	0.975
Block	7.21*	0.051	0.008	7.13	0.051	0.009
PILT-P Stimulus Type	13.23**	0.090	<0.001	13.98**	0.095	<0.001
Gain Feedback Amount	0.04	<0.001	0.843	0.01	<0.001	0.944
Loss Feedback Amount	33.24**	0.200	<0.001	34.55**	0.206	<0.001
Three-Way Interactions with Task Type and Block						
Age Group	6.858*	0.049	0.010	7.503*	0.053	0.007
BAS	8.824*	0.062	0.004	6.952*	0.050	0.009
BIS	1.176	0.009	0.280	1.399	0.010	0.239
PILT-P Stimulus Type	0.022	<0.001	0.883	0.102	0.001	0.750
Gain Feedback Amount	8.378*	0.059	0.004	11.456**	0.079	0.001
Loss Feedback Amount	3.674	0.027	0.057	4.313	0.010	0.040

Note: PILT-P = PILT-Positive, BAS = Behavioral Activation Scale (either Drive or Reward Responsiveness), BIS = Behavioral Inhibition Scale**.** *$p \leq 0.0125$ **$p \leq 0.001$

Supplemental Table S4.3

Post Hoc Regressions Predicting Mean Response Bias and Response Bias Change For the PILT-Positive and PILT-Negative

Predictor	BAS Drive											
	Step 1				Step 2				Step 3			
	b	β	t-stat	p-val	b	β	t-stat	p-val	b	β	t-stat	p-val
PILT-P Mean Bias												
Intercept	-1.24		-2.56*	0.012	-1.11			0.038	-1.19		-2.18†	0.031
Age Group	0.06	0.15	1.76	0.081	0.07	0.17	1.65	0.102	0.18	0.42	0.79	0.434
PILT-P Stimulus Type	-0.03	-0.07	-0.82	0.416	-0.04	-0.08	-0.90	0.371	-0.03	-0.07	-0.81	0.418
Feedback Amount	0.03	0.24	2.87*	0.005	0.03	0.23	2.65*	0.009	0.03	0.23	2.71*	0.008
BIS					-0.01	-0.02	-0.18	0.860	-0.01	-0.03	-0.22	0.828
BAS					-0.02	-0.06	-0.73	0.466	0.00	-0.01	-0.08	0.935
BIS x Age G									0.01	0.06	0.14	0.891
BAS x Age G									-0.04	-0.33	-0.86	0.391
Model	R2=.11; Adj R2=.09; F=5.71; p=.001				R2=.12; Adj R2=.08; F=3.51; p=.005				R2=.12; Adj R2=.07; F=2.59; p=.016			
PILT-P Bias Change												
Intercept	0.21		0.26	0.794	-0.23		-0.27	0.790	<-.01		<-.01	0.997
Age Group	-0.05	0.08	-0.86	0.390	-0.03	-0.05	-0.46	0.644	-0.34	-0.50	-0.92	0.357
PILT-P Stimulus Type	0.09	1.31	1.31	0.194	0.09	0.13	1.45	0.148	0.09	0.12	1.33	0.185
Feedback Amount	0.00	-0.02	-0.26	0.795	0.00	0.00	0.03	0.972	0.00	-0.01	-0.12	0.908
BIS					-0.06	-0.13	-1.27	0.206	-0.06	-0.13	-1.07	0.286
BAS					0.12	0.26	3.10*	0.002	0.09	0.19	1.80	0.075
BIS x Age G									0.00	0.02	0.05	0.962
BAS x Age G									0.10	0.46	1.21	0.230
Model	R2=.03; Adj R2=.01; F=1.33; p=.267				R2=.10; Adj R2=.07; F=3.03; p=.013				R2=.11; Adj R2=.06; F=2.37; p=.026			
PILT-N Mean Bias												
Intercept	-0.95		-11.60**	<0.001	-0.62		-3.97**	<0.001	-0.73		-4.20**	<0.001
Age Group	0.20	0.27	3.41**	0.001	0.23	0.31	3.40**	0.001	0.70	0.96	2.19†	0.030
PILT-P Stimulus Type	0.22	0.28	3.83**	<0.001	0.21	0.26	3.62**	<0.001	0.21	0.26	3.66**	<0.001
Feedback Amount	0.02	0.58	7.64**	<0.001	0.02	0.56	7.48**	<0.001	0.02	0.54	7.23**	<0.001
BIS					-0.02	-0.03	-0.41	0.686	0.04	0.07	0.73	0.467
BAS					-0.10	-0.20	-2.87*	0.005	-0.10	-0.19	-2.33†	0.021
BIS x Age G									-0.15	-0.69	-1.83	0.070
BAS x Age G									-0.01	-0.04	-0.14	0.892
Model	R2=.36; Adj R2=.35; F=25.86; p<.001				R2=.40; Adj R2=.38; F=18.00; p<.001				R2=.42; Adj R2=.39; F=13.48; p<.001			
PILT-N Bias Change												
Intercept	-0.35		-3.54**	0.001	-0.10		-0.51	0.613	0.07		0.31	0.757
Age Group	0.26	0.35	3.65**	<0.001	0.28	0.37	3.37**	0.001	-0.40	-0.53	-1.00	0.318
PILT-P Stimulus Type	0.08	0.10	1.12	0.266	0.07	0.08	0.95	0.342	0.06	0.08	0.90	0.371
Feedback Amount	0.01	0.13	1.49	0.140	0.00	0.12	1.30	0.195	0.01	0.14	1.53	0.127
BIS					-0.01	-0.02	-0.19	0.849	-0.07	-0.14	-1.17	0.245
BAS					-0.08	-0.15	-1.82	0.071	-0.09	-0.18	-1.78	0.077
BIS x Age									0.18	0.80	1.74	0.084
BAS x Age G									0.05	0.21	0.57	0.571
Model	R2=.09; Adj R2=.07; F=4.45; p=.005				R2=.11; Adj R2=.08; F=3.39; p=.007				R2=.14; Adj R2=.09; F=2.94; p=.007			

Predictor	BAS Reward Responsiveness											
	Step 1				Step 2				Step 3			
	b	β	t-stat	p-val	b	β	t-stat	p-val	b	β	t-stat	p-val
PILT-P Mean Bias												
Intercept	-1.24		-2.56*	0.012	-1.10		-2.07†	0.040	-1.16		-2.12†	0.036
Age Group	0.06	0.15	1.76	0.081	0.07	0.18	1.66	0.098	0.30	0.70	0.73	0.465
PILT-P Stimulus Type	-0.03	-0.07	-0.82	0.416	-0.03	-0.08	-0.86	0.392	-0.03	-0.07	-0.78	0.438
Feedback Amount	0.03	0.24	2.87*	0.005	0.03	0.24	2.79*	0.006	0.03	0.23	2.75*	0.007
BIS					0.00	-0.01	-0.14	0.886	-0.01	-0.02	-0.19	0.848
BAS					-0.03	-0.06	-0.68	0.497	-0.01	-0.02	-0.20	0.842
BIS x Age G									0.01	0.05	0.10	0.921
BAS x Age G									-0.06	-0.58	-0.64	0.523
Model	R2=.11; Adj R2=.09; F=5.71; p=.001				R2=.12; Adj R2=.08; F=3.49; p=.005				R2=.12; Adj R2=.07; F=2.52; p=.018			
PILT-P Bias Change												
Intercept	0.21		0.26	0.794	0.09		0.10	0.920	0.09		0.10	0.922
Age Group	-0.05	-0.08	-0.86	0.390	-0.03	-0.04	-0.36	0.719	-0.01	-0.01	-0.01	0.990
PILT-P Stimulus Type	0.09	0.12	1.30	0.194	0.08	0.11	1.19	0.235	0.08	0.11	1.19	0.237
Feedback Amount	0.00	-0.02	-0.26	0.795	-0.01	-0.04	-0.43	0.670	-0.01	-0.04	-0.44	0.664
BIS					-0.06	-0.13	-1.24	0.218	-0.06	-0.14	-1.10	0.272
BAS					0.11	0.13	1.49	0.139	0.12	0.14	1.29	0.198
BIS x Age G									0.02	0.08	0.17	0.863
BAS x Age G									-0.02	-0.10	-0.11	0.912
Model	R2=.03; Adj R2=.01; F=1.33; p=.267				R2=.05; Adj R2=.02; F=1.49; p=.197				R2=.05; Adj R2<.01; F=1.06; p=.396			
PILT-N Mean Bias												
Intercept	-0.95		-11.60**	<0.001	-0.40		-1.53**	0.128	-0.32		-1.07	0.286
Age Group	0.20	0.27	3.41**	0.001	0.24	0.32	3.50**	0.001	0.12	0.17	0.21	0.830
PILT-P Stimulus Type	0.22	0.28	3.83**	<0.001	0.21	0.27	3.69**	<0.001	0.20	0.26	3.58**	<0.001
Feedback Amount	0.02	0.58	7.64**	<0.001	0.02	0.57	7.54**	<0.001	0.02	0.56	7.45**	<0.001
BIS					-0.02	-0.03	-0.40**	0.692	0.04	0.09	0.83	0.409
BAS					-0.14	-0.15	-2.13†	0.035	-0.20	-0.21	-2.50†	0.014
BIS x Age G									-0.16	-0.74	-1.94	0.055
BAS x Age G									0.16	0.82	1.12	0.266
Model	R2=.36; Adj R2=.35; F=25.86; p<.001				R2=.39; Adj R2=..36; F=16.83; p<.001				R2=.41; Adj R2=.38; F=12.95; p<.001			
PILT-N Bias Change												
Intercept	-0.35		-3.54**	<0.001	0.31		0.97	0.334	0.25		0.67	0.505
Age Group	0.18	0.25	2.95*	0.004	0.20	0.27	2.66*	0.009	0.37	0.50	0.56	0.576
PILT-P Stimulus Type	0.12	0.15	1.78	0.077	0.12	0.15	1.75	0.082	0.12	0.15	1.84	0.068
Feedback Amount	0.07	0.32	3.94**	<0.001	0.07	0.32	4.01**	<0.001	0.07	0.31	3.91**	<0.001
BIS					0.03	0.06	0.62	0.539	-0.02	-0.04	-0.35	0.724
BAS					-0.19	-0.20	-2.46†	0.015	-0.13	-0.14	-1.45	0.149
BIS x Age G									0.14	0.63	1.43	0.154
BAS x Age G									-0.16	-0.81	-0.96	0.341
Model	R2=.17; Adj R2=.15; F=9.24; p<.001				R2=.21; Adj R2=.18; F=6.958; p<.001				R2=.22; Adj R2=.18; F=5.40; p<.001			

Note: b = unstandardized beta, β = standardized beta, Adj, R^2 = adjusted R^2 †p<0.05 *p<0.0125 **p≤0.001

Supplemental Table S4.4

Repeated Measures ANOVAs Investigating Effects of Age, Task Type, and Previous Trial Feedback on Reaction Time and Accuracy

Interaction Type and Factor/Predictor	Reaction Time ANOVA			Accuracy ANOVA		
	F-Statistic	Partial η^2	p-value	F-Statistic	Partial η^2	p-value
Main Effects						
Task Type	0.04	<0.001	0.852	11.25**	0.077	0.001
Previous Trial Feedback	2.20	0.016	0.140	1.60	0.012	0.208
Age Group	141.90**	0.512	<0.001	4.71	0.034	0.032
PILT-P Stimulus Type	3.18	0.023	0.077	0.80	0.006	0.374
Gain Feedback Amount	1.07	0.008	0.303	50.38**	0.271	<0.001
Loss Feedback Amount	0.28	0.002	0.597	47.32**	0.260	<0.001
Two-Way Interactions with Task Type						
Previous Trial Feedback	1.34	0.010	0.249	0.02	<0.001	0.889
Age Group	0.23	0.002	0.630	15.99**	0.106	<0.001
PILT-P Stimulus	0.25	0.002	0.622	3.33	0.024	0.070
Gain Feedback Amount	0.05	<0.001	0.819	11.22**	0.077	0.001
Loss Feedback Amount	3.47	0.025	0.065	22.08**	0.141	<0.001
Two-Way Interactions with Previous Trial Feedback						
Age Group	7.92*	0.055	0.006	2.77	0.020	0.098
PILT-P Stimulus	2.83	0.021	0.095	0.24	0.002	0.626
Gain Feedback Amount	1.41	0.010	0.237	1.16	0.009	0.283
Loss Feedback Amount	2.44	0.018	0.121	0.12	0.001	0.731
Three-Way Interactions with Task Type and Previous Trial Feedback						
Age Group	7.96*	0.056	0.005	2.91	0.021	0.091
PILT-P Stimulus	1.46	0.011	0.229	0.01	<0.001	0.927
Gain Feedback Amount	0.70	0.005	0.403	0.00	<0.001	0.962
Loss Feedback Amount	7.48*	0.053	0.007	0.36	0.003	0.551

Note: PILT-P = PILT-Positive *$p<0.0125$ **$p\leq0.001$

Supplemental Table S4.5

Post Hoc Regressions Predicting Differences in Reaction Time Post Feedback versus No Feedback During the PILT-Positive, PILT-Negative, and Across Tasks

Task Type and Predictor	b	β	t-statistic	p-value
PILT-Positive (PILT-P)				
Intercept	185.42		0.57	0.571
Age Group	-8.90	-0.03	-0.36	0.720
PILT-P Stimulus Type	-9.42	-0.03	-0.35	0.725
Feedback Amount	-3.25	-0.04	-0.47	0.642
Model Statistics	R^2=0.01; Adj R^2=-0.02; F=0.14; p=0.935			
PILT-Negative (PILT-N)				
Intercept	333.84		4.80**	<0.001
Age Group	-161.82	-0.31	-3.30*	0.001
PILT-P Stimulus Type	-72.86	-0.13	-1.50	0.137
Feedback Amount	-5.89	-0.21	-2.34†	0.021
Model Statistics	R^2=0.09; Adj R^2=0.07; F=4.26; p=0.007			
Mean of PILT-P and PILT-N				
Intercept	561.10		1.66	0.100
Age Group	-76.31	-0.27	-2.81	0.006
PILT-P Stimulus Type	-45.54	-0.15	-1.68	0.095
Gain Feedback Amount	-8.44	-0.10	-1.19	0.237
Loss Feedback Amount	-2.18	-0.15	-1.56	0.121
Model Statistics	R^2=0.07; Adj R^2=0.05; F=2.66; p=0.036			

Note: b = unstandardized beta, β = standardized beta, Adj, R^2 = adjusted R^2 †p<0.05 *p<0.0125 **p≤0.001

Supplemental Table S4.6

Repeated Measures ANOVA Investigating Effects of Age, Task Type, Block, BIS, and BAS on Response Bias for Adult and Child Age Groups

Interaction Type and Factor/ Predictor	ADULTS						CHILDREN					
	BAS Drive			BAS Reward Responsiveness			BAS Drive			BAS Reward Responsiveness		
	F-Statistic	Partial η^2	p-value	F-Statistic	Partial η^2	p-value	F-Statistic	Partial η^2	p-value	F-Statistic	Partial η^2	p-value
Main Effects												
Task Type	0.01	<0.01	0.931	0.04	<0.01	0.843	0.70	0.01	0.405	0.66	0.01	0.419
BAS	3.05	0.05	0.086	<0.01	<0.01	0.948	2.34	0.04	0.131	3.73	0.06	0.058
BIS	2.95	0.04	0.091	3.06	0.05	0.085	0.42	0.01	0.517	0.72	0.01	0.399
Stim Type	0.42	0.01	0.520	0.66	0.01	0.420	11.02*	0.15	0.001	11.52*	0.15	0.001
Gain FB	13.47**	0.17	<0.001	13.43*	0.17	0.001	2.73	0.04	0.103	4.42	0.06	0.039
Loss FB	31.02**	0.33	<0.001	38.04**	0.37	<0.001	23.04**	0.26	<0.001	23.06**	0.26	<0.001
Interactions with Task Type												
Block	0.02	<0.01	0.876	0.13	<0.01	0.717	13.84**	0.18	<0.001	15.12**	0.19	<0.001
BAS	0.33	0.01	0.570	0.21	<0.01	0.648	2.12	0.03	0.151	3.99	0.06	0.050
BIS	1.80	0.03	0.185	1.90	0.03	0.173	1.08	0.02	0.302	1.57	0.02	0.215
Stim Type	3.01	0.04	0.088	2.48	0.04	0.120	8.84*	0.12	0.004	9.21*	0.13	0.003
Gain FB	0.12	<0.01	0.728	0.09	<0.01	0.770	0.02	<0.01	0.876	0.29	<0.01	0.593
Loss FB	13.11*	0.17	0.001	16.16**	0.20	<0.001	17.53**	0.21	<0.001	17.56**	0.22	<0.001
Interactions with Task Type and Block												
BAS	5.97	0.09	0.017	3.17	0.05	0.080	3.25	0.05	0.076	3.68	0.05	0.059
BIS	1.54	0.02	0.219	1.38	0.02	0.245	0.15	<0.01	0.701	0.32	<0.01	0.573
Stim Type	0.97	0.01	0.329	0.87	0.01	0.355	2.24	0.03	0.139	2.48	0.04	0.120
Gain FB	<0.01	<0.01	0.998	<0.01	<0.01	0.988	13.98**	0.18	<0.001	18.54**	0.22	<0.001
Loss FB	0.22	<0.01	0.643	<0.01	<0.01	0.956	9.21	0.13	0.003	9.07	0.12	0.004

Note: Stim Type = Stimulus Type during the PILT-P (0=nose, 1=mouth), FB = Feedback Amount, BAS = Behavioral Activation Scale (either Drive or Reward Responsiveness), BIS = Behavioral Inhibition Scale. *p<0.0125 **p≤0.001

Supplemental Table S4.7

Post Hoc Regressions Predicting Mean Response Bias and Response Bias Change For the PILT-Positive and PILT-Negative for Adult and Child Age Groups

