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Neural And Behavioural Responses To Rewards And Losses In Early Development: A Functional Magnetic Resonance Imaging Study

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Psychology
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«NEURAL AND BEHAVIOURAL RESPONSES TO REWARDS AND LOSSES IN EARLY DEVELOPMENT: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY»

(Thesis format: Monograph)

by

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Graduate Program in «Psychology»

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Abstract

Functional magnetic resonance imaging (fMRI) was used to investigate the neural and behavioural correlates of learning from rewards and losses in children. Greater blood-oxygen-level dependent (BOLD) responses in the ventral striatum (VS) and the ventromedial prefrontal cortex (VMPFC) were found when participants received rewards compared to when they missed out on an opportunity to receive rewards. In contrast, greater BOLD responses in the anterior insula (AI) and the anterior cingulate cortex (ACC) were found when participants received losses compared to when they avoided losing. The BOLD response to rewards in the VS and VMPFC correlated positively with the tendency to select rewards. Greater incidence of early life adversity was associated with greater likelihood to select rewarding stimuli and a larger BOLD response in the VS and VMPFC to rewards. Findings suggest that the functional calibration of the mesocorticolimbic pathway is sensitive to the experience of early life adversity.

Keywords

Mesocorticolimbic dopamine pathway (MCLP), Ventral Striatum (VS), Ventromedial Prefrontal Cortex (VMPFC), Reward learning, Loss learning, Instrumental Learning, Early life adversity.

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Chapter 1 : Introduction

The capacity to select actions that lead to favourable outcomes while avoiding

actions that lead to unfavourable outcomes has both developmental and evolutionary

advantages (Delgado, 2007; Foerde & Shohamy, 2011; Heekeren, Wartenburger,

Marschner, Mell, Villringer, Reischies, 2007; Hennigan, D'Ardenne, & McClure, 2015;

Jocham, Klein, & Ullsperger, 2011; Liu et al., 2007; Liu, Hairston, Schrier, & Fan, 2011;

O'Doherty, 2004; Samanez-Larkin, Hollon, Carstensen, & Knutson, 2008; Schultz,

2000; Schultz, 2015; Wise, 2004). Opportunities to make decisions that may lead to

rewards or losses present themselves frequently; importantly, learning to make choices

that lead to advantageous outcomes and learning to avoid choices that lead to

disadvantageous outcomes is achieved via feedback after making a choice and observing

the outcome. Over time, we learn what choices are advantageous in that they lead to

rewards, and what choices are disadvantageous in that they lead to losses. The choices

that we make are motivated by the outcomes of our previous actions. If the outcome of

our action was positive, we learn to repeat the behaviour that resulted in the reward; if the

outcome was negative, on the other hand, we learn to avoid repeating the action that

resulted in the loss (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Delgado, 2007;

Schultz, 2000). This learning process involves the ability to represent the value of

rewards and losses, and to extract information from the environment about the

predictability of when and where rewards and losses are likely to occur (O'Doherty, 2004; Schultz, 2000). Critically, rewards are not defined by their physical properties, such as the subjective feeling of pleasure that a stimulus may induce. Rather, rewards are defined by the behavioural reactions that they produce (Delgado, 2007; Schultz, 2015). One important function of rewards is to serve as positive reinforcers that increase the frequency of selecting actions that lead to the acquisition of positive outcomes (Schultz, 2000). It is in this manner that rewards help guide behaviour, if a behavioural choice leads to a positive outcome, that choice is considered rewarding in that it increases the frequency of selecting the action that led to the reward in the first place.

It is evident that selecting actions that lead to rewards and avoiding actions that lead to losses is advantageous; however, a hypersensitivity to either rewards or losses beyond the normative range can have adverse consequences. For example, attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder marked by a deficit in behavioural inhibition and includes symptoms of hyperactivity, impulsivity, and inattention (Polanczyk, Willcutt, & Salum, 2014). Notably, dysfunctional reward processing including a hypersensitivity to individual instances of reward (Tripp & Alsop, 1999), excessive approach behaviours, and a limited capacity to tolerate reward delays have been implicated as common characteristics of ADHD (Carmona et al., 2009; Hommer, Bjork, & Gilman, 2011; Luman, Tripp, & Scheres, 2010; Plichta & Scheres,

2014; Plichta et al., 2009; Sagvolden & Johansen, 2005; Sonuga-Barke, 2002; Ströhle et

al., 2008; Tripp & Alsop, 1999; Tripp & Wickens, 2009; Volkow et al., 2009).

Furthermore, dysregulation in reward processing is associated with a host of other

adverse consequences such as substance abuse and pathological gambling (Bechara,

2005; Diekhof, Falkai, & Gruber, 2008; Garavan & Stout, 2005; Goudriaan &

Oosterlaan, 2004; Volkow, Fowler, & Wang, 2003; Volkow & Wise, 2005), mood

disorders including major depressive disorder (Chau, Roth, & Green, 2004; Drevets,

2001), schizophrenia (Chau et al., 2004), and eating disorders (Volkow & Wise, 2005).

In the case of addictions, it is important to note that individuals may willingly perform

actions that lead to adverse outcomes because they are insensitive to the punishment of

negative consequences, or because they are highly motivated by the prospect of gains

(Luciana, Wahlstrom, Porter, & Collins, 2012). Therefore, dysregulation in reward

processing can be the result of a heightened sensitivity to gains, or a blunted response to

losses. Considering both the advantages of learning from rewards and losses, and the vast

array of consequences associated with dysregulation of the reward system, a deeper

understanding of the underlying mechanisms of reward and loss learning is necessary.

Consequently, a growing number of studies have been dedicated to understanding the

neurobiological and environmental factors that may give rise to individual differences in

learning from rewards and losses.

The objective of the current study was to investigate reward and loss learning both at the behavioural and neural level. Functional magnetic resonance imaging (fMRI) was used to determine whether individual differences in reward/loss learning can be predicted by the magnitude of neural activity in regions associated with rewards and losses. Furthermore, the association between the experience of early life adversity and learning from rewards and losses was investigated at both the behavioural and neural level. In the following sections, the neural circuitry associated with learning from rewards and losses will be summarized. Additionally, a review of the potential for early life adversity to differentially calibrate the neural circuitry associated with rewards will be provided. Finally, the objectives and research questions of the current study will be outlined.

1 « The Neural Correlates of Rewards »

1.1 « Overview of the Mesocorticolimbic Dopamine Pathway (MCLP) »

The idea that there is an anatomically distinct neural circuitry involved in the processing of rewards was initiated by electrical stimulation studies in the early 1950's. Olds and Milner (1954) conducted a series of experiments demonstrating that animals work hard to obtain electrical stimulation in midbrain dopamine (DA) regions, including the ventral tegmental area (VTA). Not only did electrical stimulation in regions including the medial forebrain bundle, the VTA, and the hypothalamus result in learning

acquisition rates and extinction curves comparable to those of naturally occurring rewards, but also, rats developed a conditioned place preference for spatial locations where they were administered the electrical stimulation (Olds & Milner, 1954; Wise & Rompre, 1989, Wise 1996). Following these experiments, further support for the existence of a reward circuitry was provided by pharmacological manipulation and intracranial injections of drugs of abuse into regions hypothesized to be involved in processing rewards (Carlezon and Wise, 1996; Carr and White, 1983; Phillips and Fibiger, 1978). For example, Carlezon and Wise (1996) found that rats learned to lever-press for administration of phencyclidine (PCP) directly into the nucleus accumbens (NAc) shell and within the frontal cortex (Carlezon and Wise 1996).

The involvement of both the VTA and the ventral striatum/NAc in processing rewards is now well-established. However, recent studies demonstrate that the reward circuitry is far more extensive than previously thought (Haber & Knutson, 2010). The reward circuitry includes not only the VTA and NAc, but also the entire ventral striatum (VS), the substantia nigra (SN), the ventral pallidum, the anterior cingulate cortex (ACC), and the ventromedial prefrontal cortex (VMPFC; Haber & Knutson, 2010). The VS receives its main cortical input from the VMPFC and anterior cingulate cortex (ACC), and also receives dopaminergic input from the VTA. The VS projects to the ventral pallidum (VP) and to the VTA/SN, which, in turn, extends back to the prefrontal cortex

via the thalamus. In addition, there are other key regions that regulate the reward circuit including the amygdala, hippocampus, habenula, pedunculopontine nucleus, and the raphe nuclei (Haber and Knutson, 2010). In the sections that follow, the functional role of the VTA and VS within the reward circuitry will be reviewed.

1.2 « Dopamine Neurons in the VTA»

Dopaminergic signaling originating from the VTA have provided important insights into the biophysiological mechanisms that underlie reward learning. Phasic DA signaling is defined as a rapid (< 1s), spatially restricted signal driven by DA neuron burst firing (Floresco, 2015; W. Schultz & Romo, 1990). In various behavioural situations, including in instrumental learning tasks, DA neurons in the SN and VTA demonstrate this phasic activity after the presentation of natural rewards, and upon visual and auditory stimuli that predict rewards (Ljungberg, 1992; Romo & Schultz, 1990; Schultz & Romo, 1990; Schultz, 2000). In contrast, the presentation of stimuli that are predictive of rewards followed by an *absence* of the reward produce brief phasic DA dips in neural firing (Schultz, 2000; Schultz 1998). The observation that DA bursts are enhanced by unpredicted rewards and depressed by the absence of predicted rewards, demonstrates that dopaminergic bursts are not signaling reward itself, but rather, the reward prediction error (Ljungberg, 1992; Mirenowicz & Schultz, 1994; Schultz, 2000; Schultz, 2015). Additionally, more recent studies have demonstrated that the magnitude

of the phasic DA burst encodes the expected availability or receipt of large versus small

rewards (Day, Jones, & Carelli, 2011; Floresco, 2015; Sugam, Day, Wightman, &

Carelli, 2012). These elegant experiments have revealed that phasic DA bursts and dips

can serve as teaching signals that encode reward prediction errors for anticipated rewards.

DA can enhance or suppress VS activity via its actions on either D1 or D2 receptors.

Recent evidence suggests that activation of D1-like or D2-like receptors within the VS

can have different behavioural consequences—namely, approach (D1) versus avoidance

(D2; Floresco, 2015; Kravitz, Tye, & Kreitzer, 2012).

1.3 « The Striatum»

The striatum is subdivided into dorsal and ventral portions. The dorsal striatum

(DS) consists of the caudate nucleus and the putamen; the DS receives projections from

the dorsolateral prefrontal cortex and also receives dopaminergic input from the SN. The

ventral striatum (VS), on the other hand, consists mainly of the NAc and includes

portions of the putamen and ventral caudate; the VS receives cortical projections mainly

from the VMPFC and receives dopaminergic input from the VTA (Delgado, 2007). The

striatum is a region with numerous functions including habit formation, reward learning

and action control; because of its diverse functions, the striatum has been suggested to

integrate information regarding emotions, motivation, cognition and motor control. In a

recent review, the VS has been proposed to integrate cognitive and affective information

to increase the efficiency of approaching actions that lead to positive outcomes and avoiding actions that lead to negative outcomes (Floresco, 2015; *Also See* Salamone & Correa, 2009). For example, DA in the VS has been shown to influence appetitive aspects of behaviour in rats; furthermore, lesions in rat VS induce deficits in approach behaviours, implicating the importance of this neural region for motivating appetitive behaviours (Delgado, 2007; Robbins & Everitt, 1992).

Animal research has greatly contributed to our understanding of the functional role of the striatum. Early experiments with primates demonstrated that the striatum responds to the expectation of a reward (Hikosaka, 1989), and to delivery of natural rewards (Apicella, Ljungberg, Scarnati, & Schultz, 1991). Research with humans has largely confirmed the role of the VS in responding to the delivery of natural rewards, the presence of unexpected rewards, and to delivery of positive feedback after selecting a neutral stimulus (Rogers et al., 2004). One of the paradigms used with humans during an fMRI scan involved a card guessing game, during which participants were asked to guess whether the value of an upcoming card is greater than 5 or less than 5. Following the participant's choice, the actual outcome of the card was presented in addition to feedback in the form of a reward (winning $1.00) or a loss (losing $.50), depending on whether their choice was correct or incorrect. While participants were completing the task, blood oxygen-level-dependent (BOLD) responses increased in the VS during both positive and

negative feedback. Interestingly, the increase in BOLD to positive feedback remained high and slowly returned to baseline, whereas the BOLD increase to negative feedback rapidly returned to baseline (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000). These results demonstrate the role of ventral striatal activity to both positive and negative feedback; moreover, a meta-analysis of 142 neuroimaging studies in healthy adults also confirmed the functional role of the VS in processing both positive and negative feedback (Liu et al., 2011).

More recently, research has demonstrated that the BOLD activity measured in the VS is likely associated with dopaminergic signaling. Pessiglione and colleagues (2006) elegantly demonstrated the relationship between dopamine, ventral striatal activity, and behavioural choice in humans using a combination of pharmacological manipulations and fMRI (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). The pharmacological manipulations involved increasing dopaminergic function via administration of L-DOPA or reducing dopaminergic function via administration of haloperidol. Participants were scanned after the administration of L-DOPA or haloperidol and were required to complete an instrumental learning task that involved learning from a pair of stimuli associated with gains and a pair of stimuli associated with losses. The results of the experiment revealed that the magnitude of the reward prediction error as measured via ventral striatal activity varied depending on the pharmacological manipulation. Critically,

participants who were administered L-DOPA had increased VS BOLD response to positive prediction errors and also were more likely to select the most rewarding stimuli relative to participants who were administered haloperidol (Pessiglione et al., 2006). Other research groups have confirmed the role of DA in modulating VS activity to rewards using a combination of fMRI and PET, and have concluded that reward-related BOLD activity is related to dopaminergic release (Knutson & Gibbs, 2007; Schott et al., 2008).

The combination of these studies demonstrate that dopaminergic signaling to either the receipt of unexpected rewards or positive feedback after selecting stimuli associated with rewards originates from the VTA, projects to the VS and is detectable via standard fMRI procedures. Individual differences in the BOLD response within the VS can then serve as a proxy measure for individual differences in dopaminergic signaling in response to rewards and/or positive feedback. Furthermore, the magnitude of the BOLD response within the VS has also been shown to be correlated with individual differences in selecting rewarding stimuli (Pessiglione et al., 2006). Therefore, measurements of BOLD activity within the MCLP, in particular the VS, can potentially be used to determine the biological underpinnings of individual differences in selecting actions that lead to positive outcomes.

2 « The Neural Correlates of Losses »

2.1 « A Shared Neural Circuitry for Rewards and Losses»

While numerous studies have been dedicated to the study of the neurobiological correlates of rewards, the neurobiological correlates of learning from losses remain controversial (Palminteri et al., 2012). Some researchers have proposed that the same neural regions that facilitate reward learning underlie loss learning. Whereas DA bursts facilitate approaching rewards, DA dips weaken approach circuits and facilitate avoiding adverse outcomes (Palminteri et al., 2012). In accordance with this view, in patients with Parkinson's Disease (PD), L-DOPA improves learning from rewards but impairs learning from losses (Frank, Seeberger, & O'Reilly, 2004; Palminteri et al., 2009). However, this notion remains controversial because not all studies have confirmed that DA enhancers impair learning from losses (Fiorillo, 2013; Pessiglione et al., 2006). If the same neural circuitry is involved in both reward learning and loss learning, then the MCLP would be recruited when receiving rewards *and* avoiding losses. In accordance with this hypothesis, Delgado and colleagues (2000) found that the VS responds to both positive and negative feedback. However, Fiorillo (2013) suggests that DA neurons of the primate VTA are insensitive to losses and are activated only to unexpected rewards and suppressed by the absence of expected rewards (Fiorillo, 2013). Based on the notion that DA neurons in the VTA are insensitive to losses, it has been suggested that a separate neural circuitry is central to loss learning.

