Neural mechanisms of cognitive control and reward learning in children with Attention Deficit Hyperactivity Disorder

by

Carmen Noel Lukie
B.Sc. (Honours), University of Winnipeg, 2007
B.A., University of Winnipeg, 2007

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of

MASTER OF SCIENCE

in the Department of Psychology

Supervisory Committee

Neural mechanisms of cognitive control and reward learning in children with Attention Deficit Hyperactivity Disorder

by

Carmen Noel Lukie
B.Sc. (Honours), University of Winnipeg, 2007
B.A., University of Winnipeg, 2007

Supervisory Committee

Dr. Clay B. Holroyd (Department of Psychology)
Supervisor

Dr. Kimberly A. Kerns (Department of Psychology)
Departmental Member

Dr. Ulrich Mueller (Department of Psychology)
Departmental Member

Abstract

Supervisory Committee
Dr. Clay B. Holroyd, Psychology
Supervisor
Dr. Kimberly A. Kerns, Psychology
Departmental Member
Dr. Ulrich Mueller, Psychology
Departmental Member

A substantial amount of behavioural, genetic, and neurophysiological data suggest that Attention Deficit Hyperactivity Disorder (ADHD) is influenced by an underlying abnormality in the midbrain dopamine system. A previous study found that children with ADHD are unusually sensitive to the salience of rewards, mediated in part by the dopamine system (Holroyd, Baker, Kerns & Mueller, 2008). The current study aimed to replicate and expand upon the previous finding using event-related potentials (ERP) recorded from typically developing children and children with ADHD as they navigated a "virtual T-Maze" in two conditions differing on reward saliency. Children also completed a behavioural task designed to measure decision making and sensitivity to reward and punishment. Both groups of children responded to the behavioural task in a way that is indicative of increased sensitivity to reward. Unlike the previous study, the salience of reward as reflected in the ERP did not have an effect on either children with ADHD or typically developing children. However, both groups displayed a larger error-related negativity (ERN) in the condition presented second.

Table of Contents

List of Tables

List of Figures

Acknowledgments

I would like to thank my supervisor, Dr. Clay Holroyd for his limitless guidance, support and encouragement throughout this project. I also would like to thank my committee members, Dr. Kim Kerns and Dr. Ulrich Mueller for their invaluable expertise and guidance on this project. A special thank you goes out to Jennifer MacSween, Sarah Hutchison, Laurie Fitzgerald, Kate Randall, Erin Eadie, Céline Koryzma, Jeff Frazer, Megan Yim, and Michele Murphy for the many hours they devoted to recruitment and data collection. The Natural Sciences and Engineering Research Council of Canada (NSERC) and the Michael Smith Foundation for Health Research (MSFHR) generously supported this research through graduate fellowships to Carmen Lukie. The Canadian Institute for Health Research (CIHR) supported this research through an operating grant to Dr. Clay Holroyd.

Neural mechanisms of cognitive control and reward learning in children with Attention Deficit Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioural developmental disorder in school-aged children. ADHD is characterized as a pervasive pattern of difficulty sustaining attention, controlling behaviour, and marked hyperactivity in comparison with typically developing children of the same age. The DSM-IV-TR estimates prevalence to be between 3 to 7% in school aged children (American Psychiatric Association, 2000). A recent study by the government of Canada estimated the prevalence of hyperactivity-impulsivity and inattention in Canadian children 2-11 years of age. The study found that 5-17% of girls and 9-23% of boys experienced difficulties with hyperactivity-impulsivity and 1-18% of girls and 1-14% of boys reported significant difficulties caused by inattention (Romano, Baillargeon, & Tremblay, 2002). Although these estimates do not map directly onto the prevalence rates of ADHD, they provide a useful indicator of the degree to which difficulties with hyperactivity, impulsivity, and inattention affect Canadian children, families, and communities.

Currently, three subtypes of ADHD are recognized: a predominantly inattentive subtype (ADHD-PI), a predominantly hyperactive-impulsive subtype (ADHD-PHI), and a combined inattentive and hyperactive-impulsive subtype (ADHD-C) (American Psychiatric Association, 2000). Many clinicians believe that ADHD-PHI is a developmental precursor to ADHD-C. The prevalence rate of the ADHD-PHI subtype is lower, children diagnosed with ADHD-PHI tend to be younger and the majority go on to develop ADHD-C (Lahey, Pelham, Loney, Lee, & Willcutt, 2005; Baeyens, Roeyers, &

Walle, 2006). Children diagnosed with ADHD-PI are described as being lethargic, hypoactive, passive, “in a fog”, and “daydreamy”. This presentation of inattention differs from those children with ADHD-C whose difficulties with attention appear to stem from having low levels of sustained attention and high distractibility. These significant differences in symptoms, combined with a later onset of ADHD-PI, smaller differences in gender, and different rates of comorbidities have led many researchers to believe that ADHD-PI and ADHD-C may be two entirely different disorders (Barkley, 1997).

Referral and diagnosis rates of ADHD are higher in boys than girls and differ depending on the subtype of ADHD and the setting (American Psychiatric Association, 2000). In clinical settings the range has been reported to be as high as 9:1 boys to girls being diagnosed with ADHD. In community samples this difference is often much lower, with a ratio of approximately 1.5 to 1(Scahill & Schwab-Stone, 2000). Children with ADHD have significantly high rates of comorbidities; approximately 50% of children diagnosed with ADHD also meet diagnostic criteria for Oppositional Defiant Disorder or Conduct Disorder. Additionally, Mood, Anxiety, Learning, and Communication Disorders are often associated with ADHD (American Psychiatric Association, 2000).

Behaviours associated with ADHD put a significant strain on affected children and families. Parents of children with ADHD often report high levels of marital strain, lower quality of interpersonal relationships, and higher instance of stress and depression (Brown & Pacini, 1989). Appropriate and effective treatment of ADHD can considerably change the quality of life of individuals and families affected by this disorder (Rader, McCauley, & Callen, 2009). ADHD is a serious and prominent mental health concern; in

order to establish new and effective treatments, a better understanding of the underlying mechanisms of this disorder is needed.

ADHD and Executive Functions

Many of the behaviours associated with ADHD are related to difficulties with executive functions. A common way of thinking about and describing executive functions are as self-regulatory functions that include the abilities to inhibit, shift set, plan, organize, use working memory, problem solve and maintain set for future goals (Sergeant, Geurts, & Oosterlaan, 2002). It has been well established that the frontal lobes are the last neural structures to fully develop and are responsible for higher level functioning and cognitive control. Children with ADHD perform worse than typically developing children on tasks specific to frontal lobe functioning, but not on tasks tapping into temporal lobe functioning (Shue & Douglas, 1992). Four primary areas of executive functioning in which children with ADHD have shown impairments include response inhibition and execution, working memory and updating, set-shifting and task-switching, and interference control (Willcutt, Doyle, Nigg, Pennington, & Faraone, 2005). Difficulties in executive functions are stable across gender, age, and subtype and are specific to ADHD and not other possible comorbid behavioural disorders (Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2005; Pasini, Paloscia, Alessandrelli, Porfirio, & Curatolo, 2007; Seidman, 2006; Oosterlaan, Scheres, & Sergeant, 2005).

ADHD and Dopamine

Many theories regarding the cause of ADHD have been put forward in the past few decades. A theory receiving increasing support is of an underlying dopamine (DA) dysfunction. Nearly 40 years ago, Wender (1972) proposed a biochemical abnormality

underlying ADHD. Wender argued that a biochemical abnormality causes functional underactivity of the monoamine neurotransmitter system. At the beginning of the 1990's, Levy reviewed the literature and determined that an abnormality in the dopaminergic system was most likely responsible for difficulties with goal-directed behaviours observed in children with ADHD (Levy, 1991).

Currently, there is a vast amount of evidence supporting the idea that ADHD may be strongly influenced by an underlying abnormality in the midbrain DA system. Methylphenidate, the most widely used pharmacological treatment for ADHD, in use since the 1960s, targets the DA system (Kimko, Cross, & Abernethy, 1999). The mechanisms of action of methylphenidate are not specifically known, but years of research point to an ability of methylphenidate to increase synaptic levels of DA by blocking DA transporters (DATs) (Grace, 2001; Volkow et al., 1998; Cragg & Rice, 2004).

The improvement in symptoms of ADHD when levels of extracellular DA are increased, along with results from a number of animal model studies has led many researchers to propose a hypofunctioning DA system underlying the behavioural abnormalities in children with ADHD. Numerous well established rat models of ADHD suggest a dysregulation in the DA system. However, results remain mixed regarding whether this dysregulation occurs from a hyper or hypoactive DA system (van der Kooij & Glennon, 2007). The prefrontal cortex (PFC) is an area that commonly displays impairment in a number of animal models of ADHD (Davids, Zhang, Tarazi, & Baldessarini, 2003; Russell, 2002; Sullivan & Brake, 2003; van der Kooij& Glennon, 2007). The PFC receives numerous projections from the midbrain DA system, suggesting

an involvement of the mesolimbic and mesocortical DA systems in ADHD. In the spontaneously hyperactive rat, currently the best animal model of ADHD, DA neurons in the mesocortical, mesolimbic, and nigrostriatal pathways release less DA, suggesting a hypodopaminergic system is responsible for behaviours associated with ADHD (Russell, 2002; Viggiano, Vallone, Ruocco, & Sadile, 2003).

A significant role for DA dysregulation in the manifestation of ADHD has been inferred from recent advances in genetic and molecular genetics. Twin studies have placed the heritability of ADHD at approximately 80% (Spencer, 2002). Even with such high heritability, it is proving extremely difficult to separate biological effects from environmental effects. Over 20 candidate genes have been identified in molecular genetic studies of ADHD, all contributing small effects to the overall picture of ADHD (Shastry, 2004). Although the findings are not conclusive, a number of candidate genes have been significantly associated with the occurrence of ADHD, including DAT1, DRD4, and DRD5 (Gizer, Ficks, & Waldman, 2009).

The dopamine transporter gene (DAT1) has been implicated in ADHD behaviours. DAT1 is responsible for the number of dopamine transporters (DATs) available, on which methylphenidate exerts its effect (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010). Many polymorphisms have been identified in the DAT1 gene and a number of these polymorphisms have been linked to ADHD. Levels of heterogeneity in DAT polymorphisms remain high; however, it seems likely that the DAT1 gene may be involved in an underlying DA dysfunction in individuals with ADHD (Gizer et al., 2009). Recent neuroimaging studies that have found increased DAT density in striatal areas in adults with ADHD support the theory of DATs involvement (Krause,

2008; Krause, Dresel, Krause, la Fougere, & Ackenheil, 2003; but see Hesse, Ballaschke, Barthel, & Sabri, 2009). Over-expression of DAT1 in certain brain regions would result in higher levels of reuptake by the presynaptic neuron, leading to lower than normal amounts of tonic DA availability.

The dopamine D4 receptor gene (DRD4) is highly expressed in frontal areas of the brain (Floresco & Tse, 2007). Higher rates of ADHD and novelty seeking have been associated with specific polymorphisms in the DRD4 gene (El-Faddagh, Laucht, Maras, Vöhringer, & Schmidt, 2004; Grady et al., 2003; Rowe et al., 1998). Children with a specific polymorphism of the DRD4 gene tend to have greater severity of symptoms and greater persistence of symptoms over time (Langley et al., 2009; Biederman et al., 2009). Associations have also been made between the DRD5 gene and higher incidence of ADHD (Barr et al., 2000; Levy, Hay, & Bennett, 2006; Squassina et al., 2008). A number of genes coding for DA regulation in frontal regions of the brain have been implicated as playing a role in ADHD. Although the findings of these genetic studies remain inconclusive, they strongly suggest a complicated and intricate role for DA as the primary source of an underlying biochemical abnormality in ADHD.

Reinforcement Learning and Dopamine

DA activity has also been established as having a major role in reward processing and reinforcement learning. Reinforcement learning refers to the ability to use stimuli and positive and negative feedback from the environment to modify behaviour in such a way as to minimize loss or punishment and maximize gain or reward. Modern reinforcement learning theory has its roots in optimal control theory and the psychology of animal learning. Optimal control theory is a set of differential equations that is used over time to

minimize a dynamical system's state and value functions (Sutton & Barto, 1998). In the study of animal learning, Thorndike's widely accepted "Law of Effect" describes trial and error learning through reinforcement. Actions that are followed by a reward will have a stronger connection and will be more likely to recur in similar situations in the future. Likewise, actions that are followed by a punishment will be less likely to recur in similar future situations. The strength of the reward or punishment is directly linked to the likeliness of the animal to use or avoid that same action in the future (Thorndike, 1911). Modern reinforcement learning theory has proven an important approach to understanding and developing learning algorithms for multilayer neural networks.

A more recent addition to modern reinforcement learning theory is that of temporal-difference (TD) methods. The method of temporal differences is a combination of Monte Carlo and dynamic programming ideas, and based on the Rescorla-Wagner model that learning occurs whenever actual events differ from expected events. It suggests the deviations that occur between a predicted response and the actual response drives a system to learn (Sutton, 1988). One particular method of TD learning that is appealing to psychological and biological systems is the actor-critic model. In this model, the "actor" selects the actions the system will make and the "critic" criticizes those actions. The critic evaluates the results of the action taken by the actor and verifies whether things have gone better or worse than expected. These critiques act as temporal difference errors (TDEs). TDEs act as measurements of the difference or amount of error between actual compared to expected outcomes. TDEs are then able to make any necessary adjustments to the selected action in order to improve the expected outcome (Sutton, 1988). Reinforcement learning theory and the temporal difference method

provides a computational framework that lends itself to the understanding of adaptive neural networks. These computational models provide an interpretation of the activity of DA neurons in the ventral tegmental area and substantia nigra long thought to play a role in reward processing and reward dependent learning (Schultz, 1997).