Dependent Variable and Predictor	ADULTS								CHILDREN							
	BAS Drive				BAS Reward Responsiveness				BAS Drive				BAS Reward Responsiveness			
	b	β	t-stat	p-val	b	β	t-stat	p-val	b	β	t-stat	p-val	b	β	t-stat	p-val
PILT-P Mean Bias																
Intercept	-2.16		-2.24†	0.029	-2.05		-2.01†	0.049	-0.65		-1.07	0.288	-0.68		-1.13	0.261
PILT-P Stimulus Type	-0.13	-0.20	-1.76††	0.084	-0.12	-0.20	-1.69††	0.095	0.02	0.05	0.40	0.692	0.02	0.05	0.42	0.676
Feedback Amount	0.05	0.31	2.74*	0.008	0.05	0.31	2.70*	0.009	0.02	0.18	1.42	0.159	0.02	0.19	1.50	0.138
BIS	0.00	-0.01	-0.09	0.927	-0.01	-0.01	-0.12	0.903	-0.01	-0.03	-0.26	0.792	-0.01	-0.03	-0.26	0.795
BAS	-0.05	-0.12	-1.05	0.297	-0.06	-0.07	-0.66	0.513	0.00	-0.02	-0.16	0.874	0.00	-0.01	-0.05	0.956
Model Statistics	R2=.18; Adj R2=.13; F=3.52; p=.012				R2=.17; Adj R2=.12; F=3.32; p=.016				R2=.04; Adj R2=-.02; F=0.67; p=.614				R2=.04; Adj R2=-.02; F=0.67; p=.618			
PILT-P Bias Change																
Intercept	-2.42		-1.49	0.142	-2.31		-1.29	0.203	1.05		1.14	0.258	1.21		1.34	0.185
PILT-P Stimulus Type	0.23	0.22	1.88††	0.064	0.23	0.22	1.81††	0.075	0.01	0.02	0.19	0.851	0.01	0.01	0.09	0.929
Feedback Amount	0.04	0.14	1.22	0.227	0.04	0.15	1.22	0.229	-0.02	-0.15	-1.22	0.228	-0.03	-0.20	-1.66	0.102
BIS	-0.04	-0.05	-0.45	0.656	-0.03	-0.04	-0.32	0.751	-0.07	-0.18	-1.52	0.133	-0.08	-0.20	-1.63	0.109
BAS	0.18	0.29	2.49†	0.015	0.09	0.07	0.56	0.578	0.07	0.21	1.69††	0.096	0.11	0.17	1.44	0.154
Model Statistics	R2=.15; Adj R2=.10; F=2.82; p=.032				R2=.07; Adj R2=.01; F=1.24; p=.303				R2=.10; Adj R2=.04; F=1.75; p=.149				R2=.09; Adj R2=.03; F=1.55; p=.199			
PILT-N Mean Bias																
Intercept	-0.15		-0.52	0.605	-0.49		-1.03	0.305	-0.76		-3.78**	<0.001	-0.34		-1.02	0.311
PILT-P Stimulus Type	0.05	0.06	0.61	0.546	0.03	0.04	0.38	0.705	0.27	0.34	3.55**	0.001	0.27	0.34	3.56**	0.001
Feedback Amount	0.03	0.55	5.51**	<0.001	0.03	0.61	6.11**	<0.001	0.02	0.50	5.19**	<0.001	0.02	0.49	5.15**	<0.001
BIS	-0.13	-0.19	-2.08†	0.042	-0.13	-0.20	-2.12†	0.038	0.04	0.08	0.81	0.419	0.05	0.09	0.95	0.348
BAS	-0.08	-0.15	-1.51	0.136	0.02	0.02	0.17	0.867	-0.09	-0.20	-2.05†	0.045	-0.19	-0.22	-2.26†	0.027
Model Statistics	R2=.46; Adj R2=.42; F=13.56; p<.001				R2=.44; Adj R2=.40; F=12.56; p<.001				R2=.41; Adj R2=.38; F=11.44; p<.001				R2=.42; Adj R2=.39; F=11.82; p<.001			

PILT-N Bias Change																
Intercept	-0.12		-0.31	0.761	0.82		1.36	0.180	-0.05		-0.20	0.843	0.11		0.27	0.785
PILT-P Stimulus Type	0.01	0.02	0.12	0.906	0.05	0.05	0.39	0.695	0.11	0.15	1.26	0.213	0.12	0.16	1.31	0.194
Feedback Amount	0.00	-0.03	-0.21	0.838	0.00	-0.05	-0.37	0.713	0.01	0.24	2.03†	0.047	0.01	0.23	1.99††	0.051
BIS	0.10	0.15	1.23	0.223	0.10	0.16	1.31	0.196	-0.07	-0.14	-1.17	0.246	-0.07	-0.14	-1.14	0.260
BAS	-0.06	-0.11	-0.86	0.394	-0.30	-0.26	-2.14†	0.037	-0.09	-0.19	-1.64	0.106	-0.11	-0.13	-1.11	0.269
Model Statistics	R2=.03; Adj R2=-.03; F=0.54; p=.705				R2=.09; Adj R2=.03; F=1.52; p=.207				R2=.14; Adj R2=.09; F=2.63; p=.042				R2=.12; Adj R2=.07; F=2.23; p=0.76			

Note: b = unstandardized beta, β = standardized beta, Adj, R^2 = adjusted R^2 ††p<0.10 †p<0.05 *p<0.0125 **p≤0.001

Supplemental Table S4.8
Regression predicting BAS Drive

Predictors	All Participants N=140				Adults N=70				Children N=70			
	b	β	t-statistic	p-value	b	β	t-statistic	p-value	b	β	t-statistic	p-value
Intercept	2.71		32.82**	<0.001	3.03		44.74**	<0.001	2.70		27.82**	<0.001
PILT-P Bias Change	0.53	0.24	3.02*	0.003	0.45	0.29	2.55†	0.013	0.65	0.22	1.94††	0.056
PILT-N Mean Bias	-0.60	-0.25	-3.09*	0.002	-0.53	-0.25	-2.20†	0.031	-0.65	-0.25	-2.16†	0.035
Age Group	0.33	0.22	2.78*	0.006								
Model Statistics	R^2=.15; Adj R^2=.13; F=8.16; p=<.001				R^2=.15; Adj R^2=.12; F=5.86; p=.005				R^2=.12; Adj R^2=.09; F=4.54; p=.014			

Note: Residuals used for Bias variables, controlling for stimulus type and feedback amount. b = unstandardized beta, β = standardized beta, Adj, R^2 = adjusted R^2. ††p<0.10 †p<0.05 *p<0.0125 **p≤0.001

Chapter 5.

Incentive Responsivity In Children: Relations With Depression Risk, Negative Mood, And Anhedonia

Abstract

Objective: Reduced reward responsivity and altered response to loss (of reward) are observed in adults and adolescents at increased risk for Major Depressive Disorder (MDD) based on family history. However, it is unclear whether reduced behavioral responsivity to incentives is a lifelong marker of MDD risk, evident prior to the normative adolescent increase in incentive responding.

Method: Healthy 7-10-year-old children of mothers with (high-risk; N=28) or without (low-risk; N=45) a history of depression performed two signal detection tasks to assess behavioral responsivity to gain and loss of rewards. Responsivity to gain/loss was operationalized as bias towards/away from responses that received more frequent reward/punishment feedback. Differences in responsivity relating to the child's depression risk, general depressive symptoms (maternal-report), anhedonic symptoms, and negative mood symptoms were investigated via repeated measures ANOVA.

Results: No significant differences in response bias toward gain or away from loss were observed between the risk groups. However, children with elevated anhedonic symptoms showed *blunted* responsivity to gain feedback whereas *enhanced* loss responsivity related to elevated negative mood and elevated general depressive symptoms. Elevated negative mood further related to reduced reward responsivity in high-risk children, but enhanced responsivity to gain in low-risk children.

Conclusions: In childhood, individual differences in specific depressive symptoms are stronger predictors of gain approach and loss avoidance behaviors than maternal depressive history. Depressive symptoms characterized by low positive affect (anhedonia) most consistently related to gain responsivity while elevated depressed/negative mood most consistently related to loss responsivity.

5.1 Introduction

Behavioral/neural phenotypes associated with affective psychopathology risk have received much focus in recent years. Samples free of current pathology, but at increased risk for developing affective disorders given a positive family history (e.g. depression risk (Lieb et al 2002)) provide unique opportunities to parse risk-related endophenotypes from effects of a disorder. Relatedly, there has also been increasing emphasis in the literature on relating specific domains of affective functioning, such as reward expectancy, learning, and loss reactivity, to specific symptoms/risk and to predicting clinical outcome (Insel et al 2010). The application of such approaches within adolescent and adult populations has yielded compelling results including reduced response to reward with elevated depression risk (Gotlib et al 2010, McCabe et al 2012, Olino et al 2014). However, few studies have investigated reward/punishment processing in healthy or at-risk school age children. Yet, it is particularly important to study incentive-related behavior in this age period as it precedes the normative developmental rise in reward responsivity and decrease in loss response associated with transitions into/out of adolescence (Galvan 2010, Galvan & McGlennen 2013).

Over the past decade, neuroimaging and behavioral studies have consistently reported reduced response to reward in adults and adolescents with MDD (for review see (Eshel & Roiser 2010, Forbes 2011, Kerestes et al 2014)). Similarly, reduced reward response has been found in currently healthy adolescent samples at elevated risk for MDD based on a family history of depression (Gotlib et al 2010, McCabe et al 2012, Olino et al 2014). Beyond diagnostic categories, elevations in specific depressive symptoms such as anhedonia (lack of experienced pleasure) or melancholy have been linked to reduced responsivity/sensitivity to positive stimuli/outcomes in a variety of tasks/domains (Dowd & Barch 2010, Forbes et al 2010,

Pizzagalli et al 2005, Treadway et al 2009). While these lines of evidence clearly implicate reduced behavioral/neural response to reward not only in clinical depression but also in high risk states, no studies to our knowledge have evaluated whether behavioral response to reward is also reduced in school age children at high-risk for depression. This is an important developmental question as reward-related behaviors and neural systems undergo dramatic changes across development with peak reward responding observed during adolescence (for review see (Galvan 2010, Richards et al 2013)).

Of interest is whether the differences in responsivity to reward observed between high- and low-risk adolescents reflects alteration in the typical developmental process of enhanced sensitivity to reward specific to the adolescent period, or whether this phenomenon is evident more generally across development. At issue is whether the typical 'adolescent peak' in reward response is evident in low-risk populations, but attenuated in high-risk populations, thus making group differences in reward responding most evident during this normative 'peak'. Alternatively, depression risk may be associated with reduced reward responsivity throughout the lifespan, even prior to adolescence. There is only limited cross-sectional evidence for either of these hypotheses (Goff et al 2013, Kujawa et al 2014), though these studies did not exclude for current pathology in their examination of risk. Thus, studies investigating reward responsivity in *healthy* but high-risk child populations are needed to test whether this finding is specific to puberty/post-puberty or is observed across development, an issue that would inform the design of preventative interventions.

Another important underexplored question is whether the reduced responsivity discussed above is specific to reward/positive stimuli or reflects a more general blunting of incentive responsivity independent of valence. There is evidence for blunted responses to *both* positive and

negative emotional stimuli in adult MDD (Bylsma et al 2008) and in adults (Chase et al 2010, Dowd & Barch 2010, Steele et al 2007, Stoy et al 2012a) and children (Luking et al 2015) with reduced hedonic capacity. However, there are also a number of studies reporting *elevated* responsivity to negative incentives in adult MDD (Kerestes et al 2014, Schiller et al 2013) and adolescent MDD risk (Gotlib et al 2010, McCabe et al 2012). No studies to our knowledge have investigated response to loss (of reward) independently of gain responsivity in adolescent MDD, i.e. not focusing on differences between gain and loss. However, several studies report elevated response to non-incentive negative stimuli in child/adolescent MDD and risk (Monk et al 2008, Pagliaccio et al 2012). This important question of whether depression risk in school age children is characterized by blunted responses to both reward and loss or whether the alteration is more specific to reward could also have important clinical/treatment implications.

A family history of MDD confers increased risk; however only a fraction of those at high-risk (~40%) go on to develop MDD (Goodman & Gotlib 1999, Hammen et al 2008a, Hammen et al 2008b). Further, healthy children at high-risk for MDD often show elevated, subclinical levels of depressive symptoms, such as negative mood and anhedonia (Angold 1987). Thus, it is unclear whether differences between high/low-risk groups reflect elevated symptoms or risk-related mechanisms independent of current symptom severity. A recent study suggested that some neural differences in reward responsivity observed between high and low-risk adolescents were explained by symptom level (Olino et al 2014). As such, it is important to explore these symptoms in addition to risk status.

In the current study, we used age-appropriate positive and negative incentive tasks that have been well studied in the adult literature (Pizzagalli et al 2008a, Pizzagalli et al 2005) along with dimensional measures of depressive, other internalizing, and externalizing disorder

symptoms to test several hypotheses within a sample of healthy 7-10-year-old children at high-risk (maternal depressive episode history) or low-risk (no maternal psychopathology) for developing MDD. We hypothesized that high-risk children would show both reduced gain approach behavior and enhanced loss avoidance behavior relative to low-risk children. Additionally we hypothesized that children with elevated of anhedonia would show blunted gain approach and loss avoidance behavior, regardless of risk group status.

5.2 Method

Participants and Procedure

119 mothers with or without a history of depression and their 7-10-year-old children from the St. Louis, Missouri metropolitan area were enrolled in the study. Families were recruited via flyers/brochures distributed through schools and posted in the community as well as via the Research Participant Registry at Washington University School of Medicine. Prior to enrollment, mothers completed a phone screen to help determine eligibility. Children who were beyond 7-10 years, had begun menstruation (female), could not consume candy, were born prior to 35 weeks gestation, or were diagnosed previously with a psychiatric, learning, or other major medical disorder were excluded.

Data presented here were collected during the first session of a multi-session protocol. On the day of assessment, mothers provided written informed consent and children provided written assent. Mothers then completed clinical interviews and questionnaires about themselves and their child in a separate room. Children completed a 'tasty task' (discussed below), two versions of a Probabilistic Incentive Learning Task (PILT), a clinical interview, and questionnaires. The Washington University in St. Louis Institutional Review Board approved all study procedures.

Assessment of Psychopathology and Risk

Diagnostic Interviews

Given our questions regarding *risk* for depression, analyses focus on the *healthy* offspring of women with/without a history of at least one depressive episode. To determine child psychiatric history, both child and mother completed the Kiddie-Structured Assessment for Affective Disorders-Present and Lifetime Version (KSADS) (Kaufman et al 1997) administered by masters level clinicians trained to reliability. Data from dyads where only one reporter completed the KSADS (n=5; 2 high-risk) were excluded. Based on combined reports (Bird et al 1992), twelve children met criteria for externalizing or internalizing disorders and were excluded from analyses. Children with a disorder impacting ability to respond during the behavioral task (two tic, one general motor, one Cystic Fibrosis, one dyslexia) or whose mother used illicit drugs during pregnancy (maternal-report; n=3) were also excluded.

Depression risk was defined by maternal depressive episode history (past/present versus absent), established via the Structured Clinical Interview for DSM Disorders (SCID) (First 2007). Children of mothers without any lifetime psychiatric diagnosis were considered low-risk (n=45). Children of mothers who had experienced at least one depressive episode (n=28) were considered high-risk; 22 had recurrent depressive episodes. The remaining 24 mothers did not meet inclusion criteria for either group (see Supplemental Table 5.1 for diagnoses).

Symptom Measures

Children and mothers completed a variety of self-report measures designed to assess depressive symptomology, affect, mood regulation, and sensitivity to rewards/punishments (Supplemental Table 5.2). Several dimensional measures of symptoms were of interest here. Specifically, maternal-report of child depressive symptoms was obtained from the Child Depression Inventory - Parent Version (CDI-P). Child self-report was also obtained from the

Child Depression Inventory - Child Version (CDI-C). We focus on the anhedonic and negative mood subscales from the CDI-C and utilize age/gender-normalized t-scores for all measures throughout analyses. Maternal-report of child anxiety and ADHD symptoms were obtained from the Child Behavior Checklist (CBCL anxiety and ADHD subscales).

Prior to each behavioral task, children performed a 'tasty task' where they rated their current affect, consumed two pieces of candy (children chose either M&Ms© or Skittles©), and then rated their affect, the sweetness of the candy, and their liking of the candy post-tasting. Liking rating options included extremely (n=72), a lot (n=55), moderately (n=2), a little (n=0), and not at all (n=0). Ratings of candy liking did not differ based on depression risk (p=0.80).

Probabilistic Incentive Learning Task (PILT)

Task Design and Data Processing

To assess behavioral responsivity to feedback, we used versions of the probabilistic reward task developed by Pizzagalli et al (2005) and Tripp & Alsop (1999) and previously modified for use in child populations (Luking et al 2015). Durring the PILT, participants perform a difficult two-choice discrimination (indicated whether a short or long mouth/nose was presented) which is followed by occasional feedback. In the PILT-Postivive version of the task (PILT-P), children receive either candy gain or no feedback, while in the PILT-Negative version (PILT-N), children receive either candy loss or no feedback (Figure 5.1A). Children gain one candy piece for every gain feedback instance and lose one candy from a 70-piece allotment for every loss feedback instance. Importantly, gain/loss feedback during the PILT-P/N only follows a portion of correct/incorrect responses, respectively. Feedback is also delivered unequally between the two responses such that one response receives approximately three times as much feedback as the alternative reponse (See supplement for more detailed discussion of task

structure).

Behavioral responsivity to feedback is defined as the degree to which a participant preferentially selects/avoids the response receiving more frequent feedback (the RICH reponse, i.e. rich in feedback). This bias in responding (log b) is calculated via signal detection statistics across a block of trials. Given that the RICH and the alternative (LEAN) response should initially be selected with relatively equal frequency (bias near zero), general response bias and/or changes in response bias across a task reflects the influence of feedback on choice behavior and is used as the dependent measure in beahvioral analyses.

$$Response\ Bias\ (\log b) = \frac{1}{2}\log\left(\frac{RICHcorrect * LEANincorrect}{RICHincorrect * LEANcorrect}\right)$$

During reward versions of this task, children and adults who are more responsive to feedback tend to increasingly *approach* the RICH reponse followed more frequently by gain feedback even at the expense of overall accuracy, indicated by positive values/change in response bias across the PILT-P (Luking et al 2015, Pizzagalli et al 2005). Conversely, during the punishment version, children who are more responsive to feeback tend to increasingly *avoid* the RICH reponse (Luking et al 2015). They instead prefentially select/approach the LEAN response that receives less loss feedback, again at the expense of overall accuracy, indicated by negative values/change in response bias across the PILT-N.

Data Analysis

To characterize any differences in symptom levels between high and low risk groups we utilized independent sample t-tests. We also conducted correlations between child and parent reported depressive symptoms (child/parent CDI) and child-reported anhedonia and negative mood (CDI-C).