2.2 « A Distinct Neural Circuitry for Avoiding Losses»

In accordance with this view, the anterior insula (AI) and the ACC have been implicated in the experience and anticipation of negative consequences; furthermore, activity in the AI has been associated with an enhanced ability to avoid losses (Palminteri et al., 2012; Samanez-Larkin et al., 2008). Moreover, Blair and colleagues (2006) have demonstrated that regions associated with rewards and losses are distinct. The results of their experiment revealed that BOLD response in the VMPFC was greater when participants were choosing between two positive stimuli—gaining the greater reward. In contrast, the ACC showed greater BOLD response when participants had to choose between two negative stimuli—choosing the stimulus to gain the lesser punishment. While the literature in terms of a distinct network responsible for learning from losses and avoiding adverse consequences is not as reliable as the findings within the MCLP in relation to rewards, it appears that the AI and the ACC are neural regions involved in at least some aspects of loss learning.

3 « Environmental Influences on Learning from Rewards and Losses »

Investigating the neurobiological variables that may give rise to individual differences in approaching rewards and avoiding losses is necessary for understanding the biological factors that can influence behavioural approach and avoidance. However, environmental factors that can modulate the MLCP are also of great theoretical and

practical interest. Learning to select favourable outcomes and avoid unfavourable outcomes is evidently advantageous; additionally, dysregulation within the MCLP can have adverse consequences, ranging from substance abuse to ADHD. Therefore, a thorough understanding of both the neurobiological and environmental factors that can influence the MCLP are of great practical relevance.

Administration of pharmacological drugs like methylphenidate have traditionally been used to remedy ADHD (Volkow et al., 2012). This pharmacological approach however, is invasive in that it directly alters the underlying neural circuitry associated with reward and loss learning. Furthermore, the administration of pharmacological agents often induce changes in all neural regions, and not simply the regions that are associated with the maladaptive behaviour. If environmental factors can calibrate the MCLP, it may be practical to alter environmental conditions in a manner that prevents the dysregulation of the MCLP, and by extension, the maladaptive behavioural consequences associated with dysregulation of the MCLP.

A recent review by Gatze-Kopp (2011) suggests that the MCLP is sensitive to adverse life events in much the same way as the hypothalamic-pituitary-adrenal axis (HPA). The MCLP is suggested to demonstrate phenotypic plasticity in such a way that makes the reward circuitry sensitive to developmental influences including early life adversity (Gatzke-Kopp, 2011). In addition, the plasticity of the MCLP in relation to

early life events is said to have adaptive advantages. In relation to reward-learning, it is interesting to consider that the neural circuitry involved in reward learning may not only use information regarding outcomes of making choices in the immediate environment, but may also be using information regarding outcomes of choices throughout the course of development. If the MCLP is indeed plastic to early life events, and is calibrated differentially depending on the severity of early life adversity, then individual differences in the experience of adverse life events might influence both the functional response of the MCLP to rewards, and also the resultant behavioural choices.

3.1 « The Influence of Adversity on the MCLP and Behaviour»

Regarding the influence of adversity on behavioural choices to select rewards and avoid losses, the literature has been mixed. A number of research groups have shown that under acute stress, participants have a heightened propensity to approach rewards (Casement, Shaw, Sitnick, Musselman, & Forbes, 2015; Lighthall, Gorlick, Schoeke, Frank, & Mather, 2013; Mather & Lighthall, 2012; Meaney, Brake, & Gratton, 2002). In addition, individuals under stress (e.g., marital dissatisfaction), are more prone to substance abuse (Goeders, 2003). Similarly, subordinate macaques have been shown to have a greater propensity to self-administer cocaine relative to dominant macaques. Furthermore, being housed in social groups resulted in an increase in D2 receptors in dominant macaques, but no change in D2 receptor density for subordinate macaques,

implicating an association between adversity (or the absence of adversity) and individual differences within the dopaminergic system at the receptor level (Morgan et al., 2002).

The combination of these results seem to suggest that adversity increases reward sensitivity in both humans and animals. However, other research groups have found the opposite set of findings—that adversity results in a blunted reward response (Berghorst, Bogdan, Frank, & Pizzagalli, 2013; Chiara & Imperato, 1988). One important consideration in attempting to reconcile these mixed findings is that the majority of the aforementioned studies used acute stress paradigms; the influence of chronic stress or adversity experienced throughout the course of development has not been thoroughly investigated. Recently however, Boecker and colleagues (2014) found that early life adversity is associated with hypo-responsiveness in the VS during reward anticipation, but hyper-responsiveness in the right insula during reward receipt. Additionally, these patterns of findings were related to ADHD, suggesting that the influence of early life adversity on ADHD is mediated by individual differences in the calibration of the MCLP (Boecker et al., 2014).

4   « The Current Study »

The aim of the current study was to investigate the neural correlates of individual differences in learning from rewards and losses early in development. The first research question to investigate was whether the underlying neural circuitry involved in receiving

rewards and avoiding losses is the same or different. If the underlying neural circuitry is the same, the VS and VMPFC would exhibit a greater BOLD response at feedback when participants gained rewards and also when they avoided losses. In contrast, if the underlying neural circuitry involved is distinct, the VS and VMPFC would be activated in response to positive feedback, and the AI and ACC would be activated in response to negative feedback. A further research question was to determine whether differential BOLD responses to rewards and losses were predictive of selecting stimuli that were more often associated with gains and/or avoiding stimuli that were more often associated with losses. Additionally, an investigation of whether the frequency and intensity of adversity experienced early in development influenced the MCLP and/or behavioural approach/avoidance was conducted.

To this end, fMRI scans were obtained from 9-12 year old children while they were completing an instrumental learning task adapted from Pessiglione and colleagues (2006). Based on previous research, increased BOLD response in regions in the reward circuitry—specifically the VS and VMPFC—during positive feedback was expected. In contrast, an increased BOLD response in regions associated with losses—specifically the AI and ACC—during negative feedback was expected. Additionally, individual differences in the magnitude of VS activity and VMPFC activity were predicted to correlate positively with individual differences in the propensity to select the stimulus

that most frequently resulted in gains. Likewise, individual differences in the magnitude of AI and ACC activity were hypothesized to correlate positively with individual differences in the propensity to avoid the stimulus that was most frequently associated with losses. Finally, questionnaire data from the participants' mothers were obtained to determine the frequency and intensity of early life adversity. An association between early life adversity and activation within the MCLP to rewards was expected. However, based on the conflicting results of previous research, the direction of that relationship was unclear—whether an increase in the frequency and intensity of early life adversity is predictive of an enhanced or blunted neural response to rewards was unclear. The objective was simply to determine whether the MCLP is indeed sensitive to adversity experienced early in life, as suggested by Gatzke-Kopp (2011).

4.1 « Summary of Research Questions»

1) Are the neural regions associated with gaining rewards and avoiding losses the same or distinct? If they are the same, VS and VMPFC activity to receipt of rewards and avoidance of losses would be expected. If they are distinct circuits, VS and VMPFC activity to positive feedback, and AI and ACC activity to negative feedback would be expected.

2) If rewards and losses recruit the same regions, does the magnitude of VS and VMPFC activity in response to obtaining rewards and avoiding losses predict individual differences behaviourally (selecting rewards and avoiding losses)?

3) If rewards and losses recruit distinct neural circuitry:

    a. Do individual differences in the magnitude of VS and VMPFC BOLD response correlate with individual differences in learning to select stimuli associated with rewards? Based on previous research, the magnitude of VS and VMPFC BOLD activity in response to positive feedback was expected to correlate positively with a propensity to select the stimulus more frequently associated with rewards.

    b. Do individual differences in the magnitude of AI and ACC BOLD activity correlate with individual differences in learning to avoid stimuli associated losses? Based on previous research, the magnitude of AI and ACC BOLD activity in response to negative feedback was predicted to correlate positively with a propensity to avoid the stimulus more frequently associated with losses.

4) Do individual difference in the experience of early life adversity correlate with individual differences in VS and VMPFC BOLD activity in response to positive feedback? Similarly, do individual differences in the experience of early life adversity correlate with individual differences in AI and ACC BOLD activity in response to negative feedback? In other words, are regions involved in reward/loss circuitry differentially calibrated based on the experience of early life adversity?

Chapter 2 : Methods

5 « Participants »

Nineteen (11 females) typically developing children between the ages of 9 and 12 years ($M = 10.8$, $SD = 0.97$) were recruited from Western University's Child Development Participant Pool. All participants had normal or corrected to normal vision and were right-handed. Children with learning disabilities or a diagnosis of ADHD were excluded from the study because the diagnoses could confound the results of the fMRI analyses. The study was approved by Western University's Research Ethics Board and informed consent and assent were obtained from mothers and their children prior to participation in the study.

6 « General Procedure »

Trained research assistants recruited participants from the Child Development Participant Pool via telephone calls. Upon obtaining verbal agreement regarding interest in the study, children and their mothers participated in two parts of the study. After receiving informed consent from mothers and informed assent from children, we began the experimental procedures. First, children were trained for the fMRI portion of the study using a 0T-Mock Scanner. The purpose of the mock scanning procedure was to better acquaint both children and mothers with the scanning environment and to ensure that children were comfortable and capable of remaining still for an extended period of

time. While child participants were completing the mock scanning procedures, we asked mothers to complete the Early Life Experiences (ELE) questionnaire. Additionally, participants were required to complete some behavioural tasks and other questionnaires that will be used in other aspects of a larger study. If both children and their mothers agreed to continue with a real fMRI session, we booked an fMRI appointment at Robarts Research Institute for a later date. The entire mock scanning procedure and participation in other aspects of the larger study took approximately 2 hours, and participants were compensated with a $25 gift card to Chapters/Indigo/Coles for their participation.

7 « Early Life Experiences Questionnaire (ELE) »

The ELE questionnaire was administered to mothers of child participants because it is a quantifiable measure of commonly occurring adverse life events. The ELE questionnaire is a 22-item questionnaire designed to measure individual differences in the experience of both the frequency and intensity of adverse life events. An example of one questions on the ELE questionnaire is "New marriage of a parent", mothers were required to indicate if the event occurred, when it occurred (0-6 years) or (7+ years), and how stressful the event was for the child on a Likert-type scale *1 (Mildly Stressful)* to *5 (Extremely Stressful)*. To view the ELE, please see Appendix A.

8   « Instrumental Learning Task»

While inside the fMRI scanner (detailed fMRI procedures described below),

participants completed 3 runs of an instrumental learning task designed to investigate

learning from both rewards and losses (adapted from Pessiglione et al., 2006).

Participants were instructed to try and "get as many points as possible" during the course

of each run. Participants were also informed that they could win up to $10.00 if they

performed well on the task in an effort to increase their motivation to remain still during

the scanning procedures and to ensure that they attended to the task. Please note that all

participants received the $10.00 compensation at the end of the scanning procedure

regardless of their performance or capacity to remain still. During each run, 3 pairs of

neutral, black and white stimuli of common objects were presented. In the stimulus pair

associated with gains (gain-pair stimuli), selecting one of the two stimuli resulted in

positive feedback (+10 points) on 80% of trials and neutral feedback (0 points) on 20% of

trials; in contrast, selecting the other stimulus resulted in positive feedback (+10 points)

on 20% of trials and neutral feedback (0 points) on 80% of trials. In the stimulus pair

associated with losses (loss-pair stimuli), selecting one of the two stimuli resulted in

negative feedback (-10 points) on 80% of trials and neutral feedback (0 points) on 20% of

trials; and selecting the other stimulus resulted in negative feedback (-10 points) on 20%

of trials and neutral feedback (0 points) on 80% of trials. The final stimulus pair (nulls)

resulted in getting 0 points regardless of the choice—both stimuli resulted in receiving

neutral feedback (0 points) in 100% of trials. For the purposes of statistical analyses, the following four conditions were defined:

1.) Wins: instances when participants selected one of the gain-pair stimuli and won 10 points.

2.) Misses: instances when participants selected one of the gain-pair stimuli and received zero points.

3.) Losses: instances when participants selected one of the loss-pair stimuli and lost 10 points.

4.) Avoids: instances when participants selected one of the loss-pair stimuli and received zero points (Please See Figure 1).

To increase statistical power, wins, misses, avoids, and losses were defined based on the outcome of the choices that participants made, regardless of whether or not they chose the most probabilistically advantageous stimulus. For example, wins were defined as instances when participants won 10 points regardless of which stimulus they selected. Similarly, losses were defined as instances when participants lost 10 points regardless of the stimulus that they chose.
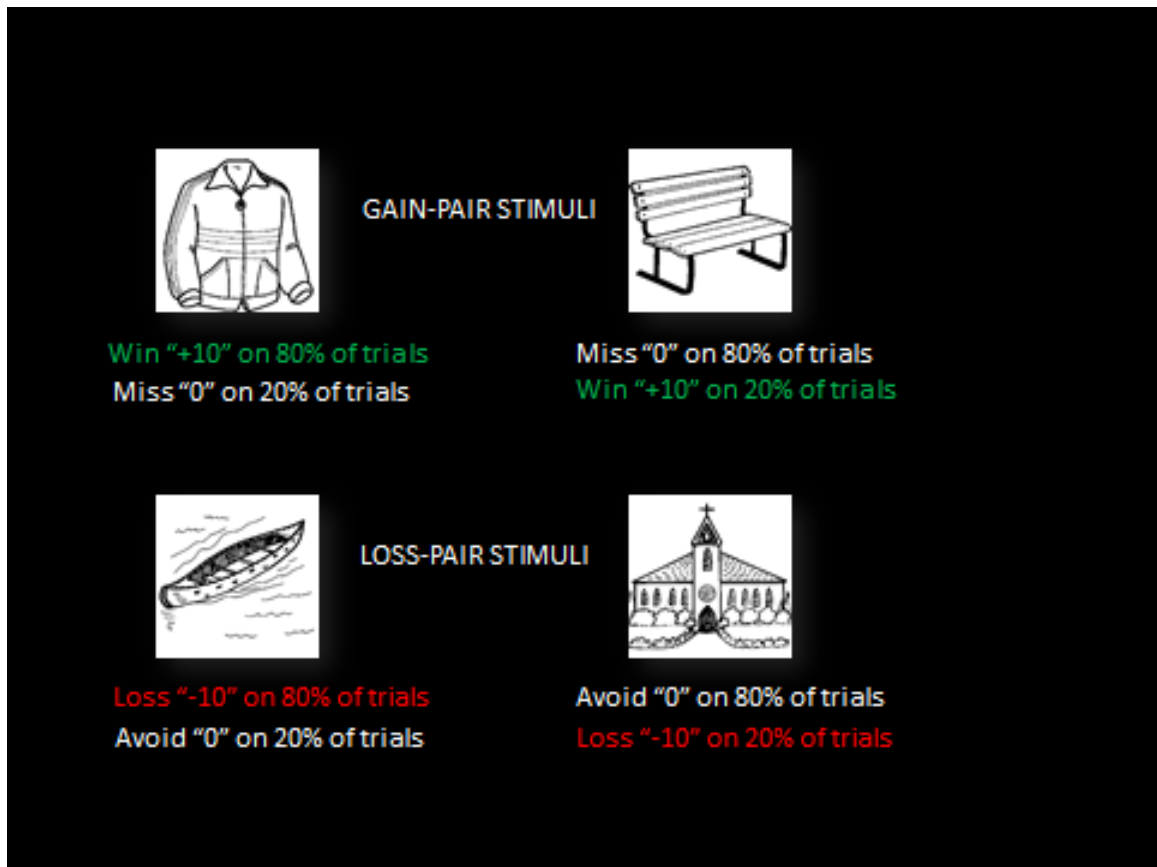
Figure 1. Visual demonstration of the four conditions in the instrumental learning task(wins, misses, avoids, losses).

9   « Event-Related fMRI Data Acquisition»

The imaging procedure was conducted using a 3-Tesla Siemens Magnetom Prisma scanner and a Siemens Prisma 32-channel head coil. Functional T2* weighted images were acquired using an echo-planar imaging (EPI) pulse sequence. Slices were obtained in an ascending, interleaved order (TR = 686 ms; TE = 30 ms; FOV=192 x 192

mm; flip angle = 54°; voxel size = 3 mm^3, 64 x 64 matrix). A total of 3 runs of functional

data were collected from each participant, each functional run consisted of 650 volumes

and lasted for approximately 7 minutes. During the course of the functional runs,

participants were instructed to complete the instrumental learning task (described above).

