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The Effects of Early Life Stress on Decision Making Under Risk, Response Inhibition, and Error Processing as Risk Factors for Cocaine Addiction

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By

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B.S., The College of William and Mary, 2006

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An abstract of
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Abstract

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By Amanda Elton

Early life stress is associated with an increased risk for drug addiction, but little is understood about how traumatic events in childhood mediate adverse outcomes in adulthood. Eleven adults with early life stress histories (ELS group), eleven men with cocaine dependence (Cocaine group), and fifteen healthy comparison subjects (Control group) participated in an fMRI study of response inhibition and decision making under risk. In a stop-signal task, groups did not differ in stop-signal reaction time, a measure of response inhibition. However, exploratory analyses determined that both ELS males and cocaine-dependent subjects failed to display adaptive slowing following failed stops. Neuroimaging data identified diminished striatal and insula responses in the ELS subjects compared to the Control group for errors of commission; a regression analysis of Childhood Trauma Questionnaire (CTQ) total scores across these trials indicated a dose-effect relationship between early life stress and insula hypoactivity following errors of commission. Despite reduced adaptive slowing behavior, cocaine-dependent individuals displayed greater error-related activations in the striatum – but not insula – compared with the Control group. These results implicate early life stress in an inability to adapt behavior to a changing environment, potentially through reduced insula activity related to poor recognition of errors. The behavioral results from a decision making task revealed no group differences among females in choice selection. However, ELS males and Cocaine males were more likely than Control males to make risky decisions for small rewards. fMRI results indicated that decision making activated the bilateral striatum in the Control group but not the ELS or Cocaine groups. A regression analysis of decision making trials and CTQ total scores further revealed that early life stress results in decreased engagement of the striatum and frontal cortical regions during decision making under risk. These results suggest that early life stress may affect the processes of reward valuation and choice selection through altered neurodevelopment of striatal and frontal brain regions. This research provides a novel understanding of the effects of early life stress on cognitive processes and their behavioral consequences and identifies potential brain mechanisms through which early life stress may increase risk for addiction.

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INTRODUCTION

Drug addiction is a pervasive problem and a major burden for society. The costs of addiction extend from drug-related crime and imprisonment, addiction treatment, poor general health and loss of productivity, as well as far-reaching indirect effects on the family and society. A 2004 report by the Office of National Drug Control Policy estimated the overall cost of illicit drug abuse in the United States in 2002 as $180.9 billion and rising (Office of National Drug Control Policy, 2004). Understanding the etiology of addiction in order to focus on prevention efforts and enhance current treatment methods would serve to minimize its socioeconomic impact as well as improve the health and well-being of the many individuals affected.

Risk factors for drug use, abuse, and addiction

The problem of drug addiction cannot be reduced to simple genetic fate or exposure to a single external agent. Rather, risk for addiction is conferred through multiple interacting environmental and genetic factors. Twin studies suggest genetics influence drug use and addiction risk for males more than females (van de Bree et al., 1998), thereby implying that the environment plays a larger determining role in the risk for drug use disorders in females compared to males. Furthermore, environmental factors are more closely related to drug use than drug abuse and dependence, at least for some drugs (Kendler and Prescott, 1998; van de Bree et al., 1998). The following describes the risk associated with the specific environmental factor posed by childhood adversity.

Childhood adversity as a risk factor for drug abuse and addiction

Childhood trauma is a recognized risk factor for a multitude of negative outcomes in later life, including drug use and addiction (Felitti et al., 1998). In fact, more than half of all drug-abusing individuals entering treatment for drug addiction report a childhood history of physical or sexual abuse (Pirard et al., 2005). Other forms of childhood maltreatment, including emotional abuse, emotional neglect and physical neglect, while less studied, are also prevalent in drug-abusing populations at frequencies higher than the general population (Medrano et al., 1999). In a sample of drug-abusing women, 40% had experienced at least one form of childhood abuse, of which 27% had been sexually abused (Brady et al., 1994). Of a group of drug-addicted women studied by Fullilove and colleagues (1993), 32% reported childhood physical abuse and 42% had suffered childhood sexual abuse (reviewed by Medrano et al., 1999). Dunn et al. (1994) found that of a group of 100 men in a drug abuse treatment program, 25% had experienced physical abuse, 25% emotional abuse, 6% sexual abuse, and 18% multiple types of abuse during childhood.

Other research has identified relationships between childhood trauma histories and drug-use variables. A seminal study of over 8,000 subjects conducted by the Centers for Disease Control and Prevention (CDC) found significant associations between forms of abuse, neglect, and household dysfunction during childhood and early initiation of drug use as well as self-reported drug addiction (Dube et al., 2003). In men, emotional abuse has been associated with a younger age of first alcohol use and a greater severity of drug abuse, while, for women, sexual abuse, emotional abuse, and overall maltreatment

have been associated with a younger age of first alcohol use (Hyman et al., 2006). Compared to drug abusers without a lifetime history of physical or sexual abuse, abused subjects exhibit greater drug addiction-related functional impairments (Pirard et al., 2005). These data, supported by other studies, provide overwhelming evidence to support the contention that a history of maltreatment and early life trauma predisposes to drug abuse problems later in life.

Childhood adversity is associated with persistent sensitization of the stress response

Research to indentify factors linking childhood maltreatment with depression in adulthood (Bagley and Ramsay, 1985; Felitti et al., 1998, McCauley et al., 1997) have identified long-term effects of child abuse on stress response systems, possibly related to disrupted cerebral cortical control of limbic regions involved in the stress response. The hypothalamic-pituitary-adrenal (HPA) axis response to a psychosocial stressor (the Trier Social Stress test, Kirschbaum et al., 1993) was assessed in women with and without major depression and with or without histories of childhood physical or sexual abuse (Heim et al., 2000). It was found that women with childhood abuse histories and without a diagnosis of major depression had an increased plasma adrenocorticotropic hormone (ACTH) response to the stressor compared with controls and depressed women without childhood abuse histories. Women who had been victims of child abuse and had a diagnosis of major depression exhibited a significantly increased plasma cortisol response to the stressor compared to all other groups. Similarly-defined groups of males undergoing a dexamethasone/corticotropin-releasing factor (CRF) test displayed a similar

pattern of HPA-axis dysregulation (Heim et al., 2008). Men with childhood abuse histories had an increased ACTH and cortisol response to the test compared to non-abused men. Additionally, abused men with major depression exhibited increased ACTH and cortisol responses relative to both control men and depressed men without abuse histories. HPA-axis hyperactivity has also been identified in preclinical models of early life stress in which young animals are separated from their mothers for repeated and prolonged periods of time (Plotsky and Meaney, 1993; Ladd et al., 1996; Kalinichev et al., 2002; Sanchez, 2006). These studies suggest that early life stressors result in a persistent, perhaps permanent, sensitization of the stress response and thereby enhance an individual's susceptibility to stress-related psychiatric disorders such as major depression or drug dependence.

Childhood adversity is associated with altered brain development

Childhood abuse and neglect are associated with altered prefrontal cortical functioning. Physical neglect during infancy has been associated with delayed cognitive development (Strathearn et al., 2001). A behavioral and PET neuroimaging study of children adopted from Romanian orphanages also found evidence of disrupted prefrontal cortical functioning, including inattention, impulsivity, decreased cognitive functioning, and decreased glucose metabolic rates in the prefrontal cortex (Chugani et al., 2001). Roy (2002) found that emotional neglect scores on the Childhood Trauma Questionnaire (CTQ) were associated with lower cerebrospinal fluid concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid, and the dopamine metabolite homovanillic acid,

indicating that this form of neglect may impair serotonin and dopamine neurotransmission. A study in young children (3-6 years) noted decreased performance on three measures of cognitive functioning in both abused and neglected children versus non-maltreated children (Hoffman-Plotkin and Twentyman, 1984). A PET study observed that histories of childhood physical and/or sexual abuse were associated with decreased neuronal viability, as measured by *N*-acetylaspartate/creatine ratio, in the right dorsolateral prefrontal cortex in patients with generalized anxiety disorder (Matthew et al., 2004). These studies suggest a strong association between childhood maltreatment and long-term deficits in cognitive functioning, perhaps related to decreased activity in prefrontal cortical circuits responsible for executive functioning due to changes in dendritic density, number of synapses, or receptor density.

Exploring the link between childhood adversity and risk for drug abuse

The use of behavioral and functional neuroimaging responses to tasks representing functional probes of brain processes is a powerful approach to exploring the neurobiology of psychiatric disorders. Deficits in response inhibition and decision making are reflected in the diagnostic hallmarks of drug addiction. This thesis research explored the hypothesis that deficits in the neural representation of behavioral inhibitory control and/or choice behaviors under conditions of risk transduce the impact of childhood maltreatment on a heightened risk for drug abuse and addiction.

Response inhibition and error processing

The clinical classification of drug dependence is dependent upon evidence for inability to stop prepotent or habitual drug-seeking and -use behaviors. Stop-signal tasks measure an individual's ability to inhibit a prepotent motor response after the response has been initiated. These tasks are often used as an indicator of the ability to exert cognitive control of ongoing behavior. A typical stop-signal task requires a subject to respond to a series of frequent "Go" stimuli but inhibit their response following the less frequent presentation of a "stop signal." The stop signal, either an auditory or visual stimulus, is presented after a variable delay relative to the Go stimulus ("stop-signal delay"), presumably after the motor response to the Go stimulus has been initiated.

The Stop-signal reaction time (SSRT) is the time it takes to inhibit the go process after the display of the stop signal and is a measure of individual stopping latency. The stop-signal reaction time can be calculated using the average reaction time to Go signals, average stop-signal delay, and percentage of successful stops on Stop trials. The result of this calculation yields an SSRT composed of the time to encode the stop signal, the time for the "stop" neurons to intercept the "go" neurons, and the time to make a motor response during Go trials (Liddle et al., 2009).

Logan and Cowan (1984) developed a model to explain the behavior observed in stop-signal tasks. Their theory suggests that there are neural stop processes and go processes, and the outcome – respond or do not respond – depends on which process finishes first. More recently, fMRI and animal lesion studies have further characterized the brain regions involved in different aspects of stop-signal tasks. Eagle and colleagues

(2007) assessed the effects of lesions to the rat orbitofrontal cortex and subthalamic nucleus on Go trial reaction time, stop-signal reaction time, and percentage correct stops on stop trials. Lesions to the orbitofrontal cortex resulted in increased stop-signal reaction times and worse stop trial accuracy without affecting go reaction times. Lesions to the subthalamic nucleus caused decreased Go trial reaction times and a reduced ability to stop in response to a stop signal, implicating a role for the subthalamic nucleus in stopping without affecting stop-signal reaction time. Furthermore, Narayanan and Laubach (2008) found that inactivation of the rat dorsomedial prefrontal cortex resulted in attenuated post-error slowing during a reaction time task.

Neuroimaging studies of inhibitory control in humans expand upon the findings from animal studies. The neural circuitry for Go processes has been proposed to include the motor pathway involving supplementary motor area, putamen, subthalamic nucleus, globus pallidus, thalamus and motor cortex, whereas stopping processes appear to rely on the interception of the motor pathway at the level of the subthalamic nucleus and globus pallidus by the right inferior frontal cortex and pre-supplementary motor area (Aron and Poldrack, 2006, Aron et al., 2007).

Impulsive behavior is characteristic of both individuals with histories of childhood maltreatment (Grilo et al., 1999; Brodsky et al., 2001, Chugani et al., 2001, Cuomo et al., 2008) and cocaine dependence (Biggins et al., 1997; Levin et al., 1998, Moeller et al., 2001). Performance on stop-signal tasks further demonstrates that cocaine abusers have decreased inhibitory control (Fillmore and Rush, 2002) relative to control subjects. It has been suggested that a longer stop-signal reaction time, a measure of inhibitory control, exhibited by cocaine dependent subjects on stop-signal tasks may be

more closely related to decreased performance monitoring than inhibitory control, *per se* (Li et al., 2006a). Although reaction time and response accuracy generally adaptively increase in response to errors or increasing task difficulty (Rabbitt, 1966), cocaine addicts showed less slowing in response to failed stops for stop signals compared with controls (Garavan et al., 2003). A follow-up study used fMRI to show that the brain regions engaged during post-error slowing consisted of parts of the prefrontal cortex (Li et al, 2008). Another human neuroimaging study found that cocaine abusers exhibited decreased activation of selective brain regions involved in inhibitory control (anterior cingulate cortex, pre-supplementary motor area, insula) during an inhibitory control task – a Go/No-Go task – relative to control subjects (Kaufman et al., 2003), implicating a disrupted functioning of these brain regions in cocaine dependence. The present study investigated the potential role of decreased inhibitory control related to childhood maltreatment as a risk factor for cocaine abuse and addiction.

An fMRI study of sex differences in a stop-signal task found that, during stop signal inhibition, males showed increased activation in the middle, medial and superior frontal gyri, cingulate cortex, insula, globus pallidus and putamen compared to female subjects (Li et al., 2006b). The reverse contrast revealed no areas where activation was greater for women than for men. However, a median split analysis comparing female subjects with fast versus slow SSRTs indicated that females activate the posterior caudate (tail) to correctly inhibit their responses (Li et al., 2006b). The results from this study suggest that men and women employ different strategies to countermand motor responses, a difference that may contribute to observed sex differences in the response of drug-addicted individuals to treatment.