To characterize behavior on the PILTs, a repeated measures ANOVA was conducted to investigate how response bias changed as a function of Task Type (PILT-P, PILT-N) and Block (first, last). An additional repeated measures ANOVA was conducted to describe effects of Task Type on mean discriminability (see supplement).

To test hypotheses regarding incentive responsivity, depression risk status, anhedonia, negative mood, and depressive symptoms, a repeated measures ANOVA was conducted with response bias as the dependent variable. Task Type (PILT-P, PILT-N) and Block (first, last) served as repeated measures, analyses focus on effects of Task Type and the interaction of Task Type and Block. Risk Group (high, low) and PILT-P stimulus type (mouth, nose) were included as between-subjects factors. Covariates of interest included general depressive symptoms (CDI-P total t-score), anhedonia (CDI-C subscale t-score), and negative mood (CDI-C subscale t-score); interactions between covariates of interest and Risk Group were also investigated. Anxiety and ADHD symptom levels (CBCL subscale t-scores) were also included as covariates to control for other symptomology though we did not have specific hypotheses regarding these measures. Post-hoc regressions were conducted to determine the direction of significant effects within the full sample and within each risk group separately. For regressions involving the full sample, all between-subjects factors and covariates were entered as a first step followed by the interaction of Risk Group and covariates of interest in the second step; within group regressions included one step with Stimulus Type and covariates as predictors.

5.3 Results

Participant Characteristics and Individual Difference Measures

Descriptive statistics and symptom measure intercorrelations are displayed in Tables 5.1 and 5.2. High- and low-risk groups were matched demographically, with no significant

differences in sex, ethnicity, age, pubertal development, or family income. Child self-report of general depressive symptoms, anhedonia, and negative mood did not significantly differ across risk groups (Table 5.1). Maternal-report of child ADHD symptoms also did not differ significantly across groups. However, high-risk mothers did report significantly higher levels of depressive symptoms and anxiety symptoms in their children relative to low-risk mothers, a pattern is consistent with prior literature (Gotlib et al 2010). As expected, and consistent with the extant literature, child-report and maternal-report of child depressive symptoms were not significantly related (Achenbach et al 1987).

Table 5.1: Demographic And Clinical Characteristics Of Healthy Children At Low- And High-Risk For Developing Depression

	Low Risk N = 42	High Risk N = 27	t/X^2
Gender (% male) [a]	53.3	53.6	0.98
Age in years [b]	8.99 (1.12) 7.02 - 10.68	8.69 (1.21) 7.01 - 10.83	1.05
Pubertal Development Scale [b]	1.53 (0.53)	1.54 (0.43)	-0.13
Ethnicity (% white) [a]	48.9	50.0	1.17
Family Income [b]	12.02 (7.09) 1 - 21	11.18 (7.30) 1 - 21	0.49
Child Depression Inventory - Child [b]			
Total T-score	49.02 (13.66) 37 - 83	53.70 (14.59) 37 - 77	-1.37
Anhedonia Subscale T-Score	48.19 (10.45) 37 - 83	52.44 (10.59) 37 - 75	-1.67
Negative Mood Subscale T-score	53.67 (15.49) 39 - 91	55.52 (15.92) 39 - 80	-0.49
Child Depression Inventory - Parent [b, c]			
Total T-score	41.36 (5.54) 34 - 61	47.79 (8.12) 35 - 67	-3.69**
Child Behavior Checklist [b, c]			
Anxiety Subscale T-score	51.35 (2.98) 50 - 63	55.75 (6.19) 50 - 70	-3.51**
ADHD Subscale T-Score	52.44 (5.45) 50 - 78	54.93 (6.83) 50 - 75	-1.62

Note: Family Income Level coded in 21 increments of $5,000 starting with 1= $1-$5,000 and ending with 21 = >$100,000. [a] = n (and percentage) are reported along with chi-square statistic. [b] = mean (and standard deviation) range are reported along with t-statistic. [c] = Equal variance assumption not met, thus the t-statistic was computed based on unequal variances. ** p = 0.001

Table 5.2: Intercorrelations Amongst Symptom Measures

	1	2	3	4	5
1) CDI-C Total T-score					
2) CDI-C Negative Mood Subscale T-	0.96**				
3) CDI-C Anhedonia Subscale T-score	0.88**	0.76**			
4) CDI-P Total T-score	0.19	0.11	0.20#		
5) CBCL Anxiety Disorder Subscale T-	0.12	0.09	0.09	0.41**	
6) CBCL ADHD Subscale T-score	0.20#	0.17	0.17	0.64**	0.36**

Note: CDI-C = Child Depression Inventory Child Self-Report, CDI-P = Child Depression Inventory Parent Report, CBCL = Child Behavior Checklist, ADHD = Attention Deficit Hyperactivity Disorder, ** $p < 0.01$, * $p < 0.05$, # $p < 0.10$

Behavioral Task Results

There were significant effects of Task Type and Block on response bias (Task Type effect, $F(1,70) = 52.33$, $p < 0.001$; Task Type x Block interaction, $F(1,70) = 18.31$, $p < 0.001$; Supplemental Table 5.4, Figure 5.1B). During the PILT-P, response bias was significantly greater than zero during all blocks (all $p < 0.01$), i.e. children learned to approach the more frequently rewarded response. However, bias did not significantly increase across the PILT-P blocks (Block effect; $F(1,71) = 2.44$, $p = 0.123$). During the PILT-N, response bias was significantly less than zero during all blocks (all $p < 0.001$), i.e. children learned to avoid the response more frequently paired with loss feedback. Response bias also became significantly more negative from the first to last block of the PILT-N (main effect of Block during PILT-N; $F(1,71) = 16.80$, $p < 0.001$).

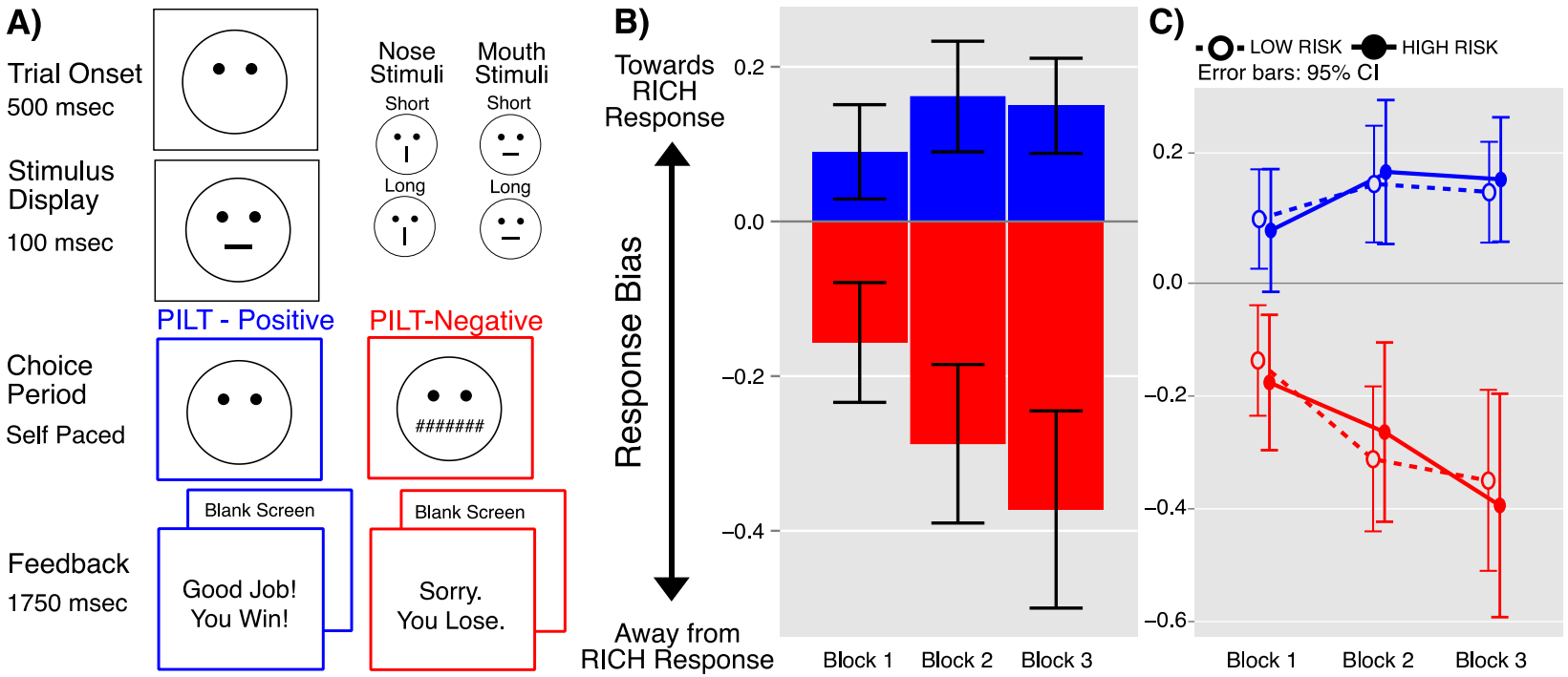


Figure 5.1: Probabilistic Incentive Learning Task Diagram And Response Bias

Note: A) Schematic diagrams of negative and positive Progressive Incentive Learning Task (PILT) versions. B) Response bias within each block of 40 trials for the PILT-Positive (blue) and PILT-Negative (red). C) Response bias during each block of the PILT-Positive/Negative by Risk Group (Low-Risk = open circles/dotted lines; High-Risk = closed circles/solid lines)

Does Incentive Responsivity Relate to Risk Group Status?

Contrary to our predictions, no significant effects of risk group were observed on incentive responsivity (Risk Group effect, $F(1,58) = 0.37$, $p = 0.547$; Task Type x Risk Group interaction, $F(1,58) = 0.01$ $p = 0.941$; Task Type x Block x Risk Group interaction, $F(1,58) = 0.03$, $p = 0.870$; Figure 5.1C).

Relations between Incentive Responsivity and Symptom Levels

Response bias change across tasks differed based on child-reported anhedonic symptoms ($F(1,58) = 5.34$, $p = 0.024$), child-reported negative mood levels ($F(1,58) = 4.19$, $p = 0.045$), and maternal-report of child general depressive symptoms ($F(1,58) = 6.08$, $p = 0.017$) (Figure 5.2A). Further, the relation between response bias change across each task (PILT-P/PILT-N) and negative mood differed based on Risk Group ($F(1,58) = 5.39$, $p = 0.024$; Figure 5.2B, Supplemental Tables 5.7-5.9). Post-hoc hierarchical regression analyses were conducted to determine whether interactions reflected relations within the PILT-P, PILT-N, or both. No significant interactions with Task Type alone or effects/interactions of ADHD or anxiety symptoms were observed (Supplemental Table 5.6).

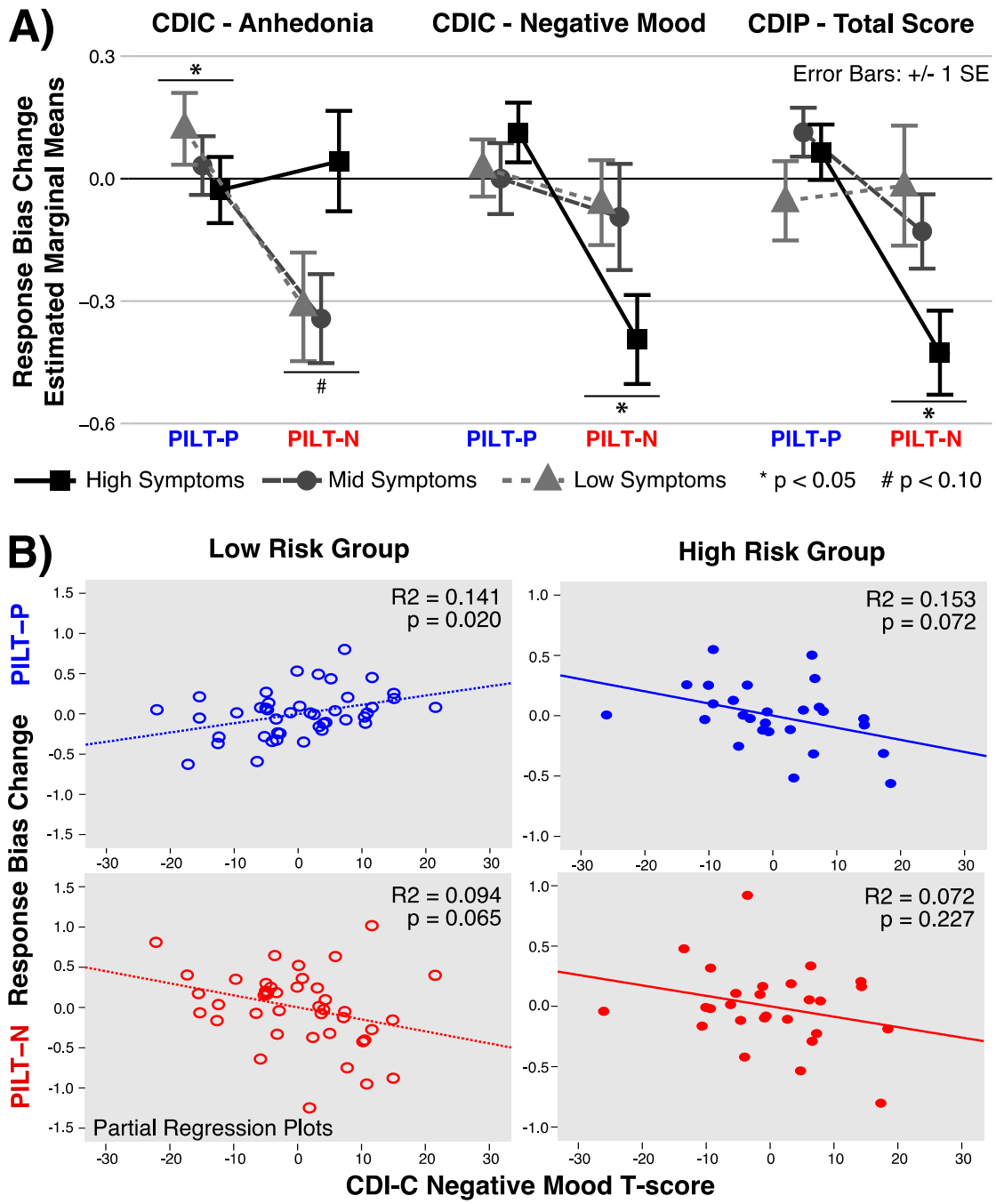


Figure 5.2: Response Bias Change Relations With Anhedonia, Negative Mood, And General Depressive Symptom Levels

Note: CDI-C = Child Depression Inventory – Child Self-Report, CDI-P = Child Depression Inventory – Parent Report, PILT-P = PILT-Positive (blue), PILT-N = PILT-Negative (red). A) Interactions of Task Type and Symptom Level (Anhedonia, Negative Mood, General Depressive Symptoms-CDIP). B) Partial regression plots depicting Negative Mood prediction of response bias change for each task type and risk group.

PILT-Positive: Across risk groups, elevated anhedonic symptoms significantly related to reduced gain approach behavior (β = -0.38, t = -2.03, p = 0.046; Supplemental Table 5.5, Model 1). Reduced gain approach behavior also related to elevated negative mood, but only amongst *high-risk* children (β = -0.59, t = -1.90, p = 0.072; Figure 5.2B). *Low-risk* children with elevated negative mood showed *enhanced* gain responsivity (β = 0.55, t = 2.43, p = 0.020; Figure 5.2B). Negative mood and general depressive symptoms did not significantly predict PILT-P bias change (all p > 0.25; Supplemental Table 5.7, Model 1).

PILT-Negative: Across risk groups, both elevated negative mood symptoms (child-report CDI-C) and general depressive symptoms (maternal-report CDI-P) were significant and independent predictors of *enhanced* loss avoidance (negative mood β = -0.41, t = -2.29, p = 0.026; CDI-P β = -0.33, t = -2.01, p = 0.049; Figure 5.2). Conversely, anhedonic symptoms were only a weak predictor of *blunted* loss avoidance (β = 0.31, t = 1.75, p = 0.085; Supplemental Table 5.5, Model 1).

5.4 Discussion

The aim of the current study was to investigate relations between behavioral responsivity to gain and loss feedback, MDD risk (based on maternal depressive history), and severity of specific depressive symptoms within healthy school age children. First, in contrast to adolescent neuroimaging findings, children's *behavioral* responsivity to gain and loss feedback did not differ based on maternal depressive history. Second, reduced gain approach behavior was related to elevated anhedonic symptoms across risk groups and was related to elevated negative mood symptoms in high-risk children. Third, in low-risk children, enhanced gain approach behavior was related to elevated negative mood symptoms. Fourth, across risk groups, enhanced loss

avoidance behavior related to both elevated negative mood and elevated maternal-report of child general depressive symptoms.

Depression Risk and Incentive-Related Behavior

Contrary to our hypotheses, we did not find a significant effect of depression risk on either gain or loss responsivity. This was notable given evidence of reduced *neural* responsivity to gain/positive stimuli with elevated MDD risk in the adolescent literature.(Gotlib et al 2010, McCabe et al 2012, Monk et al 2008, Olino et al 2014) The first concern when interpreting this null results is power. With that said, the current high-risk sample includes 28 children while previous adolescent neuroimaging studies report significant group differences using high-risk samples roughly half our size (N=17 Monk et al (2008)(Monk et al 2008), N=14 Olino et al (2014)(Olino et al 2014), N=13 Gotlib et al (2010)(Gotlib et al 2010), N=14 Goff et al (2013)(Goff et al 2013)). Thus, we are better powered to detect between group differences of the size observed in the extant adolescent neuroimaging literature; yet, it is likely that differences in incentive responsivity between groups at high-/low-risk for MDD are simply small during childhood and increase during adolescence based on the normative developmental shift in reward motivation. For example, a cross-sectional study investigating extreme early life stress/neglect as a risk factor for MDD observed reduced ventral striatal responses to happy faces within high-risk adolescents (11-15 years), but not in the child group (5-10 years).(Goff et al 2013) Larger longitudinal studies that follow participants from early childhood through adolescence are needed to explicitly test this hypothesis.