Each run consisted of 44 trials containing 20 gain-pair stimulus conditions, 20 loss-pair

stimulus conditions, and 4 null conditions. Stimulus pairings (gain-pair, loss-pair, and

nulls) were presented for 3000 ms in a random order. Participants were required to select

a stimulus by means of a button press; pressing the left button with the 2D finger resulted

in selection of the stimulus presented on the left side of the screen, and pressing the right

button with the 3D finger resulted in selection of the stimulus presented on the right side

of the screen. After the participant made their selection, feedback appeared in the center

of the screen for 1000 ms with either "+10", "-10", "0" or "Too Slow" if they did not

make a selection within the 3000 ms. In between feedback and the following stimulus

presentation, we included an intertrial-interval (ITI) of 1000-5000 ms which consisted of

a black screen with a fixation cross. A total score was displayed at the bottom of the

screen when the run was complete, and a final screen was displayed that said "Great job,

you won 'x' points", where x was the total number of points the participant obtained

during that run. After the completion of all 3 functional runs, we collected a high-

resolution T1-weighted anatomical image using a 3D MPRAGE pulse sequence (192

slices; voxel size = 1 mm^3, 256 x 256 matrix). The entire fMRI procedure took

approximately 1 hour to complete and participants were compensated $10.00 cash and with a $25.00 gift card to Chapters/Indigo/Coles for their participation. For a visual depiction of the fMRI procedure, please see *Figure* 2.
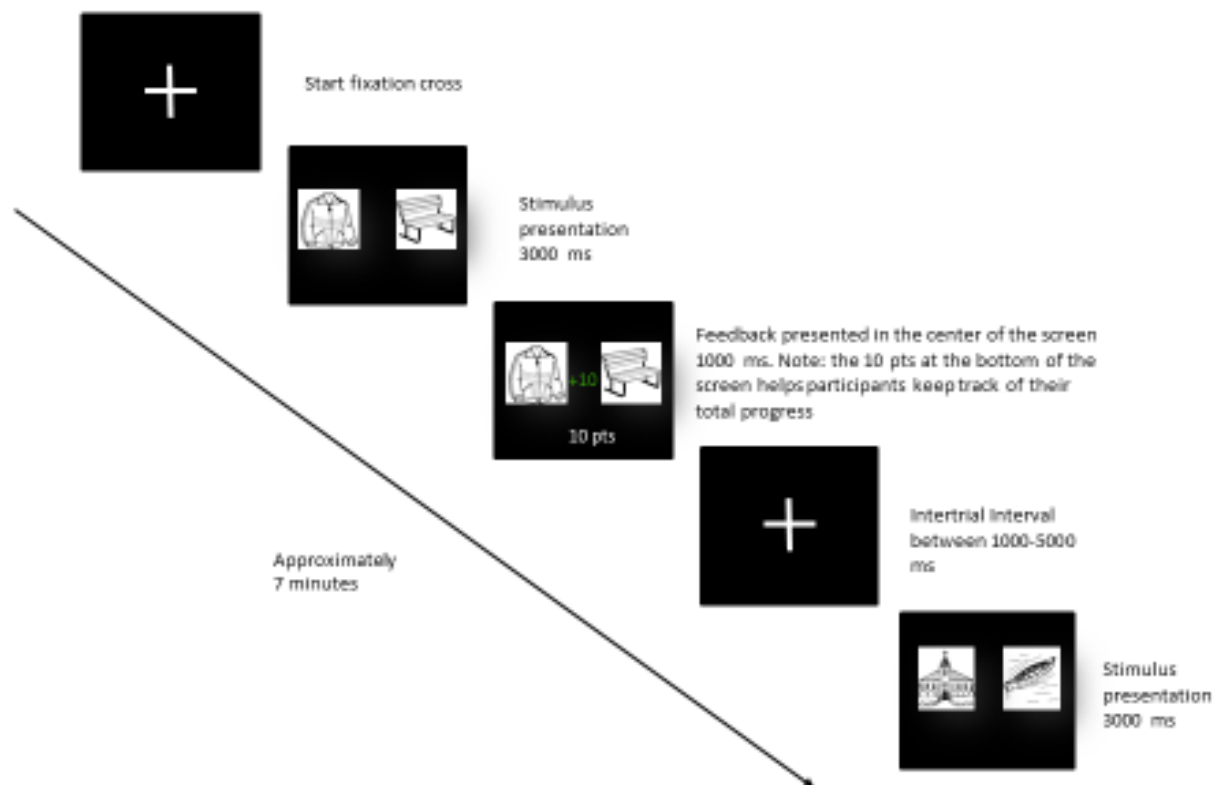
Figure 2. This figure is an illustration of the fMRI task, participants viewed a fixation cross, followed by a stimulus set, the participants then made a choice via button press and received feedback. An intertrial interval between 1000-5000 ms

was included before the presentation of the next stimulus. Each stimulus was
presented for 3000 ms and there were 44 trials in total.

9.1 « fMRI Data Preprocessing and Analysis»

Following fMRI data acquisition, all data were preprocessed using Statistical

Parametric Mapping 12 (SPM 12). First, all functional runs were realigned to the first

functional volume collected, and we ensured that none of the participants exceeded 3 mm

of motion in translation or rotation. Next, we performed coregistration of functional and

anatomical data. We then normalized all single subject data to Montreal Neurological

Institute (MNI) space, and finally, we spatially smoothed the data using an 8 x 8 x 8 mm

Gaussian kernel. After completion of all standard preprocessing procedures, we obtained

onsets for the following conditions: wins, misses, avoids, losses, and nulls, which

allowed us to determine exactly at what time points the conditions occurred for each

participant. We then created single subject maps for each participant by creating general

linear models (GLMs). The GLM for each participant consisted of 5 predictors: wins,

misses, avoids, losses, and nulls; 6 regressors were also included in the GLM for the

motion parameters (3 directions in translation x,y,z; and 3 directions in rotation roll,

pitch, yaw). BOLD response was modelled using a canonical hemodynamic response

function (HRF). Single-subject contrast images for wins vs. misses and losses vs. avoids

were obtained and finally, group contrasts for both wins vs. misses and losses vs. avoids

were also acquired. Region of interest (ROI) data were obtained using the MarsBar

Region of Interest toolbox for SPM. We extracted ROI parameter estimates (β) for the

left and right VS, VMPFC, left and right AI, and ACC (Please See Table 1 for a list of

regions and their corresponding coordinates). All coordinates for the ROIs were obtained

from prior studies investigating the MCLP, using similar procedures and MNI space

(Blair et al., 2006; Pessiglione et al., 2006).

Table 1. Regions of interest and their [x,y,z] coordinates at the centre of the sphere. VS = ventral striatum, VMPFC = ventromedial prefrontal cortex, AI = anterior insula, and ACC = anterior cingulate cortex.

Region of Interest	MNI coordinates at Centre of Sphere (x,y,z)	Radius of Sphere (mm)
Left VS	x = -14, y = 10, z = -9	7 mm
Right VS	x = 14, y = 10, z = -9	7 mm
VMPFC	x = -1, y = 47, z = -18	10 mm
Left AI	x = -40, y = 21, z = -8	10 mm
Right AI	x = 40, y = 24, z = -8	10 mm
ACC	x = 8, y = 26, z = 36	10 mm

Chapter 3 : Results

10 « Behavioural Results »

10.1 « Learning to Select Favourable Outcomes and Avoid Unfavourable Outcomes »

Prior to proceeding with the imaging analyses, an investigation of whether

participants learned the reward and loss contingencies presented in the instrumental

learning task was conducted. The learning curves in *Figure 3* are visual depictions of

observed behavioural choices. *Figure 3* shows on a trial by trial basis the proportion of

participants that chose the correct stimulus in the gain-pair condition (in green) and

selected the incorrect stimulus in the loss-pair condition (in red). For example, to obtain

the data points for trial 1 in *Figure* 3, we first determined how many participants received

a gain-pair condition at trial 1, we then calculated the proportion of those participants

who selected the stimulus that most often resulted in rewards and plotted that percentage

as the data point at trial 1. Similarly, we determined how many participants received a

loss-pair condition at trial 1, and calculated the proportion of participants who selected

the incorrect stimulus at trial 1. These calculations were repeated for all subsequent trials.

As demonstrated in *Figure 3*, it is evident that across the trials, the proportion of

participants who chose the correct stimulus (the one associated with a greater frequency

of obtaining rewards) increased, while the proportion of participants who chose the

incorrect stimulus (the one associated with a greater frequency of obtaining losses)

decreased.
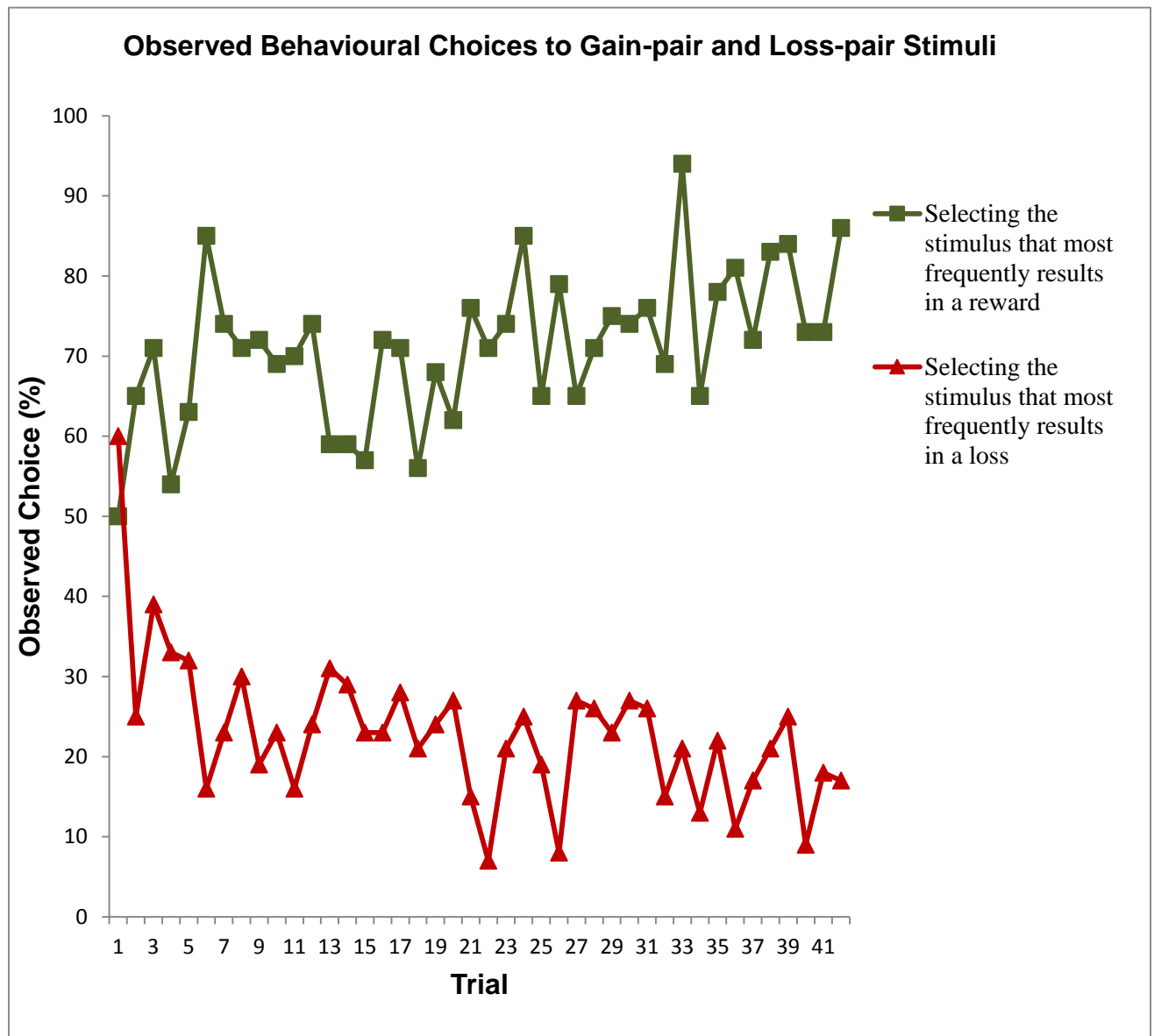
Figure 3. Observed behavioural choice to gain-pair and loss-pair stimuli.

10.2 « Gain-Pair and Loss-Pair Accuracy »

Accuracy for gain-pair conditions and loss-pair conditions were measured separately. For the gain-pair condition, accuracy was defined as the percentage of instances across all runs that the participant selected the "correct" stimulus (the stimulus that most frequently resulted in rewards). For the loss-pair condition, accuracy was defined as the percentage of instances across all runs that the participant avoided the "incorrect" stimulus (the stimulus that most frequently resulted in losses). A paired-samples t-test was conducted to compare accuracy on the gain-pair condition with accuracy on loss-pair condition. Accuracy scores on the gain-pair condition ($M = 75.91$, $SD = 13.34$) and accuracy on the loss-pair condition ($M = 79.09$, $SD = 13.94$) did not differ significantly from one another; $t(18) = 0.929$, $p = .365$. These results indicate that the average accuracy on gain-pair conditions did not differ significantly from the average accuracy on loss-pair conditions.

Next, whether accuracy on gain-pair conditions was correlated with accuracy on loss-pair conditions was investigated. A Pearson correlation was conducted and demonstrated that there was not a statistically significant relationship between gain-pair accuracy and loss-pair accuracy, $r(17) = .403$, $p = .087$. Although the relationship between gain-pair accuracy and loss-pair accuracy was not statistically significant, the scatter plot in *Figure 4.* shows that there is a trend towards a positive correlation; such

that participants who scored high in accuracy in the gain-pair condition also scored high in accuracy in the loss-pair condition. However, given that the correlation between the two conditions was not statistically significant, gain-pair accuracy and loss-pair accuracy were treated as separate scores for all of the following analyses (in other words, an overall accuracy score was not obtained).

No Correlation Between Gain-Pair and Loss-Pair Accuracy

r (17)= .403, p = .087
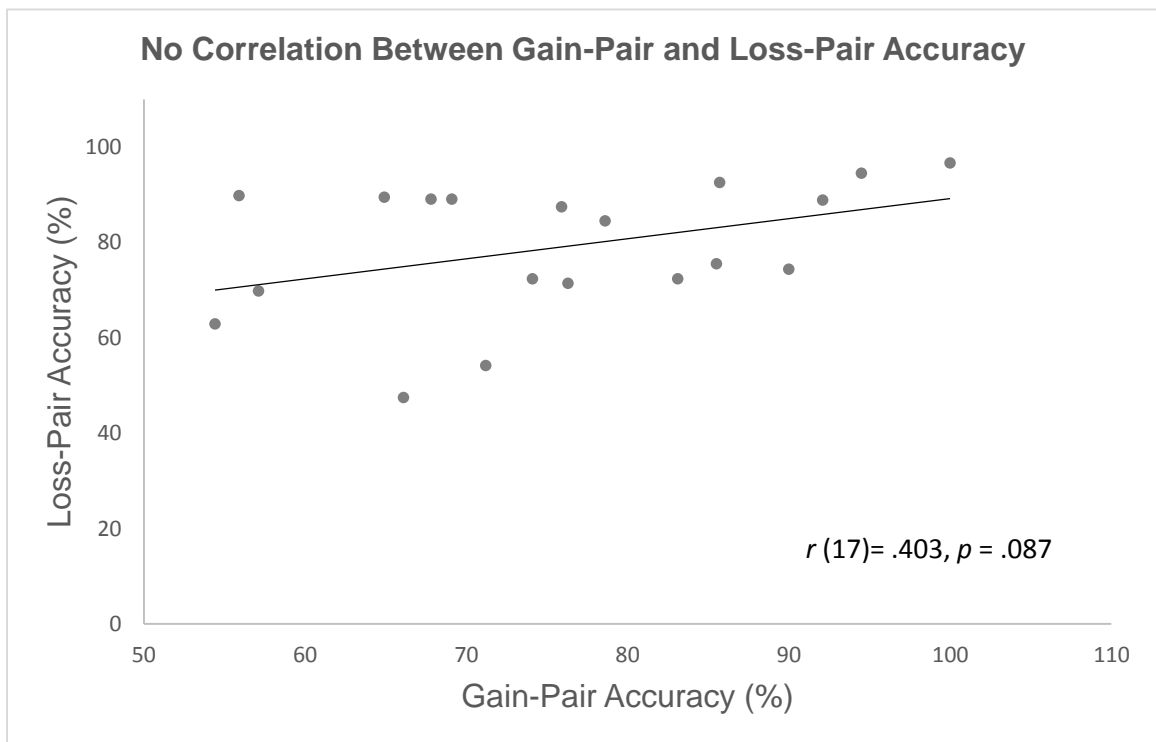
Figure 4. Scatter-plot showing no correlation between gain-pair and loss-pair accuracy.