In 1991, Ljungberg, Apicella and Schultz used microelectrodes to record activity from single DA neurons in two Macaca fascicularis monkeys during a reinforcement learning task. Performance on a spatial delayed alternation task was cued by a light and the monkeys were rewarded a drop of juice for correct lever pulls. Phasic activity of DA neurons significantly increased in response to unexpected rewards. After the monkeys learned to associate reward delivery with the light, the phasic burst occurred in response to the light. In trials where the incorrect lever was pulled or the reward was not delivered as expected, a significant decrease in phasic DA activity was observed (Ljungberg, Apicella, & Schultz, 1991; Ljungberg, Apicella, & Schultz, 1992). These findings suggested that DA neurons respond to salient stimuli that hold behavioural motivation and incentives for reward.

Similar results were replicated by Schultz et al. (1993), in microelectrode recordings from two monkeys trained in three different tasks (spatial choice, instructed spatial and delayed response task). DA neurons fired phasically at either the time of instruction, or the time of trigger, depending on which held a salient reward cue for the specific task. DA neurons decreased firing rates when the reward was expected, but not delivered (Schultz et al., 1993). DA neurons appeared to transfer learning; rather than firing to the delivery of the reward, DA firing propagated back in time to the first

indication that reward delivery was imminent. As discussed below, this finding provides in vivo support for reinforcement learning.

The strongest DA responses occur when an unexpected reward occurs or is better than anticipated. When a reward is predicted, there is no significant change in the firing rate of DA neurons. When rewards are omitted or are worse than anticipated, there is a decrease in DA firing rates. These results taken together and replicated over many studies suggest that DA neurons report the actual occurrence of rewards in comparison to what was expected. The change in firing strength serves as a measure of the magnitude of the error in the prediction of the reward (Schultz, 2002). The common characteristics of the pattern of activity of DA neurons and Sutton's actor-critic theory of TDEs have been noted by many researchers.

The actor-critic theory has inspired numerous models of information processing in the basal ganglia (see Joel, 2002 for review). Montague, Dayan, and Sejnowski (1996) developed a theoretical model incorporating how the previously observed activity of the mesencephalic dopamine system could result in learning. They fit this model to a number of the previously described animal experiments and their results led them to suggest that the phasic increases and decreases of DA delivery from the ventral tegmental area to cortical and subcortical structures delivers reward prediction errors (RPEs) (Montague, Dayan, & Sejnowski, 1996). These RPEs have been suggested to act as TDEs that serve as an internal reward or teaching signal, enabling the system to learn from reinforcement (Suri, 2002; Egelman, Person, & Montague, 1998). Animal studies combined with computational modeling studies provide strong evidence in favour of a midbrain DA system that encodes RPE signals.

The substantia nigra (SN) and the ventral tegmental area (VTA) are two areas in the midbrain that contain the largest distribution of dopaminergic neurons. From these two nuclei, three major dopaminergic pathways arise. From the SN, the nigrostriatal pathway projects axons into the caudate nucleus and putamen of the striatum. The mesolimbic and mesocortical pathways both originate in the VTA. The mesolimbic pathway innervates the nucleus accumbens, the olfactory bulb, as well as other limbic structures. The mesocortical pathway innervates the prefrontal cortex, anterior cingulate cortex, and other frontal cortex structures (Bentivoglio & Morelli, 2005). A role for motivation and reward has been established in the mesolimbic dopamine pathway. The mesocortical dopamine pathway has connections to the PFC and plays a vital role in areas of cognitive control. DA plays a role in the flexibility and stability of behaviour by adjusting neurochemical equilibriums between many brain structures, both at the molecular level of receptors, and at the systems level (Cools, 2008).

Reinforcement Learning and ADHD

A number of theoretical models that incorporate deficiencies in reinforcement contingencies observed in children with ADHD have been developed. Many of these theories follow earlier observations of Wender (1974) who acknowledged that children with ADHD are less sensitive to feedback from their environment. As a result of this insensitivity to reinforcement, children with ADHD are quick to become bored and require higher levels of reinforcement. One of the first theories influenced by Wender's observations suggested that children with ADHD have an increased threshold for rewards and require larger and more frequent reinforcement compared to typically developing children (Haenlein & Caul, 1987). Douglas and Parry (1994) theorized that children with

ADHD are significantly more sensitive to reward, more likely to seek out immediate rewards, and more likely to become distracted and frustrated by anticipated rewards.

Crone et al (2003) found that children with ADHD have a deficit in approach tendencies in the presence of a forthcoming reward, rather than a deficit in reacting to punishment or negative feedback. Crone suggested that this supports the theory that children with ADHD have a deficit in the reward, rather than avoidance system. Similarly, Iaboni et al (1997) found that the heart rate of children with ADHD habituated to reward more quickly than a control group, suggesting that children with ADHD habituate to rewards at an increased rate. Reinforcement has a stronger effect on the performance of children with ADHD compared to typically developing children. Children with ADHD are also more likely to choose immediate rewards, regardless of the recent reward history or if the delayed reward is larger in magnitude (see Luman, 2005 for review).

A recent study used heart rate responses (HRR) and heart rate variability (HRV) as measures of mental effort. During a time reproduction task, it was found that children with ADHD had a lower frequency HRV in conditions without reinforcement, suggesting that they require reinforcement to engage in the task (Luman, Oosterlaan, Hyde, Van Meel, & Sergeant, 2007). In a follow up study, heart rate and skin conductance were monitored while participants completed a decision making task. Children with ADHD had elevated heart rate responses following rewards in comparison to a control group (Luman, Oosterlaan, Knol, & Sergeant, 2008). However, in a study designed to investigate whether reward frequency or magnitude was more influential on

reinforcement learning in children with ADHD, neither was found to have a significant effect (Luman, Van Meel, Oosterlaan, Sergeant & Geurts, 2009).

In 1994, Bechara, Damasio, Damasio, and Anderson designed the Iowa Gambling Task (IGT), which simulates real-life decision making in the way that it factors punishment, reward, and uncertainty of outcomes. Participants are required to make a series of single card selections from four decks of cards, the goal being to maximize reward by the end of the task. Two of the decks deliver small immediate rewards, but also smaller punishments and are advantageous for long term gain. The other two decks provide high immediate rewards, but are associated with higher punishment and will ultimately lead to a net loss. The task requires that actions resulting in large immediate rewards are inhibited in favour of actions with increased long term gain, but smaller immediate rewards. The IGT is believed to measure the ability to postpone immediate gratification in favour of delayed rewards and has been largely associated with orbitofrontal cortex (OFC) functioning (Bechara et al., 1994). A reverse version of the IGT was developed in which participants are faced with immediate punishments on every card selection and a variable reward schedule. In this task, advantageous decks deliver large immediate punishment and larger rewards and disadvantageous decks deliver smaller immediate punishments and smaller rewards (Bechara, Tranel & Damasio, 2000).

Following suit with the general development of the PFC, the OFC continues to develop into adulthood (Happaney, Zelazo, & Stuss, 2004). As the OFC continues to develop, the ability to delay immediate gratification in favour of long term rewards strengthens. Young children tend to respond to the IGT in a manner similar to that observed in patients with OFC lesions. With increasing age, children are able to learn to

select from the advantageous decks more quickly (Crone, Bunge, Latenstein, & van der Molen, 2005; Crone, & van der Molen, 2004). The age at which OFC development allows for children to sufficiently learn to select from the advantageous decks on the IGT is still unknown (but see Kerr & Zelazo, 2004; Garon & Moore, 2007).

Only a handful of studies have examined the performance of individuals with ADHD on the IGT. Adolescents and adults chose significantly more from disadvantageous decks in comparison to control participants (Malloy-Diniz, Fuentes, Leite, Bechara, & Correa, 2007; Toplak, Jain, & Tannock, 2005). Impaired performance of adolescents with ADHD on the IGT was not related to intelligence or working memory. Additionally, parent ratings of hyperactivity and impulsivity were significantly correlated with performance on the IGT in adolescents with ADHD, but not in a control group (Toplak et al., 2005). Results remain mixed as one study reported that children with ADHD did not perform differently than a group of typically developing children on either the standard or reverse versions of the IGT (Geurts, van der Oord & Crone, 2006). One possible confound in this study was that children with all three subtypes of ADHD were included. Garon, Moore and Waschbusch (2006) examined performance of children with ADHD-C on the original IGT and found that they made more selections from the disadvantageous decks than did a typically developing comparison group. Children with ADHD-C also failed to show a learning curve throughout the task. Recently, Masunami, Okazaki and Maekawa (2009) explored T-patterns in card selections on the IGT in a group of children with ADHD and a control group. T-patterns are complex time patterns detected using a heuristic bottom-up pattern detection algorithm that take into consideration the time interval between ongoing events. This method allows for detection

of patterns between temporally distant events and is useful in exploring decision making strategies. Children with ADHD had fewer T-patterns to punishments, and had many T-patterns to rewards, supporting a notion that children with ADHD have a high sensitivity to rewards. Examining the neural mechanisms responsible for reinforcement learning and how these mechanisms may be impaired will lead to an increased understanding of reinforcement learning deficits in children with ADHD.

Although a number of behavioural tasks have examined the effect of frequency, predictability, and immediacy of reward delivery on the performance of children with ADHD, fewer studies have examined the impact of reward salience and how this might be neurologically interpreted differently in children with ADHD. Using differing levels of monetary incentives, Slusarek and Velling (2001) found that children with ADHD performed at a level below that of typically developing children when the incentives were minimal. When the monetary incentives were increased, children with ADHD performed at a rate similar to the control group, indicating that the group with ADHD required higher levels of reinforcement in order to adequately perform the task.

In an interesting series of studies, the impact of social and monetary rewards on performance of a go/no-go task was investigated. Children with ADHD as well as a control group showed a larger improvement in cognitive control in response to monetary incentives over social rewards. However, between the two groups, children with ADHD responded significantly better than the control group in the social incentive condition (Kohls, Herpertz-Dahlmann, & Konrad, 2009; Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009). Indeed, the impact of social compared to monetary rewards interacted with individual differences including reward seeking and empathy. Children scoring high

on a measure of reward seeking were better able to improve their response inhibition in the monetary reward condition, whereas children with greater empathic skills were able to benefit from social rewards. In addition, a positive relationship was observed between higher scores on a measure of reward seeking and increasing cognitive control in conditions where there was a monetary incentive (Luman, Van Meel, Oosterlaan, Sergeant, & Geurts, 2009).

DA's role in reinforcement learning combined with an underlying DA dysfunction in children with ADHD led Grace (2001) to propose that difficulties with reward learning and cognitive control in children with ADHD arise from inflated phasic DA responses to both major and minor rewards and punishments. Due to abnormally low tonic DA availability in the ventral striatum and nucleus accumbens, phasic bursts in response to rewarding stimuli will reach a ceiling regardless of the actual magnitude of the reward. Similarly, phasic DA decreases in response to anticipated rewards that are not delivered are also amplified, resulting in amplification of both positive and negative RPE signals.

Largely based on behavioural data and animal models, Sagvolden, Johansen, Aase, and Russell (2005) proposed the Dynamic Developmental theory of ADHD. The Dynamic Developmental theory suggests that due to a hypofunctioning DA system, children with ADHD experience altered reinforcement of novel behaviour and deficient extinction of previously reinforced behaviours. In turn, Sagvolden predicts that RPE signals are smaller in children with ADHD. A hypofunctioning mesolimbic DA system reduces the time available to associate behaviours and reinforcements in children with ADHD. Due to this shortened window of time, children with ADHD will experience

difficulties with attention, motor impulsiveness, hyperactivity, and varied behavioural responses, or a failure to inhibit response.

A recent study by Cockburn and Holroyd (submitted) sought to investigate Grace (2001) and Sagvolden's (2005) theories using a computational modeling approach. Results from animal studies and behavioural studies with children with ADHD were computationally simulated. The simulation found that the absolute size of the prediction error does not play a significant role in eliciting ADHD behaviours. Rather, it was found that asymmetrically large positive and small negative dopamine prediction error signals best accounted for the ADHD-like behaviours in the previous studies (Cockburn and Holroyd, submitted). This finding suggests that children with ADHD may be relatively more sensitive to reward or positive feedback in comparison to punishment or negative feedback. Specifically, the model suggests that this asymmetry in the reward prediction system may manifest in impaired extinction of reinforced behaviours as the positive RPE signals would be stronger than the negative RPE signals.

ADHD and the Error Related Negativity

Holroyd, Kerns, Mueller, and Baker (2008) used event related potentials (ERPs) to study reward processing in children with ADHD. This approach was based on the recent theory by Holroyd and Coles (2002) that integrates the activity of the mesencephalic dopamine system (MDS) with a specific component of the ERP called the error related negativity (ERN). The reinforcement learning – error related negativity (RL-ERN) theory holds that when an individual makes an error, a negative RPE is generated, indicating that the actual outcome was worse than expected. This RPE is calculated by the basal ganglia and is conveyed via the MDS to the anterior cingulate cortex (ACC).

The theory states that phasic DA changes (RPEs) are delivered via the MDS to the apical dendrites of ACC motor neurons, eliciting an ERN. By modulating the size of the excitatory postsynaptic potentials at the apical dendrites, negative RPEs following disinhibited responses elicit a large ERN, whereas positive RPEs following inhibited responses generate a larger positivity and consequently a smaller ERN. The ACC then uses this information to modify performance on the task (Holroyd and Coles, 2002).

The ERN is derived by obtaining the difference wave of ERP recordings to reward or correct trials and ERP waveforms from no reward or incorrect/error trials. The ERN component represents the difference in activity in the brain on correct versus error trials, capturing variance in the ERP associated with both reward and error trials (Holroyd, Pakzad-Vaezi, & Krigolson, 2008). The ERN appears to be generated in the ACC and its amplitude regulated by the magnitude of phasic increases or decreases in the DA system (Holroyd & Coles, 2002). Thus, the amplitude of the ERN acts as a measure of the difference between the actual outcome and the expected outcome carried as a RPE to the ACC. The ACC is then able to use the information provided by this signal to adjust or modify behaviour accordingly.