It is also important to note that the studies investigating depression risk discussed above focus on neural responsivity to incentives/positive stimuli rather than behavior. There is evidence suggesting that neural markers may either be more sensitive to group differences (larger effect

size) (Dawson 2008, Ibanez et al 2012, Manoach & Agam 2013) or predict future increases in symptoms.(Bress et al 2013a, Morgan et al 2013) It is also possible that *healthy* high-risk children are able to employ compensatory strategies eliminating differences in behavior (in low-demand laboratory situations) despite potential differences in neural function. Future studies are needed to investigate whether incentive processing differences are (more) evident under stress or after mood induction or whether this finding represents an important developmental difference between school age children and adolescents.

Factors Relating to Gain Approach Behavior

As hypothesized, children who reported elevated anhedonic symptoms also showed reduced gain approach behavior. This result is conceptually consistent with previous PILT-P studies in non-clinical adult (Huys et al 2013, Pizzagalli et al 2005) and non-clinical low-risk child (Luking et al 2015) samples. This finding is also conceptually consistent with the adolescent neuroimaging literature where reduced striatal response to gain feedback relates to reduced daily experience of positive affect.(Forbes et al 2009) Reduced gain approach behavior was also observed in high-risk children who reported elevated negative mood. This relation is not surprising given the extant literature pointing to *reduced* striatal response to positive feedback/stimuli with elevated depressive symptoms and positive attenuation theories of emotional reactivity in MDD.(Clark et al 1994, Forbes et al 2010, Forbes et al 2007, Olino et al 2014) However, the opposite pattern of *elevated* gain approach behavior was observed in *low-risk* children endorsing similar levels of elevated negative mood. This interesting and unexpected finding could suggest that low-risk children display an adaptive response to elevated negative mood by actively seeking out reward, in contrast to high-risk children who, with the same elevations in negative mood, show reward avoidance. Given that high- and low-risk groups

endorsed similar levels of negative mood symptoms, differences in behavioral relations cannot be interpreted as being based on negative mood severity. However, in addition to the interpretation above, other factor(s) not examined here, that may differ across groups, such as parenting style, dampening of positive affect, and the relation between levels of positive and negative mood, may mediate the group difference in this relation. As no other studies, to our knowledge, have compared relations between gain responsivity and negative mood symptoms in similar populations, future studies are needed to first replicate this group difference and then examine potential mediators.

Factors Relating to Loss Avoidance Behavior

Across risk groups, elevated loss avoidance related to both elevated child-reported negative mood and maternal-report of child depressive symptoms (CDI-P). These relations are consistent with negative potentiation theories of emotion reactivity in MDD, where current negative mood is thought to potentiate responsivity to negative stimuli.(Beck 1976, Scher et al 2005) It is interesting that both negative mood and CDI-P related to reduced loss responsivity and explained unique variance in loss-related behavior given that the two reports are not significantly related in this study or the extant literature.(Achenbach et al 1987) This provides further support for using maternal and child reports as separate predictors of behavior, a strategy that some investigators have begun to use when investigating neural response to incentives/affective stimuli.(Bress et al 2012, Pagliaccio et al 2012) Future studies are needed to replicate this finding and to explore the mechanisms of these unique predictions.

Given prior adult and child work relating elevated anhedonia/reduced hedonic capacity to blunted responsivity to both gain and loss feedback,(Chase et al 2010, Luking et al 2015, Steele et al 2007) we expected to observe reduced loss avoidance in children reporting elevated

anhedonic symptoms. While we did observe a negative relation between anhedonic symptoms and loss avoidance, it was only a trend level relation (p=0.085). However, given the extant literature supporting blunted reactivity with elevated anhedonia, and that the direction of the relation between loss responsivity and anhedonia is in the opposite direction of that with negative mood and CDI-P, we suggest that future studies utilize anhedonia and negative mood as separate predictors particularly of loss-related behavior.

Limitations/Future Directions

We focused on maternal history of psychopathology to define MDD risk. Although maternal MDD is among the most robust risk factors for MDD, there are other sources of risk that we did not investigate, such as trauma/stress and paternal psychopathology. Future studies defining 'risk' in different ways are needed to replicate the current null result of risk status and the significant dimensional relations between symptoms and behavior. The generalizability of the current results is also somewhat limited by our exclusion of children with any type of past/current pathology given that onset of disorders such as GAD and ADHD often predates MDD diagnosis and maternal MDD also confers increased risk for these disorders. Thus, although excluding such children is necessary for investigating true effects of 'risk' versus pathology, future studies are needed to determine whether MDD risk relates to incentive processing in children with different types of pathology.

Conclusions

Although MDD risk based on a maternal history of depression was not significantly related to either gain or loss responsivity in healthy school age children, individual differences in children's subclinical depressive symptom severity did predict both types of behavior. The current results show continuity with the extant adult literature in that anhedonic symptoms

related to reduced reward responsivity and elevated negative mood symptoms related to elevated loss responsivity. This suggests that mechanisms subserving relations between specific depressive symptoms and incentive-related behaviors may be conserved across development. However, high- and low-risk children showed differing directions in the relation between negative mood and gain responsivity. If this finding reflects a true difference in behavior, maintaining elevated gain approach despite negative mood may indicate resilience and be a proactive target for intervention. This unexpected finding would be an important issue for future study. In sum, our results support examining reports of specific depressive symptoms by different reporters as separate predictors of incentive-related behavior. Developmental differences in these relations between school age and adolescence may be important to inform risk trajectories or developmentally specific approaches.

5.5 Supplemental Information

Probabilistic Incentive Learning Task (PILT)

Task Design

To assess behavioral responsivity to gain/loss feedback we used versions of the probabilistic reward task developed by (Heerey et al 2008); (Pizzagalli et al 2005); (Tripp & Alsop 1999)) and previously modified for use in child populations (Luking et al 2015). All children completed the PILT-P followed by the PILT-N and each task was comprised of three blocks of 40 trials.

During both tasks either a short or long mouth/nose is briefly presented (stimulus type counterbalanced across participants and differed for each task for a given child) (Figure 5.1A). Children then indicate via a button press which stimulus was shown. Stimuli are presented in a pseudorandom order (50% long trials, 50% short trials) and one of the two responses is preferentially incentivized such that during the PILT-P/N correctly/incorrectly selecting that response, designated the 'RICH' response, is scheduled to receive 3 times as much gain/loss feedback as the alternate, 'LEAN', response. Which of the two buttons corresponded to the 'RICH' response and which buttons indicated the 'short' versus 'long' stimulus were counterbalanced across participants. During practice children were told that only some correct/incorrect responses would receive feedback during the PILT-P/N respectively and that a blank screen would follow remaining responses. Importantly, children were not informed that one response would receive more frequent feedback.

To increase difficulty, and thus incorrect responses that could receive feedback, a perceptual mask (row/column of pound signs) replaced the nose/mouth stimulus during the PILT-N. However, the absolute number of gain/loss feedback instances and the exact rich to lean

feedback ratio did differ across participants during both PILTs as a function of accuracy (all $p < 0.001$). While this is not uncommon for the PILT, particularly in children (Luking et al 2015), it is important to note that neither amount nor ratio of RICH:LEAN feedback events for either task significantly differed across risk groups (all $p > 0.14$) and the ratio of rich to lean feedback was not significantly related to any covariates of interest (all $p > 0.13$).

Data Processing

As in previous studies, individual trials where reaction time (RT) did not fall within +/- three standard deviations of a participants' mean RT or RT or did not fall between 2500 and 150 msec were excluded (Luking et al 2015, Pizzagalli et al 2005). Performance and behavioral responsivity to incentive feedback were examined via discriminability (log d) and response bias statistics respectively. Log b/d were calculated as in previous PILT studies, using all trials in a block (40 here) and adding 0.5 to counts of the four event types (Pizzagalli et al 2005).

$$Discriminability\ (\log d) = \frac{1}{2}\log\left(\frac{RICHcorrect * LEANcorrect}{RICHincorrect * LEANincorrect}\right)$$

As expected given the addition of a perceptual mask to the PILT-N, discriminability was significantly lower in the PILT-N than PILT-P (main effect of Task Type; $F(1,70) = 24.14$, $p < 0.001$; Supplemental Table 5.5). Discriminability did not differ significantly based on risk group (main effect of Risk Group, $F(1,70) = 1.40$, $p = 0.240$; interaction of Task Type and Risk Group, $F(1,70) < 0.01$, $p = 0.968$).

Supplemental Table S5.1

Comorbid Diagnoses for High-Risk and Other-Risk Groups via Structured Clinical Interview for DSM Disorders (SCID)

SCID - Past or Present	High MDD-Risk N = 28	Other-Risk N = 21
MDD	7	--
Bipolar II	1	--
Bipolar I	--	3
Anxiety	--	7
Anxiety & MDD	10	--
MDD, Anxiety & Substance	6	--
Substance abuse/dependence	--	3
Substance & MDD	4	2 (use during pregnancy)
Substance & Schizophrenia	--	1
Substance, Schizophrenia, & Anxiety	--	1
Never Disordered via SCID, but previous diagnosis/medication from other clinician	--	4

Note: MDD = Major Depressive Disorder

Supplemental Table S5.2
Individual Difference Questionnaires Administered but not Analyzed by Reporter/Subject

CHILD SELF REPORT

Positive and Negative Affective Scales - Child Version (Laurent et al 1999)
Behavioral Inhibition/Behavioral Activation Scales - Child Version (Muris et al 2005)
Response To Positive Affect Scale (Feldman et al 2008)

Child Pleasure Scale (Kazdin 1989)

Children's Emotion Management Scale (Zeman et al 2001)
Mood and Feelings Questionnaire (Angold et al 1995)

Life Events Checklist

Children's Response Styles Questionnaire (Abela et al 2007)
Guilt Inventory (Jones et al 2000)
Handedness Form

MOM ABOUT CHILD

Mood and Feelings Questionnaire (Angold et al 1995)

Child Pleasure Scale (Kazdin 1989)

Emotion Regulation Checklist (Shields & Cicchetti 1997)
Child Sleep Habits Questionnaire (Owens et al 2000)

Life Events Checklist

MOM SELF REPORT

Positive and Negative Affective Scales (Watson et al 1988)
Behavioral Inhibition/Behavioral Activation Scale (Carver & White 1994)
Response To Positive Affect Scale (Feldman et al 2008)
Snaith Hamilton Pleasure Scale (Snaith et al 1995)
Beck's Depression Inventory (Beck et al 1996)
Ruminative Responses Scale (Treynor et al 2003)
Emotion Regulation Questionnaire (Garnefski & Kraaij 2007)

Supplemental Table S5.3
Repeated Measures ANOVA investigating effects of Task Type, Block, and Stimulus Type on Response Bias

Interaction Type	Factor/Covariate	F-Statistic	P-Value
Main Effects	Task Type	49.39	< 0.001
	PILT-P Stimulus Type	1.29	0.261
Interactions with Task Type	PILT-P Stimulus Type	0.80	0.376
	Block	17.62	< 0.001
Interactions with Task Type and Block	PILT-P Stimulus Type	1.64	0.205

Note: PILT-P = Probabilistic Incentive Learning Task - Positive

Supplemental Table S5.4
Repeated Measures ANOVA investigating effects of Task Type, Risk Group, and Stimulus Type on Mean Discriminability

Interaction Type	Factor/Covariate	F-Statistic	P-Value
Main Effects	Task Type	22.54	< 0.001
	PILT-P Stimulus Type	5.62	0.021
	Risk Group	1.40	0.240
Interactions with Task Type	PILT-Positive Stimulus Type	29.07	< 0.001
	Risk Group	< 0.01	0.968

Note: PILT-P = Probabilistic Incentive Learning Task - Positive

Supplemental Table S5.5

Repeated Measures ANOVA investigating effects of Task Type, Block, Stimulus Type, Risk Group, and Symptom levels on response bias

Interaction Type	Factor/Covariate	F-Statistic	P-Value
Main Effects	Task Type	1.46	0.232
	Risk Group (0=Low-Risk, 1=High-Risk)	0.37	0.547
	PILT-P Stimulus Type	1.83	0.181
	CDIC Negative Mood	0.01	0.931
	CDIC Anhedonia	0.12	0.728
	CDIP General Depressive Symptoms	1.12	0.295
	CBCL Anxiety Problems	2.64	0.110
	CBCL ADHD Problems	0.02	0.897
Two-Way Interactions with Risk Group	CDIC Negative Mood	0.96	0.332
	CDIC Anhedonia	0.46	0.499
	CDIP General Depressive Symptoms	0.51	0.478
Two-Way Interactions with Task Type	Block	0.56	0.456
	Risk Group (0=Low-Risk, 1=High-Risk)	0.01	0.941
	PILT-P Stimulus Type	0.52	0.473
	CDIC Negative Mood	2.87	0.096
	CDIC Anhedonia	1.62	0.208
	CDIP General Depressive Symptoms	0.57	0.453
	CBCL Anxiety Problems	2.50	0.119
	CBCL ADHD Problems	0.10	0.756
Three-Way Interactions with Task Type and Risk Group	CDIC Negative Mood	0.78	0.381
	CDIC Anhedonia	0.62	0.435
	CDIP General Depressive Symptoms	0.02	0.883
Three-Way Interactions with Task Type and Block	Risk Group (0=Low-Risk, 1=High-Risk)	0.03	0.870
	PILT-P Stimulus Type	1.08	0.303
	CDIC Negative Mood	**4.19**	**0.045**
	CDIC Anhedonia	**5.34**	**0.024**
	CDIP General Depressive Symptoms	**6.08**	**0.017**
	CBCL Anxiety Problems	0.33	0.569
	CBCL ADHD Problems	1.53	0.221
Four-Way Interactions with Task Type, Block, and Risk Group	**CDIC Negative Mood**	**5.39**	**0.024**
	CDIC Anhedonia	3.57	0.064
	CDIP General Depressive Symptoms	< 0.01	0.975

Note: CDIC = Child Depression Inventory Child Self-Report, CDIP = Child Depression Inventory Parent Report, CBCL = Child Behavior Checklist, ADHD = Attention Deficit Hyperactivity Disorder, PILT-P = Probabilistic Incentive Learning Task - Positive. All symptom measures reflect age/gender-normalized t-scores.

Supplemental Table S5.6

Post Hoc Regressions Response Bias Change (Block 3 – Block 1) for Each Task Type (Positive and Negative)

Model	Predictors	PILT-Positive			PILT-Negative		
		St. Beta	T-score	P-value	St. Beta	T-score	P-value
1	Model Fit Statistics	R2=.14; Adj R2=.06; F=1.72; p=.131			R2=.21; Adj R2=.13; F=2.69; p=.022		
	PILT-P Stimulus Type	0.08	0.69	0.493	**0.25**	**2.19**	**0.032**
	Risk Group (0=low; 1=high)	0.01	0.04	0.967	-0.02	-0.13	0.895
	CDIC Negative Mood	0.18	0.98	0.333	**-0.41**	**-2.29**	**0.026**
	CDIC Anhedonia	**-0.38**	**-2.03**	**0.046**	0.31	1.75	0.085
	CDIP Total	0.19	1.15	0.254	**-0.33**	**-2.01**	**0.049**
	CBCL Anxiety Symptoms	0.09	0.61	0.547	0.14	1.02	0.312
	CBCL ADHD Symptoms	0.07	0.48	0.635	0.28	1.82	0.074
2	Model Fit Statistics	R2=.29; Adj R2=.18; F=2.67; p=.011			R2=.21; Adj R2=.09; F=1.74; p=.100		
	PILT-P Stimulus Type	0.13	1.08	0.283	0.23	1.88	0.065
	Risk Group (0=low; 1=high)	0.19	0.22	0.827	0.33	0.34	0.734
	CDIC Negative Mood	**0.67**	**2.99**	**0.004**	**-0.47**	**-2.01**	**0.050**
	CDIC Anhedonia	**-0.80**	**-3.49**	**0.001**	0.36	1.52	0.134
	CDIP Total	0.34	1.47	0.146	-0.26	-1.06	0.293
	CBCL Anxiety Symptoms	0.07	0.55	0.585	0.14	1.02	0.313
	CBCL ADHD Symptoms	0.06	0.37	0.714	0.26	1.65	0.104
	Risk Group x Negative Mood	**-2.19**	**-3.36**	**0.001**	0.33	0.47	0.638
	Risk Group x Anhedonia	**2.50**	**2.78**	**0.007**	-0.34	-0.36	0.722
	Risk Group x CDIP Total	-0.56	-0.66	0.509	-0.36	-0.40	0.690

Note: CDIC = Child Depression Inventory Child Self-Report, CDIP = Child Depression Inventory Parent Report, CBCL = Child Behavior Checklist, ADHD = Attention Deficit Hyperactivity Disorder, PILT-P = Probabilistic Incentive Learning Task - Positive All symptom measures reflect age/gender normalized t-scores.

Supplemental Table S5.7

Post Hoc Repeated Measures ANOVAs Investigating Effects of Task Type, Stimulus Type, and Symptom Levels on Response Bias Change (Block 3 – Block 1) Within Low and High-Risk Groups

Risk Group	Interaction Type	Factor/Covariate	F-Statistic	P-Value
Low-Risk Group	Main Effect	PILT-P Stimulus Type	1.08	0.305
		CDIC Negative Mood	0.13	0.723
		CDIC Anhedonia	0.01	0.908
		CDIP Total	0.31	0.580
		CBCL Anxiety Symptoms	1.87	0.180
		CBCL ADHD Symptoms	1.96	0.171
	Interaction with Task Type	PILT-P Stimulus Type	0.38	0.539
		CDIC Negative Mood	**9.27**	**0.004**
		CDIC Anhedonia	**7.82**	**0.008**
		CDIP Total	1.39	0.246
		CBCL Anxiety Symptoms	0.00	0.982
		CBCL ADHD Symptoms	0.60	0.443
High-Risk Group	Main Effect	PILT-P Stimulus Type	4.24	0.053
		CDIC Negative Mood	**4.72**	**0.042**
		CDIC Anhedonia	1.71	0.206
		CDIP Total	0.78	0.386
		CBCL Anxiety Symptoms	0.40	0.536
		CBCL ADHD Symptoms	1.17	0.293
	Interaction with Task Type	PILT-P Stimulus Type	0.93	0.345
		CDIC Negative Mood	0.02	0.876
		CDIC Anhedonia	0.09	0.761
		CDIP Total	4.07	0.057
		CBCL Anxiety Symptoms	0.62	0.441
		CBCL ADHD Symptoms	0.48	0.498

Note: CDIC = Child Depression Inventory Child Self-Report, CDIP = Child Depression Inventory Parent Report, CBCL = Child Behavior Checklist, ADHD = Attention Deficit Hyperactivity Disorder, PILT-P = Probabilistic Incentive Learning Task - Positive. All symptom measures reflect age/gender-normalized t-scores.