Decision making under risk

Drug-addicted individuals will attempt to obtain and use drugs, despite clear, negative consequences. Cocaine self-administration studies in rats suggest that deficient reward processing may be a contributing factor to the development of cocaine addiction (Koob and Le Moal, 2001; Kreek and Koob, 1998; Robinson and Berridge, 2003). In human subjects, laboratory tasks involving gambling choices also implicate dysregulation of the perceived value of rewards in drug addiction (Grant et al., 2000; Bechara et al., 2002). Bechara and colleagues (2001) found that drug abusers persist longer in making disadvantageous decisions in a gambling task relative to controls; patients with lesions to the ventromedial prefrontal cortex make even poorer decisions compared to drug abusers. Interestingly, deficits in ventral frontal cortex activity have been associated with cocaine dependence (Goldstein and Volkow, 2002). Since reward valuation and decision making under risk are functions known to be disrupted in cocaine addicts, we explored the effects of childhood maltreatment on the neural processes related to reward valuation under conditions of risk. These processes engage an increasingly articulated set or network of brain areas, in addition to the ventromedial prefrontal cortex.

In a task of parametrically-modulated reward options and known probability, brain regions implicated in decision making under risk included the middle frontal gyrus, inferior frontal gyrus, and orbitofrontal gyrus (Rogers et al., 1999). Selection of low probability/high reward versus high probability/low reward choices was associated with activation of the anterior cingulate cortex (Rogers et al., 2004; Smith et al., 2009). Brain regions including the dorsal and ventral striatum and ventromedial prefrontal cortex were

shown to code for value of a potential choice, displaying increased activity related to potential gains and decreased activity related to potential losses (Tom et al., 2007).

The striatum has become increasingly recognized for its role in executive functions, particularly decision making. The dorsal striatum seems to be involved in learning the associations between actions and rewarding outcomes and in execution of goal-directed behavior (Balleine et al., 2007). The ventral striatum may be involved in the representation of expected reward and motivation for choosing the option with the highest predicted value (Heekeren et al., 2007). Ventral striatal activity has also been shown to code prediction error, increasing in activation following the receipt of an unexpected reward (Heekeren et al., 2007; Trepel et al., 2005), and it has been suggested that ventral striatal activity during decision making is related to its role in signaling prediction error (Hare et al., 2008; Hunt, 2008).

The lack of skin conductance response of patients with amygdala lesions to losses in a gambling task suggests that the amygdala is involved in the processing of negative outcomes in certain tasks (Bechara et al., 1999). The anterior cingulate cortex, well known for coding conflict, has also been shown to increase activity in response to monetary loss or a decrease in expected reward, with a suggested role in modifying future behavior (Fujiwara et al., 2009; Taylor et al., 2006; Williams et al., 2004).

Given the previous research regarding neural and behavioral control deficits in individuals with early life stress histories and in cocaine-dependent individuals, I hypothesized that diminished functioning of cortical and subcortical networks involved in reward valuation and inhibitory control due to early life stress contributes to an increased

vulnerability for drug addiction. This vulnerability may factor into drug use initiation and the subsequent lack of control of drug use in many early life trauma victims.

This thesis focuses on the impact of early life stress on the behavioral and neural representations of inhibitory control and decision making under risk, with a consideration of the implications of observed effects on risk for drug abuse and addiction.

METHODS

This study used a cross-sectional design to indentify behavioral and neural indicators of risk for addiction in healthy adults deemed to be "at-risk" based on early life stress histories. A cocaine-dependent group made up the second cross section, and adults with neither early life stress histories nor current or past drug abuse or dependence made up a control group. Early life stress histories were assessed using interviews and retrospective self-rating questionnaires.

Subjects

This study was approved by the Emory University Institutional Review Board (IRB), as well as the Research and Development (R&D) Committee of the Atlanta Veterans Administration Medical Center (VAMC). All subjects signed informed consents indicating that they understood and agreed to participate in the study.

Four subject populations were recruited for this study: non-drug-abusing subjects without histories of early life stress ("Controls"), non-drug-abusing subjects with histories of early life stress ("ELS group"), cocaine-dependent subjects without histories of early life stress, and cocaine-dependent subjects with histories of early life stress. For the thesis requirements from this "in-progress" study, the cocaine-dependent groups were combined into one group ("Cocaine group") as a representative population of cocaine-dependent individuals. Study subjects were identified from admissions to the Substance Abuse Treatment Program (SATP) at the Atlanta Veterans Administration Medical

Center (VAMC) and from the Emory Conte Center. To minimize the confounds posed by different drug dependencies and treatment decisions, this research focused on treatment-seeking persons with cocaine dependence.

For all subjects, the absence of drug dependencies other than cocaine and nicotine were confirmed by a SCID interview (First et al., 1997) (3 cocaine-dependent subjects were positive for alcohol dependence). Current mood, anxiety or other Axis I disorders were also assessed in this interview and subjects positive for such disorders were excluded from the study. However, lifetime histories of depression or anxiety disorders were permitted to ensure ELS subjects without drug abuse disorders were not simply resilient rather than at-risk as theoretically predicted. Other exclusion criteria were assessed based on physical exam or medical history and included a positive history of loss of consciousness of greater than 1 min, significant current or prior cardiovascular disease (hypertension, arrhythmias), HIV, diabetes, history of hospitalization within the previous six months for a medical illness, deafness, blindness or other significant sensory impairment. All subjects were free of psychotropic medication for at least 30 days at the time of fMRI acquisitions and were screened for any contraindications for fMRI studies including non-removable metal (e.g., cardiac pacemakers, bullets), medication (e.g., beta-blocker) or claustrophobia. Additionally, all females were given a urine pregnancy test to validate a lack of pregnancy.

Cocaine-dependent subjects had a diagnosis of cocaine dependence according to DSM-IV criteria. A urine screen for cocaine, as well as amphetamines, opiates, benzodiazepines, barbiturates, marijuana, phencyclidine, and tricyclic antidepressants was administered on the day of MRI acquisitions. The day of the scan occurred while in

treatment after at least one week of drug abstinence in order to control for acute withdrawal effects and treatment effects. One cocaine-dependent subject tested positive for cocaine on the day of the fMRI scan due to self-reported cocaine use two days prior. Data from this subject was included in all analyses.

Subject assessments

Interviews

- A **Structured Clinical Interview for DSM-IV Axis I Disorders** (SCID-I; First et al., 1997) was conducted for each subject to assess for the presence of Axis I disorders. Current Axis I disorders other than cocaine or nicotine dependence were considered exclusion criteria for the study.
- **The Childhood and Early Family Environment Interview** was used to assess for histories of childhood trauma related to birth complications, major accidents or illnesses, parental separation or death, parent-child interactions, physical and emotional neglect, and physical, emotional and sexual abuse. This interview is especially useful for determining the timing and nature of stressful events.

Self-rating questionnaires

The following self-rating questionnaires were completed by each subject using paper and pencil:

- **Childhood Trauma Questionnaire** – Childhood trauma histories were quantified using the abbreviated, 25-item version of the Childhood Trauma Questionnaire (CTQ, Bernstein et al., 2003). This questionnaire employs self-report ratings of the occurrence and frequency of events related to five different forms of child maltreatment: physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect.
- **Life Experiences Survey** – To control for the effects of recent adulthood stressors, the Life Experiences Survey (Sarason et al., 1978) was administered. This survey is a 43-item questionnaire that assesses for the occurrence of a variety of potentially stressful life events over the previous year, as well as a self-rating of the extent to which each event had a positive or negative impact on the subject's life.
- **The Aggression Questionnaire** – The Aggression Questionnaire (TAQ) contains 29 items that make up four scales measuring physical aggression, verbal aggression, anger, and hostility. A total score was also calculated as the sum of the four subscales (Buss et al., 2000).
- **The Hassles Scale** – The Hassles Scale indicates the presence and severity of 117 hassles that may have occurred over the previous month (Kanner et al., 1981).
- **Connors Adult ADHD rating scale** – Attention-deficit hyperactivity disorder (ADHD) symptoms were assessed using the Connors Adults ADHD rating scale – Self report: Long Version (CAARS – S:L), a 66-item self-report questionnaire (Conners et al., 1999). The CAARS measures inattentive symptoms,

hyperactivity, impulsivity, problems with self-concept, DSM-IV inattentive symptoms, DSM-IV hyperactive symptoms, and total ADHD symptoms. There is also an inconsistency index, which helps to identify random or careless responding.

- **The Beck Depression Inventory** – The Beck Depression Inventory (BDI) is a 21-item self-report instrument used to determine the severity of depression symptoms (Beck et al., 1961).
- **The Barratt Impulsiveness Scale** – The Barratt Impulsiveness Scale, 11th version (BIS-11; Barratt, 2000) is 30-item self-report measure of impulsive personality traits related to attention, motor impulsivity, self-control, cognitive complexity, perseverance, and cognitive instability. Three second-order factors are also assessed: attentional impulsiveness, motor impulsiveness, and nonplanning impulsiveness. A total score was obtained by summing the scores on the first-order factors (Patton et al., 1995).
- **The NEO-Five Factor Inventory** – The NEO-Five Factor Inventory (NEO-FFI) consists of 60 items that measure five personality factors: extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience (Costa Jr. and McCrae, 1992).
- **The Personality Diagnostic Questionnaire** – The Personality Diagnostic Questionnaire-4th Edition (PDQ-4) is a 99 item true-false questionnaire which assesses for DSM-IV personality disorders (Hyler, 1997).

Pre- and Post-scan ratings

Two questionnaires were administered both immediately prior to and immediately following the scan:

- **Spielberger State-Trait Anxiety Inventory** The State-Trait Anxiety Inventory (STAI; Spielberger, 1983) was used to distinguish between a subject's feelings of anxiety as a situational state or as a general trait. There are two (state and trait) 20-item scales.
- **The Positive Affect Negative Affect Scale** – The Positive Affect Negative Affect Scale (PANAS) is a 20-item self-report questionnaire that was used to measure the emotional states that the subject was feeling at the moment. It provides a score for both negative and positive emotions (Watson et al., 1988).

Tasks

Stop-signal task: While lying in the scanner, subjects performed a task of inhibitory behavioral control (Figure 1). Subjects viewed a screen on which random alphabetical letters were displayed one at a time. Each letter was presented for 1 second, with a fixed inter-stimulus interval of 3 seconds. Subjects were instructed to press a button on a response box as quickly as possible following the onset of the presentation of the letter (the "go signal"). In 25% of the trials, determined randomly, a white box (the "stop signal") appeared around the letter at a variable time following the onset of the go signal.

The subjects were instructed to withhold their response to the go signal whenever the white box appeared. The delay of the stop signal was varied depending on subject performance, such that a correct inhibition of a response caused the delay of the stop stimulus to increase by 50 ms (making it harder to inhibit the next response), and an incorrect response during a stop trial decreased the stop signal delay by 50 ms (making it easier to inhibit the next response). The stop signal delay was initially set at 250 ms. There were 300 trials, of which 75 were stop trials. The variability of the stop-signal delay in response to subject performance was intended to allow each subject to correctly inhibit a response approximately 50% of the time. Therefore, the average stop-signal delay was different for each subject but the level of stopping difficulty was controlled. Subjects practiced the task outside the scanner prior to the scan until they understood the task.

Roulette Task: While lying in the MR scanner, subjects performed a task of decision-making under risk (Figure 2). Each subject was told that they had $20.00 to start the task and this amount was displayed on the top of the screen at the beginning of the task. A roulette-style wheel with six equal sections appeared at the beginning of each trial, of which two sections were one color (red or blue) and displayed a certain monetary reward and four sections were a different color (red or blue) and displayed a different monetary reward, yielding a more likely and a less likely outcome The reward contingencies for each trial were pseudo-randomized so that subjects' choice of a color would decide between one of the following pairs of reward contingencies: $0.00 vs. $2.00, $0.20 vs. $1.80, $0.40 vs. $1.60, $0.60 vs. $1.40, $0.80 vs. $1.20 and $1.00 vs. $1.00, where the

larger reward was always displayed on the color represented by the least likely outcome. Additionally, for each trial, the subject chose under conditions of a bet of either $0.50 or $1.00 that a "roulette ball" would land on one of the two colors. The amount of the bet was predetermined by the computer and was represented by a coin displayed in the center of the wheel. The time it took to make a color selection (no time limit imposed) constituted the decision making phase of the task. Following a decision, the anticipation phase of the task would commence in which a white ball would spin around the roulette wheel and stop on one of the sections. A correct guess added the monetary reward associated with the chosen color to the subject's "total" shown on the top of the screen and resulted in the display of the word "win" with the amount won. An incorrect guess resulted in the loss of the bet from the total and feedback was displayed as the word "lose" and the amount of the bet. The revelation of the loss or gain results was considered the outcome phase of the task. This design allows the separate consideration of whether childhood maltreatment influences the neural representation of discrete aspects of risk choice related to decision making, anticipation or receipt/omission of reward,

Sensory-motor control trials consisted of $0.00 displayed on all sections, regardless of color, and a $0.00 bet (a coin with 0 cents printed on it). The ball rolled around the roulette wheel as with every other trial following a decision, and the outcome of the trial was displayed as either "lose $0.00" or "win "$0.00," depending on the outcome. The subject was assured before the start of the task that their decision during such trials could never affect their total earnings. A 10-trial practice session allowed each subject to become fluent with the task prior to the scan. Subjects' understanding of the

task was confirmed verbally at the completion of the practice session, and the option was always given to complete an additional practice session if desired.