10.3 « No Effect of Sex or Age on Gain-Pair/Loss-Pair Accuracy »

To ensure that there was no effect of sex on either gain-pair or loss-pair accuracy, the group was split by sex: females (n = 11) and males (n = 8) and independent samples t-tests for gain-pair and loss-pair accuracy were conducted. Gain-pair accuracy in females (*M* = 79.77, *SD* = 11.64) did not differ significantly from gain-pair accuracy in males (*M* = 70.6, *SD* = 14.45). Leven's test indicated equal variances (*F* = .042, *p* = .841) and the independent samples t-test was not significant, *t*(17) = 1.534, *p* = .143. Similarly, loss-pair accuracy in females (*M* = 75.34, *SD* = 15.08) did not differ significantly from loss-pair accuracy in males (*M* = 84.25, *SD* = 11.06); Leven's test (*F* = .619, *p* = .442); *t*(17) = -.413, *p* = .176.

To ensure that there were no effects of age on either gain-pair or loss-pair accuracy, Pearson correlations between age (in months) and accuracy on gain-pair and loss-pair conditions were conducted independently. Age (*M* = 129.84, *SD* = 11.64) did not correlate significantly with gain-pair accuracy, *r*(17) = -.125, *p* = .610. Similarly, age did not correlate significantly with loss-pair accuracy, *r*(17) = -.323, *p* = .178.

10.4 « Reaction Time (RT) »

Next, an investigation of whether reaction time (RT) measured in milliseconds (ms) differs between gain-pair and loss-pair conditions using a paired samples t-test was

conducted. RT in the loss-pair condition ($M = 1259.42$, $SD = 98.24$) was significantly greater than the RT in gain-pair condition ($M = 1162.69$, $SD = 150.16$), $t(18) = 3.626$, $p = .002$. These findings are consistent with those reported by Pessiglione and colleagues (2006) who also found that RT in the loss-pair condition was significantly greater than RT in the gain-pair condition using the same task with adults. *Figure 5* illustrates the difference in RT between loss-pair and gain-pair conditions.

Average RT in the Loss-Pair Condition is Significantly Greater than Average RT in the Gain-Pair Condition
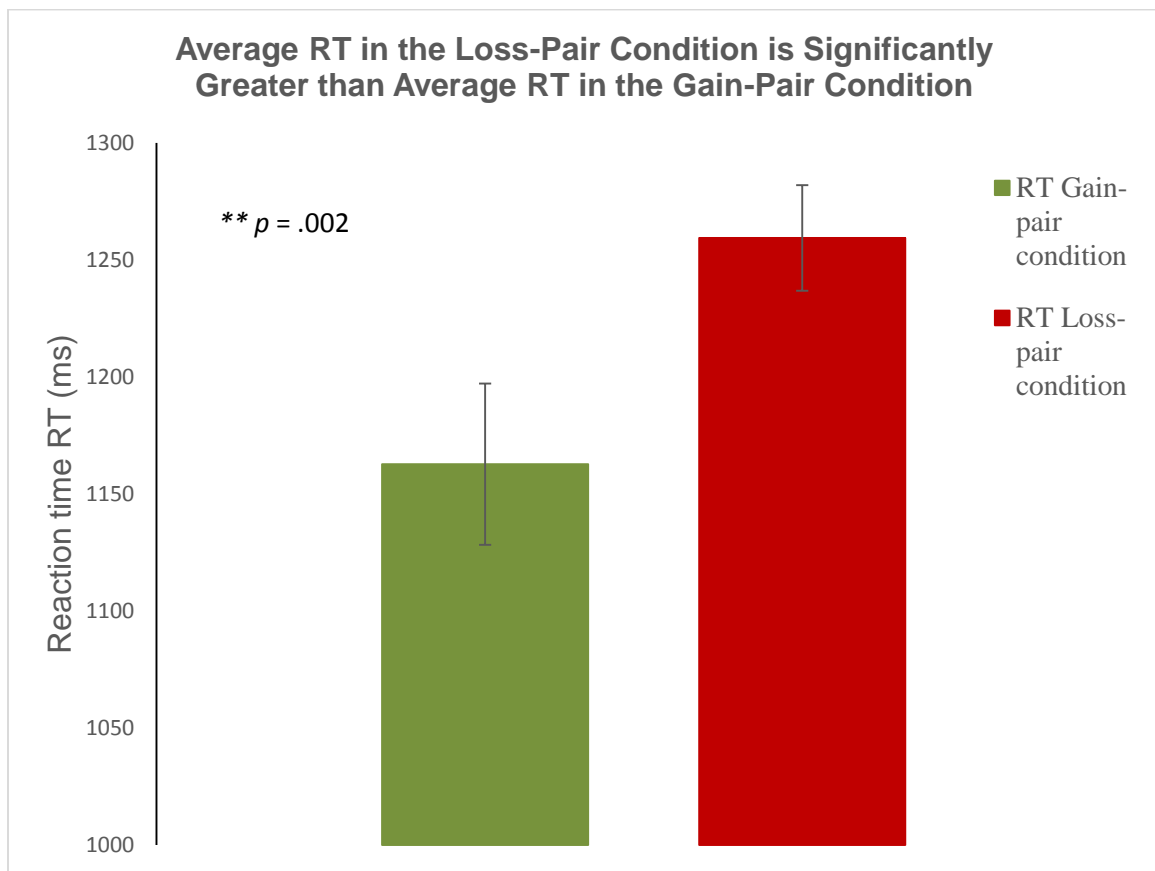
Figure 5. Bar-plot showing the difference in RT between loss-pair and gain-pair conditions

10.5 « No Effect of Sex or Age on Gain-Pair/Loss-Pair RT »

Once again, to ensure that there was no sex difference in RT during either the gain-pair or loss-pair conditions, participants were grouped by sex (females n = 11) and males (n = 8). Independent samples t-tests for both gain-pair and loss-pair RT revealed that for gain-pair conditions, RT was not significantly different between females (*M* =

11.97.55, $SD = 172.32$) and males ($M = 1114.75$, $SD = 104.99$). Levene's test for equality

of variances was not significant ($F = 2.608$, $p = .125$) and the t-test was not significant,

$t(17) = 1.201$, $p = .246$. Similarly, for loss-pair RT, there was no difference between

females ($M = 1260.26$, $SD = 118.53$) and males ($M = 1258.25$, $SD = 68.90$). Levene's test

indicated equal variances ($F = 2.609$, $p = .125$), and the t-test was not significant, $t(17) =$

.043, $p = .966$. Finally, there was no effect of age on either gain-pair or loss-pair accuracy

as determined via Pearson correlations between age (in months) and RT. Age ($M =$

129.84, $SD = 11.64$) did not correlate significantly with gain-pair RT, $r(17) = -.035$, $p =$

.885. Likewise, age did not correlate significantly with loss-pair RT, $r(17) = -.135$, $p =$

.583.

11 « Research Question 1 »

11.1 « Do the VS and VMPFC Show a Greater BOLD Response in Wins Relative to Misses? »

To replicate previous findings that the MCLP, specifically the VS and VMPFC,

are more active during gaining rewards (wins) relative to missing out on an opportunity

to gain rewards (misses), a group contrast for wins vs. misses was obtained. *Figure 6*

shows the group contrast for wins contrasted against misses (wins vs. misses) at a

statistical threshold of $t = 2.878$, $p < .005$ (uncorrected). As predicted, regions within the

MCLP (VS and VMPFC) were significantly activated in response to wins at feedback

relative to misses.
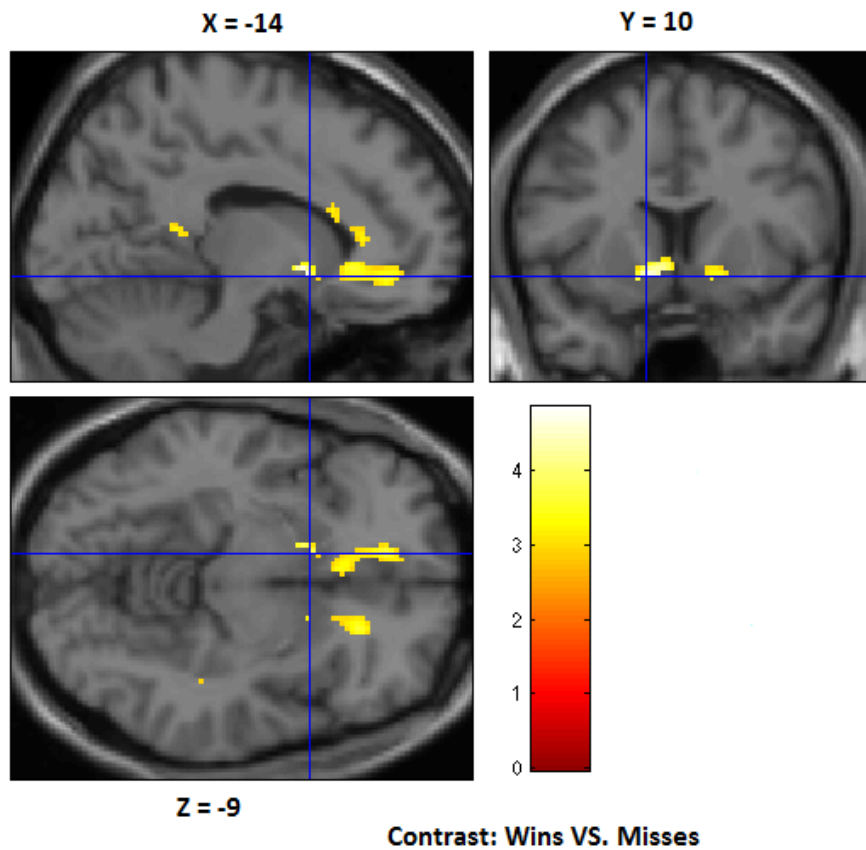
Figure 6. Group contrast for wins vs. misses [x = -14, y = 10, z = -9] at a statistical threshold of t = 2.878, p < .005. MNI T1.img template. Regions that show more activation during wins relative to misses include bilateral VS and VMPFC.

11.2 « Do the AI and ACC Show a Greater BOLD response in Losses Relative to Avoids? »

Similarly, to determine whether the AI and ACC were more active during losses relative to avoiding a loss (avoids), a group contrast for losses vs. avoids was obtained.

Figure 7 shows the group contrast for losses contrasted against avoids (losses vs. avoids)

at a statistical threshold of $t = 3.61$, $p = .001$ (uncorrected). The group contrast reveals

robust error network activity, including greater bilateral AI and ACC BOLD response in

losses relative to avoids. *Table 2* is a summary of statistics for significant clusters of

activation for the wins vs. misses and losses vs. avoids contrasts.

Figure 7. Group contrast for losses vs. avoids [x = 40, y = 24, z = -8], at a statistical threshold of t = 3.61, p < .001. MNI T1.img template. Regions that show more activation during losses relative to avoids include bilateral AI and ACC.

Table 2. Statistics for ROIs within the wins vs. misses and losses vs avoids contrasts.
Note: Coordinates denote the location of peak activation.

Contrast	MNI Coordinates [x,y,z]	Region	Statistics
Wins vs. Misses	[-16, 8, -6]	Left Ventral Striatum (VS)	$t = 4.85, p = .000$
	[14, 8, -4]	Right Ventral Striatum (VS)	$t = 3.67, p = .001$
	[-16, 14, -8]	Venromedial Prefrontal Cortex (VMPFC)	$t = 3.60, p = .001$
Losses vs. Avoids	[-36, 26, -4]	Left Anterior Insula (AI)	$t = 7.19, p = .000$
	[40, 20, -6]	Right Anterior Insula (AI)	$t = 11.56, p = .000$
	[6, 36, 38]	Anterior Cingulate Cortex (ACC)	$t = 12.63, p = .000$

11.3 « Does Avoiding a Loss Recruit the Same Neural Regions as Gaining a Reward? »

To determine whether the patterns of brain activity observed in gaining rewards and avoiding losses are the same or distinct, group-level contrasts for wins vs. misses, and avoids vs. losses were conducted. If the underlying neural circuitry is the same, the VS and VMPFC were expected to become active to both wins and avoids, relative to misses and losses, respectively. *Figure 8* shows the group contrast for avoids vs. losses at a statistical threshold of $t = 2.878$, $p < .005$ (uncorrected), and demonstrates that the BOLD responses in the VS and VMPFC were not significantly greater in avoids relative to losses.
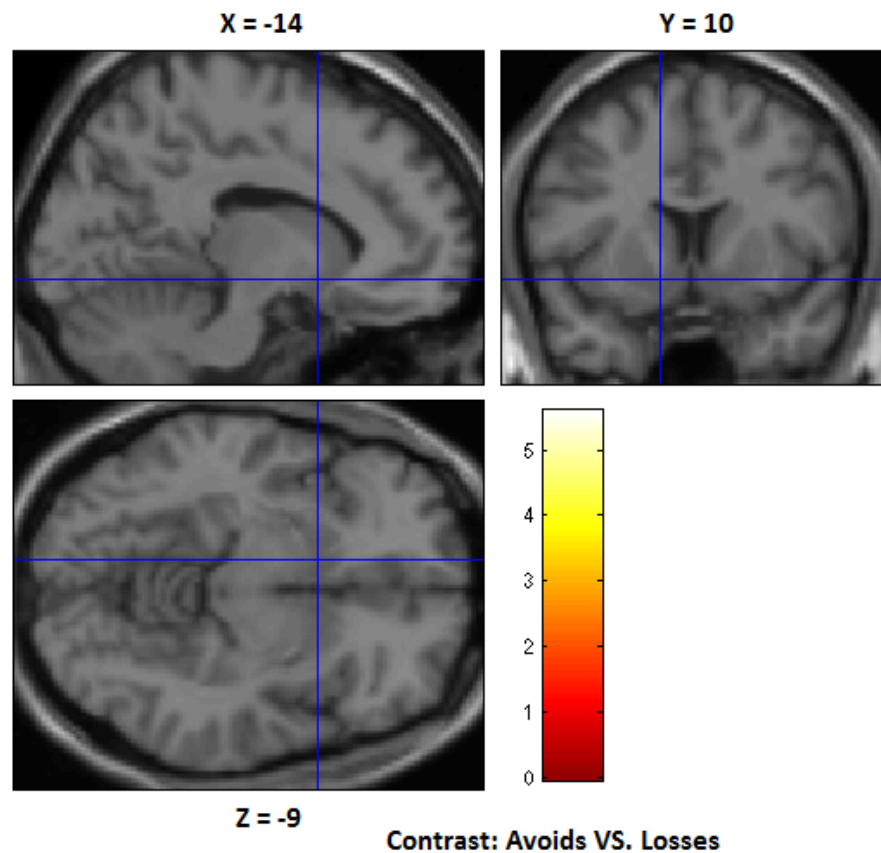
Figure 8. Group contrast for avoids vs. losses [x = -14, y = 10, z = -9] at a statistical threshold of t = 2.878, p < .005. MNI T1.img template. There were no clusters of significant activity in VS or VMPFC.