Supplemental Table S5.8

Post hoc Regressions Within Low and High-Risk Groups Predicting Response Bias Change (Block 3 – Block 1) for Each Task Type (Positive and Negative)

Risk Group	Predictors	PILT-Positive Bias Change St. Beta	T-score	P-value	PILT-Negative Bias Change St. Beta	T-score	P-value
Low-Risk	Model Fit Statistics	R2=.34; Adj R2=.23; F=3.08; p=.015			R2=.16; Adj R2=.02; F=1.11; p=.375		
	PILT-P Stimulus Type	0.08	0.53	0.600	0.16	0.99	0.331
	CDIC Negative Mood	**0.55**	**2.43**	**0.020**	-0.48	-1.91	0.065
	CDIC Anhedonia	**-0.63**	**-2.70**	**0.010**	0.39	1.48	0.148
	CDIP Total	0.11	0.50	0.618	-0.25	-1.00	0.325
	CBCL Anxiety Symptoms	0.23	1.42	0.164	0.15	0.83	0.412
	CBCL ADHD Symptoms	0.15	0.74	0.463	0.30	1.29	0.205
High-Risk	Model Fit Statistics	R2=.22; Adj R2=-.01; F=0.95; p=.483			R2=.36; Adj R2=.17; F=1.88; p=.135		
	PILT-P Stimulus Type	0.18	0.87	0.396	0.35	1.89	0.073
	CDIC Negative Mood	-0.59	-1.90	0.072	-0.35	-1.25	0.227
	CDIC Anhedonia	0.25	0.80	0.431	0.28	1.01	0.326
	CDIP Total	0.24	0.97	0.346	-0.41	-1.84	0.081
	CBCL Anxiety Symptoms	-0.03	-0.14	0.887	0.18	0.89	0.383
	CBCL ADHD Symptoms	0.08	0.30	0.767	0.27	1.11	0.280

Note: CDIC = Child Depression Inventory Child Self-Report, CDIP = Child Depression Inventory Parent Report, CBCL = Child Behavior Checklist, ADHD = Attention Deficit Hyperactivity Disorder, PILT-P = Probabilistic Incentive Learning Task - Positive. All symptom measures reflect age/gender normalized t-scores.

Chapter 6.

Reduced Hedonic Capacity/Approach Motivation Relates to Blunted Responsivity to Gain and Loss Feedback in Children

This chapter is in press at the Journal of Clinical Child and Adolescent Psychology. My contributions to this paper included data collection, data analysis, and writing.

Reference: Luking KR, Neiman JS, Luby JL, & Barch DM. Reduced Hedonic Capacity/Approach Motivation Relates to Blunted Responsivity to Gain and Loss Feedback in Children. Journal of Clinical Child and Adolescent Psychology (2015) 10.1080/15374416.2015.1012721

Abstract

Objective: Adolescents and adults with Major Depressive Disorder or elevated depressive symptoms show reduced reward responses and tend to show enhanced responses to negative stimuli. However, reward-related behaviors and adaptive responses to negative feedback undergo dramatic changes across puberty. Thus, key questions remain regarding how altered incentive processing relates to depressive and anhedonic symptoms in pre-pubertal child populations. Method: Twenty-four non-clinical pre-pubertal children aged 7-10 years (15 male; 16 Caucasian) completed two signal detection tasks that assessed behavioral responsivity to candy gain and loss feedback, respectively. These tasks were based on Pizzagalli's probabilistic reward task where asymmetric feedback leads to greater bias towards the more frequently rewarded response in more hedonic or non-depressed adults. We further modified the task to create a version where incorrect responses could result in losses from an original allotment of candy. Children and parents/guardians also completed individual difference questionnaires to assess the child's depressive symptoms, general affect, and hedonic capacity/approach motivation. Results: Regressions indicated a relation between hedonic capacity/approach motivation (child self report) and response bias in both gain and loss tasks. No significant relations were observed between depressive (child self report), internalizing (parent report), or externalizing symptoms (parent report) and bias in either the gain or loss task in this small sample. Conclusions: These results suggest that reduced hedonic capacity/approach motivation is associated with blunted responses to both gain and loss feedback in pre-pubertal children.

6.1 Introduction

The relation between Major Depressive Disorder (MDD) and blunted response to reward has been consistently documented both in adult and adolescent MDD literatures (for recent reviews see Auerbach, Admon, & Pizzagalli, 2014; Bogdan, Nikolova, & Pizzagalli 2013; Eshel & Roiser, 2010; Forbes & Dahl, 2012; Treadway & Zald, 2011). Behavioral and neural responses to reward are similarly reduced in adults/adolescents without current clinically diagnosed depression, but with elevated depressive symptoms or at elevated risk for developing depression (Bress, Smith, Foti, Klein, & Hajcak, 2012; Kujawa, Proudfit, & Klein, 2014; McCabe, Woffindale, Harmer, & Cowen, 2012; Pizzagalli, Jahn, & O'Shea, 2005). Conversely, *enhanced* responses to incentive loss and negative affective stimuli have been reported in adults and adolescents with clinically diagnosed depression, elevated depressive symptoms, or elevated risk for developing MDD (Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997; Gotlib et al., 2010; Holmes & Pizzagalli, 2007; McCabe, Cowen, & Harmer, 2009; Monk et al., 2008; Santesso, Steele, Bogdan, Holmes, & Deveney, 2008b). However, reward-related behaviors, adaptive response to negative feedback, and incidence of mood pathology, undergo dramatic changes from childhood to adulthood (Crone, Zanolie, Van Leijenhorst, Westenberg, & Rombouts, 2008; Galvan, 2010; Geier & Luna, 2009; Kessler et al., 2005; Luking, Luby, & Barch., 2014; Richards, Plate, & Ernst, 2013; van den Bos, Cohen, Kahnt, & Crone, 2012; van Duijvenvoorde, Zanolie, Rombouts, Raijmakers, & Crone, 2008). Thus, key questions remain regarding how altered incentive processing relates specifically to self-reported hedonic capacity and other depressive symptoms within pre-pubertal child populations.

Anhedonia, the lack of experienced pleasure, is a key symptom of MDD (APA, 2013). Findings of reduced responsivity to reward in adults with MDD and healthy adults with elevated

anhedonic/depressive symptoms are consistently observed across many task types and components of incentive processing (Dowd & Barch, 2010; Pizzagalli et al., 2009; Santesso et al., 2008a; Schaefer, Putnam, Benca, & Davidson, 2006; Sloan, Strauss, Quirk, & Sajatovic, 1997; Treadway, Bossaler, Shelton, & Zald, 2012; Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). The probabilistic reward task developed by Tripp & Alsop (1999) and used extensively by D. A. Pizzagalli, and others, has proven to be a valuable tool for evaluating behavioral shifts driven by reward. In this task one of two responses receives reward feedback more frequently, this asymmetry typically induces bias towards the more frequently rewarded response. However, individuals with elevated anhedonic depressive symptoms (Pizzagalli et al., 2005), current MDD (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008b), and remitted depression (Pechtel, Dutra, Goetz, & Pizzagalli, 2013) show less of this response bias, indicating reduced behavioral responsivity to reward. Reduced response to reward is similarly well documented across experimental modalities in the adolescent MDD literature (for recent reviews see Auerbach et al., 2014; Forbes & Dahl, 2012). Adolescents with MDD or elevated depressive symptoms are less able to use reward contingencies to improve performance (via cognitive control) (Hardin, Schroth, Pine, & Ernst, 2007; Jazbec, McClure, Hardin, Pine, & Ernst, 2005), are less sensitive to incentive magnitude (Forbes, Shaw, & Dahl, 2007), and show reduced neural responsivity to reward feedback (Bress et al., 2012; Forbes et al., 2006; Forbes et al., 2010).

Within negative affective domains the effects of MDD/depressive symptoms are more mixed. The negative potentiation theory of emotion reactivity in MDD suggests that reactivity to negative stimuli is enhanced as negative mood states prime cognitive and attention biases towards congruent stimuli (Beck, 1976; Scher, Ingram, & Segal, 2005). There is experimental evidence supporting this hypothesis both within the basic neuroscience literature and in patient

groups. For example, amygdala reactivity to negative stimuli is enhanced following induction of negative mood states (Berna et al., 2010; Wang, LaBar, & McCarthy, 2006), and MDD/high-risk groups, who experience greater negative mood relative to control/low-risk groups, tend to show *enhanced* behavioral/neural responsivity to negative pictures/feedback (Elliott et al., 1997; Foland-Ross et al., 2013; Gotlib et al., 2010; Hamilton & Gotlib, 2008; Holmes & Pizzagalli, 2007; Kellough, Beevers, Ellis, & Wells, 2008; Ladouceur et al., 2005; McCabe et al., 2012; Monk et al., 2008; Santesso et al., 2012; Santesso et al., 2008b; Tucker, Luu, Frishkoff, Quiring, & Poulsen, 2003). However this effect is not universal and other theories, such as Emotion Context Insensitivity (ECI), hypothesize a general *reduction* in reactivity to both positive and negative stimuli in MDD (Rottenberg, Gross, & Gotlib, 2005; Rottenberg, 2007) A recent meta-analysis of studies investigating emotional reactivity in MDD by Bylsma et al., 2008 reports significantly *blunted* reactivity to negative as well as positive stimuli in MDD across studies. Further support for ECI is provided by studies specifically investigating anhedonic symptoms within the incentive literature. These studies report *blunted* behavioral and neural responsivity to both positive and negative incentives in individuals with elevated anhedonia in patient and control groups (Chase et al., 2010; Dowd & Barch, 2010; Steele, Kumar, & Ebmeier, 2007, Stoy et al., 2012). As no studies, to our knowledge, have investigated how responsivity to loss of incentive relates to MDD or anhedonic symptoms specifically in children, it is unclear whether potentiated or blunted responses to loss/negative stimuli will be observed with elevated symptoms at these ages.

Although relations between MDD and responsivity to affective stimuli/incentive feedback are strikingly similar in the adolescent and adult literatures, normative responses to positive and negative incentives change dramatically from childhood through adulthood. These

developmental changes may impact how depressive symptoms relate to gain and loss responsivity in pre-pubertal populations relative to adolescents and adults. From a typical developmental standpoint, adolescents show markedly elevated sensitivity to reward relative to both children and adults, who tend to show similar responses to reward (Galvan, Hare, Parra, Penn, & Voss, 2006; Luking et al., 2014; Paulsen, Carter, Platt, Huettel, & Brannon, 2011; Richards et al., 2013; van den Bos et al., 2012). Conversely, emerging evidence suggests that children are particularly reactive to loss/negative feedback relative to adults and adolescents (Luking et al., 2014; van den Bos et al., 2012; van Duijvenvoorde et al., 2008; van Leijenhorst, Crone, & Bunge, 2006). Thus, it seems especially important to investigate responding to both gains and losses in pre-pubertal populations, as loss may be a particularly powerful domain for detection of individual difference relations in this age group.

It is also important to note that although we have chosen to focus on MDD/depressive symptoms to motivate the current study, altered responsivity to incentives, as well as anhedonia, play prominent roles in psychopathology beyond MDD. For example, behavior on the probabilistic reward task also relates to ADHD in children (Tripp & Alsop, 1999), bipolar disorder in adults (Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008a), and comorbid MDD and substance abuse in adolescents (Boger et al., 2014). Altered responsivity to incentives is also observed in schizophrenia (Dowd & Barch, 2012; Heerey, Bell-Warren, & Gold, 2008), disordered eating (Loxton & Dawe, 2001), oppositional defiant disorder (Humphreys & Lee, 2011), and anxiety (Bress, Meyer, & Hajcak, 2013b; Johnson, Turner, & Iwata, 2003). Further, patterns of gain/loss sensitivity within diagnostic (risk) groups often differ depending on comorbid disorders (e.g. Humphreys & Lee, 2011; Kujawa et al., 2014). Given these relations, and that relative incidence of types of pathologies change over development (i.e. age of onset for

anxiety disorders is earlier than for MDD and incidence of anxiety disorders is greater than that of MDD, particularly in childhood (Kessler et al., 2005), we take care to control for both externalizing (indexing ADHD, oppositional defiant, and conduct disorder symptoms) and internalizing (indexing anxiety and depression) symptoms in our analyses although our hypotheses center on depressive symptoms.

While gain and loss behaviors relate to depressive symptoms even within non-clinical populations from adolescence onward, how such behaviors relate to depressive symptoms and hedonic capacity during childhood remains an important open question. Thus, the current study aims to investigate such relations while controlling for other types of symptoms related to gain/loss processing (i.e. internalizing and externalizing). To assess gain responsivity, children completed a modified version of the probabilistic reward task used extensively in the adult depression literature (Pizzagalli et al., 2008b; Pizzagalli et al., 2005), where children earned candy following some correct responses. To assess loss responsivity a second modified version of the traditional task was completed, in which children lost candy from an original allotment following some incorrect responses. Although we operationalize gain responsivity and loss responsivity as the tendency of such feedback to influence behavior and investigate each separately, it is important to note that neural systems responsive to gain and loss and involved in approach/avoidance behaviors are not entirely unique (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Delgado, Stenger, & Fiez, 2004; Knutson, Westdorp, Kaiser, & Hommer, 2000). Thus, gain and loss responsivity are not necessarily orthogonal. However, as previous literature using the probabilistic reward task focuses on responsivity to gain, and different symptom types (e.g. internalizing versus externalizing) relate differentially to reward/punishment sensitivity, we form separate hypotheses for gain and loss responsivity.

The adult probabilistic reward task literature clearly points to reduced responsivity to gain feedback in individuals with MDD or elevated anhedonic depressive symptoms (Huys, Pizzagalli, Bogdan, & Dayan. 2013; Pizzagalli et al., 2008b; Pizzagalli et al., 2005). Thus, we hypothesize that reduced self-reported hedonic capacity or elevated depressive symptoms will relate to reduced behavioral responsivity to gain feedback in our child sample. Further, given evidence of blunted responsivity to negative stimuli with elevated anhedonic depressive symptoms or reduced hedonic capacity in adults, we expect lower self-reported HC/AM to similarly relate to lower loss responsivity in our pre-pubertal sample. The adult MDD literature has been inconsistent in regards to how general depressive symptoms relate to loss responsivity. Further, different conceptual models of negative stimuli processing in MDD make different predictions with ECI predicting blunted responsivity to negative stimuli/feedback and negative potentiation predicting enhanced responsivity to negative stimuli/feedback, with neither model having been examined in children. Therefore, it is unclear whether or how general depressive symptoms will relate to behavioral loss sensitivity.

6.2 Method

Participants

Twenty-eight children along with a parent/guardian participated in this study. Two children were unable to understand and follow instructions for the behavioral tasks and two adults failed to complete reports on the child, thus four children are excluded from analyses. The remaining 24 children were aged 7-10 years (mean 8.21, standard deviation 0.98) and were predominately male (n=15; 62.5%) and Caucasian (n=16; 66.7%). All children were pre-pubertal, established via parent/guardian Pubertal Staging Questionnaire reports (Carskadon & Acebo, 1993; Petersen, Crockett, Richards, & Boxer, 1988). A history of diagnosed mental illness, either

for the child or immediate family members (adult report), and inability to consume sugar or dislike of sweet candies served as exclusion criteria. Despite a lack of reported pre-existing diagnoses (no clinical interviews were conducted), parent reports of internalizing/externalizing behaviors on the Child Behavior Checklist (CBCL) fell within the 'borderline to clinical' range for five children (Achenbach, 1991). Thus, we characterize the sample as 'non-clinical' rather than 'healthy'.

Participants were recruited from the St. Louis, Missouri metropolitan area via the research participant registry at Washington University in St. Louis. Adults completed a phone screen to determine the children's eligibility prior to enrolling in the study. Parents/guardians provided written informed consent and children provided written assent at the beginning of the in-person assessment. The Washington University in St. Louis Institutional Review Board approved all study procedures.

Procedure

On the study day adults provided consent and completed questionnaires in an adjacent room. Before beginning behavioral tasks, children tasted two candy pieces of their choice (M&M's® or Skittles®) and rated how much they liked the candy. Two children reported liking the candy 'moderately', four reported 'quite a bit', and eighteen reported 'extremely' (response options also included 'not at all' and 'a little'). Next, children completed two versions of a modified probabilistic incentive learning task (PILT) based on (Heerey et al., 2008; Pizzagalli et al., 2005; Tripp & Alsop, 1999), one where small candy pieces could be gained (PILT-Positive) (Figure 6.1A) and another where candy could be lost (PILT-Negative) (Figure 6.1B) from an original allotment (the order of PILT-P/PILT-N was counterbalanced across participants). Between the two PILTs children completed several individual difference questionnaires with the

assistance of the experimenter. Finally, children completed a post-test questionnaire where they rated affective responses to winning/losing candy.

Individual Difference Measures

Adults completed the Child Behavior Checklist (CBCL) (Achenbach, 1991), parent report version of the Child Depression Inventory (CDI-P) (Kovacs, 1985), and a demographics form. Children completed self-report forms designed to assess depressive symptoms [Child Depression Inventory (CDI-C) (Kovacs, 1985); Short Mood and Feelings Questionnaire (MFQ) (Angold et al., 1995)], general affect [child version of the Positive and Negative Affective Scale (PANAS-C) (Laurent et al., 1999)], and hedonic capacity or reward/punishment sensitivity [modified version of the Child Pleasure Scale (CPS) (Kazdin, 1989); child version of the Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS-C) (Muris, Meesters, de Kanter, & Timmerman, 2005)]. See Table 6.1 for descriptive statistics.

The PANAS-C has positive and negative affective subscales. The positive affect scale is comprised of 15 positive words (e.g. happy, interested, energetic). Children rate the extent to which they experience that emotion, responses range from 1 "very slightly or not at all" to 5 "Extremely", and responses are summed to create a total score. The positive affect scale shows good internal consistency (0.89) and construct validity in that it negatively relates to depressive symptom severity (Laurent et al., 1999).

The CPS consists of 30 items such as "you are eating your favorite ice cream", "Your teacher tells you and your parents what a terrific student you are", "Your mother/father gives you a big hug" and the child rates how happy they would feel in that situation (1=not at all, 2=happy, 3=very happy). CPS responses are summed to create a total score. The CPS shows adequate internal consistency ranging from 0.91 to 0.96 and criterion validity, i.e. children with diagnosed

MDD show significantly lower scores on the CPS than children not diagnosed with depression (Kazdin, 1989; Steele, Phipps, & Srivastava, 1999).