Each of the six combinations of reward contingencies, in addition to control trials, was presented eight times, with four of each of the reward trials requiring a $0.50 bet and four requiring a $1.00 bet, giving a total of 56 consecutive trials. Each subject performed the 56 trials twice. ELS and Control subjects were awarded the nearest whole dollar amount earned in both runs of the task. The cocaine-dependent subjects were compensated in vouchers that could be redeemed for food, clothing, and other goods at the VAMC.

Image Acquisition

Images were acquired on a Siemens Magnetom Trio 3T whole body MRI scanner with TIM gradients (Siemens Medical Solutions, Inc., Malvern, PA, USA). T2*-weighted images were acquired using a gradient echo-planar (EPI) pulse sequence (34 axial slices, matrix = 64 x 64, FOV = 192 mm, slice thickness = 3 mm, gap = 1 mm gap, TR = 2.0 sec; TE = 30 ms; flip angle = 90°, voxel size = 3 x 3 x 3 mm^3). Subjects responded to the tasks on a button box using their dominant hand. The task order of the experiment consisted of the first run of the Roulette Task, the stop-signal task, and then the second run of the Roulette Task. Total scan time was approximately 50 minutes.

Data Analysis

Behavioral data analysis

All statistical tests of behavioral data were performed using SPSS Statistics 17.0 software.

Stop-signal task: The following behavioral outcomes were calculated for each subject: percent successful stops on stop trials, mean reaction time on go trials, mean stop-signal delay, stop-signal reaction time, percent reaction time decrease for go trials following a stop signal (post-signal slowing; PSS), percent reaction time decrease for go trials following a correct stop (post-correct stop slowing; PCSS), and percent reaction time decrease following an error of commission on stop trials (post-error slowing; PES). These measures were compared between Control, ELS, and Cocaine groups by one-way analysis of variance with a Dunnett post hoc test of main effects. Independent samples t-tests were used to assess sex differences.

Stop-signal reaction time (SSRT), a measure of stopping latency, was calculated as described by Logan and Cowan (1984). The average stop-signal delay for an individual was subtracted from a percentile go reaction time. Go reaction time was adjusted using the percent failed stops on stop trials. For example, if a subject correctly inhibited responding on 50% of stop trials, the percentile go reaction time would simply be the median reaction time. If only 40% of stop trials were inhibited (60% failed stops), then the 60^{th} percentile go reaction time would be used.

Post-signal slowing, a measure of behavioral adaptation to stop signals, was calculated as the percentile difference in go trial reaction time following a stop signal compared to go trials that did not follow a stop signal. Post-signal slowing is composed of both slowing following failed stops (post-error slowing) and slowing following successful stops (post-correct stop slowing). Post-error slowing as a measure of behavioral adaptation to failures to withhold responding was calculated as the percentile difference in go trial reaction time following a failed stop compared to go trials that did not follow a stop signal. In order obtain a broader understanding of the behaviors related to post-signal slowing, given that this measure is composed of differing proportions of post-error trials and post-successful stop trials depending on the individual, a post-correct stop slowing measure was also calculated. Post-correct stop slowing was calculated as the percentile difference in go trial reaction time following a successful stop compared to go trials that did not follow a stop signal.

Exploratory analyses were conducted to assess ELS versus Control group differences for males only and females only in order to preliminarily explore sex-specific effects of ELS on response inhibition.

Roulette Task: A one-way analysis of variance (ANOVA) and a Dunnett post-hoc test was performed to test for group differences in the percentage of trials that subjects in the Control group versus the ELS group and Cocaine group chose the most likely outcome out of the 96 decision-making trials that made up the two runs of the Roulette Task. A two-way repeated measures ANOVA assessed the effects of group on the percentage choice of the most likely outcome across the six levels of reward contingencies.

Exploratory analyses were conducted using the above methods to assess for group differences for males only, as well as ELS group females versus Control group females only in order to assess sex-specific effects of ELS on decision making under risk.

fMRI data analysis

Data preprocessing and statistical analyses were performed using Statistical Parametric Mapping version 5 (SPM5) software (Wellcome Department of Imaging Neuroscience, University College London, U.K.). Image preprocessing involved slice timing, realignment, normalization, and smoothing using an 8 mm^3 full width at half maximum (FWHM) Gaussian kernel. Statistical analysis methods were either one-sample t-tests (decision making epoch for activations for individual groups), multiple regression analyses (CTQ total scores), or independent sample t-tests (all others), unequal variances assumed, with age and sex as covariates.

Stop-signal task: For the Stop-signal task, five first-level contrasts were conducted and compared at the second-level between the Control group and ELS group as well as between the Control group and Cocaine group: Go, Successful Stops (successful withholding of a response to a stop signal), Failed Stops (errors of commission during stop trials), Successful Stops > Go trials and Failed Stops > Go trials.

A total CTQ score was computed and used as a regressor in regression analyses to determine the effects of the degree/severity of childhood maltreatment in a combined

Control and ELS group (N=24) on the contrasts Successful Stops > Go and Failed Stops > Go, controlling for age and sex.

Roulette Task: Contrasts for the Roulette Task consisted of the decision making versus control ($0) trials, the decision making period parametrically modulated by reward contingencies for the least likely outcome, the anticipatory period modulated by the potential reward, the anticipatory period modulated by the bet, winning outcomes, and losing outcomes.

The CTQ total score was also used in linear regression analyses in a combined Control and ELS group (N=26) to determine the effects of the degree of childhood maltreatment on the decision making trials versus control trials contrast as well as decision making trials modulated by reward contingencies, while controlling for age and sex.

RESULTS

Subjects

Fifteen control subjects and 11 subjects with histories of early life stress were enrolled in the study (Table 1). The ELS and Control groups were matched for age (control: 30.1 ± 8.4 years, ELS: 30.9 ± 8.0 years; mean ± SD), sex (control: 8 male, 7 female; ELS: 5 male, 6 female), race (control: 8 Caucasian, 5 African American, 1 Asian/Pacific Islander, 1 Middle Eastern/Asian; ELS: 4 Caucasian, 4 African-American, 2 Hispanic), and education (control: 16.2 ± 1.3 years, ELS: 16.4 ± 2.1 years; mean ± SD). A third group of cocaine-dependent subjects consisted of eleven African-American males (age: 50.6 ± 4.7 years; education: 13.2 ± 1.9 years; mean ± SD). Data collected using self-report questionnaires is also reported in Table 1 (Note that data is missing from four of the cocaine-dependent subjects). Of the seven cocaine-dependent subjects for which early life stress data was available, one subject was identified as having a history of childhood trauma. Due to limited numbers of cocaine-dependent subjects without childhood trauma histories, any results concerning this population are reported as a combined cocaine-dependent group, regardless of early life stress status.

Stop Signal Task:

Behavioral results

Data from one ELS subject, one Control subject, and two cocaine-dependent subjects were omitted from behavioral and fMRI analyses due to incomplete or inadequate task response data. An additional cocaine-dependent subject was omitted from the fMRI analysis due to excessive head motion. All three omitted cocaine-dependent subjects had negative early life stress histories.

There were no group differences in stop-signal reaction time (Figure 3). There were also no significant differences between groups on percent correct stops, post-signal slowing, post-correct stop slowing, or post-error slowing (Table 2). However, a paired t-test indicated that Control subjects slowed significantly more following errors of commission compared with successful stops ($p = 0.005$), whereas the same analysis found no significant differences between these measures in the ELS group ($p = 0.991$) or the cocaine-dependent subjects (0.887).

Exploratory analyses indicated significant sex differences in task performance measures. A separate analysis of only female subjects revealed significant differences between ELS and Control groups in post-signal slowing (Control: 5.7 ± 1.9%, ELS: 21.3 ± 9.2%; mean ± standard deviation; $p = 0.003$), post-correct stop slowing (Control: 0.7 ± 9.1%, ELS: 21.3 ± 13.4%; mean ± standard deviation; $p = 0.014$), and post-error slowing (Control: 9.3 ± 6.3%, ELS: 24.4 ± 7.6%; mean ± standard deviation; $p = 0.006$), where ELS subjects exhibited greater adaptive slowing tendencies. Although ELS females had a

longer mean SSRT (212 ± 61 ms) than Control females (168 ± 50 ms), this difference was not statistically significant (p = 0.234) (Figure 4, Table 3).

While ELS was associated with greater slowing and slightly longer SSRTs in female subjects, an opposite pattern of effect of ELS was seen for male subjects. Control males displayed significantly greater slowing following errors on stop trials compared to ELS males (Control: 22.3 ± 10.9%, ELS: 6.4 ± 8.1%; mean ± SD; p = 0.012). Other measures of slowing were not significantly different between groups. There was also no significant difference in SSRT between ELS males (175 ± 68 ms) and Control males (183 ± 54 ms) (Figure 4, Table 3).

Slowing following stop trials was greater in Control males compared to the all-male Cocaine group (Control: 17.1 ± 3.1%, Cocaine: 7.5 ± 8.4%; mean ± SD; p = 0.010). The Control males slowed more than the Cocaine group following failed stops (Control: 22.3 ± 10.9%, Cocaine: 8.0 ± 7.0%; mean ± SD; p = 0.005) but not following successful stops (Control: 10.9 ± 9.1%, Cocaine: 7.1 ± 17.5%; mean ± SD; N.S.). There was no significant difference in SSRT between the Cocaine group (170 ± 63) and Control males (183 ± 54) (Table 3).

Given the preliminary sex-specific effects of early life stress status on adaptive slowing behavior, separate correlation analyses for males and females were used to determine the influence of severity of childhood maltreatment on task behavioral measures. For Control and ELS males combined, there were no significant correlations between total CTQ scores and measures of slowing or stop-signal reaction time. For females, total CTQ scores significantly correlated with post-signal slowing (R= 0.672, p = 0.023) and post-correct stop slowing (R= 0.715, p = 0.013), but not post-error slowing

(R = 0.463, p = .152). These results provide evidence that childhood maltreatment in females can affect adaptive behavior in adulthood.

When the Control and ELS groups were combined and the behavioral data analyzed to compare sexes, no differences between males and females were found in SSRT (p = 0.751, N.S.), PES (p = 0.742, N.S.), PSS (0.842, N.S.), or PCSS (0.965). However, there were significant within- group sex differences, where ELS females slowed more than ELS males following stop trials (p = 0.050), especially for failed stops (p = 0.007). Conversely, Control males demonstrated greater slowing than Control females on the same measures: PSS (p = 0.018) and PES (p = 0.025) (Table 3).

fMRI results

Significant group differences were noted for the blood oxygen level-dependent (BOLD) responses for Go trials (Table 4), and for both Successful Stops (Table 5) and Failed Stops (Table 6) at a statistical threshold of $p < 0.005$ and $k \geq 20$.

For Go trials, the Control group activated the medial (polar) prefrontal cortex more than the ELS group. The ELS group displayed extensive activations that were greater than the Control group during Go trials in the left inferior frontal cortex (BA 44), thalamus, caudate, bilateral precentral gyrus, left putamen, right inferior parietal cortex, and precuneus. There were no activations related to Go trials which differed between the Control group and Cocaine group.

For Successful Stops, the Control group exhibited greater activations in the medial (polar) prefrontal cortex and precuneus compared to the ELS group. Activations

were greater for the ELS group relative to Controls in the right thalamus and caudate nucleus (associative striatum). The Control group activated the bilateral inferior parietal lobules, middle temporal gyrus, and left precuneus more than the Cocaine group.

For Failed Stop trials, the Control group activated the medial (polar) prefrontal cortex more than the ELS group. Greater activations were seen for ELS subjects compared to Control subjects in the precuneus and left precentral gyrus. A greater activation was also seen in the Cocaine group in the right precentral gyrus compared to the Control group.

For Successful Stops > Go, the Cocaine group exhibited significant activations in the left posterior superior temporal sulcus and superior temporal gyrus (Table 7a). No significant clusters were identified for the Successful Stops > Go contrast for the Control or ELS groups using a statistical threshold of $p < 0.005$ and $k \geq 20$

Significant group differences were, however, noted for neural responses related to response inhibition (Table 7b). Controls showed a significantly greater activation relative to ELS subjects for Successful Stops > Go trials in the right inferior frontal gyrus (pars triangularis). However, the ELS group exhibited significantly greater activations than the Control group in the posterior cingulate cortex and bilateral thalamus. The Control group activated the middle and superior temporal gyri, as well as the right insula, more than the Cocaine group for Successful Stops > Go trials.

Early life stress, estimated using CTQ total scores, was treated as a continuous variable across both ELS and Control groups. For the regression analysis of CTQ total scores and the contrast of Successful Stops > Go, lower CTQ scores were associated with greater activation in the right inferior frontal gyrus/middle frontal gyrus and the left

inferior parietal lobe (Table 9a).

Significant group activations for error processing, represented by the contrast Failed Stops > Go, are reported in Table 8a at a statistical threshold of $p < 0.005$ and $k \geq 20$. Whereas the Control group activated the left caudate nucleus, left amygdala, right putamen, bilateral inferior frontal gyri, and left middle frontal gyrus for the Failed Stops > Go contrast, the Cocaine group activated the left caudate nucleus, right globus pallidus, thalamus, right putamen, and the left amygdala. No significant clusters of activation were identified for the Failed Stops > Go contrast for the ELS group.

Significant group differences were also identified for neural responses related to error processing (Table 8b). Controls showed a significantly greater activation relative to ELS subjects for Failed Stops > Go trials in the right inferior frontal gyrus, dorsal and ventral striatum, and a cluster spanning the right insula, precentral gyrus and inferior frontal gyrus (pars operculum). There were no significant clusters for which ELS subjects exhibited greater activations than Control subjects. However, significant clusters were identified in the bilateral ventral striatum for the Cocaine group compared to the Control group (Table 8b).