A comparison of *Figure 6* (wins vs. misses), and *Figure 8* (avoids vs. losses), reveals that while the BOLD responses in the VS and VMPFC were significantly greater in wins relative to misses, the same neural regions were not significantly more active when participants avoided a loss relative to when they received a loss (Please See *Figure 9*).
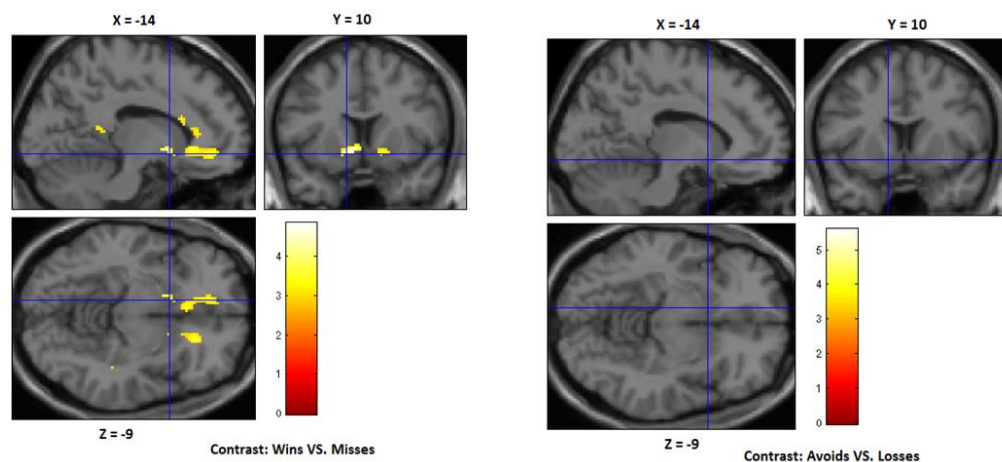
Figure 9. A comparison of the wins vs. misses and avoids vs. losses contrasts [x = - 14, y = 10, z = -9] both at a statistical threshold of t = 2.878, p < .005. MNI T1.img template.

To further demonstrate that gaining a reward (wins) results in a different pattern of neural activity in comparison to avoiding a loss (avoids), wins vs. avoids were directly contrasted against one another at a statistical threshold of $t = 2.878, p < .005$ (uncorrected). *Figure 10* demonstrates that the BOLD response in the right VS and VMPFC was greater in wins relative to avoids.
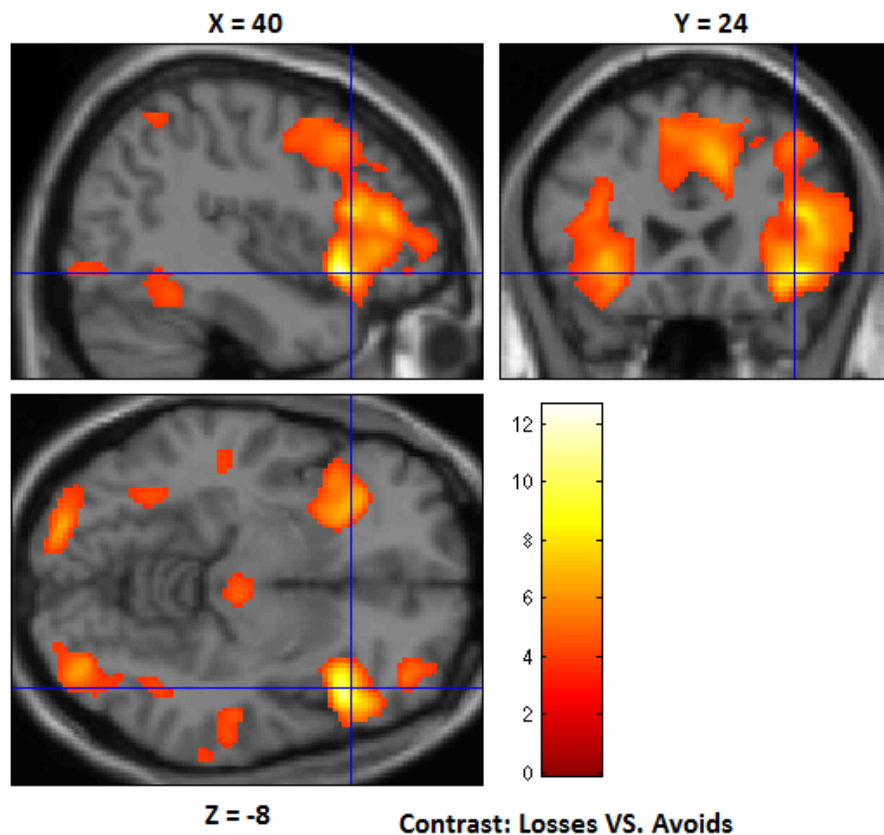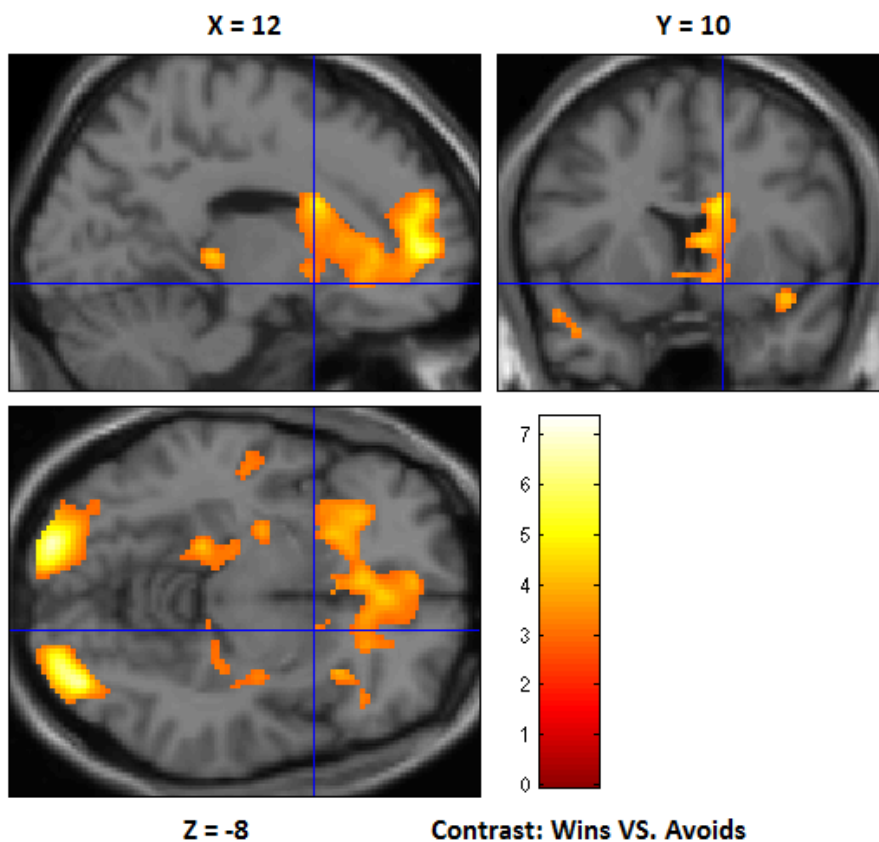
Figure 10. Group contrast for wins vs. avoids [x = 12, y = 10, z = -8] at a statistical threshold of t = 2.878, p < .005. MNI T1.img template. Regions that show more activation during wins relative to avoids include the right VS and VMPFC.

12 « Research Question 2 »

12.1 « Do the BOLD Responses in the VS and VMPFC Correlate with Gain-Pair Accuracy? »

We previously determined that the VS and the VMPFC are more significantly activated to wins relative to misses. Based on previous research, individual differences in

the magnitude of the VS and VMPFC BOLD response were expected to correlate with

accuracy on the gain-pair condition, such that participants with a greater BOLD response

in the regions of the MCLP (VS and VMPFC) would select the stimulus associated with

rewards more often. Individual differences in β in the left VS in the wins vs. misses

contrast (M = 1.78, SD = 1.85) were correlated with gain-pair accuracy and a positive

correlation r(17) = .5088, p = .026 was found. These results indicate that the greater the

BOLD response in the left VS during wins relative to misses the better the participant's

performance on the gain-pair condition (selecting the stimulus that is most frequently

associated with rewards). Similarly, the BOLD response in the right VS during wins vs.

misses (M = 1.50, SD = 1.50) correlated positively with gain-pair accuracy, r(17) =

.5356, p = .018; and the BOLD response in the VMPFC during wins vs. misses (M =

0.77, SD = 2.59) correlated marginally with gain-pair accuracy, r(17) = .463, p = .045.

Please refer to *Figures 11-13* for the scatter-plots illustrating the relationships.
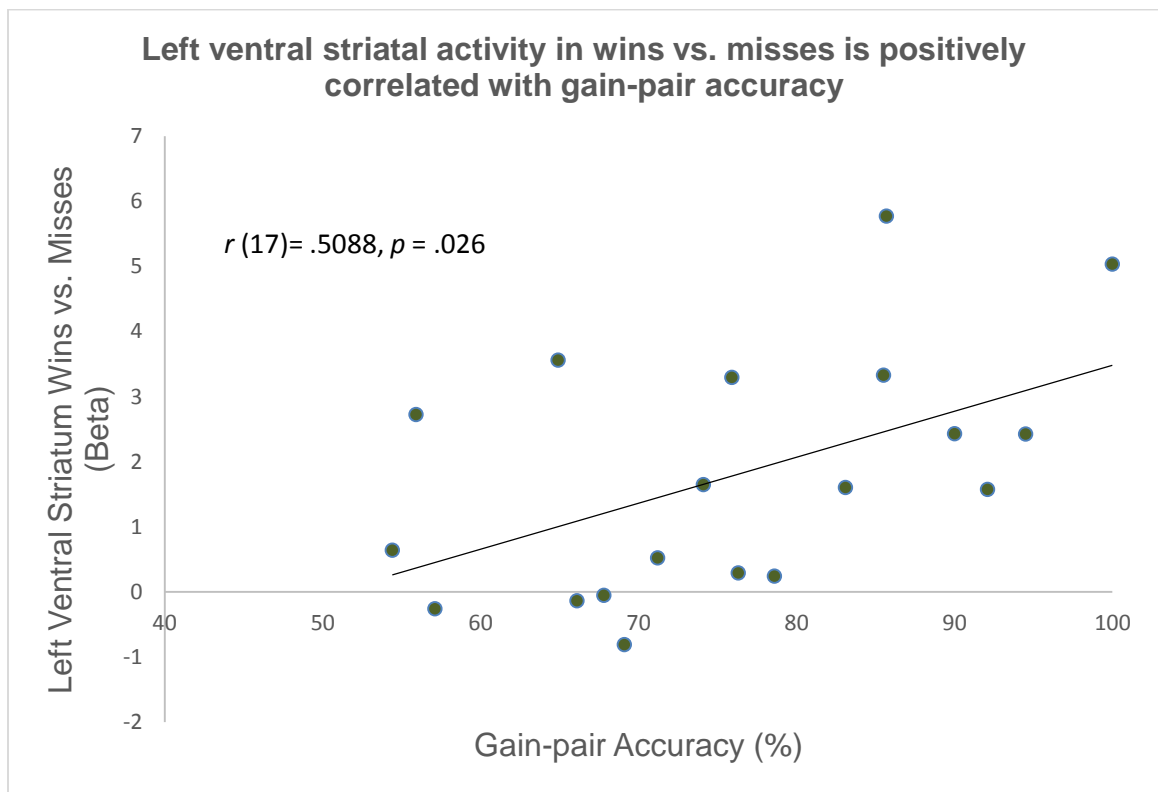
Figure 11. Scatter-plot of the correlation between activity left VS in wins vs. misses (β) and gain-pair accuracy (%).

Right ventral striatal activity in wins vs. misses is positively correlated with gain-pair accuracy

r (17) = .5356, *p* = .018

Right Ventral Striatum Wins vs. Misses (Beta)
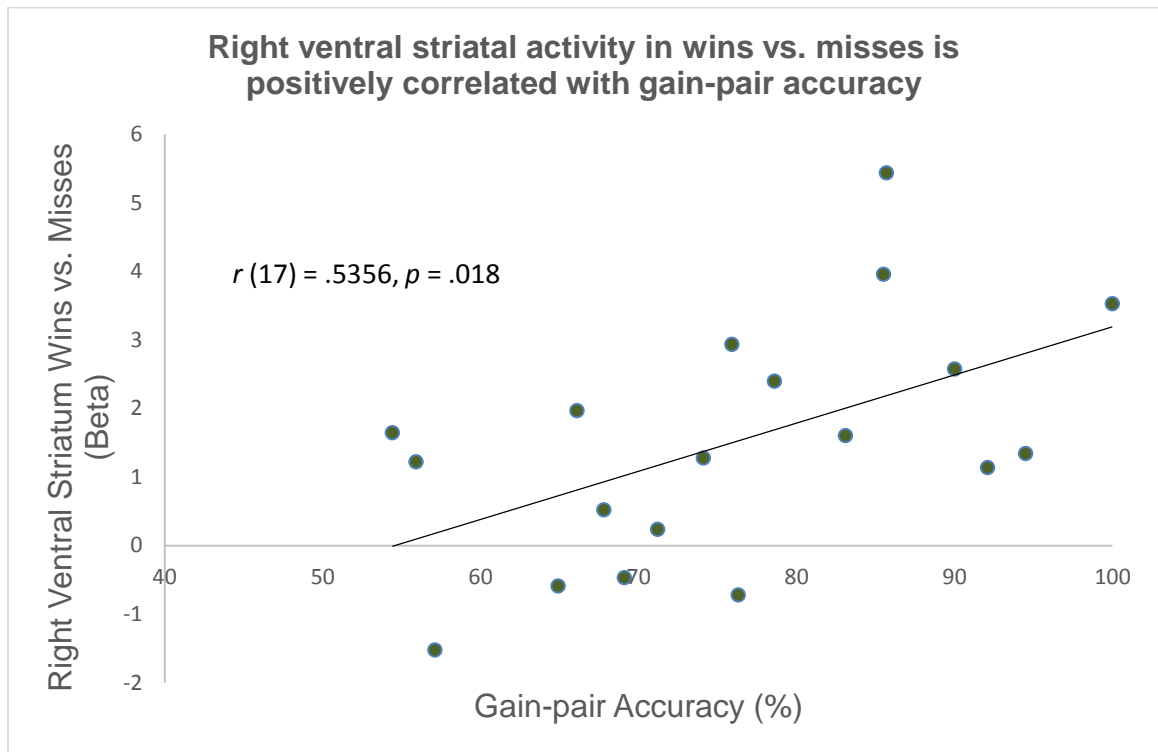
Gain-pair Accuracy (%)

Figure 12. Scatter-plot of the correlation between activity right VS in wins vs. misses (β) and gain-pair accuracy (%).
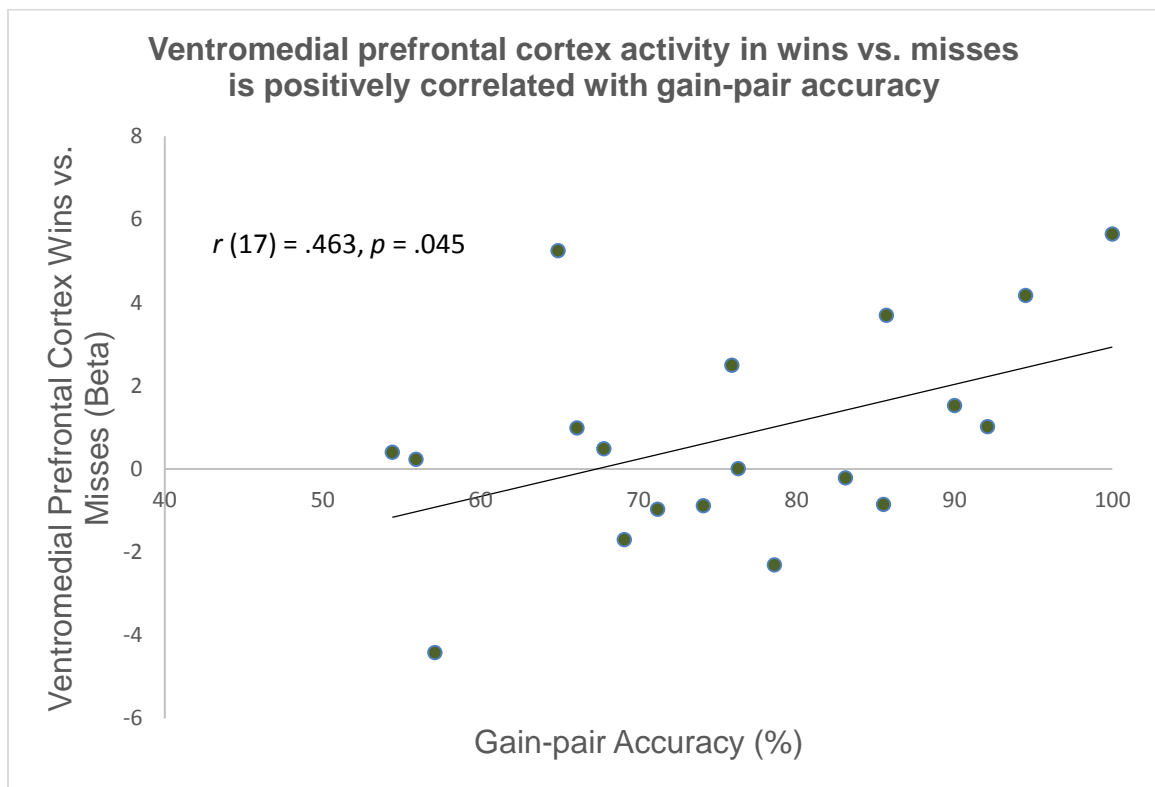
Figure 13. Scatter-plot of the correlation between activity VMPFC in wins vs. misses (β) and gain-pair accuracy (%).