The ACC is a specialized area of the neocortex that receives projections from dopaminergic cells located in the lateral portion of the VTA as well as from a smaller number of cells in the medial part of the SN pars compacta (Bentivoglio & Morelli, 2005). As well, the ACC receives projections from the limbic lobe, including the OFC and amygdala (Morecraft & Van Hoesen, 1998). The ACC extends numerous projections to many areas of the brain, including areas in the brainstem responsible for motor production and directly to motor neurons in the spinal cord (Devinsky, Morrell, & Vogt,

1995). Research suggests that the ACC may provide a location in which motor intentions are transformed into actions (Holroyd, Nieuwenhuis, Mars, & Coles, 2004). The input of the MDS to the ACC makes it likely that the ACC uses the prediction error signal carried by the MDS to modify action selection (Holroyd & Coles, 2002). The ACC receives input from many areas and integrates emotional and motivational factors and their impact on motor activity or behavioural actions (for review see Bush, Luu, & Posner, 2000).

A number of studies have supported the ACC as the source of the ERN (Dehaene, Posner, & Tucker, 1994; Miltner, Braun, & Coles, 1997). Herrmann and colleagues (2002) used the Low Resolution Tomography method (LORETA) to determine the brain electrical sources of the ERN. They found evidence of the ERN being generated in the ACC. Dipole modeling was also found to support the prediction that the ERN is generated in the ACC (van Veen & Carter, 2002). Other studies have supported the role of MDS in the generation of the ERN. Administration of amphetamine, a DA agonist, resulted in an increase in the amplitude of the ERN (de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004). Alternatively, administration of the DA antagonist haloperidol resulted in a decrease in the amplitude of the ERN (de Bruijn et al., 2006). The influence of drugs and medications, whose primary action is on the DA system, result in amplitude changes in the ERN.

The ERN has been shown to exist in two different conditions. The first is in on speeded reaction time tasks such as the Erikson flanker task, and is called the response ERN or rERN. This ERN usually appears immediately after an error has been committed. The other type of ERN occurs after negative feedback is presented in trial and error feedback tasks and is called the feedback ERN or fERN (Miltner, Braun & Coles,1997).

Both response and feedback ERNs are measured as the difference between incorrect and correct ERPs. The amplitude of the ERN is affected by motivation, fatigue, and interest in the task (Gehring, Goss, Coles, Meyer, & Donchin, 1993). In one study, after a two hour period had elapsed and ERN amplitude had decreased, motivation was increased by offering a monetary incentive as well as by highlighting social comparisons. Differences in the increase of the ERN and performance on the ongoing task after increasing motivation varied greatly across individuals (Boksem, Meijman, & Lorist, 2005).

There is overwhelming evidence that children with ADHD have abnormalities in the midbrain DA system and display differences in reinforcement learning in comparison to typically developing children. If abnormalities in the phasic firing of the midbrain DA system are responsible for the difficulties seen in behavioural reinforcement learning tasks, the ERN will provide a non-invasive method with which to measure this dysfunction. The magnitude and direction of differences in the amplitude of the fERN in children with ADHD compared to a typically developing control group will help to decipher the precise abnormality in the midbrain DA system of individuals with ADHD. If Grace's (2001) hypothesis of exaggerated phasic DA increases and decreases is correct, the fERN of children with ADHD should be larger in comparison to typically developing children. Alternatively, if Sagvolden's (2005) model is correct, and phasic DA bursts are smaller due to decreased levels of tonic DA availability, then the fERN will be smaller in children with ADHD.

A number of studies have investigated error processing on speeded response time tasks in individuals with ADHD. The rERN is produced as soon as individuals become aware that an error has been committed. On speeded response time tasks, a rERN is

elicited by the error itself rather than by the feedback informing a participant their response was incorrect. Children with ADHD make more errors and are less likely to show post-error slowing as a strategy for reducing error commission on speeded response time tasks (Jonkman, van Melis, Kemner, & Markus, 2007; O'Connell et al., 2009; van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007; Wiersema, van, & Roeyers, 2005). A reduced rERN is elicited by errors on speeded response time tasks such as the stop signal task (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005), the Erikson Flanker task (van Meel et al., 2007), and a go/no-go task (O'Connell et al., 2009) in individuals with ADHD. However, other studies have reported the rERN to be the same across individuals with ADHD and control groups (Jonkman et al., 2007; Wiersema et al., 2005; Wiersema, van, & Roeyers, 2009; Zhang, Wang, Cai, & Yan, 2009).

Another study investigated the fERN in children with ADHD. Children participated in a guessing game that required them to wait for feedback to determine if the response was better or worse than expected. Children with ADHD displayed a larger fERN to losses than did a typically developing control group. These results suggest that children with ADHD have an increased sensitivity to unfavourable outcomes (van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005). However, reward and non reward stimuli were not counterbalanced and the fERN produced was atypical, making it unclear whether it was the fERN that was indeed being measured (Holroyd, Baker, Kerns, & Müller, 2008).

Holroyd et al (2008) recruited 14 boys with ADHD-C and 13 typically developing boys all aged 8 – 13 years and had participants navigate their way through a "virtual T-maze" in search of rewarding stimuli ($0.05) while an ongoing ERP was recorded.

Midway through the experiment, after two blocks of 50 trials were completed, children were physically awarded the amount of money they had accumulated. Holroyd et al (2008) did not find a significant difference in overall fERN amplitude between groups; however, an unexpected interaction was found between group and time (pre and post payment). The fERN of typically developing children decreased from the first to the second half of the experiment. On the other hand, the fERN of children with ADHD increased in the second half of the experiment, post payment. These results suggest that children with ADHD may not have been initially motivated to perform the task when presented with abstract performance feedback. Other ERP components did not differ between the groups, suggesting that both groups were attending to the task at hand and that the difference in the fERN is unique to the levels of motivation across group and time. However, due to the design of the preliminary study, it is not possible to determine if the increase in amplitude of the fERN post payment in children with ADHD might have occurred solely as a function of time regardless of payment. Additionally, this interaction was found post hoc and is more likely to be a statistical artifact than if the result had been predicted prior to analysis.

The current study was designed to replicate and expand upon the preliminary Holroyd et al (2008) study in a number of ways. A new sample of typically developing children and children with combined subtype ADHD was recruited. All children were carefully screened and potentially diagnosed with ADHD, as well as common comborbid disorders including ODD, CD, GAD, and depression. In the current study all children completed the T-maze task under two conditions, a "points" condition in which rewards are abstract, and a "money" condition with salient, monetary rewards. In the money

condition, participants were awarded their earnings in Canadian nickels that were added to a jar within their sight. The presentation of the two conditions was counterbalanced across subjects to control for fatigue and order effects. If children with ADHD are indeed more sensitive to the saliency of the reward than typically developing children, I will expect to see an interaction in group by condition. It is predicted that children with ADHD will have an increased fERN in the money condition in comparison to the typically developing children. This difference in fERN amplitude is expected to occur irrespective of which condition was presented first.

Methods

Participants

A total of 68 children were recruited from Victoria and surrounding communities to participate in the study. Children were recruited via newsletters sent home from school, posters placed in the offices of local pediatricians, and an advertisement in a local parent magazine. Nine of these participants did not meet criteria for a diagnosis of ADHD (see below), 11 participants did not return to the study for the second session, 4 participants were excluded due to excessive ERP artifacts, and 3 participants were not able to complete the ERP session. The study was comprised of two separate experimental sessions carried out at the University of Victoria. During the first session, a clinical psychology graduate student administered the Wechsler Abbreviated Scale of Intelligence (WASI) (Psychological Corporation, 1999) and the Wechsler Individual Achievement Test – II (WIAT-II) (Psychological Corporation, 2002) to the participant. Also during the first session, an upper level clinical graduate student administered the Diagnostic Interview for Children and Adolescents (DICA) (Reich, 2000) to a parent or

primary caregiver of the participant. The DICA interview was audio recorded and a second blind rater later confirmed diagnoses.

All of the children with ADHD included in the sample had a previous diagnosis made by a qualified healthcare practitioner (i.e. registered psychologist, pediatric psychiatrist or neurologist, developmental pediatrician, family physician). In addition, to be included in the study, participants had to meet criteria for a diagnosis of ADHD on the DICA by both the primary and secondary raters; participants not meeting the DSM-IV diagnostic criteria for ADHD combined subtype were excluded from analysis (N=9). None of the children presenting as typically developing met criteria for a diagnosis of ADHD. Additionally, participants were required to have an IQ above 85 and evidence of learning disabilities (a common comorbidity within this population) were noted. Because ADHD is a complex disorder and has high levels of comorbid externalizing and internalizing disorders, the DICA also assessed whether participants met diagnostic criteria for Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), Generalized Anxiety Disorder (GAD), or a major depressive episode past or present. The occurrence of comorbid disorders was obtained to rule out potentially confounding factors, as well as to better characterize the sample. A short version of the Conner's Rating Scale Revised (Conners, 1997) was completed by parents and was sent home with participants to be given to their teacher. Teachers were asked to complete the questionnaire, reporting on the child's behaviour off medication, and return the questionnaire in a prepaid envelope directly to the researchers. Parents and teachers were also asked to complete the Behaviour Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy, & Kenworthy, 2000).

Nineteen children with combined type ADHD (10.05 ± 1.75 years old) and twenty-two typically developing children (10.54 ± 1.5 years old) were included in the analyses (see table 1 for group demographics and characteristics). The two groups did not differ in age ($t[39] = 1.152$, $p = 0.256$) or IQ (ADHD = 113.79 ± 10.05; Controls = 115.82 ± 12.07; $t[39] = 0.579$, $p = 0.566$). Of the children diagnosed with ADHD, 10 had no history of medication use, 8 were currently taking medication, and 1 had a previous history of medication use but was not currently on medication.

During the second session, children participated in a computerized T-Maze task (Baker and Holroyd, 2009) while ongoing EEG was recorded. Following the T-Maze, participants completed original and reverse child-friendly versions of the Iowa Gambling Task (IGT) (Bechara et al., 1994; Bechara et al., 2000). The details of the task and data acquisition procedures are described below. For this second session, all participating children were required to stop taking any stimulant medications for the treatment of ADHD 24 hours prior to participating in the EEG experiment. None of the children in the current study were taking medications for conditions other than ADHD. Participants all had normal or corrected-to-normal vision. Parents received a $10.00 honorarium following each session, as well as reimbursement for any parking costs. Children received a small toy following each session and also received their earnings for the T-Maze task (approximately $5.00) following the second session. Parents and children provided written assent and consent prior to participating in each session. The experiment was approved by the human subjects review board at the University of Victoria and was

	Controls n = 22			ADHD n = 19		
	Mean	S.D.	Range	Mean	S.D.	Range
Gender (M:F)	16:6			12:7		
Age (years)	10.64	1.50	8-13	10.05	1.75	8-13
FSIQ (standard score)	115.82	12.07	91-139	113.79	10.05	91-129
Inattention (t-score)	50.75	8.35	41-72	78.74	8.41	62-95
Hyperactivity/Impulsivity (t-score)	50.05	7.93	40-69	80.92	16.40	55-116
	Number of participants			Number of participants		
Learning Disability (Reading:Math)	2:0			1:5		
Medication (current)	0			8		
ADHD	0			19		
ODD	1			10		
CD	0			0		
MDE	1			3		
GAD	0			2		

Table 1. *Group characteristics.* FSIQ = Full Scale Intelligence Quotient as measured by the Wechsler Abbreviated Scale of Intelligence. Incidence of learning disabilities was determined through discrepancy analysis from reading and math subtests on the Wechsler Individual Achievement Test – II. Inattention and Hyperactivity scores are an average of ratings on the Conner's Rating Scale Revised from parents and forms that were returned by teachers (N=35). Eight children in the ADHD sample were currently taking medication (1 participant was taking Adderall, 1 was taking Ritalin, 1 was taking Dexedrine, 2 participants were taking Concerta, and 3 were currently on Biphentin). Diagnosis were based on the Diagnostic Interview for Children and Adolescents where ADHD = Attention Deficit Hyperactivity Disorder – Combined type, ODD = Oppositional Defiant Disorder, CD = Conduct Disorder, MDE = Major Depressive Episode (numbers include both present and past episodes), GAD = Generalized Anxiety Disorder.

conducted in accordance to the ethical standards prescribed in the 1964 Declaration of Helsinki.

Procedure

During the second session, participants were seated comfortably in front of a computer monitor in an electromagnetically shielded room. The first task required participants to navigate their way through a simple T-shaped "virtual maze", the goal being to find reward stimuli (Baker and Holroyd, 2009). The initial image displayed the length of the base alley in the maze with a green double arrow at the end of the alley indicating the participant could choose to turn left or right. This image remained on the screen until the participant made their decision by pressing a button on a stimulus response (SR) box. To select the left alley, they pressed button 1 with their left index finger, and to enter the right alley they pressed button 2 with their right index finger. Once a choice was made, the image of the selected alley appeared (500 ms) followed by an image of either an apple or an orange (1000 ms). At the beginning of the task, participants were informed that one image (either the apple or the orange randomly assigned) indicated that they received a reward and that the other image indicated no reward (Figure 1). The mappings between images and reward and no reward stimuli were counterbalanced across participants. Participants were told to navigate the maze in such a way as to maximize their reward earnings. On each trial, the type of feedback stimulus was randomly selected (50% probability of receiving reward or no-reward feedback); however the participants were not informed of this. The feedback image was followed by a blank screen (1000 ms) and then the next trial began. Participants completed two versions of the T-maze each comprised of four blocks containing 50 trials. Blocks were

interspersed with rest breaks, the duration of which was controlled by the participant. In the "points" version of the T-maze, each rewarding stimulus was worth 5 points and the non-reward was worth 0 points. In the "money" version of the T-maze, every time a rewarding stimulus was found the participants were awarded 5 cents. The amount of money earned was placed in a glass jar during every rest period, allowing the participant to visually see their earnings. Participants were told they would take home however much money they accumulated by the end of the experiment. The order of presentation of points and money conditions was counterbalanced between participants.