The regression of CTQ total scores on the contrast of Failed Stops > Go revealed greater activation of the right insula and left putamen with decreasing CTQ scores (Table 9b).

Roulette Task

Behavioral results

Control subjects earned an average of $54.92, ELS subjects earned an average of $53.01, and cocaine-dependent subjects earned an average of $55.40 over the two runs of the Roulette Task (There were no statistically significant group differences).

There was no significant difference between subject groups in percentage choice of the most likely outcome across all reward trials at a significance level of $p = 0.05$ (Controls: 61.9%; ELS group: 54.7%; Cocaine group: 56.7%). Controls were more likely than cocaine-dependent subjects to choose the most likely outcome for the $0.80/$1.20 reward contingency ($F(2,34) = 3.768$; $p = 0.030$, Dunnett post-hoc test). However, there were no other significant group differences in the impact of varying risk on percentage choice of the most likely outcome for any other reward contingencies (Fig. 5). In an exploratory analysis of sex differences in the effects of early life stress on decision making under risk, no differences were revealed between ELS females and Control females for any levels of reward contingencies (Fig. 6). However, compared to ELS males, Control males were more likely to choose the most likely outcome for the choices between $0.80 and $1.20 ($F(2,21) = 5.083$; $p = 0.031$, Dunnett post-hoc test) and between $0.60 and $1.40 ($F(2,21) = 3.304$; $p = 0.034$, Dunnett post-hoc test) (Fig. 7a). Control males were also more likely than cocaine-dependent males to choose the most likely outcome for the $0.80/$1.20 reward contingency ($F(2,21) = 5.083$; $p = 0.018$, Dunnett post-hoc test) (Figure 7b). Thus, early life stress is associated with more risky choice

behavior in males.

fMRI results

An initial contrast analysis sought to isolate the group-level neural correlates of the influence of risk on choice behavior. In healthy comparison subjects, the contrast of decision-making trials versus control trials revealed bilateral clusters in the ventral striatum ($p < 0.01$, $k \geq 20$) (Fig. 8, Table 10). The same contrast for ELS subjects revealed extensive activations involving midbrain, precentral gyrus, superior/medial frontal gyrus/supplementary motor area, superior temporal gyrus, cingulate gyrus, parahippocampal gyrus, and visual and somatosensory cortex (Fig. 9, Table 10), whereas cocaine-dependent subjects activated premotor and motor cortex, thalamus, lingual gyrus, and superior temporal gryus/insula regions (Figure 10, Table 10).

An independent samples t-test of the same contrast comparing healthy controls to individuals with early trauma histories (Controls greater than ELS and ELS greater than Controls) revealed no significant clusters at a threshold of $p < 0.005$, $k \geq 20$. There was also no significant difference at this threshold between the Control group and Cocaine group for decision making > control trials.

Given the sex-specific differences in decision making observed in the behavioral data, exploratory sex-specific analyses of the imaging data were carried out for the decision making component of the Roulette Task. The comparison of Control males versus ELS males identified a cluster in the medial frontal gyrus with significantly greater activation in the Control males (MNI coordinates -3, 36, 39; $p < 0.01$; $k = 23$).

The same comparison for females identified a cluster in the right ventral striatum that was greater in Control versus ELS females (MNI coordinates 18, 6, -6; $p < 0.005$, $k = 11$).

Further analysis of the influence of risk on decision making explored neural activations related to the changing levels of reward contingencies or risk. For Control subjects, the first level contrast of decision making modulated by reward for the least likely outcome identified clusters in the dorsomedial prefrontal cortex, mid-cingulate gyrus, and bilateral posterior parietal cortex ($p < 0.01$, $k \geq 20$) (Table 11a). There were no significant clusters for the same parametric analysis for the ELS or Cocaine groups at the same threshold.

The second level contrast of Controls greater than ELS subjects for decision making modulated by reward contingencies revealed a cluster in the right ventral striatum ($p = 0.01$, $k \geq 10$) (Table 11b). No clusters survived the same threshold for contrast of ELS subjects greater than Control subjects. Relative to the cocaine-dependent subjects, the Control group exhibited greater neural representation of decision making modulated by reward contingencies for the supplementary motor area, left insula, right anterior cingulate cortex, ventrolateral prefrontal cortex, and dorsomedial prefrontal cortex (Table 11b).

Regression analyses identified brain regional activations during risk-biased decision making that were modulated by the severity of childhood maltreatment. For the decision making versus control trial contrast, increasing CTQ scores were associated with increasing activation of the medial frontal gyrus, ventral anterior cingulate cortex, caudate, left inferior frontal gyrus, left insula, right middle and left superior temporal gyri, and inferior and superior parietal lobules (Table 12). For the same contrast,

decreasing CTQ scores were associated with increased activation of the dorsal striatum, left and right middle frontal gyri, left superior frontal gyrus, right inferior frontal gyrus, posterior cingulate cortex, precuneus, and middle occipital gyrus (Table 12).

Regression analyses for decision making modulated by reward contingencies revealed no brain regions that were linearly related to CTQ total scores.

Second level contrasts for the *anticipation* period revealed one cluster in which the Control and ELS group differed. For the anticipation of reward, the Control group exhibited a greater activation of the right precentral gyrus (MNI coordinates 33, -27, 54; $p < 0.005$, $k = 24$) compared to the ELS group. There were no differences in neural responses related to reward anticipation between the Control and Cocaine groups.

For trials in which the *outcome* was a win, Control subjects activated the supplementary motor area, pre-supplementary motor area, right globus pallidus, cuneus, right precentral gyrus, and mid-cingulate cortex more than ELS subjects (Table 13). The pattern of activation for loss outcomes closely resembled that for wins for the contrast of Controls greater than ELS, and included the supplementary motor area, bilateral globus pallidus, right precentral gyrus and cuneus (Table 13).

The comparison of the Control group with the Cocaine group revealed greater activations for win outcomes in the cocaine-dependent individuals in the left inferior frontal gyrus, insula, and cingulate regions (Table 14). A similar but more extensive pattern of activation was apparent for the contrast of the Cocaine group > Control group for loss outcomes, which included parahippocampal gyrus, inferior frontal gyrus, precentral gyrus, cingulate gyrus, and cuneus (Table 14).

DISCUSSION

The findings of this study suggest that early life stress histories affect the behavioral and neural representation of response inhibition and decision making under risk, with the most pronounced effects being sex-specific. While ELS females exhibited more pronounced adaptive slowing in the stop-signal task than Control females, Control males displayed greater slowing following errors of commission than ELS males. On the other hand, group behavioral differences on the Roulette Task were evident in male subjects but absent in female subjects. Results from the fMRI data also suggest that early life stress may alter the neural basis of inhibitory control and decision making under risk.

Response Inhibition: Stop-signal task

Consistent with the finding of Garavan and colleagues (2003), cocaine addicts in this study showed less slowing in response to failed stops for stop signals compared with controls. Cocaine addiction is thus associated with a lesser influence of error detection and processing on the adaptation of behavior. Similarly, male subjects with early life stress histories also exhibited significantly less slowing than controls following failed stops. Furthermore, only the Control group showed a behavioral distinction between correct and incorrect responses to stop trials. These findings could indicate either a lack or awareness of committed errors (Hester et al., 2009) or an impairment in implementing adaptive slowing behaviors. However, the Cocaine group and male ELS group did not have significantly different stop-signal reaction times than the Control group. This

finding fits consistently with the contention of Li et al. (2006a) that longer stop-signal reaction times sometimes observed in cocaine addicts are most closely related to deficits in adapting to task errors. These results support the proposed link between early life stress and inhibitory control processes – performance monitoring, specifically – as a risk factor for cocaine addiction in men. Deficits in performance monitoring and error processing in drug abusers have been reported by a number or studies (Kauffman et al., 2003; Foreman et al., 2004; Li et al., 2006a; Hester et al., 2009). However, this is the first study, to my knowledge, in which deficits in behavioral slowing have been observed in individuals with early life stress histories that are at risk for drug use disorders.

Female subjects with early life trauma histories, on the other hand, slowed more in response to errors, as well as to correct stops, than did their Control counterparts and had non-significantly longer stop-signal reaction times. Control females also slowed less than Control males following stops trials and errors of commission. An interpretation of these results would imply that females typically have poorer behavioral control compared to males, and that childhood stress may induce a hypervigilant state associated with greater restraint on behavior for females. Indeed, an fMRI study of healthy control subjects by Li and colleagues (2006b) found than males had greater cortical and subcortical activations than females during a stop-signal task, whereas the opposite contrast revealed no significant clusters. The above study did not report sex differences in stop-signal reaction time or post-error slowing, potentially because it did not control for important contributing variables such as early life stress history; the present study may be the first to report sex differences in the behavioral aspects of the stop-signal task.

Whether or not female cocaine addicts display deficits in inhibitory control has

yet to be studied. Therefore, it remains to be determined whether the effects of early life stress on inhibitory control in females could contribute to a risk for addiction.

The stop-signal task revealed greater activations in the medial prefrontal cortex (Brodmann Area (BA) 10) for Control subjects versus ELS subjects for Go trials, correct stop trials, and failed stop trials. Evidence from patients with medial frontal lobe lesions highlights the importance of this brain region for response inhibition, as these patients make increased errors of commission (Drewe, 1975; Leimkuhler and Mesulam, 1985). This region has been hypothesized to be involved in biasing attention towards external stimuli requiring fast responses (Gilbert et al., 2006), consistent with the demands of a stop-signal task. The deficits in medial prefrontal cortical activations observed in this study imply that it may be a neurodevelopmental target of childhood stress. This prospect is supported by the fact that the prefrontal cortex continues to develop throughout childhood (Fuster, 2002) and is involved in the regulation of the HPA-axis stress response and therefore a target of stress hormones (Azra and Seema, 2007; Diorio et al., 2003). The medial prefrontal cortex has also been implicated in drug addiction and relapse (Volkow et al., 2005; Grusser et al., 2004; Park et al., 2002). Decreased functioning in this region in the ELS subjects, therefore, may represent a risk factor for addiction.

The ELS group displayed greater activations than the Control group during Go trials in a number of regions involved in motor response initiation and execution, including the thalamus, caudate nucleus, precentral gyrus, and putamen. These activations may be related to a stronger commitment to go processes, faster go response times, and consequently, the greater number of errors of commission seen in the ELS

group.

Control subjects showed significantly greater activation compared to ELS subjects for Successful Stops > Go in the right inferior frontal gyrus, a region believed to be crucial for inhibitory control (Aron et al., 2004; Aron et al., 2003a). Moreover, the functional response of this region exhibited an inverse linear relationship with total CTQ scores during successful stopping, lending further support to the role of early life stress in negatively impacting inhibitory control processes in the brain. Theoretically, the diminished ability to engage this critical brain region in response to demands for inhibiting response tendencies (e.g., impulsive drug use) underlies the predisposition of individuals with childhood maltreatment histories to drug abuse and addiction.

For Failed Stops > Go, the Control group showed greater activation than the ELS group in the caudate/globus pallidus and right insula/inferior frontal gyrus regions. The insula has been implicated in error awareness (Klein et al., 2007; Hester et al., 2009) as well as post-error slowing (Li et al., 2008). The caudate nucleus has a known role in certain inhibitory control tasks (Aron et al., 2003b, Vink et al., 2004) and is therefore believed to not only be involved in execution of motor responses but also inhibition of responses. Cortico-striatal-thalamic loops are important components of behavior, and inhibitory control is believed to involve a loop of projections between the lateral orbitofrontal cortex, ventromedial caudate, medial globus pallidus, and thalamus (Cummings, 1993). The striatum, and its dopaminergic innervations, are also implicated in the coding of violations of expected outcomes as prediction error signals, which are, in turn, critical to the recruitment of behavioral adaptations that constitute learning. The evidence from this study suggests that Control subjects are better able to recruit this

network compared to ELS subjects in order to successfully adapt their behavior during failed stop trials.

Consistent with the Control and ELS group differences for the Failed Stops > Go contrast, the regression analysis of CTQ total score and Failed Stops > Go revealed an inverse relationship between CTQ scores and activation of the right insula and ventral striatum. This suggests that the impact of childhood maltreatment on adaptive behavior following error detection is mediated through its effects on the insula and striatum. The results also support a dose-effect relationship such that more severe childhood maltreatment is associated with increasing neurodevelopmental deficits in this neural network.

As opposed to the ELS group, for the contrast of Failed Stops > Go, the Cocaine group activated ventral striatum more than the comparison subjects. This result is in opposition to my hypothesis that the ELS group and the Cocaine group would show similar neural deficits in inhibitory control. The effects observed in the ELS group and in the regression analysis point to specific costs of early life stress on inhibitory control networks that are not seen in cocaine-dependent subjects (most of whom lack significant childhood maltreatment histories). On the contrary, cocaine addiction appears to enhance the response of the ventral striatum to errors of commission. The lack of behavioral slowing in response to failed stops, however, suggests that there is a dissociation in this group between neural responses to errors and implementation of behavioral changes, the former involving the ventral striatum and the latter perhaps depending on the insula (Li et al., 2008).

Differences between the Cocaine group and the Control group were not as

extensive as for the ELS group versus Control group. The results for these comparisons should be viewed with caution, particularly with regards to potential Type II error, as only 8 cocaine-dependent subjects provided usable stop-signal task data.