The BAS component of the BIS/BAS consists of 13 items such as, "I get thrilled when good things happen to me", "I get very excited when I would win a contest", "When I see an opportunity to get something that I want, I go for it right away". Responses range from 1 (very true for me) to 4 (very false for me), responses are reverse scored and summed to create a total score. Muris et al.'s BAS has shown adequate internal consistency (0.81) and criterion validity in children, relating to personality traits associated with elevated reward responding (Muris et al., 2005).

The CDI-C consists of 27 sets of items designed to assess different depressive symptoms. Responses on each item set are rated on a scale from 0 to 2 such that higher values indicate greater severity (e.g., 0=I have fun in many things, 1=I have fun in some things, 2=Nothing is fun at all). Items are summed to produce a total score; age and gender normed t-scored total scores are used in the current study. Internal consistencies have been reported from .71 to .94, test-retest reliability is very good ranging from .66 to .90, and shows strong construct validity in a number of studies (Kovacs, 1985; Saylor, Finch, Spirito, & Bennett, 1984; Sitarenios & Kovacs, 1999).

The CBCL consists of 118 items describing behavioral problems such as, "Feels he/she has to be perfect", "Nervous, high-strung, or tense", "Sets fires". The parent then rates on a 3-point scale, from 0 (not at all true) to 2 (true or often), the extent to which each item was true for the child in the past 6 months. Items are summed to create Internalizing (Anxious=Depressed, Withdrawn, and Somatic Complaints) and Externalizing (Aggressive and Destructive) problems subscales; age and gender normed t-scored totals for each subscale are used in the current study.

Internalizing and Externalizing Problems Subscales show excellent internal consistency and test-retest reliability, both >.90 for each subscales as well as strong construct validity (Achenbach & Rescorla, 1991; Nakamura, Ebesutani, Bernstein, & Chorpita, 2009).

All measures were developed specifically for use in the respective population (either child or parent report) and have shown adequate internal consistency and validity. Specifically, within the current sample Cronbach's Alpha (Table 6.1) was above or near the .7 rule-of-thumb cutoff which indicates adequate internal consistency.

Given the conceptual relation between hedonic capacity (CPS), approach motivation (BAS), and positive affect (PANAS-P), strong intercorrelation amongst measures (CPS and BAS $r(28) = 0.45$, $p = 0.017$; CPS and PANAS-P $r(27) = 0.48$, $p = 0.012$; BAS and PANAS-P $r(27) = 0.54$, $p = 0.004$), and the lack of an a priori hypothesis regarding a specific questionnaire/scale versus another, Z-scored total scores from the CPS, BAS, and PANAS-P were summed to create a composite score, hedonic capacity/approach motivation (HC/AM), where greater values indicate greater HC/AM.

Table 6.1: Descriptive Statistics For Individual Difference Measures

Questionnaire	Scale	Range	Mean	Standard Deviation	Cronbach's Alpha	Coefficient of Variation (median centered)
Child Behavior Checklist	Internalizing T-Score	34 – 64	48.79	8.71	0.77	20.5%
	Externalizing T-Score	33 – 64	48.75	8.87	0.83	20.2%
Child Depression Inventory	Child Report Total T-score	35 – 54	43.58	5.09	0.70	11.6%
Positive and Negative Affect Scales	Positive Affect Subscale	48 – 72	60.83	7.56	0.778	12.5%
Behavioral Inhibition/ Behavioral Activation Scales	Behavioral Activation Scale	30 – 51	38.92	6.28	0.87	17.2%
Child Pleasure Scale	Total Score	30 – 59	45.67	8.07	0.87	17.6%
Hedonic Capacity/Approach	Motivation Composite Score	-4 – 4	0.00	2.39		

Probabilistic Incentive Learning Tasks

We employed a modified version of the probabilistic reward task developed by Heerey et al. (2008), Pizzagalli et al. (2005), and Tripp & Alsop, (1999) termed the PILT-Positive (PILT-P) to assess reward sensitivity (Figure 6.1A). To make the task more child-friendly we utilized small candy pieces rather than money as the incentive, and reduced the number of trials relative to previous studies. As in previous versions of this task, either a short or long nose/mouth is briefly presented within a cartoon face (stimuli are presented in a pseudorandom order- 50% long trials, 50% short trials). Participants then indicate which stimulus was presented via button press. During the PILT-P a portion of correct responses are followed by gain feedback indicating one candy piece was won. Remaining correct, and all incorrect, responses are followed by a blank screen. Importantly, this intermittent gain feedback is delivered asymmetrically such that one of the two responses (deemed the 'RICH' response) is scheduled to receive gain feedback three times more often than the alternative 'LEAN' response. Whether the 'RICH' response corresponded to the right or left button and whether that button indicated the short or long stimulus was counterbalanced across participants. Participants were not informed that one response would selectively receive more feedback, however, they were aware that not all correct responses would receive gain feedback.

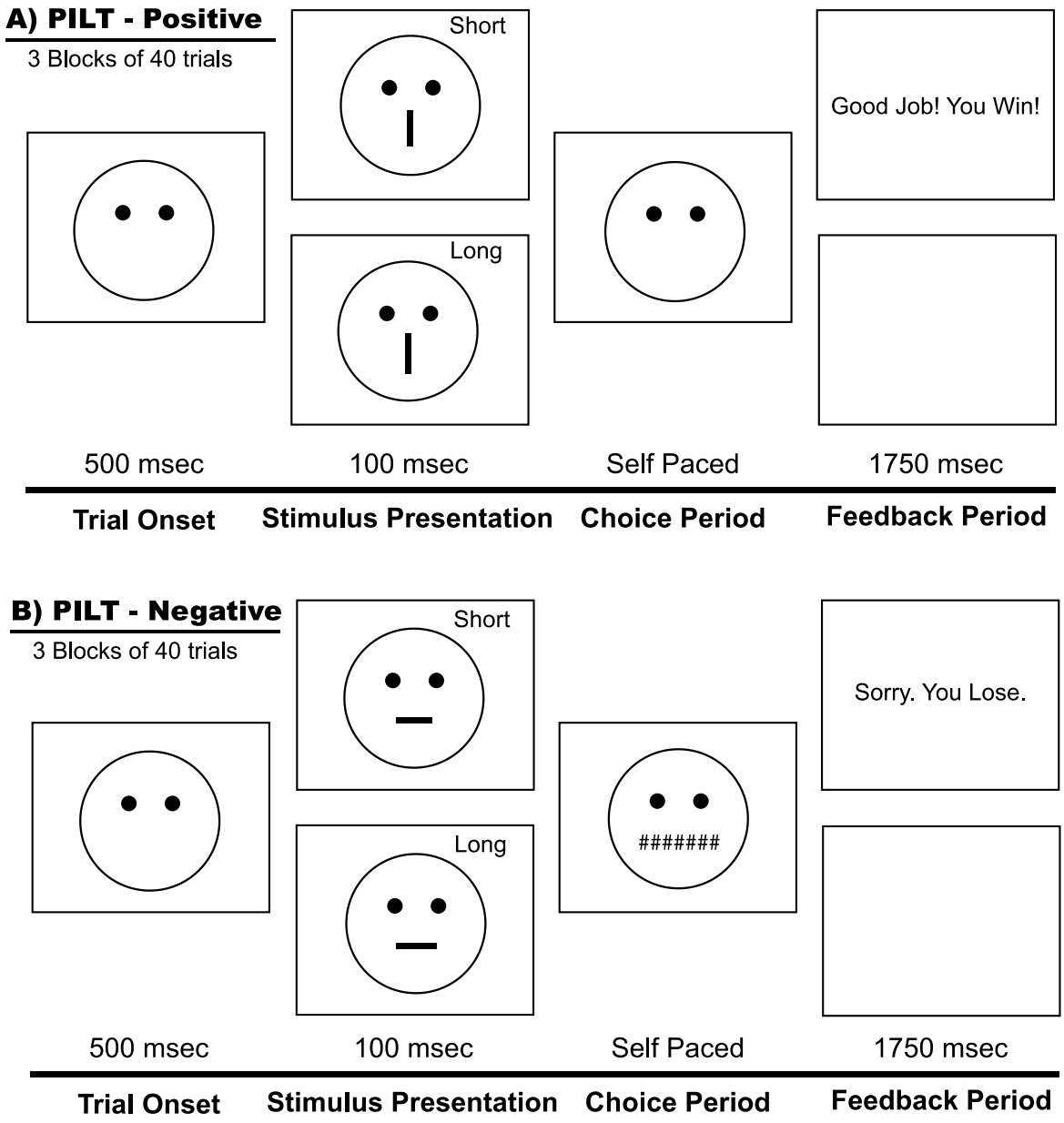


Figure 6.1: Probabilistic Incentive Learning Task (PILT)
Schematics for (A) Positive and (B) Negative task versions

To assess behavioral sensitivity to loss of reward we further modified the PILT to deliver loss feedback; the loss version of the task is termed PILT-Negative (PILT-N). A perceptual mask (row/column of pound signs) replaced the nose/mouth stimulus to decrease task accuracy (PILT-P mean accuracy = 70.5%, sd = 8.2%; PILT-N mean accuracy = 55.3%, sd = 6.6%). This was necessary in order to ensure a sufficient number of trials in which to provide loss feedback. All other task parameters remained the same, except now feedback followed a portion of incorrect responses, again in an asymmetric fashion, and feedback indicated that one candy piece would be lost from an original allotment of 70 candy pieces.

Before beginning each of the PILT tasks children performed 20 practice trials followed by three 40-trial task blocks. Within each task block 12 (in)correct 'RICH' responses and 4 (in)correct 'LEAN' responses were selected to receive candy feedback (loss/gain respectively). Between each block the child and experimenter stood and stretched for approximately 30 seconds.

Data Processing

Individual trials were excluded from analysis either if reaction time (RT) did not fall within +/- three standard deviations of a participants' mean RT or if RT did not fall between 2500 and 150 msec (Pizzagalli et al., 2005). On average less than 5% of trials within a task were excluded for a given subject based on RT criteria. General task performance and responsivity to incentive feedback were examined via discriminability (log d) and response bias (log b) statistics respectively. Log b/d were calculated as in previous PILT studies, using all trials in a block (40 here) and adding 0.5 to the number of each of the four event types (Pizzagalli et al., 2005). Greater values for log d indicate better discrimination between the short and long stimuli. More positive response bias values indicate a greater propensity to select the 'RICH' button response

whereas more negative values indicate a greater shift away from making the 'RICH' button response.

$$Discriminability\ (\log d) = \frac{1}{2}\log\left(\frac{RICHcorrect * LEANcorrect}{RICHincorrect * LEANincorrect}\right)$$

$$Response\ Bias\ (\log b) = \frac{1}{2}\log\left(\frac{RICHcorrect * LEANincorre\square t}{RICHincorrect * LEANcorrect}\right)$$

6.3 Results

Response Bias in the PILT-P and PILT-N

To determine whether response bias changed across the PILT-P/N, a repeated measures ANOVA was conducted for each task with Block (1, 2, 3) as the repeated measure and response bias was the dependent variable. One-sample t-tests were conducted to determine whether bias at the end of the task (Block 3) differed from zero for the PILT-P and PILT-N.

For the PILT-P, bias in B3 differed from zero (t (1,23) = 3.01, p = 0.006) such that participants as a whole tended to select the rich response more frequently than the lean response. Further, response bias increased across the task as a function of block (F (2,23) = 3.21, p = 0.049) (Figure 6.2). For the PILT-N, bias in B3 significantly differed from zero (t (1,23) = -3.72, p = 0.001) such that participants as a whole selected the rich response, more frequently followed by loss feedback, *less* frequently than the lean response. Bias also became more negative across the task as a function of block F (2,23) = 4.54, p = 0.016 (Figure 6.2).

Table 6.2: Intercorrelations Amongst Predictors

Measure	1	2	3	4	5	6	7
1) CDI-C total t-score							
2) CBCL Internalizing Subscale	0.05 (.82)						
3) CBCL Externalizing Subscale	0.08 (.73)	0.64 (<.01)					
4) Hedonic Capacity/Approach Motivation	0.14 (.51)	0.01 (.95)	0.06 (.77)				
5) PILT-P Response Bias in Block 3	0.07 (.76)	0.09 (.67)	-0.22 (.30)	0.42 (.04)			
6) PILT-P Change in Response Bias: Block 3 - Block 1	0.50 (.01)	-0.02 (0.93)	0.06 (.78)	0.03 (.90)	0.08 (.70)		
7) PILT-N Response Bias in Block 3	0.22 (.31)	-0.11 (.60)	-0.39 (.06)	-0.42 (.04)	-0.24 (.26)	0.24 (.27)	
8) PILT-N Change in Response Bias: Block 3 - Block 1	-0.07 (0.74)	-0.17 (.42)	-0.37 (.08)	-0.61 (<.01)	-0.19 (.38)	0.11 (.61)	0.68 (<.01)

Note. Pairwise correlations between dependent variables and predictors in regression analyses; *r* (p-value). Measure abbreviations refer to; CDI-C (Child Depression Inventory – Child Version; total t-score reported), CBCL (Child Behavior Checklist; total t-scores reported); PILT-P (PILT-Positive), PILT-N (PILT-Negative).

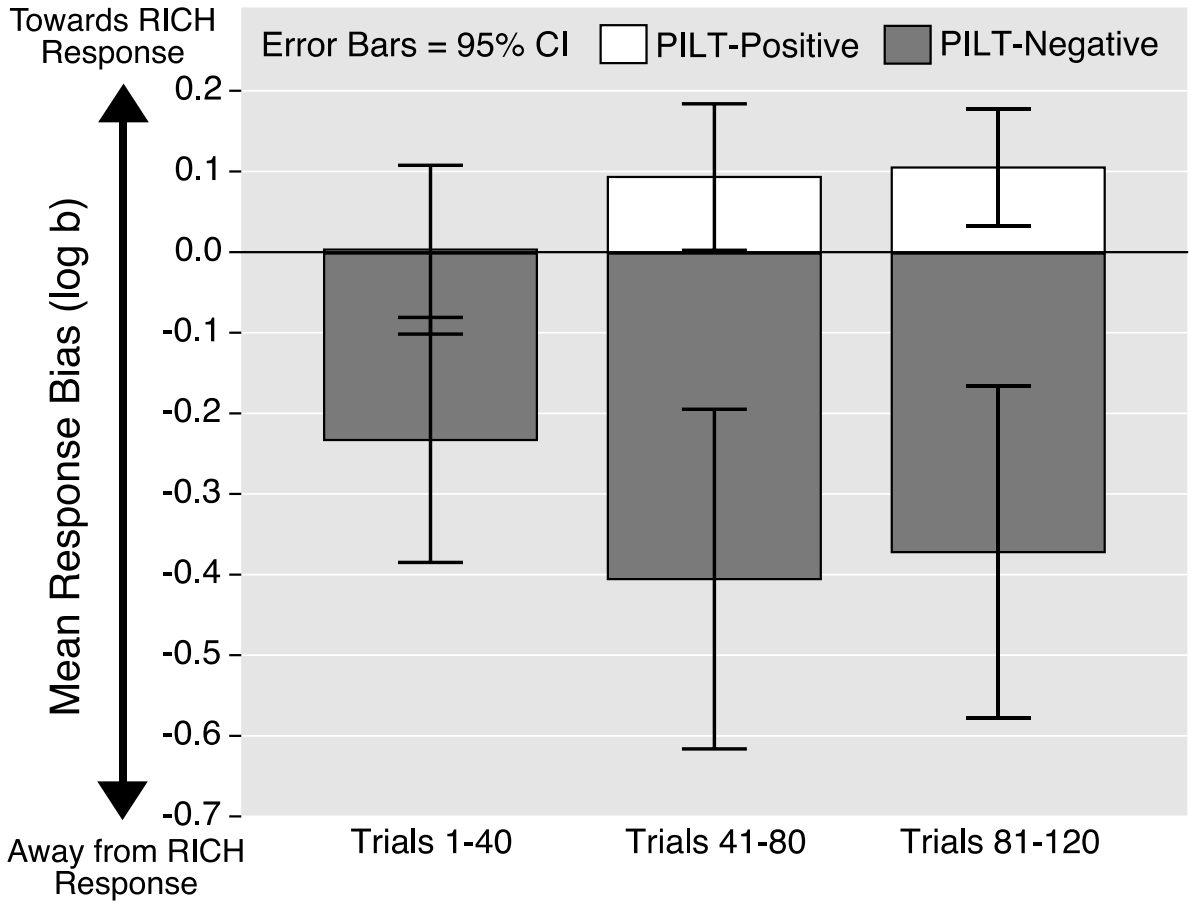


Figure 6.2: PILT-Positive And PILT-Negative Response Bias
Response bias across the PILT-Positive (white bars) and PILT-Negative (gray bars).

Relations between Task Order/Stimuli and Discriminability

Univariate ANOVAs were conducted to determine whether mean discriminability during the PILT-P and PILT-N differed based on PILT-P order (first or second), PILT-P stimulus (mouth or nose), or the interaction of order and stimulus. Mean discriminability in the PILT-P and PILT-N did not vary as a function of either PILT-P order or stimulus type (all $p > .17$).

Relations between Response Bias and Individual Difference Measures

Four regressions were conducted to assess relations between response bias and task order/stimulus type, depressive symptoms (CDI-C t-score), internalizing symptoms (CBCL subscale t-score), externalizing symptoms (CBCL subscale t-score), and HC/AM. Internalizing and externalizing subscales were chosen because each indexes a number of symptoms (e.g. internalizing subscale assesses both anxious and depressive symptoms), balancing the need to control for symptoms that show relations with gain/loss responsivity with the need to maximize degrees of freedom.

Dependent measures included response bias in block 3, and 'bias change' or the difference in block 3 and block 1 response bias (B3-B1), for both gain and loss tasks. A *Bonferroni* Correction (0.05/4 = 0.0125) was used to determine significance within regression analyses testing our hypotheses.

Tests for multicollinearity indicated that a very low level of multicollinearity was present (*VIF* = 1.8 for Internalizing T-Score; *VIF* = 1.7 for Externalizing T-Score; *VIF* < 1.2 for all other variables). See Table 6.2 for bivariate correlations between all predictors and dependent variables.