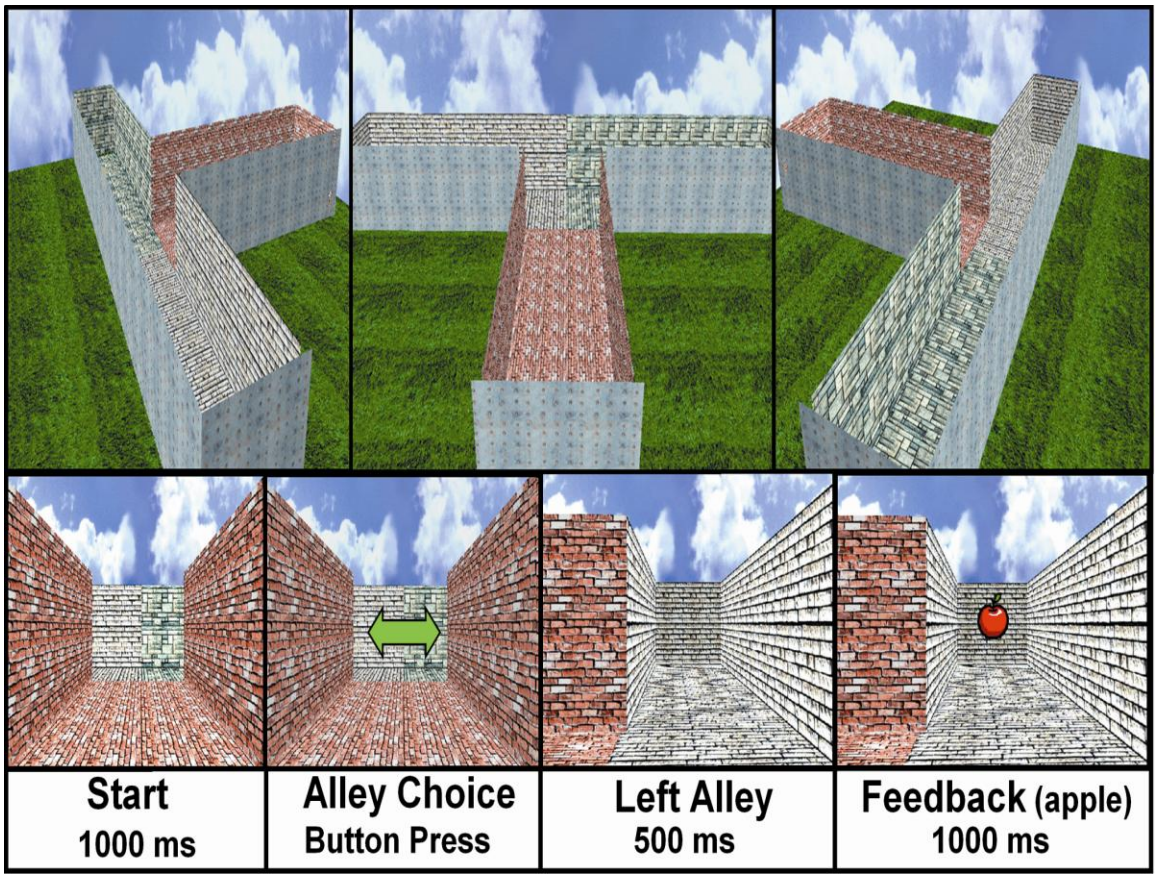

Figure 1. View of the layout of the T-Maze and images displaying the sequence of events during a single trial of the T-maze Task (please note, the double arrow was magnified in this figure for the purpose of clarity) (Baker & Holroyd, 2009).

During the condition presented second, regardless whether it was money or points, both children with ADHD as well as typically developing children displayed difficulties remaining focused. The experminters verbally encouraged participants to select the alley in which they believed the reward was hidden as soon as the green double arrow appeared. This encouragement was intended to help keep children motivated, engaged and focused on the task, as well as help them proceed through the second T-maze task in a timely fashion.

Following the T-Maze task, participants were given modified child friendly versions of the Iowa Gambling Task, both the original and reverse versions (Bechara et al., 1994; Bechara, Tranel, & Damasio, 2000). The task began with an image of a donkey centered on the lower part of the screen and four identical doors spread evenly across the upper part of the screen (Crone and van der Molen, 2004; Figure 2). Participants were told that they were to "knock" on one door at a time, represented correspondingly by buttons 'A', 'D', 'G', and 'J' on a keyboard, the goal being to find as many apples as possible to "feed" the "hungry donkey". In the original version every door selection resulted in a number of apples, but the rewards were higher for doors 'A' and 'D' than for doors 'G' and 'J'. In addition, sometimes when a participant selected a door they were awarded the apples but a variable number of apples were also taken away; punishments were greater on doors 'A' and 'D' compared to doors 'G' and 'J' (Figure 2). Selections that resulted in a loss of apples were random, with a higher frequency, but smaller quantity of punishment associated with doors 'A' and 'G' and a less frequent, but larger punishment associated with doors 'D' and 'J'. The task was structured in such a way that choices from doors 'A' and 'D' resulted in an overall net loss and choices from doors 'G'

and ‘J’ in an overall net gain (see Crone et al., 2004, for gain and loss probabilities). The participants were told that their goal was to find as many apples by the end of the game as possible by selecting from the four doors. Participants were not told of the reward and punishment schedules that were associated with each of the doors, but were informed that some doors might be more helpful than others in successfully completing the task. In the reverse version of the task, with every door selection the participant had apples taken away, losses were higher from doors ‘G’ and ‘J’ than from doors ‘A’ and ‘D’. On a random selection of trials, the participant was awarded apples in addition to the apples they lost. Rewards were higher from doors ‘G’ and ‘J’ compared to doors ‘A’ and ‘D’.

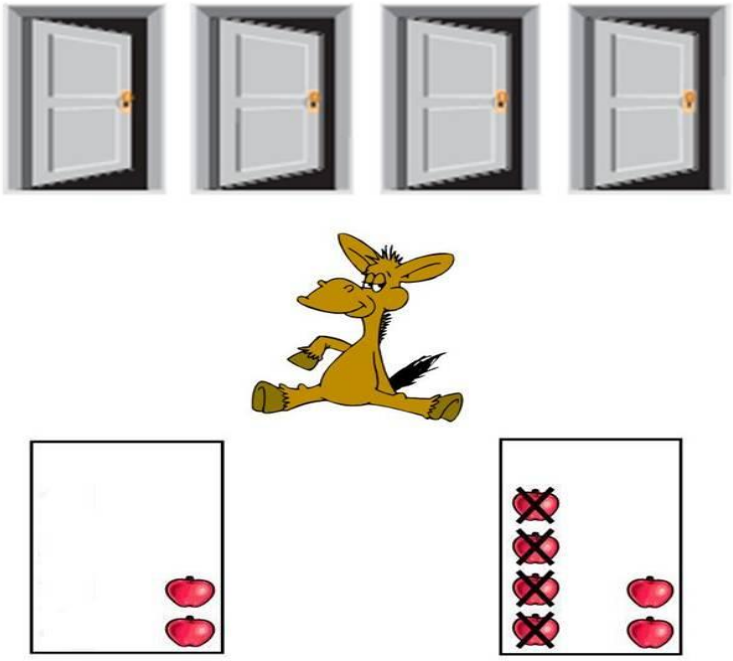

Figure 2. View of the layout of the modified donkey IGT. Top image shows presentation of the 4 doors indicating that participants should make a door selection. Bottom images display two possible outcomes on the original task, the image on the left showing when participants are rewarded apples, and the image on the right displaying feedback when apples are both rewarded and taken away (Crone et al., 2004).

The reverse task was also structured in such a way that choices from doors ‘A’ and ‘D’ resulted in an overall net loss and choices from doors ‘G’ and ‘J’ in an overall net gain. Performance on the IGT was determined by the calculation of a difference score for each the original and reverse tasks. The number of door selections from the disadvantageous doors was subtracted from the number of door selections from the advantageous doors [(G + J) – (A + D)]. In addition, a difference score was calculated between the original and reverse IGT tasks (difference score on reverse task subtracted from the difference score on the original task). The order of presentation of the original and reverse tasks was counterbalanced across participants.

Data Acquisition and Analysis

During the T-maze, the EEG was recorded from 19 electrode sites using BrainVision Recorder Software (Brainproducts, GmbH, Munich, Germany). The electrodes were mounted in a fitted nylon cap with a standard 10-20 layout and referenced to a common ground. The horizontal electrooculogram (EOG) was recorded from the external canthi of both eyes, and the vertical EOG recorded from the suborbit of the right eye and electrode channel Fp2 for the purpose of artifact correction. Inter-electrode impedances were kept below 10kΩ and two electrodes were placed on the right and left mastoids. The EEG data was sampled at a rate of 250 Hz and amplified by low-noise electrode differential amplifiers with a frequency response of DC 0.017-67.5 Hz (90dB octave roll off).

Post processing was performed using Brain Vision Analyzer software (Brainproducts, GmbH). The EEG data were filtered through a phase-shift-free Butterworth filter with a passband of 0.10-20 Hz. An 800 ms epoch of data extending

from 200 ms prior to feedback stimulus onset to 600 ms following the stimulus was extracted from the continuous EEG for analysis. Ocular artifacts were removed using the eye movement correction algorithm described by Gratton, Coles, and Donchin (1983). The epochs were re-referenced to linked mastoid electrodes and baseline corrected by subtracting from each sample the average activity recorded at that electrode during the 200 ms interval preceding stimulus onset. Muscular and other artifacts were removed using a ±200μV level threshold and a ±50μV step threshold rejection criteria.

ERPs were created for each electrode and participant by averaging the single-trial EEG according to feedback type (reward or no-reward) separately across the points and money conditions. The fERN was measured at electrode site FCz, where it typically reaches maximum amplitude (Miltner, Braun & Coles, 1997; Holroyd & Krigolson, 2007). The fERN was determined for each participant by subtracting the average ERP elicited by the reward feedback from the average ERP elicited from the no-reward feedback (Holroyd and Coles, 2002; Holroyd & Krigolson, 2007). The peak amplitude was determined by identifying the peak negativity of the difference waveform between 200 and 400 ms following feedback onset. ERP as well as behavioural measures were analyzed using the statistical package for the social sciences (SPSS 17.0).

Results

There were no significant effects of gender, age, medication, or a diagnosis of comorbid ODD on any of the behavioural or electrophysiological measures. Groups significantly differed on measures of inattention and hyperactivity/impulsivity as assessed by the Conner's (inattention: ADHD = 78.74; Controls = 50.75; $t[39] = -10.67$, $p < 0.001$; hyperactivity/impulsivity: ADHD = 80.92; Controls = 50.05; $t[39] = -7.51$, $p <$

0.001). A three-factor ANOVA on response time was carried out as a function of condition (within subject: money, points), order (money first, points first) and group (ADHD, control). Main effects of condition, group, and order were not significant, however, an interaction between condition and order was significant ($F[1,34] = 14.465$, $p = 0.001$, E.S. = 0.298). When participants were separated based on completing money or points first, a significant difference in response time was only found for those participants who completed points first and money second (points = 900.62 ms; money = 648.19 msc; $t[17] = -4.054$, $p = 0.001$) (Figure 3). The difference for participants completing money first and points second showed a trend towards significance (money = 795.76 ms; points = 694.54 ms; $t[19] = 1.546$, $p = 0.139$).

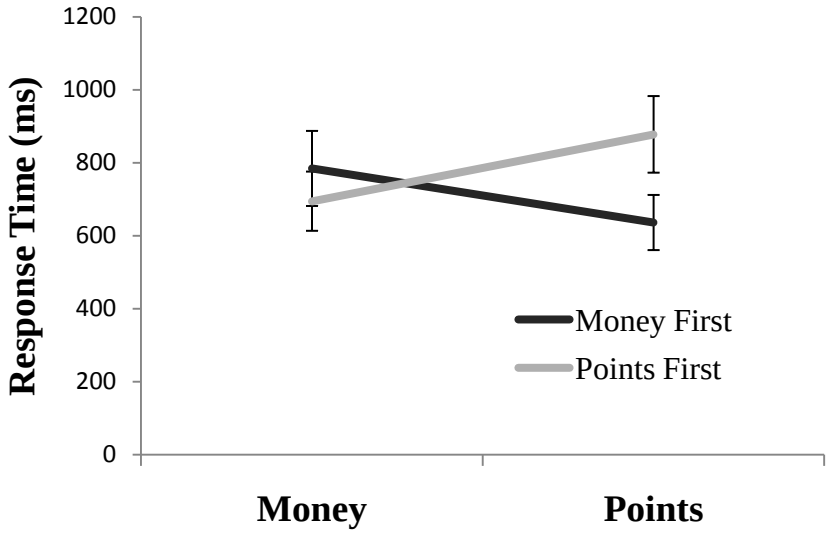

Figure 3. Response times in the T-maze task as a function of order (money first, points first), collapsed across group (ADHD, control). Error bars indicate standard errors of the mean.

Figure 4 illustrates the ERPs recorded at channel FCz associated with reward and

no-reward feedback. The data underwent an artifact rejection procedure which discarded an average of 2.5% and 1.4% of trials for children with ADHD and typically developing children respectively, leaving the data relatively artifact free. An additional 27% and 13% of trials for children with ADHD and typically developing children, respectively, were corrected for eye movement artifact.

The fERN was significantly different from zero for typically developing children (controls = -5.70 μV, S.D. = 3.08, $t[21] = -8.672$, $p < 0.001$), and for children with ADHD (ADHD = -5.60 μV, S.D. = 5.18, $t[18] = -4.71$, $p < 0.001$) (Figure 5). Consistent with their identification as the fERN, the difference waves were maximal at channel FCz. Although children with ADHD exhibited a high degree of variability in fERN amplitude, these results confirm that the T-maze task successfully elicited the fERN in both groups.