12.2 « Do the BOLD Responses in the AI and ACC Correlate with Loss-Pair Accuracy? »

The group contrast for losses vs. avoids revealed significant activity in bilateral AI and also in the ACC. To determine whether BOLD responses in the AI or ACC in losses vs. avoids correlated with accuracy on the loss-pair condition, Pearson correlations were computed between the ROIs and loss-pair accuracy. The BOLD response (β in losses vs. avoids contrast) in neither the left AI ($M = 3.22$, $SD = 2.16$), the right AI ($M =$

3.16, *SD* = 1.53), nor the ACC (*M* = 2.73, *SD* = 1.74) correlated with loss-pair accuracy

(*M* = 79.09, *SD* = 13.94). These results demonstrate that the BOLD response observed in

the losses vs. avoids contrast did not predict individual differences in avoiding the

stimulus that most frequently resulted in a loss. Please refer to *Figures 14-16* for scatter-

plots illustrating the relationships between bilateral AI, ACC and loss-pair accuracy.
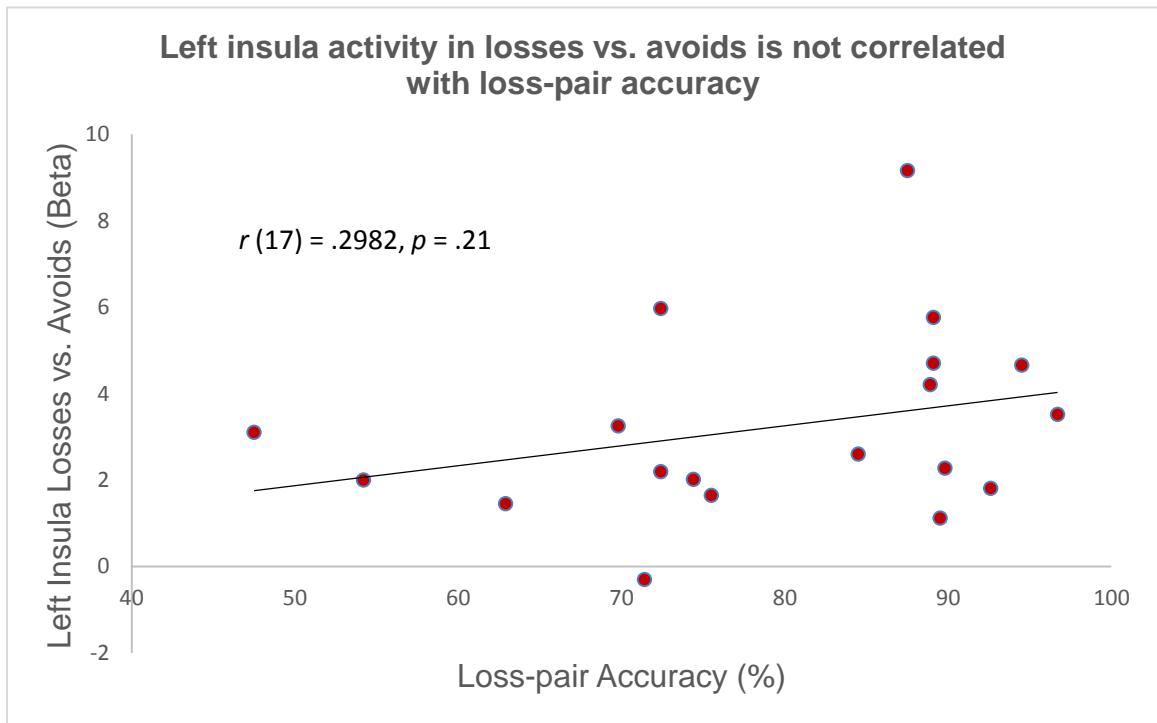
Figure 14. Scatter-plot of the correlation between activity in the left AI in losses vs. avoids (β) and loss-pair accuracy (%).
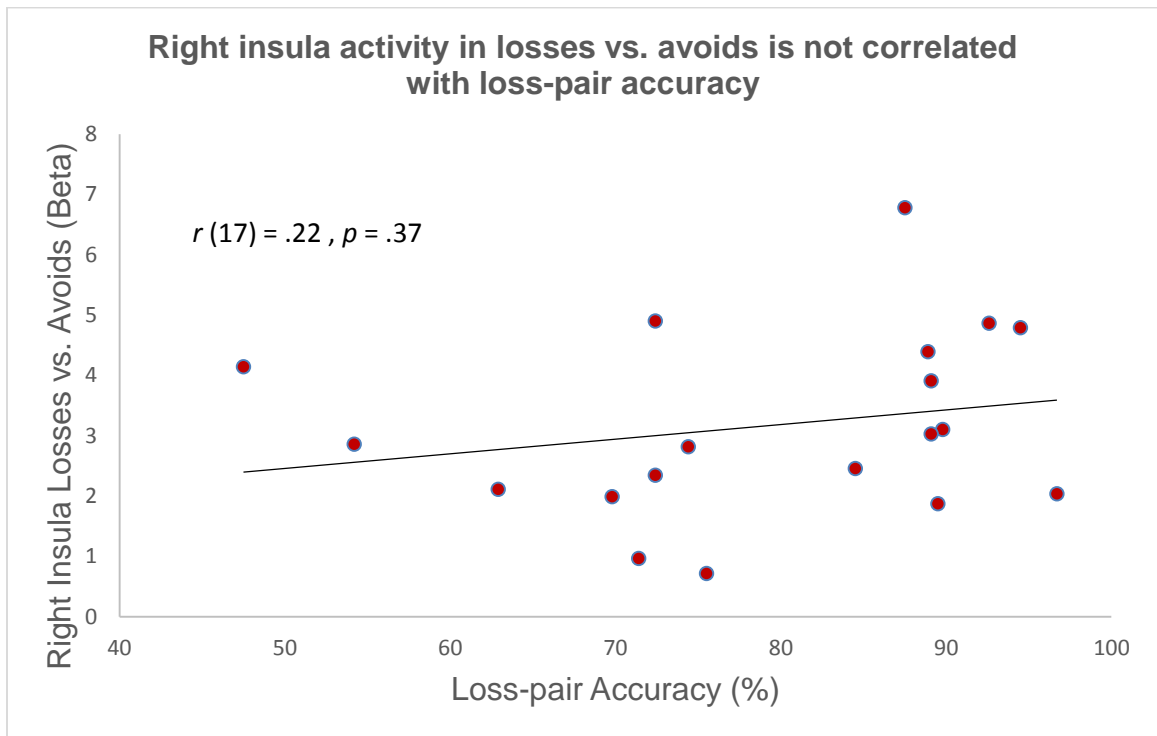
Figure 15. Scatter-plot of the correlation between activity in the right AI in losses vs. avoids (β) and loss-pair accuracy (%).
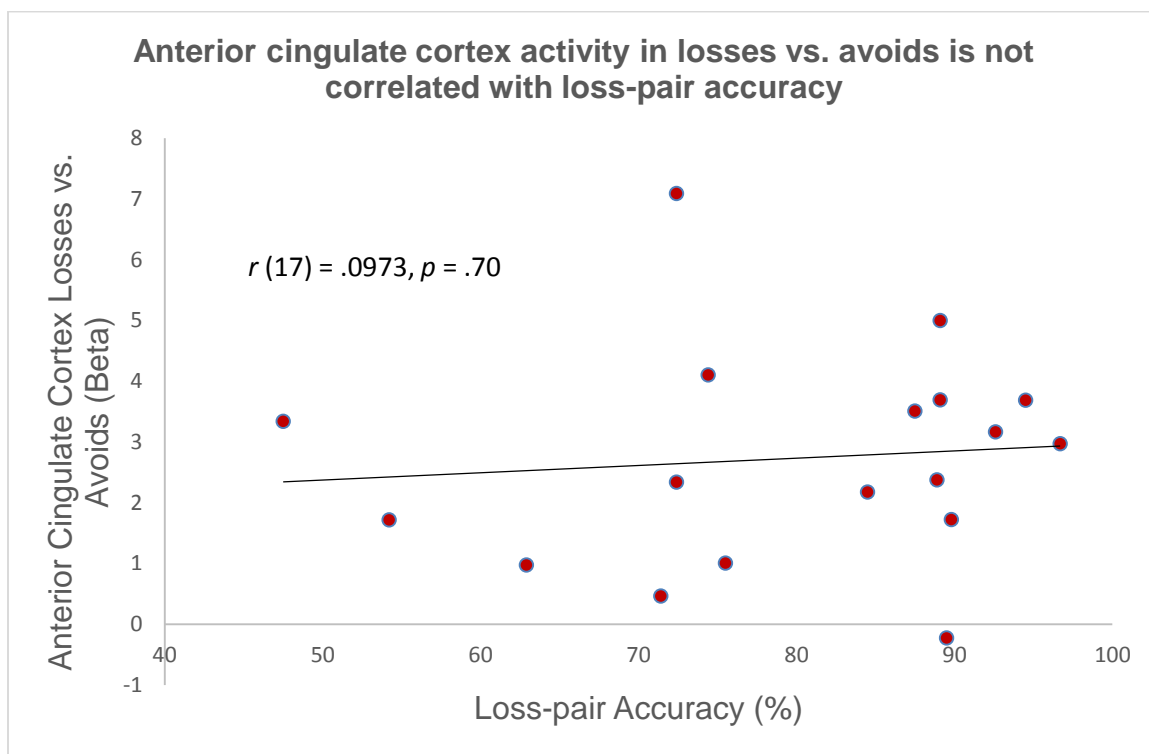
Figure 16. Scatter-plot of the correlation between activity in the ACC in losses vs. avoids (β) and loss-pair accuracy (%).

13 « Research Question 3»

13.1 « Does Early Life Adversity Correlate with VS and VMPFC Activity in Wins vs. Misses? »

To examine whether the experience of early life adversity influenced the response

of the MCLP (VS and VMPFC in particular) to rewarding feedback, Pearson correlations

were conducted between the total adversity score and left VS, the right VS, and the

VMPFC activity in wins vs. misses. The relationship between the ELE total adversity

score (M = 12.47, SD = 7.95) and beta in the left VS in the wins vs. misses contrast (M = 1.78, SD = 1.85) was positive $r(17)$ = .5961, p = .007. Similarly, there was a positive correlation between the total adversity score and beta in the right VS during wins vs. misses (M = 1.50, SD = 1.50), $r(17)$ = .5084, p = .026; and beta in the VMPFC during wins vs. misses (M = 0.77, SD = 2.59), $r(17)$ = .5521, p = .014. These results demonstrate that early life adversity had an influence on the BOLD response to rewarding feedback in regions within the MCLP. Please refer to *Figures 17-19* for scatter-plots of the relationships.

Total adversity is positively correlated with left ventral striatal activity in wins vs. misses

r (17) = .5961 , **p* = .007

Left Ventral Striatum Wins vs. Misses (Beta)