PILT-Positive

Task order, stimulus type, CDI-C t-score, Externalizing t-score, and Internalizing t-score, were all non-significant predictors in both PILT-P regressions (Table 6.3). HC/AM significantly positively predicted PILT-P bias during block 3 indicating that children with lower HC/AM show less bias towards the more frequently rewarded RICH response at the end of the PILT-P (Table 6.3, Figure 6.3). HC/AM was not a significant predictor of PILT-P bias change.

Table 6.3: Regressions Predicting Task Behavior

Dependent Variable	Predictors	PILT-Positive				PILT-Negative			
		R^2	Adj. R^2	Std. Beta	F/t statistic	R^2	Adj. R^2	Std. Beta	F/t statistic
Response Bias (Block 3)	Model Statistics	0.49	0.31		2.73 (p = 0.05)	0.47	0.28		2.47 (p = 0.07)
	Task Order			0.39	2.04			-0.04	-0.19
	PILT-P Stimulus			-0.16	-0.91			0.20	1.07
	CDI-C			0.10	0.55			0.27	1.49
	CBCL Internalizing			0.30	1.29			0.21	0.88
	CBCL Externalizing			-0.52	-2.289			-0.55	-2.35
	HC/AM			0.51*	2.81*			-0.42	-2.26
Response Bias Change (B3-B1)	Model Statistics	0.43	0.23		2.15 (p = 0.10)	0.49	0.30		2.67 (p = 0.05)
	Task Order			-0.38	-1.88			< 0.01	0.01
	PILT-P Stimulus			-0.23	-1.23			-0.01	-0.07
	CDI-C			0.49	2.56			0.04	0.23
	CBCL Internalizing			0.05	0.18			0.08	0.32
	CBCL Externalizing			0.13	0.53			-0.38	-1.66
	HC/AM			-0.15	-0.76			-0.59*	-3.28*

Note. Regression Analyses with task properties, depressive/internalizing/externalizing symptoms, and hedonic capacity/approach motivation (HC/AM) predicting PILT-Positive (PILT-P) and PILT-Negative response bias (in Block 3 and difference in response bias between Block 3 and Block 1 [B3-B1]). Predictor abbreviations refer to; CDI-C (Child Depression Inventory – Child Version), CBCL (Child Behavior Checklist). Std. Beta = Standardized Beta. Adj. R^2 = Adjusted R squared. * p<.0125

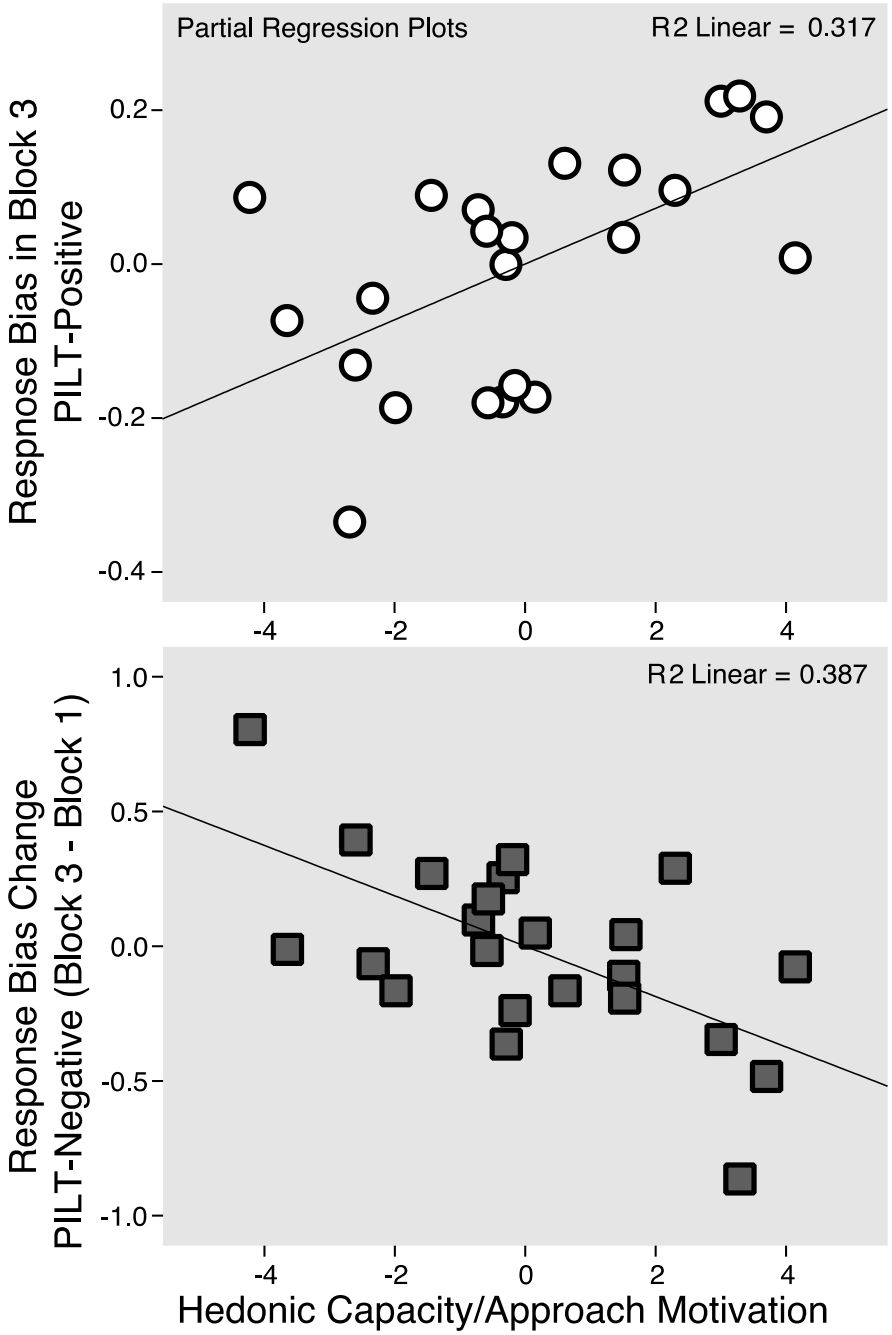


Figure 6.3: Response Bias And Hedonic Capacity/Approach Motivation
Partial regression plots of Hedonic Capacity/Approach Motivation (HC/AM) with response bias in Block 3 of PILT-Positive (white circles) and change in response bias across PILT-Negative (gray squares) controlling for PILT-P order/stimulus and depressive symptoms, internalizing symptoms, and externalizing symptoms. Results indicate greater responsivity to both gain and loss feedback in children with elevated HC/AM.

PILT-Negative

Again, task order, stimulus type, CDI-C t-score, Externalizing t-score, and Internalizing t-score, were all non-significant predictors in both PILT-N regressions (Table 6.3). HC/AM significantly negatively predicted PILT-N bias change indicating that less hedonic children were less able to shift bias away from the more frequently punished RICH across the PILT-N (Table 6.3; Figure 6.3). HC/AM was not a significant predictor of PILT-N block 3 bias.

Qualitatively similar patterns of relations between behavior and predictors were observed for both the PILT-P and N when child's sex and parent reports of child anxiety and depressive symptoms from the CBCL were included as separate predictors (in place of combined 'internalizing' symptoms).

HC/AM Post-hoc Analyses

Given the relation observed between response bias and HC/AM, additional post-hoc correlations were run to determine whether HC/AM was related to amounts of feedback, ratio of rich to lean feedback, and mean discriminability during the two tasks. For both the PILT-P and PILT-N, HC/AM was not significantly related to amount of feedback (PILT-P $r(22)=-.18$, $p=.386$; PILT-N $r(22)=-.06$, $p=.768$), ratio of rich to lean feedback events (PILT-P $r(22)=.12$, $p=.573$; PILT-N $r(22)=.22$, $p=.305$), or mean discriminability (PILT-P $r(22)=-.25$, $p=.235$; PILT-N $r(22)=-.13$, $p=.546$). Thus, relations between HC/AM and response bias were not likely driven by participants with high/low HC/AM experiencing differing amounts of feedback/ ratio of that feedback or showing differing ability to distinguish long/short stimuli.

6.4 Discussion

This goal of this study was to examine how behavioral responsivity to gain and loss feedback relates to hedonic capacity/approach motivation and dimensional sub-clinical

depressive symptoms within a non-clinical pre-pubertal child sample. To do so we developed child-friendly gain and loss versions of a signal detection task that has been well studied in the adult literature. Like in adult studies, children in the current study learned to preferentially select the response paired more frequently with candy gain during the PILT-P (Pizzagalli et al., 2008b; Pizzagalli et al., 2005). In the PILT-N, children successfully learned to shift behavior away from the response more frequently followed by candy loss. Interestingly, the degree of these behavioral shifts related to hedonic capacity/approach motivation, such that less hedonic children showed blunted response bias in both the PILT-P and PILT-N.

The current finding of reduced responsivity to gains in children with lower hedonic capacity/approach motivation is conceptually consistent with the adult literature where during this task, individuals with depression or elevated anhedonic depressive symptoms show reduced reward responsivity (Huys et al., 2013; Pizzagalli et al., 2008a; Pizzagalli et al., 2008b; Pizzagalli et al., 2005). This result has several important clinical and developmental implications. First, the PILT-P seems to be a useful tool for assessing a child's ability to adaptively respond to incentive feedback, mirroring the utility of monetary versions of the same task in adults. Second, non-clinical pre-pubertal child populations are able to report on levels of hedonic capacity/approach motivation in a way that meaningfully relates to behavior. Third, given the similarity between these findings in pre-pubertal children and those in adults, it is likely that the mechanisms subserving relations between individual differences in reward responsivity and hedonic capacity/approach motivation are similar across development, although longitudinal studies investigating the trajectory of such behavior/individual difference relations across development are needed. Finally, although other studies using combined child/adolescent groups have reported relations between general depressive symptoms and reduced neural responsivity to

rewards versus losses (Bress, Foti, Kotov, Klein, & Hajcak, 2013a; Bress et al., 2012), this is the first study, to our knowledge, in a non-clinical pre-pubertal sample demonstrating a relation between reduced response to reward and lower hedonic capacity/approach motivation specifically.

In the PILT-N children with lower hedonic capacity/approach motivation showed reduced shifts in behavior away from the more frequently punished response, i.e. reduced loss avoidance behavior. Overall this finding, in conjunction with results from the PILT-P, supports a pattern of blunted responsivity to valenced incentive feedback, positive or negative, in children with lower hedonic capacity. Although no adult studies using an individual differences approach have investigated responsivity to loss using similar signal detection tasks, adult neuroimaging studies also observe blunted responses to negative/positive stimuli with elevated levels of anhedonia (Chase et al., 2010; Dowd & Barch, 2010; Steele et al., 2007). This pattern is also reported in adolescents/children where elevated depressive symptoms or a maternal history of MDD (but not anxiety disorder) relate to reduced differentiation in neural responses to gain and loss feedback, a finding conceptually consistent with 'blunted' response to valenced feedback (Bress et al., 2012; Kujawa et al., 2014). Although our results indicating blunted loss responsivity are consistent with those of the adult anhedonia literature and child/adolescent depressive symptom/risk literature, studies comparing behavior in adult MDD groups to healthy controls during similar signal detection tasks with loss have either yielded null results or suggested enhanced responsivity in depressive groups (Henriques & Davidson, 2000; Henriques, Glowacki, & Davidson, 1994; Santesso et al., 2008b).

Likely explanations for the mixed findings in the adult literature and differences from the current study include the use of individual difference versus clinical/control group comparisons

and heterogeneity within clinical groups. MDD is a heterogeneous disorder, patients can present with depressed mood or anhedonia, or both (APA, 2013), and MDD often co-occurs with other disorders (such as substance use and anxiety disorders) that have also been linked to disrupted incentive processing as discussed in the introduction. Other studies investigating gain/loss sensitivity note qualitatively different patterns of responsivity across groups depending on these co-morbidities (Humphreys & Lee, 2011; Johnson et al., 2003; Kujawa et al., 2014). Given MDD's heterogeneity and high rate of comorbidity, it is reasonable to hypothesize that the mixture of symptoms and comorbidities within a given clinical group differs across studies. As such, focusing on between group comparisons rather than relations to specific symptom dimensions (e.g., anhedonia versus depressed mood) likely contribute to the frequency of mixed findings in the MDD versus non-depressed literature.

Our analytical approach enabled testing for relations between behavior and specific domains (e.g., hedonic capacity/approach motivation) while simultaneously assessing depression and other potentially relevant dimensions of behavior (e.g. internalizing and externalizing symptoms). This is a particularly useful approach if individual depressive and other symptoms (e.g. anhedonia, depressed mood, anxiety, ADHD, externalizing symptoms) show different directional effects on responsivity to loss of incentive such as elevated loss responses with greater depressed mood or anxiety, and blunted loss responses with increasing anhedonia or externalizing symptoms. In our *non-clinical* child sample this approach suggested a positive relation between hedonic capacity/approach motivation and loss responsivity, while significant effects of depressive, internalizing, and externalizing symptoms on response bias were not observed. However, it is possible that relations between PILT-P/N task behavior and depressive or externalizing symptoms, in addition to hedonic capacity/approach motivation, would be found

in a larger sample or in a clinical sample where hedonic capacity would likely relate to depressive symptoms. Although depressive symptoms and hedonic capacity are typically thought to negatively correlate, in the current sample, and other child studies with larger sample sizes (Kingsbury, Coplan, Weeks, & Rose-Krasnor, 2013; Muris et al., 2005), self-reported reward sensitivity and depressive symptoms were unrelated. Future studies are needed to more fully test relations between child self-reported hedonic capacity and other depressive symptoms and whether each explains unique variance in behavioral responsivity to gain/loss.

Differences in development and incentive type between the current study and the adult literature may also contribute to somewhat discrepant results across age. While we utilize primary incentives (candy), the adult literature has exclusively employed monetary incentives that may be less affectively salient and thus tie more loosely to 'hedonic' responses in the case of loss, especially if participants are already being paid a base rate for their time/effort. Further, it is likely that loss of an incentive such as candy/money differs qualitatively from interpersonal loss, such as loss of friendship and other types of social loss that likely induce enhanced negative responses in depressed/risk populations. Also, children seem to be particularly sensitive to feedback signaling loss of reward as evidenced by both behavioral and neuroimaging studies (Crone, Bunge, Latenstein, & van der Molen, 2005; Crone et al., 2008; Luking et al., 2014; van den Bos et al., 2012). As such, there may be more variation in loss-related behavior within child populations, aiding detection of relations between symptom levels and loss-related behavior.

Limitations and Future Directions

As the main limitation of this study is the small sample size, larger future studies are needed to replicate and then extend these findings into clinical and risk populations. The ethnic breakdown of our sample reflects that of the greater St. Louis area and the sample did not include

significantly different percentages of males and females. Nonetheless, the generalizability of findings should be assessed in samples that are non-white and with greater female representation. It will also be important for future studies to establish both the stability of behavior/individual difference relations across development and the test/re-test reliability of the PILT-P and PILT-N in this age group. Further, as loss feedback in the current study signals both an error and loss of something appetitive (candy), future studies capable of disentangling error and punishment/loss signals and relating the associated responses specifically with individual differences in hedonic capacity and other depressive symptoms are warranted. Our results highlight the relation between hedonic capacity and loss-avoidance behavior, in addition to gain-approach behavior. Future studies are needed to evaluate whether including hedonic capacity as a separate predictor (in addition to other depressive symptoms and internalizing/externalizing symptoms) can help rectify discrepant findings within the MDD literature regarding loss/negative affective domains.

Chapter 7.

Conclusions And Future Directions

The preceding chapters examined relations between gain/loss responsiveness and differences in 1) developmental stage, 2) self-reported incentive sensitivity, and 3) risk for MDD in healthy children, as well as interactions between incentive sensitivity and developmental stage/MDD risk. Importantly, we investigated these questions using tasks/methods where responsiveness to gain feedback and loss feedback were not interdependent and thus were dissociable. Overall we found that while children and adults showed similar striatal and behavioral response to gain feedback, children were more responsive to loss feedback than adults behaviorally and within the insula. Both elevated gain approach and loss avoidance behavior related to elevated incentive sensitivity assessed via a number of self-report measures, and gain approach and loss avoidance predicted unique variance in self-reported motivation. Importantly, relations between approach/avoidance behavior and self-report measures did not interact with developmental stage or level of MDD risk. Finally, while children at relatively high- and low-risk for MDD showed similar levels of gain approach and loss avoidance behaviors, low-risk children with elevated self-reported negative mood showed *elevated* gain approach while high-risk children with similar levels of negative mood showed *reduced* gain approach behavior.

7.1 Age And Incentive Responsiveness: Summary And Implications

In chapter two we developed a candy version of the standard monetary Card Guessing Game (CGG), a task used extensively in the incentive processing literature (Delgado et al 2000, Delgado et al 2004, Forbes et al 2010). Results showed that regions in the striatum and limbic system shown to be sensitive to monetary incentives in the extant literature also respond differentially to candy gain and loss feedback within healthy young adults. Chapters three and four then investigated how neural and behavioral responsiveness to incentive feedback, respectively, differed in child and young adult groups. In both studies we found no significant

age differences in responses to gain feedback. Children and adults showed similar striatal response to candy gain feedback during the CGG and similar levels of gain approach behavior during the Probabilistic Incentive Learning Task utilizing positive feedback (PILT-P). These findings suggest that more basic components of reward processing do not show large differences between child and adult groups.

Given the extant literature, this similarity between child and adult striatal response to gain seems at least somewhat independent of incentive type/delivery. Although no studies have directly compared neural responsiveness to primary and secondary incentives in child and adult populations, our striatal findings using candy (primary) incentives delivered post scan complement those obtained with positive facial expressions (primary - delivered during scan) (Somerville et al 2011), non-incentivized positive feedback (potentially secondary – delivered during scan) (van Duijvenvoorde et al 2008), money (secondary – delivered post scan) (Galvan et al 2006), and points (secondary – delivered/redeemed post scan) (van den Bos et al 2009). None of the studies discussed, including our own, were designed to separate responses to feedback receipt, thought to index 'liking', from anticipatory responses, thought to index 'wanting'. Instead all tasks focused on response to receipt of incentives. Recent evidence in adults and adolescents suggests that striatal responses during anticipation and receipt of incentives show different developmental trajectories (Hoogendam et al 2013). Thus, while it seems that children and adults respond similarly to *receipt* of reward/positive feedback, it is possible that differences in striatal responses would be observed during *anticipation* or other components of reward processing.