No overall difference in fERN amplitude was observed between the two groups ($t[39] = -0.076$, $p > 0.05$). FERN amplitude was further investigated with a 3-way ANOVA with condition (money, points) as a within subjects factor and group (ADHD, control) and order (money first, points first) as between subjects factors. None of the main effects were statistically significant ($p > .05$) and the interaction between condition and order was the only significant interaction (Wilks' Lamdba = 0.779, $F[1,37] = 10.518$, $p < 0.005$ E.S. = 0.221). Separate paired t-tests within those participants doing money first or points first showed a significant difference in fERN amplitude between conditions for those participants completing money first (money first = - 4.376 μV; points second = -6.605 μV; $t[20] = 2.435$ $p < 0.025$), and for those participants completing points first (points first = -4.795 μV; money second = -6.837 μV; $t[19] = -2.291$, $p < 0.05$, Figure 6).

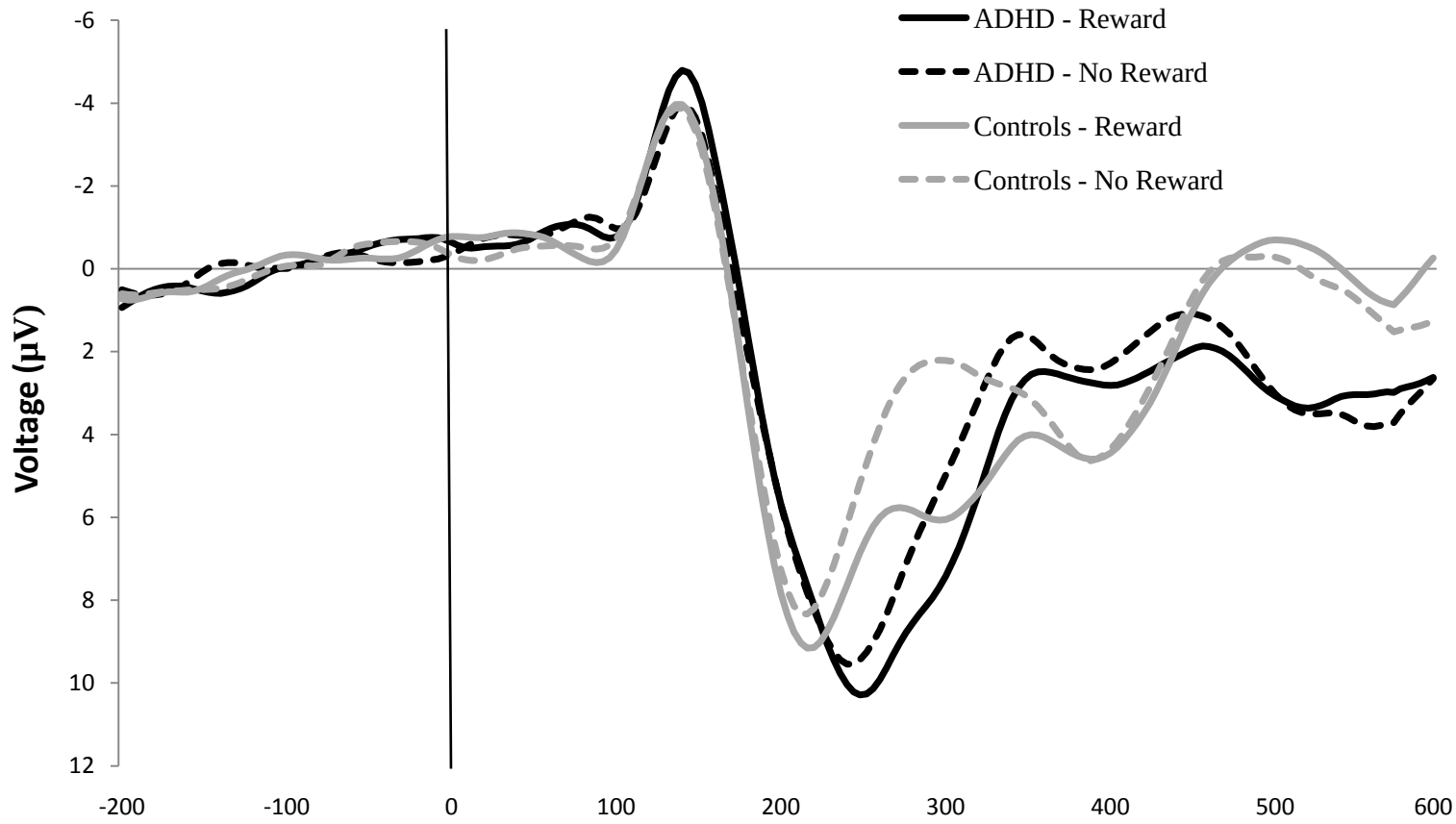

Figure 4. Event-related brain potentials elicited by reward and no-reward feedback, for children with ADHD and typically developing children. Feedback onset occurs at 0 ms. Data recorded at channel FCz. Note that negative is plotted up by convention.

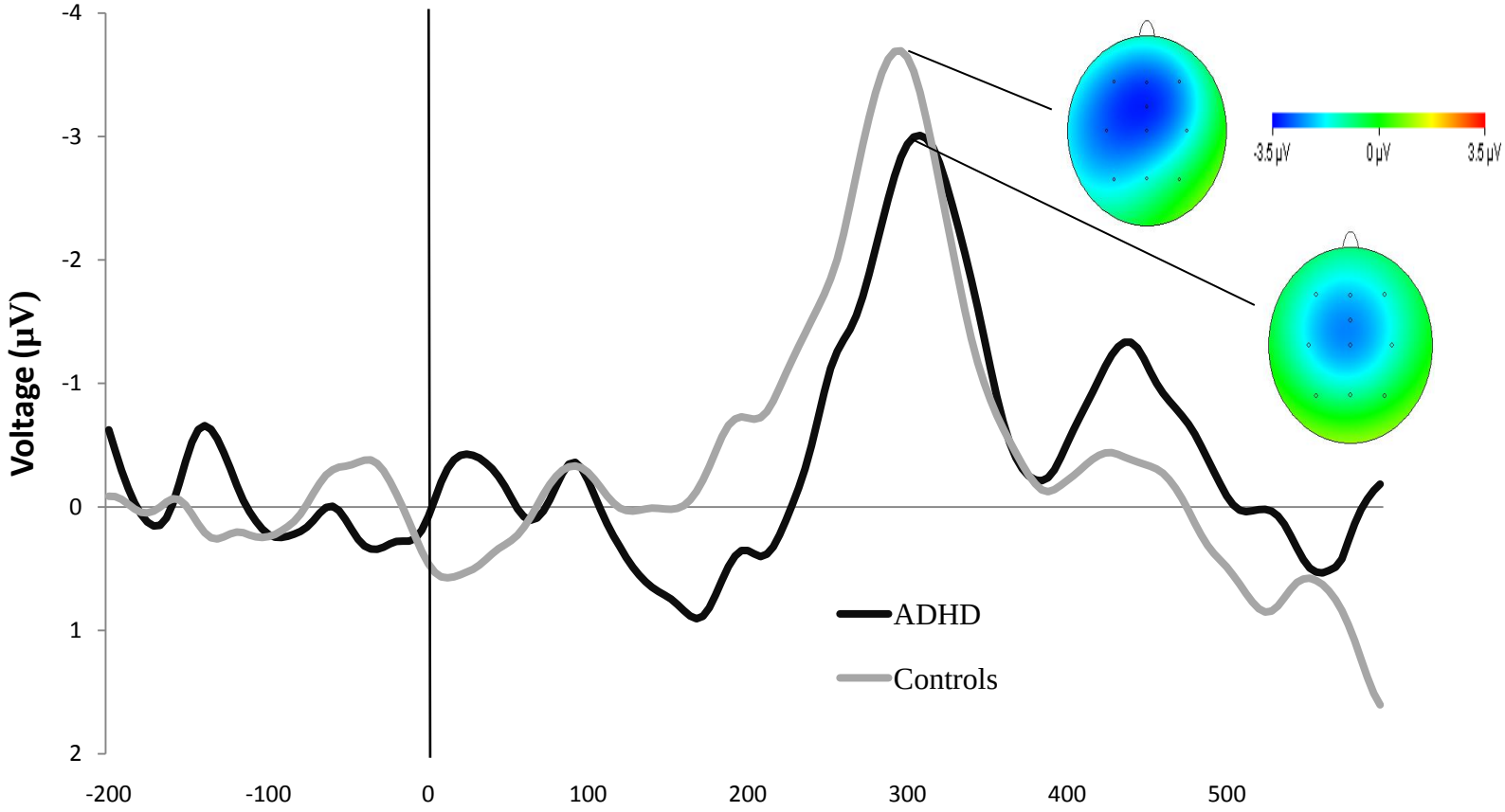

Figure 5. Feedback error-related negativity difference waves and corresponding scalp distributions for children with ADHD and typically developing children. Feedback onset occurs at 0 ms. Data recorded at channel FCz. Note that negative is plotted up by convention.

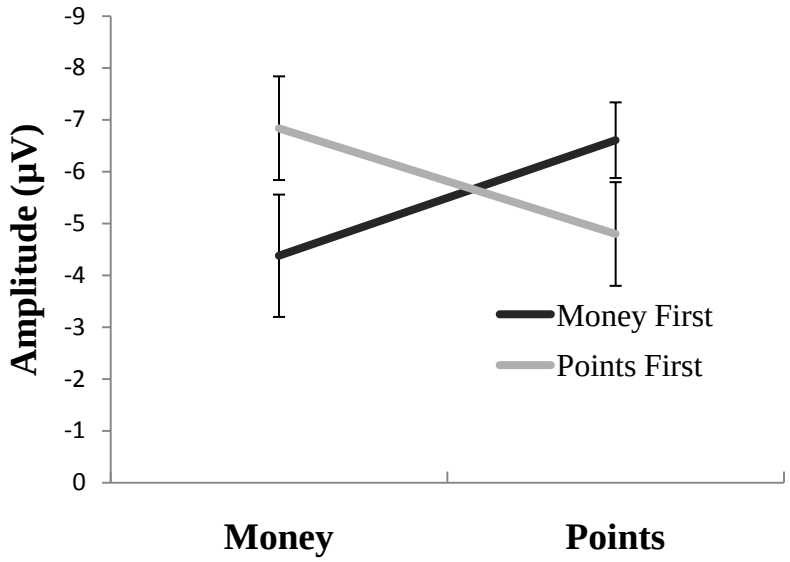

Figure 6. Feedback error-related negativity amplitude as a function of order (money first, points first), collapsed across group (ADHD, control). Error bars indicate standard errors of the mean.

Overall performance on the IGT reverse and original tasks were not correlated ($r = -0.101$, $p > 0.05$). An ANOVA with IGT performance (original, reverse) as a within subjects factor and group (ADHD, control) and order (original first, reverse first) as between subjects factors found that both children with ADHD and typically developing children performed better on the reverse IGT (reverse difference score = 18.44) than on the original IGT (original difference score = 1.33; $F[1, 35] = 12.23$; $p < 0.005$). All interactions were not significant.

There were no significant correlations between parent and teacher ratings of inattention and hyperactivity with the amplitude of the fERN or with IGT performance ($p > .05$) both collapsed across groups and for the children with ADHD separately. Intelligence as measured by the WASI FSIQ was also not significantly correlated with

performance on the IGT or with fERN amplitude ($p > .05$). Across groups, there was a significant correlation between the overall difference score between the two IGT conditions and the amplitude of the fERN ($r = -0.445$, $p < 0.01$). On further analysis, this correlation appears to be driven by the amplitude of the fERN in the second condition ($r = -0.540$ $p < 0.001$) (Figure 7), with a trend towards significance for the first condition ($r = -0.286$ $p = 0.088$). When an outlier was removed from analysis (fERN = -22.1810, IGT = 24) and the correlations were rerun, the findings remained unchanged.

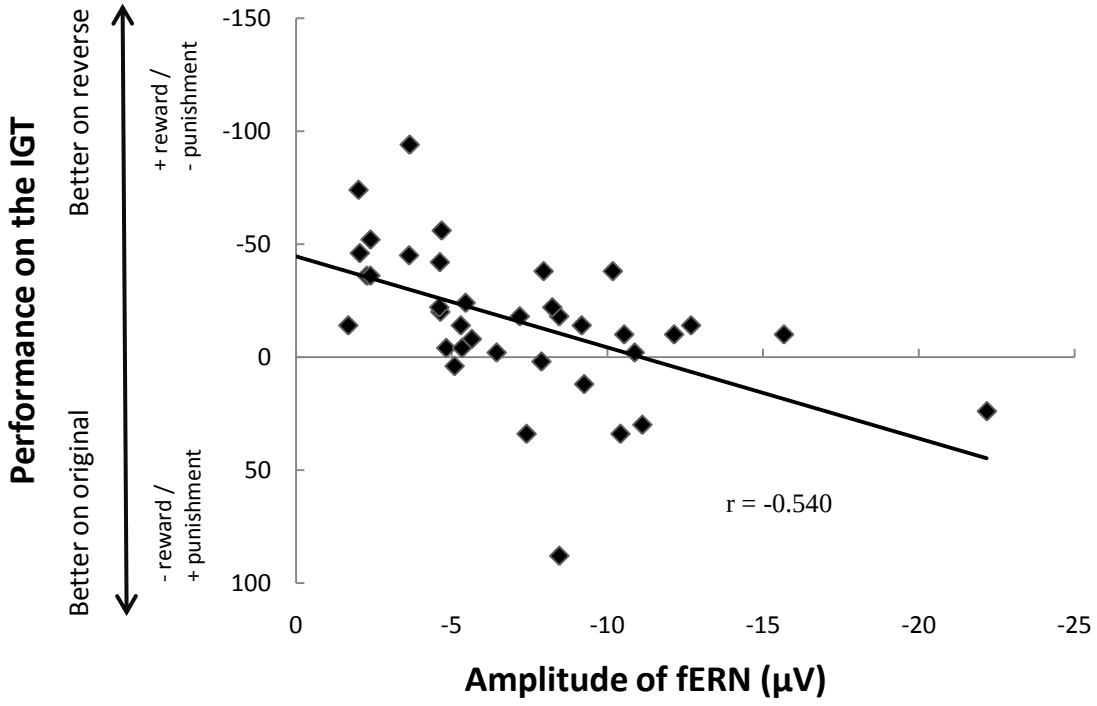

Figure 7. FERN amplitude for the second condition as a function of performance on the IGT tasks (difference score on reverse task subtracted from the difference score on the original task). A higher score on the performance on the IGT indicates that participants performed better on the original task in comparison to the reverse task. Participants scoring higher on the original version of the IGT may have diminished sensitivity to reward or increased sensitivity to punishment (- reward/+ punishment). Alternatively, participants scoring higher on the reverse version of the IGT may have increased sensitivity to reward or diminished sensitivity to punishment (+ reward/- punishment).