Influence of risk on choice behavior: Roulette Task

Although subjects in the ELS and Cocaine group were slightly more likely to choose the less likely (riskier) outcome than the Control group, the differences were most significant for the $1.20 vs. $0.80 choice. The fact that the difference was most evident at for this particular choice suggests that the ELS males and cocaine-dependent subjects are more willing to make a risky decision (choice of $1.20) at a lower relative potential reward value than are male control subjects. In other words, the curve of the graph of percent choice of most likely outcome across reward values (risk levels) drops off quickly for the Cocaine and ELS groups at the $1.20 vs. $0.80 decision but drops off for Control subjects at the $1.40 vs. $0.60 decision.

The activations for control subjects during the decision-making period of the Roulette Task were concentrated primarily in ventral striatal regions and to a lesser extent, in the dorsal striatum. On the other hand, activations for the ELS group were diffuse but involved strong visual cortex activations, whereas the Cocaine group primarily activated motor cortex. Surprisingly, this task did not activate any of the expected prefrontal regions, i.e. orbitofrontal cortex or dorsolateral prefrontal cortex, typically seen in decision making tasks (Rogers et al., 2004). The involvement of the striatum in decision making has been suggested to revolve around the deliberation of

risky responses (Matthews et al., 2004), the coding of choice values and motivation (ventral striatum, Wickens et al., 2007), and goal-directed action selection and initiation (dorsal striatum, Balleine et al., 2007). A lack of frontal activations could be related to a transition from reflective to automated decision making (Daw et al., 2005), as each of the choices was repeated 16 times over the course of the two runs of the task.

Although the females in the Control and ELS groups did not exhibit significant behavioral differences in the Roulette Task, results from the imaging data indicate a effect of early life trauma on engagement of the right striatum during decision making under risk. For males, a group difference was observed in the medial frontal gyrus, where Control males had a greater activation. This region is known to be critical for decision making (Rushworth et al., 2007), and may be related to a greater response conflict in the Control males versus ELS males (Ridderinkhof et al., 2004). As an extension of this monitoring role, the medial frontal cortex is also believed to signal a need for increased cognitive control and behavioral flexibility (Ridderinkhof et al., 2004), functions that may be diminished in males with early life stress histories.

The contrast for the decision making period modulated by reward for the least likely outcome (varying risk level) was used as a measure of the processes involved in reward valuation and decision making under risk. Only the Control group showed a neural response sensitivity to changing reward contingencies, even at the low voxel-level threshold of $p = 0.01$. The Control group showed a parametric modulation of activations in the superior frontal gyrus, medial frontal gyrus, and left and right inferior parietal lobules. Previous work by Tom and colleagues (2007) has demonstrated that sensitivity of these brain regions – in addition to the striatum – to potential rewards and losses

during decision making is correlated with behavioral loss aversion. The comparison of the Control group and ELS group suggests that the right striatum is more engaged for choices under increasing levels of risk in control subjects than individuals with early life stress histories. These outcomes suggest that ELS subjects have a decreased sensitivity to the relative value of potential rewards and decreased aversion to potential losses, providing a neural basis for the greater risk-taking behavior seen in this group during decision making.

The regression analyses provide a clearer understanding of which decision making-related brain regions are most impacted by childhood maltreatment. Lower CTQ scores (less abuse or neglect) were associated with a greater engagement of a number of the frontal brain regions often implicated in decision making (Rogers et al., 1999), as well as the striatum, which the current task appears to primarily rely on. This outcome indicates that greater severity of maltreatment is related to diminished functioning of these brain regions during decision making. In contrast, increasing CTQ scores were related to greater brain-wide activations, which may indicate decreased efficiency of decision making processes.

Improper reward valuation may be a crucial risk factor for drug use and addiction. Cocaine addicts place high value on immediate reward and discount potential negative outcomes of drug abuse. In a similar manner, deficits in reward valuation may influence decision making with regard to initial drug use and/or relapse in individuals with early life stress histories. The comparison of cocaine addicts to comparison subjects in this study, however, did not reveal significant differences in striatal regions related to changing reward contingences. Rather, the Control group showed greater engagement of

a number of brain regions related to risk taking and decision making (i.e. anterior cingulate cortex, insula, medial frontal gyrus, ventrolateral prefrontal cortex) compared to cocaine-dependent subjects. While the current study does not provide evidence that these deficits are related to early life stress deficient processing of risk and reward represents another plausible risk phenotype for addiction.

Limitations

Some of the major limitations to this study include small sample sizes and the absence of key comparison groups. While the samples recruited for this study produced significant neural activations for many aspects of the two tasks and resolved several group differences in both behavioral and fMRI data, the significant sex effects that were observed in the behavioral outcomes resulted in profound within-group variability. Future work should allow sufficient numbers of subjects to stratify these samples by sex. Furthermore, the effects of ELS in females were significant for behavioral slowing measures of the stop-signal task, but the importance of these effects for addiction risk could not be determined without a comparison group of female cocaine-dependent subjects. Recruitment of separate groups of cocaine-dependent subjects based on early life stress status but matched on other variables would also have benefitted this study. The Cocaine group differed from the Control and ELS groups on two important variables: age and drug use history. It is possible that these variables affected the observed results for this group, making this sample less than ideal for comparison with the other two groups. The direct comparison of cocaine-dependent individuals that have

early life stress histories to those without such histories would provide a means to remove the effects of these confounding variables. Lastly, the ELS group was recruited to represent individuals who are at risk for developing a drug use disorder. However, the criterion that this group could not have current or a previous history of drug abuse or dependence creates the possibility that this sample is composed more of resilient rather than at-risk individuals.

Conclusions

The hypothesis that early life stress negatively affects the processes of decision making under risk and response inhibition, thereby resulting in an increased susceptibility for cocaine addiction, would be supported if the differences between the ELS and Control groups were similar to the differences between the Cocaine and Control groups. Behaviorally, this appears to be the case. Both ELS males and cocaine-dependent males displayed deficits in behavioral adaptation to errors on the stop-signal task. Additionally, both ELS males and cocaine-dependent males chose the more risky, least likely outcomes for certain reward contingencies relative to Control males. However, fMRI data did not reveal consistent similarities between Control versus ELS and Control versus Cocaine contrasts.

There are several ways to interpret the above observations. First, it is possible that early life stress alters behavior through specific neural mechanisms, and these effects were not observed in the Cocaine group because only one out of the eleven cocaine-dependent subjects had a positive history of early life stress. Nonetheless, the behavioral

effects of early life stress related to response inhibition and decision making under risk may be more important in risk for drug dependence than the underlying neural effects. It is also possible that the increased risk for addiction identified by epidemiologic studies in individuals with early life stress may be due to the effects of stress on other behaviors not tested by this study. Finally, some of the functional brain changes observed in the Cocaine group, but not the ELS group, could have occurred as a result of years of cocaine use, which is believed to alter neural systems (Koob and Le Moal, 2001). There are likely to be a number of different genetic and environmental factors in addition to early life stress that could increase risk for addiction. However, it is not clear whether each factor or interacting groups of factors increases risk though similar neural and behavioral phenotypes or whether there are perhaps multiple paths that could lead to the same outcome.

Further study of cocaine-dependent individuals will be required to determine whether there is a link between the effects of early life stress histories on response inhibition and decision making under risk and vulnerability for cocaine dependence. Additionally, the results of this study, especially concerning sex differences, remain preliminary due to the small sizes of the samples. Nonetheless, this study provides novel insight into the effects of early life stress on decision making under risk and inhibitory control, the major diagnostic hallmarks of drug abuse and addiction.

Figure 1 Schematic illustration of the stop-signal task

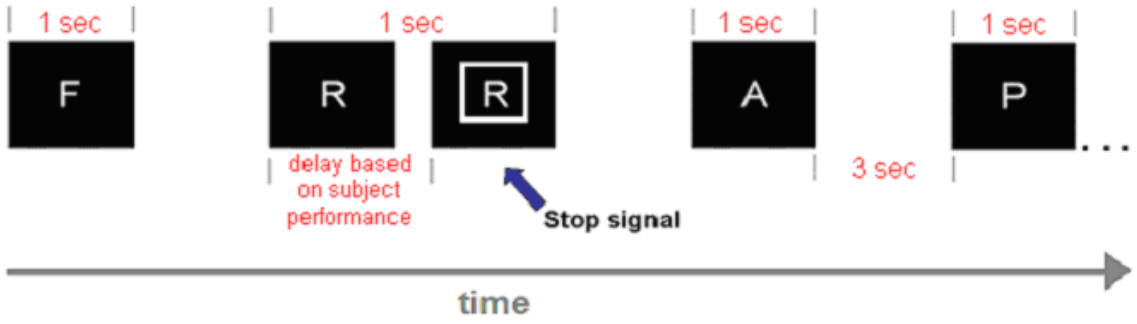


Figure 2 Schematic illustration of the Roulette Task

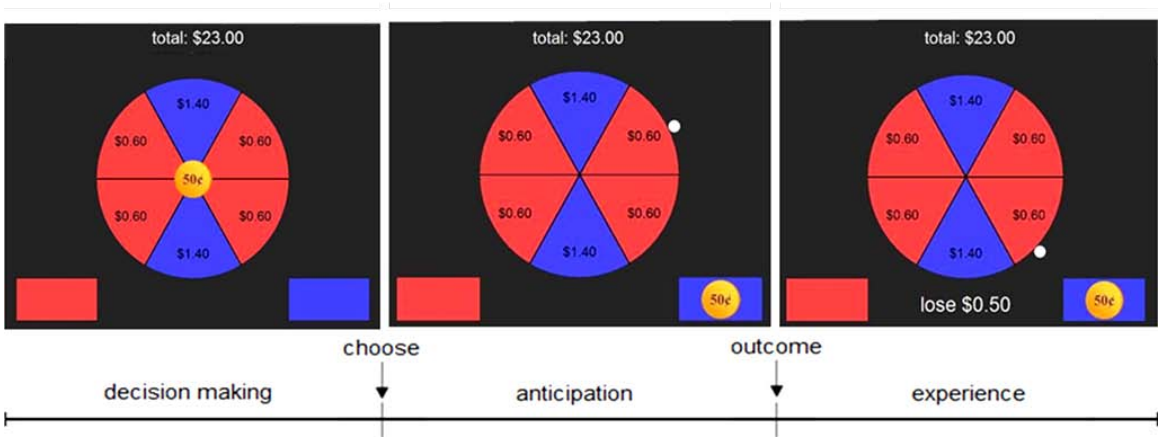


Table 1 Subject demographic, maltreatment history, and clinical variables

Demographic Data		Control	ELS	Cocaine All
	Total N	15	11	11 (7)
Age (Years)	Mean ± SD	29.5 ± 8.4	30.8 ± 7.5	50.6 ± 4.7
Sex	Male	8	5	11
	Female	7	6	0
Race	Caucasian	8	4	0
	African-American	5	5	11
	Hispanic	0	2	0
	Asian or Pacific Islander	1	0	0
	Middle-Eastern/Asian	1	0	0
Education (Years)	Mean ± SD	16.2 ± 1.3	16.4 ± 2.1	13.2 ± 1.9
Self-Report Questionnaires				
CTQ	Physical Abuse	5.5 ± 0.9	9.2 ± 3.2**	(7.29 ± 1.98)
	Emotional Abuse	5.9 ± 1.6	10.1 ± 3.4**	(9.86 ± 3.08)**
	Sexual Abuse	5.1 ± 0.3	6.0 ± 3.3	(5.14 ± 0.38)
	Physical Neglect	5.3 ±0.6	7.6 ± 3.5*	(7.00 ± 2.31)
	Emotional Neglect	5.9 ± 1.2	10.6 ± 4.0**	(10.57 ± 5.13)*
	Total	27.7 ± 2.8	43.5 ± 13.1**	(39.86 ± 10.70)*
TAQ	Physical	13.8 ± 3.9	19.4 ± 7.6*	(23.43 ± 4.79)**
	Verbal	11.2 ± 4.0	13.2 ± 5.0	(15.57 ± 2.76)
	Anger	10.6 ± 4.9	13.3 ± 6.0	(16.29 ± 2.23)
	Hostility	11.6 ± 4.5	14.5 ± 5.9	(22.86 ± 2.97)*
	Total	47.2 ± 16.1	60.3 ± 21.8	(78.1 ± 6.4)*
BDI	Total	1.2 ± 1.3	3.3 ± 3.4	(6.3 ± 6.7)*
BIS	Total	59.3 ± 11.5	61.8 ± 8.4	(71.0 ± 11.7)*
CAARS	Total	56.3 ± 39.0	56.4 ± 21.9	(79.0 ± 59.1)