It is also important to note that while studies generally report similar child and adult striatal responses to reward, most of these studies also report age differences in cortical

responses. As we restricted our neuroimaging analyses to the subcortex and insula, it is not clear whether we would have observed similar cortical age differences. However, our own results in chapter three, and those of other developmental studies, suggest that age differences in activation reported in the literature may be influenced by behavior (Church et al 2010, Somerville et al 2011, van den Bos et al 2012). For example, in chapter three age effects within striatal regions were no longer significant after controlling for win-stay/lose-shift behavior. Given that surprisingly few studies in the developmental incentive literature have attempted to match child and adult groups on performance or otherwise account for age differences in task behavior, it is unclear the extent to which age differences in cortical response to rewards are explained by age differences in task behavior (see (Somerville et al 2011, van den Bos et al 2012) for developmental neuroimaging studies that do control for/investigate behavior). This issue is particularly relevant for more complex incentive learning/risk taking tasks, such as the IGT, where both behavior and cortical activation patterns vary dramatically with age. The relation we observe between striatal response to feedback in our simple guessing task and individual differences in basic win-stay/lose-shift behavior provides yet more evidence for the need to consider task behavior in developmental neuroimaging studies (see (Church et al 2010) for extended commentary).

The similarity in child and adult striatal response to gain feedback discussed above is also consistent with the lack of significant age differences in gain approach behavior on the PILT reported in chapter four, as striatal response to reward (fMRI and EEG methodologies) has been linked to PILT-P response bias (Bress & Hajcak 2013, Santesso et al 2008a). However, the null effect of age on gain-related response bias is somewhat at odds with the extant behavioral incentive literature. Specifically, other behavioral studies that examine learning rates from

positive versus negative feedback often highlight that children show *reduced* learning rates for reward information, or reduced effects of reward on expected value, relative to adults (van den Bos et al 2012, van der Schaaf et al 2011). Importantly though, these paradigms are more complex than the PILT, often requiring maintenance/integration of several response options with unique/changing probabilistic characteristics. Further, these tasks deliver either positive or negative feedback for every response, making it difficult to dissociate approach and avoidant behavior. Although additional studies are needed to directly test this hypothesis, given the current results it seems that age differences in learning rates from reward information most likely do not stem from differences in basic reward sensitivity, but may relate to more complex/cognitive components of reward processing.

Unlike the gain results discussed above, we observed significant age-related differences in both neural and behavioral responses to loss feedback. Specifically, children showed elevated responsiveness to loss within the dorsal/posterior insula, as well as elevated responsiveness to loss during the PILT-N. As no studies have investigated insular response to loss feedback in child and adult groups, it is difficult to integrate the insula finding with the extant developmental literature. However, in adults, the dorsal/posterior insula shows positive connectivity with sensory/motor regions, mid/posterior cingulate cortex, and amygdala (Cauda et al 2012, Cauda et al 2011, Cloutman et al 2012, Deen et al 2011, Roy et al 2013) facilitating its role in visceral and motor responses to negative stimuli (see (Mast 2013) for review), representing/evaluating negative internal states such as pain (Kurth et al 2010), and response to negative incentive outcomes (Liu et al 2011). Interestingly, a recent study investigating age-related changes in amygdala functional connectivity observed strong positive connectivity between the amygdala and dorsal/posterior insula during childhood, which weakened into adulthood (Gabard-Durnam

et al 2014). It is unclear how stronger positive functional coupling between the amygdala and posterior insula may influence responses to loss feedback within the insula. However, it is possible that this pattern indicates that the dorsal/posterior insula is more strongly integrated with neural systems involved in affective processing/responding; if so, BOLD responses within the dorsal/posterior insula may relate more strongly to affective responding during childhood than adulthood when responses may reflect integration between affective, motor, and sensory systems as suggested by adult studies of insula connectivity and function. Future studies are needed to examine whether age differences in amygdala-posterior insula connectivity mediate the elevated behavioral response to loss we observe in children relative to adults.

Children also demonstrated greater behavioral responsiveness to loss feedback relative to adults. Specifically, children showed greater avoidance of responses paired with more frequent loss feedback than adults. Other studies have noted that children are particularly sensitive to the frequency of loss feedback, avoiding options with frequent feedback even at the expense of overall earnings (Aite et al 2012, Crone et al 2005), and show greater learning rates for negative feedback than adults (van den Bos et al 2012, van der Schaaf et al 2011). However, all of the extant studies provided both gain and loss/negative feedback within the same task, and gain or loss feedback followed all responses. The use of separate gain and loss tasks in chapter four allowed us to examine loss-related behaviors specifically, rather than a trade-off between gain and loss responsiveness. Further, we were able to examine subsequent effects on RT and accuracy when incorrect responses did and did not receive loss feedback. These analyses highlighted that although children showed stronger avoidance behavior than adults, relative to adults they also showed greater reductions in overall accuracy during the PILT-N (versus PILT-P) and showed the greatest slowing following loss feedback. Together these findings suggest that

loss feedback is better able to facilitate acquisition of response bias, i.e. enhanced avoidance of frequent punishment, in childhood relative to adulthood, but at the cost of both accuracy and speed. One potential explanation for these behavioral results may be that loss/negative feedback is simply more affectively salient for children than adults. While our data are not able to directly test this hypothesis and no studies have examined the neural underpinnings of differences in PILT-N behavior, such a hypothesis is consistent with the neuroimaging findings in chapter three where children showed elevated response to loss within the posterior insula. Future developmental studies are needed to examine whether age differences in insular activation mediate age differences in loss avoidance behavior on the PILT-N by combining the PILT-N and other fMRI paradigms.

There are very few studies spanning child and adult ages in primates investigating changes in reward/punishment-related neurotransmitter systems over development. The few developmental studies that have been conducted focus on the dopaminergic (DA) system and tend to have small sample sizes and often offer conflicting results (see (Wahlstrom et al 2010) for review). Most relevant to the current results, there is some evidence that Dopamine Type 1 (D1) and Dopamine Type 2 (D2) receptor expression show different relations with age. Specifically, one human study reported both elevated D1 (sometimes associated with "go" or reward learning) related mRNA/protein amounts in adults relative to children and elevated measures of D2 (sometimes associated with "no-go" or loss learning) receptors in children relative to adults (Rothmond et al 2012). However, there is also evidence that densities of both receptor types decline from childhood to adulthood or show no change over this age range (see (Wahlstrom et al 2010) for review). Further, there is limited evidence that dopamine levels increase, at least in PFC, from childhood through adulthood in non-human primates (Goldman-

Rakic & Brown 1982, MacBrown & Goldman 1977). In human adults, D1 and D2 receptor function/prevalence have been linked to enhanced punishment and reward learning/behaviors respectively, effects that may also be mediated by DA synthesis (Cools et al 2009, Frank et al 2009, Frank & Hutchison 2009, Frank et al 2007). Interestingly these somewhat dissociable relations to reward and punishment responsiveness have been explored in the same tasks that show changes in learning rates from reward/punishment from childhood to adulthood, i.e. the Frank Task and the Probabilistic Reversal Learning Task (van den Bos et al 2012, van der Schaaf et al 2011). Thus, if children do in fact show relatively elevated D2-like receptor density, and reduced DA synthesis compared to adults, it would be conceptually consistent with the elevated response to loss we observe. However, future studies exploring how DA system function relates to behavior over development are needed to directly test this hypothesis. Such studies should also consider other transmitter systems beyond DA and functional/structural connectivity within reward-related neurocircuitry as it is likely that other factors beyond DA also influence relations between age and loss avoidance behaviors.

Changes in DA system function have been linked to the adolescent typical increases in risk taking and reward responding as discussed in the introduction (Wahlstrom et al 2010). By extension it is theorized that increases in DA availability, and associated behaviors, in part subserve the evolutionary role of adolescence, via encouraging exploration and separation from the family, which then allows for new experiences and sexual partnerships resulting in increased genetic diversity/health of offspring (see (Spear 2000) for commentary). Such evolutionary hypotheses are difficult to falsify and thus test, however, they can be useful thought experiments. Although entirely speculative, it is possible that the elevated response to loss, specifically prepotent avoidant ‘lose-shift’ responses, we observed may be an important feature of childhood

from an survival/evolutionary perspective. Childhood is a particularly vulnerable time in that while children experience increased independence and motor ability relative to infancy/toddlerhood, they do not have the life experience or cognitive skills to take informed risks. As such, it may be particularly important from a safety/survival perspective for children to learn rapidly, often in one trial, from punishment/negative feedback, and it may be less important for elevated reward responding to drive additional risk-taking. While it is not possible to evaluate the evolutionary 'purpose' of the elevated response to loss we observe during childhood, it is interesting to speculate regarding how this age difference may be beneficial from a developmental perspective.

7.2 Depression Risk And Incentive Responsiveness: Summary And Implications

Chapter six examined gain approach and loss avoidance behaviors in healthy children at relatively high and low-risk for developing MDD. Although the PILT has not been examined in high-risk populations defined by maternal depressive history, adults and adolescents with MDD or adults with remitted MDD show reduced gain approach behavior (Boger et al 2014, Pechtel et al 2013a, Pizzagalli et al 2008a). As such we hypothesized that high-risk children would show reduced gain approach behavior on the PILT-P and might also show enhanced loss avoidance behavior on the PILT-N based on neuroimaging work in adult MDD and adolescent risk populations (Eshel & Roiser 2010, Gotlib et al 2010). However, contrary to our hypotheses high and low-risk children showed similar levels of both gain approach and loss avoidance behavior. High-risk groups typically report elevated depressive and anhedonic symptoms relative to healthy comparison groups, but it is unclear whether elevated symptom levels mediate group effects on gain approach behavior (see (Olino et al 2014) for commentary). The current null

result is not surprising if, as other studies investigating response to affective/incentive stimuli have suggested (Dowd & Barch 2010, Olino et al 2014), group differences in symptoms/hedonic capacity fully mediate group effects, given that our high and low-risk groups did not differ in self-reported anhedonic symptoms. However, it is also possible that effects of MDD risk on incentive responsiveness are small prior to puberty. To address this question, longitudinal studies are needed to directly compare effect sizes over development. However two studies investigating *neural* response to positive affective/incentive stimuli suggest that effects of MDD risk are small in childhood (Kujawa et al 2014) or are larger in adolescence than childhood (Goff et al 2013). Investigating how children with elevated MDD risk, elevated subclinical symptoms, and/or relatively reduced response to reward during childhood may deviate from the typical developmental trajectory of an increasing response to reward peaking in adolescence may shed light on the mechanisms contributing to the increase in incidence of MDD observed over adolescence.

Interestingly, despite exhibiting similar levels of approach/avoidance behavior and self-reported negative mood (via Child Depression Inventory) at the group level, high- and low-risk children reporting elevated negative mood showed very different patterns of gain approach behavior in relation to self-reported mood. Specifically, high-risk children reporting elevated negative mood showed *reduced* gain approach behavior while low-risk children reporting similarly elevated negative mood actually showed *enhanced* gain approach behavior. This relation was not hypothesized as elevated depressive symptoms (including negative mood) are typically related to reduced reward responsiveness. However, given that elevated neural response to reward has been linked to resilience to depression (Bress et al 2013a), the positive relation between approach behavior and negative mood in low-risk children may serve as a protective

factor evident this group. Longitudinal studies are needed to test this hypothesis, but given the novelty of this finding replication is critical prior to initiating such prospective studies.

Elevated negative mood also related to elevated loss avoidance behavior, and this relation did not differ based on MDD risk. It is important to note that although negative mood and anhedonia are both gateway symptoms of MDD (APA 2013), they show different relations with loss avoidance behavior across the studies discussed here. Specifically, reduced hedonic capacity or elevated anhedonia related to *reduced* loss avoidance in chapters four, five, and six while elevated negative mood related to *elevated* loss avoidance. The one other study, to our knowledge, that has included measures of anhedonic and negative mood symptoms as separate predictors of reactivity to negatively valenced stimuli, reports strikingly similar results to chapter six (Saxena et al Under Review). It should be noted that negative mood and anhedonia were not strongly positively related in chapter six or in Saxena et al. As such, future studies in clinical populations, where anhedonia and negative mood are typically strongly positively related, are needed to determine whether these relations are similarly dissociable at higher symptom levels. However, given the results of chapter six, and that in chapter five, PILT behavior did not significantly relate to CDI total scores (which combines negative mood and anhedonia subscales), future studies should consider examining these two core components of depressive symptomology as separate predictors particularly when investigating responsiveness to negative stimuli.

7.3 Individual Differences in Incentive Responsiveness: Summary and Implications

Chapters four, five, and six investigated relations between gain and loss-related response bias and self-reported incentive sensitivity indexed via several different questionnaires. These

questionnaires have been designed to assess different conceptual constructs such as hedonic capacity, motivation, affect, and depressive symptomology. However, in both child and adult populations, self-reports on these measures are often strongly correlated. Interestingly, all of the incentive sensitivity questionnaires we assessed showed qualitatively similar relations to gain and loss behaviors. Specifically, individuals reporting elevated incentive sensitivity, i.e. elevated BAS drive, reduced anhedonic symptoms, or elevated hedonic capacity composite scores (BAS, child pleasure scale, and positive affect), showed both elevated gain approach and elevated loss avoidance behavior.

Previous studies in non-depressed adults have linked elevated melancholic depressive symptoms (i.e. reduced incentive sensitivity) to reduced gain approach behavior on the PILT-P (Pizzagalli et al 2005). Similarly, the results of chapter six show that elevated self-reported anhedonia and reduced gain approach behavior predict reduced gain approach behavior in a healthy child population. However, no studies utilizing the PILT-P have related behavior to self-report on other types of incentive sensitivity scales. The similarity in relations with behavior across the self-report measures is not necessarily surprising. However, it is not clear from the current studies whether each questionnaire is predicting common or unique variance in PILT-P behavior as chapter four, five, and six each focused on different incentive sensitivity measures. However, chapter four and five did include separate predictors of PILT behavior, chapter four included BIS and BAS (drive or reward responsiveness) as simultaneous predictors, and chapter five included psychopathology symptomology. In both of these chapters, behavior on the PILT specifically related to the incentive sensitivity measure of choice and was not significantly related to BIS or internalizing/externalizing symptomology. Together these results suggest that behavior on the PILT relates to incentive sensitivity specifically, rather than global

internalizing/externalizing symptoms or behavioral inhibition (BIS). However, our results do not suggest that behavior relates to a specific component or incentive sensitivity construct as measured via self-report questionnaires.

No studies in the extant literature have utilized a version of the PILT delivering loss feedback following incorrect responses. Thus, it was unclear whether anhedonia (or other incentive sensitivity measures) would relate to PILT-N behavior. Across chapters four, five, and six individuals that reported *reduced* incentive sensitivity also showed reduced loss avoidance behavior, further highlighting the relation between incentive sensitivity and avoidance behavior. These findings are consistent with a growing literature in adults suggesting that individuals reporting reduced incentive sensitivity (i.e., elevated anhedonia assessed via pleasure scales) show blunted affective and behavioral responses to *both* positive and negative stimuli/feedback (Chase et al 2010, Dowd & Barch 2010, Saxena et al Under Review, Steele et al 2007). Studies reporting 'blunted' responding to both positive and negative stimuli typically interpret blunted responses to positive and negative stimuli as the effect of a single process, rather than the result of separable processes specific to 'positive' versus 'negative' blunting. However, while these studies relate affective reactivity to positive and negative stimuli to self-reported anhedonia, none of these studies, to our knowledge, have examined whether reactivity to positive and negative stimuli predict *unique* variance in self-reported anhedonia. Interestingly, results from chapter four suggested that gain approach and loss avoidance behavior do in fact predict *unique* variance in incentive sensitivity (here BAS drive or motivation) suggesting multiple processes contributing to incentive sensitivity (motivation). Thus, incentive sensitivity may reflect both responsiveness to gain, and responsiveness to the loss of rewards, with each of these two constructs contributing independent predictive variance. This result is even more intriguing given

that the questionnaires used in chapters four, five, and six exclusively index responsiveness to putatively positive events/outcomes and not 'loss' of appetitive outcomes. Further, the BIS subscale of the BIS/BAS, which indexes affective reactivity to negative events, did not significantly relate to PILT-N behavior. Future studies that also assess and relate self-reported affective reactivity to loss of appetitive stimuli and behavioral/neural responsivity to receipt of aversive 'punishment' stimuli (versus loss of appetitive stimuli), in addition to gain, are needed to replicate and extend these results.

It is also important to note that the relations between incentive sensitivity and PILT behavior discussed above did not differ based on developmental stage (chapter four) or risk for depression (chapter six). These findings suggest that the mechanism linking motivated behavior and self-reported incentive sensitivity may be conserved both across development and across risk for psychopathology. Similarly, studies investigating relations between hedonic capacity and affective/behavioral response to positive/negative stimuli within adult clinical and patient groups have also reported qualitatively similar relations between hedonic capacity and responses to positive/negative stimuli across group distinctions (Chase et al 2010, Dowd & Barch 2010, Steele et al 2007). However, longitudinal studies are certainly needed to explicitly test this relation as individuals age and high-risk offspring move through adolescence and adulthood.

7.4 General Conclusions

The current results highlight the importance of responsiveness to loss feedback, a component of incentive responding that has not been explored from developmental or psychopathology perspectives in the child literature. While the vast majority of the developmental incentive literature both in healthy and depressed/high-risk groups has focused on response to gain feedback or positive affective stimuli, the current results suggest that childhood

is a time of elevated neural and behavioral responsiveness to loss feedback. Further, we show evidence that individual differences in incentive sensitivity and depressive symptomology relate to behavioral responsiveness to losses as well as gains. This finding has significant implications not only for theories regarding psychopathology and development, but also incentive processing and motivation more generally. Specifically, new theories of anhedonia and motivation are needed which reflect drive to obtain positive outcomes, but also drive to avoid losing rewards that have already been obtained.

Future work is needed to expand upon these findings, specifically investigating how responsiveness to both gain and loss in childhood may predict trajectories of incentive responding across adolescence. Longitudinal work is also needed to examine how relations between gain/loss responsiveness and risk for pathology may change across development. Together such studies could further inform whether treatments targeting incentive sensitivity during childhood may reduce risk for psychopathology by 'normalizing' the developmental trajectory of incentive sensitivity for a given individual.

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