Total Adversity (ELE)
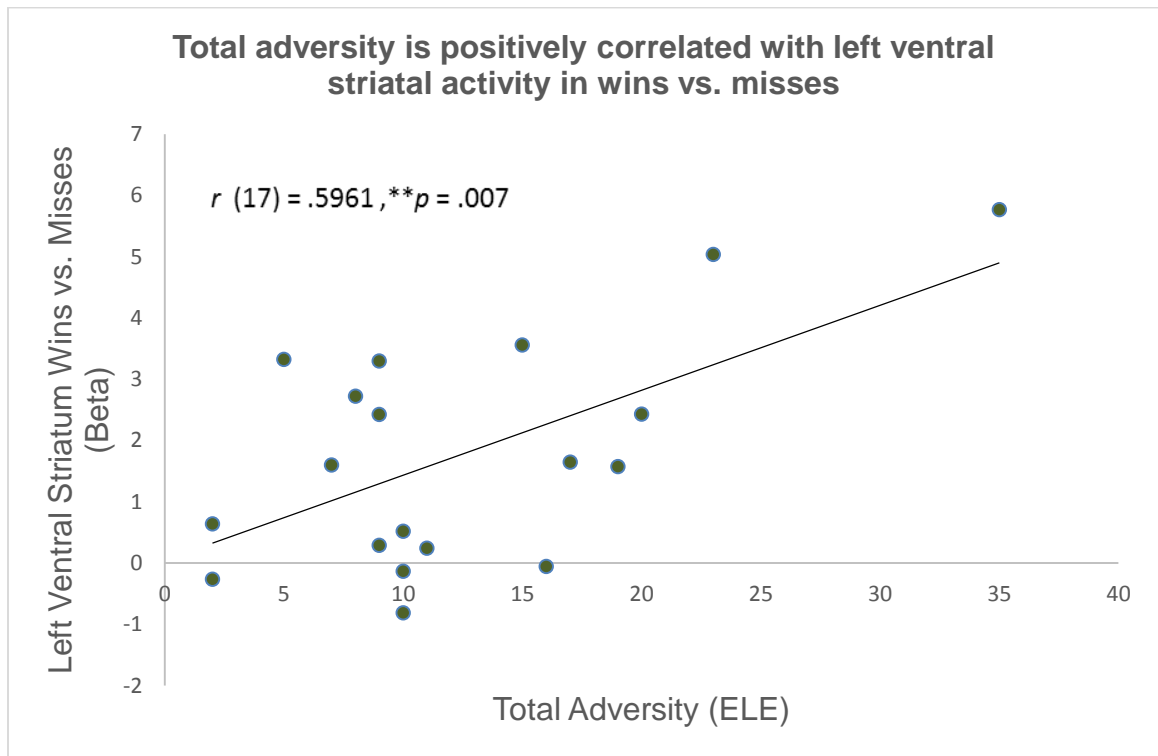
Figure 17. Scatter-plot of the correlation between left ventral striatal activity in wins vs. misses (β) and total adversity (ELE).
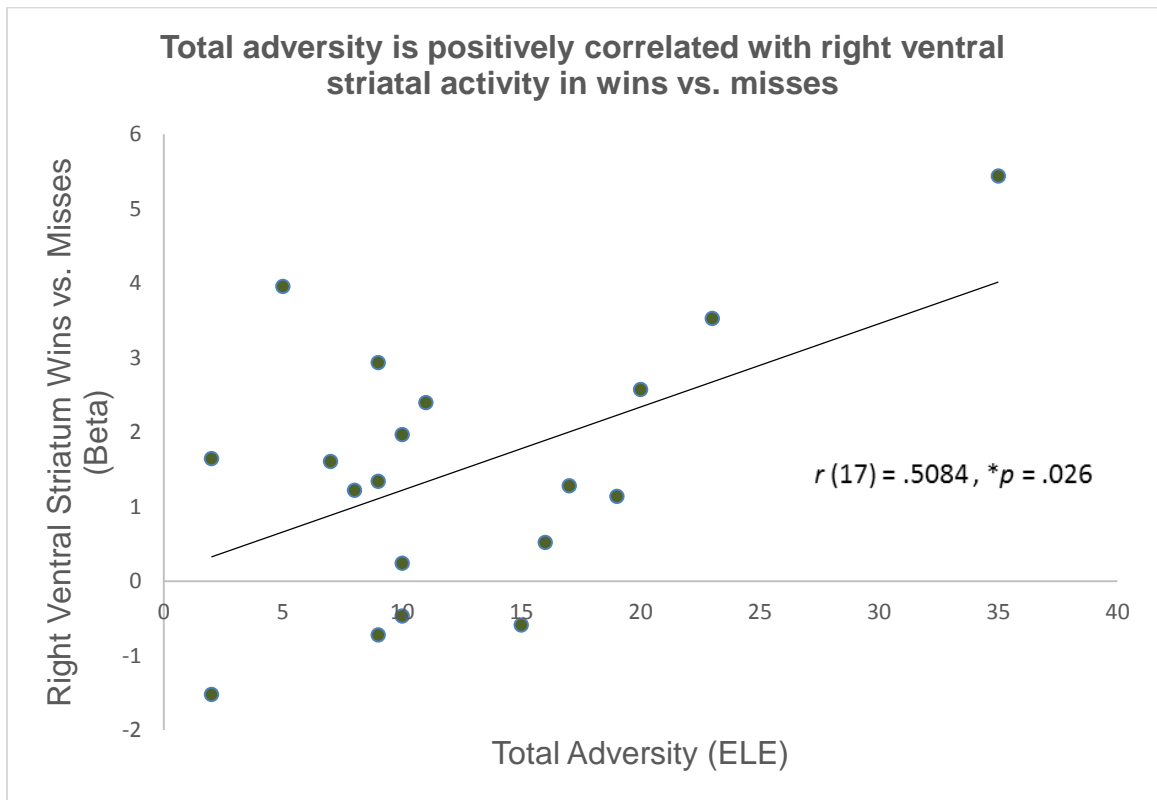
Figure 18. Scatter-plot of the correlation between right ventral striatal activity in wins vs. misses (β) and total adversity (ELE).
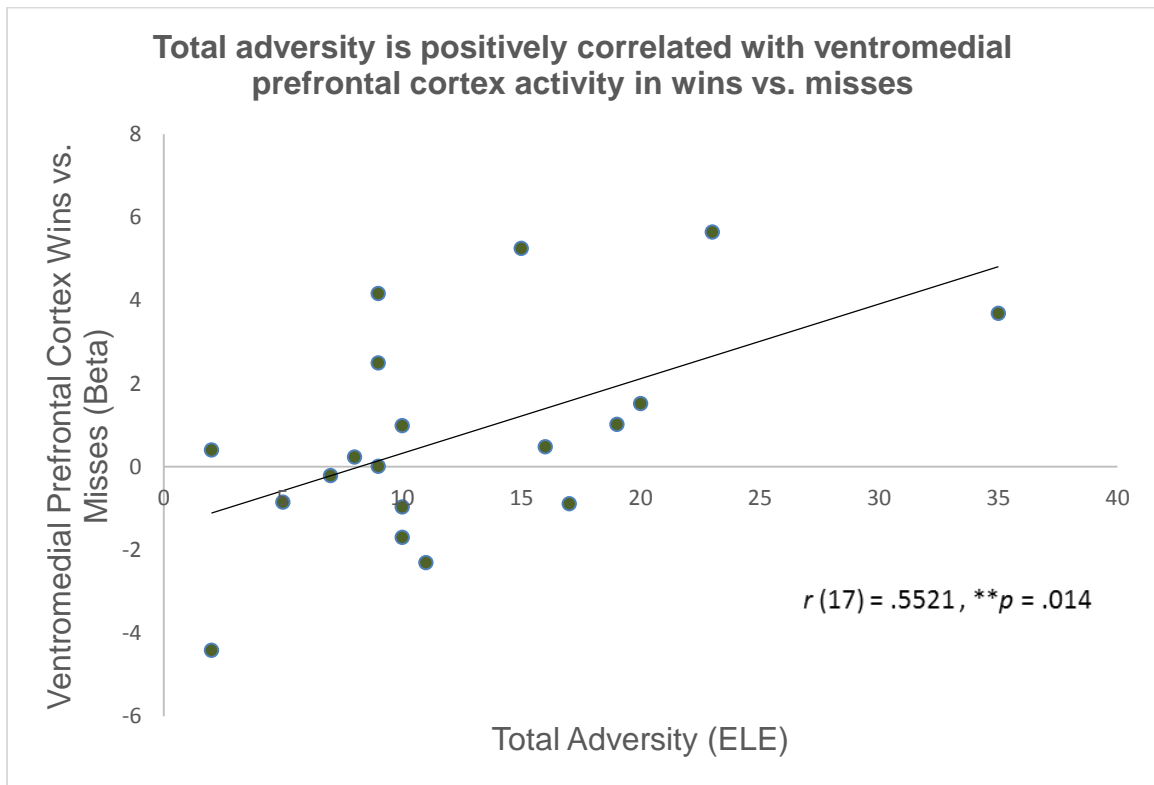
Figure 19. Scatter-plot of the correlation between right ventral striatal activity in wins vs. misses (β) and total adversity (ELE).

13.2 « Does the Experience of Early Life Adversity Predict Gain-Pair Accuracy? »

Given the positive relationship between adversity experienced early in life and greater activation within regions of the MCLP, and given that those same regions were predictive of gain-pair accuracy behaviourally, we conducted a correlation between ELE scores ($M = 12.47$, $SD = 7.95$) and gain-pair accuracy ($M = 75.91$, $SD = 13.34$). Indeed, the results demonstrated that total adversity was positively correlated with gain-pair

accuracy *r*(17) = .526, *p* = .02 (Please refer to *Figure 20*). However, the relationship

between total adversity and accuracy seems to be specific to gain-pair accuracy, total

adversity did not correlate with loss-pair accuracy (*M* = 79.09, *SD* = 13.94), *r*(17) =

.4424, *p* = .06.
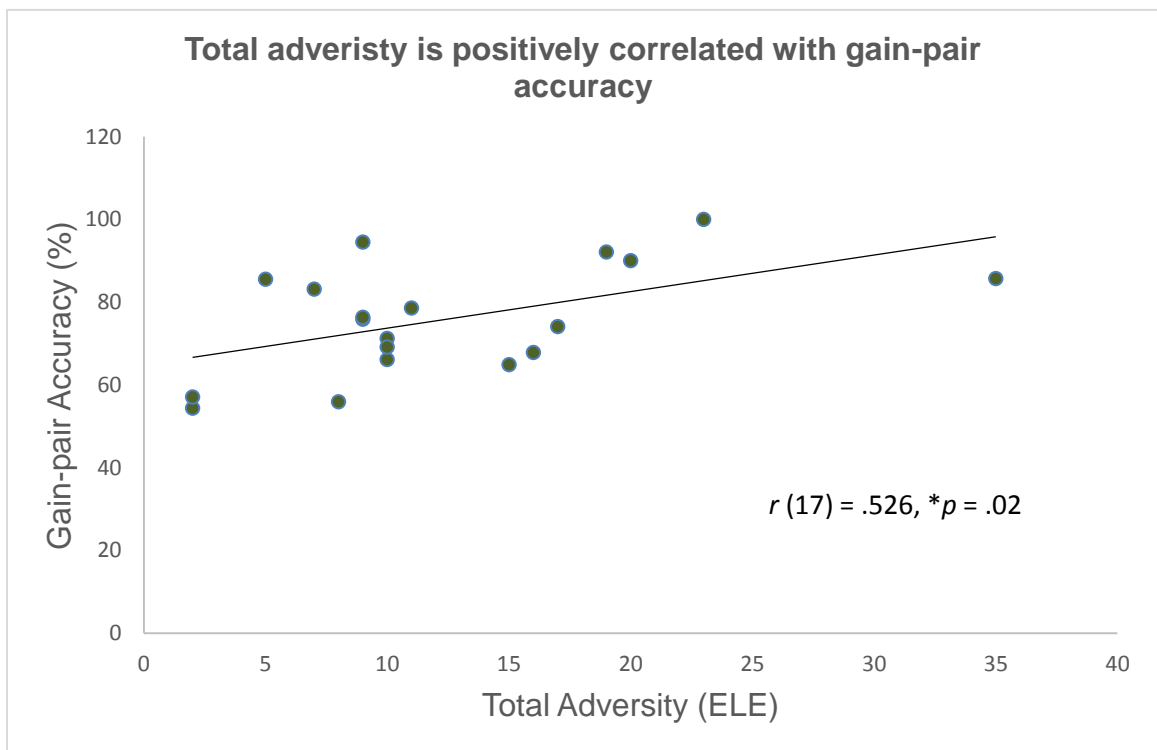
Figure 20. Scatter-plot of the correlation between gain-pair accuracy (%) and total adversity (ELE).

13.3 « Does Early Life Adversity Correlate with AI and ACC Activity in Losses vs. Avoids? »

Next, whether the neural regions involved in feedback to losses exhibit a similar phenotypic plasticity was investigated. Bilateral AI and ACC activity were correlated with total adversity scores from the ELE separately and the results revealed that there was no significant relationship between adversity and any of the regions active during feedback to losses. The total adversity score ($M = 12.47$, $SD = 7.95$) did not correlate with activity in the left AI ($M = 3.22$, $SD = 2.16$) in losses vs. avoids, $r(17) = -.104$, $p = .67$; it did not correlate with activity in the right AI ($M = 3.16$, $SD = 1.53$), $r(17) = .199$, $p = .413$; nor did it correlate with activity in the ACC ($M = 2.73$, $SD = 1.74$), $r(17) = .3278$, $p = .17$.

Chapter 4 : Discussion

Learning from rewards and losses guides future decision making and is advantageous; moreover, previous research has demonstrated that dysregulation within the MCLP can have adverse consequences. In light of these considerations, the present study examined both the neural and the behavioural correlates of reward and loss learning early in development. Furthermore, whether regions within the MCLP are sensitive to the presence of early life adversity was investigated.

14 « Behavioural Findings»

At the behavioural level, RT in the loss-pair condition was significantly greater than RT in the gain-pair condition. These findings are consistent with those reported by Pessiglione and colleagues (2006) who used the same task in an adult cohort. This difference in RT in the gain-pair and loss-pair conditions could be because participants first attend to the most salient stimulus in each pair, and then chose/avoid that option. For example, in the gain-pair condition, the salient stimulus is the "correct" stimulus, participants attend to that stimulus and then select it. In contrast, in the loss-pair condition, the salient stimulus is the "incorrect" stimulus, participants first attend to the incorrect stimulus and then avoid that stimulus. The process of attending to a stimulus

and selecting it would take less time than attending to a stimulus and then selecting the other stimulus in the pair.

15   « fMRI Findings and Brain-Behaviour Correlations»

First, previous findings that the VS and VMPFC exhibit a greater BOLD response during gaining rewards (wins) relative to missing out on an opportunity to gain rewards (misses) were replicated. Consistent with previous findings (Floresco, 2015; Pessiglione et al., 2006; Rogers et al., 2004), a greater BOLD response in the bilateral VS and the VMPFC in wins relative to misses was found. Furthermore, individual differences in the BOLD response in the MCLP were correlated with behavioural performance, such that the BOLD response in the bilateral VS and VMPFC correlated positively with gain-pair accuracy. These results demonstrate that the greater the BOLD response in the aforementioned regions, the more frequently participants selected the stimulus that was more often associated with rewards. Additionally, this relationship provides evidence for the functional role of the VS and VMPFC in influencing behaviour. Consistent with these findings, a recent review characterizes the VS as a region that integrates cognitive and affective information to increase the efficiency of selecting actions that lead to positive outcomes (Floresco, 2015; *See Also* Pessiglione et al.,2006).

Previous research has demonstrated that the AI and ACC are involved in the experience and anticipation of negative consequences (Blair et al., 2006; Palminteri et al.,

2012; Samanez-Larkin et al., 2008). Based on these findings, conditions when participants lost point against conditions when they avoided losing points were contrasted. Consistent with previous findings, the BOLD response was greater in the bilateral AI and ACC in losses relative to avoids. However, Samanez-Larkin and colleagues (2008) reported that AI activity to losses predicted participants' ability to avoid subsequent losses. Contrary to these findings, we did not find a relationship between AI or ACC activity and loss-pair accuracy. These results demonstrate that while the AI and ACC respond to the feedback of losses, they do not necessarily guide future choices. The finding that BOLD responses within regions of the MCLP correlate positively with subsequent behavioural choice and that BOLD responses within the AI and ACC *do not* correlate with behavioural choice, might be reflective of the anatomical connection between the striatum and the motor cortex. The basal ganglia including regions of the striatum were traditionally viewed as motor regions because of the white matter fiber tracts that connect the regions with the motor cortex; therefore, it could be that neural activity within the striatum in response to rewards could be efficiently transmitted to the motor cortex thereby influencing actions to select the rewarding stimulus.

15.1 « Avoiding a Loss is not Processed the Same Way as Gaining a Reward »

Some researchers have found that the same neural regions that respond to gaining

rewards are activated when participants avoid losses. This notion stems from the idea that

DA bursts facilitate approach behaviours, while DA dips facilitate avoidance behaviours

(Delgado et al., 2000; Frank et al., 2004; Palminteri et al., 2009, 2012). However, other

researchers have hypothesized that an entirely separate neural system is activated in

response to losses. According to the latter hypothesis, DA neurons within the VTA are

insensitive to losses—they activate only to unexpected rewards and become suppressed

in the absence of predicted rewards (Fiorillo, 2013). We hypothesized that if approaching

rewards and avoiding losses rely upon the same neural circuitry, fMRI activation in VS

and VMFPC would be observed both when participants gain reward and when they avoid

losses. However, the findings reveal that while the VS and VMPFC were significantly

activated in wins versus misses, they were not activated in avoids versus losses. These

findings provide support for the hypothesis that DA neurons within the VTA are

insensitive to losses and become activated only to rewards. Avoiding a loss is not

processed in the same way as gaining a reward—at least at the neural level and with a

developmental cohort. Some of the inconsistent findings might reflect differences in the

samples used; for example, some of the previous research that demonstrates that the same

neural circuitry is involved in gaining rewards and avoiding losses used patients with

Parkinson's disease (Frank et al., 2004). Furthermore, it is important to disambiguate rewards and losses within the task, many of the tasks administered in previous studies included rewards and losses within the same stimulus pairing. For example, stimulus "A" resulted in a reward 80% and a loss 20%; whereas stimulus "B" resulted in a reward 20% and a loss 80% of time (Frank et al., 2004). Using tasks that are designed in this way make it particularly difficult to disambiguate what the participants' choice means; selecting A could be approaching a reward or avoiding a loss. One of the advantages of the task used in this study is that it separates gain-pair and loss-pair stimuli, such that stimulus "A" predicts reward most of the time and stimulus "B" predicts receiving 0 points most of the time. In other words, the task designed by Pessiglione and colleagues (2006) and used in this study, separates rewards and losses in a manner that makes it easier to interpret the participants' behaviour. These differences in the tasks used to engage the MCLP could explain some of the inconsistent findings.