* $p < 0.05$
** $p < 0.005$

Figure 3 Lack of group differences in stopping latency for the stop-signal task

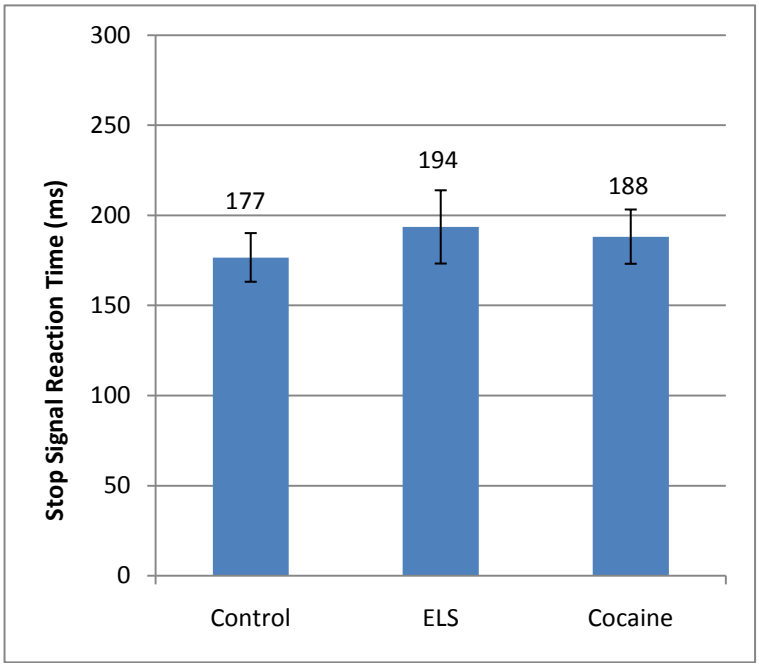


Table 2 Performance data for the stop-signal task

	Control (N=14)	ELS (N=10)	Cocaine (N=9)
Correct Stops	42.1%	37.4%	39.0%
Go Reaction Time (ms)	739	590	760
Stop-Signal Delay (ms)	582	434	610
Stop-Signal Reaction Time (ms)	177	194	170
Post-Signal Slowing	12.2%	14.4%	7.5%
Post-Error Slowing	16.8%	15.4%	8.0%
Post-Correct Stop Slowing	6.5%	15.3%	7.1%

Figure 4 Lack of effect of subject group or sex on stopping latency for the stop-signal task

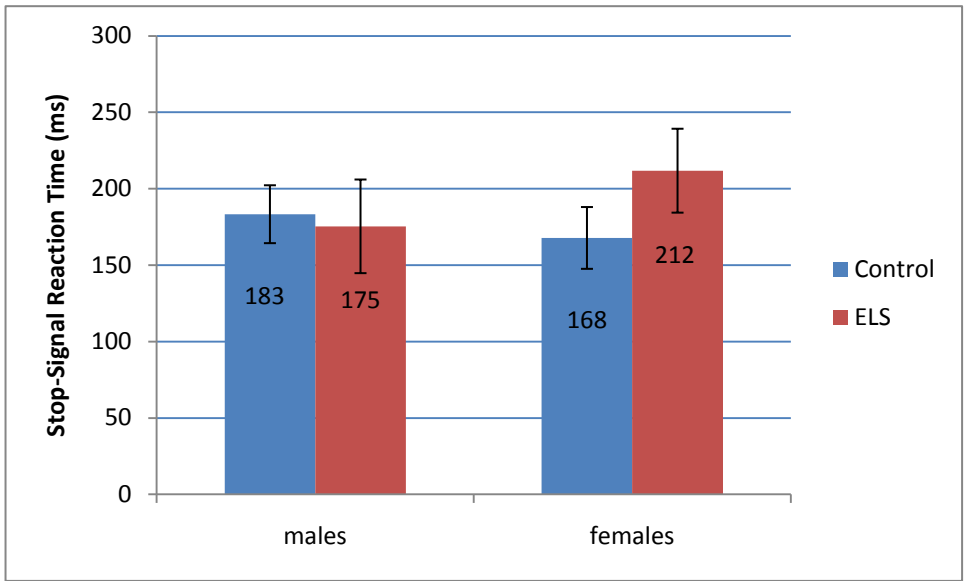


Table 3 Performance data for the stop-signal task by sex

	Control Female (N=6)	**ELS** Female (N=5)	**Control** Male (N=8)	**ELS** Male (N=5)	**Cocaine** Male (N=8)
Correct Stops	44.4%	38.5%	40.4%	36.3%	39.0%
Go Reaction Time (ms)	839	669	663	512	760
Stop-Signal Delay (ms)	683	488	506	379	610
Stop-Signal Reaction Time (ms)	168	212	183	175	170
Post-Signal Slowing	5.8%	21.3%	17.1%	7.5%	7.5%
Post-Error Slowing	9.3%	24.4%	22.3%	6.4%	8.0%
Post-Correct Stop Slowing	0.7%	21.3%	10.9%	9.3%	7.1%

Table 4 Effect of childhood maltreatment on the neural processing correlate of controlled motor responses

Go *Control > ELS*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Medial Frontal Gyrus	10	-3	57	3	28	3.22
Go *ELS > Control*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Inferior Frontal Gyrus	44	-45	12	15	45	3.88
	Thalamus		9	-6	15	144	3.58
	Precentral Gyrus	6	-30	0	36	59	3.48
	Precuneus	7	-18	-60	45	25	3.39
	Precentral Gyrus	4	57	-12	36	35	3.39
	Precuneus	7	24	-57	45	22	3.13
	Putamen		-27	-6	15	29	3.10
	Inferior Parietal Lobule	40	39	-39	42	26	3.04

Table 5 Effect of childhood maltreatment on the neural basis of response inhibition

Successful Stops *Control > ELS*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Precuneus	19	33	-84	36	22	3.19
	Medial Frontal Gyrus	10	15	63	6	18	3.01
Successful Stops *ELS > Control*			**x**	**y**	**z**	**k**	**Z**
	Thalamus		6	-9	15	53	3.21
	Caudate		3	18	12	33	3.06
Successful Stops *Control > Cocaine*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Inferior Parietal Lobule	40	45	-66	42	190	3.90
	Superior Temporal Gyrus	21	60	-3	-12	24	3.72
	Precuneus	19	-30	-66	42	35	3.32
	Inferior Parietal Lobule	39	-48	-66	39	47	3.27

Table 6 Effect of childhood maltreatment on the neural basis of error processing

Failed Stops *Control > ELS*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Medial Frontal Gyrus	10	-6	60	6	18	3.17
Failed Stops *ELS > Control*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Precuneus	7	-15	-57	42	23	3.54
	Precentral Gyrus	6	-30	-6	36	29	3.31
Failed Stops *Cocaine > Control*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Precentral Gyrus	6	33	-15	39	23	3.39

Table 7 Neural correlates of response inhibition

a. Localization of neural processing related to response inhibition in cocaine addicts

Successful Stops > Go *Cocaine*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Superior Temporal Sulcus	22	-54	-42	9	40	3.90
	Superior Temporal Gyrus	22	-51	3	0	28	3.82

b. Group differences in neural processing related to response inhibition

Successful Stops > Go *Control > ELS*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Inferior Frontal Gyrus	45	57	27	24	19	3.03
Successful Stops > Go *ELS > Control*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Posterior Cingulate	30	9	-45	21	14	3.72
	Thalamus		-6	-27	9	18	3.24
	Thalamus		6	-36	9	11	2.84
Successful Stops > Go *Control > Cocaine*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Middle Temporal Gyrus	21	57	-3	-15	31	4.14
	Superior Temporal Gyrus	42	-63	-15	12	20	3.30
	Insula	13	42	-9	12	63	3.18

Table 8 Error processing-related neural activations

a. Group-level neural correlates of error processing

Failed Stops > Go *Control*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Caudate Nucleus		-15	6	24	71	4.64
	Amygdala		-24	0	-9	52	3.81
	Precentral Gyrus	6/44	-51	9	12	24	3.66
	Middle Frontal Gyrus	47	-45	45	-6	58	3.55
	Putamen		15	9	6	212	3.49
	Inferior Frontal Gyrus	44	45	9	27	21	3.11
Failed Stops > Go *Cocaine*			**x**	**y**	**z**	**k**	**Z**
	Caudate Nucleus		-18	-12	21	50	3.94
	Globus Pallidus		27	-15	0	39	3.94
	Thalamus		18	-9	15	26	3.77
	Putamen		24	9	-3	25	3.51
	Amygdala		-21	3	-12	78	3.50

b. Group differences in the neural correlates of error processing

Failed Stops > Go *Control > ELS*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Caudate Nucleus		-18	0	24	72	4.21
	Caudate Nucleus/		9	6	3	71	3.85
	Ventral Striatum		12	3	-6		3.75
	Insula/	13	45	6	18	47	3.37
	Inferior Frontal Gyrus/	9	45	9	30		3.17
	Precental Gyrus	44	51	0	9		2.93
Failed Stops > Go *Control > Cocaine*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Cuneus	18	15	-78	15	21	2.99
Failed Stops > Go *Cocaine > Control*			**x**	**y**	**z**	**k**	**Z**
	Putamen		18	15	-3	33	3.58
	Ventral Striatum		-9	18	-6	62	3.18
			-18	15	0		3.14

Table 9 Severity of childhood maltreatment is associated with reduced neural responses for response inhibition and error processing demands

a. Response inhibition

Successful Stops > Go -CTQ Regression		**BA**	**x**	**y**	**z**	**k**	**Z**
	Inferior Parietal Lobule/	40	-51	-42	27	63	3.92
	Superior Temporal Gyrus/	22	-63	-42	24		3.28
	Supramarginal Gyrus	40	-39	-45	36		2.94
	Inferior Frontal Gyrus/	45	51	24	24	61	3.33
	Middle Frontal Gyrus/	46	42	27	27		2.94
	Middle Frontal Gyrus	9	33	24	42		2.91

b. Error processing

Failed Stops > Go -CTQ Regression		**BA**	**x**	**y**	**z**	**k**	**Z**
	Insula	13	45	6	18	20	3.20
	Putamen		-15	12	-6	34	3.18

Figure 5 Choice behavior in the Roulette Task for changing levels of reward contingencies

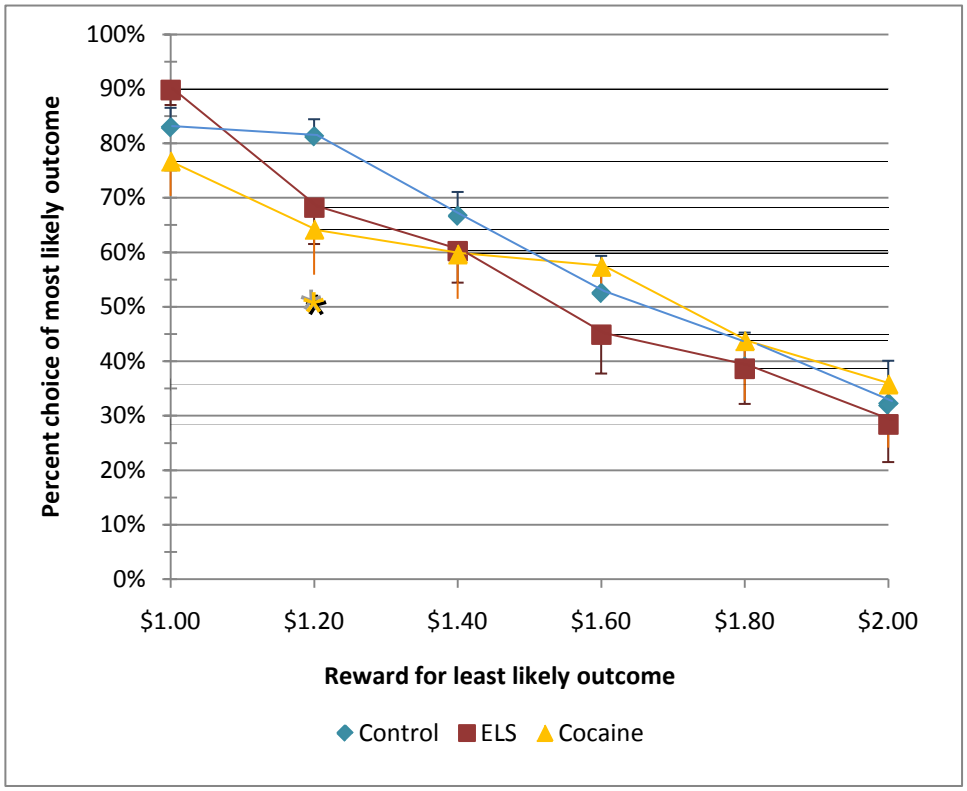


Figure 6 Choice behavior of female subjects in the Roulette Task for changing levels of reward contingencies