Discussion

As was found in the previous study, there were no significant group differences in the amplitude of the fERN. Post hoc findings from the previous study (Holroyd et al., 2008) found that the amplitude of the fERN increased during the second half of the T-Maze task, post payment, in children with ADHD, but decreased in typically developing children. However, there were a number of limitations with that study. First, it was not possible to differentiate the effect of monetary payment from other possible causes of a change in fERN amplitude (i.e., time on task, fatigue, etc.). Additionally, the findings in the previous study were post hoc, increasing the likeliness that they resulted from a statistical fluke. A final limitation was that a measure of intelligence was not included, making it impossible to determine whether groups differed on IQ and the possible effect intelligence may have had on the outcome.

The current study corrected for these limitations of the previous study: the order of presentation of the points and money conditions were counterbalanced across participants, a measure of IQ was included, and an attempt was made to replicate the original post-hoc finding. On the basis of the previous findings, I predicted that the fERN in children with ADHD would be larger in comparison to typically developing children only in the condition in which participants were awarded money instead of points. Instead, I found that there were no differences in fERN amplitude between groups or between money and points conditions. The current study found an increase in fERN amplitude for children with ADHD and typically developing children in the second condition, regardless of whether it was money or points. Although these results show the same pattern as was found in the previous study for the children with ADHD (who

exhibited an increase in fERN amplitude from the first to the second conditions), they are inconsistent with the previous results for the typically developing children (who exhibited a trend for a decrease in fERN from the first to the second conditions). Notably, in the present study children with ADHD exhibited a considerably higher level of variability in fERN amplitude in comparison with that of the typically developing children.

In adults, the amplitude of the fERN has been shown to be correlated with the degree of task engagement (Yeung, Holroyd, & Cohen, 2005), fatigue and motivation (Boksem, Meijman, & Lorist, 2006) and shows strong context dependence (Holroyd, Larsen, & Cohen, 2004). Additionally, the amplitude of the fERN is sensitive to tasks in which money was used to increase motivation (Rongjun, Yuejia, Zheng, & Xiaolin, 2007; San Martín, Manes, Hurtado, Isla, & Ibañez, 2010). Monetary incentives were found to significantly reduce the effects of sleep deprivation on the amplitude of the rERN in adults. This effect was demonstrated by an increase in amplitude of the rERN following the addition of a monetary incentive (Hsieh, Li, & Tsai, 2010). Hemodynamic activation of the rostral ACC was stronger in response to monetary losses than to losses not involving money (Taylor et al., 2006). Fewer studies have looked at the effect of monetary incentive in children and adolescents, and no one has looked at the effect of money on the fERN in comparison with a more abstract ‘points’ reward condition. Van meel et al. (2005) had children with ADHD and typically developing children play a gambling game in which they could win or lose money. They found that children with ADHD had a more negative mean amplitude following monetary losses than did typically developing children, but did not find differences between groups following monetary

gains. These findings might suggest that children with ADHD are particularly sensitive to monetary punishment. However, as previously mentioned, reward and no reward stimuli were not counterbalanced in Van meel's study and the fERN produced was atypical making the results difficult to interpret. The current study did not penalize children with a loss of money; instead the no-reward condition resulted in no gain of points or money. It may be possible that the lack of difference between groups was due to the fact that children were not penalized money in the no-reward conditions.

Children are spending an increasing amount of time playing video games. One study found American children aged 10-19 spend approximately 8 hours per week playing video games (Cummings & Vandewater, 2007). A large majority of video games operate on a points system, with better performance on the game resulting in a higher score. Hence, the saliency of abstract points may be increased for the present generation of children and adolescents, decreasing the gap of saliency between 5 points and 5 cents.

The T-Maze task given to participants in the current study was twice as long as in the original study. To the best of my knowledge, there have not been any studies to date that have examined the optimal length of time for ERP studies in children with or without ADHD, nor have any studies examined fatigue in adults in a feedback related task. In an ERP study that had adults perform a no/no-go task for 60 minutes, it was found that the rERN decreased with time due to mental fatigue (Kato, Endo, & Kizuka, 2009). However, the demands placed on participants during a speeded task are much heavier than on the current feedback related task, and our task took between 35-45 minutes to complete and included numerous breaks.

The amplitude of the fERN increased in the second condition, regardless of whether the children completed points or money first. In addition to the fERN being larger in the second condition, response times were also found to be significantly shorter in the second condition. These findings are consistent with the possibility that the children became increasingly engaged in the task with time, for the following reasons. Engagement in the task was increased by encouraging participants to look for a pattern or to develop a strategy to maximize their rewards. As the children's focus and attention decreased, an additional tactic was used by experimenters to increase engagement in the task. Participants were encouraged to stay engaged in the task by selecting the alley they believed the reward to be in as quickly as they could following the appearance of the green double arrow. Children were verbally encouraged for their performance on the reward finding task, as well as their ability to stay focused on the task and to select an alleyway as soon as the green double arrow appeared. These verbal instructions coincide with shorter response times in the second condition, and correspond in time with the observed increase in the amplitude of the fERN. Thus this increase in fERN amplitude may have been due to the fact that the children were more focused and engaged with the task, as revealed by the faster button presses in response to the experimental instructions. A higher degree of task engagement and interest has been associated with larger fERN amplitudes (Yeung et al., 2005).

The encouragement of the participants' ability to remain focused on the task and respond quickly may have acted as a social incentive above and beyond the reward incentives they were already receiving. In an interesting series of studies, the impact of social and monetary rewards on the performance on a go/no-go task was examined.

Children with ADHD and a typically developing control group both showed improvement in cognitive control in response to monetary and social rewards. Between the two groups, children with ADHD were more sensitive to social incentives in comparison with a control group (Kohls, Herpertz-Dahlmann, Konrad, 2009; Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009). The impact of social compared to monetary rewards interacted with individual differences including reward seeking and empathy. It has been shown that the fERN increased when participants believed they were competing online against other participants (Van Meel, & Van Heijningen, 2010). A study involving adults found an increase in amplitude of the rERN when participants were told their performance was being evaluated by a research assistant (Hajcak, Moser, Yeung & Simons, 2005). A similar effect has been observed in children. Children who performed a speeded response time task in front of an audience displayed a larger rERN in comparison to a group working alone (Kim, Iwaki, Uno & Fujita, 2005). In the current study, children were praised for remaining focused on the task throughout the second condition and for quick responses. Children's awareness of the fact that their responses were being watched may have increased, subsequently increasing engagement in the task.

The effect of verbal encouragement for faster responses in the second condition of the T-maze is difficult to interpret and is a limitation in the current study. It is possible that encouragement of faster response times increased attention and focus on the task, consequently increasing engagement. Alternatively, experimenter feedback regarding response times may have accentuated the fact that performance was being monitored. It is unclear through what mechanism evaluation of performance may act to increase the

amplitude of the ERN. Further research is needed to understand the effects of external encouragement or evaluation on behavioural and psychophysiological responses.

A recent study using the T-Maze to elicit the fERN found no differences in amplitude between children, adolescents, and young adults (Montazer-Hojat & Holroyd, 2010). However, previous studies have demonstrated that children display a reduced rERN in comparison with older adolescents and adults (Segalowitz & Dywan, 2009; Wiersema, van der Meere, & Roeyers, 2007). In addition to the development of the dopamine system throughout childhood, it has also been suggested that there is considerably more latency jitter across individuals, as well as from trial to trial within children, possibly contributing to the reduced ERN amplitude observed in children (Segalowitz & Dywan, 2009). Individual differences in sensitivity to punishment and reward (as measured by the BIS/BAS) modulated the amplitude of the rERN on a Flanker task in young adults (Boksem, Tops, Kostermans, & De Cremer, 2008). A similar recent finding showed that individuals scoring high on a measure of empathy had a larger fERN on the T-maze task in comparison to those with low empathy scores (Lukie & Holroyd, 2010). Individual differences have a strong influence on the fERN, but were not measured in the current study.

Previous ERN studies involving children with ADHD have reported mixed findings. Some studies found that children with ADHD showed a larger rERN (Burgio-Murphy et al., 2007), some a reduced rERN (van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007; Wiersema, vander Meere, & Roeyers, 2005), and some reported no differences in rERN amplitude between children with ADHD and typically developing children (Liotti, Pliszka, Perez, Kothmann, & Woldorv, 2005). A major criticism and

possible source of variability between studies is whether children were aware when they had committed an error (Segalowitz & Dywan, 2009). Another difficulty in reliably measuring the rERN is the variability in the timing of the internal error detection with respect to the timing of the individual's motor response. These technical complexities make evaluating rERN results, especially with child participants, difficult. Eppinger, Mock, and Kray (2009) examined differences in rERN and fERN amplitude in typically developing children in comparison with adults. Their results suggested that children are less able than adults to build an internal representation of the correct response and therefore rely more on external feedback to guide learning. In the current study, a fERN was measured and children were reminded every 50 trials which stimulus was the reward. Using a feedback task to elicit the fERN circumvents the technical difficulties associated with the rERN in child studies. Additionally, use of a feedback task allows us to better generalize to everyday situations as children commonly learn to guide their behaviour from external feedback, such as rewards and punishments (Shiller & Schneider, 2003).

On the original version of the IGT, both typically developing children and children with ADHD made more selections of doors with high immediate rewards and higher punishments, ultimately resulting in larger overall loss. On the reverse version of the IGT both groups made more selections from doors that delivered high immediate punishment and higher rewards, in the long term resulting in overall gain. Both groups performed better on the reverse version of the IGT in comparison to the original version of the IGT, suggesting that they are relatively hypersensitive to reward or insensitive to punishment.

Previous studies have found that performance on the original version of the IGT improves with age. Older children out perform younger children and improvement continues throughout adolescence into adulthood (Crone & van der Molen, 2004; Hooper, Luciana, Conklin, & Yarger 2004). However, a recent study found performance on a modified version of the original IGT improved up until approximately age 14, after which performance was not significantly different from those of adults (Cauffman, Shulman, Claus, Banich, Steinberg, & Graham, 2010). Crone, Bunge, Latenstein, and van der Molen (2005) had children complete modified versions of the original and reverse IGT tasks, and found that children aged 7-15 years learned to differentiate between advantageous and disadvantageous decks more quickly in the reverse task than in the original task. It may be that when anticipating long term goals, individuals tend to focus more on reward than punishment.

Previous studies have found that adolescents (Toplak et al., 2005) and children with ADHD show impaired performance on modified versions of the IGT (Garon et al., 2006; Bubier & Drabick, 2008; Wang, Zhu, Wang & Wang, 2008). Luman, Oosterlaan, Knol, and Sergeant (2008) reported that children with ADHD respond similarly to typically developing children when the frequency of punishments increased, but were impaired when the magnitude of punishments were altered. Wang (2008) included children with ADHD-PI and ADHD-C and did not observe any differences between groups. The results of the current study support the findings reported by Geurts (2006) who found children with ADHD performed similarly to typically developing children. Toplak et al. (2005) found no correlation between IQ and performance on the IGT, but did find that increased parental ratings of hyperactivity and impulsivity were correlated

with IGT performance in adolescents with ADHD. The current study found no relationship between performance on the IGT with either IQ or parental ratings of hyperactivity/impulsivity or inattention.

Interestingly, children who performed better on the original IGT task in comparison to the reverse IGT had a larger fERN. Children who were better able to learn to pick from the advantageous decks in the original IGT task were better able to avoid those decks that delivered larger punishments. Superior performance on the original version of the IGT may be due to hypersensitivity to punishment, or hyposensitivity to reward. This finding suggests that those individuals who are more sensitive to punishment or less sensitive to reward on the IGT show this same sensitivity to punishment in the ERP, manifested as increased fERN amplitude. Note that variation in fERN amplitude, which is determined as the difference between the ERPs to correct and error feedback, could be due to variation in the neural response to either type of feedback. For example, a recent study including individuals with substance dependence found a smaller fERN in those individuals who learned more efficiently from negative feedback (in comparison to positive feedback) on a behavioural task. The reduced fERN found in these punishment-sensitive individuals was found to be driven by a decreased reward signal rather than a decreased error signal (Baker, Stockwell, Barnes & Holroyd, in press). Note further that the finding in the current study was post-hoc and should be investigated further in future studies. Studies that have examined individual differences, including a measure of sensitivity to punishment, have not found a relationship between a high sensitivity to punishment and performance on the IGT (Davis, Patte, Tweed, & Curtis, 2007; Franken & Muris, 2005).

The current study aimed to expand upon and replicate the findings of the original study by Holroyd et al (2008). Instead, no differences were found between typically developing children and children with ADHD. Both groups had a larger fERN in the second condition, regardless of reward saliency, and this increase corresponded with faster behavioural response times. Additionally, groups performed similarly on a behavioural decision making task designed to measure sensitivity to rewards and punishments.