16 « The MCLP is Sensitive to Early Life Adversity»

Gatzke-Kopp (2011) suggests that the MCLP demonstrates plasticity to adversity experienced early in development. Changes in DA signaling within the MCLP are proposed to be adaptations to adversity; and the severity of early life adversity is proposed to predict individual differences in dopaminergic function. To test this hypothesis, the frequency of early life adversity (measured via ELE) was correlated with

MCLP BOLD responses during wins versus misses. A positive correlation between adversity and activity within the VS and VMPFC was found. These findings are consistent with the idea that the MCLP shows phenotypic plasticity, such that the greater the amount of adversity experienced in early development, the greater the magnitude of the BOLD response in regions within the MCLP when participants received rewards. In addition, an association between early life adversity and behaviour was found; once again, early life adversity was positively correlated with gain-pair accuracy.

These findings are consistent with previous research that demonstrates a relationship between adversity and a behavioural sensitivity to rewards (Casement et al., 2015; Goeders, 2003; Lighthall et al., 2013; Mather & Lighthall, 2012; Meaney et al., 2002). However, these results provide not only behavioural evidence demonstrating a relationship between adversity and a tendency to select rewarding stimuli, but also, they demonstrate a relationship between the MCLP and adversity experienced in early development. These findings are of particular interest because they demonstrate that the MCLP tracks not only information regarding the outcomes of choices in the immediate environment, but is also sensitive to adverse events that occur throughout the course of early development. The idea that environmental factors might influence the MCLP is of practical relevance given the important role of the MCLP in learning to select rewards, and that dysregulation within the MCLP has a host of adverse consequences, including

ADHD, (Carmona et al., 2009; Hommer, Bjork, & Gilman, 2011; Luman, Tripp, & Scheres, 2010; Plichta & Scheres, 2014; Plichta et al., 2009; Sagvolden & Johansen, 2005; Sonuga-Barke, 2002; Ströhle et al., 2008; Tripp & Alsop, 1999; Tripp & Wickens, 2009; Volkow et al., 2009). If we begin to understand the role of environmental adversity in calibrating the MCLP, we may begin to better understand what gives rise to individual differences in susceptibility to substance abuse, ADHD, schizophrenia and other disorders of the dopaminergic system. A better understanding of both the neurobiological and environmental influences on the MCLP and disorders associated with dysregulation of the MCLP, can inform evidence-based clinical practice.

17 « Limitations »

The present study has several limitations that should be taken into consideration when interpreting the findings. First, the small sample size (n = 19) makes it difficult to generalize our findings to the population at large. Furthermore, the sample consisted predominantly of Caucasian families from a middle to upper-middle class socioeconomic status, once again compromising the generalizability of our findings. The fact that many of the participants were from middle to upper-middle class socioeconomic status has implications with regards to the findings in relation to the ELE questionnaire. It has previously been determined that low socioeconomic status is associated with the experience of early life adversity, and with the current sample, the assessment of extreme

conditions of early life adversity that are typically correlated with low socioeconomic status and parental education were not possible to investigate.

Beyond sample characteristics, the ELE questionnaire has both its merits and drawbacks. The ELE questionnaire required mothers of child participants to indicate how stressful commonly occurring adverse life events were for their child. Given that the ELE questionnaire was completed by the mothers (and not the participants themselves), mothers may not have accurately estimated how stressful the adverse life event was for their child. It is quite possible that some mothers may have under/over-estimated how stressful the event was for their child. The reason that the ELE was used despite this limitation is that other questionnaires that assess adversity in early childhood often use measures of traumatic events. We were not interested in only the presence of extremely traumatic events, but also, how typically occurring stressful life events might influence individual differences in the function of the MCLP. One further limitation in the treatment of early life adversity using the ELE was that all types of adversity were aggregated in the total adversity measure. However, the types of events on the ELE are quite diverse (*Appendix A*) and range from issues pertaining to the stability of the early life environment (e.g., moving residences or changing schools), to events that may have longer lasting influences (e.g., serious illness or death of an immediate family member). One interesting future direction could be to separate early life events into different

categories and observe whether it is a particular type of adversity that influences the MCLP more than others. Similarly, the ELE includes measures of when the adverse life event occurred (between 0-6 years or 7 + years), it would be interesting to investigate whether or not the timing of early life adversity influences the MCLP and subsequently behaviour. The underlying research question would be to determine whether differential calibration of the MCLP based on early life adversity has a sensitive period. These types of an analyses were not conducted in the current study because of limitations associated with the small sample size.

A further limitation is related to the design of our fMRI protocol, an inter-trial interval between the stimulus presentation and feedback was not included. Therefore, differences in BOLD activity to the anticipation versus receipt of rewards cannot be determined, as suggested by some recent evidence (Boecker et al., 2014). Additionally, the stimuli that were used in the paradigm were not natural rewards, they were simply drawings of everyday objects. It would be interesting to determine whether the MCLP responds more robustly to natural rewards, such as pictures of appetizing foods or attractive faces in contrast to pictures of foods that typically illicit disgust and unattractive faces. Using stimuli that are more likely to be present in the natural environment might increase the external validity of the study.

In the present study, age-related changes in the function of the MCLP or in behavioural performance were not investigated. It is possible that as participants approach adolescence, they would be more sensitive to the prospect of rewards as previous research has determined that adolescence is a period of risk-taking and novelty seeking. In future work, the development trajectory of reward and loss learning at the behavioural level, the structural level of the nervous system, and the functional response of the MCLP in response to rewards and losses will be determined. Finally, in the present study, a consideration of how variability within the genome might influence the BOLD response in the MCLP to rewards, and whether gene-environment interactions might explain individual differences at both the neural and behavioural level were not included. In future work, both environmental and genetics data will be included in the analyses. Future studies should also investigate the influence of early life adversity on the structure of the MCLP using diffusion tensor imaging (DTI; for an analysis of white matter fiber tracts within regions of the MCLP) and voxel-based morphometry (for an analysis of individual differences in gray matter volume). Gaining an understanding of how genes and the environment (and/or their interaction) might influence both the structure and function of the MCLP will help shed light onto what gives rise to individual differences in reward learning.

18 « Concluding Remarks »

The present study replicated previous findings that regions within the MCLP (VS and VMPFC) show a greater BOLD response to gaining rewards relative to missing out on rewards. Furthermore, the results demonstrated that individual differences in the magnitude of the BOLD response within the VS and VMPFC correlated positively with selecting the stimulus that resulted in a reward most often. In contrast, the AI and ACC demonstrated greater BOLD responses to receiving losses relative to avoiding losses. However, neither the activity in the AI nor the ACC was predictive of behavioural performance in avoiding the stimulus that most often resulted in a loss. Additionally, while the VS and VMPFC exhibited a greater BOLD response to gaining rewards relative to missing out on rewards; the same regions did not show increased BOLD activity in avoiding a loss relative to receiving a loss. These findings suggest that the neural underpinnings of gaining rewards are not the same as the neural underpinnings of avoiding losses—at least in a developmental sample. Finally, the MCLP was found to demonstrate a phenotypic plasticity to adversity experienced early in childhood. The frequency and intensity of adverse life events experienced throughout the course of development correlated positively with VS and VMPFC activity when participants obtained a reward relative to when they missed out on receiving a reward. Moreover, early life adversity correlated positively with the behavioural propensity to select the stimulus that most frequently resulted in rewards (*Figure 21* is a visual schematic

outlining these relationships). The finding that the MCLP is sensitive to early life

adversity is of particular importance because it demonstrates that the MCLP tracks

information regarding the outcome of choices in both the immediate environment, and

also throughout ontogeny. The combination of these findings can help delineate what

factors contribute to individual differences in learning to select actions that are favourable

and avoid actions that are unfavourable.
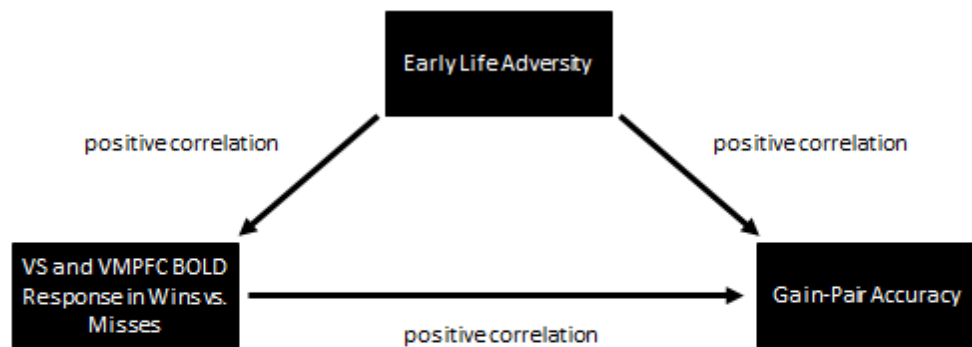
Figure 21. Diagram showing the relationships between adversity, MCLP BOLD response, and gain-pair accura

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Appendices

Appendix A: Early Life Experiences Questionnaire

Early Life Experiences Questionnaire

Participant code: _____

Your relationship to the child: _____

Mother's occupation _____

Mother's Highest level of Education:
(Please circle)

1. Elementary school
2. High-school
3. Professional certificate, college diploma
4. Bachelor's degree
5. Master's (MA, MSc, MBA)
6. Professional school (dentistry, law, medicine, etc) / Phd

Father's occupation _____

Father's Highest level of Education:
(Please circle)

1. Elementary school
2. High-school
3. Professional certificate, college diploma
4. Bachelor's degree
5. Master's (MA, MSc, MBA)
6. Professional school (dentistry, law, medicine, etc) / Phd

Household income
(Please circle)

1. Less than $40,000
2. 40,000 to 49,999
3. 50,000 to 59,999
4. 60,000 to 69,999
5. 70,000 to 79,999
6. 80,000 to 89,999
7. 90,000 to 99,999
8. 100,000 to 109,999
9. 110,000 to 119,999
10. Greater than 120,000

Please provide some information about your child and the related pregnancy:

Child's sex: _____ Male / _____ Female

What was your child's gestational age at birth (e.g., full-term is 40 weeks)? _____ weeks

How much did your child weigh when s/he was born? _____ lbs _____ oz, OR _____ gm

Were there any complications during the pregnancy, such as illnesses or preexisting conditions in the mother that may have affected the baby (e.g., high blood pressure)? When in the pregnancy did these complications occur (e.g., first month, second month, etc)?

_____

_____

Were there any complications during the newborn period (e.g., blood infection)?

_____

_____

Did you take any vitamins or supplements (e.g., iron, folic acid) before (or during) your pregnancy? Please specify.

_____

Is your child currently taking any medications? Please specify.

_____

Has your child ever had problems at school (e.g., fighting, not paying attention in class)? If so, please explain.

_____

_____

One important goal of our study is to learn how early experiences impact the development of children's thinking and brain functioning. We are therefore asking you to report on various events that may have occurred in your child's life, when they occurred, and how stressful they were to your child. If your child has not experienced a listed event, please check "not experienced" for that event. If your child has experienced a stressful event that is not listed, please report the event under "Other."

Listed below are events that can occur in life and can be stressful for families and young children. *Please indicate which events your child has experienced and the time period in which s/he experienced them. Also, please indicate how stressful the event was for your child at the time that it occurred.* A rating of 1 would indicate a mildly stressful event, a rating of 3 would suggest a moderately stressful event, while a rating of 5 would signify an extremely stressful event.

	0-6 Years old. (Check)	7+ Years old. (Check)	Not Exp. (circle)	1 = Mildly Stressful 3 = Moderately Stressful 5 = Extremely Stressful (circle)				
New marriage of a parent			0	1	2	3	4	5
Detention of a parent in jail or comparable institution			0	1	2	3	4	5
Major change in sleeping habits			0	1	2	3	4	5
Death of close family member:			0	1	2	3	4	5
Father			0	1	2	3	4	5
Mother			0	1	2	3	4	5
Brother			0	1	2	3	4	5
Sister			0	1	2	3	4	5
Grandmother			0	1	2	3	4	5
Grandfather			0	1	2	3	4	5
Other			0	1	2	3	4	5
Death of a family pet			0	1	2	3	4	5
Major change in eating habits (much more or much less food intake)			0	1	2	3	4	5
Death of a close friend			0	1	2	3	4	5
Serious illness or injury of close family member:			0	1	2	3	4	5
Father			0	1	2	3	4	5
Mother			0	1	2	3	4	5
Brother			0	1	2	3	4	5
Sister			0	1	2	3	4	5
Grandmother			0	1	2	3	4	5
Grandfather			0	1	2	3	4	5

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		0	1	2	3	4	5
Spouse							
Other _____		0	1	2	3	4	5
Major change in closeness of family members		0	1	2	3	4	5
Gaining new family member (through birth, adoption, family member moving in, etc.)		0	1	2	3	4	5
Change of residence		0	1	2	3	4	5
Change of school		0	1	2	3	4	5
Parental loss of employment		0	1	2	3	4	5
Parent's new job		0	1	2	3	4	5
Major personal illness or injury		0	1	2	3	4	5
Move of close friend		0	1	2	3	4	5
Major change in social activities (increased or decreased participation)		0	1	2	3	4	5
Major change in living conditions of family (building new home, remodeling, etc.)		0	1	2	3	4	5
Divorce of parents		0	1	2	3	4	5
Serious illness or injury of close friend		0	1	2	3	4	5
A parent's engagement		0	1	2	3	4	5
Reconciliation of parents		0	1	2	3	4	5

Other recent experiences which have had an impact on your child's life. **List and rate:**	0-6 Years old. (Check)	7+ Years old. (Check)	1 = Mildly Stressful 3 = Moderately Stressful 5 = Extremely Stressful (circle)				
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5

Curriculum Vitae

Niki Hosseini-Kamkar

EDUCATION

MSc. Developmental Psychology, Western University, London, Ontario

2013 - Present

Supervisor: Dr. J. Bruce Morton

BA Psychology, Western University, London, Ontario

2008 - 2012

Area of Study: *Developmental Cognitive Neuroscience*

RESEARCH EXPERIENCE

Publications

Nicholson, A.A., **Hosseini-Kamkar, N.** , Fallowfield, H., & Morton J.B.(2015). The neural correlates of cognitive behavioural self-regulation in early development. *Western Undergraduate Psychology Journal, 3*(1).

Hosseini-Kamkar, N. & Morton, J.B. (2014). Sex differences in self-regulation: An evolutionary perspective. *Frontiers in Neuroscience.*

Hosseini-Kamkar, N. (2014).The A1 allele of the Taq1 A polymorphism in association with addiction: A review. *Western Undergraduate Psychology Journal, 1*(1), Article 10

Presentations

Hosseini-Kamkar, N. (2015). Closing the Gap Between Neuroscience and Education: Proposal for the Parents Reaching Out Regional Grant. *Oral Presentation at TVPIC,* London, Ontario.

Fallowfield, H., **Hosseini-Kamkar, N.**, & Morton, J.B. (2014). Individual Differences in Cognitive and Behavioural Self Regulation: A Multi-Level Approach for Assessing Genetic and Environmental Influences Early in Development. *Poster presented at Minds on Minds Symposium,* London, Ontario.

Grants and Awards

NSERC Postgraduate Scholarship-Doctoral PGS-D, *$63,000*   2015-2016

Marilyn (Pack) McClelland Award in Psychology, $550   2015
Awarded to a full-time graduate student conducting research related to children.
Selection was based on academic achievement, research productivity and quality of research publications.

2014 - Present

CHRI , $7,500
Funding in support of "Individual Differences in Cognitive and Behavioural Self-Regulation Early in Development".

Western Graduate Research Scholarship , $10,000   2014 - Present

Western Open Access Fund , $2,270   August 2014
Funding provided for Frontiers open access publishing fee.

Western Graduate Research Scholarship , $10,000   2013 - 2014

Fanshawe College Award of Academic Excellence, $750 *Awarded to full-time students who were on the Dean's Honour Roll*	December 2007

Relevant Work Experience

Research Assistant in Cognitive Development and Neuroimaging Laboratory, Western Universit	2013 - 2014
Research Assistant, The Brain and Mind Institute, Western University	2011 - 2012
Research Assistant, Cognitive Psychology Laboratory, Western University	
	2009 – 2011
Research Assistant, Regional Mental Health Care, London Ontario	Summer 2009