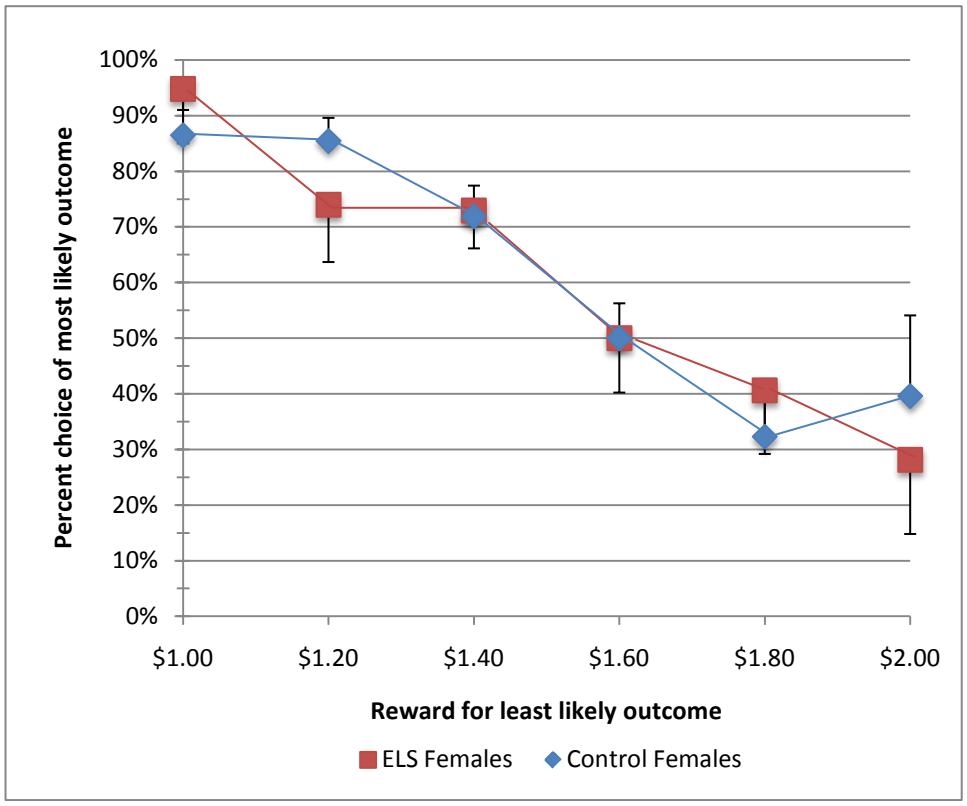
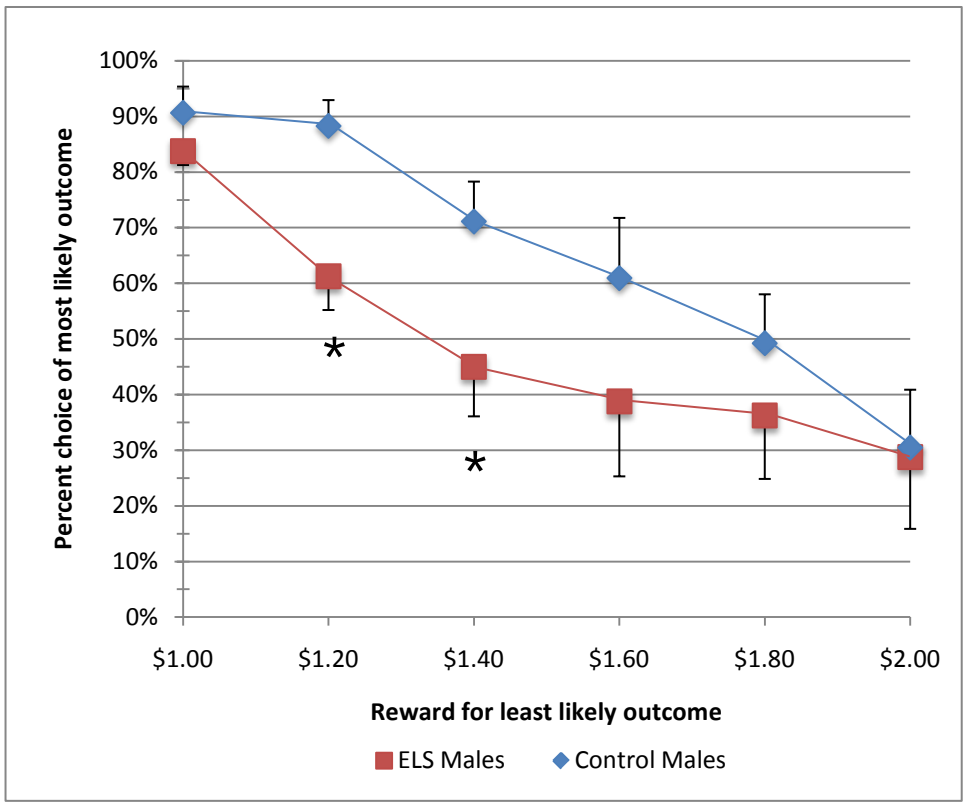


Figure 7 Choice behavior of male subjects in the Roulette Task for changing levels of reward contingencies

a. Early life stress status is associated with decreased choice of the most likely outcome for the $1.20/$0/80 and $1.40/$0.60 reward contingencies in males



b. Cocaine dependence is associated with decreased choice of the most likely outcome for the $1.20/$0/80 reward contingency in males