Future Directions

Continued collection of data, as well as replications of the current study are vital next steps to increase confidence in the current findings. The T-Maze task used in the current study was twice as long as in the original study. This increase in length of time of the experiment made it difficult for both groups of children to remain focused and engaged in the task. As a strategy to increase engagement, researchers encouraged children to select an alley as soon as the stimuli appeared indicating they were able to make a selection. In future studies, reducing the number of trials should decrease the need for researchers to encourage faster responses as the demand on children's sustained attention will not be as great.

The current study found an interesting correlation between performance on the original and reverse versions of the IGT and the fERN. The structure of the IGT is not able to differentiate whether increased sensitivity to punishment or decreased sensitivity to reward might be driving the larger amplitude in the fERN. Future studies should incorporate the probabilistic selection task (Frank, Seeberger & O'Reilly, 2004) to

separate and further examine individual differences in learning from positive or negative feedback and the relationship to the fERN.

Another interesting future study includes examining the difference of monetary and social rewards on the amplitude of the fERN in both typically developing children, as well as children with ADHD. Both groups of children responded positively to social encouragement. Finally, future fERN studies including measures of individual differences such as empathy and sensitivity to punishment and reward that appear to influence the amplitude of the ERN will be important.

References

American Psychiatric Association. (2000). *Diagnostic and satistical manual of mental disorders (4th ed. text revision).* Washington, DC: Author.

Baeyens, D., Roeyers, H., & Walle, J. V. (2006). Subtypes of attention-Deficit/Hyperactivity disorder (ADHD): Distinct or related disorders across measurement levels? *Child Psychiatry & Human Development, 36*, 403-417.

Baker, T., & Holroyd, C. (2009). Which way do I go? Neural activation in response to feedback and spatial processing in a virtual T-maze. *Cerebral Cortex, 19*, 1708-1722.

Baker, T. E., Stockwell, T., Barnes, G., & Holroyd, C. B. (in press). Pathways to addiction: At the intersection of brain, cognition and personality. *Addiction Biology.*

Banaschewski, T., Becker, K., Scherag, S., Franke, B., & Coghill, D. (2010). Molecular genetics of attention-deficit/hyperactivity disorder: An overview. *European Child & Adolescent Psychiatry, 19*, 237-257.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin, 121*, 65-94.

Barr, C. L., Wigg, K. G., Feng, Y., Zai, G., Malone, M., Roberts, W., et al. (2000). Attention-deficit hyperactivity disorder and the gene for the dopamine D5 receptor. *Molecular Psychiatry, 5*, 548.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*, 7-15.

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain: A Journal of Neurology, 123,* 2189-2202.

Bentivoglio, M., & Morelli, M. (2005). The organization and circuits of mesencephalic dopaminergic neurons and the distribution of dopamine receptors in the brain. In S. B. Dunnett, M. Bentivoglio, A. Björklund & T. Hökfelt (Eds.), *Handbook of chemical neuroanatomy, vol 21, dopamine* (pp. 1-106). Amsterdam: Elsevier.

Biederman, J., Petty, C., Ten Haagen, K., Small, J., Doyle, A., Spencer, T., et al. (2009). Effect of candidate gene polymorphisms on the course of attention deficit hyperactivity disorder. *Psychiatry Research, 170,* 199-203.

Boksem, M. A. S., Meijman, T. F., & Lorist, M. M. (2005). Effects of mental fatigue on attention: An ERP study. *Cognitive Brain Research, 25,* 107-116.

Boksem, M., Tops, M., Kostermans, E., & De Cremer, D. (2008). Sensitivity to punishment and reward omission: Evidence from error-related ERP components. *Biological Psychology, 79,* 185-192.

Brown, R. T., & Pacini, J. N. (1989). Perceived family functioning, martial status, and depression in parents of boys with attention deficit disorder. *Journal of Learning Disabilities, 22.*

Bubier, J., & Drabick, D. (2008). Affective decision-making and externalizing behaviors: The role of autonomic activity. *Journal of Abnormal Child Psychology:, 36,* 941-953.

Burgio-Murphy, A., Klorman, R., Shaywitz, S., Fletcher, J., Marchione, K., Holahan, J., et al. (2007). Error-related event-related potentials in children with attention-deficit

hyperactivity disorder, oppositional defiant disorder, reading disorder, and math disorder. *Biological Psychology, 75,* 75-86.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences, 4,* 215-222.

Castellanos, F. X. (1997). Toward a pathophysiology of attention-deficit/hyperactivity disorder. Cools, R. (2008). Role of dopamine in the motivational and cognitive control of behavior. *Neuroscientist, 14,* 381-395.

Cauffman, E., Shulman, E., Claus, E., Banich, M., Steinberg, L., & Graham, S. (2010). Age Differences in Affective Decision Making as Indexed by Performance on the Iowa Gambling Task. *Developmental Psychology, 46,* 193-207.

Cockburn, J. & Holroyd, C.B. (2010). Focus on the positive: Computational simulations implicate asymmetrical reward prediction error signals in childhood Attention-Deficit/Hyperactivity Disorder. Manuscript submitted for publication.

Cragg, S. J., & Rice, M. E. (2004). DAncing past the DAT at a DA synapse. *Trends in Neurosciences, 27,* 270.

Crone, E. A., Bunge, S. A., Latenstein, H., & van der Molen, M. W. (2005). Characterization of children's decision making: Sensitivity to punishment frequency, not task complexity. *Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence, 11,* 245-263.

Crone, E. A., Richard Jennings, J., & van, d. M. (2003). Sensitivity to interference and response contingencies in attention-Deficit/Hyperactivity disorder. *Journal of Child Psychology & Psychiatry & Allied Disciplines, 44,* 214-226.

Crone, E. A., & van, d. M. (2004). Development changes in real life decision making: Performance on a gambling task previously shown to depend on the ventromedial prefrontal cortex. *Developmental Neuropsychology, 25*, 251-279.

Cummings, H., & Vandewater, E. (2007). Relation of adolescent video game play to time spent in other activities. *Archives Of Pediatrics & Adolescent Medicine, 161,* 684-689.

Davids, E., Zhang, K., Tarazi, F. I., & Baldessarini, R. J. (2003). Animal models of attention-deficit hyperactivity disorder. *Brain Research Reviews, 42*, 1.

Davis, C., Patte, K., Tweed, S., & Curtis, C. (2007). Personality traits associated with decision-making deficits. *Personality & Individual Differences, 42*, 279-290.

de Bruijn, Ellen R. A., Hulstijn, W., Verkes, R. J., Ruigt, G. S. F., & Sabbe, B. G. C. (2004). Drug-induced stimulation and suppression of action monitoring in healthy volunteers. *Psychopharmacology, 177*, 151-160.

de Bruijn, E. R. A., Sabbe, B. G. C., Hulstijn, W., Ruigt, G. S. F., & Verkes, R. J. (2006). Effects of antipsychotic and antidepressant drugs on action monitoring in healthy volunteers. *Brain Research, 1105*, 122-129.

Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science, 5*, 303-305.

Devinsky, O., Morrell, M., & Vogt, B. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain: A Journal Of Neurology, 118*,279-306.

Douglas, V. L., & Parry, P. A. (1994). Effects of reward and nonreward on frustration and attention in attention deficit disorder. *Journal of Abnormal Child Psychology, 22*, 281.

Egelman, D. M., Person, C., & Montague, P. R. (1998). A computational role for dopamine delivery in human decision-making. *Journal of Cognitive Neuroscience, 10*, 623-630.

El-Faddagh, M., Laucht, M., Maras, A., Vöhringer, L., & Schmidt, M. H. (2004). Association of dopamine D4 receptor (DRD4) gene with attention-deficit/hyperactivity disorder (ADHD) in a high-risk community sample: A longitudinal study from birth to 11 years of age. *Journal of Neural Transmission, 111*, 883-889.

Eppinger, B., Mock, B., & Kray, J. (2009). Developmental differences in learning and error processing: Evidence from ERPs. *Psychophysiology, 46*, 1043-1053

Floresco, S. B., & Tse, M. T. (2007). Dopaminergic regulation of inhibitory and excitatory transmission in the basolateral amygdala-prefrontal cortical pathway. *Journal of Neuroscience, 27*, 23-23.

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: Cognitive reinforcement learning in Parkinsonism. *Science, 306*, 1940-1943.

Franken, I., & Muris, P. (2005). Individual differences in decision-making. *Personality & Individual Differences, 39*, 991-998.

Garon, N., Moore, C., & Waschbusch, D. A. (2006). Decision making in children with ADHD only, ADHD-anxious/depressed, and control children using a child version of the Iowa gambling task. *Journal of Attention Disorders, 9*, 607-619.

Garon, N., & Moore, C. (2007). Developmental and gender differences in future-oriented decision-making during the preschool period. *Child Neuropsychology, 13*, 46-63.

Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science, 4,* 385-390.

Geurts, H. M., Verté, S., Oosterlaan, J., Roeyers, H., & Sergeant, J. A. (2005). ADHD subtypes: Do they differ in their executive functioning profile? *Archives of Clinical Neuropsychology*, *20,* 457-477.

Geurts, H., van der Oord, S., & Crone, E. (2006). Hot and Cool Aspects of Cognitive Control in Children with ADHD: Decision-Making and Inhibition. *Journal of Abnormal Child Psychology, 34,* 813-824.

Gizer, I. R., Ficks, C., & Waldman, I. D. (2009). Candidate gene studies of ADHD: A meta-analytic review. *Human Genetics, 126,* 51-90.

Grace, A. A. (2001). Psychostimulant actions on dopamine and limbic system function: Relevance to the pathophysiology and treatment of ADHD. In M. V. Solanto, A. F. T. Arnsten, F. X. Castellanos, M. V. Solanto, A. F. T. Arnsten & F. X. Castellanos (Eds.), *Stimulant drugs and ADHD: Basic and clinical neuroscience*. (pp. 134-157). New York, NY US: Oxford University Press.

Grady, D. L., Chi, H., Ding, Y., Smith, M., Wang, E., Schuck, S., et al. (2003). High prevalence of rare dopamine receptor D4 alleles in children diagnosed with attention-deficit hyperactivity disorder. *Molecular Psychiatry, 8,* 536.

Haenlein, M., & Caul, W. F. (1987). Attention deficit disorder with hyperactivity: A specific hypothesis of reward dysfunction. *Journal of the American Academy of Child & Adolescent Psychiatry, 26,* 356-362.

Hajcak, G., Moser, J.S., Yeung, N., & Simons, R.F. (2005). On the ERN and the significance of errors. *Psychophysiology, 42,* 151-160.

Happaney, K., Zelazo, P. D., & Stuss, D. T. (2004). Development of orbitofrontal function: Current themes and future directions. *Brain & Cognition, 55,* 1-10.

Herrmann, M. J., Römmler, J., Ehlis, A., Heidrich, A., & Fallgatter, A. J. (2004). Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (pe). *Cognitive Brain Research, 20,* 294-299.

Hesse, S., Ballaschke, O., Barthel, H., & Sabri, O. (2009). Dopamine transporter imaging in adult patients with attention-deficit/hyperactivity disorder. *Psychiatry Research: Neuroimaging Section, 171,* 120-128.

Holroyd, C. B., Baker, T. E., Kerns, K. A., & Müller, U. (2008). Electrophysiological evidence of atypical motivation and reward processing in children with attention-deficit hyperactivity disorder. *Neuropsychologia, 46,* 2234-2242.

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review, 109,* 679-709.

Holroyd, C. B., & Krigolson, O. E. (2007). Reward prediction error signals associated with a modified time estimation task. *Psychophysiology, 44,* 913-917.

Holroyd, C. B., Larsen, J. T., & Cohen, J. D. (2004). Context dependence of the event-related brain potential associated with reward and punishment. *Psychophysiology, 41,* 245-253.

Holroyd, C. B., Nieuwenhuis, S., Mars, R. B., & Coles, M. G. H. (2004). Anterior cingulate cortex, selection for action, and error processing. In M. I. Posner, & M. I.

Posner (Eds.), *Cognitive neuroscience of attention*. (pp. 219-231). New York, NY US: Guilford Press.

Hooper, C., Luciana, M., Conklin, H., & Yarger, R. (2004). Adolescents' Performance on the Iowa Gambling Task: Implications for the Development of Decision Making and Ventromedial Prefrontal Cortex. *Developmental Psychology, 40,* 1148-1158.

Hsieh, S., Li, T., & Tsai, L. (2010). Impact of monetary incentives on cognitive performance and error monitoring following sleep deprivation. *Sleep: Journal of Sleep and Sleep Disorders Research, 33,* 499-507

Iaboni, F., & Douglas, V. I. (1995). Effects of reward and response costs on inhibition in ADHD children. *Journal of Abnormal Psychology, 104,* 232.

Joel, D., Niv, Y., & Ruppin, E. (2002). Actor–critic models of the basal ganglia: New anatomical and computational perspectives. *Neural Networks, 15,* 535.

Jonkman, L. M., van Melis, J. J. M., Kemner, C., & Markus, C. R. (2007). Methylphenidate improves deficient error evaluation in children with ADHD: An event-related brain potential study. *Biological Psychology, 76,* 217-229.

Kato, Y., Endo, H., & Kizuka, T. (2009). Mental fatigue and impaired response processes: Event-related brain potentials in a Go/NoGo task. *International Journal of Psychophysiology, 72,* 204-211.

Kerr, A., & Zelazo, P. D. (2004). Development of "hot" executive function: The children's gambling task. *Brain & Cognition, 55,* 148-157.

Kim, E.Y., Iwaki, N., Uno, H., & Fujita, T. (2005). Error related negativity in children: The effect of an observer. *Developmental Neuropsychology, 28,* 871-883.

Kimko, H. C., Cross, J. T., & Abernethy, D. R. (1999). Pharmacokinetics and clinical effectiveness of methylphenidate. *Clinical Pharmacokinetics, 37,* 457-470.