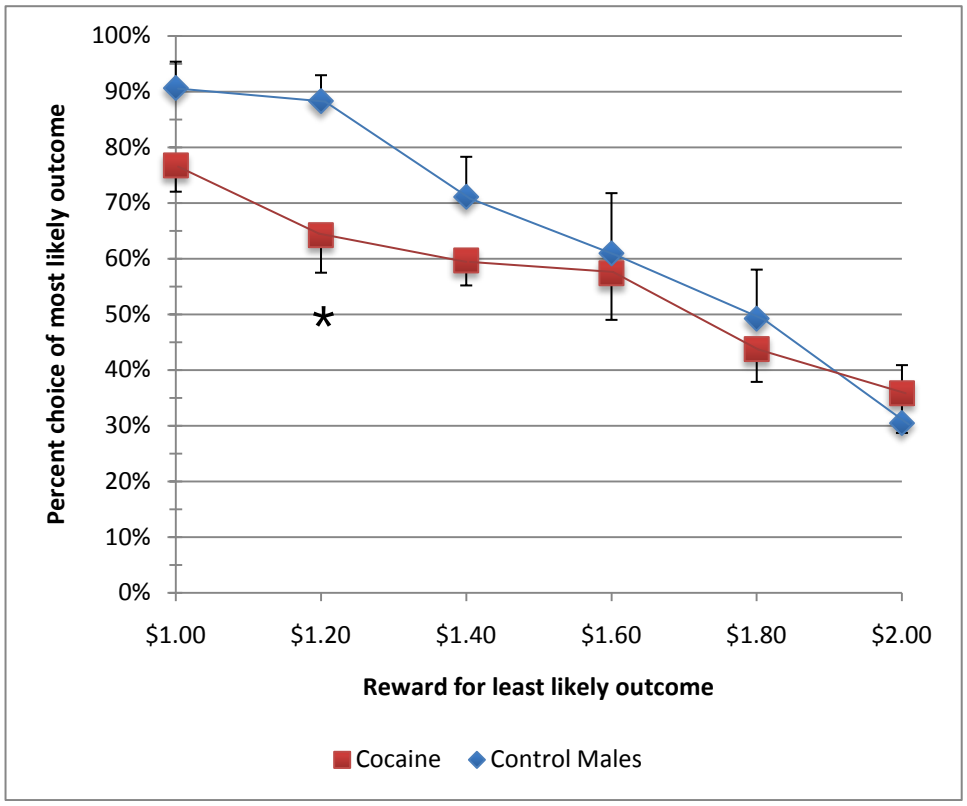


Figure 8 Decision making-related neural activations – Control group

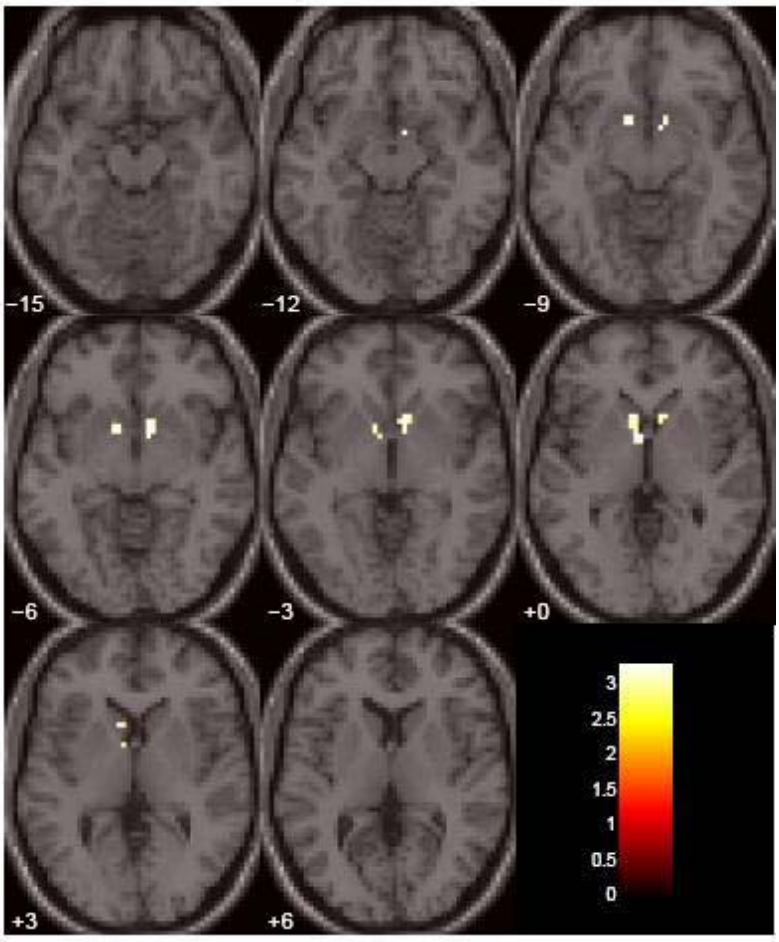


Figure 9 Decision making-related neural activations – ELS group

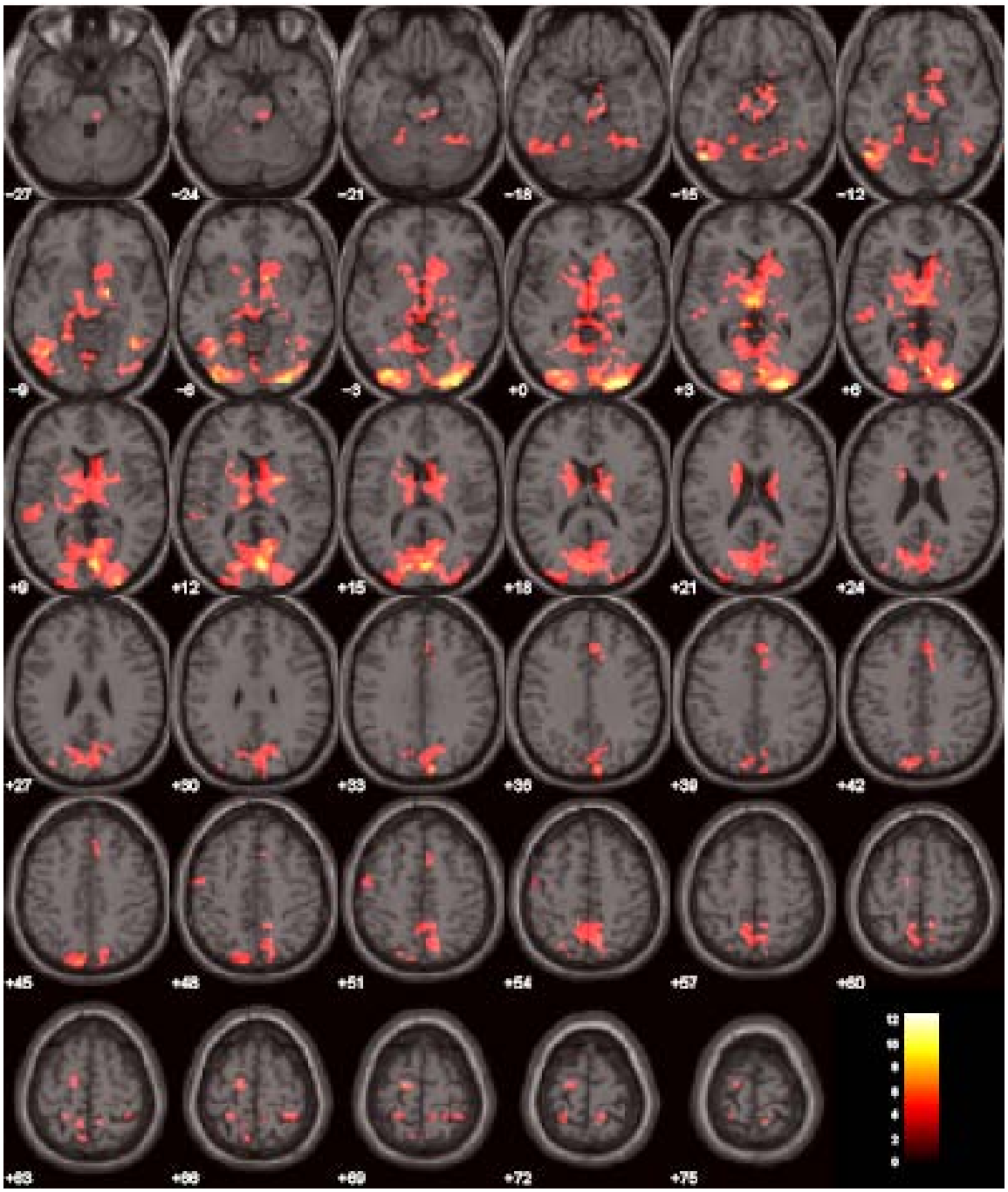


Figure 10 Decision making-related neural activations – Cocaine group

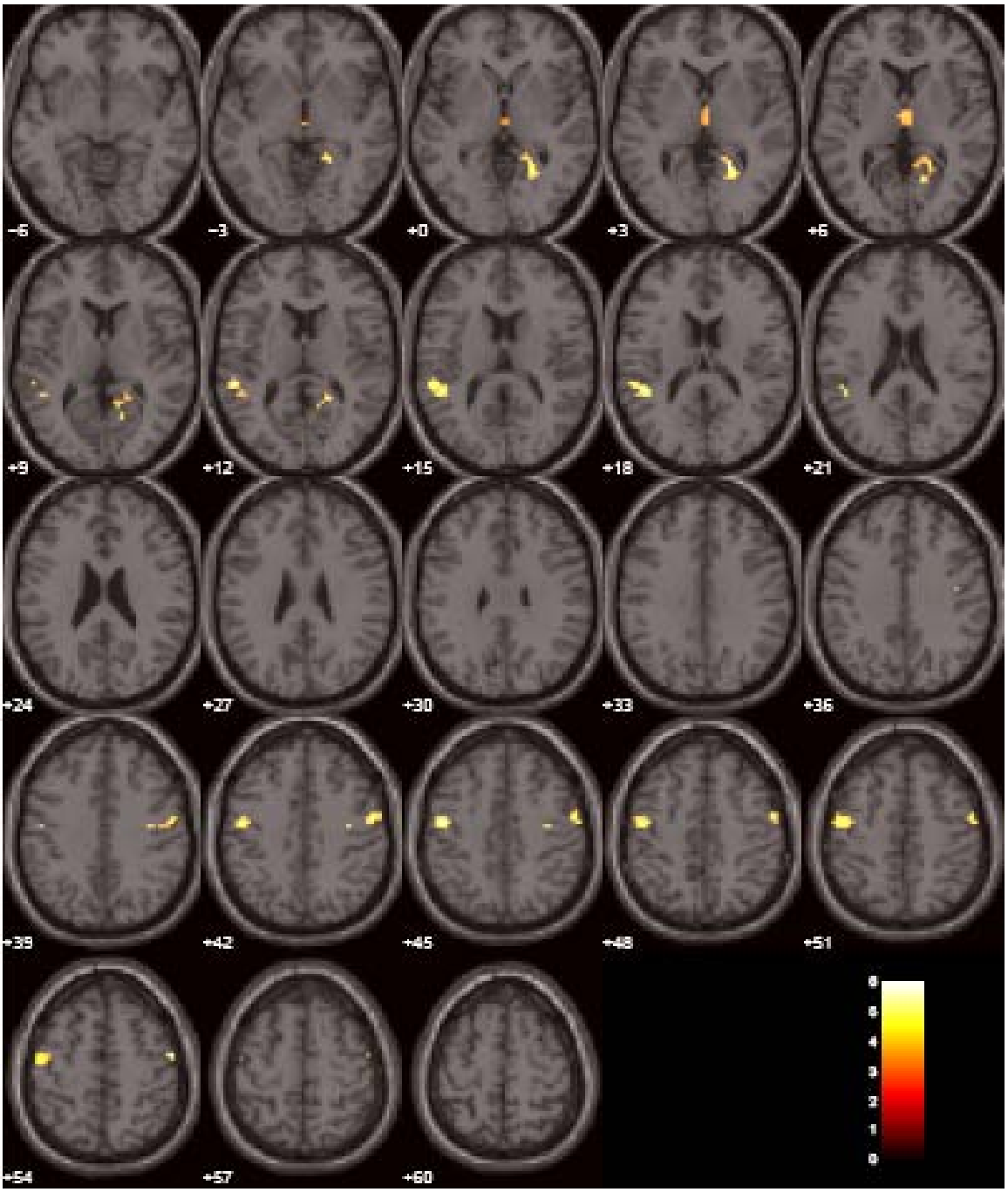


Table 10 Group-level decision making-related neural activations

Decision Making > Control *Control*		**x**	**y**	**z**	**k**	**Z**
	Striatum	9	3	-9	21	2.72
	Striatum	-12	6	-9	25	2.58
Decision Making > Control *ELS*	**BA**	**x**	**y**	**z**	**k**	**Z**
	Middle Occipital Gyrus 18	27	-96	3	1585	4.79
	Superior Frontal Gyrus/ 6	-15	-15	69	32	3.81
	Medial Frontal Gyrus/					
	Supplementary Motor Area					3.09
	Parahippocampal Gyrus 27	27	-30	-3	36	3.20
	Cingulate Gyrus 32	9	24	42	77	3.09
	Superior Temporal Gyrus 41	-54	-36	9	62	3.06
	Precentral Gyrus 4	-48	-9	51	21	3.05
	Postcentral Gyrus 5	36	-45	66	24	2.93
	Postcentral Gyrus 5	-21	-45	63	24	2.85
Decision Making > Control *Cocaine*	**BA**	**x**	**y**	**z**	**k**	**Z**
	Precentral Gyrus 6	54	-6	54	43	3.61
	Parahippocampal Gyrus/ 30	21	-51	3	62	3.51
	Posterior Cingulate/					2.93
	Lingual Gyrus					2.74
	Precentral Gyrus 4	-48	-9	45	58	3.49
	Superior Temporal Gyrus/ 42	-54	-36	12	47	3.37
	Insula 13	-45	-42	18		3.26
	Thalamus	0	-12	6	28	2.59

Table 11 Neural correlates of decision making modulated by level of risk

a. Neural correlates of decision making modulated by level of risk in Control subjects

Decision Making x Reward Contingency *Control*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Superior Frontal Gyrus	8	15	45	48	28	3.61
	Inferior Parietal Lobule	7	42	-72	48	183	3.48
	Medial Frontal Gyrus/	8	-3	30	45	74	3.18
	Superior Frontal Gyrus	6	-12	30	63		2.83
		8	-6	33	57		2.72
	Inferior Parietal Lobule	40	-54	-57	48	64	3.02
	Cingulate Gyrus	23	-3	-18	33	20	2.76
	Precuneus	7	-3	-72	39	48	2.62

b. Group differences in the neural correlates of decision making modulated by level of risk

Decision Making x Reward Contingency *Control > ELS*		**x**	**y**	**z**	**k**	**Z**
	Putamen	15	6	-6	15	3.43

Decision Making x Reward Contingency *Control > Cocaine*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Mid-Cingulate Cortex	24	21	-18	45	95	4.19
	Insula		-30	-6	18	58	3.68
	Medial Frontal Gyrus	24	-18	-3	51	79	3.64
	Anterior Cingulate Cortex	32	-12	42	6	70	3.07
	Ventrolateral Prefrontal Cortex	47	33	42	-6	37	2.99
	Insula	13	-36	-15	12	21	2.85
	Superior Frontal Gyrus	9	-12	45	33	20	2.80

Table 12 Dose-effect relationship between severity of early life stress and decision making-related neural activations

Decision Making > Control CTQ Regression		**BA**	**x**	**y**	**z**	**k**	**Z**
	Middle Temporal Gyrus/	39	57	-69	18	8353	5.42
	Supramarginal Gyrus/	40	63	-48	39		5.30
	Inferior Parietal Lobule	40	66	-42	30		5.28
	Caudate/		-12	27	-6	601	4.96
	Anterior Cingulate/	24	-6	21	-6		4.80
	Medial Frontal Gyrus	11	6	48	-12		4.59
	Precentral Gyrus/	4	15	-36	75	178	4.93
	Medial Frontal Gyrus	6	6	-27	72		4.61
	Superior Parietal Lobule	7	-21	-63	69	70	4.61
	Insula		-36	0	15	84	4.02
	Superior Parietal Lobule	7	27	-60	69	47	4.07
	Supplementary Motor Area	6	18	-9	57	20	3.68
	Inferior Frontal Gyrus	45	-51	21	15	24	3.62
	Cuneus	18	-12	-87	27	22	3.28
Decision Making > Control -CTQ Regression		**BA**	**x**	**y**	**z**	**k**	**Z**
	Thalamus/		6	-6	18	188	6.33
	Caudate		18	-9	24		4.91
	Lingual Gyrus	18	-9	-81	3	79	6.23
	Middle Occipital Gyrus	19	-30	-96	18	31	5.71
	Precuneus	19	-21	-84	42	234	5.71
	Medial Frontal Gyrus	10	18	63	6	30	5.56
	Superior Frontal Gyrus	6	-18	9	72	72	5.51
	Middle Frontal Gyrus	6	36	-9	69	90	5.14
	Inferior Frontal Gyrus	46	48	42	15	84	5.11
	Lingual Gyrus/	19	-15	-54	-3	82	4.86
	Posterior Cingulate	29	-3	-39	6		4.54
	Middle Frontal Gyrus	10	-36	48	6	21	3.90
	Putamen		18	12	-6	25	3.49

Table 13 Effect of early life stress on the neural responses to monetary gain or loss in the Roulette task

Win Outcomes *Control > ELS*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Supplementary Motor Area	6	9	-3	60	30	4.07
	Mid-Cingulate Cortex	24	6	-3	48	99	3.80
	Precentral Gyrus	6	48	0	15	32	3.68
	Globus Pallidus		12	6	-3	56	3.36
	Supplementary Motor Area	6	45	-12	63	38	3.34
	Pre-Supplementary Motor Area	6	21	3	60	38	2.97
Loss Outcomes *Control > ELS*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Supplementary Motor Area	6	9	-6	63	65	3.96
	Globus Pallidus		12	6	-6	94	3.43
	Cuneus	17	-9	-87	9	39	3.39
	Precentral Gyrus	6	45	-12	63	29	3.27
	Left Globus Pallidus		-9	0	-6	35	3.17

Table 14 Effect of cocaine dependence on the neural responses to monetary gain or loss in the Roulette task

Win Outcomes	

Cocaine > Control		**BA**	**x**	**y**	**z**	**k**	**Z**
	Mid-Cingulate Cortex	24	-24	-21	48	22	3.37
	Precentral Gyrus	7	18	-48	42	40	3.34
	Middle/Medial Frontal Gyrus	8	24	9	39	83	3.28
	Claustrum		27	12	15	49	3.13
	Insula	13	-36	9	12	246	3.05
	Inferior Frontal Gyrus		-39	45	6	74	2.87
Loss Outcomes *Cocaine > Control*		**BA**	**x**	**y**	**z**	**k**	**Z**
	Precuneus	31	24	-45	42	91	3.90
	Parahippocampal Gyrus	30	27	-54	0	188	3.54
	Inferior Frontal Gyrus	47	39	24	-15	122	3.38
	Precentral Gyrus	24	-24	-21	48	70	3.30
	Cingulate Gyrus	8	24	9	39	94	3.30
	Inferior Frontal Gyrus	45	-54	21	21	557	3.18

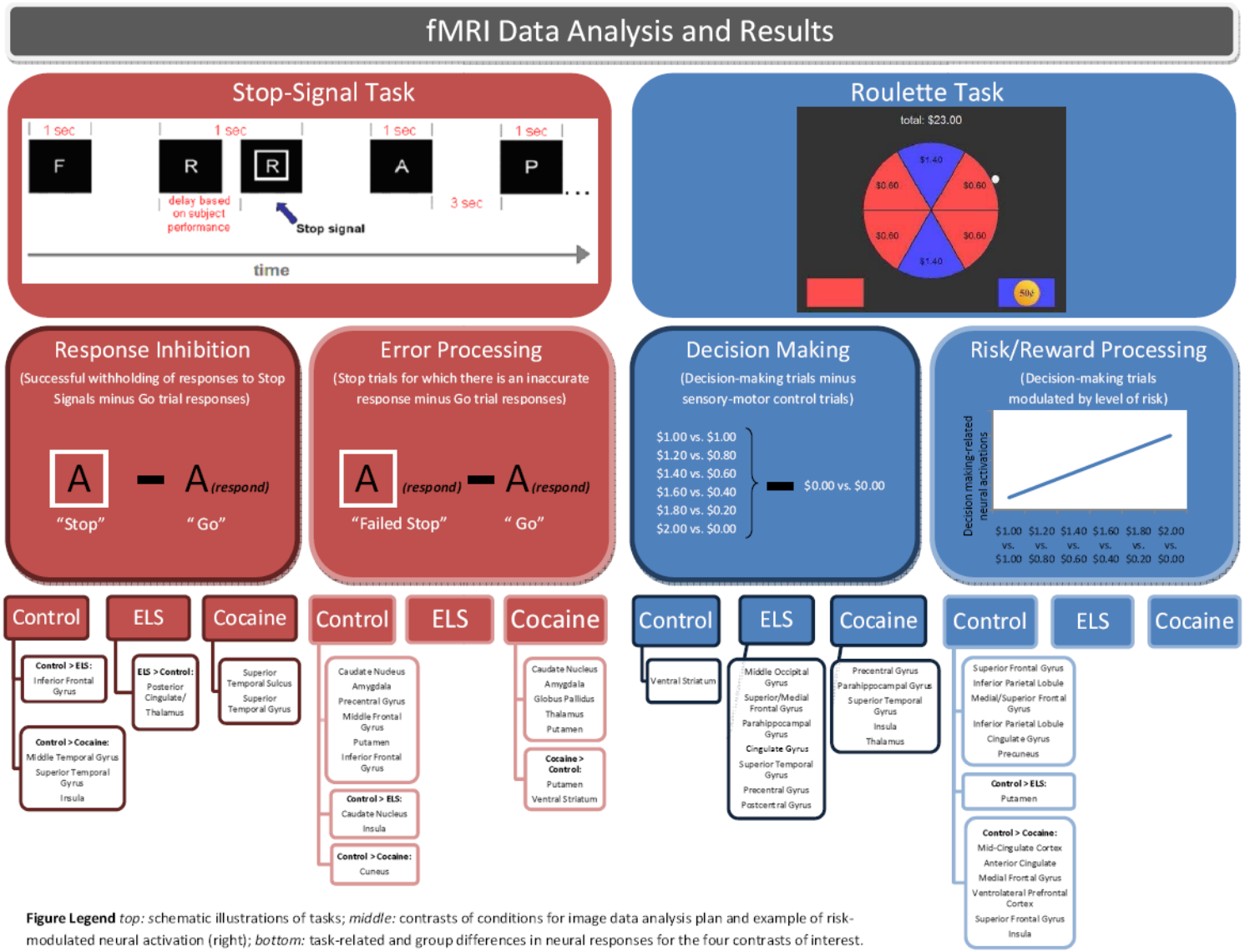


Figure Legend *top:* schematic illustrations of tasks; *middle:* contrasts of conditions for image data analysis plan and example of risk-modulated neural activation (right); *bottom:* task-related and group differences in neural responses for the four contrasts of interest.

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