Kohls, G., Herpertz-Dahlmann, B., & Konrad, K. (2009). Hyperresponsiveness to social rewards in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). *Behavioral and Brain Functions, 5,* 20-31.

Kohls, G., Peltzer, J., Herpertz-Dahlmann, B., & Konrad, K. (2009). Differential effects of social and non-social reward on response inhibition in children and adolescents. *Developmental Science, 12,* 614-625.

Krause, J. (2008). SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder. *Expert Review of Neurotherapeutics, 8,* 611-625.

Krause, K., Dresel, S. H., Krause, J., la Fougere, C., & Ackenheil, M. (2003). The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder. *Neuroscience & Biobehavioral Reviews, 27,* 605.

Lahey, B. B., Pelham, W. E., Loney, J., Lee, S. S., & Willcutt, E. (2005). Instability of the DSM-IV subtypes of ADHD from preschool through elementary school. *Archives of General Psychiatry, 62,* 896-902.

Langley, K., Fowler, T. A., Grady, D. L., Moyzis, R. K., Holmans, P. A., Van, d. B., et al. (2009). Molecular genetic contribution to the developmental course of attention-deficit hyperactivity disorder. *European Child & Adolescent Psychiatry, 18,* 26-32.

Levy, F. (1991). The dopamine theory of attention deficit hyperactivity disorder (ADHD). *Australian and New Zealand Journal of Psychiatry, 25,* 277-283.

Levy, F., Hay, D. A., & Bennett, K. S. (2006). Genetics of attention deficit hyperactivity disorder: A current review and future prospects. *International Journal of Disability, Development & Education, 53*, 5-20.

Liotti, M., Pliszka, S. R., Perez, R., Kothmann, D., & Woldorff, M. G. (2005). Abnormal brain activity related to performance monitoring and error detection in children with ADHD. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 41*, 377-388.

Ljungberg, T., Apicella, P., & Schultz, W. (1991). Responses of monkey dopamine neurons to external stimuli: Changes with learning. In G. Bernardi, et al. (Eds.), *The basal ganglia III.* (pp. 487-494). New York, NY US: Plenum Press.

Ljungberg, T., Apicella, P., & Schultz, W. (1992). Responses of monkey dopamine neurons during learning of behavioral reactions. *Journal of Neurophysiology, 67*, 145-163.

Lukie, C.N. & Holroyd, C.B. (2010, February). Neural Mechanisms of Individual Differences in Personality Traits. Poster session presented at the 38th annual meeting of the International Neuropsychological Society, Acapulco, Mexico.

Luman, M., Oosterlaan, J., Hyde, C., Van Meel, C. S., & Sergeant, J. A. (2007). Heart rate and reinforcement sensitivity in ADHD. *Journal of Child Psychology & Psychiatry, 48*, 890-898.

Luman, M., Oosterlaan, J., Knol, D. L., & Sergeant, J. A. (2008). Decision-making in ADHD: Sensitive to frequency but blind to the magnitude of penalty? *Journal of Child Psychology & Psychiatry, 49,* 712-722.

Luman, M., Oosterlaan, J., & Sergeant, J. A. (2005). The impact of reinforcement contingencies on AD/HD: A review and theoretical appraisal. *Clinical Psychology Review, 25*, 183-213.

Luman, M., Van Meel, C. S., Oosterlaan, J., Sergeant, J. A., & Geurts, H. M. (2009). Does reward frequency or magnitude drive reinforcement-learning in attention-deficit/hyperactivity disorder? *Psychiatry Research, 168,* 222-229.

Malloy-Diniz, L., Fuentes, D., Leite, W. B., Bechara, A., & Correa, H. (2007). Impulsive behavior in adults with attention deficit/hyperactivity disorder: Characterization of attentional, motor and cognitive impulsiveness. *Journal of the International Neuropsychological Society, 13*, 693-698.

Masunami, T., Okazaki, S., & Maekawa, H. (2009). Decision-making patterns and sensitivity to reward and punishment in children with attention-deficit hyperactivity disorder. *International Journal of Psychophysiology, 72,* 283-288.

Miltner, W. H. R., Braun, C. H., & Coles, M. G. H. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence. *Journal of Cognitive Neuroscience, 9*, 788.

Montague, P. R., Dayan, P., & Sejnowski, T. J. (1996). A framework for mescencephalic dopamine systems based on predictive hebbian learning. *Journal of Neuroscience, 16*, 1936-1947.

Montazer-Hojat, S., & Holroyd, C.B. (2010, May). Developmental Changes in Feedback Error-related Negativity (fERN):An Electrophysiological Study of the Brain Error Processing System. Poster session presented at the 12th annual meeting of the North West Cognition and Memory Society, Bellingham, Washington.

Morecraft, R. J., & Van Hoesen, ,G.W. (1998). Convergence of limbic input to the cingulate motor cortex in the rhesus monkey. *Brain Research Bulletin, 45*, 209-232.

O'Connell, R. G., Bellgrove, M. A., Dockree, P. M., Lau, A., Hester, R., Garavan, H., et al. (2009). The neural correlates of deficient error awareness in attention-deficit hyperactivity disorder (ADHD). *Neuropsychologia, 47*, 1149-1159.

Oosterlaan, J., Scheres, A., & Sergeant, J. A. (2005). Which executive functioning deficits are associated with AD/HD, ODD/CD and comorbid AD/HD+ODD/CD? *Journal of Abnormal Child Psychology, 33*, 69-85.

Pasini, A., Paloscia, C., Alessandrelli, R., Porfirio, M. C., & Curatolo, P. (2007). Attention and executive functions profile in drug naive ADHD subtypes. *Brain & Development, 29*, 400-408.

Rader, R., McCauley, L., & Callen, E. C. (2009). Current strategies in the diagnosis and treatment of childhood attention-deficit/hyperactivity disorder. American *Family Physician, 79*, 657-665.

Romano, E., Baillargeon, R.H., & Tremblay, R.E. (2002). Prevalence of hyperactivity-impulsivity and inattention among Canadian children: Findings from the first data collection cycle (1994-1995) of the national longitudinal survey of children and youth (DOI: SP-561-01-03E). Hull, Quebec: Human Resources Development Canada Publications Centre. Retrieved from: http://www.hrsdc.gc.ca/eng/cs/sp/sdc/pkrf/publications/research/2002-000170/SP-5610201E.pdf

Rongjun, Y., Yuejia, L., Zheng Y., & Xiaolin, Z. (2007). Does the FRN in brain potentials
reflect motivational/affective consequence of outcome evaluation? *Progress in Natural Science, 17*,136-143

Rowe, D. C., Stever, C., Giedinghagen, L. N., Gard, J. M. C., Cleveland, H. H., Terris, S. T., et al. (1998). Dopamine DRD4 receptor polymorphism and attention deficit hyperactivity disorder. *Molecular Psychiatry, 3*, 419.

Russell, V. A. (2002). Hypodopaminergic and hypernoradrenergic activity in prefrontal cortex slices of an animal model for attention-deficit hyperactivity disorder — the spontaneously hypertensive rat. *Behavioural Brain Research, 130*, 191.

Sagvolden, T., Aase, H., Johansen, E. B., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Sciences, 28*, 397-468.

San Martín, R., Manes, F., Hurtado, E., Isla, P., & Ibañez, A. (2010). Size and probability of rewards modulate the feedback error-related negativity associated with wins but not losses in a monetarily rewarded gambling task. *NeuroImage, 51*, 1194-1204.

Scahill, L., & Schwab-Stone, M. (2000). Epidemiology of ADHD in school-age children. *Child and Adolescent Psychiatric Clinics of North America, 9*, 541-555.

Schultz, W., Apicella, P., & Ljungberg, T. (1993). Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *The Journal of Neuroscience, 13*, 900-913.

Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. *Current Opinion in Neurobiology, 7,* 191-197.

Schultz, W. (2002). Getting formal with dopamine and reward. Neuron, 36(2), 241.

Segalowitz, S., & Dywan, J. (2009). Individual differences and developmental change in the ERN response: implications for models of ACC function. *Psychological Research, 73,* 857-870.

Seidman, L. J. (2006). Neuropsychological functioning in people with ADHD across the lifespan. *Clinical Psychology Review, 26,* 466-485.

Sergeant, J. A., Geurts, H., & Oosterlaan, J. (2002). How specific is a deficit of executive functioning for attention-Deficit/Hyperactivity disorder? *Behavioural Brain Research, 130,* 3.

Shastry, B. S. (2004). Molecular genetics of attention-deficit hyperactivity disorder (ADHD): An update. *Neurochemistry International, 44,* 469.

Shiller, V., & Schneider, M. (2003). *Rewards for kids!: Ready-to-use charts and activities for positive parenting*. Washington, DC US: American Psychological Association.

Shue, K. L., & Douglas, V. I. (1992). Attention deficit hyperactivity disorder and the frontal lobe syndrome. *Brain and Cognition, 20,* 104-124.

Slusarek, M., & Velling, S. (2001). Motivational effects on inhibitory control in children with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry, 40,* 355.

Spencer, T. J. (2002). Attention-deficit/hyperactivity disorder. *Archives of Neurology, 59,* 314-316.

Squassina, A., Lanktree, M., De Luca, V., Jain, U., Krinsky, M., Kennedy, J., et al. (2008). Investigation of the dopamine D5 receptor gene (DRD5) in adult attention deficit hyperactivity disorder. *Neuroscience Letters, 432*, 50-53.

Sullivan, R. M., & Brake, W. G. (2003). What the rodent prefrontal cortex can teach us about attention-deficit/hyperactivity disorder: The critical role of early developmental events on prefrontal function. *Behavioural Brain Research, 146*, 43.

Suri, R. E. (2002). TD models of reward predictive responses in dopamine neurons. *Neural Networks, 15*, 523.

Sutton, R. S. (1988). Learning to predict by the method of temporal differences. *Machine Learning, 3*, 9-44.

Sutton, R. S., & Barto, A. G. (1998). *Reinforcement learning*: An introduction. Cambridge, MA: MIT Press.

Taylor, S., Martis, B., Fitzgerald, K., Welsh, R., Abelson, J., Liberzon, I., et al. (2006). Medial Frontal Cortex Activity and Loss-Related Responses to Errors. *Journal of Neuroscience, 26*, 4063-4070

Thorndike, E. L. (1911). Animal intelligence. experimental studies. Oxford England: Macmillan.

Toplak, M. E., Jain, U., & Tannock, R. (2005). Executive and motivational processes in adolescents with attention-deficit-hyperactivity disorder (ADHD). *Behavioral and Brain Functions,1*, 8-8.

van, der Kooij. K., & Glennon, J. C. (2007). Animal models concerning the role of dopamine in attention-deficit hyperactivity disorder. *Neuroscience & Biobehavioral Reviews, 31*, 597-618.

van Meel, C. S., Heslenfeld, D. J., Oosterlaan, J., & Sergeant, J. A. (2007). Adaptive control deficits in attention-deficit/hyperactivity disorder (ADHD): The role of error processing. *Psychiatry Research, 151*, 211-220.

van Meel, C. S., Oosterlaan, J., Heslenfeld, D. J., & Sergeant, J. A. (2005). Telling good from bad news: ADHD differentially affects processing of positive and negative feedback during guessing. *Neuropsychologia, 43*, 1946-1954.

Van Meel, C., & Van Heijningen, C. (2010). The effect of interpersonal competition on monitoring internal and external error feedback. *Psychophysiology, 47*, 213-222.

van Veen, V., & Carter, C. S. (2002). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience, 14*, 593-602.

Viggiano, D., Vallone, D., Ruocco, L. A., & Sadile, A. G. (2003). Behavioural, pharmacological, morpho-functional molecular studies reveal a hyperfunctioning mesocortical dopamine system in an animal model of attention deficit and hyperactivity disorder. *Neuroscience & Biobehavioral Reviews, 27*, 683.

Volkow, N. D., Wang, G. -., Fowler, J. S., Gatley, S. J., Logan, J., Ding, Y., et al. (1998). Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *American Journal of Psychiatry, 155*, 1325-1331.

Wang, Y., Zhu, Z., Wang, P., & Wang, Z. (2008). The effect of rewards and punishment on affective decision-making in children with two subtypes of ADHD. *Acta Psychologica Sinica, 40*, 975-986.

Wender, P. H. (1972). The minimal brain dysfunction syndrome in children. I. the syndrome and its relevance for psychiatry. II. A psychological and biochemical model for the syndrome. *The Journal of Nervous and Mental Disease, 155*, 55-71.

Wender, P. H. (1974). Some speculations concerning a possible biochemical basis of minimal brain dysfunction. *Life Sciences, 14,* 1605-1621.

Wiersema, J. R., van der Meere, J., & Roeyers, H. (2005). ERP correlates of impaired error monitoring in children with ADHD. *Journal of Neural Transmission, 112,* 1417-1430.

Wiersema, J., van der Meere, J., & Roeyers, H. (2007). Developmental changes in error monitoring: An event-related potential study. *Neuropsychologia, 45,* 1649-1657.

Wiersema, J. R., van der Meere, J., & Roeyers, H. (2009). ERP correlates of error monitoring in adult ADHD. *Journal of Neural Transmission, 116,* 371-379.

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Pennington, B. F., & Faraone, S. V. (2005). Validity of the executive function theory of attention-Deficit/Hyperactivity disorder: A meta-analytic review. *Biological Psychiatry, 57,* 1336-1346.

Yeung, N., Holroyd, C., & Cohen, J. (2005). ERP Correlates of Feedback and Reward Processing in the Presence and Absence of Response Choice. *Cerebral Cortex, 15,* 535-544.

Zhang, J., Wang, Y., Cai, R., & Yan, C. (2009). The brain regulation mechanism of error monitoring in impulsive children with ADHD—An analysis of error related potentials. *Neuroscience Letters, 460,* 11-15.